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LUND
UNIVERSITY

DOCTORAL DISSERTATION

Doctoral dissertation for the degree of Doctor of Philosophy (PhD) at the Faculty of Medicine at Lund University to be publicly defended on June 14th, 2024, at 13.00 in Agardh Hall, CRC, Jan Waldenströms gata 35, Malmö.

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Title and subtitle: Aspects on efficacy in endovascular treatment with drug eluting stents and balloons in the repair of stenotic vessel lesions with special reference to local drug therapy.

Abstract:

Background: The need for vascular procedures for certain disease-specific causes is a major issue for health care today. This thesis will focus on endovascular treatment for PAD and malfunctioning haemodialysis access. Although many other vascular diseases and anatomic regions sometimes need to be managed with endovascular procedures, PAD and haemodialysis access together account for a significant part of the daily vascular operative production. The incidence of PAD is heavily increasing in society due to the ageing population and lifestyle issues, and an essential part of this pathological and metabolic issue is the increasing burden of diabetes mellitus in developed countries around the world. Also, the need for haemodialysis is increasing, partly due to the same reasons discussed earlier. For the last decades, the treatment of both PAD and malfunctioning haemodialysis access is increasingly being performed by interventional methods, which come with an increasing burden of handling intimal hyperplasia and other adverse treatment effects. These lead to early restenosis that significantly impairs the clinical results of the performed procedures as well as the patient's quality of life. New drug adjunctive angioplasty methods have been developed to deal with these postangioplasty problems. Studies are needed to evaluate their efficacy and safety compared to standard procedures.

Methods: Three RCTs and one retrospective observational cohort study were performed, all comparing drug eluting endovascular therapy with standard endovascular therapy in specified settings. The aim was to clarify an acceptable safety profile and possibly demonstrate superior treatment results with drug eluting technology.

I. Randomisation of 50+50 subjects in a single blinded, parallel group, clinical trial, comparing drug eluting angioplasty against conventional angioplasty when treating malfunctional haemodialysis access in the upper extremity.
II. Randomisation of 100+100 subjects in a single blinded, parallel group, clinical trial, comparing drug eluting stenting against standard bare metal stenting when treating arterial lesions in the superficial femoral artery or the popliteal artery in subjects with chronic limb threatening ischemia.
III. Nationwide observational cohort study, with data from SWEDVASC and NDR, analysing and comparing the results of drug eluting therapy in endovascular treatment of lower limb ischemia in subjects with and without diabetes mellitus.
IV. Randomisation of 35+35 subjects in a single blinded, parallel group, clinical trial, comparing drug eluting angioplasty against conventional angioplasty when treating complex crural arterial lesions in subjects with chronic limb threatening ischemia.

Results: Studies I and II did not completely fulfil the prestudy enrolment criteria. They were analysed and could not show any safety issues or superior results with drug eluting technology. Study III showed that subjects with diabetes mellitus and chronic limb threatening ischemia, treated with drug eluting methods, had superior amputation-free survival (HR 0.712 [CI 0.562-0.901], p=0.005). Study IV did not show any differences in primary outcome variables at one-year follow-up. However, amputation-free survival as a secondary outcome variable was significantly better among subjects treated with drug coated balloons (OR 0.31[CI 0.10-0.96], p=0.042).

Conclusion: The aggregated results signal a possible positive treatment effect with drug eluting technology compared to standard treatment. Unfortunately, two of the performed trials became underpowered and could not support a conclusion in favour of drug eluting technology. More and larger randomised studies are needed to clarify the role of drug eluting technologies in the treatment of vascular diseases.

Key words: Drug eluting, Drug coated, Angioplasty, Endovascular, Stent, Paclitaxel, Chronic limb threatening ischemia, Haemodialysis access, Diabetes Mellitus, Randomized trial.

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Coverphoto: Death of Seneca by Peter Paul Rubens (AD 1612)

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To my beloved family
For their support and patience
Åsa, Matilda, Johanna, and Ebba

“Cogito, ergo sum”

Rene Descartes, AD 1596-1650

French rationalist philosopher, mathematician, and scientist. He was the private tutor of Queen Christina of Sweden. He died from pneumonia on a cold winter day in Stockholm.

“Optimum est pati quod emendare non possis”

Seneca the Younger, 4 BC – AD 65

Roman stoic philosopher. After the Pisonian conspiracy, he died in Rome by his own knife, ordered by Nero, the Roman emperor. (From Moral Letters 107; IX)

“Life is short. That´s all there is to say. Get what you can from the present - Each of us lives only now, this brief moment”

Marcus Aurelius, AD 121-180

Roman emperor and stoic philosopher. He died in Sirmium, today a small Serbian city, where ten Roman emperors were born. He was the last of the five “good emperors”, and his death ended the two centuries long “Pax Romana”. (From Meditations 3; X)

Table of Contents

List of scientific papers

This thesis is based on the following manuscripts, referred to by their Roman numerals and reprinted with permission from their respective publisher.

I. Fransson T, Gottsäter A, Abdulrasak M, Malina M, Resch T. Drug eluting balloon (DEB) versus plain old balloon angioplasty (POBA) in the treatment of failing dialysis access: A prospective randomized trial. J Int Med Res. 2022 Mar;50(3):3000605221081662. doi: 10.1177/03000605221081662. PMID: 35354342; PMCID: PMC8978321.

II. Fransson T, Gottsäter A, Abdulrasak M, Malina M, Resch T. Randomized clinical Trial Comparing drug Eluting Stent Zilver PTX® Versus Bare Metal Stent Zilver Flex® for Treatment of Lesions in Femoral and Popliteal Arteries in Chronic Limb Threatening Ischemia. Vasc Endovascular Surg. 2023 Oct;57(7):706–716. doi: 10.1177/15385744231171746. Epub 2023 Apr 21. PMID: 37085152.

III. Fransson T, Sturedahl AD, Resch T, Björn E, Gottsäter A. Nationwide Study of the Outcome of Treatment of Lower Extremity Atherosclerotic Lesions With Endovascular Surgery With or Without Drug Eluting Methods in Patients With Diabetes. J Endovasc Ther. 2024 Apr 5:15266028241241967. doi: 10.1177/15266028241241967. Epub ahead of print. PMID: 38577781.

IV. Fransson T, Mohammed Y, Gottsäter A, Resch T. Prospective randomized clinical trial comparing paclitaxel coated balloon versus conventional balloon angioplasty for treatment of infragenicular complex arterial lesions in critical limb threatening ischemia. The CRURAL DEB study. Submitted.

An overall glance at the thesis

PAPER	AIM	METHOD	RESULTS
Drug eluting balloon (DEB) versus plain old balloon angioplasty (POBA) in the treatment of failing dialysis access: A prospective randomized trial.	To compare the results of angioplasty with drug coated and non-coated standard balloons when treating arteriovenous (AV)-fistulas and AV-grafts.	Single centre, single blinded, randomised parallel group trial.	There were no differences in primary outcome variables. The study did not reach the planned number of enrolments.
Randomized clinical trial comparing drug eluting stent Zilver PTX® versus bare metal stent Zilver Flex® for treatment of lesions in femoral and popliteal arteries in chronic limb threatening ischemia.	To compare results of drug coated and non-coated stents when treating stenoses or occlusions in the femoropopliteal (FP) arterial segment.	Single centre, single blinded, randomised parallel group trial.	There were no differences in primary outcome variables. The study did not reach the planned number of enrolments.
Nationwide study of the outcome of treatment of lower extremity atherosclerotic lesions with endovascular surgery with or without drug eluting methods in patients with diabetes.	To investigate the results of drug coated treatment in patients with diabetes compared to treatment in patients without diabetes by merging two large nationwide registries (SWEDVASC and NDR).	Nationwide observational retrospective cohort study.	Patients with diabetes suffering from critical limb threatening ischemia had a significantly lower risk for amputation or death in comparison with patients without diabetes when treated with drug eluting technology.
Prospective randomized clinical trial comparing paclitaxel coated balloon versus conventional balloon angioplasty for treatment of complex infragenicular arterial lesions in critical limb threatening ischemia. The CRURAL DEB study.	To compare results of angioplasty with drug coated and non-coated standard balloons when treating arterial stenoses or occlusions in below-the-knee arteries in subjects with chronic limb threatening ischemia (CLTI).	Single centre, single blinded, randomised parallel group trial.	There were no differences in primary outcome variables. The secondary outcome variable amputation-free survival was significantly better in the group treated with drug coated balloons.

Foreword

Finalising this research project with a doctoral thesis has been a distant goal for many years, with a frequent unsure feeling about a possibly unrealistic task that might not be important. At age 57, why keep going when it, in a bigger perspective, probably will not change much in everyday real life? The reason is that this, in most senses, is an inward journey. It has been an educational process overall, although one as, in my case, has clinical and medical experience and knowledge in the field of interest for almost three decades.

Although I did not consider it initially, I´ve learned important things, not only regarding some different theoretical circumstances. Generally, you will run into various administrative and practical issues that you need to confront. This most commonly involves people, and people, as you know, are different. So, from this smaller perspective, you will probably not be the same person after the examination, which is swiftly approaching.

From the beginning, I was not actually interested in the health care professions at all, after finishing four years of technical gymnasium in biochemistry. The life, though, took some mysterious ways. After completing the military services at the Swedish lifeguard dragoons (at this time in history, compulsory for young men), I was supposed to continue with my preliminary plans for my future life. At this point in my life, I was pretty convinced about studying quantum physics and astronomy by applying for a university education in physics, but I had unfortunately missed the application deadline and was forced to wait another year. And waiting was just what I was doing, struggling at a temporary, quite dull work as a carpenter, but as you know, you need to earn money to live…

I soon realised there are other higher education programs you can start twice a year, so being bored, I decided to apply for some of these programs that would begin in the spring semester. One was to study for a medical degree and become a medical doctor. Actually, this was slightly unrealistic, as my grades were not high enough, but you never know…

As expected, I did not qualify at first, second, or third admission, and I completely forgot this and was planning for my “real” applications later that year. Suddenly, one day, while still working as a carpenter, I got a telephone call. Cell phones didn´t exist, and the call had been forwarded to the office, where my boss now held the telephone.

The person on the other end was calling from the Medical Faculty in Lund. She swiftly explained that there were so many drop-offs this first semester that they had decided to fill up the course by calling people who had applied, starting at the top of the list from the third admission. I certainly was not at the top of the list, but she

said that many had not answered or had other plans, which was not extraordinary as it was 10 o´clock in the morning and a long way into the semester.

So here I was on an ordinary Thursday at work, and the education had been going on for seven weeks. I should start on Monday, and I had to decide on the spot; otherwise, she would continue the calls further down the list.

I looked at my curious boss and asked him if I could end my employment on the spot because maybe I should become a doctor instead. Fortunately, he said that I could quit, which was not obvious, and I then replied to the woman on the telephone that I´d be there on Monday.

Confused and excited, I went straight home that same Thursday, saying goodbye to my work colleagues, and started to get things fixed for this relatively large deviation of my life. Three days to get hold of a place to stay, among other things, is not a great deal of time, but friends are valuable, as we all know…

On that Monday, a new path in my life, one that I had not considered earlier, started.

Another fantastic part of this story is all the coincidences. This Thursday, my mother was at home because she had an appointment with her hairdresser (usually, nobody was at home at this time). She answered the phone call just when she was on her way out through the front door and forwarded the telephone number to my work (my boss). Then, the woman from the faculty also bothered to call my boss to get in contact with me (she could have continued down the list). Suppose these things had not happened in that continuous leap of instances. In that case, I´d probably spend my days today looking into microcosmos or macrocosmos and not dealing so much with people, which is more or less the essence of being a surgeon.

I´ve never regretted this change of plans (my mother always said that someone had this plan for my life), although it became quite different from what I thought about my future profession at that time. On the other hand, I de facto, in parallel with my medical education, graduated from several courses at the institution for astronomy in Lund in a peculiar way so as not to abandon this idea completely (which I finally did anyway). I consider that a medical doctor is, at least for many people, in general, a profession with social credibility and great possibilities to interact with or influence other people's lives, and maybe this was the right choice for me as a person, although I´m not 100% sure about this even to this day. Eventually, I´ll be …

Early in my career, I realised that I´m actually rather practical, making it reasonable to head for a surgical profession, which at the beginning was not pinpointed. Again, it is the interactions with people that affect your life path, and at my first position as a young doctor, I met colleagues who affected my life in the direction towards choosing general and vascular surgery. At this time, all vascular procedures were performed with surgical methods, and the endovascular era had not commenced at all. My picture of the surgeons who performed vascular procedures was like a

picture of the Ghostbusters and their motto, “Who do you want to call?” because they were always the “rescue” when things got out of hand. I saw them doing a lot of appreciated “saves” when colleagues ran into trouble. It was here that I made my choice. I stayed with these colleagues to become a general and vascular surgeon. (Vascular Surgery became a speciality of its own in 2006 when I was already a consultant)

So, it began…

After years of vascular surgical training, you slowly and continuously confronted the growing endovascular development, which was primarily accounted for by our radiology colleagues. Seeing the theoretical and practical opportunities for the patients made me realise that this will profoundly affect future vascular surgical therapy, and quite early, I started to collaborate with colleagues at different radiology departments who rather unselfishly supported and educated me in these techniques. Finally, I did become quite an experienced open AND endovascular surgeon, although I am still learning and improving my skills to this day. Throughout these years, I also have come to realise, in some circular perspective, that in real life, there does not actually exist any vascular surgeon that can perform all the daily vascular workload at the highest level of quality, a level that should be the least acceptable for most patients in need for a vascular procedure. It should be considered a myth that a vascular surgeon is supposed to expertly manage all vascular procedures, and no hypothetical patient wants such a surgeon.

Being focused on open surgical procedures for revascularisation of ischemic extremities for the last decade, this circumstance leads us back to the why and what regarding this thesis. The endovascular options for revascularisation increased rapidly with increasing efficacy, and an increasing portion of ischemic subjects were offered this minimally invasive treatment, a shift that, in many cases, was well supported. Focus, obviously at this time in my career, shifted towards the endovascular portfolio, which so far only was discussing mechanic properties and solutions for the increasing need for reinterventions during and after endovascular treatments as the biological response after angioplasty and stents hampered the optimisation of the treatment efficacy. It was at this time that a combined pharmaceutical and mechanic solution saw light with the development of drug coated balloons and stents. This was an inspiring theoretical solution, and the initial results seemed promising. A seed was sown that eventually led to the idea of this research project as part of a doctoral degree.

And we started 2012…

Some of these 12 years are put into this book, and it can be said as Jean Jacques Rousseau, the famous Genevan philosopher during the Ages of Enlightenment, put it, -*Patience is bitter, but its fruit is sweet*-.

It has been a primarily rewarding but sometimes irritating process, and during more extended periods, it was hard to see an actual meaningful ending. Writing this today, I instead feel enlightened and proud that I continued (I suppose you need to suffer from slight OCD). I end my foreword of this achievement with some amazing head-on quotes formulated by one of the brightest minds and scientists of all time. Some of the quotes can be applied to this work, and my thoughts and others can guide you all in other aspects of life.

"Fear or stupidity has always been the basis of most human actions".

"If A is success in life, then A equals x + y + z. Work is x; y is play; and z is keeping your mouth shut."

"Only a life lived for others is a life worthwhile".

"All of science is nothing more than refinement of everyday thinking".

"The path to a lazy compromise is a one-way street. There is no U-turn and no stopping".

"Never do anything against conscience even if the authority demands it".

"Wisdom is not a product of schooling but of the life-long attempt to acquire it".

-Albert Einstein-

List of abbreviations

ABI	Ankle brachial index
ACE	Angiotensin converting enzyme
ACEI	Angiotensin converting enzyme inhibitor
AE	Adverse events
AF	Atrial fibrillation
AFS	Amputation-free survival
AK	Above Knee
AMI	Acute myocardial infarction
AMP	Amputation
AMS	Absorbable magnesium scaffold
AR	Absolute risk (ARR=absolute risk reduction)
ARB	Angiotensin receptor blocker
AS	Anatomical success
ASA	Acetylsalicylic acid
AUC	Appropriate Use Criteria
AV	Arteriovenous
AVF	Arteriovenous fistula
AVG	Arteriovenous graft
BB	Brachiobasilic
BC	Brachiocephalic
BES	Balloon-expandable stent
BK	Below knee
BMS	Bare metal stent
BMT	Best medical treatment
BP	Blood pressure
BP	Bypass
BS	Binary stenosis
BTK	Below the knee
CAD	Coronary arterial disease
CCB	Calcium channel blockers
CD	Clinically driven
CDC	Central dialysis catheter
CE	Conformite´ Europeenne

DFU	Diabetic foot ulcer
CHD	Congestive heart disease
CHF	Congestive heart failure
CI	Confidence interval
CILO	Cilostazol
CKD	Chronic kidney disease
CLI	Critical limb ischemia
CLTI	Chronic limb threatening ischemia
COPD	Chronic obstructive pulmonary disease
CRYO	Cryoplasty balloon treatment
CS	Clinical success
CTA	Computed tomography angiography
CTO	Chronic total occlusion
CUT	Cutting balloon angioplasty
CV	Cardiovascular
CVD	Cerebrovascular disease
CVS	Central vein stenosis
DA	Directional atherectomy
DAPT	Dual antiplatelet therapy
DCB	Drug coated balloon
DEB	Drug eluting balloon
DES	Drug eluting stent
DET	Drug eluting therapy
DFU	Diabetic foot ulcer
DM	Diabetes mellitus
DSA	Digital subtraction angiography
DUS	Duplex ultrasound
EFS	Event-free survival
ENDO	Endovascular
ERS	Everolimus eluding resorbable scaffold
ESRD	End stage renal disease
EVT	Endovascular treatment
FDA	Food and Drug Administration
FEM	Femoral
FF-	Freedom from -

FP	Femoropopliteal
HbA1c	Haemoglobin A1c or glycated haemoglobin
HEL	Helical (stent)
HPPTA	High pressure percutaneous transluminal angioplasty
HR	Hazard ratio
HRQoL	Health related quality of life
IC	Intermittent claudication
ICD	Ischemic cardiac disease
IH	Intimal hyperplasia
INR	International normalised ratio
IP	Infrapopliteal
IPF	Index of patency function
IPR	Inpatient registry
ISR	In-stent restenosis
ITT	Intention to treat
IVL	Intravascular lithotripsy
IVP	Intervention-free period
IWS	Interwoven stent
KDOQI	Kidney Disease Outcomes Quality Initiative
Kt/V	K*(t/V) (K= dialyzer clearance ml/min; t=time; V=volume of body water)
LA	Laser atherectomy
LDL	Low density lipoprotein
LLL	Late lumen loss
LS	Limb salvage
MAE	Medical adverse events
MACE	Major adverse cardiovascular events
MALE	Major adverse limb events
MIP	Maximum intensity projections
ML	Median length
MRA	Magnetic resonance angiography
NDR	National Diabetes Registry
NOAC	Novel oral anticoagulants
OA	Orbital atherectomy
OR	Odds ratio

OS	Overall survival
P 1-3	Popliteal artery part 1-3
PA	Popliteal artery
PAA	Popliteal artery aneurysm
PAD	Peripheral arterial disease
PaP	Primary assisted patency
PBP	Prosthetic bypass
pBP	Primary bypass
PCI	Percutaneous coronary intervention
PDR	Prescribed drug register
POBA	Plain old balloon angioplasty
POP/Pop	Popliteal artery
PP	Primary patency
pp	per protocol
PSV	Peak systolic velocity
PSVR	Peak systolic velocity ratio
PTA	Percutaneous transluminal angioplasty
PTFE	Polytetrafluoroethylen (ePTFE = expanded PTFE)
PTX	Paclitaxel
PVD	Peripheral vascular disease
QoL	Quality of Life
RC	Radiocephalic
RC	Rutherford category
RCT	Randomised controlled trial
RR	Restenosis rate
RR	Relative risk (RRR=relative risk reduction)
SAE	Serious adverse events
SAPT	Single antiplatelet therapy
sBP	Secondary bypass
SE	Standard error
SES	Self-expanding stent
SF	Stent fracture
SFA	Superficial femoral artery
SG	Stentgraft
SP	Secondary patency

SV	Stent to vessel (ratio)
SWEDVASC	Swedish National Vascular Registry
SWEDPAD	Swedish drug-elution trial in peripheral arterial disease
TASC	Transatlantic intersociety consensus
TIG	Tigris® (stent)
TLR	Target lesion revascularisation
TP	Toe pressure
$TcPO_2$	Transcutaneous oxygen pressure
TG	Triglycerides
TS	Technical success
TVR	Target vessel revascularisation
VBP	Vein bypass
WIfI	Wound, Ischemia, foot Infection

Definitions

Absolute risk	Absolute risk refers to the actual probability of an outcome occurring in a specific group regardless of any other factors. ARR represents the difference in event rates between the experimental and control groups.
Ambispective	Having both prospective and retrospective components.
Anastomosis	A cross connection between two components, such as two blood vessels.
Aneurysm	An abnormal blood-filled swelling of an artery or vein, resulting from a localised or general weakness in the wall of the vessel.
Angioplasty	The mechanical widening of narrowed or obstructed blood vessels with the use of balloons.
Angiosome	This relates to a three-dimensional unit of skin and underlying tissue, vascularised by a source artery termed an *arteriosome* and drained by a vein termed a *venosome*. It is a concept often used by specialists in plastic surgery.
Ankle brachial index	Ratio of the blood pressure at the ankle and the blood pressure in the upper arm (*brachium*).
Antegrade	Directed forward.
Arteriovenous access	Surgically constructed connection/anastomosis between an artery and a superficial vein with the purpose of using it as an inflow and outflow for a haemodialysis procedure.
Atherectomy	A surgical procedure to remove plaque from an artery.
Autologous	Derived from part of the same individual.
Binary stenosis	Binary restenosis is defined as a reduction in the percent diameter stenosis of 50% or more. The term "binary" means that patients are placed in 2 groups: those with ≥50% stenosis and those with <50% stenosis.
Binary restenosis	See above. Restenosis means the recurrence of a stenosis.

Bypass	Going past or around. An alternative passage is created to divert a bodily fluid around a damaged organ. For example, going past an occluded vessel.
CLTI	A clinical syndrome defined by the presence of objective peripheral artery disease (PAD) in combination with rest pain, gangrene, or lower limb ulceration for at least two weeks duration.
Cohort	In statistics, a demographic grouping of people, especially those in a defined age group or having a common characteristic.
Composite	From two or more constituent materials. In vascular surgery, it refers to when different conduits or materials are used together. (Composite bypass – from autologous vein AND prosthetic material)
Confidence interval	In statistics, a confidence interval (CI) is an interval expected to typically contain the parameter being estimated. More specifically, given a confidence level (95% or 99% are typical levels), a CI is a random interval that contains the parameter being estimated (95% or 99%) of times.
Critical limb ischemia	See CLTI. An older nomenclature.
Crural (vessel)	Latin crūrālis, from crūs (“leg”). In vascular surgery, this accounts for the vessels in the lower leg below the knee joint and below the popliteal artery.
Cryoplasty	Dilation of an artery combined with cryotherapy, i.e. the balloon is inflated with nitrous oxide at a temperature of -10° C, in order to reduce the restenosis rate.
Cumulative	That is formed by an accumulation of successive additions. In statistics incorporating all current and previous data over time up to the present or at the time of measuring or collating.
Cutting balloon	A specialised angioplasty technique, with sharp blades incorporated in the balloons to facilitate a crack open of a stenosed or occluded artery.
Debulking	Partially removing. In vascular endovascular surgery, this addresses the partial removal of plaque or debris from inside the diseased artery in an effort to improve the results of angioplasty or stenting in heavily calcified arteries.

Directional atherectomy	A variant of endovascular atherectomy when you shear plaques from the arteries in a specified direction.
Dissection	In this context, dissection can be a solution for passing obstructed vessels by dissecting a passage in the wall of the artery, but more commonly, it refers to a complication after angioplasty when the different layers in the arterial wall separate from each other, negatively affecting the flow. This situation is most often managed with a "bailout" stent.
Dysfunctional access	Not performing its proper or intended function regarding a haemodialysis circuit.
Embolectomy	Surgical removal of an embolus to relieve an embolus. Rudolf Virchow introduced the word in 1848. Latin embolus ("piston"), from Ancient Greek ἔμβολος (émbolos, "peg, stopper"), usually a blood clot or other matter carried by the bloodstream and causing a blockage or occlusion of a blood vessel.
Endarteriectomy	A surgical procedure to remove plaque from an artery. The endarterium is the lining of an artery. (Also, *endarterectomy*)
*Thromb*endarteriectomy	This is the same as above but also involves blood clots. (Also, *thrombendarterectomy*)
Endoaneurysmorraphy	A surgical procedure to treat aneurysms by suturing its walls to restore the blood vessel's normal size.
End-to-end	Connecting two ends to each other, i.e. the ends of two vessels.
End-to-side	Connecting one vessel to the side of the other vessel.
Endothelium	A thin layer of flat epithelial cells that lines the heart, serous cavities, lymph vessels, and blood vessels.
Endovascular	Endo- from Ancient Greek ἔνδον (éndon, "inner; internal"). Vascular procedure within a blood vessel, by percutaneous access.
Excipient	An ingredient that is intentionally added to a drug for purposes other than the therapeutic or diagnostic effect. In this context, we refer to "carriers" for the different drugs on balloons or stents that are supposed to be eluted in the wall of arteries at balloon inflation or stent delivery to reduce the restenosis rate.

Haemodialysis access	With access to the blood circuit, dialysis removes waste products from the blood in kidney failure. To perform this, you must have repeated access to the blood circulation, which usually means a tunnelled dialysis catheter, arteriovenous fistula, or graft.
Hazard (rate)	The frequency at which the event of interest occurs per unit of time, given that it has not yet happened up until that time
Hazard ratio	In survival analysis, the hazard ratio (HR) is the ratio of the hazard rates corresponding to the conditions characterised by two distinct levels of a treatment variable of interest.
HbA1c	Glycated haemoglobin (glycohaemoglobin, or haemoglobin A1c).
Head-to-head	Direct one-to-one comparison.
Homograft (Homologous)	Surgical graft transplant or tissue between genetically different individuals of the same species. Synonym – Allograft.
Hybrid surgery	Something of mixed origin or composition. In this case, a procedure consisting of both open surgery and endovascular intervention.
Hyperlipidaemia	Excess quantity of lipids in the blood, usually derivates from cholesterol metabolism. This can be a symptom of several medical conditions. It is one of the most critical risk factors for PAD/CAD/CVD.
Incidence	The act of something happening or the extent or the relative frequency of something happening. In statistics, a measure of the rate of new occurrence of a given medical condition in a population within a specified period.
In-stent restenosis	Recurrence of a stenosis inside a previously deployed vascular stent. This is an essential problematic issue in endovascular surgery.
Infragenicular vessel	Means infra=below and genu=knee. Vessels below the knee level.
Infrainguinal vessel	Means infra=below and inguinal= something of groin origin or pertaining to the groin. In vascular surgery, it relates to vessels below the inguinal ligament (groin) and outside the abdomen.

Infrapopliteal vessel	Means infra=below and popliteal=something of popliteus origin (area behind the knee) or pertaining to the popliteus. It is a synonym for below the knee, infragenicular, and crural.
In-situ	Means to leave something in its original place or position. In vascular surgery, it relates to when you leave the vein bypass in its original place instead of removing it and reversing the vein.
Interposition	The act of interposing, the state of being interposed or being placed between. In vascular surgery, it means putting a graft between the ends of a resected vessel.
Intermittent claudication	Intermittent=presenting at intervals, periods, or situations and Claudication= from Latin claudicātiō ("limping", noun), from claudicō ("to limp, halt, be lame"). In PAD, this is a situation of episodic pain and limping when the circulation to lower limbs limits the physiological possibility of walking due to a shift towards anaerobic combustion when tissue oxygenation becomes insufficient due to vessel stenoses.
Intima	The innermost part of an anatomical tubular structure, particularly an artery. The thin lining inside the blood vessels is essential in protecting from vessel thrombosis.
Intimal hyperplasia	A process by which the cell population increases within the innermost layers of the arterial wall, and the intima becomes thicker. This is a situation that often develops after angioplasty and stenting due to the vessel response. This leads to restenosis that is not due to arteriosclerosis.
Juxtaanastomotic	Juxta= near together or in close proximity, and the word anastomosis. In vascular surgery, it means something closely related to an anastomosis.
Lithotripsy	Litho- ("relating to a stone or calculus") + Ancient Greek τρῖψῐς (trîpsis, "rubbing, friction"). In endovascular intervention, a technique to handle calcifications in the treatment of PAD. Simultaneously, when performing angioplasty, the vessel is treated with ultrasound shock waves to crush the plaques and facilitate the dilatation.

Meta-analysis	A systematic procedure for statistically combining the results of multiple similar studies.
Multicollinearity	In statistics, multicollinearity, or collinearity, is a situation where the predictors in a regression model are linearly dependent.
Nominal diameter	Relates to the normal diameter or the actual diameter when measured. It should be compared to oversizing, which occurs when choosing a stent or balloon proportionally larger than the nominal diameter.
Odds	The ratio of the probability of an event happening to that of it not happening.
Odds ratio	An odds ratio (OR) is a statistic that quantifies the strength of the association between two events, A and B. The odds ratio is defined as the ratio of the odds of A in the presence of B and the odds of A in the absence of B, or equivalently (due to symmetry), the ratio of the odds of B in the presence of A and the odds of B in the absence of A. Two events are independent if and only if the OR equals 1, i.e., the odds of one event are the same in either the presence or absence of the other event.
Orbital atherectomy	A variant of endovascular atherectomy, where you shear plaques from the arteries by a rotating drill-like device working in all directions simultaneously.
Overfitting	This is a situation in statistical modelling in which an analysis corresponds too closely or exactly to a particular dataset and may, therefore, fail to fit additional data or predict future observations reliably.
Patency	Patent=open, unconcealed, or conspicuous. In vascular surgery, it relates to the openness (of a tube, such as a blood vessel or catheter) and the relative absence of blockage or obstruction.
Peak systolic velocity	Peak relates to the highest level. Systolic is associated with the contractive phase of the heart cycle. Velocity relates to the speed of blood inside the vessels. It is the highest speed of blood inside the vessel during the heart contraction.

Peak systolic velocity ratio	See above. If you measure the speed at a stenosis, the velocity will rise in a functional relationship to the degree of stenosis. If you compare this to the velocity in a normal part of the vessel, you can calculate a ratio. A ratio >2.0-2.5 is significant and relates to physiologically relevant stenosis.
Percutaneous	Takes place through the skin and involves a puncture.
Photoablative	Ablation in medicine refers to the removal of a body part, tumour, or organ. Photo refers to light (Latin). In vascular interventions, photoablative means using laser light to perform atherectomy by vaporisation. It is a special form of debulking or crossing technique.
Physiological malfunction	Relates to access circuit function. A dialysis access can still be clinically functional, but when measuring hemodynamic parameters of the access, these can sometimes repeatedly fall outside an optimal interval. This situation may sometimes proceed to a clinically relevant malfunction.
Predilatation	Dilatation prior to some other procedure, usually to facilitate the procedure.
Postdilatation	Dilatation following another procedure, usually when the result of the primary procedure is unsatisfactory.
Prevalence	The quality or condition of being prevalent, wide extension, or spread. In statistics, this means the total number of cases of a disease in a given statistical population at a given time divided by the number of individuals in that population.
Primary endpoint	Primary endpoints are typically efficacy measures that address the main research question.
Primary patency	Refers to the uninterrupted flow of blood through a treated blood vessel without the need for additional interventions. It is the duration of time from the initial intervention until the blood vessel needs to be retreated or is occluded.
Primary assisted patency	Refers to a hybrid measure that combines aspects of both primary and secondary patency. It relates to the time from the initial intervention until the subsequent intervention is needed to maintain blood flow, and the vessel may not have failed to a level of thrombosis or occlusion.
Primary prevention	Medically intervening before any health effects occur.

Prospective study	Prospective relates to something likely or expected to happen or happen either in the near or far future. In statistics, such a study has an experimental design that looks forward in time and observes events as they happen.
Randomised study	This is a study with a prospective design that randomly assigns subjects to an experimental group and a control group.
Recirculation	This is the process when a defined volume of liquid circulates again at a defined place in a flow circuit. In vascular access intervention, this phenomenon appears when the same portion of blood passes through the dialyser multiple times, leading to a very inefficient dialysis process. The reason is often stenoses in the access circuit that limit the blood flow.
Recoil	Refers to starting or falling back, a rebound. In vascular surgery, it occurs after angioplasty when the vessel is unable to stay fully open. If the recoil is considerable, you must support the vessel interior with a scaffold, usually a vascular stent.
Relative risk	Relative risk compares the risk of an outcome between exposed and unexposed groups. RRR represents the difference in event rates expressed relative to the control event rate. It is usually expressed as a percentage.
Renal replacement therapy	(RRT) is a therapy that replaces the normal blood-filtering function of the kidneys, including dialysis (haemodialysis or peritoneal dialysis), hemofiltration, and hemodiafiltration. Another form of RRT is a renal transplant.
Residual stenosis	Refers to remaining or leftover. In vascular surgery, it means that some degree of stenosis remains in the treatment area after the procedure is finalised. It principally means that the procedure was a technical failure.
Restenosis	Recurrence of an earlier treated stenosis.
Retrograde	Directed backwards.

Retrospective study	Retrospective relates to something in the past, contemplating or looking backwards. In statistics, such a study has an experimental design that looks back in time and assesses events that have already occurred. The outcome for each subject is already known when the project starts.
Secondary endpoint	Secondary outcomes are those that are more exploratory in nature or for which effects may be too small to detect from your sample but are still of interest and valuable to assess.
Secondary patency	Refers to the duration (or situation) of time that a blood vessel remains open after the initial intervention, even if subsequent interventions are required to restore blood flow and the vessel has failed to the level of thrombosis or occlusion.
Secondary prevention	Identifying diseases in the earliest stages, before the onset of signs and symptoms, and medically intervening.
Statins	A class of medications that reduce the risk and mortality of cardiovascular disease in people at high risk. They are the most prescribed cholesterol-lowering drugs, known as HMG-CoA reductase inhibitors. There are multiple variants of this drug. atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin.
Statistical power	The level of statistical power tells us how strong a hypothesis test is at detecting an effect in the study population.
Stenosis	Latin stenōsis, from Ancient Greek στένωσις (sténōsis, "narrowing"), from στενόω (stenóō, "to confine, to contract"). For vascular surgeons, this means narrowing a vessel.
Stent	The word "stent" derives from the name of an English dentist, Charles Thomas Stent. It is a tube-like device inserted inside vessels to keep the passage open. Stents are used in many other areas of medicine and surgery besides vascular procedures.
Stochastic	Randomly determined.
Subclinical malfunction	Similar to physiological malfunction.

Suprainguinal vessel	Supra=above and inguinal relates to the groin (See infrainguinal). It means the intraabdominal vessels supplying the lower limbs with blood.
Systematic	Methodical, regular, and orderly. Procedurally orderly determined.
Thiazides	Refers to a class of diuretics based on the chemical structure of benzothiadiazine. They are commonly used as antihypertensive agents. The thiazide drug class was discovered and developed at Merck and Co. in the 1950s. The first approved drug of this class was chlorothiazide.
TLR	The procedure when the same earlier treated lesion is retreated.
TVR	The procedure when the same earlier treated vessel is retreated.
Tertiary intervention	Managing disease medically post diagnosis to slow or stop disease progression.
Vessel preparation	This is the procedure by which the vessel is prepared for the main treatment. Usually, vessel preparation is performed with atherectomy, lithotripsy, or cutting devices, but even standard plain balloon angioplasty is commonly used before placing a stent or a drug eluting device.

Abstract

Background: The need for vascular procedures for certain disease specific causes is a major issue in health care today. This thesis will focus on endovascular treatment for peripheral arterial disease (PAD) and malfunctioning haemodialysis access. Although many other vascular diseases and anatomic regions sometimes need to be managed with endovascular procedures, PAD and haemodialysis access together account for a significant part of the daily vascular operative production.

The incidence of PAD is heavily increasing in society due to the ageing population and lifestyle issues, and an essential part of this is the increasing burden of diabetes mellitus. Also, the need for haemodialysis is increasing, partly due to the same reasons mentioned earlier.

For the last decades, the treatment of both PAD and malfunctioning haemodialysis access is increasingly being performed by interventional methods, which come with an increasing burden of handling intimal hyperplasia (IH) and other adverse treatment effects. IH leads to early restenosis that significantly impairs the clinical results of the performed procedures as well as the patient's quality of life. New drug adjunctive angioplasty methods have been developed to overcome these postangioplasty problems, and there is a need for studies that evaluate the efficacy and safety of these compared to the standard procedures.

Methods: Three randomised controlled trials (RCT)s and one retrospective observational cohort study were performed, all comparing drug eluting endovascular therapy with standard endovascular therapy in specified settings. The aim was to clarify an acceptable safety profile and possibly demonstrate superior treatment results with drug eluting technology.

I. Randomisation of 50+50 subjects in a single blinded, parallel group, clinical trial, comparing drug eluting angioplasty against conventional angioplasty when treating malfunctional haemodialysis access in the upper extremity.
II. Randomisation of 100+100 subjects in a single blinded, parallel group, clinical trial, comparing drug eluting stenting (DES) against standard bare metal stenting (BMS) when treating arterial lesions in the superficial femoral artery or the popliteal artery in subjects with chronic limb threatening ischemia (CLTI).
III. Nationwide observational cohort study, with data from the Swedish National Vascular Registry (SWEDVASC) and Swedish National Diabetes Registry (NDR), analysing and comparing the results of drug eluting therapy in endovascular treatment of lower limb ischemia in subjects with and without diabetes mellitus (DM).

IV. Randomisation of 35+35 subjects in a single blinded, parallel group, clinical trial, comparing angioplasty using drug coated balloons (DCB) against conventional angioplasty when treating complex crural arterial lesions in subjects with CLTI.

Results: Study I and II did not ultimately reach the preset enrolments. They were analysed and could not show any safety issues or improved results with drug eluting technology. Study III showed that subjects with DM and CLTI, treated with drug eluting methods, had superior amputation-free survival (HR 0.712 [CI 0.562-0.901], p=0.005). Study IV did not show any differences in primary outcome variables at one-year follow-up. However, amputation-free survival as a secondary outcome variable was significantly better among subjects treated with drug coated balloons (OR 0.31[CI 0.10-0.96], p=0.042).

Conclusion: The aggregated results suggest a possible positive treatment effect with drug eluting technology compared to standard treatment. Unfortunately, two of the performed trials became underpowered and could not clearly support a conclusion in favour of drug eluting technology. More and larger randomised studies are needed to clarify the role of drug eluting technologies in the treatment of vascular diseases.

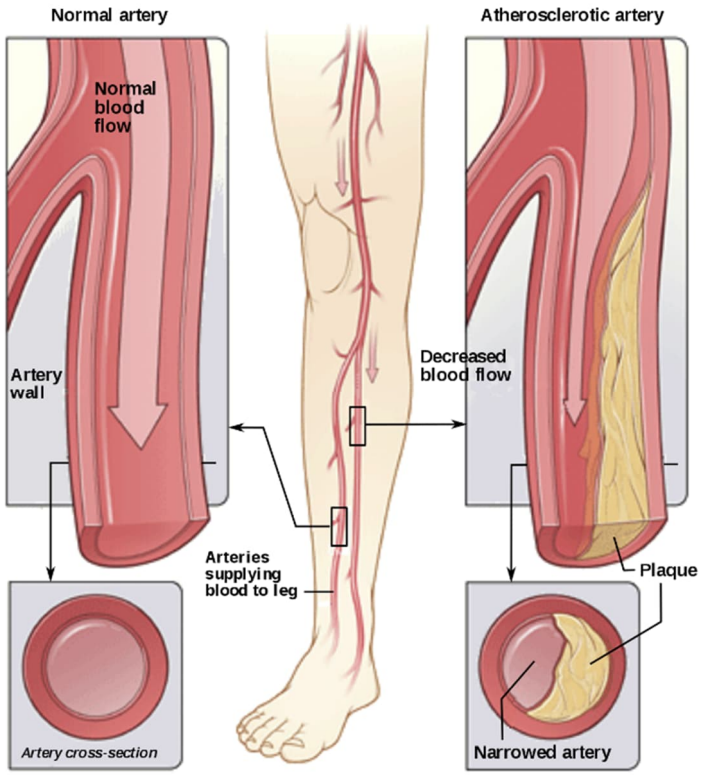
Introduction

This thesis deals with two of the most common problems vascular surgeons face in their daily practice, namely, peripheral arterial diseases - PAD and revisions of malfunctional haemodialysis access. Over the last decades, the development of these procedures has evolved from exclusively being performed with open vascular surgery to a situation where most cases are performed with endovascular methods. In the setting of PAD, this development has simultaneously led to a decreased number of amputations,[1] and regarding revision of a malfunctional access, the endovascular method is today the first line treatment in almost all relevant cases[2].

Peripheral arterial disease

Peripheral arterial disease - PAD is a disorder affecting all the arteries in the body, excluding those supplying the brain and the heart (cerebrovascular disease – CVD and coronary artery disease – CAD). PAD most commonly affects the arterial supply to the legs, and it also constitutes a significant part of the peripheral vascular diseases – PVD, which also includes diseases involving veins and lymphatics.

Decreasing arterial circulation to the lower extremities affects more than 236 million worldwide and increases with age[3-12]. It can give rise to functional disabilities of different severity as well as ischemic ulcers or limb amputations. Asymptomatic PAD with an objectively decreased perfusion to the lower limb is also a marker and risk factor for both serious CVD and CAD, eventually leading to stroke or myocardial infarction. PAD is associated with poor quality of life and a high risk of major adverse cardiovascular events - MACE (myocardial infarction, stroke, or cardiovascular death) and major adverse limb events - MALE (peripheral revascularisation or major limb amputation)[13 14]. The survival of subjects with symptomatic PAD is also clearly affected, as seen in PAD trials[15-17], with a short-term mortality between 5.4-9.5%. The risk of developing chronic limb threatening ischemia - CLTI and eventually facing an amputation is around 11%[18]. Conservatively treated subjects with CLTI have an 18% mortality rate and a 27% amputation rate at 12 months[19]. See Picture I.



Picture I. Schematic view of PAD in lower extremities.

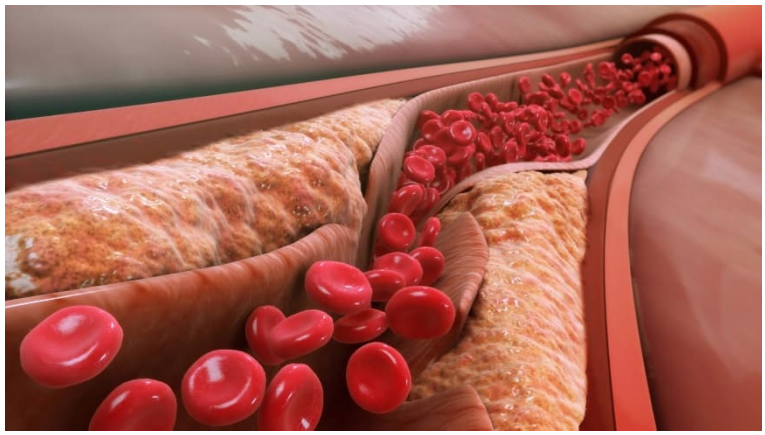
(By Jmarchn - Own work, CC BY-SA 3.0, https://commons.wikimedia.org/w/index.php?curid=31200275)

Aetiology

Major risk factors for developing PAD are cigarette smoking, renal insufficiency, diabetes mellitus (DM), hypertension, hypercholesterolemia, and obesity. Genetic factors can play a significant role, but usually, the most critical determinants of PAD are unhealthy lifestyle factors such as diet and a low amount of physical activity[3-6].

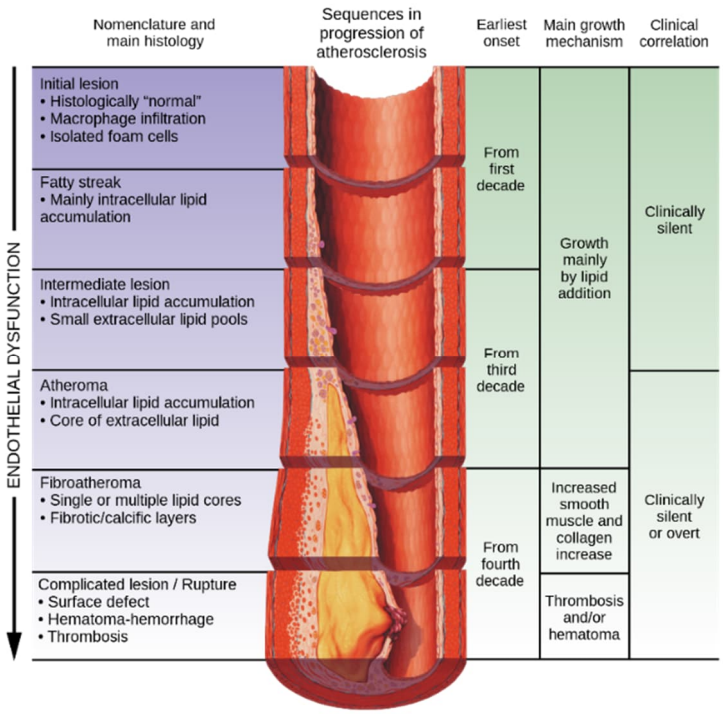
Atherosclerosis

In most cases, PAD develops from atherosclerosis, a condition primarily caused by the storage of blood compounds and active inflammation in the vessel wall, which will give rise to plaques composed of fat, cholesterol, and calcium, among other compounds. These plaques give rise to narrowing of the artery and, ultimately, a total occlusion[20]. See Pictures II, III, and IV.



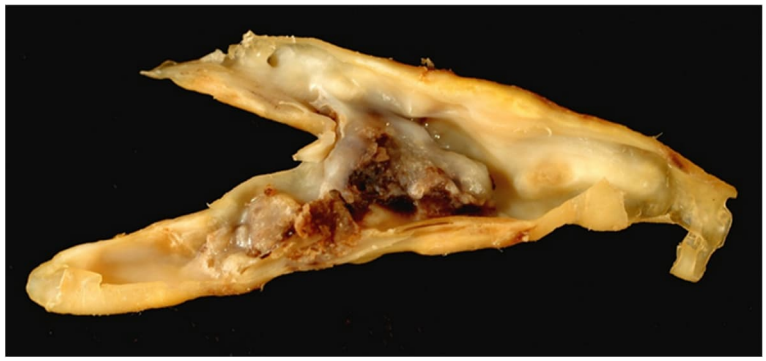
Picture II. Schematic picture of vessel atherosclerosis narrowing the arterial lumen.

(By Manu5 - http://www.scientificanimations.com/wiki-images/, CC BY-SA 4.0, https://commons.wikimedia.org/w/index.php?curid=67489698)



Picture III. Table showing the development of atherosclerotic disease.

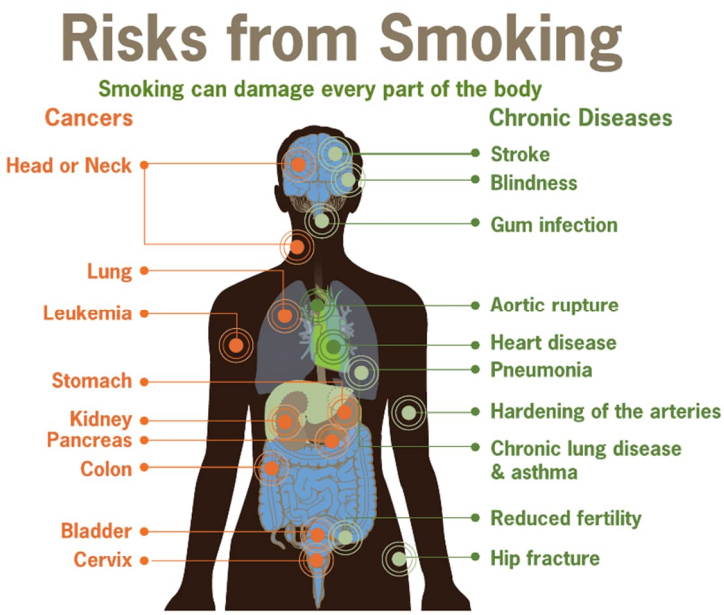
(By YitzhakNat - Own work and based on. Made with MS Visio., CC BY-SA 4.0, https://commons.wikimedia.org/w/index.php?curid=121967143)



Picture IV. Photo of an excised atherosclerotic plaque.
(By Ed Uthman, CC BY 2.0, https://commons.wikimedia.org/w/index.php?curid=1208790)

Smoking

Smoking is a significant contributor to PAD, and smoking cessation has profound effects on both the symptoms and cardiovascular risk[21]. Smoking cessation combined with physical activity and secondary preventive medications can significantly affect the effective walking distance. Smoking also affects the results of vascular procedures and their prognosis[22]. See Picture V.



Picture V. Schematic view of the human body showing some of the diseases caused by smoking.
(By CDC - This file was derived from: Tobacco Use-CDC Vital Signs-September 2010.pdf, Public Domain, https://commons.wikimedia.org/w/index.php?curid=20852937)

Diabetes Mellitus

The prevalence of DM is increasing in society in a pandemic way[23 24], profoundly affecting health care services. DM affects over 450 million people worldwide[23 25], causing atherosclerosis through effects on platelets, endothelial cells, and smooth muscle cell function[26].These effects make DM one of the leading risk factors for PAD[25-28]. PAD can manifest itself as intermittent claudication (IC) or CLTI with rest pain or ulceration[29 30]. Both conditions are associated with increased long-term mortality[31 32]. DM also has a negative impact on the long-term prognosis regarding acute myocardial infarction (AMI) and major amputation after invasive endovascular treatment of both IC and CLTI[33-47]. The incidence of amputations is very high among subjects suffering from DM compared to the general population[48 49], but the incidence can be decreased by offering more vascular surgical procedures[50].

Subjects with DM have a 2- to 4-fold increased prevalence of PAD, higher rates of complications after vascular intervention, and worse outcomes overall[43 51-54]. The distribution of vascular disease is also different and more distally located[55]. DM often causes a phenomenon- called arterial media sclerosis, which is a condition with stiff, uncompressible lower leg arteries that affect the possibility of registering adequate ankle pressures. Usually, toe pressures must be measured on subjects with a diagnosis of DM to confirm a diagnosis of PAD[46]. Foot ulcers and limb amputations are of significant concern in the population with DM and PAD. Specific considerations may apply to subjects with DM regarding the choice of revascularisation methods, that more often possibly should be performed by open surgery, which seems to offer superior results in the diabetic cohort with complicated ulcers[56].

Effect of gender

There is a difference between male and female subjects regarding the presentation and symptoms of PAD. The results of interventions also differ. Women usually have equal or better overall results after revascularisation regardless of the choice of method[57-61], but in some specified settings, worse outcomes can be expected, as in the treatment of FP arterial disease[62 63]. Women with PAD also more often present with CLTI or atypical symptoms in the leg[64 65]. It is essential to keep these differences in mind, as in some settings, one must consider that some treatment modalities are not as effective in female subjects[66]. The interconnection, with sometimes worse results, can be mainly explained by the fact that females more often have small calibre vessels.

Intermittent claudication – IC

Most subjects with objective signs of vascular impairment in the lower legs are asymptomatic for a long time, as the body can compensate for arterial narrowing by increasing the vessel area and developing collateral pathways. When symptoms appear, most suffer from a limited walking distance before a need to rest. Asymptomatic subjects, as well as most subjects with IC, should not be treated invasively, as conservative measures such as smoking cessation, training, preventive cardiovascular medications, and lifestyle changes have good clinical results. Exercise programs have a good effect on IC symptoms[67-72], and the walking distance can also be further effectively improved by non-operative active interventions such as supervised exercise programs[73-76]. Surgery or endovascular procedures should only be considered in highly selected cases. The critical outcome for these subjects is quality of life (QoL), which generally corresponds poorly to most infrainguinal endovascular procedures, which have limited efficacy in the long-time perspective. However, QoL may be improved after endovascular intervention in the short- and medium-time perspective[77 78]. The reason is that improvement by conservative modes is more durable than endovascular procedures, given that the latter often needs to be revised several times during a long follow-up period, which increases the cumulative procedural risk. Conservative treatment has virtually no risks at all, and with training, the body also learns to tolerate higher levels of anaerobic cellular combustion.

Chronic Limb Threatening Ischemia – CLTI

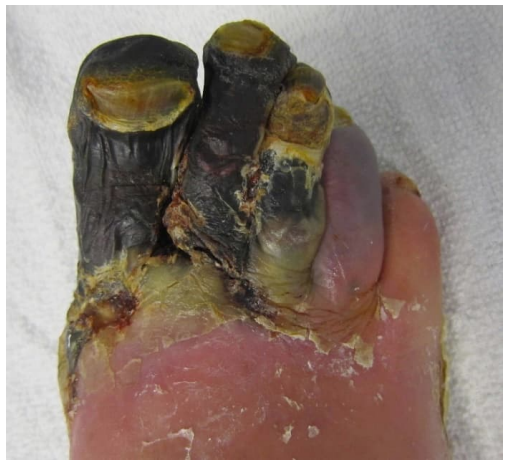
CLTI caused by PAD is an increasing clinical challenge in our ageing populations[18 23 41 79-85], partly related to the increasing burden of DM[23 41 43]. The life expectancy and quality of life in a PAD population, frequently also hampered by multiple comorbidities, is usually poor[79 81-85].

Only a minor part of subjects with unspecified PAD will deteriorate to CLTI, and in PAD population registries, the prevalence of amputation reaches 1%[61]. When an objective diagnosis of CLTI is at hand, this seriously affects the risk for death or amputation in the short perspective, with a one-year amputation rate of 6-38%[80]. The five-year survival is worse than for most common cancer forms, with a mortality rate of 29-48%[80]. The treatment results and survival after intervention are also worse[86].The distribution of arterial lesions in CLTI is also more distally located with more critical stenoses in the popliteal and crural region[87]. See Picture VI.

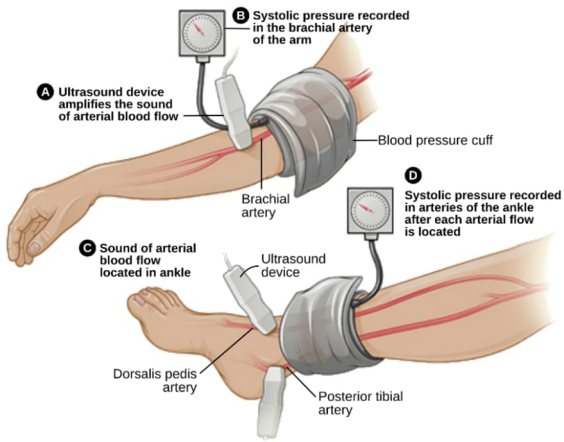
Diagnosis of Peripheral Arterial Disease - PAD

A history of symptoms, together with a physical exam, is essential and usually sufficient to make a diagnosis. The diagnosis can be confirmed by measuring the

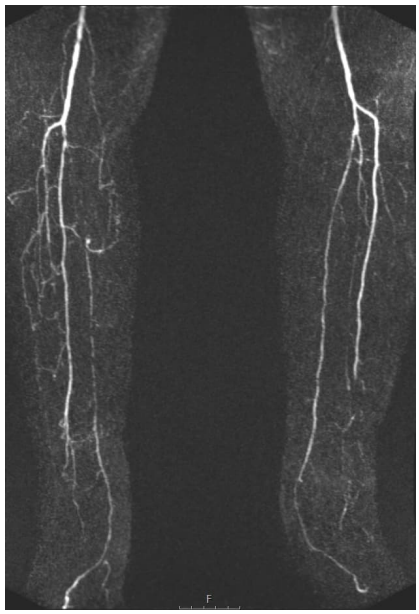
ankle brachial index (ABI), sometimes combined with a treadmill examination. Distal tissue perfusion can be examined with toe pressures and distal tissue oxygenation by measuring transcutaneous oxygen pressure ($TcPO_2$). If invasive treatment is considered, you must further examine the patient to obtain vascular anatomy in order to select the appropriate revascularisation method. This examination can be done with duplex ultrasound - DUS, computerised tomography angiography – CTA, magnetic resonance tomography angiography – MRA, or a conventional selective angiography[8 10 29]. See Pictures VII and VIII.



Picture VI. Photo showing gangrene of forefoot (RC VI or Fontaine IV).
(By James Heilman, MD - Own work, CC BY-SA 3.0, https://commons.wikimedia.org/w/index.php?curid=14572015)



Picture VII. Schematic view showing how to perform an ankle brachial index.
(By Jmarchn - Own work, CC BY-SA 3.0, https://commons.wikimedia.org/w/index.php?curid=31168075)



Picture VIII. MRA of the infragenicular arterial circulation.

PAD can be classified according to different scales to make comparisons easier and reporting more reproducible[88]. See Tables 1-5.

Fontaine classification	
I	Asymptomatic
IIa	IC > 200m
IIb	IC <200m
III	Rest pain
IV	Ulcer or Gangrene

Table 1. Fontaine classification. Rene Fontaine, French cardiologist, 1954[89].

Rutherford categories	
I	Mild IC
II	Moderate IC
III	Severe IC
IV	Rest pain
V	Minor tissue loss
VI	Major tissue loss or gangrene

Table 2. Rutherford categories. R B Rutherford, American vascular surgeon, 1986, revised 1997[90].

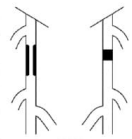
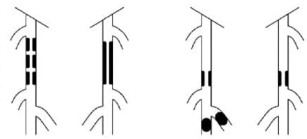
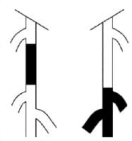
TASC A lesions • Single stenosis ⩽10 cm in length • Single occlusion ⩽5 cm in length	
TASC B lesions • Multiple lesions (stenoses or occlusions), each ⩽5 cm • Single stenosis or occlusion ⩽15 cm not involving the infrageniculate popliteal artery • Heavily calcified occlusion ⩽5 cm in length • Single popliteal stenosis	
TASC C lesions • Multiple stenoses or occlusions totaling >15 cm with or without heavy calcification • Recurrent stenoses or occlusions after failing treatment	
TASC D lesions • Chronic total occlusions of CFA or SFA (>20 cm, involving the popliteal artery) • Chronic total occlusion of popliteal artery and proximal trifurcation vessels	

Table 3. TASC II classification of femoropopliteal arterial disease[91].

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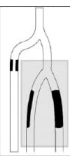
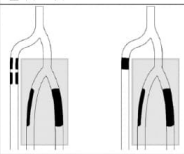
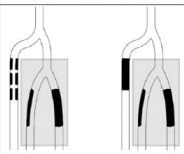
TASC A lesions Single focal stenosis, ⩽5 cm in length, in the target tibial artery with occlusion or stenosis of similar or worse severity in the other tibial arteries.	
TASC B lesions Multiple stenoses, each ⩽5 cm in length, or total length ⩽10 cm or single occlusion ⩽3 cm in length, in the target tibial artery with occlusion or stenosis of similar or worse severity in the other tibial arteries.	
TASC C lesions Multiple stenoses in the target tibial artery and/or single occlusion with total lesion length >10 cm with occlusion or stenosis of similar or worse severity in the other tibial arteries.	
TASC D lesions Multiple occlusions involving the target tibial artery with total lesion length >10 cm or dense lesion calcification or non-visualization of collaterals. The other tibial arteries occluded or dense calcification.	

Table 4. TASC II classification of infrapopliteal arterial disease[92].

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The Wound, Ischemia, and Foot Infection (WIfI) classification system.
This consists of 3 components graded separately from 0 (none) to 3 (severe). One component may be dominant but the specific combination of scores is used to estimate the risk of limb amputation at 1 year and the need for or benefit of revascularization.

Wound (W)		
Grade	Ulcer	Gangrene
0	None	None
1	Small, Shallow	None
2	Deep with exposed bone, joint, or tendon	Limited to digits
3	Extensive, deep, and involving forefoot and/or midfoot with or without calcaneal involvement	Extensive and involving forefoot and/or midfoot Full Thickness heel necrosis with or without calcanael involvement

Ischemia (I)		
Grade	ABI Ankle systolic pressure	Toe pressure or transcutaneous oximetry
0	>0.80 > 100 mmHg	>60 mmHg
1	0.60-0.80 70-100 mmHg	40-60 mmHg
2	0.40-0.59 50-69 mmHg	30-39 mmHg
3	<0.40 <50 mmHg	<30 mmHg

Foot infection (fI)	
Grade	Clinical manifestation
0	No symtoms or signs of infection
1	Infection indicated by ≥ 2 of the following: • Local swelling or induration • Erythema 0.5 -2.0 cm around ulcer • Local tenderness or pain • Local warmth • Purulent discharge (thick, opaque to white or sanguieous)
2	Infection as described above with: • Erythema > 2cm around ulcer • Involving structures deeper than skin and subcutaneous tissues (eg, abcess, osteomyelitis, septic arthritis, fascitis) • No signs of systemic inflammatory response (see below)
3	Infection as described above with ≥ 2 signs of systemic inflammatory response syndrome: • Temperature > 38˚C or < 36˚C • Respiratory rate > 20/min or PaCO2 < 32 mmHg • Heart rate > 90/min • WBC > 12000/µL or < 4000/µL or 10% immature forms

Table 5. WIfI classification system of PAD. Joseph L Mills Sr 2010[93].

Non-interventional treatment - Best Medical Treatment (BMT)

CATEGORY	TREATMENT	COMMENTS
Smoking cessation	Stop tobacco use, with or without pharmacological or behavioural treatment[10 94].	Active smoking increases the risk of failure of vascular procedures[22].
Glycaemic control	Lower HbA1c to target (<53 mol/L) levels with anti-diabetic therapy[6 46 95].	Glycaemic control may reduce microvascular complications, improve wound healing, and lower the risk for infections[6 46 95].
Antiplatelet drugs	Clopidogrel 75mg x 1 or ASA 75mgx1 is recommended[96-98].	Combination therapy with ASA and low-dose rivaroxaban 2.5mg twice daily may reduce cardiovascular complications[16 96].
Lipid lowering drugs	With manifest PAD, treat with statins ± adjunctive to LDL<1.4mmol/L[10 99].	Lowering LDL has a high impact on cardiovascular risk. MALE is reduced[100 101].
Blood pressure control	BP < 130/80 mmHg is a recommended goal[10 102 103].	No contraindications against beta-blocker use. ACEI[102-104] and ARB reduce cardiovascular events in PAD[102 103].
Physical activity	Physical exercise 3-5 times a week reduces cardiovascular risk factors[10 102 105].	Healthy diet, weight, and waist circumference are correlated to cardiovascular risk[10 102].

When diagnosed with PAD, it is essential to manage all risk factors to lower the risk for peripheral vascular complications but also to accomplish an overall reduction of cerebrovascular and cardiovascular events, as there is an interconnection between

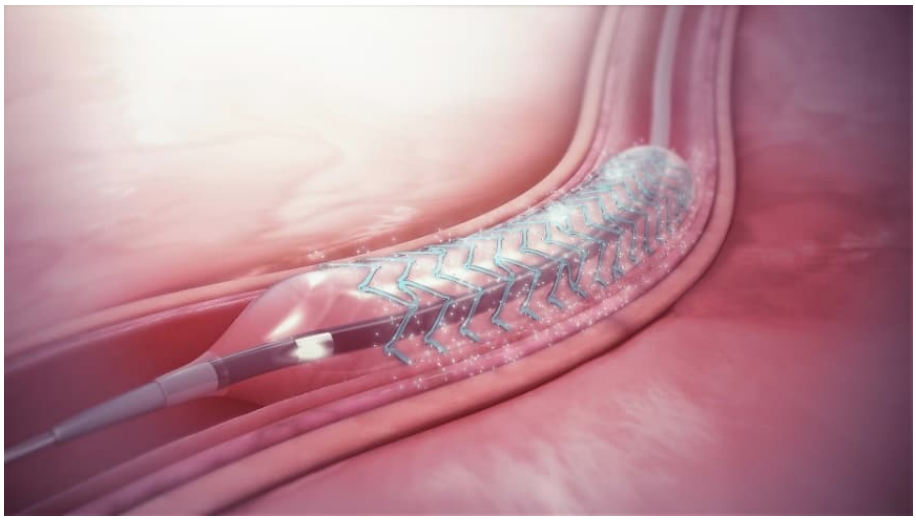
all the risks[10]. Lifestyle factors such as smoking, diet, weight, waist circumference, and physical activity are of paramount importance. In patients with DM, the blood sugar levels often need to be managed medically, and it is vital to treat hyperlipidaemia[99]. For circulation, single antiplatelet therapy (SAPT) is prescribed, and adjunctive treatment with a low dose NOAC might be considered as this may reduce the cardiovascular risks further[96 106 107]. The blood pressure needs to be appropriately managed, and angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARB) are of extra value in PAD due to the considerable reduction in cardiovascular risk[102].

Surgical, Endovascular, or Hybrid treatment

All patients with confirmed CLTI who are ambulant without other short-term life limiting diseases should be evaluated for surgical or endovascular treatment. This may also apply to subjects with a severe walking impairment where conservative regimes have failed. Younger, still employed subjects who cannot perform their daily tasks can also be considered for invasive treatment early if the lesions are not too surgically complicated. Proximal lesions in the aortoiliac axis and common femoral artery may, therefore, be more often managed operatively as the procedures have good long-term results and usually low procedural risk. See Pictures X-XII.

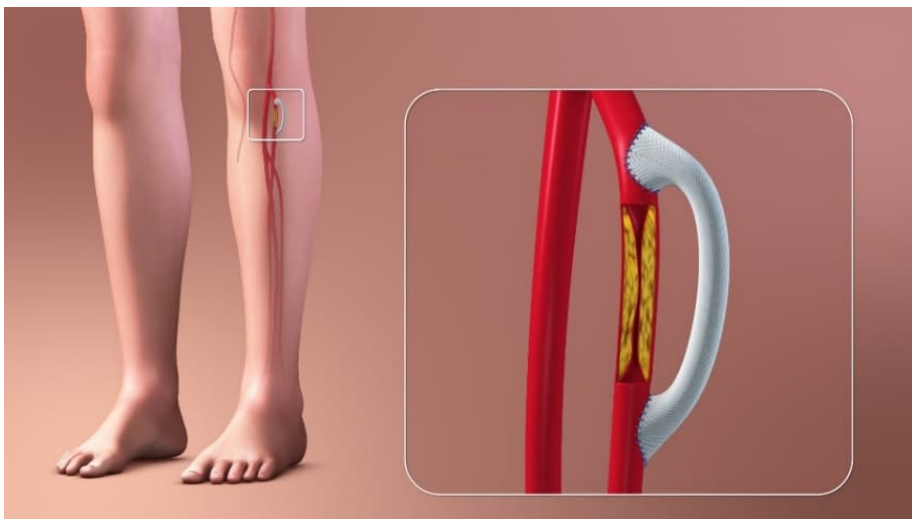
The most common surgical methods include arterial endarterectomy or surgical bypass. Endovascular methods include balloon angioplasty with or without intravascular stents. Drug coated balloons and stents may possibly reduce the restenosis rate, and further study of this is a major topic of this thesis. In certain instances, interventions are performed simultaneously with both open and endovascular methods, so-called" hybrid operations." See Picture IX.

Picture IX. Photo showing a "hybrid operation" theatre.
(By Pfree2014 - Own work, CC0, https://commons.wikimedia.org/w/index.php?curid=36622337)



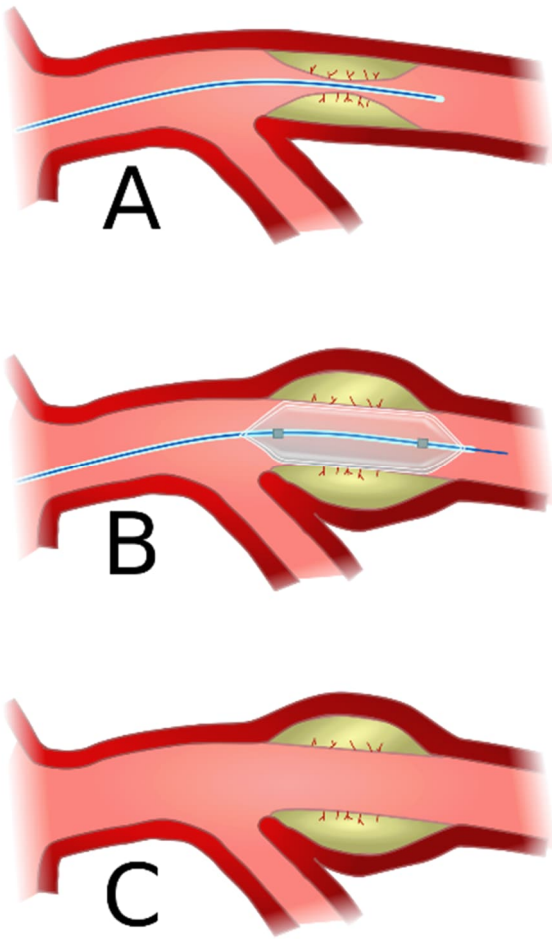
Picture X. Schematic view of the deployment of a drug eluting balloon-expandable stent.

(By https://www.scientificanimations.com/ - http://www.scientificanimations.com/wiki-images/, CC BY-SA 4.0, https://commons.wikimedia.org/w/index.php?curid=70777398)



Picture XI. Principal view of a bypass procedure in the lower limbs.

(By https://www.scientificanimations.com - https://www.scientificanimations.com/wiki-images/, CC BY-SA 4.0, https://commons.wikimedia.org/w/index.php?curid=91336494)



Picture XII. Schematic view of balloon angioplasty.
(By own work - this file, CC BY-SA 3.0, https://commons.wikimedia.org/w/index.php?curid=19334307)

Haemodialysis access

When performing haemodialysis[108-110], one form of renal replacement therapy, repeated access to the circulation, is needed to achieve filtering of the blood. Usually, subjects have sessions 2-4 times a week for a couple of hours every time. The efficacy of dialysis (Kt/V) is better if the available access has a high-volume flow. However, too extended values of high-volume flow in an arteriovenous coupled access may lead to an arterial “steal” situation when the circuit takes too much blood, giving less circulation for the distal limb. This can sometimes seriously

affect the distal arterial circulation, forcing an abandonment of the circuit by ligation or, if possible, performing a flow-limiting operation[110-112]. See Picture XIII.

The importance of achieving safe repeated vascular access with sufficient flow was apparent already in the early phases of the evolving haemodialysis technique. The basic features are:

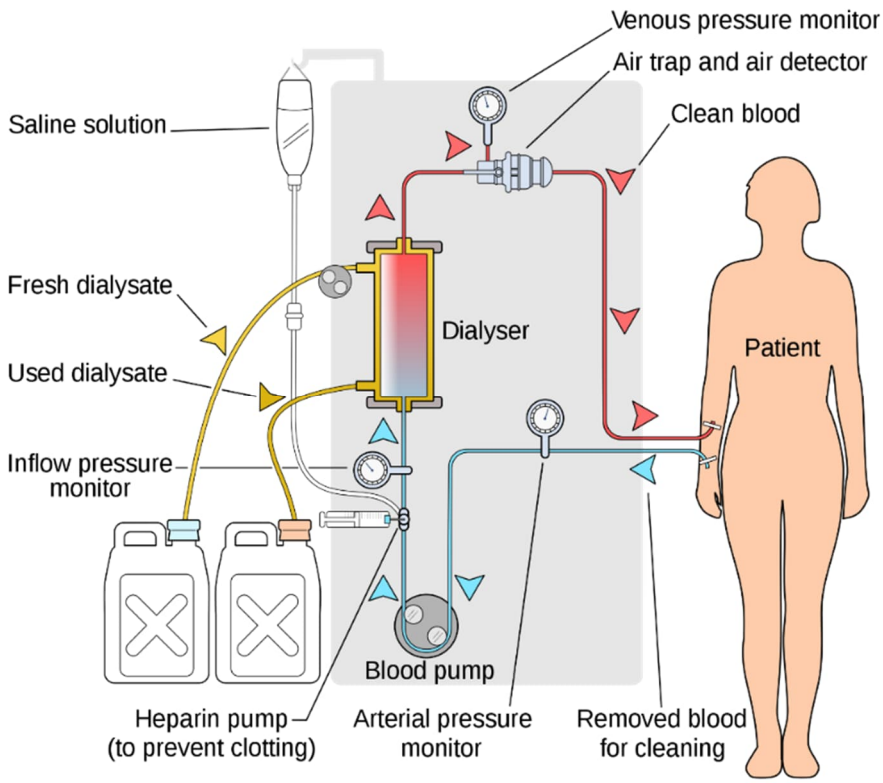
I. Easy repetitive access to blood circulation.

II. Blood flow can easily be “stopped” at the end of the procedure.

III. Durable long-term function with few reinterventions.

IV. Freedom from major complications

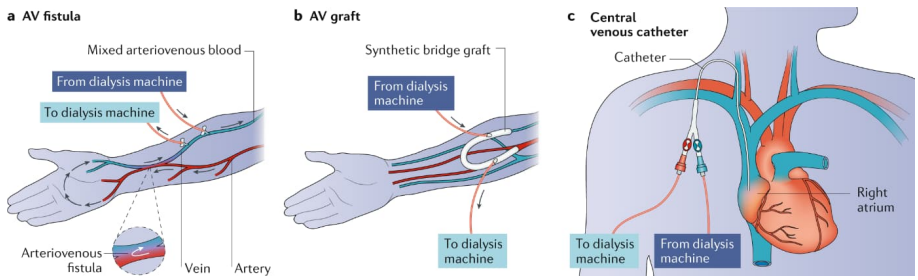
V. Resistance to infection.



Picture XIII. Schematic view of how haemodialysis is performed.

(By This W3C-unspecified vector image was created with Inkscape . - Own work from Image:Haemodialysis schematic.gif., CC BY 3.0, https://commons.wikimedia.org/w/index.php?curid=3411574)

There are three standard methods to establish permanent vascular access for dialysis. Arteriovenous fistula (AVF), synthetic arteriovenous graft (AVG), or a central intravenous tunnelled, cuffed, double-lumen catheter (CDC). An arteriovenous fistula is surgically constructed by anastomosing a superficial, usually upper extremity, vein to an artery. These fistulae need to mature often for at least 6 to 12 weeks, usually longer, before being accessed for dialysis. If the superficial vein available is in poor condition, you may, in some instances, put a synthetic vascular graft between the inflow artery and a suitable outflow vein. These grafts can usually be used after a couple of days, but the durability is not as good as with an autologous AVF. The last and least attractive solution is a permanent catheter, but it has limitations as the risk for infection is increased, and it may affect the future possibilities of constructing an AVF or AVG[113-117]. See Picture XIV.



Picture XIV. Schematic view showing the major types of haemodialysis access.
(Adopted from https://doi.org/10.1038/s41581-020-0333-2; Copyright © 2020, ©Springer Nature Limited)

When performing dialysis with an AVF or AVG, you insert two needles, which serve as a "feed" and "return" for the dialysis pump circuit. With all these weekly punctures and a high-volume flow in the access, problems with stenoses and sometimes aneurysms eventually occur, which might give rise to bleeding or decrease haemodialysis efficacy.

In accordance with the K/DOQI guidelines, patients in haemodialysis care frequently receive an upper extremity arteriovenous AV fistula or graft [115 117 118], in line with the concept of choosing the "right access at the right time for the right patient". With continuous regular use, these circuits, as mentioned above, will often develop significant stenoses [119 120]. Stenoses of AV fistulas and grafts are a very frequent problem that often compromise optimal dialysis. Haemodialysis patients are usually intensely monitored, and when access malfunction is noticed, this will prompt further investigation and intervention. Signs of a malfunctional access force you to consider a revision, which today usually is performed with an endovascular method, using angioplasty balloons and stents, sometimes with drug coatings as an adjunctive for improving the durability of these revision procedures that often are short. This issue is another major topic of this thesis.

National registries

SWEDVASC – Swedish National Registry for Vascular Surgery[121].

This registry started in 1987, and from 1994, all Swedish hospitals performing vascular procedures have signed up for participation. The registry is regularly validated, and many scientific reports have been published based on SWEDVASC data. Approximately 60% of *all* treatments registered are performed with endovascular methods. The procedure coverage is >95%. Approximately 10,000 vascular procedures are performed yearly in thirty-five hospitals with vascular services.

Ref: www.ucr.uu.se/swedvasc/om-swedvasc/om-swedvasc

In SWEDVASC, health-related quality of life (HRQoL) is continuously registered using validated questionnaires at the one- and twelve-month postprocedural follow-up. Objective evaluation of patency is non-mandatory.

NDR – National Diabetes Registry[122].

This registry was founded in 1996 and covers more than 85% of adult (>18 years) subjects diagnosed with DM. Since 2018, children have also been included, with a coverage of almost 100%. In the registry, you may collect data regarding clinical characteristics, risk factors, laboratory analyses of diabetes-related complications, and individual medical treatments.

Ref: ndr.registercentrum.se/om-diabetesregistret/nationella-diabetesregistret-aer-till-foer-att-foerbaettra-varden/p/rJ-SvDC65

DiaD – Swedish Dialysis Access Database[123].

This national sub-registry collects information about haemodialysis patients and their types of access, function, complications, and revisions.

A brief history of vascular surgery and the rise and fall of open vascular procedures

Before the early 1900s, ligation was the only method available to deal with vascular problems. Ligatures were already described between the fourth and seventh centuries, and written evidence exists from the Byzantine surgeon Paul of Aegina in treating aneurysms, varicose veins, and arterial injuries. Techniques of ligation were further developed by famous surgeons such as Ambroise Pare´ and William Hunter. Further development was later dependent on the development of

microscopes and magnification loupes during the 19th century by Carl Zeiss, Ernst Abbe, and Charles Louis Chevalier. Edwin Theodore Saemich perfected the work by constructing functioning surgical loupes in 1876. With loupes and microscopes, the understanding of vessel microanatomy and physiology increased significantly as it was understood that preservation of endothelium was essential to prevent thrombosis. Clinical observations from famous surgeons such as Virchow, Paget, and Billroth improved the understanding of the coagulation process. In 1888, Rudolf Matas (1860-1957), the "father" of vascular surgery, chose not to ligate and instead performed the first endoaneurysmorraphy when he saved the arm of a young farm worker with a traumatic brachial artery aneurysm[124]. In 1923, Matas also performed the first successful ligation of the abdominal aorta for a syphilitic aneurysm[125].

In 1891, Alexander Jassinowsky reported the first successful arterial repairs in animals. J.B Murphy performed the first end-end anastomosis in 1896 when he saved a young man that had been shot in the groin, and he also developed the invagination technique for vascular anastomosis in 1897.

In 1902, there was a breakthrough when Alexis Carrel (1873-1944) described the triangulation method for constructing an anastomosis, and Dr Carrel is considered the pioneer of modern vascular surgery. He received the Nobel Prize for his achievements in vascular anastomosis and transplantation in 1912. The technique was further improved together with Charles Claude Guthrie (1880-1963), who insisted on aseptic techniques and the importance of including the tunica intima in the completion of an anastomosis. In 1906, they jointly published the "patch method", a principle still used today in vascular surgery, i.e. the "Carrel patch" technique[126]. Together, they attempted to bridge arterial discontinuity with the interposition of vein grafts, but in the same year, it was Jose Goyanes in Madrid who performed the first clinical vein interposition graft.

Early in the former century, experiments were also conducted regarding sutureless anastomosis of arteries. The most well-known physician was Erwin Payr, who experimented with magnesium tube conductors to connect vessels. Success was accomplished in a laboratory setting but not in the real world.

During World War I, further efforts were made to repair vessels in an attempt to save extremities, and both Alexis Carrel and Rene Leriche (1879-1955) served as military surgeons, further trying to increase success with vascular suturing and repairs. Although the US only participated in the last year, 1917-1918, figures from the causalities show that more than 4000 US soldiers lost a leg due to battlefield trauma. Only 13% lost their leg on the battlefield, whereas the remaining soldiers lost their leg in the surgical ward in an attempt to save the leg. However, infections and vascular techniques were still considerable problems to overcome. Rene Leriche is a portal figure in vascular surgery. Although considered very conservative, he trained many later renowned vascular surgeons such as Michael DeBakey, Jao Cid dos Santos, Rene Fontaine, and Jean Kunlin. He is also famous for "Leriche

Syndrome", with the triad of claudication, impotence, and absence of femoral pulses[127].

Leriche had tried to reestablish flow with an interposition vein graft in a thrombosed artery already in 1909, but this was unsuccessful because he did not know the extent of thrombosis (at this time still, there were no diagnostic measures available to delineate the extent of thrombosis). Angiography was not clinically available until two decades later, as described in the next chapter. The concept of thrombendarteriectomy was also popularised by Jao Cid dos Santos (1907-1975), but it suffered from the same problems with a lack of diagnostic procedures. He succeeded many years later, in 1946, in performing the first successful operation, but that was after heparin was discovered in 1916 and angiography was made available. Heparin was made clinically useful by work from Gordon Murray (1894-1976)[128 129], published in 1936, who successfully used heparin in experimental arterial surgery. With heparin, it was possible to succeed even though the intima was not fully sutured or integrated into the repair.

The discovery of heparin is one of the most important discoveries in the history of vascular surgery because so much technical development is entirely dependent on the possibility of keeping patients anticoagulated during surgery or in the postoperative period. Heparin was discovered in 1916 by a medical student, Jay McClean (1890-1957), working with professor W.H. Howell (1860-1945), but was not useful due to toxicity. The process of purifying heparin for clinical use was performed by Charles Best (1899-1978)[130 131], and this was finalised in 1928. Charles Best was also a major part of the discovery and purification of insulin in 1921, along with Frederick Banting (1891-1941).

In 1948 Jean Kunlin (1904-1991)[132 133], a younger coworker of Rene Leriche, revived the technique for venous bypass grafting, a method already proposed in 1913 by Jaeger. By this achievement, modern vascular surgery was born, and the method of venous surgical bypass was broadly adopted. The technique evolved by establishing the in-situ technique at two centres in the late 50s to make the surgery less traumatic. The pioneering work was done by Paul Cartier (1919-2008) and Karl Hall (1917-2001)[134], but vein valve destruction was still problematic in the hands of other surgeons, and the technique did not become very popular. Karl Hall developed a retrograde vein valve stripper in 1968, a type that still can be seen in use. 1984, Cartier published his results of 850 in situ bypasses with a 75% five-year patency rate. The method was popularised again in 1979 when Leather et al. reported excellent results with a more simplified technique for valve destruction[135]. Leather later published results of 2058 in situ bypasses between 1975-1995. The cumulative patency rates were 91%, 81%, and 70 % after 1, 5, and 10 years, respectively and with a ten-year limb salvage rate of 90%[136]. These results are impressive even in a modern setting. Several later randomised studies comparing in situ technique with reversed vein technique have shown no differences in results[137-141]. The vascular procedures were becoming more and more familiar and widespread.

Regarding more central vascular surgery, such as aortic, visceral, and carotid repair, these areas of vascular surgery were more complicated. However, the vascular surgical techniques for suturing, grafting, and heparinisation were quite well developed at this time, and angiographic studies were available. Jaques Oudot (1934-), a French vascular surgeon who performed research on arterial homografts and experimental aortic occlusions, replaced a thrombosed aortic bifurcation with a homograft in 1950, the first aortic bifurcation graft[142-145]. In 1951, he performed the first cross-over bypass between the external iliac arteries for a similar diagnosis. A few months earlier, Norman E Freeman (1903-1975) and Frank H Leeds (1914-2003) performed the first crossover revascularisation with the superficial femoral artery[146].

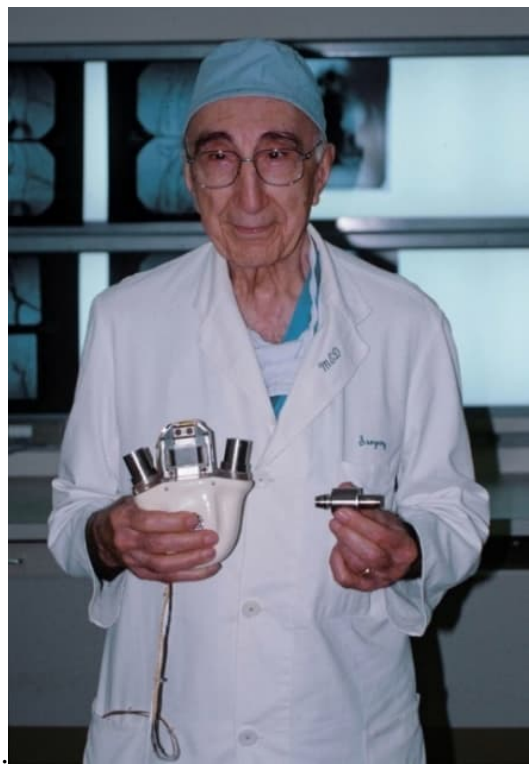
Regarding reconstructive surgery of the carotid arteries, this began in Buenos Aires, when Raul Carrea did the first case of revascularisation by performing an anastomosis between the internal and external carotid artery in 1951[147]. The first successful endarterectomy with primary closure was performed by Michael DeBakey (1908-2008) in 1953[148]. Felix Eastcott (1917-2009) performed the first published case of an operation with end-end anastomosis between the common carotid and internal carotid artery with success in 1954[149]. See Picture XV.

Charles Dubost (1914-1991) did the first resection of an abdominal aortic aneurysm (AAA) with restoration of arterial continuity with a homograft in 1951[150 151]. Rapid development followed with the growing availability of synthetic vascular conduits. Arthur Voorhees (1921-1992) pioneered the evolution of synthetic grafts as he worked with Arthur Blakemore (1897-1970). He developed the Vinyon-N graft, which he constructed from parachutes, and performed animal experiments[152]. The first graft was placed in a patient with aortic aneurysm rupture in 1952 at Columbia University. After that, there was a continuous search for optimal synthetic grafts using Orlon®, Teflon®, Nylon®, and Dacron®. Today, grafts are commonly produced from polyester fibres or ePTFE.

Extensive series of aortic surgery appeared in the literature in the 70s, and there were comparisons between aortic endarterectomy and aortic grafting, showing superiority for grafting. In 1981, E.S Crawford (1922-1992) published his 25-year experience with aortoiliac reconstructions in 1004 cases[153], and later, D.E Szilagyi (1939-1975) reported his experience with 1748 aortobifemoral bypasses with a 68% 20-year patency[154]. Closing into the 90s, when the endovascular phase had just started, the first endovascular treatments of aortic aneurysms were performed in 1990 by Juan Parodi (1942-). Today, 80% of AAA are treated with EVAR[155 156] and only 22% of PAD[157] treatments are performed with open surgical procedures. With this further evolving situation, problems with sufficient education and performance regarding open vascular surgery are to be expected in the future[155].

Another essential achievement worth mentioning was the balloon embolectomy catheter, also called the “Fogarty catheter”, after the developer Thomas Fogarty

(1934-)[158]. He performed the first balloon embolectomy in 1961, and the patient made an excellent recovery from acute limb ischemia. He had been working with these balloons for years during his education and residency. Before his invention, embolectomy was a cumbersome procedure with multiple arteriotomies, flushing, Esmarch compression, vein strippers, and corkscrew devices, with a success rate well below 50%. His catheters are estimated to have saved the lives and limbs of more than 20 million patients[159]. Despite this, in recent years, his technique for solving acute ischemic issues has been overrun by modern endovascular methods with pharmaco-mechanical devices or aspiration devices for handling the problem without the need for an operation. Thomas Fogarty is also famous for many other inventions besides his well-renowned winery in California, which produces excellent wines that are well worth tasting.



Picture XV. Michael DeBakey (1908-2008). American cardiovascular surgeon. He performed the first carotid endarterectomy in 1953 and also the first patch-graft angioplasty in 1958. He also developed the first Dacron vascular graft. Here he is in a picture, 94 years old, still surgically active.

(Public Domain, https://commons.wikimedia.org/w/index.php?curid=878078)

A brief history of angioplasty and stenting, a journey towards the endovascular revolution

The angioplasty technique traditionally depends on the possibility of x-rays and performing angiograms. Today, some interventionists actually perform angioplasty treatments in different regions with the sole guidance of duplex ultrasound (DUS).

X-ray beams were discovered by Wilhelm Conrad Roentgen (1845-1923) at the end of the 19th century[160] [161]. During the first decades of the 20th century, scientists performed arterial visualisation experiments using contrast material in cadavers and animals. Necessary steps were taken during the 20s, primarily by the Portuguese neurologist Edgar Moniz[162](1874 -1955), who developed the cerebral angiography technique[163]. Moniz is also famous for the prefrontal leucotomy, for which he received the Nobel Prize in 1949. His colleague Reynaldo Cid dos Santos (1880-1970) performed the first aortogram in Lisbon 1929. These diagnostic procedures were cumbersome and often carried a risk of complications, as they were done with a direct puncture technique. See Picture XVI.

Picture XVI. Portrait of Egaz Moniz (1874-1955), Portuguese neurologist and Nobel Prize laureate for the prefrontal leucotomy. Developer of the technique for cerebral angiography.

(By José Malhoa - Oliveira, V. "Quadros Médicos: Egas Moniz, por José Malhoa". Acta Med Port 2014 Sep-Oct;27(5):669-671, Public Domain, https://commons.wikimedia.org/w/index.php?curid=58677779)

In 1952, Sven-Ivar Seldinger (1921-1998) developed the "Seldinger" technique for safe catheterisation of vessels, which was an important achievement for the continuous development of the endovascular techniques for different vascular treatments[164 165]. Although many other modalities are now available for diagnostic purposes, conventional angiograms remain the gold standard in some settings.

Charles Theodore Dotter (1920-1985), an American radiologist, is often credited with the creation of a new speciality, interventional radiology. Percutaneous transluminal angioplasty (PTA) was his landmark achievement, sometimes also called the "Dottering procedure"[166-171]. Later, he introduced the concept of arterial stenting when he placed a coil spring graft in the femoral artery of a dog[172].

In parallel, another essential achievement was seen with the development of low osmolality and non-ionic contrast agents, which were less dangerous and less painful for the patients. A significant contributor was Torsten Almén, professor of radiology at Lund University[173-176].

Further improvement of the angioplasty technique in peripheral arteries was made by Werner Porstmann (1921-1982), a German radiologist, who was the first to close a ductus arteriosus by catheter technique in 1967[177], and, in 1973, developed a non-distensible "corset" balloon that allowed vessel dilatation to a size far larger than the introduced catheter[178]. The latter was further developed by Andreas Gruntzig (1939-1985), a German radiologist, who would later also perform the first coronary angioplasty (PTCA) in 1977[179-181].

During the development of peripheral and coronary angioplasty, shortcomings were realised. With the increasing use of this technology, the issues of acute occlusion or stenosis due to dissection or recoil had to be solved. The exploration of stent treatment started both in peripheral and coronary lesions. Although development has always been pioneered in the coronary field, considerable improvements have been made simultaneously in all peripheral vascular settings.

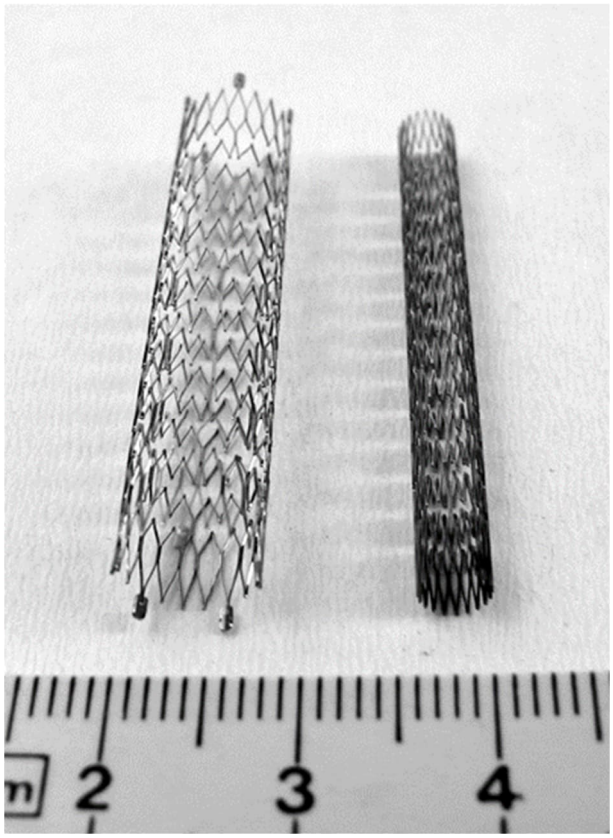
The first coronary stents were placed by Ulrich Sigwart (1941-) and Jaques Puel (1946-2008) in 1986[182 183], and these were self-expandable in design (Wallstent®). The first balloon-expandable stents (Palmaz-Schatz®) were developed by Julio Palmaz (1945-) and Richard A Schatz (1952-)[184], and these stents were placed in patients for the first time in both peripheral and coronary arteries in 1987. Dr Palmaz stented an iliac artery in a German patient in Freiburg that year. The Palmaz-Schatz® stent was the first stent that got FDA approval for coronary treatment in 1994, by then, it had already been approved for use in peripheral arteries since 1991. Other collaborations moved forward simultaneously, as with the group led by Gary Roubin, who worked with the Italian radiologist Cesare Gianturco (1905-1995)[185] in the construction of the Roubin-Gianturco stents (Flexstent®).

Within only a couple of years, >80% of the coronary interventions were performed with stents after important randomised controlled trials (RCT) regarding the use of

balloon-expandable Palmaz-Schatz® stents were published[186] [187], making percutaneous coronary intervention (PCI) treatment with stents the standard of care.

Simultaneously randomised investigations of these stents in femoropopliteal (FP) arterial lesions were performed, but in the early phase, the results were disappointing, with 5 RCT showing results similar to standard angioplasty[188-192]. This was a reminder that coronary and peripheral interventions, although similar, have important anatomic and technical differences. The superficial femoral artery is anatomically challenging to treat with endovascular techniques. See Picture XVII.

A significant proportion of complex modern interventional endovascular techniques rely on stenting as this overcomes recoil and dissections. It does not, however, deal with the issue of restenosis due to neointimal proliferation. So, with stents, the interventionist got a tool to eliminate common mechanical problems but was left with problems with the frequent development of late restenosis due to subintimal hyperplasia, an issue that needs other solutions.



Picture XVII. Photo of a deployed and an undeployed stent.
(By Frank C. Müller - Own work, CC BY-SA 2.5, https://commons.wikimedia.org/w/index.php?curid=3406054)

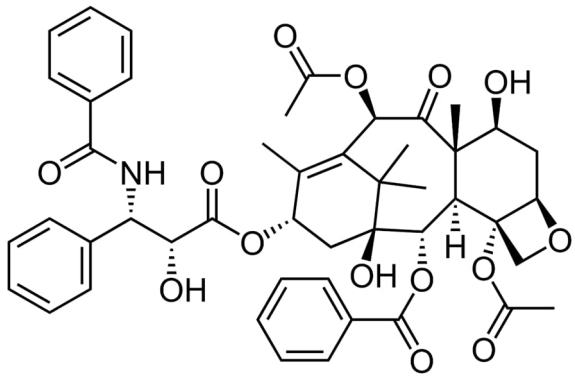
The era of drug eluting adjunctive angioplasty and stent techniques started with the developments in coronary revascularisation[193 194]. After applying a standard of care with balloon-expandable stents in coronary revascularisation, large studies showed a restenosis rate reaching 15-30% in less than six months[195 196]. Experiments with different stent coatings and infusion of different immunomodulating compounds were examined in animal studies in an effort to reduce the rate of restenosis[197].

The first drug eluting commercial device was a sirolimus-eluting coronary stent, first placed in a patient by Jose Eduardo Sousa (1934-2022), a Brazilian cardiologist, in 1999. He was also the first to place Palmaz-Schatz® stents in the coronary arteries in 1987. The development led to the first generation of drug eluting stents, Cypher® (Bx Velocity) (Johnson & Johnson) and Taxus® (Boston Scientific). The Cypher® stent was coated with sirolimus, also known as rapamycin, which is produced by the bacteria *Streptomyces Hygroscopius*. In contrast, the Taxus® stent is coated with paclitaxel, a compound extracted from the Pacific Yew *(Taxus Baccata)*. Both compounds have heavy immunomodulating effects and are used to treat certain cancer forms and to suppress organ rejection in transplantation surgery. These stents were examined in large, randomised studies against BMS. The TAXUS and SIRIUS trials included > 1000 subjects each, and both showed highly significant improvements in efficacy compared to BMS[198 199]. Cypher® was the first DES to get Food and Drug Administration (FDA) approval 2003.

A substantial setback was the publication in 2007 showing an increased risk of death and myocardial infarction due to late stent thrombosis produced by problems with the stent polymer coatings[200]. This led to the development of the later generations of coronary stents with new platforms and adjunctive drug coatings[201]. DES is today still considered the standard of care in PCI, and very few indications for BMS are left, as concluded in the Norwegian NORSTAT[202] randomised study including >9000 subjects as well as in large metanalyses[203].

The most crucial drawback of DES is still the need for long-term treatment with dual antiplatelet therapy (DAPT) or similar anticoagulative therapies. Regarding drug eluting stents for PAD, the first device was the paclitaxel-coated Zilver PTX® self-expanding stent, which was FDA-approved in 2012, almost ten years after the first coronary DES.

A critical reflection regarding the continuous improvement of endovascular procedures and devices is that an essential part of the development involved US-based research faculties, but most pioneer treatments in humans were performed outside the US, as in Europe, because their regulatory bodies are less strict and demanding. In Europe, you only need to CE mark a product, but in the US, you need approval from the FDA, which forces the companies to perform relevant studies for each product for the US market, which is not the case in Europe.



Picture XVIII. The chemical structure for Paclitaxel.

(By Calvero. - Selfmade with ChemDraw., Public Domain, https://commons.wikimedia.org/w/index.php?curid=1703615)

The technique with drug eluting balloons developed after the use of DES has flourished. The reason for further development was that all lesions were not suitable for stenting, and in PAD, stenting was not as effective as in coronary procedures. Delivery of drugs during angioplasty is technically more challenging, so the techniques for binding and delivery had to be explored further. Around the millennium, groups were working on technical solutions for drug delivery in angioplasty and stenting, foremost in Tubingen, Germany, under the supervision of Christian Herdeg[204-206] and at Massachusetts Institute for Technology (MIT), US, under the supervision of Elazer Edelman[207-210]. Necessary steps were then taken by Ulrich Speck, head of contrast media research at Schering in Berlin, when he, in 1999, used contrast media as a carrier for local drug delivery in a porcine coronary model[211]. An intracoronary bolus of a Taxane-Iopromide solution led to an apparent reduction of neointimal formation, although the time of application was short[212 213]. See Picture XVIII.

Experiments with coated balloons started in 2001, and simultaneously, the randomised RAVEL study was presented at the European Society for Cardiology (ESC) congress in Stockholm. This showed a highly significant reduction of restenosis rate after deployment of sirolimus-coated stents compared to BMS in coronary revascularisation[214]. Despite serious doubts about the efficacy of a single-dose treatment, animal trials with different drug coated balloon prototypes began in 2002, showing that one coating efficiently reduced neointimal formation[215]. Human randomised trials with DCB in coronary in-stent restenosis started in 2003 with the PACCOCATH ISR I/II trials, showing positive results[216 217].

The first human PAD trial was the THUNDER (Local Taxane with Short Exposure for Reduction of Restenosis in Distal Arteries) trial directed by Gunnar Tepe. This study showed a significant reduction of late lumen loss (LLL) and target lesion

revascularisation (TLR)[218]. This study was followed by the FEMPAC trial, which also studied the same concept in FP arterial lesions, showing excellent results[219]. These Paccocath® coated balloons were the pioneers in the DCB evolution in the peripheral artery setting, and they consisted of a specific matrix called Paccocath® mixed with paclitaxel and Ultravist®, an x-ray contrast medium[220 221]. Studies were also performed to determine the effect of balloon inflation times[222], which proved to be acceptably short. The evolution has been swift from here, with sixteen different DCBs and seven DESs on the European market today, all with varying concepts regarding indication, active drugs, doses, and carriers. This thesis should be seen from this perspective.

A brief history of vascular access and haemodialysis

The idea of haemodialysis by filtrating blood was already described by Thomas Graham in Glasgow in 1850. Abel and Roundtree performed the first experimental haemodialysis in animals in 1913, and the first haemodialysis treatment in man was conducted in Germany in 1924 by George Haas (1886-1971). He used a glass cannula for arterial and venous access in the arm of a young boy. Repeated access to the circulation was a significant limitation, as was vascular thrombosis. When heparin was available in 1928, the problem with coagulation was reduced.

The first step towards an "artificial kidney was taken in 1937 when William Thalhimer (1884-1961) used the increasing knowledge regarding membrane technology, anticoagulation, and quantification of uraemia to perform successful haemodialysis on dogs. The first dialysis apparatus as renal replacement therapy was developed in 1943-1947 by Willem Kolff (1911-2009)[223] and Nils Alwall (1904-1986)[224].

Doctor Kollf performed the first successful haemodialysis on a young woman in 1943 using the "rotating drum kidney" he had developed. After 12 treatments, no vessels were left for access, as the technique necessitated new punctures of arteries and veins each time.

Access to the blood circuit was a considerable limitation for performing haemodialysis on a repeated basis. In 1960, Belding Scribner (1921-2003) used external Teflon tubing, operatively placed between the radial artery and a forearm vein[225 226]. The first patient, Clyde Shields, lived for eleven years with this method of haemodialysis. The shunt worked for a couple of months before it needed to be replaced. The "Quinton-Scribner shunt" was an essential step in the history of haemodialysis.

In 1961, James E. Cimino (1928-2010) and Michael J. Brescia (1933-2023) developed a technique for direct repeated venipuncture for haemodialysis. They

also noted that traumatic arteriovenous fistulas in Korean war veterans seldom affected their general health. The idea of surgically constructed arteriovenous fistulas was not new, as it was performed in the 1930s for children paralysed by polio.

This led to the first construction of an arteriovenous (AV)-fistula for haemodialysis in 1965[227]. The idea came from Cimino and Brescia, and this access is called the “Cimino-Brescia” fistula. However, the operation was performed by Kenneth Appel, a surgeon in New York. This achievement was an immense breakthrough in haemodialysis care. The technique evolved from a side-to-side anastomosis to the method currently in use with the end-to-side anastomosis, developed by Lars Rohl in 1968[228].

Simultaneously, techniques for central vein access were developed mainly from the subclavian or femoral vein routes, and they were explored first by Stanley Sheldon and Josef Erben[229] already in 1961.

In the 1970s, different non-autologous grafts were tried for arteriovenous bridging and repeated access with limited success until 1976, when L.D Barker presented the first 72 cases with expanded PTFE grafts for haemodialysis. They remain the mainstay for graft access procedures today.

The surgically created AV fistula is still the first option to consider today when planning for continuous haemodialysis[113 116 230]. Sometimes, the conditions for such a procedure are limited when today's choice is an early cannulation ePTFE graft, much like the type used in the 1970s.

Although the construction of the AV circuit is still performed by traditional open surgery, most revision procedures are performed with endovascular treatment today. Trials with endovascular constructions of AV access by thermal fusion of a target artery and vein have been published lately, but the technique is not scientifically or practically yet fully adopted for broad clinical use[231-233].

Extended scientific analysis of medical and interventional aspects in PAD and Haemodialysis Access

Aspects of epidemiology and risks concerning PAD

Calculations show that the prevalence of PAD in the population reaches 12%, and the prevalence of CLTI among these is estimated to be 11%[12 234]. The prevalence is age-dependent, with 20% of adults aged more than seventy having an objective PAD diagnosis. More than 6.5 million subjects suffer from CLTI, and the prognosis foresees that this figure will further increase as the "metabolic syndrome", DM, and smoking are increasing in prevalence.

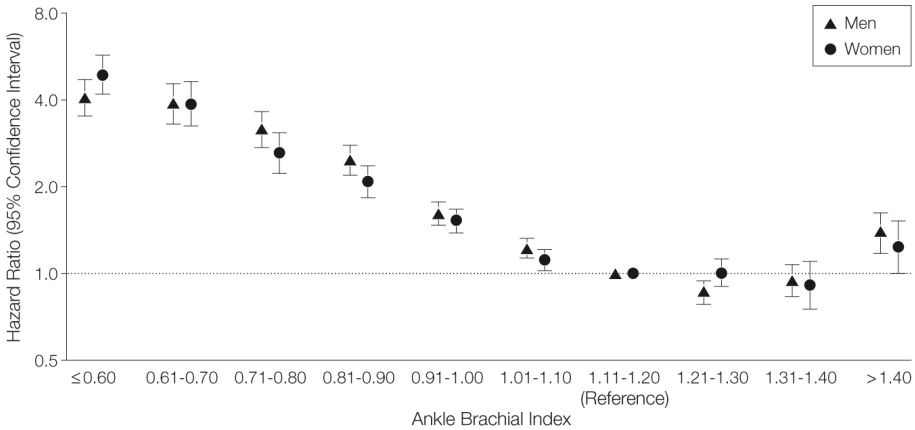
Approximations say that 5-10% of subjects with asymptomatic PAD or IC will progress to CLTI over a five-year period[12 234]. Important independent risk factors for the progress of PAD to CLTI are age, smoking, DM, and end stage renal disease (ESRD), and progression is calculated to be 7.5% the first year after referral and 2.2% yearly after that[234].

The overall age-adjusted death rate for PAD reaches 14.8 per 100.000, and only 20-30% of subjects with PAD die of non-cardiovascular related issues, and the annual cardiovascular event rate, including AMI, stroke, and death is 5-7%[12 234]. See Picture XIX.

The natural history of PAD tells us that the incidence of CAD is 30-50%, and for carotid artery stenosis, 15-25%. The lifetime risk for PAD is estimated to be 20-30%. The one-year limb salvage rate in conservatively treated CLTI can be as good as 57%, with a survival rate of 75% and AFS rate reaching 51%[11 12 235 236].

In PAD patients with IC, the amputation rate is 6% at three years, and with CLTI, the rate of death or amputation is 20% per year. The general rate of amputations declined during the first decade of the 21st century but is now increasing again, primarily due to the increasing prevalence of DM[11 12 235 236].

PAD can, therefore, unfortunately, be expected to cause an increasing vascular surgery workload ahead of us.



Picture **XIX. Diagram showing hazard ratio for total mortality in men and women by ankle brachial index at baseline for all studies combined in the ABI Collaboration[237].**
(Adopted from https://doi:10.1001/jama.300.2.197; Copyright © 2008, ©American Medical Association)

Aspects of epidemiology and risks concerning PAD in subjects with DM

The connection between PAD and DM needs particular attention as 20-30% of PAD subjects have concomitant DM[238]. The prevalence of PAD in a DM cohort ranges from 27% to 76%, and this cohort has a heavy risk for amputation, 4-fold compared to a national average[238]. DM is, as mentioned, heavily increasing in the population, leading to an increased PAD prevalence[23]. The prevalence has increased by >200% over the last 20 years in some regions[238]. Today, the estimates are that 537 million people have DM, and the prognosis is that we will see an increasing prevalence, reaching 783 million in 2045[46]. Cardiovascular disease accounts for >50% of the mortality in type II DM[238]. The mortality rate for a subject with DM, PAD, and DFU is well above 50% at five years[46].

DM impairs endothelial function, and much of the effects are mediated by nitric oxide. This leads to increased atherogenesis. Important negative mediators are hyperglycaemia, excess free fatty release, and insulin resistance, leading to vasoconstriction, inflammation, and thrombosis. Impaired vascular smooth muscle function and impaired platelet function are other essential steps in the pathophysiological process[236].

The prevalence of abnormal ABI in subjects with a normal glucose tolerance test is 7% compared to 21% in those with a pathological test, and fasting blood sugar level relates to risk for PAD[28 236]. It is known that ABI has limited effectiveness for detecting PAD in a diabetic cohort[239], and other diagnostic tests such as TP or $TcPO_2$

need to be considered for a more reliable objective evaluation of the distal circulation and the following prognosis for the ulcer healing process.

The prevalence of DM increases the risk for IC, with 3.5 in men and 8.6 in women. The relative risk (RR) for lower extremity amputation is 12.7 with a DM diagnosis and 23.5 if aged 65-74 years[236].

DM changes the pattern of PAD[55 240 241]. Arterial lesions are more distally located with a corresponding higher complexity of distal calcifications.

Approximately 25%-90% of amputations are associated with DM[238], and the increased risk is not only contributed to the increased prevalence of PAD but also to peripheral neuropathy, autonomic neuropathy, foot deformities, and infection[238]. The problem with DFU is a well-defined problem with a high risk for amputation, and DFU precedes 85% of annual non-traumatic amputations with a yearly incidence of DFU at 2% and a lifetime risk reaching 34%[46 242]. Revascularisation is a crucial part of the multidisciplinary treatment of DFU or CLTI in subjects with DM.

Aspects concerning best medical treatment in PAD

There are few specific randomised studies regarding the pharmaceutical treatment of risk factors in PAD, and proposals are also interpolated from studies regarding the risk reducing therapy of cardiac and cerebral vascular events. There are multiple vital parts of an optimal best preventive treatment for PAD, and besides drugs, the first and most essential aspects are smoking cessation, physical exercise, and diet, and the positive effects of these matters are well documented[10 99 105].

The use of drugs for prevention is well documented in five different areas: Lipid lowering treatment, antihypertensive treatment, single antiplatelet treatment, dual pathway or dual platelet treatment, and antidiabetic treatment.

Lipid lowering treatment

The basis for this treatment is the reduction of LDL and TG levels, and all PAD patients receiving medical treatment with statins will have a significant risk reduction regarding MACE. The goal is LDL < 1.4 mmol/L or a 50% reduction from index levels. Statins also seem to improve the walking distance in subjects with IC, reduce the amputation rate and may improve graft patency. Combinations with ezetimibe and/or proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors are effective if target levels are not reached[6 10 99-101 103].

Antihypertensive treatment

Reduction of blood pressure has significant effects on CV events and mortality. According to guidelines, the treatment threshold is 140/90 mmHg, and the blood pressure target should be as low as 120-130/70-80 mmHg in subjects < 65 years. First-line treatment should be ACEIs or ARBs, as they specifically reduce CV events in a PAD cohort. Multiple drugs are commonly needed, and the first-line adjunctive treatment is calcium channel blockers (CCB) or thiazides. Beta-blockers are not contraindicated but have not been thoroughly evaluated in CLTI[6 10 29 102-104 243-245].

Antiplatelet therapy

Single antiplatelet treatment is a portal therapy for symptomatic PAD preventive treatment[6 96 103], whereas there is no data supporting treatment in asymptomatic PAD subjects. The Antithrombotic Trialists' Collaboration showed that SAPT reduces CV events by 25% in most subjects with an unspecified CV risk[97]. The CAPRIE trial showed that clopidogrel was more effective than ASA, with a small ARR of 0.5%, with a related RRR of 8.7%[98]. Ticagrelor was shown to be more effective than clopidogrel in CAD (PLATO-trial[246]) but not in PAD (EUCLID-trial[247]).

Dual Pathway or Dual Platelet therapy

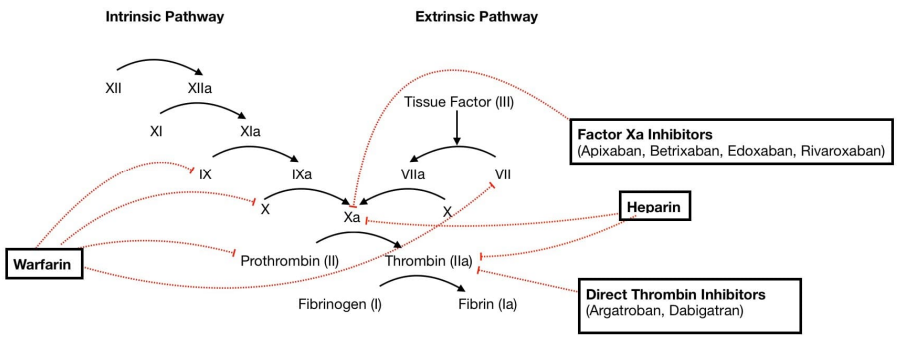
Recent randomised trials have explored the effects of different combinations of antithrombotic treatment to further reduce CV complications. Warfarin and ASA have been investigated both in CAD to reduce recurrent AMI and in CVD to reduce recurrent stroke. The WARSS-trail[248] compared ASA 325mg against warfarin with no differences in the rate of stroke or death. The WARIS-II[249] instead compared ASA 160mg against warfarin (INR 2.0-2.5) + ASA 75mg and warfarin (INR 2.8-4.0). Single ASA was significantly inferior in preventing a new CAD event. The WAVE-trial[250] did a similar comparison in PAD subjects. They randomised between SAPT and warfarin (INR 2.0-3.0) +SAPT and did not show an advantage in CV events but more frequent life-threatening bleedings in the cohort receiving the combination therapy. The Dutch BOA study[251] compared ASA and warfarin after bypass surgery for PAD without overall differences, which though were shown in a subgroup analysis.

The CHARISMA-trial[252] investigated DAPT against SAPT in subjects with documented cardiovascular disease or multiple risk factors. Endpoints were MI, stroke, or CV death, and did not show any benefits with DAPT. The CASPAR trial[253] did a similar randomisation after bypass surgery for PAD, without overall differences, but with a subgroup analysis showing a possible superior efficacy for DAPT in prosthetic grafts.

The first trial studying the combination of SAPT and low-dose new oral anticoagulant (NOAC) (rivaroxaban) was the COMPASS-trial[107]. They randomised 27395 subjects with stable atherosclerotic vascular disease into three groups receiving rivaroxaban 2.5mgx2 + ASA 100mg, rivaroxaban 5mgx2, or ASA 100mg. The first group had fewer CV events but more major bleedings than those with only ASA. The high-dose group was not superior to SAPT. A COMPASS subgroup analysis[16], focusing on subjects with PAD or carotid disease, came to the same conclusion that the combination treatment was superior (HR 0.72 [CI 0.57-0.90], p=0.0047). However, a higher frequency of non-fatal and non-critical bleeding was noted.

The VOYAGER-trial[106] randomised 6564 subjects after PAD revascularisation to SAPT alone or Rivaroxaban 2.5mgx2 + ASA, showing a significantly lower incidence (15% reduction) of a composite outcome (ALI, major amputation, MI, ischemic stroke or death), but with a significantly higher frequency of bleedings, with an incidence at three years of 5.94% vs 4.06% in the rivaroxaban vs placebo groups respectively.

Treatment with dual pathway therapy is considered standard treatment in stable PAD subjects without excess bleeding risk[6 96 103]. See Picture XX.



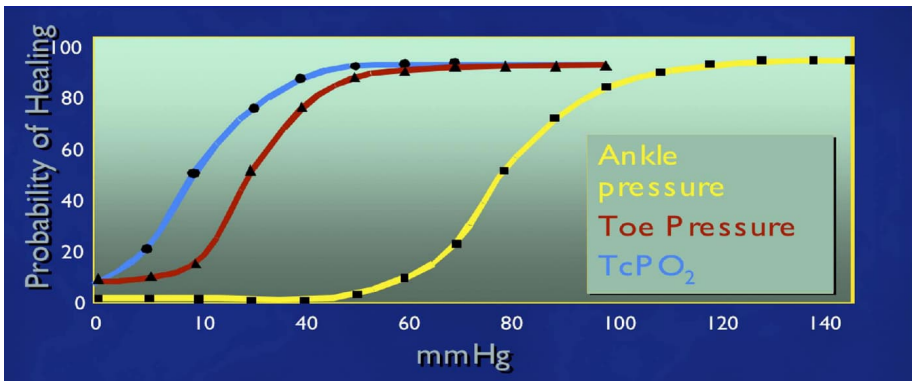
Picture XX. Picture showing major classes of anticoagulants, including warfarin, heparin, direct thrombin inhibitors, and factors Xa inhibitors. This figure illustrates the sites within the coagulation cascade at which these major classes of anticoagulants exert their effects.
(By SteveKong3 - Own work, CC BY-SA 4.0, https://commons.wikimedia.org/w/index.php?curid=85965621.)

Antidiabetic therapy

As discussed earlier, thorough control of blood sugar levels is beneficial in reducing the progression of PAD and cardiovascular events overall. The target for HbA_{1c} is < 7% or < 53mmol/L. Glucagon-like peptide-1 receptor agonists (GLP1-RA) reduce CV events compared to placebo in patients with type 2 diabetes and may reduce the amputation rate. Sodium-glucose co-transporter 2 (SGLT2) inhibitors also reduce CV events[254].

Aspects regarding conservative treatment of PAD

Not to be forgotten in the discussion of revascularisation procedures in CLTI is the non-operative alternative[255]. Frail or elderly patients with CLTI have a high early mortality after admission. This is seen in combination with a low risk of immediate limb-related complications[256]. It is essential to emphasise a palliative limb care option in selected cases and ensure that subjects with CLTI are examined by experienced physicians with the knowledge and competence to deal with these complex consultations. Looking at meta-analyses regarding conservative treatment of usually non-reconstructable CLTI, there is a 27% amputation rate at 12 months, with corresponding AFS reaching 60%[19]. Meta-analyses regarding octogenarians show that they have a 32 % mortality the first year after a revascularisation procedure[257], which is vital to keep in mind, as is the fact that parameters other than perfusion are essential for limb salvage[258] and ulcers de facto heal, although the perfusion is objectively suboptimal[259]. See Picture XXI.

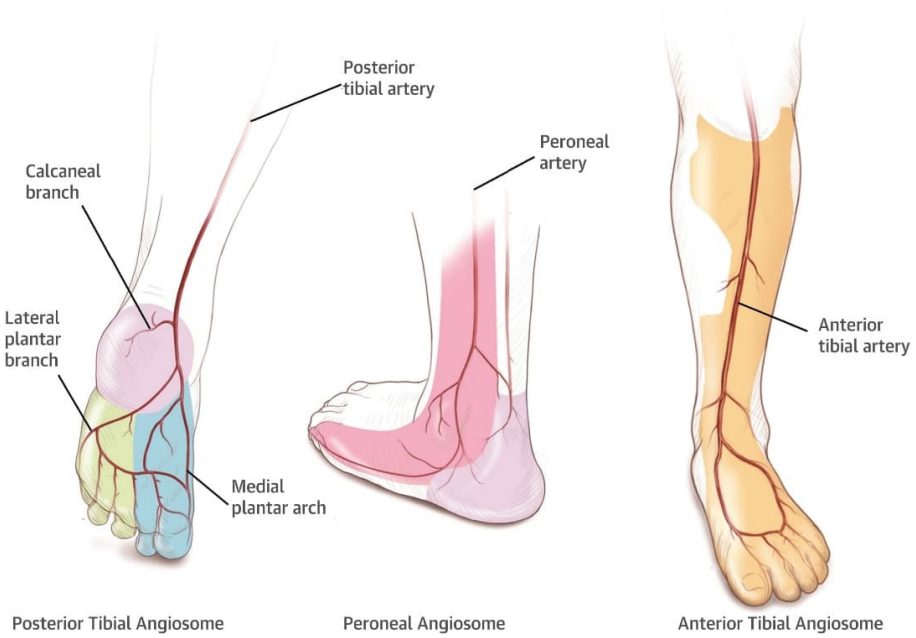


Picture XXI. Picture showing hemodynamics and probability of healing of a diabetic foot ulcer[259].
(Adopted from https://doi.org/10.1016/j.jvs.2010.06.012; Copyright ® 2010, ® Elsevier)

Aspects of direct or indirect revascularisation in PAD

For years, there has been an ongoing discussion regarding the value of direct vs indirect revascularisation to optimise wound healing and improve limb salvage. The concept was instituted already in 1992[260]. Logically, clinicians would opt to revascularise the vessel directly feeding the related angiosome if the target vessel is accessible and open to the foot. There are no high-quality trials, and the data for a few meta-analyses performed are of low quality. One important reason is that pedal arch patency, which is an essential factor, often is not accounted for. Some earlier studies, however, support direct revascularisation[10 261-269]. It also seems less critical

in open vascular revascularisation, where wound healing rates seem similar with indirect revascularisation[270]. One large systematic review and one guideline document regarding PAD in DM with diabetic foot ulcer (DFU), both from 2023, conclude that available data does not support a superiority for direct revascularisation for wound healing, limb salvage, or mortality and due to the low-quality data the certainty of evidence is very low[46 56]. See Picture XXII.



Picture XXII. Picture showing the angiosomes of the foot and ankle[271].

(Adopted from https://doi.org/10.1016/j.jacc.2016.04.071; © 2016 by the American College of Cardiology Foundation. Published by Elsevier.)

Aspects regarding invasive treatment in subjects with DM and PAD

Subjects with diabetes mellitus and PAD belong to a group that may need particular concerns regarding indications and methods for invasive treatment. As mentioned, the disease pattern is different[55 240 272]. There is also a high prevalence of CLTI in the contralateral limb at follow-up after a vascular procedure, which needs to be accounted for. In a 6-year period, 50% develop CLTI that requires intervention in the contralateral limb[273]. Specific effects of revascularisation in subjects with DM and PAD have been discussed for years, and publications have argued for worse results in subjects with DM compared to the population with only PAD[35-38 43 47 274-

[279]. There has also been a discussion regarding different theories behind any differences in outcome[280-286]. At the same time, there are also publications telling us that revascularisation can seemingly be performed with similar results in both groups[287-297]. The positive effects of drug eluting therapy have been an exciting topic, specifically in subjects with DM, as the mechanism for the disease is different, and a superior effect with DET in DM has been proposed[298]. The choice of method, open or endovascular surgery, has also been debated. It is common in PAD guidelines to argue for an endovascular first strategy, but some publications[46] argue instead for autologous bypass when possible, as this may lead to more efficient wound healing and superior patency, a proposition that was also concluded in recent guidelines regarding DM and CLTI[56 95 299-301]. However, this was before the publication of BASIL-2, and the situation has not been clarified as this study showed results in the opposite direction, though not explicitly investigating subjects with DM. The Italian Guidelines (meta-analysis) for the treatment of diabetic foot syndrome published in 2023[302], including BASIL-2, argue for no crucial differences between endovascular and open surgery when treating subjects with DM, PAD, and foot ulcers. However, there were more reinterventions and slower ulcer healing in the DET group, but also significantly less serious adverse events (SAE). When treating subjects with DM interventionally for IC, they seem to have more severe complications both after endovascular and open surgery[33 34]. This is essential to address when selecting subjects with DM for treatment, and it is important to be sure that medical treatment and other risk factors are entirely controlled[303 304].

To conclude, data regarding the specific effects of DM in revascularisation points in different directions, *but* the earlier prevailing idea that revascularisation of subjects with DM and CLTI is of no use is an opinion that should be rendered obsolete as modern results are entirely reasonable and comparable[95]. It seems reasonable that both types of procedures are relevant, and decision-making is essential. Patients should also have the opportunity to be treated at a vascular centre with all the necessary competences in place on a daily basis.

Pivotal trials regarding infrainguinal surgical or endovascular treatment of lower extremity ischemia

Even though not being a part of this thesis, you need to understand the tremendous open vascular surgical development since Jean Kunlin performed the first vein bypass for lower extremity ischemia[132] in Paris in 1948. Since then, the evolving open surgical procedures have been the backbone of the effort to reduce lower extremity amputations. For example, a vein bypass has very high primary patency, secondary patency, and limb salvage rates, reaching 55%, 70%, and 90%,

respectively, at ten years[136]. However, these procedures are medically and technically demanding for the patient and the surgeon.

Being a less invasive and less technically demanding treatment both for the patient and surgeon but still achieving reasonable treatment efficacy, endovascular procedures have increased significantly over the last decades[305]. This revolution has completely changed the education of vascular surgeons, making it more challenging to become a highly skilled or experienced bypass surgeon, as the bulk of daily vascular procedures are performed mostly with endovascular techniques.

There is currently still no complete consensus regarding how to choose between open and endovascular methods, and the most extensive randomised studies to date are difficult to interpret and show somewhat conflicting results[306 307]. The patient populations are complex, and the scientific obstacles for good, reliable randomised comparisons are enormous, and many vascular patients will eventually also fall outside the scope of randomised trials[308].

Recent guidelines, as mentioned, often recommend an "endovascular first" strategy, which, in relation to the collected scientific evidence, seems reasonable, being aware of the fact that, in specific settings, only low-quality data is available[8 9 29 46]. Many of the RCTs comparing endovascular treatment against open surgery do not show any large differences[307 309-316]. You can also find a rather extensive number of articles presenting results from different large observational cohort studies or sometimes conjugates of other studies presented as meta-analyses[302]. Very few of these recommend or advocate open revascularisation as a routine procedure for treating clinically ischemic limbs. This circumstance, together with increasing age and comorbidities, suggests that the bulk of our patients may be better off with less invasive procedures, which seem to have comparable short and mid-term results.

However, we still need to consolidate the ability to perform open surgical vascular procedures, which is clearly a more challenging task today if one wants to deliver acceptable results in selected cases.

Recommendations in some guidelines remain open surgery with bypass in specific settings if autologous vein is available, if the patient has a low or medium risk, if life expectancy is long, and if lesions >250mm. This conclusion is based on the BASIL-1 trial, and long-term patency in open reconstructions with vein grafts is generally high[10 287 317].

No randomised trials are comparing the best methods of open and endovascular treatment of subjects with IC, and it is essential to emphasise that there are still some recent publications in favour of bypass surgery in more specific settings, mainly regarding endpoints such as long-term results, complex wound healing, and DM[318 319]. See Table 7.

Pivotal trials of femoropopliteal non-drug adjunctive angioplasty in lower extremity ischemia

Conventional balloon angioplasty is the foundation for endovascular treatment and a method that more recent technologies must be compared to in different settings. The results of plain standard angioplasty are reasonable when treating short de novo lesions, as shown by Nguyen et al. In a cohort of subjects with 90% TASC A and B lesions, they had primary patency rates reaching 46% and 37% at 3 and 5 years[320].

There are apparent shortcomings when treating longer lesions (>250mm) where the one-year patency only reaches 15%[321]. The same applies to treating in-stent restenosis with an expected one-year patency of 28-37%[322]. Regarding small calibre arteries in the FP region, results may favour angioplasty over bare metal stents[323].

All the shortcomings have led to further development of the angioplasty technique. A simple method of using longer inflation times may give significantly better technical results[324 325].

Cryoplasty or cutting balloon devices are further developments of the angioplasty technique, and RCTs have been performed to compare these methods with standard care. Cryoplasty has not presented clearly superior results and is seldomly used today[326-329]. Cutting balloon treatment has shown conflicting results and not as good outcomes as many expected in clinical direct randomised comparisons[330 331], but may be used in selected cases of complex/fibrotic stenoses.

Other speciality balloons, i.e. the Serranator® and Angiosculpt® devices, both using scoring technology, have been evaluated in non-randomised settings in single arm registries with promising results in the FP region[332 333], but their role in femoral or popliteal artery treatment is still not purely defined.

One other recent development of the angioplasty technique is the lithotripsy method, which is a vessel preparation technique for severe or medium calcified arteries, where it disrupts the arteriosclerotic plaques and is mainly followed by drug coated balloon angioplasty or stenting to complete the treatment. The initial results are promising[334].

To conclude, angioplasty is an integral part of the endovascular toolbox in treating arterial lesions in the FP region, at least as a vessel preparator. However, the scientific evidence for single treatment with only PTA may apply only to selected uncomplicated cases with short lesions. See Table 8.

Pivotal trials of infrapopliteal non-drug adjunctive angioplasty in lower extremity ischemia

In the treatment of infrapopliteal (IP) arterial lesions, conventional balloon angioplasty is still an essential and fundamental method, although new and more advanced technologies are increasingly being used in the field. The primary patency monitored after one year reaches 48-63%[335 336] and after three years, 24-60%[337-339], with lesion length as a critical factor for worse results, as shown by Schmidt et al., with a three-month primary patency rate of 31% in lesions with a mean length of 180mm[340].

A recent metanalysis, published in 2023, using data from 11 RCTs, shows a binary restenosis rate of 60% at 12 months[341]. The corresponding limb salvage rate after plain balloon angioplasty is as high as 91% at five years[342], and there is a well-known discrepancy between vascular primary patency after treatment and an index limb amputation, which is an effect of timely reinterventions and the burden of tissue loss at the index procedure[343]. Problems with a high degree of calcification and occlusions give rise to postangioplasty slow flow phenomena in almost 20% of cases that seriously affect the limb salvage rates[344], and the degree of media calcification in crural arteries is highly correlated to the risk of major amputation[345 346].

In a randomised trial of plain angioplasty with or without adjunctive cilostazol treatment, there was no difference between groups, but the restenosis rate was >80% at three months in both groups with an uncategorised length of lesions, which is a high number reflecting the medium and long term issues with simple angioplasty when treating the crural arteries[347].

A randomised pilot trial using an atherectomy device as an adjunct has shown promising results regarding improved treatment efficacy in the IP arteries[348]. Regarding other angioplasty techniques, there are no accurate direct comparisons of other speciality balloons in this anatomic area, but scoring technology has shown promising results in a recent feasibility study[349], and lithotripsy angioplasty is also evaluated in the non-randomised Disrupt PAD III study with promising results[350].

The conclusion regarding angioplasty in IP lesions is firstly, similar to FP arterial lesions that single conventional balloon angioplasty should primarily be considered in selected short and uncomplicated lesions or as a vessel preparator; secondly, that there may be of clinical value to treat more than one outflow vessel if possible, as was shown in a randomised study from 2018[351], with superior wound healing efficacy but without differences in limb salvage rate.

Pivotal trials of femoropopliteal drug eluting angioplasty in lower extremity ischemia

Adjunctive drug eluting angioplasty treatment in the superficial femoral and popliteal arteries has been reasonably well studied, with several randomised studies. Most angioplasty balloons in use are coated with paclitaxel and a carrier. The carrier constitutes different chemical compounds in all the manufactured CE-marked balloons on the market.

The randomised studies performed are heterogeneous regarding included subjects and outcome variables, but the large majority of studies show superiority for DCB when directly compared to conventional angioplasty ± optional or primary BMS[219 352-374]. Most studies include subjects with lesion lengths less than 100mm and show consistency regarding the results even though different balloon platforms and excipients are used. The primary patency at one, three, and five years reaches 54-86%[353 355 357 358 360 364 367 368 372], 70%[366], and 61%[352], respectively. The study with the most extended median lesion lengths (>150mm) could not prove a difference in the primary outcome, which is in line with the mechanical issues when treating long lesions with or without adjunctive techniques[375].

The discussion regarding any mortality risks with paclitaxel use[376] led to a period of debates and scrutiny of vascular registries around the world. Currently, regarding mortality, drug eluting treatment is considered safe, as shown in the largest randomised prospective registry concerning drug eluting therapy[377]. There is also a discussion regarding the risk of amputations using paclitaxel, as presented by Katsanos et al[378]. In a meta-analysis, they argued for a higher amputation rate in the drug eluting cohort that corresponded to the total paclitaxel dose given. This was driven by high-dose products and mostly from studies investigating CLTI in the infragenicular region, as the In. Pact DEEP study[379], which was aborted after 12 months of follow-up due to safety issues and the SINGA-PACLI trial[380], where >50% of the study subjects were on haemodialysis. The five-year follow-up from In. Pact DEEP[381] did not show a higher amputation rate.

The discussion is ongoing but has not led to any restrictions in the FP region, where pharmacokinetic studies have not proven effects on wound healing and amputations in the treatment of CLTI subjects[382]. Studies have suggested that there may be an issue with distal particulate embolisation of paclitaxel crystals, which differ significantly across balloon platforms[383-385].

This discussion also has affected the arguments for choosing another bioactive drug, as in coronary revascularisation. A recent randomised study compared sirolimus-eluting balloons with paclitaxel-eluting balloons with a proven non-inferiority[386]. Randomised studies have also shown that low-dose paclitaxel balloons are as effective as high-dose balloons[387 388].

Sub-analysis of long lesion (median lesion length >250mm) treatment in randomised controlled trials shows a significantly better result after drug coated balloon treatment compared to standard balloon angioplasty[321].

So, in conclusion, considering the overall randomised scientific evidence currently available, as well as results from meta-analyses, drug eluting adjunctive treatment in angioplasty of FP lesions should strongly be considered[389-397]. See Table 9.

Pivotal trials of infrapopliteal drug eluting angioplasty in lower extremity ischemia

When performing angioplasty in the infragenicular region, you encounter the same issues as discussed above, as the results of non-drug adjunctive treatments have limitations regarding the development of binary stenoses and the need for, often, repeated TLR procedures already in the short and medium-term follow-up.

The use of DCBs in these small calibre vessels has been studied in a few randomised controlled studies, and more RCTs are planned or currently ongoing. The results so far have been discrepant as some of the studies were not able to conclude a clear superiority for DCB treatment[380 381 398-400]. A few studies have results that are significantly in favour of DCB treatment, with freedom from TLR rates at 12 months between 71-90% compared to 23-59% with standard angioplasty [401-404].

The risks with paclitaxel use in the IP arteries have also been discussed both regarding mortality and amputations[378 405]As previously discussed, there are no clear concerns regarding mortality today, and no clear conclusions have been made so far regarding the risk for amputation after the use of DCBs in the infragenicular region. This effect has also not been seen in later meta-analyses[406-409] of IP endovascular treatment.

The recent meta-analyses also came to different conclusions. Some were not able to conclude a clear superiority[406 410] for DCB, while others showed benefits regarding primary patency, rate of binary stenosis, and rate of TLR in the short-term perspective (6 months), but less clearly at 12 months[407 408].

In conclusion, regarding the treatment of crural arterial lesions, there is an ongoing controversy regarding the place for DCB, as the results are divergent. A recent meta-analysis concluded that the results of standard angioplasty treatment regarding primary patency rates and TLR rates in these randomised trials are 10-20% units higher than usually accounted for in trial power calculations[341]. Further studies are needed to draw a reasonable conclusion, taking into account the modern-day results after plain balloon angioplasty. See Table 10.

Pivotal trials of femoropopliteal bare metal stenting and stentgraft treatment in lower extremity ischemia

Treatment with BMS in FP lesions has been a significant part of the endovascular treatment of PAD and is still frequently used. RCTs have been conducted since the late 1990s, and stentgraft (SG) treatment has also been investigated in a few trials. Early results are not impressive but since the groundbreaking ABSOLUTE trial[411] in 2007, there has been a row of RCTs comparing BMS with PTA, with different primary outcomes, out of which the majority speaks in favour of BMS[189 192 411-415]. Although the studies are heterogeneous regarding indication, median lesion length, and rate of total occlusions, there is a general trend toward some form of BMS superiority against standard PTA.

The studies of SG treatment compared to PTA also show better results in analogy with the former studies[416 417]. In two SG studies, the VIASTAR and VIBRANT, SG (Viabahn®) are compared against BMS. VIBRANT[418] did not show the same improved primary patency at three years that VIASTAR[419] could demonstrate after two years.

In the ISAR-STATH study with three treatment arms, DCB+BMS was superior to both PTA + BMS and direct atherectomy (DA)[420]. Recent meta-analyses conclude that BMS has better short-term outcomes compared to standard PTA. Not surprisingly, the long-term superiority is questioned[392 393 421], with a sometimes problematic development of in-stent restenosis. Therefore, BMS seems to be inferior to drug eluting treatment in the FP segment[392 393 421 422].

The problem with in-stent restenosis after stenting with bare metal stents is well known for interventionists, and it constitutes a not negligible part of femoral artery interventions. Five RCTs have compared the results of DCB and PTA in these complicated ISR lesions, with consistently superior results for DCB[423-427]. One study compared SG treatment with PTA and showed superior results[428]. When treating these lesions with laser atherectomy, there is one comparative trial showing superior results with atherectomy + DCB versus only DCB[429], and another comparing atherectomy + PTA with PTA alone, also with superior results[430]. Older comparative studies with atherectomy devices alone against PTA produced worse results than standard PTA[431]. A recent trial using photoablative technique before DCB or DCB alone did not show any differences[432]. Comparative trials using cutting balloon technology have not demonstrated superior results[433].

In conclusion, you probably need to consider other alternatives before you decide to treat an FP lesion with a bare metal stent, although it seems superior to standard PTA. Other possible treatment alternatives seem to have advantages[392 395]. Open cell stents also have concerns regarding intimal hyperplasia and in-stent restenosis, which you also must consider. See Table 11.

Pivotal trials of infrapopliteal bare metal stenting in lower extremity ischemia

Non-drug adjunctive stenting for IP lesions has been used for more than 30 years, mostly to overcome suboptimal results after plain balloon angioplasty. Few randomised studies comparing stents against PTA in IP lesions have been published, and they include self-expanding and balloon-expanding stents as well as carbostents and resorbable stents. The results are divergent[415 434-440], and the latest RCT from 2023 did not show any differences compared to PTA in treating lesions lengths up to 80mm[434]. Primary patency at 12 months in RCTs reaches 35-56%[437 438]. Looking at an important meta-analysis, including 640 patients with IP stenting, the primary patency and limb salvage at 12 months were 73% and 98 % for balloon-expandable stents and 79% and 96% for self-expanding stents[441]. Target vessel revascularisation was 18% and 6% for BES and SES, respectively. They also conclude that drug eluting stents seem to be more effective.

In conclusion, with a relatively high restenosis rate, the definitive role of non-drug adjunctive stent in below-the-knee (BTK) treatment can be considered as a potential bailout treatment in failed PTA, even though better options may be available. It should not be regarded as a primary treatment, and other alternatives should always be considered in IP stenting situations. See Table 12.

Pivotal trials of femoropopliteal drug eluting stenting in lower extremity ischemia

Only two different DES are available for FP use in the US and EU markets. Namely, the Zilver PTX®, the first DES for peripheral use, and the Eluvia®, which later was examined in the EMINENT study, the most extensive randomised comparison against BMS[442]. This study showed clear DES superiority after 12 months with a primary patency of 83% compared to 74% with BMS ($p<0.01$) in lesion lengths of 75mm. The Zilver PTX® has shown a superior event-free survival at five years with lesion lengths at 65mm[443], but the trial setting in the Zilver PTX® trial was complicated with a sequential double randomisation process. In both studies, a significant proportion of subjects suffered from IC. The 11 RCTs available[442-451] are heterogenous, with two trials comparing DES against DCB without significant differences[447 448]. With the exception of the SIROCCO trial[450], the first DES RCT, that used sirolimus-coated stents, all the other trials use paclitaxel coated devices. One RCT compares Zilver PTX® against Eluvia® head-to-head in FP lesions with a mean lesion length of 85mm, with superior results regarding TLR at 24 months for Eluvia®, which is a slow-release device[445]. Falkowski et al. compared Zilver PTX® against Zilver Flex® in 2020[446], similar to our trial II in this thesis. They

showed superior results with DES regarding TLR and binary restenosis at three years. There seems to be greater efficacy with DES against BMS in specific settings, which is also supported in some meta-analyses[421 452]. Clear superiority against DCB and the appropriateness in long lesions are more questionable. In a recent meta-analysis of 4847 subjects from both RCTs and retrospective registries treated for FP lesions >150mm, the primary patencies at 12 months reached 68%, 67%, 74%, and 83% for BMS, SG, DES, and DCB, respectively[422]. Another meta-analysis including 1889 subjects from seven RCTs comparing DES and BMS could *not* show superiority for DES[453]. A meta-analysis analysing data from both RCTs and registries comparing DES and DCB in FP lesions[454], showed a modest superiority for DES against only DCB, but when comparing DES to atherectomy + DCB, DES was inferior, reflecting that the issue of the mechanical properties and calcium burden in FP disease is a significant factor. In a recent, very nicely presented meta-analysis, including 38 trials with 6026 subjects[421], comparing all multiple modalities for FP treatment, you may see interesting differences. See Table 6.

In conclusion, the most appropriate treatment in each setting is still not fully clarified, and high-quality data is still lacking, so more research needs to be provided. With available data, it seems clear that some form of advantage for using drug eluting therapy when treating FP lesions is to be expected, and specifically concerning DES, it may be appropriate as primary treatment in short and medium-long lesions or as bailout after PTA. With deployment, you must relate to the randomised study by Miki et al., when they randomised Zilver PTX in superficial femoral artery lesion to either 1- or 2-mm oversizing, showing increased postimplantational intimal hyperplasia with a higher SV ratio[455]. See Table 13.

Table 6. The table highlights comparisons between different modalities in treating FP lesions, showing odds ratios (OR) and corresponding 95% confidence intervals (CI).

Comparisons	PP 6m	PP 12m	PP 24m	TLR 6m	TLR 12m	TLR 24m
BMS vs PTA	5.14 (2.46-10.58)	2.02 (1.35-3.01)	2.47 (1.23-4.56)	0.04 (0.00-0.57)	0.40 (0.23-0.69)	0.30 (0.14-0.68)
SG vs PTA	*Not specified*	4.52 (1.89-11.14)	3.55 (1.07-10.72)	*NS*	0.27 (0.08-0.90)	0.20 (0.06-0.62)
DCB vs PTA	4.20 (2.50-6.91)	3.50 (2.34-5.23)	3.11 (1.89-5.00)	0.22 (0.10-0.59)	0.24 (0.15-0.36)	0.33 (0.21-0.48)
DES vs PTA	15.24 (5.42-39.64)	4.05 (1.99-8.27)	7.10 (2.56-16.46)	*NS*	0.25 (0.10-0.58)	0.28 (0.10-0.73)
BMS vs SG	*Not specified*	*NS*	*NS*	*NS*	*NS*	*NS*
BMS vs DCB	*NS*	0.58 (0.33-0.99)	*NS*	*NS*	*NS*	*NS*
BMS vs DES	*NS*	0.50 (0.25-0.99)	*NS*	*NS*	*NS*	*NS*
SG vs DCB	*Not specified*	*NS*	*NS*	*NS*	*NS*	*NS*
SG vs DES	*Not specified*	*NS*	*NS*	*NS*	*NS*	*NS*
DCB vs DES	0.28 (0.10-0.80)	*NS*	*NS*	*NS*	*NS*	*NS*

Pivotal trials of infrapopliteal drug eluting stenting in lower extremity ischemia

In the beginning, the stents used in BTK treatment were coronary drug eluting stents. One of the first more extensive trials evaluating DES in the crural setting was PaRADISE, a non-randomised single arm trial (PReventing Amputations using Drug eluting StEnts), showing only 6% cumulative amputations at three years[456]. They placed 228 DES 83% Cypher® and 17% Taxus® stents in subjects with Rutherford Category (RC) IV-VI and crural lesions, with a mean stented length of 60mm.

There is a shortage of randomised trials regarding DES in infragenicular arteries[457-464]. Most are performed with balloon-expandable stents, and only one recent trial studied the efficacy of self-expanding drug eluting stents, i.e. the SAVAL trial published in 2023, that did not show superior results compared to standard PTA in crural lesions up to 140mm[458].

Early in 2024, Varcoe et al. published results with an Everolimus-coated resorbable scaffold in IP arteries and focal lesions with a median length of 45mm, with highly superior results compared to PTA at 12 months[457]Resorbable scaffolds are the latest idea for handling early or acute problems with recoil and dissections. They have the advantage of leaving nothing behind in the medium and long term.

Siablis et al. compared DCB and DES in lesions up to 150mm, with improved efficacy for DES at six months[460]. Otherwise, comparisons have been made against PTA with optional BMS. In the PADI, ACHILLES, and YUKON-BTK trials, DES seems superior in the long term at 1,3- and 5-year follow-up[459 461 462].

With less than ten RCTs performed, knowledge is limited regarding the place for DES in IP treatment. Available data speaks for an advantage in short and medium-long lesions against PTA±BMS. Meta-analyses are divergent regarding the efficacy of DES[408 409 465-468].

A reasonable conclusion is that DES should be considered in the treatment of IP lesions as there seems to be a scientifically reproducible superiority against PTA/BMS in lesions of short and medium lengths. In comparison with DCB, any advantage is unclear, and it is probably wise to consider DCB as an alternative in long lesions. See Table 14.

Pivotal trials of infrainguinal use of debulking methods in lower extremity ischemia

There are few randomised comparisons between different approaches using available debulking devices. The debulking devices usually consist of mechanical atherectomy devices that work by directional or orbital shearing and thermal or laser-driven devices.

Regarding de novo FP lesions, the randomised evidence for their use is scarce, with few studies showing superiority and ten studies showing equal results compared to standard therapy[469-478]. Clear superiority is only shown in one study at six months[472]. Recent meta-analyses point in different directions, with the latest also including ISR, argue for superiority when using debulking devices[479-481].

Looking at the cases with ISR, the scenario is similar[429-432], with only four randomised studies that show conflicting results, however, including the largest randomised trial of debulking strategies for FP lesions, this indicates a highly significant improvement of the TLR rate at 6m (26% vs 48%, $p<0.005$)[430]. One study compared orbital and directional atherectomy head-to-head, with a result in favour of the directional techniques[482].

In the IP region, there are so far only three randomised comparisons[348 483 484], but the two latest trials are probably underpowered and cannot show significant treatment differences due to the low number of participants, although the numerical differences are highly dispersed[483 484].

The more than ten years old CALCIUM 360 trial is still the only randomised study supporting superiority for debulking strategies in this region[348]. Meta-analyses also including retrospective studies argue for clearly superior results[485 486].

In conclusion, scientific evidence for the consistent use of debulking devices is problematically scarce, and more high-quality evidence is needed to support their systematic use in standard care. See Table 15.

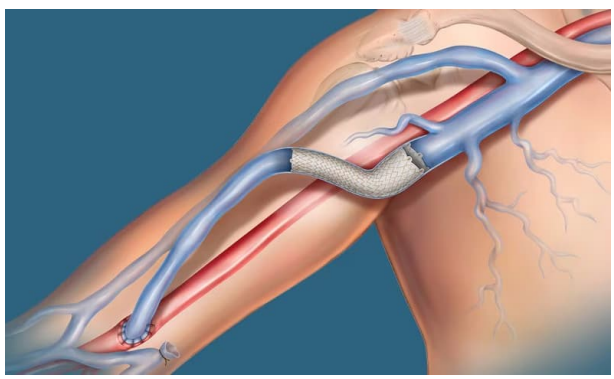
Pivotal trials regarding non-drug adjunctive endovascular treatment of malfunctional haemodialysis access in upper extremities

Regarding non-thrombosed AV-grafts or AV-fistulas, there are extremely few direct comparisons between surgical and endovascular treatment, and today, most access revisions are performed with endovascular methods, although the juxta anastomotic stenoses scientifically still may perform slightly better after open surgical revision,

as Argyriou et al. concluded already 2015[487], by performing a meta-analysis of four different non-randomised cohort studies[488-491]. The study by Brooks et al. from 1987[492] is the only study that compares open revision with angioplasty in a randomised setting when treating graft venous anastomosis stenoses with Gruntzig dilatation catheters at the Swedish Hospital in Seattle, US.

Endovascular treatments are somewhat more comprehensively compared. Simple PTA is commonly performed with often acceptable results in dialysis access maintenance with primary patency rates at six months between 27-63%[2]. Randomised comparisons of PTA and BMS are few and, to some extent, outdated, and none of them show any crucial differences in using these first-generation devices[493-495]. Later non-randomised cohort studies suggest treatment effects in favour of BMS vs. PTA[496-498].

The vascular community has increased the use of SGs when approaching outflow lesions, in line with several RCTs that show substantial improvements regarding treatment efficacy in comparison with PTA[499-507]. The place for BMS in haemodialysis access outflow lesions is nowadays questionable. There is only one randomised study by Shemesh et al.[508], directly comparing BMS and SG, showing improved treatment efficacy with SG. Kavan et al.[503], also had a small BMS group in their RCT with three treatment arms, showing similar results. See Picture XXIII.



Picture XXIII. Schematic picture showing a Brachiobasilic AV-fistula treated with an SG to solve an access outflow issue.

(*Adopted from illustrations by Mike Austin. Copyright© 2018. C.R. Bard, Inc.*)

Regarding speciality balloons, most commonly cutting balloon devices, there are a couple of randomised comparisons between cutting balloon treatment and standard PTA or high-pressure PTA (HPPTA)[509-513]. The results are conflicting, but the choice of cutting devices may be warranted in certain instances. See Tables 16 and 17.

Pivotal trials regarding drug eluting endovascular treatment of malfunctional haemodialysis access in upper extremities

As our studies are focused on this recently implemented drug eluting technology, it is important to highlight where we stand today regarding knowledge and recommendations. Starting with DES, there are still no direct comparisons regarding their efficacy in this field today, and the place of this treatment in the armamentarium is unclear. A few small recent single arm studies have proved their safety and shown acceptable results[514-517], but no recommendations can be made so far.

The DCBs have been the focus for the last few years regarding endovascular treatment in different vascular regions. Our knowledge of their use in this field will improve as more randomised trials are published in the future. Concerning the use of DCBs in the treatment of vascular access dysfunction, results from RCTs are so far wildly divergent, and the endpoints are varying[518-540]. Three different late meta-analyses from 2023 are though in favour of DCB use in the treatment of dysfunctional AV-access[541-543]. See Table 18.

Tables showing randomised trials of specified infrainguinal endovascular treatments for PAD and endovascular revisions of haemodialysis access (Tables 7-18)

Table 7. Randomised studies comparing open surgery and endovascular intervention in infrainguinal lower limb ischemia.

Reference	Study	Year	Sites	Indication	Lesions	Treatment	Subjects	Primary endpoint	Follow up (years)	Results
Van Walraven et al[315]	SUPERB	2024	6	CLTI/IC	SFA (AK)	BP vs SG	62/63	PP	5	PP 1y;49% vs 36% (p=0.608)
Enzmann et al[544]		2023	1	CLTI/IC	SFA/POP	VBP vs BMS	106/103	PP, SP	4	SP 4y;73% vs 50% (p=0.021)
Bradbury et al[306]	Basil-2	2023	41	CLTI	Crural +/-	VBP vs Endo	172/173	AFS	2 (min)	AFS;37% vs 47% (p=0.037)
Bosiers et al[310]	Zilverpass	2023	13	CLTI/IC	SFA (AK)	PBP vs DES	107/113	PP	5	PP;41% vs 50% (p=0.69)
Farber et al[307]	BEST-CLI 1	2022	150	CLTI	Infrainguinal	VBP vs Endo	718/716	MALE+ Death	7	Events;43% vs 57% (p<0.001)
Farber et al[307]	BEST-CLI 2	2022	150	CLTI	Infrainguinal	BP vs Endo	197/199	MALE+ Death	7	Events;43% vs 48% (p=0.12)
Meecham et al[545]	Basil-1	2019	27	CLTI	SFA/POP	BP vs BMS	128/183	FF-MALE, AFS	3	FF-MALE;67% vs 56% (p=0.04)
Eleissawy et al[311]		2019	2	CLTI/IC	Flush SFA	BP vs Endo	25/28	PP, PaP, SP	1	PP 1y;72% vs 65% (p=0.623)
Meecham et al[546]	Basil-1	2018	27	CLTI	Infrainguinal	pBP vs sBP	190/49	AFS	7	PP 7y;60% vs 40% (p=0.04)
Bjorkman et al[309]		2018	6	RC II-IV	SFA	PBP vs DES	18/23	SP	2	SP 2y;71% vs 56% (p=0.83)
Popplewell et al[314]	Basil-1	2017	27	CLTI	IP	VBP vs PTA	56/48	AFS	5	AFS 5y;36% vs 15% (p=0.1)
McQuade et al[313]		2010	1	CLTI/IC	SFA (AK)	PBP vs SG	46/40	PP, SP	4	PP 4y;58% vs 59% (p=0.807)
Bradbury et al[547]	Basil-1	2010	27	CLTI	Infrainguinal	BP vs PTA	228/224	AFS	3 (min)	OS >2y;HR 0.61 (0.50-0.75) (p=0.009)
Bradbury et al[548]	Basil-1	2010	27	CLTI	Infrainguinal	BP vs PTA	228/224	AFS	3 (min)	AFS;VPB>PBP (p=0.008)
Lepantalo et al[549]		2009	15	CLTI/IC	SFA (AK)	PBP vs SG	21/23	PP	3	PP 1y;95% vs 48% (p=0.02)
Adam et al[550]	Basil-1	2005	27	CLTI	Infrainguinal	BP vs PTA	228/224	AFS, OS	1 (min)	Events >2y;HR 0.37 (0.17-0.77) (p=0.008)
Van der Zaag et al[551]	BASIC	2004	18	RC I-IV	SFA /(AK)	VBP vs SG	25/31	PP	2	PP 1y;82% vs 43% HR 2.24 (0.9-5.58)
Wolf et al[316]		1993	8	CLTI/IC	Iliac/Fem/Pop	Surgery vs PTA	133/130	PP, LS	4	PP 4y;57% vs 58% NS
Holm et al[312]		1991	2	CLTI/IC	Iliac/Fem/Pop	Surgery vs PTA	49/53	n/a	1	PP 1y;62% vs 60% NS

Table 8. Randomised studies involving non-drug adjunctive angioplasty methods in the treatment of femoropopliteal arterial lesions.

References	Year	Sites	Allocation	Device	Company	Indication	CTO	Median lesion length (mm)	Primary endpoints	Follow up	Results
Tepe et al[552] (Disrupt PAD III)	2022	45	IVL n=153 PTA n=153	Shockwave M^5 IVL Balloon	Shockwave Medical	RC II-IV	26% vs 31% NS	101 vs 97 NS	PP	24m	PP 2y;70% vs 51% p=0.003
Banerjee et al[553]	2012	4	Cryo+BMS n=45 PTA+BMS n=45	Polar Cath	Boston Sci	RC III-V *Only DM*	48% vs 34% NS	93 vs 120 NS	BS 12m	12m	BS 1y;29% vs 56% p=0.01
Fossaceca et al[327]	2012	1	Cryo n=24 PTA n=24	Polar Cath	Boston Sci	RC II-VI *Only DM*	*Not spec.*	*Not spec.*	BS 6,12 m	12m	PP12m;36% vs 47% p=0.122
Poncyljusz et al[331]	2012	1	Cut n=30 PTA n=30	Cutting balloon	Boston Sci	RC II-IV	10% vs 7% NS	31 vs 36 NS	PP, BS 12m	12m	BS 1y pp;13% vs 36% p=0.049
Shammas et al[473]	2011	1	Cryo n=20 PTA n=20	Polar Cath	Boston Sci	RC I-V	*Not spec.*	24 vs 26 NS	PP 6m	6m	TLR 6m;15% vs 11% NS
Diaz et al[326]	2010	1	Cryo n=86 PTA n=69	Polar Cath	Boston Sci	RC I-V	*Not spec.*	*Not spec.*	PP	36m	PP 3y;49% vs 56% p=0.14
Jahnke et al[554]	2010	?	Cryo n=40 PTA n=46	Polar Cath	Boston Sci	RC I-V	23% vs 30% NS	35 vs 37 NS	PP 9m	15m	PP 9m;79% vs 67% p=0.14
Spiliopoulos et al[329]	2010	1	Cryo n=24 PTA n=26	Polar Cath	Boston Sci	RC III-VI	23% vs 15% NS	11.9 vs 12 NS ISR: 39% vs 47% NS	PP, BS, TLR, TS	36m	FF-TLR 3y;34% vs 48% p=0.04 PP 3y;59% vs 55% p=0.894
Amighi et al[330]	2008	2	Cut n= 21 PTA n=22	Cutting balloon	Boston Sci	F IIb-IV	29% vs 23% NS	<50	BS 6m	6m	BS 6m;62% vs 32% p=0.048

Table 9. Randomised studies involving DCB ± BMS in the treatment of femoropopliteal arterial lesions.

Reference	Year	Sites	Allocation	Device	Company	Dose (µg/mm²)	Indication	CTO	Median lesion length (mm)	Primary endpoints	Follow up	Results
Teichgraber et al[555] (EFFPAC)	2022	11	DCB n=85 PTA n=86	Luminor 35	iVascular S.L.U.	3.0	RC II-IV	17% vs 22% NS	59 vs 56 NS	PP, TLR	60m	PP 5y;61% vs 53% p=0.040 FF-TLR 5y;82% vs 74% p=0.050
Liao et al[353]	2022	1	DCB n=30 PTA n=30	Orchid	Acotec Scientific	3.0	RC II-V	64% vs 67% NS	91 vs 93 NS	PP, TLR	12m	PP 1y;83% vs 48% p=0.005 TLR 1y;4% vs 28% p=0.001
Ni et al[354]	2022	15	DCB n=93 PTA n=99	ZENFlow	Zylox Medical Devvice Inc.	3.0	RC III-V	29% vs 44% p=0.04	70 vs 55 p=0.07 ISR 14;11% NS	LLL 6m	12m	0.50mm vs 1.69mm p<0.001 PP 1y;54% vs 31% p<0.001
Shishehbor et al[355] (Chocolate Touch)	2022	34	DCB n=16 PTA n=152	Lutonix Chocolate Touch	BARD TriReme Medical	2.0	RC II-IV	*Not spec.*	78 vs 79 NS	PP 12m	12	PP 1y;68% vs 79% p=0.04
Nowakowski et al[356] (BIOPAC)	2021	5	DCB n=33 PTA n=33	PAK	Balton Sp zoo	3.0	RC II-IV	44% vs 26% p=0.13	65 vs 59 NS	LLL 6m	36m	0.52mm vs 1.1mm p<0.01 TLR 3y,29% vs 59% p=0.02
Zhang et al[357]	2021	14	DCB n=155 PTA n=154	Freeway	Eurocor	3.0	RC II-V	*Not spec.*	70 vs 72 NS	TLR 6m	12m	TLR 1y;3% vs 13% p=0.005
Sachar et al[358] (RANGER II SFA)	2021	67	DCB n=278 PTA n=98	Ranger	Boston Scientific	2.0	RC II-IV	18% vs 30% P=0.02	83 vs 80 NS	PP, TLR	12m	PP 1y;83% vs 66% p=0.0013 TLR 1y;6% vs 17% p=0.0011
Ye et al[359]	2021	12	DCB n=100 PTA n=100	Reewarm PTX	Endovastec Co.	3.0	RC II-V	49% vs 55% NS	96 vs 91 NS	LLL 6m TLR, MAE	12m	0.5mm vs 1.2mm p<0.001 TLR 1y;15% vs 29% p<0.05
De Boer et al[375] (RAPID)	2019	8	DCB+IWS n=80 PTA+IWS n=80	Legflow Supera	Cardionovum Abbot	3.0	RC II-VI	76% vs 70% NS	158 vs 158 NS	PP	24m	PP 2y;55% vs 48% p=0.957
Tacke et al[360] (FREEWAY)	2019	13	DCB+BMS n=105 PTA+BMS n=99	Freeway	Eurocor	3.0	RC II-V	64% vs 64% NS	77 vs 83 NS	TLR 6m	12m	PP 1y;77% vs 61% p=0.027 TLR 1y;8% vs 18% p=0.064
Iida et al[374] (IN.PACT JAPAN) (MDT-2113)	2019	11	DCB n=68 PTA n=32	In.Pact (MDT-2113)	Medtronic	3.5	RC II-IV	16% vs 16% NS	92 vs 89 NS	PP, TLR Composite	24m	PP 2y;80% vs 47% p<0.001 TLR 2y;9% vs 21% p=0.177
Du et al[361]	2019	10	DCB n=54 PTA n=57	Orchid	Acotec Scientific	3.0	RC II-V *Only DM*	50% vs 46% NS	153 vs 143 NS	LLL 6m BS, TLR	24m	0.14mm vs 1.13mm p<0.01 TLR 2y;15% vs 37% p<0.01
Brodmann et al[362] (ILLUMENATE EU)	2018	18	DCB n=222 PTA n=72	Stellarex	Philips	2.0	RC II-IV	19% vs 19% NS	72 vs 71 NS	PP, TLR	24m	PP 2y;76% vs 61% p=0.025 FF-TLR 2y;89% vs 72% p<0.001
Albrecht et al[363] (CONSEQUENT)	2018	11	DCB n=78 PTA n=75	SeQuent Please OTW	B.Braun	3.0	RC II-IV	23% vs 29% NS	137 vs 126 NS	LLL 6m PP, TLR Walk	24m	PP 2y;47% vs 31% p=0.006 TLR 2y;19% vs 40.6% p=0.007 Walk 2y;172m vs 52m p=0.001
Steiner et al[364] (RANGER I SFA)	2018	10	DCB n=71 PTA n=34	Ranger	Boston Scientific	2.0	RC II-IV	34% vs 34% NS	60 vs 68 NS	PP, TLR	12m	PP 1y;86% vs 52% p=0,002 TLR 1y;9% vs 27% p=0.030
Xu et al[365] (ACOART)	2018	10	DCB n=100 PTA n=100	Orchid	Acotec Scientific	3.0	RC II-V	57% vs 52% NS	147 vs 152 NS ISR 27;23% NS	PP, TLR	24m	PP 2y;65% vs 31 % p<0.001 FF-TLR 2y;87% vs 59% p<0.001

Reference	Year	Sites	Allocation	Device	Company	Dose (µg/mm²)	Indication	CTO	Median lesion length (mm)	Primary endpoints	Follow up	Results
Schneider et al[366] (IN.PACT SFA)	2018	57	DCB n=220 PTA n=111	In.Pact Admiral	Medtronic	3.5	RC II-IV	26% vs 19% NS	89 vs 88 NS	PP, TLR	60m	PP 3y;70% vs 45% p<0,001 TLR 3y;15% vs 31% p=0.002 Death 3y;11% vs 2% p=0.006
Krishnan et al[367] (ILLUMENATE Pivotal)	2017	43	DCB n=200 PTA n=100	Stellarex	Philips	2.0	RC II-IV	19% vs 18% NS	80 vs 89 NS	PP, TLR, LS, OS	12m	PP 1y;76% vs 58% p=0.003 TLR 1y;8% vs 17% p=0.023
Rosenfield et al[368] (LEVANT 2)	2015	54	DCB n=316 PTA n=160	Lutonix	BARD	2.0	RC II-V	21% vs 22% NS	63 vs 63 NS	PP Composite	12m	PP 1y;65% vs 53% p=0.020 FF events;84% vs 79% p=0.005
Scheinert et al[369] (BIOLUX P-1)	2015	5	DCB n=30 PTA n=30	Passeo-18 Lux	Biotronik	3.0	RC II-V	38% *Not spec.*	51 vs 69 NS	LLL 6m TLR 6,12	12m	0.51mm vs 1.04mm p=0.033 TLR 1y;16% vs 53% p=0.020
Tepe et al[370] (THUNDER)	2015	3	DCB n=48 PTA n=54	Paccocath	B.Braun	3.0	RC I-V	27% vs 26% NS	75 vs 74 NS ISR 17;11% NS	LLL 6m	6m (60)	0.4mm vs 1.7mm p<0.001 TLR 5y;21% vs 56% p=0.0005
Scheinert et al[371] (LEVANT 1)	2014	9	DCB n=49 PTA n=52	Lutonix	BARD	2.0	RC II-V	20% vs 22% NS	81 vs 80 NS	LLL 6m	24m	0.46mm vs 1.07mm p=0.016
Liistro et al[372] (DEBATE-SFA)	2013	2	DCB+BMS n=53 PTA+BMS n=51	In.Pact Admiral	Medtronic	3.0	RC III-VI	54% vs 69% p=0.10	94 vs 96 NS	BS 12m	12m	BS 1y;17% vs 47.3% p=0.008
Werk et al[373] (PACIFER)	2012	3	DCB n=44 PTA n=47	In.Pact Pacific	Medtronic	3.0	RC II-V	23% vs 38% NS	77 vs 66 NS ISR 16;13% NS	LLL 6m	12m	-0.006 vs 0.67 mm p=0.002 MAE 1y;7% vs 35% p=0.003
Werk et al[219] (FEMPAC)	2008	2	DCB n=45 PTA n=42	“Prototype”	Bavaria Medicine Indena	3.0	RC I-IV	19% vs 13% NS	47 vs 40 NS ISR 10;4% NS	LLL 6m	24m	0.3mm vs 0.8mm p=0.031 TLR 6m;7% vs 33% p=0.0024

Table 10. Randomised studies involving DCB in endovascular treatment of infrapopliteal arterial lesions.

Reference	Name	Year	Sites	Allocation	Device	Company	Dose (µg/mm²)	Indication	CTO	Median lesion length (mm)	Primary endpoints	Follow up	Results
Fransson et al (submitted)	CRURAL-DEB	2024	1	DCB n=35 PTA n=35	Ranger Sterling	Boston Scientific	2.0	RC IV-VI	81% vs 89% NS	150 vs 100 NS	PP 12m	12m	PP 1y;48% vs 48% p=0.99 AFS 1y;88% vs 68% p=0.042
Liistro et al[398]	IN.PACT-BTK	2022	9	DCB n=23 PTA n=27	In.Pact 014 DCB	Medtronic	3.5	RC IV-V	Only CTO	215 vs 218 NS	LLL 9m	9m	LLL 9m;0.9 vs 1.3 mm p=0.07
Liistro et al[401]	DEBATE-BTK	2022	1	DCB n=65 PTA n=67	In.Pact Amphiron DCB	Medtronic	3.5	RC IV-VI *Only diabetics*	78% vs 82% NS	129 vs 131 NS	FF MAE 60 TLR	60m	FF TLR 5y;63% vs 54% p=0.07 OS 5y;66% vs 40% p=0.0032
Patel et al[380]	SINGA-PACLI	2021	2	DCB n=70 PTA n=68	Passeo-18 Lux	Biotronik	3.0	RC IV-VI	35% vs 30% NS	90 vs 82 NS	PP 6m	12m	PP 6m;43% vs 38% p=0.48 AFS 1y;59% vs 78% p=0.01
Zeller at al[381]	IN.PACT-DEEP	2020	13	DCB n=239 PTA n=119	In.Pact Amphiron DCB	Medtronic	3.5	RC IV-VI	39& vs 46% NS	102 vs 129 p=0.002	FF TLR 60 OS, LS	60m	FF-TLR 5y;69% vs 78% p=0.236
Liistro et al[402]	AcoArt-I BTK	2020	1	DCB n=52 PTA n=53	Litos DCB	Acotec Scientific	3.0	RC IV-VI	68% vs 67% NS	168 vs 187 NS	LLL 6m FF TLR 12m	12m	LLL 6m;0.51 vs 1.31 mm p<0.001 FF-TLR 1y;90% vs 59% p<0.001
Jia et al[403]	AcoArt-II BTK	2020	11	DCB n=61 PTA n=59	Litos DCB	Acotec Scientific	3.0	RC IV-VI	75% vs 83% NS	170 vs 180 NS	PP, TLR 6m	12m	PP 6m;75% vs 28% p<0.001
Mustapha et al[399]	Lutonix- BTK	2019	51	DCB n=287 PTA n=155	Lutonix	BARD Peripheral	2.0	RC III-V	36% vs 33% NS	112 vs 95 NS	PP+FF AMP	6m	PP/FF-amp;74% vs 63% NS
Haddad et al[404]		2017	1	DCB n=48 PTA n=45	Luminor14	iVascular	3.0	RC IV-VI	*Not spec.*	*Not Spec.*	PP 12m	12m	PP 1y;65% vs 17% p=0.006 TLR 1y;23% vs 71% p=0.009
Zeller et al[400]	BIOLUX P-II	2015	6	DCB n=36 PTA n=36	Passeo-18 Lux	Biotronik	3.0	RC II-V	*Not spec.*	113 vs 115 NS	L-PP 6m	12m	Loss of PP 6m 17% vs 26% p=0.298

Table 11. Randomised studies involving SG or BMS in endovascular treatment of femoropopliteal arterial lesions.

Reference	Year	Sites	Allocation	Device	Company	Indication	CTO	Median lesion length (mm)	Primary endpoints	Follow up	Results
Ko et al[556] (PARADE I)	2019	11	Spot n=59 Long n=66	Smart Smart	Cordis	RC I-V	90% vs 88% NS	245 vs 238 NS	PP, 12m	12m	PP 1y;86% vs 73% p=0.158
Iida et al[557] (SM-01)	2019	17	BMS n=51 PTA n=52	Smart *50% bailout*	Cordis	RC I-III	29% vs 13% p=0.057	92 vs 99 NS	PP, TLR	36m	PP 3y;73% vs 51% p=0.033 TS;100% vs 48% p<0.001
Laird et al[558] (TIGRIS)	2018	36	TIG n=197 BMS n=70	Tigris Lifestent	GORE BD Interventional	RC II-IV	42% vs 37% NS	108 vs 118 NS	PP, TLR 12m	36m	PP 2y;56% vs 50% p=0.60 SF;0% vs 33% p<0.001
Zeller et al[559] (MIMIC)	2016	8	HEL n=50 BMS n=26	BioMimics3D Lifestent	Veyran Medical BARD Peripheral	RC I-IV	44% vs 46% NS	66 vs 63 NS	CD TLR 6, 24m	24m	PP 2y;72% vs 55% p=0.05 FF-TLR 2y;91% vs 76% p=0.135
Lammer et al[419] (VIASTAR)	2015	7	SG n=72 BMS n=69	Viabahn *Not spec.*	GORE	RC II-V	79% vs 70% NS	190 vs 173 p=0.056	PP, TLR 12m	24m	FF-TLR 2y;80% vs 62% p=0.13 PP 2y;63% vs 41% p=0.04
Rastan et al[415] (ETAP)	2015	9	BMS n=119 PTA n=127	Lifestent *Not spec.*	BARD Peripheral	RC II-V	*Not Spec.*	41 vs 43 NS	PP, TLR 24m	24m	PP 2y;64% vs 31% p<0.001 TLR 2y;22% vs 60% p<0.001
Chalmers et al[412] (SUPER)	2013	17	BMS n=74 PTA n=76	Smart *Not spec.*	Cordis	RC I-V	96% vs 91% NS	123 vs 117 NS	PP, BS 12m	12m	BS 1y;47% vs 44% NS TS;92% vs 68% p<0.001
Geraghty et al[418] (VIBRANT)	2013	19	SG n=72 BMS n=76	Viabahn *Not spec.*	GORE	RC I-V	61% vs 57% NS	200 vs 160 NS	PP, TLR 36m	36m	PP 3y;24% vs 26% p=0.392 PaP 3y;89% vs 70% p=0.04
Brancaccio et al[560]	2012	1	BMS n=25 PTA n=25	*Not spec.*		RC III-VI	80% vs 56%	*Not spec.*	BS 12m	12m	BS 1y;30% vs 50% p=0.231 Embolic load > BMS p=0.031
Laird et al[414] (RESILIENT)	2012	24	BMS n=134 PTA n=72	Lifestent *40% Bailout*	BARD Peripheral	RC I-III	26% vs 15% NS	71 vs 64 NS	TLR 12m	36m	FF-TLR 3y;75% vs 42% p<0.001 CS 3y;63% vs 18% p<0.001
Dick et al[413] (ASTRON)	2009	3	BMS n=34 PTA n=39	Astron *Not spec.*	Biotronik GmbH	RC III-V	38% vs 39% NS	82 vs 65 p=0.022	BS 6m	12m	BS 1y;34% vs 61% p=0.028
Saxon et al[417]	2008	25	SG n=97 PTA n=100	Viabahn *Not spec.*	GORE	RC I-V	*Not spec.*	70 vs 70 NS	PP 12m	12m	PP 1y;65% vs 40% p=0.0003
Krankenberg et al[561] (FAST)	2007	11	BMS n=123 PTA n=121	Luminexx *Not spec.*	C.R BARD	RC I-V	37% vs 25% p=0.053	45 vs 45 NS	BS 12m	12m	BS 1y;32% vs 39% p=0.377
Schillinger et al[411] (ABSOLUTE)	2007	?	BMS n=51 PTA n=53	*Not spec.*		RC III-V	37% vs 32% NS	101 vs 92 NS	BS 12m	24m	BS 2y;46% vs 69% p=0.031
Grenacher et al[562]	2004	1	BMS n=71 PTA n=53	Palmaz *Not spec.*	Cordis	F IIa-IV	27% vs 38% NS	<50 NS	PP 12, 24m	36m	PP 2y;49% vs 66% NS CS 2y;71% vs 77% NS
Becquemin et al[192]	2003	4	BMS n=115 PTA n=112	Palmaz *15% Bailout*	Johnson & Johnson	F IIb-IV	20% vs 20% NS	*Not spec.*	BS 12m	48m	BS 1y;35% vs 32% p=0.85 EFS;44% vs 57% p=0.017
Saxon et al[416]	2003	1	SG n=15 PTA n=13	Hemobahn *Not spec.*	GORE	RC NS	20% vs 0% NS	74 vs 63 NS	PP	24m	PP 2y;87% vs 25% p=0.002
Cejna et al[190]	2001	4	BMS n=77 PTA n=77	Palmaz *Not spec.*	Johnson & Johnson	RC I-V	45% vs 32% NS	26 vs 22 NS	PP 12m	24m	PP 2y;53% vs 53% NS

Reference	Year	Sites	Allocation	Device	Company	Indication	CTO	Median lesion length (mm)	Primary endpoints	Follow up	Results
Grimm et al[191]	2001	?	BMS n= PTA n=	Palmaz *Not spec.*	Cordis	RC NS	43% vs 13% NS	28 vs 31 NS	Not spec	36m	PP 3y;62% vs 68% NS
Zdanowski et al[189]	1999	1	BMS n=15 PTA n=17	Strecker *Not spec.*	Boston Scientific	*Not spec.*	*Only occlusions*	ML (all) 73	PP, BS 12m	12m	BS 1y;50% vs 25% p=0.033
Vroegindeweij et al[188]	1997	1	BMS n=24 PTA n=27	Palmaz *Not spec.*	Johnson & Johnson	RC I-III	19% vs 17% NS	<50 NS	PP 12m	24m	PP 1y;62% vs 74% p=0.22

Table 12. Randomised studies with non-drug adjunctive stenting of infrapopliteal arterial lesions

References	Year	Name	Sites	Allocation	Device	Company	Indication	CTO	Median lesion length (mm)	Primary endpoints	Follow up	Results
Ahn et al[434]	2023	SENS-BTK	18	BMS n=58 PTA n=61	Xpert *Not spec.*	Abbott Vascular	RC IV-VI	*Not spec.*	69 vs 83 NS	LS, TLR 12	12m	No differences
Rastan et al[415]	2015	ETAP *(poplitea)*	9	BMS n=119 PTA n=127	Lifestent	BARD Peripheral	RC II-V	*Not Spec.*	41 vs 43 NS	PP, TLR 24	24m	PP 2y; 64% vs 31% p<0.001 TLR 2y; 22% vs 60% p<0.001
Schulte et al[435]	2015	EXPAND	11	BMS n=45 PTA n=47	Astron Pulsar *Not spec.*	Biotronik	RC III-V	*Not spec.*	34 vs 39 NS	CS 12	12m	No differences
Brodmann et al[437]	2011		1	BES n=21 PTA n=33	Motion Explorer Amphiron Deep	Biotronik Invatec	RC IV-VI	30% vs 30% NS	28 vs 79 p<0.001	CS 12	12m	PP 12m; 35% vs 48% NS CS 12m;39% vs 80% p=0.006
Rand et al[436]	2011	InPeria II (Carbostent)	6	BES n=44 PTA n=44	Carbostent *Not spec.*	Sorin Biomedica	RC IV-V	19% vs 27% NS	21 vs 21 NS	CS, LS 3, 9	9m	BS 9m; 24% vs 35% NS
Randon et al[438]	2010		1	BMS n=16 PTA n=22	*Not spec.* *Not spec.*		RC IV-VI	Overall 64%	*Not spec.*	PP 12, 24	24m	PP12m; 56% vs 66% p=0.974
Bosiers et al[439]	2009	AMS INSIGHT	13	AMS n=60 PTA n=57	AMS Pleon Explorer	Biotronik Biotronik	RC IV-V	*Not spec.*	10.6 vs 12 NS	PP 6	12m	PP 6m; 32% vs 58% p=0.013
Rand et al[440]	2006	InPeria I (Carbostent)	3	BES n=24 PTA n=27	Carbostent Bijou	Sorin Biomedica Boston Scientific	F III-IV	n=2 n=4	Overall 24	PP 6	12m	PP 6m; 80% vs 46% p<0.05

Table 13. Randomised studies involving DES in endovascular treatment of femoropopliteal arterial lesions.

Reference	Year	Sites	Allocation	Device	Company	Indication	CTO	Median lesion length (mm)	Primary endpoints	Follow up	Results
Fransson et al[444]	2023	1	DES n=27 BMS n=22	Zilver PTX Zilver Flex	Cook Medical Cook Medical	RC IV-VI	96% vs 95% NS	220 vs 250 NS	TLR, PP	24m	TLR 2y;41% vs 36% NS PP 2y;33% vs 41% NS
Goueffic et al[442] (EMINENT)	2022	58	DES n=508 BMS n=267	Eluvia DES *Not Spec.*	Boston Scientific	RC II-IV	42% vs 40% NS	76 vs 72 NS	PP, TLR	36m	PP 1y;83% vs 74% p<0.01
Park et al[451] (PARADE II)	2022	8	Spot n=48 Long n=55	Zilver PTX Zilver PTX	Cook Medical	RC II-V	73% vs 85% p=0.126	239 vs 245 NS	PP, TLR 12	12m	FF-TLR 1y;72% vs 92% p=0.044
Muller-Hulsbeck et al[445] (IMPERIAL)	2021	65	DES n=156 DES n=309	Zilver PTX Eluvia	Cook Medical Boston Scientific	RC II-IV	30% vs 31% NS	82 vs 87 NS	BS, PP, TLR	24m	TLR 2y; 20% vs 13% p=0.0495 PP 2y; 77% vs 83% p=0.1008
Falkowski et al[446]	2020	1	DES n=126 BMS n=130	Zilver PTX Zilver Flex	Cook Medical Cook Medical	RC II-V	*Not Spec.*	94 vs 128 p=0.000	TLR, BS, RC-improve	36m	TLR 3y;14% vs 31% p=0.001 BS 3y;16% vs 35% p=0.004
Goueffic et al[563] (BATTLE)	2020	10	DES n=86 BMS n=85	Zilver PTX Misago	Cook Medical Terumo	RC II-V	38% vs 35% NS	70 vs 76 NS	FF-ISR 12	24m	FF-ISR 1y;91% vs 89% p=0.64
Bausback et al[448] (REAL PTX)	2019	5	DES n=75 DCB n=75	Zilver PTX *Not spec.*	Cook Medical	RC II-V	52% vs 53% NS	155 vs 150 NS	PP 12m	36m	PP 3y;56.7% vs 42.4% p=0.17
Liistro et al[447] (DRASTICO)	2019	1	DES n=96 DCB n=96	Zilver PTX In.Pact Pacific	Cook Medical Medtronic	RC III-VI	64% vs 60% NS	141 vs 146 NS	BS 12m	12m	BS 1y;21% vs 22% NS
Miura et al[449]	2018	25	DES n=85 BMS n=85 BMS+CILO n=85	Zilver PTX Misago Misago	Cook Medical Terumo Terumo	RC II-IV	51;37;39% NS	111/96/101 NS	BS 12m	12m	BS 1y;21%/28%/12% p=0.052
Dake et al[443] (Zilver PTX)	2016	55	DES n=236 PTA n=238	Zilver PTX *Not Spec.*	Cook Medical	RC II-VI	33% vs 27% NS	66 vs 63 NS	EFS, PP, 12	60m	EFS 5y;80% vs 59% p<0.01 PP 5y;66% vs 43% p<0.01
Duda et al[450] (SIROCCO)	2006	6	DES n=47 BMS n=46	Sirocco SMART	Cordis Cordis	RC I-IV	69% vs 57% NS	85 vs 81 NS	BS 6m	24m	BS 2y;23% vs 21% p>0.05

Table 14. Randomised studies comparing DES against PTA/BMS/DCB in the treatment of infrapopliteal arterial lesions.

Reference	Name	Year	Sites	Allocation	Device	Company	Indication	CTO	Median lesion length (mm)	Primary endpoints	Follow up	Results
Varcoe et al[457]	LIFE-BTK	2024	50	ERS n=173 PTA n=88	Espirit BTK *Not spec.*	Abbott Vascular	RC IV-V	*Not spec.*	44 vs 45 NS	TLR, BS, LS, PP	12m	FFevent;74% vs 44% p<0.001
Van Overhagen et al[458]	SAVAL	2023	14	DES n=130 PTA n=71	Saval DES *Not spec.*	Boston Scientific	RC IV-V	31% vs 28% NS	68 vs 69 NS	PP 12m	36m	PP 12m 68% vs 76% p=0.8552
Spreen et al[459]	PADI	2017	3	DES n=74 PTA ± BMS n=67	Taxus *Not spec.*	Boston Scientific	RC IV-VI	*Not spec.*	21 vs 23 NS	PP 6m	60m	PP 6m;48% vs 35% p=0.096 FF AMP 5y;32% vs 20% p=0.043 FF TLR 5Y;26% vs 15% p=0.041
Siablis et al[460]	IDEAS	2014	1	DES n=25 DCB n=25	*Not spec.* In.Pact Amphiron	Medtronic	RC III-VI	23% vs 12% NS	127 vs 148 NS	BS 6m	6m	BS 6m;28% vs 58% p=0.0457
Bosiers et al[463]	DESTINY	2012	?	DES n=78 BMS n=76	Xience V Vision	Abbott Abbott	RC IV-V	15% vs 17% NS	16 vs 19 NS	PP 12m	12m	PP 1y;85% vs 54% p=0.001 FF TLR 1y;91% vs 66% p=0.001
Rastan et al[462]	YUKON-BTK	2012	?	DES n=82 BMS n=79	Yukon *Not spec.*	Translumina	RC III-V	*Not spec.*	*Not spec.*	FF TLR, AMP	12/36m	No differences at 12m 3y;AMP 3% vs 12% p=0.03 3y;TVR 9% vs 20% p=0.06
Scheinert et al[461]	ACHILLES	2012	16	DES n=99 PTA n=101	Cypher Select *Not spec.*	Cordis	RC III-V	81% vs 75% NS	27 vs 27 NS	PP, BS, TLR 12	12m	BS 1y;22% vs 42% p=0.019 PP 1y;75% vs 57% p=0.025
Falkowski et al[464]		2009	2	DES n=25 BMS n=25	Cypher Select Sonic	Cordis Cordis	RC III-V	*Not spec.*	17 vs 18 NS	RR, TLR 6	6m	RR 6m;16% vs 76% p<0.001 TLR 6m;12% vs56% p<0.05

Table 15. Randomised studies involving debulking techniques in the treatment of infrainguinal arterial lesions.

References	Year	Sites	Allocation	Device	Company	Indication	Region	CTO	Median lesion length (mm)	Primary endpoints	Follow up	Results
Shammas et al[564] (JET-RANGER)	2022	11	JET + DCB n=31 PTA + DCB n=16	Jetstream XC Ranger DCB In.Pact DCB	Boston Scientific Boston Scientific Medtronic	RC II-V	FP	23% vs 44% NS	108 vs 112 NS	TLR 12m	24m	FF-TLR 2y;88% vs 80% p=0.3380
Babaev et al[482]	2022	1	DA + DCB n=30 OA + DCB n=30	HawkOne DAS Diamondback 360	Medtronic Cardiovascular Systems	RC I-IV	FP	43% vs 43% NS	151 vs 142 NS	Luminal gain and plaque volume reduction	n/a	Luminal gain and plaque volume reduction DA>OA p=0.003-0.009 Number of bailout stents OA>DA p=0.02
Böhme et al[432] (PHOTOPAC)	2021	3	LA +DCB n=30 PTA + DCB n=31	Excimer CVX-300 In.Pact	Spectranetics Medtronic	RC I-V	FP+ISR	27% vs 26% NS	126 vs 159 NS	BS 12m	24m	PP 2y;57% vs 54% p=0.851
Cai et al[470]	2020	1	DA +DCB n=45 PTA +DCB n=49	SilverHawk/TurboHawk Orchid DCB	Medtronic Acotec Scientific	RC III-V	FP	*Not spec.*	113 vs 111 NS	PP 24m	24m	PP 2y;67% vs 55% p=0.377

References	Year	Sites	Allocation	Device	Company	Indication	Region	CTO	Median lesion length (mm)	Primary endpoints	Follow up	Results
Zeller et al[471] (DEFINITIVE AR)	2017	10	DA + DCB n=48 DCB n=54	SilverHawk/TurboHawk Cotavance	Medtronic Bayer HealthCare	RC II-IV	FP	25% vs 33% NS	107 vs 94 NS	BS 12m	12m	1y;34% vs 36% 0.48
Dippel et al[430] (EXCITE ISR)	2015	40	LA + PTA n=169 PTA n=81	Turbo Elite /Turbo Tandem *Not specified*	Spectranetics	RC I-IV	FP+ISR	31% vs 37% NS	196 vs 193 NS	FF TLR 6m	12m	FF TLR 6m;74% vs 52% p<0.005
Dattilo et al[472] (COMPLIANCE 360)	2014	9	OA + PTA n=25 PTA n=25	Diamondback 360 *Bailout stent 78%*	Cardiovascular Systems	RC II-IV	FP	*Not Spec.*	56 vs 87 NS	FF TLR 6m	12m	FF TLR 6m;77% vs 11% p<0.001
Gandini et al[429]	2013	1	LA + DCB n=24 PTA + DCB n=24	Turbo Elite Freeway	Spectranetics Eurocor	RC IV-VI	FP+ISR	*Not spec.*	224 vs 226 NS	PP 12m	12m	PP 1y;67% vs 38% p=0.01
Brodmann et al[431]	2013		DA n=9 PTA n=10	SilverHawk Opta Pro	Covidien/Ev3 Cordis	*?*	FP+ISR	*Not spec.*	76 vs 67 NS	IMT	6m	DA inf vs PTA
Shammas et al[473]	2011	2	DA + PTA n=29 PTA n=29	SilverHawk *Bailout stent 62%*	Ev3	RC I-V	FP	*Not spec.*	96 vs 82 NS	TLR 12m	12m	TLR 1y;11% vs 17% NS
Tielbeek et al[474]	1996	?	DA n=38 PTA n=35	Simpson Atherocath	DVI	RC I-III	FP	N=1 N=2	<50 <50	*Not spec.*	24m	PP 2y;44% vs 67% p=0.06
Vroegindeweij et al[475]	1992	?	DA n=16 PTA n=14	Simpson Atherocath	DVI	RC I-III	FP	N=0 N=3	<25 <25	*Not spec.*	18m	PP 1y;25% vs 77% p=0.017
Lammer et al[476]	1992	?	Excimer laser n=37 Nd:YAG laser n=40 PTA n=39	308nm XeCl/Ceram Optec 1064nm Nd:YAG	MAX10, Technolas CL60 Surgical Lasers	RC I-IV	FP	100%	84 83 67	*Not spec.*	12m	No differences at 12m
Huppert et al[477]	1992	?	Excimer laser n=32 Dye laser n=32 PTA n=32	308nm XeCl/Ceram Pulsed dye laser *Not specified*	Max10, Technolas MDL 2000, Candela	RC II-V	FP	*Not spec.*	62 63 65	*Not spec.*	12m	No differences at 12m
Belli et al[478]	1991	1	LA n=34 PTA n=34	Spectraprobe PLR Cardiolase 4000	Trimedyne	RC I-IV	FP	100%	60 vs 80 NS	*Not spec.*	12m	No differences at 12m
Zeller et al[483] (OPTIMIZE BTK)	2022	7	OA + DCB n=32 PTA + DCB n=34	Diamondback 360 Lutonix 014 DCB	Cardiovascular Systems Bard Peripheral	RC III-V	IP	44% vs 35% NS	101 vs 79 NS	PP 24m	24m	PP1y;88% vs 54% p=0.076
Rastan et al[484]	2021	2	DA +DCB n=40 DCB n=40	SilverHawk/TurboHawk Lutonix 014 DCB	Medtronic Bard Peripheral	RC III-V	IP	22% vs 18% NS	192 vs 161 NS	PP 6m	12m	PP 6m;49% vs 34% p=0.241
Shammas et al[348] (CALCIUM 360) Pilot trial	2012	8	OA + PTA n=25 PTA n=25	Diamondback 360	Cardiovascular Systems	RC IV-VI	IP	*Not spec.*	91 vs 69	TS	12m	FF-MAE 1y;93% vs58% p=0.006

Table 16. Randomised studies involving cutting balloon angioplasty against conventional or high-pressure PTA (HPPTA) in the treatment of malfunctional AV-access.

References	Product	Year	Sites	Lesion	CB/PTA	Primary endpoints	Results
Aftab et al[509]	CB, BSci	2014	1	AVF	36/35	PP 6m	6m; 66% vs 40% (p=0.01) HPPTA
Murakami et al[510]	*Not spec.*	2023	1	AVF	60/62	AS, CS, PP 6m	6m; 33% vs 16% (p=0.002)
Rasuli et al[511]	Flextome, BSci	2015	1	AVF	19/20	PP 3, 6, 12m	6m; 27% vs 42% (p=0.36) HPPTA
Saleh et al[512]	CB, BSci	2014	3	AVF/AVG	316/307	AS, CS, PaP 6,12m	6m; 86% vs 56% (p=0.037)
Vesely et al[513]	*Not spec.*	2005	27	AVG	173/167	PP 6m	6m; 48% vs 40%) (p=0.37)

Table 17. Randomised studies comparing SG and conventional PTA in the treatment of malfunctional AV-access with outflow lesions.

References	Study	Product	Year	Sites	Lesion	SG/PTA	Primary endpoints	Results (PP, otherwise stated)
Dolmatch et al[499]	AVeNEW	Covera, BD	2023	24	AVF	142/138	PP 6m, AE 30d	6m; 79% vs 48% (p<0.001)
Kavan et al[503]		Fluency+, BARD	2019	1	AVG	20/20	PP, SP, TVR12m	12m; frequency TVR; 1.4 vs 2.8 (p=0.015)
Mohr et al[504]	REVISE	Viabahn, GORE	2019	30	AVG	131/138	PP 24m	24m; frequency TVR; 3.7 vs 5.1 (p=0.005)
Yang et al[507]		Viabahn, GORE	2018	1	AVG	49/49	PP, TVR 3, 6m	6m; 71% vs 28% (p<0.001)
Falk et al[500]	RESCUE	Fluency+, BARD	2016	23	AVF/AVG	132/143	PP 6m, AE 30d	6m; 66% vs 12% (p<0.001)
Haskal et al[501]	RENOVA	Flair, BARD	2016	28	AVG	138/132	PP, IFP, AE 24m	24m; 27% vs 13% (p<0.001)
Vesely et al[506]	*REVISE*	*Viabahn, GORE*	*2016*	*31*	*AVG*	*131/138*	*PP 6m*	*6m; 52% vs 34% (p=0.006)*
Rajan et al[505]		Viabahn, GORE	2015	3	AVF	9/5	PP 3,6 12m	12m; 29% vs 0% (p<0.01)
Haskal et al[502]	*FLAIR*	*Flair, BARD*	*2010*	*?*	*AVG*	*97/93*	*PP, TVR, AE 6m*	*6m; 51% vs 23% (p<0.001)*

Table 18. Randomised studies involving DCB in the treatment of dysfunctional AV-access in the upper extremities.

References	Year	Sites	DCB/ PTA	Lesion	Product	Dose (µg/mm^2)	Carrier	Primary endpoint	Follow up	Results
Goo et al[565]	2024	5	94/92	AVG	In.Pact, Medtronic	3.5	Urea	PP 3, 6m	12	PP 6m;65% vs 42% (p=0.001)
Hsieh et al[566]	2023	1	20/20	SG	Ranger, Boston Sceintific	2.0	Transpax	LLL 6m,	6	1.82 vs 3.63 mm p=0.001 PP6m;80% vs 42% p=0.005
Lookstein et al[529]	2023	29	170/160	AVF	In.Pact, Medtronic	3.5	Urea	PP, SAE 6m	36	PP 36m;43% vs 29% (p<0.001)
Maleaux et al[530]	2023	7	51/52	AVF/AVG	APERTO, Cardionovum	3.0	Ammonium salt	Function 12m	12	FF TVR;12m 20% vs 10% (p=0.612)
Zhao et al[540]	2023	11	116/118	AVF	AcoArtOrchid, ACOTEC	3.3	Magnesium stearate	PP 6m	12	PP 6m;91% vs 67% (p<0.001)
Fransson et al[519]	2022	1	22/20	AVF/AVG	Advance PTX, COOK	3.0	None	TLR and Function 12m	12	FF TLR 12m;24% vs 16% (p>0.05)
Novak et al[533]	2022	1	38/38	AVF/AVG	SeQuent Please, B.Braun	3.0	Resveratrol	PP 12m. Time to TLR	12	Time to TLR;181 vs 98 d (p=0.019)
Karunanithy et al[522]	2021	20	106/106	AVF	Lutonix, BARD	2.0	Polysorbate/ Sorbitol	Time to loss PP	12	Time to loss of PP;44 vs 45 d (p=0.44)
Pang et al[534]	2021	1	20/20	AVF/AVG	In.Pact, Medtronic	3.5	Urea	PP 12m	12	PP 12m;65% vs 30% (p=0.007)
Therasse et al[537]	2021	3	60/60	AVF/AVG	Passeo-18 Lux, Biotronik	3.0	BTHC	LLL 6m	12	LLL 6m;0.64 vs 1.13 mm (p=0.082)
Yin et al[539]	2021	10	78/83	AVF	Aperto, Cardionovum	3.0	Ammonium salt	PP 6m	12	PP 6m;65% vs 37% (p<0.001)
Karmota et al[521]	2020	2	30/30	AVF	Lutonix, BARD	2.0	Polysorbate/ Sorbitol	PP 3,6, 12m	12	PP 12m;97% vs 90% (p=0.029
Kim et al[523]	2020	1	20/19	AVF/AVG	In.Pact, Medtronic	3.5	Urea	TS, CS, PP	36	PP 36m;55% vs 49% (p=0.714)
Liao et al[528]	2020	1	22/22	AVG	In.Pact, Medtronic	3.5	Urea	PP 6m	12	PP 6m;41% vs 9% (p=0.006)
Moreno-Sanchez et al[532]	2020	4	71/69	AVF/AVG/CVS	Passeo-18 Lux, Biotronik	3.0	BTHC	PP 6, 12m	12	PP 12m;53% vs 47% (p=0.51)
Trerotola et al[538]	2020	23	141/144	AVF	Lutonix, BARD	2.0	Polysorbate/ Sorbitol	PP 6m, SAE 30d	24	PP 24m27% vs 24% (p=0.09) Time to TLR; 322 vs 207 d (p<0.0001)
Bjorkman et al[518]	2019	1	18/18	AVF	In.Pact, Medtronic	3.5	Urea	TLR	12	Time to TLR;110 vs 193 d (p=0.006)
Swinnen et al[536]	2019	3	68/60	AVF	In.Pact, Medtronic	3.5	Urea	LLL 3,6 12m	12	ΔLLL 12m;0.12mm (p=0.0003)
Irani et al[520]	2018	1	59/60	AVF/AVG/CVS	In.Pact, Medtronic	3.5	Urea	PP, BS 6m	12	PP 12m;51% vs 34% (p=0.04)
Maleaux et al[531]	2018	3	33/31	AVF	In.Pact, Medtronic	3.5	Urea	PP (clin) 3, 6, 12	12	PP 12m;42% vs 39% (p=0.95)
Kitrou et al, JVIR[525]	2017	1	20/18	CVS	Lutonix, BARD	2.0	Polysorbate/ Sorbitol	IVP 6m	6	IFP 179.0 vs 124.5 d (p=0.026)
Roosen et al[535]	2017	3	16/18	AVF/AVG	In.Pact, Medtronic	3.5	Urea	Time to TLR	12	Time to TLR; 130 vs 189 d (p=0.197)
Kitrou et al, EJR[524]	2015	1	20/20	AVF/AVG	In.Pact, Medtronic	3.5	Urea	TS, PP 12m	12	PP 12m; 35% vs 5% (p<0.001)
Kitrou et al, JVIR[526]	2015	1	20/20	AVF	In.Pact, Medtronic	3.5	Urea	TS, CS, TLR	12	Time to TLR; 308 vs 161 d (p=0.03)
Lai et al[527]	2014	1	10/10	AVF	SeQuent Please, B.Braun	3.0	Resveratrol	PTA-free patency rate 6m	12	IFP 251.2 vs 103.2 d (p<0.01)

Research aims

Users of minimally invasive endovascular techniques for treating PAD or malfunctioning haemodialysis access are familiar with the technical drawbacks as early restenosis and the development of neointimal hyperplasia, seriously limiting the longevity of the performed procedures.

Combining mechanical angioplasty and stent treatments with certain cytotoxic or cytomodulating drugs has been used and tried in different settings for some decades, and the first device that got governmental FDA approval in 2003 was the Cypher® stent (Cordis Corporation) for coronary artery stenosis[567]. The first device for peripheral use was the stent platform Zilver PTX® (Cook Medical) in 2012[568]. The reason for this drug adjunctive is the diminished inflammatory postangioplasty response and reduced formation of neointimal hyperplasia due to inhibition of the smooth muscle cell proliferation in the arterial wall, with an expectation for improved primary patency and improvement of the reintervention rate.

This thesis aims to compare the efficacy of drug eluting devices against standard angioplasty or stenting techniques in different scenarios in an effort to clarify aspects of optimal treatments in these situations.

By performing three randomised studies covering, first angioplasty of malfunctional AV-fistulas or grafts for haemodialysis, second stenting of FP atherosclerotic disease in CLTI, and third angioplasty of complex infragenicular arteriosclerotic lesions in CLTI, this thesis will cover three essential fields for angioplasty/stent treatment. The fourth study was designed as a large national retrospective observational cohort study assessing the effect of drug eluting technology in treating subjects with DM and PAD and comparing the results to subjects without DM.

The aims were set early in the era of drug eluting treatment, and during the data collection, new important insights were collected in the vascular surgical community. However, the urge for even more scientific data for optimal decision-making remains. This thesis will hopefully be relevant to the history of evaluating drug eluting technologies.

Specified aims for each trial included in this thesis

I. To clarify the superiority and safety of DCB treatment over standard PTA treatment in malfunctional haemodialysis access.

II. To clarify the superiority and safety of DES treatment over BMS treatment in treating FP arterial lesions in subjects with CLTI.

III. To clarify the superiority and safety of DET in treating subjects with DM and PAD.

IV. To clarify the superiority and safety of DCB treatment over PTA treatment in treating IP arterial lesions in subjects with CLTI.

Ethical considerations

As in all human scientific research, you must be fully aware of the ethical regulations we are obliged to follow in all situations that may appear. All studies that are part of this thesis were approved by the regional ethics committee at Lund University, and the studies fully complied with the regulations of the Declaration of Helsinki[569].

Most of our research is performed in a strictly clinical setting, randomly comparing two governmentally approved angioplasty devices with identical technical risks for acute complications. Fully applying with the regulations regarding clinical trials, all participants gave written informed consent. Hypothetically treating the same patient outside the study protocol does not require informing the patient regarding your exact choice of angioplasty device.

Direct, randomised, head-to-head comparisons between approved products are rarely performed because the regulations are, in some ways, more complicated than ethically necessary.

In our context, there were no real ethical challenges in our studies, so it was unproblematic to fulfil all ethical considerations and regulations. Unfortunately, by doing this, we also, in certain circumstances, lost potential study subjects for reasons that did not always, in the broader perspective, seem wise regarding an optimal scientific evaluation of the drug eluting efficacy.

All subjects enrolled in the national quality registries have signed written consent when in contact with health care services.

Specified ethical issues and approvals for this thesis

I. The trial protocol was approved by the Regional Research Ethics Committee in Lund, Sweden (Dnr: 2012/305). All participants provided written informed consent and were informed regarding participation by the treating physician before scheduled therapy. The reporting of this study conforms with the CONSORT statements[570].

II. The trial protocol was approved by the Regional Research Ethics Committee in Lund, Sweden (Dnr: 2012/306). All participants provided written informed consent and were informed regarding participation by the treating physician before scheduled therapy. The reporting of this study conforms with the CONSORT statements[570].

III. The trial protocol was approved by the Regional Research Ethics Committee in Lund, Sweden (Dnr: 2016/232 and Dnr: 2016/544). According to Swedish law, individual consent is not required to report patients to national quality healthcare registries or to be included in a study like this (Patient Data Act 24 2008:355, chapter 7).

IV. The trial protocol was approved by the Regional Research Ethics Committee in Lund, Sweden (Dnr: 2014/599). All participants provided written informed consent and were informed regarding participation by the treating physician before scheduled therapy. The reporting of this study conforms with the CONSORT statements[570].

Materials and methods

Methodology of the four studies in the thesis at a glance

	Paper I	Paper II	Paper III	Paper IV
Study design	Prospective, single centre, parallel, single blinded, randomised clinical trial (1:1).	Prospective, single centre, parallel, single blinded, randomised clinical trial (1:1).	Retrospective observational cohort study	Prospective, single centre, parallel, single blinded, randomised clinical trial (1:1).
Study sample	Subjects scheduled for endovascular treatment of malfunctional haemodialysis access.	Subjects scheduled for endovascular treatment of CLTI with arterial lesions in the SFA or P1	Subjects in SWEDVASC who have undergone endovascular surgery for IC or CLTI.	Subjects scheduled for endovascular treatment of CLTI with BTK arterial lesions
Enrolment period	2014-2017	2013-2015	2013-2015	2016-2020
Methods	Randomisation of subjects close to the scheduled intervention by blinded envelopes. 25+25 in two blocks Study treatment is drug coated balloon angioplasty, and control treatment is standard balloon angioplasty. Volume flow monitoring and clinical assessment. Comparison of groups regarding freedom from TLR at 6 and 12 months. Freedom from access circuit revascularisation at 6 and 12 months. Validation of functionality at 12 months.	Randomisation of subjects close to the scheduled intervention by blinded envelopes. 25+25 in four blocks Study treatment is drug eluting stent, and control treatment is standard BMS. DUS and clinical assessment at discharge, 1, 6, 12, and 24 months. Comparison of groups regarding primary patency and TLR at discharge, 1, 6, 12, and 24 months.	Identification of subjects with DM through NDR. Baseline registries from IDR regarding ICD codes and length of stay. Pharmaceutical medication retrieved from PDR. Mortality was identified from the National Cause of Death Register. Comparison of subjects with and without DM treated for IC or CLTI with or without drug eluting methods. Median time follow-up for amputation or mortality was 607 days and for reinterventions 522 days.	Randomisation of subjects close to the scheduled intervention by blinded envelopes. 35+35 envelopes Study treatment is drug coated balloon angioplasty, and control therapy is standard balloon angioplasty. MRA at 12 months and clinical assessment at 1, 6, and 12 months. Comparison of primary patency at 12 months.
Data analysis	Outcomes were analysed with the chi^2 test, and time-to-event data were analysed with Kaplan-Meier survival curves and log-rank tests. Survival data is also presented with values ± SE %.	Outcomes were analysed with the chi^2 test, and time-to-event data were analysed with Kaplan-Meier survival curves and log-rank tests. Survival data is also presented with values ± SE %.	Primary and secondary outcomes presented as incidence rates with 95% Poisson intervals. Cox regression models. Kaplan-Meier curves. Multiple imputations with logistic regression for missing values.	Outcomes were analysed with the chi^2 test, and time-to-event data were analysed with Kaplan-Meier survival curves and log-rank tests. Survival data is also presented with values ± SE %. Cox regression models for OR and CI 95%
Clinical Trial Registration	NCT05173857	NCT05296031	n/a	NCT 02750605

Overall settings

Papers I, II, and IV in this thesis are based on data from subjects treated at the Department of Thoracic and Vascular Surgery, Skåne University Hospital, Malmö, and the Department of Surgery, Blekinge County Hospital, Karlskrona. The treatments at Blekinge County Hospital were performed by vascular surgeons from Skåne University Hospital. The Vascular Centre at Skåne University Hospital is a tertiary referral centre for vascular surgery and vascular diseases with a total catchment population for primary, secondary, and tertiary cases reaching 1.7 million inhabitants. Skåne University Hospital is the third largest University Hospital in Sweden. See Picture XXIV.

Study populations

I. Patients at Skåne University Hospital scheduled for balloon angioplasty for malfunctioning haemodialysis access. They regularly had haemodialysis treatment at the dialysis units in Malmö, Lund, or Trelleborg. The planned number of enrolments was 50 + 50 subjects. The total number of included subjects with written consent who were randomised was 48. The trial treatment was given to 25 subjects, and the control treatment to 23. Three subjects in each group had to be excluded from the analysis due to faulty inclusion. Analysed subjects finally were 42 (28 male and 14 female), 22 in the trial arm and 20 in the control arm.

II. Patients at Skåne University Hospital scheduled for endovascular treatment for CLTI caused by lesions in the FP arteries. The planned number of enrolments was 100 + 100. The total number of included subjects with written consent who were randomised was 48. One subject had treatment of both limbs. The trial treatment was given to 27 limbs, and the control treatment to 22. All inclusions were correct (26 males and 22 females), and all were fully analysed.

III. Subjects included in SWEDVASC and the NDR were merged according to the study plan. All data were de-identified.

IV. Patients at Skåne University Hospital scheduled for endovascular treatment for CLTI caused by lesions in the infragenicular arteries. Two subjects were included at Blekinge County Hospital. The planned number of enrolments was 35 + 35. The total number of included subjects with written consent that were randomised was 64, and as six subjects got bilateral inclusion, mainly outside the respective study period, we reached 70 enrolled limbs.

All inclusions were correct (50 males and 14 females), and all but two cases with missing MRA were fully analysed.

Preinterventional imaging

I. All participants had undergone a DUS examination of the AV Access (Philips iU22 system; Philips Healthcare B.V, Best, the Netherlands). Some also performed CTA, showing access outflow, inflow, and the thoracic outflow region. This is necessary for case planning.

II. All participants had undergone vascular imaging with DUS, MRA, or CTA as the standard of care, which was not protocolised. This is necessary for case planning.

III. In this retrospective register study, this issue is not specified.

IV. All participants had undergone protocolised vascular imaging with MRA (Siemens Healthineers, Erlangen, Germany) Magnetom (Sola, Avanto or Aero) 1.5T with PA and 18 Body Matrix and a total of 10ml of intravenous Gadovist®. Some subjects had also been evaluated with DUS.

Picture XXIV. Photo showing the administrative offices of the Vascular Centre, Skåne University Hospital.

(Av Jorchr - Eget arbete, CC BY 3.0, https://commons.wikimedia.org/w/index.php?curid=15732176)

Postinterventional imaging and follow-up

I. No protocolised imaging was used in the follow-up period, and imaging was only performed on demand. Subjects were followed clinically at the dialysis units. At the haemodialysis unit, monthly recordings of volume flow (Transonic HD03 Haemodialysis Monitor; Transonic Systems Inc., Ithaca.,NY, USA) were undertaken as part of routine care.

II. Protocolised imaging with DUS at discharge, 1, 6, 12, and 24 months. Scheduled clinical controls, including ABI assessment, were also performed.

III. This issue is not specified in detail in this retrospective register study. All patients in SWEDVASC are routinely seen at 1 and 12 months postoperatively, and objective visualisation of patency is non-mandatory.

IV. Protocolised imaging with MRA at 12m (Siemens Healthineers, Erlangen, Germany) Magnetom (Sola, Avanto or Aero) 1.5T with PA and 18 Body Matrix and 10 ml of intravenous Gadovist®. Some subjects have also been evaluated with DUS for different reasons. A clinical follow-up was scheduled at 1, 6, and 12 months.

Data collection methods

In the three randomised studies, most workflow was performed via official charts, patient files, and images. Data was also collected in separate research files. Images were interpreted by the corresponding author, who is also the author of this thesis. All the collected data was transferred to research databases. All data was collected and stored in line with relevant data regulation acts.

In the observational cohort study (III), data was collected from two large registries that were merged according to the trial protocol. The collected data was interpreted and statistically modelled as specified by the protocol and the relevant statistical methods. Our intuition never handled the database. The registries have centres for statistical analyses, which provide calculations and relevant results for the publications.

Data handling, power calculations and statistical methods

Trial I

The initial null hypothesis was formulated as drug eluting balloon PTA performing at least 50% better than POBA regarding primary patency and freedom from reintervention during 12 months of follow-up. This calculation specified an alpha level of 5% and a power of 90% to show clinical superiority. The prespecified enrolment was set to 50 patients in each group according to pretrial calculations. At the time of trial set-up, we investigated some earlier smaller pilot studies to get hands on a reasonable cut-off value regarding efficacy[571].

Normal distribution was not assumed. Median values are presented for continuous variables with interquartile ranges and tested with the Mann-Whitney U-test. Categorical variables, on the other hand, were analysed using the chi-square test and Fisher's exact test.

Kaplan-Meier and survival curves were used to present time-to-event data, and any differences were compared with the log-rank test. This survival data is presented with values ± standard error in %.

P values <0.05 were assumed to be significant.

Data was analysed using IBM SPSS Statistics 25 (SPSS Inc, Chicago, Ill).

Trial II

The sample size was calculated according to the hypothesis that DES would perform at least 50% better than BMS regarding restenosis, as shown in earlier studies [572-574]. In an optimal setting with low-risk patients, the restenosis rate in DES treatment of FP lesions can be as low as 14-17% at one year [573 575 576]. The restenosis rates at 12 months in a cohort with only CLTI and long lesions are higher, reaching at least 35% in earlier studies of BMS treatment [574] and 23% in earlier DES studies on long FP lesions [575]. The sample size in this study, to perform 50% better than a restenosis rate of 30-40%, thus reached 100 subjects in each group, with a power of 85% and an alfa level of 5%.

Normal distribution was not assumed. Median values are presented for continuous variables with interquartile ranges and tested with the Mann-Whitney U-test. Categorical variables, on the other hand, were analysed using the chi-square test and Fisher's exact test.

Kaplan-Meier and survival curves were used to present time-to-event data, and any differences were compared with the log-rank test. This survival data is presented with values ± standard error in %.

P values <0.05 were assumed to be significant.

Data was analysed using IBM SPSS Statistics 28 (SPSS Inc, Chicago, Ill).

Trial III

Unless stated otherwise, descriptive statistics are presented as mean and standard deviation for numerical variables and count and percentages for categorical variables. Primary and secondary outcomes were examined using incidence rates with 95% Poisson confidence intervals. We constructed crude Kaplan Meier curves and performed Cox regression adjusted for the following variables at baseline: age, sex, smoking, any cardiovascular disease, lipid lowering treatment, aspirin, and oral anticoagulants. Multiple imputations with logistic regression, 20 imputations, and 15 iterations were used for missing values in the smoking variable.

Due to the low number of secondary outcome events, separate Kaplan-Meier curves and Cox regression analyses of total mortality and amputation were only calculated for CLTI patients. MACE was only calculated for IC patients due to statistical problems with fulfilling the proportional hazards assumption. No analyses were performed regarding cardiovascular death, AMI, and stroke.

P values <0.05 were assumed to be significant.

Data was analysed using IBM SPSS Statistics 28 (SPSS Inc, Chicago, Ill).

Trial IV

Calculations were performed with input from similar earlier studies[577]. The primary patency at 12 months when using conventional angioplasty in the crural arteries across all complexities has been reported as between 26% and 68%, and in the subgroup of complicated cases (TASC D or long lesions) between 26% and 37% or even lower[335 337 340 403 577-581]. Accepting the high restenosis rate with conventional angioplasty in complex infragenicular arterial lesions, a calculation was formulated with a rate of restenosis reaching 70% in the PTA arm[340].

To obtain a 50% reduction of binary restenosis or occlusion in the DCB group, 31 subjects were needed in each arm to reach a power=0.8 and α=0.05. When compensating for a 10% loss of subjects during the study period, we got the stipulated number of 35 limbs in each group.

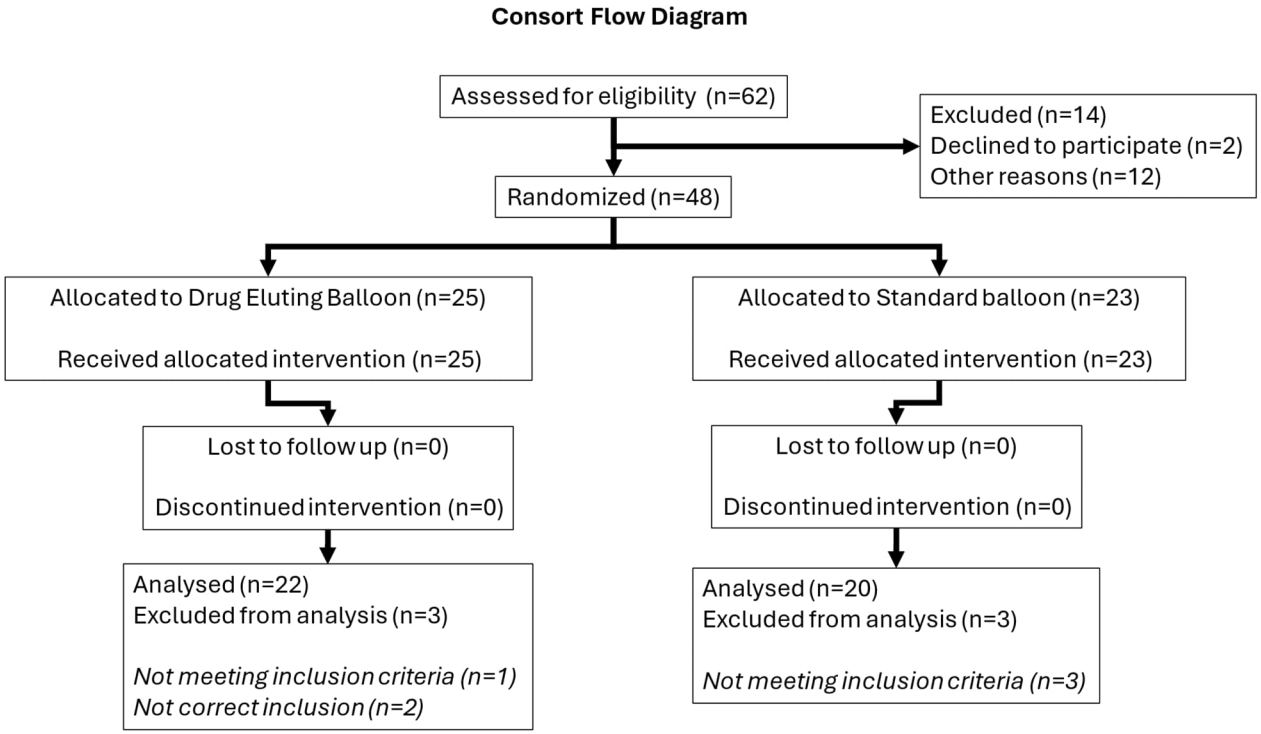
Normal distribution was not assumed. Median values are presented for continuous variables with interquartile ranges and tested with the Mann-Whitney U-test. Categorical variables, on the other hand, were analysed using the chi-square test or Fisher exact test.

Kaplan-Meier and survival curves were used to present time-to-event data, and any differences were compared with the log-rank test. This survival data is presented both with values ± standard error (SE) in percent. Results are also presented as odds ratio (OR) with a 95% confidence interval (CI).

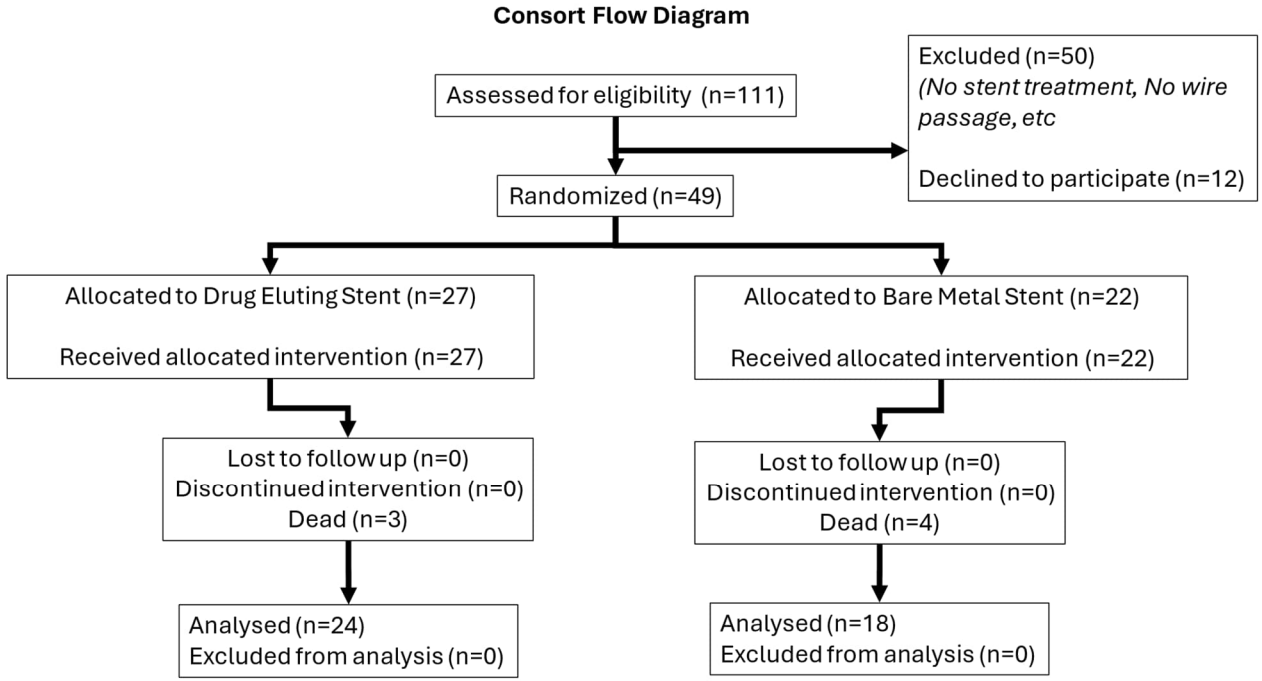
P values <0.05 were assumed to be significant.

Data was analysed using IBM SPSS Statistics 28 (SPSS Inc, Chicago, Ill).

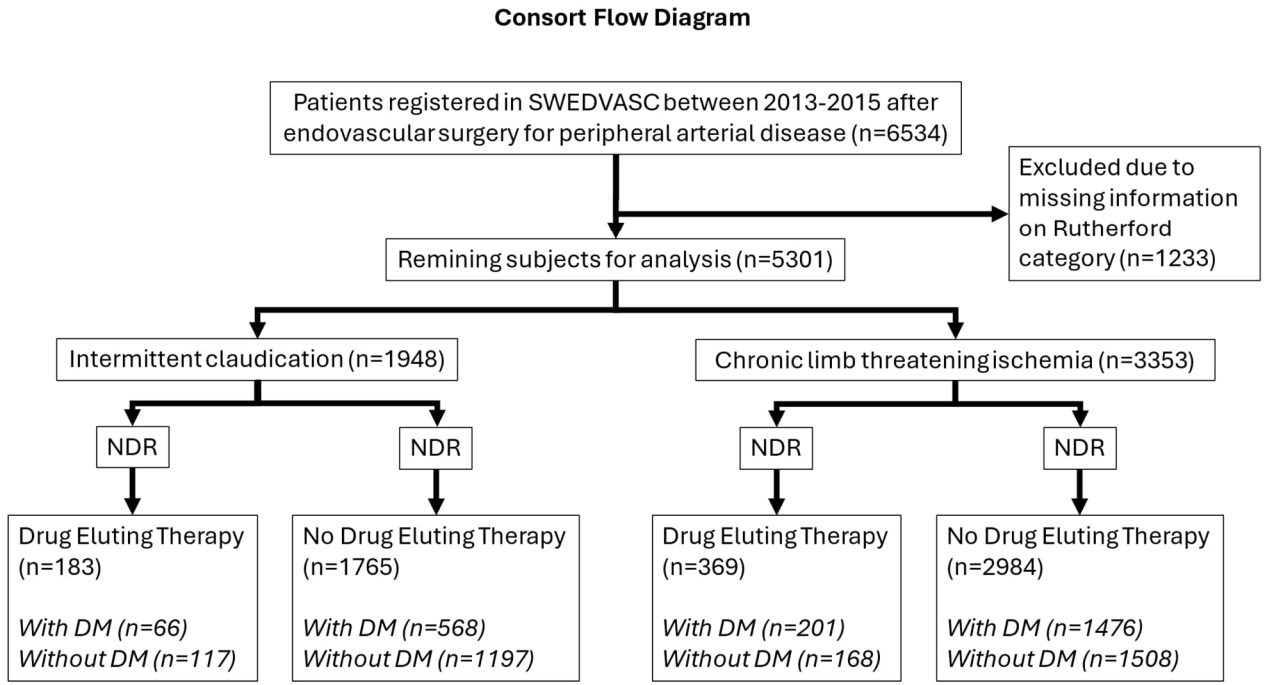
Consort Flowchart I



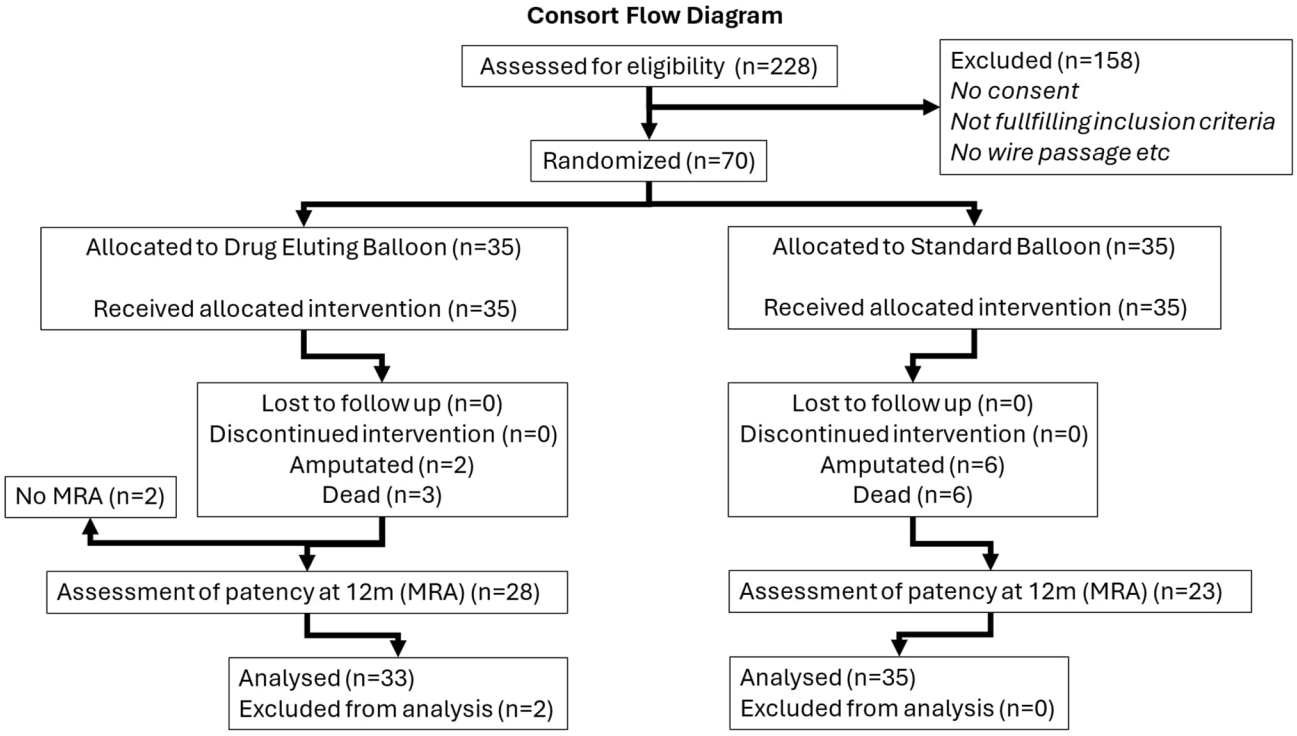
Consort Flowchart II



Consort Flowchart III



Consort Flowchart IV



Results

Main overall findings

The overall interpretation is that the three RCTs have reasonably comparable groups without scientifically essential deviations. Trials I and II suffer from a low number of participants, and no firm conclusions can be made. No apparent safety issues can be seen. In trial IV, there were unexpected numbers of deaths and amputations, making the trial functionally underpowered regarding the primary endpoint variables, as patency per protocol was objectively validated only at 12 months. No difference in the primary endpoint was shown. The deaths and amputations were mostly in the PTA group and recalculated as amputation-free survival. This was significantly higher in the group treated with DCB 88% vs 68% (OR 0.31 [CI 0.10-0.96], p=0.042). A similar outcome was seen among CLTI subjects with diabetes compared to subjects without diabetes in trial III (HR 0.712 [0.562-0.901], p=0.005).

Specific results of Trial I

Endpoints
Primary endpoints
Freedom from target lesion revascularisation (TLR) at 6 and 12 months
Freedom from access circuit revascularisation at 6 and 12 months
Functional access at 12 months
Secondary endpoints
Time to first target lesion revascularisation (TLR)
Survival at 12 months
Procedural and access related complications
Procedural technical performance

Picture XXV. Endpoints in trial I.

Primary endpoints

There were no significant differences between the groups regarding freedom from TLR (3 vs 4, p=1.000) or access circuit primary patency at 12 months (2 vs 4, p=0.665). The number of patients with functional access at 12 months was similar (70% vs 77%, p=0.592). Two circuits were lost, one in each group. See Pictures XXVI-XXVIII.

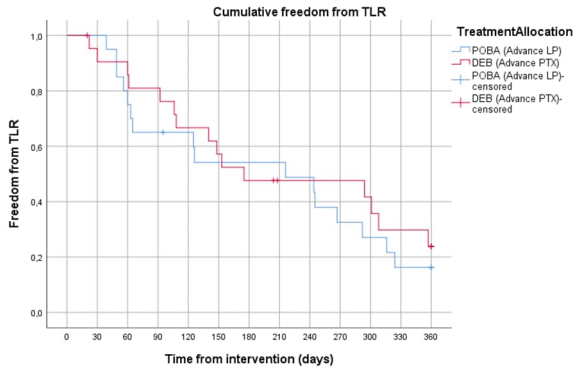
Secondary endpoints

The median time to TLR was similar in both groups (125 vs 140 days, p=0.861). There was no access related SAE and no difference in mortality at 12 months, the latter reaching 10% vs 14% (p=0.716), respectively. During follow-up, no significant differences were detected between groups regarding the total number of TLR procedures (31 vs 36, p=0.917) and access circuit reinterventions (44 vs 49, p=0.768). The median number of interventions and the number of TLR specific interventions were similar in both groups. See Pictures XXVI-XXVIII.

The technical procedural success was 100% in both groups, but the radiological technical success was unexpectedly low, only 68% vs 55% in the DEB and PTA groups, respectively. There was no significant difference between the groups.

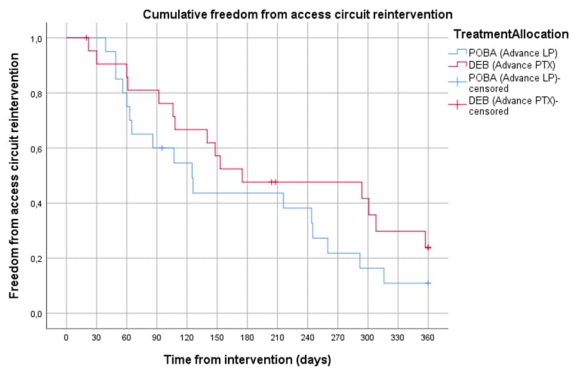
	POBA (n=20) (%)	DEB (n=22) (%)	P value
Mortality 12m	2 (10)	3 (14)	0.716
Access related SAE 12 months	0	0	1.000
Access circuit thrombosis 12 months	1	0	0.288
Any access related complication 12 months	4 (20)	1 (4)	0.122
Freedom from TLR 12 months	3 (16 ± 9)	4 (24 ± 10)	1.000
Freedom from TLR 6 months	10 (54 ± 11)	10 (48 ± 11)	1.000
Access circuit primary patency 12 months	2 (11 ± 7)	4 (24 ± 10)	0.665
Access circuit primary patency 6 months	8 (44 ± 11)	10 (48 ± 11)	0.764
Functional access 12 months	14 (70)	17 (77)	0.592
Median number of TLR interventions 12 months	1 (1-2)	1 (0-3)	0.917
Median number of access circuit interventions 12 months	2 (1-3)	2 (1-3)	0.768
Time to first TLR (days)	125 (57-261)	140 (6-294)	0.861
Number of duplex scans 12 months	3 (1-5)	3 (1-5)	0.789

Picture XXVI. Table showing results in Trial I. Comparison between treatment with Plain Old Balloon Angioplasty (POBA) and Drug Eluting Balloon (DEB). Time to first Target Lesion Revascularisation (TLR) and number of duplex scans are presented as medians with interquartile ranges. Life table data is presented with numbers and (% ± SE). The other variables are presented as numbers with percentages.



	1 months	3 months	6 months	9 months	12 months
POBA	20 (100 ± 0)	13 (65 ± 11)	10 (54 ± 11)	9 (33 ± 11)	3 (16 ± 9)
DEB	20 (95 ± 5)	17 (81 ± 9)	10 (48 ± 11)	8 (48 ± 11)	4 (24 ± 10)
	$P = 0.49$	$P = 0.50$	$P = 1.00$	$P = 0.75$	$P = 1.00$

Picture XXVII. Figure showing cumulative freedom from TLR in Trial I. Comparison between treatment with Plain Old Balloon Angioplasty (POBA) and Drug Eluting Balloon (DEB). Kaplan-Meier curve showing cumulative freedom from Target Lesion Revascularisation (TLR). The corresponding table highlights the number of patients at risk (% ± SE) at specific points and p-values for each point.



	1 months	3 months	6 months	9 months	12 months
POBA	20 (100 ± 0)	12 (60 ± 11)	8 (44 ± 11)	4 (22 ± 10)	2 (11 ± 7)
DEB	20 (95 ± 5)	17 (81 ± 9)	10 (48 ± 11)	8 (48 ± 11)	4 (24 ± 10)
	p=0.49	p=0.32	p=0.76	p=0.31	p=0.66

Picture XXVIII. Figure showing cumulative freedom from access circuit reintervention in Trial I. Comparison between treatment with Plain Old Balloon Angioplasty (POBA) and Drug Eluting Balloon (DEB). Kaplan-Meier curve showing cumulative freedom from access circuit reintervention. The corresponding table highlights the number of patients at risk (% ± SE) at specific points and p-values for each point.

Specific results of Trial II

Endpoints
Primary endpoints
Primary patency at 12 and 24 months
TLR at12 and 24 months
Secondary endpoints
Clinical success at 12 and 24 months
Secondary patency at 12 and 24 months
Survival at 2 and 5 years
SAE upto 24 months
MALE upto 24 months
Technical success

Picture XXIX. Endpoints in Trial II.

Primary endpoints

No differences were noticed regarding the primary efficacy endpoints, which were similar in both groups. Freedom from TLR at 12 and 24 months was 73% vs 63% (p=0.468) and 64% vs 59% (p=0.754), and primary patency rates at 12 and 24 months were 41% vs 44% (p=0.804), and 41% vs 33% (p=0.584) in the BMS and DES groups, respectively. See Pictures XXX, XXXII, and XXXIII.

Secondary endpoints

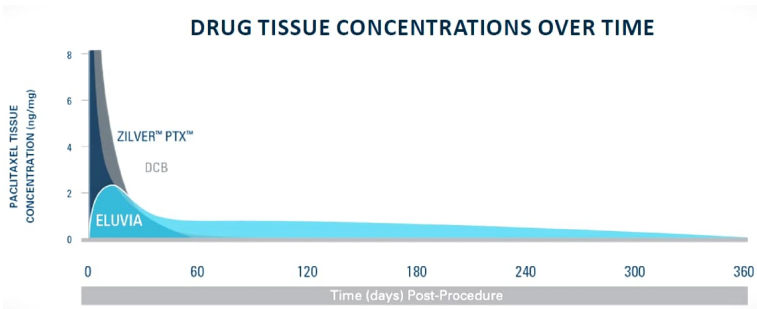
The in-hospital technical success (TS) rates were suboptimal in both groups, 64% vs 67 % (p=0.825) in the BMS and DES group, respectively, and with a predischarge early loss of patency in 6 cases. Secondary patency in the BMS and DES group was 55% vs 59% (p=0.740) and 50% vs 44% (p=0.698) at 12 and 24 months. There were no significant differences regarding improvements in RC at 1, 6, 12, and 24 months, and the rates of conversion to surgical bypass were 23 % and 11 % (p=0.274), respectively, in the BMS and DES groups. There were no differences in mortality, and the five-year survival was 77% and 78% (p=0.966) in the BMS and DES groups, respectively. The difference between BMS and DES regarding median time to TLR was not significant, 295 days vs 127 days (p=0.121). Rates of MALE were 23% vs 30% (p=1.000), and SAE rates were 41% vs 37% (p=0.586), respectively, in the BMS and DES groups at two years. There was a tendency (p=0.060) towards a difference between the groups in amputation rate at 24 months. Four patients (15%) were amputated in the DES group, whereas no amputations occurred in the BMS group. There was also a tendency towards a difference regarding subjects at risk for TLR at six months, 95 ± 5 % vs 74 ± 8% (p=0.076) in the BMS and DES group,

respectively, corresponding to a tendency for higher rates of target lesion occlusion as a primary event in the DES group compared to the BMS group, although not significant, 14% vs 37% (p=0.065). See Pictures XXX, XXXII, and XXXIII.

Regarding the presented results in comparison with the results of the IMPERIAL trial[445], Picture XXXI schematically highlights the pharmacological difference regarding drug concentrations between these two self-expanding DES, the only ones available on the market for peripheral use (Zilver PTX® and Eluvia®).

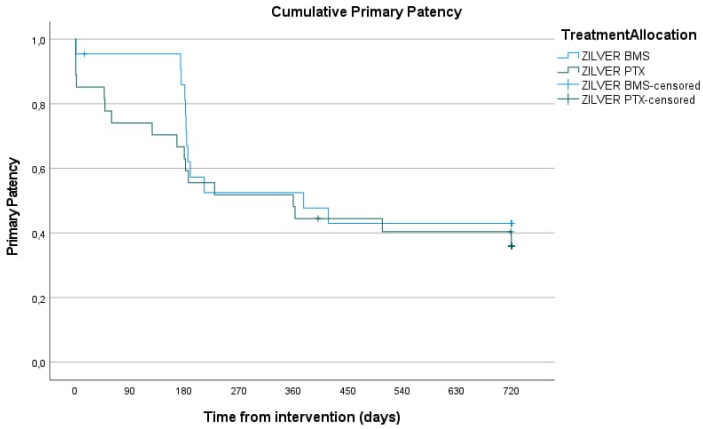
	BMS (n=22) (%)	DES (n=27) (%)	P value
TLR 12 months	6 (27)	10 (37)	0.468
TLR 24 months	8 (36)	11 (41)	0.754
Primary patency 12 months	9 (41)	12 (44)	0.804
Primary patency 24 months	9 (41)	9 (33)	0.584
Secondary patency 12 months	12 (55)	16 (59)	0.740
Secondary patency 24 months	11 (50)	12 (44)	0.698
Mortality 2 years	4 (18)	3 (11)	0.482
Mortality 5 years	5 (23)	6 (22)	0.966
Amputation rate 24 months	0 (0)	4 (15)	0.060
Major adverse limb events (MALE) 24 months	5 (23)	8 (30)	0.586
Serious adverse events (SAE) 24 months	9 (41)	10 (37)	1.000
Conversion to bypass	5 (23)	3 (11)	0.274
Time to TLR (days)	295 (206-348)	127 (1-234)	0.121
Occlusion of treated lesion as primary event	3 (14)	10 (37)	0.065
Time to occlusion	213 (183--)	94 (36-198)	0.161
Improvement RC 1 months	0 (0-3)	3 (0-3)	0.136
Improvement RC 6 months	3 (1-4)	3 (2-4)	0.903
Improvement RC 12 months	3 (0-4)	3 (1-4)	0.973
Improvement RC 24months	4 (3-4)	3 (2-4)	0.199

Picture XXX. Table showing results in Trial II. Comparison between treatment with Zilver® Flex bare metal stent (BMS) and Zilver® PTX drug eluting stent (DES). Time to target lesion revascularisation (TLR), occlusion, and improvement of Rutherford classes (RC) are presented as medians with interquartile ranges. The other variables are presented as numbers with percentages.



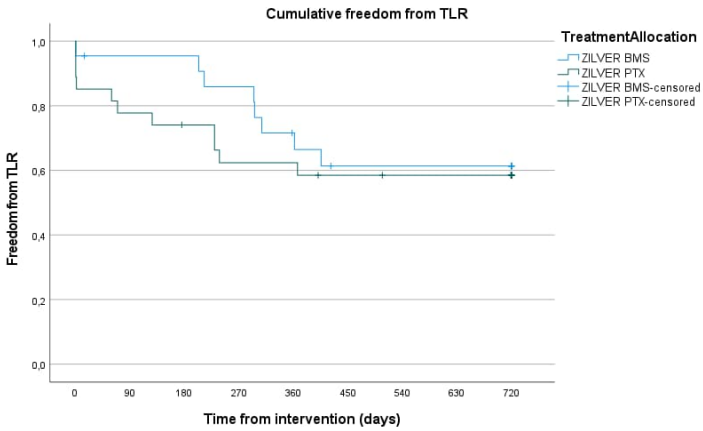
Picture XXXI. Schematic diagram depicting the pharmacokinetic profile of Eluvia® versus Zilver PTX® paclitaxel release over 12 months based on preclinical pharmacokinetic analysis. Data for Eluvia on file at Boston Scientific Corporation. Data for Zilver PTX is available from Dake MD, Van Alstine WG, Zhou Q, Ragheb AO[582].

(*Adopted from EVT VOL.4, NO.6 2016 © 2016 Bryn Mawr Communications II, LLC)*



	1 month	6 months	12 months	24 months
Zilver® Flex BMS	20 (95 ± 5)	18 (86 ± 8)	11 (52 ± 11)	9 (43 ± 11)
Zilver® PTX DES	23 (85 ± 7)	18 (67 ± 9)	14 (52 ± 10)	9 (40 ± 10)
	p=0,543	p=0,232	p=0,897	p=0,584

Picture XXXII. Figure showing cumulative primary patency in Trial II. Comparison between treatment with Zilver® Flex bare metal stent (BMS) and Zilver® PTX drug eluting stent (DES). Kaplan-Meier curve showing the cumulative primary patency. The corresponding table highlights the number of patients at risk (% ± SE) at specific points and p-values for each point.



	1 month	6 months	12 months	24 months
Zilver® Flex BMS	20 (95 ± 5)	20 (95 ± 5)	14 (72 ± 10)	11 (61 ± 11)
Zilver® PTX DES	23 (85 ± 7)	19 (74 ± 8)	16 (62 ± 9)	12 (58 ± 10)
	p=0,543	p=0,076	p=0,754	p=0,698

Picture XXXIII. Figure showing cumulative freedom from TLR in Trial II. Comparison between treatment with Zilver® Flex bare metal stent (BMS) and Zilver® PTX drug eluting stent (DES). Kaplan-Meier curve showing cumulative freedom from target lesion revascularisation (TLR). The corresponding table highlights the number of patients at risk (% ± SE) at specific points and p-values for each point.

Specific results of Trial III

Endpoints
Primary endpoints
Survival without amputation
Reintervention for PAD
Secondary endpoints
All cause mortality
Cardiovascular mortality
Major amputation
Major adverse cardiovascular events (MACE)
Myocardial infarction (MI)
Stroke

Picture XXXIV. Endpoints in Trail III.

Primary endpoints

CLTI patients with DM treated with drug eluting methods had a lower risk for amputation or mortality after adjustment compared to patients treated without drug eluting methods (HR 0.712 [0.562-0.901], P=0.005), but there were no differences regarding reinterventions for PAD. See Table 19 and Pictures XXXVI-XXXVII. There were no differences among IC patients treated with and without drug eluting methods, irrespective of the presence or absence of DM.

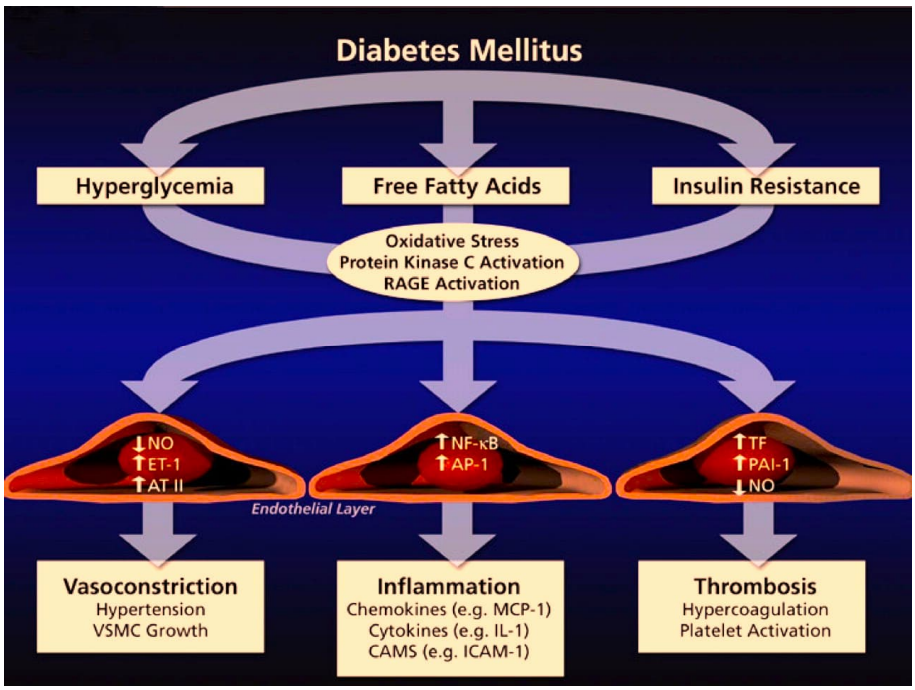
Secondary endpoints

Regarding secondary outcomes, total mortality was lower in patients with DM treated with drug eluting technology compared to those who were treated with standard endovascular technology. The difference was largest around 12 months (p=0.001) of follow-up and later followed by a "catch-up" phenomenon. No other differences concerning secondary variables (amputation and MACE) were seen between those treated with and without drug eluting methods among IC or CLTI patients with or without DM.

Regarding the presented results, as discussed earlier in this thesis, it is important to remember specific issues in subjects with DM *and* PAD regarding overall treatment effects with DET, as it may have interesting theoretical implications. Picture XXXV schematically delineates the metabolic connection between DM and PAD.

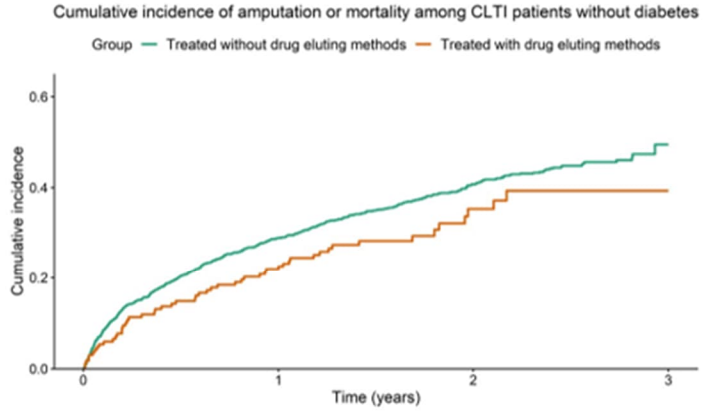
Table 19. Table from Trial III showing hazard ratios (HR) with 95% confidence intervals (CI) for patients treated with drug eluting methods compared to patients treated without drug eluting methods among patients with CLTI with and without DM, respectively.

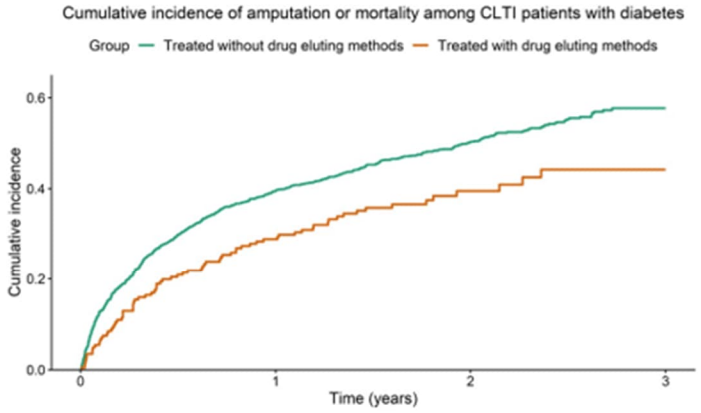
Model	HR (95% CI)	p-value	Outcome	Subgroup
Adjusted	0.712 (0.562-0.901)	0.005	Amputation or mortality	CLTI with diabetes
Unadjusted	0.698 (0.552-0.883)	0.003	Amputation or mortality	CLTI with diabetes
Adjusted	0.797 (0.600-1.057)	0.115	Amputation or mortality	CLTI without diabetes
Unadjusted	0.783 (0.591-1.037)	0.088	Amputation or mortality	CLTI without diabetes
Adjusted	0.849 (0.619-1.165)	0.309	Reintervention for PAD	CLTI with diabetes
Unadjusted	0.895 (0.654-1.227)	0.490	Reintervention for PAD	CLTI with diabetes
Adjusted	0.702 (0.486-1.016)	0.061	Reintervention for PAD	CLTI without diabetes
Unadjusted	0.715 (0.495-1.032)	0.073	Reintervention for PAD	CLTI without diabetes



Picture XXXV. Schematic picture delineating the metabolic abnormalities that characterise DM in relation to PAD.

(Adopted from https://doi.org/10.1161/01.CIR.0000091257.27563.32; ©Circulation 2003; © American Heart Association, Inc.)



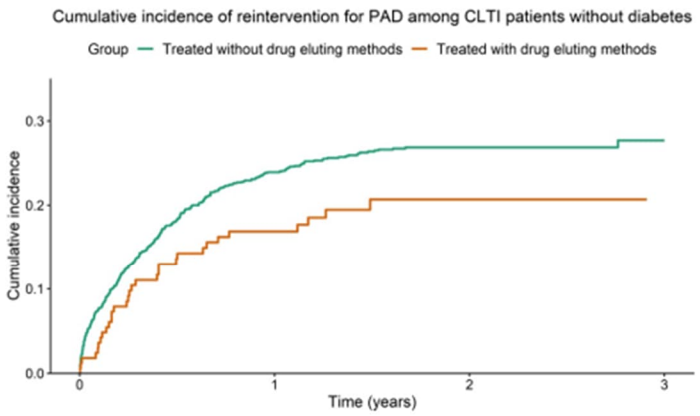


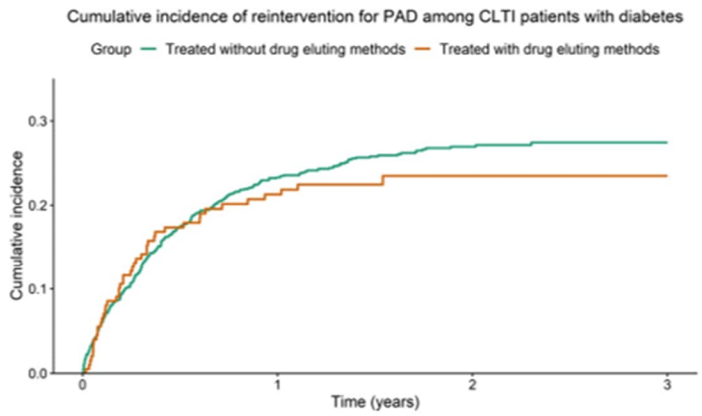
Year	0	1	2	3
DE methods	168	131 (78±3.2%)	40 (24±4.4%)	1 (<1±5.0%)
No DE methods	1508	1073 (71±1.2%)	468 (31±1.4%)	19 (1±2.7%)

Year	0	1	2	3
DE methods	201	143 (71±3.2%)	51 (25±3.7%)	4 (2±4.3%)
No DE methods	1476	893 (61±1.3%)	411 (28±1.4%)	16 (1±1.7%)

Figure from Trial III showing incidence of amputation or mortality in diabetic and nondiabetic subjects with CLTI . Crude rates of the composite variable amputation or mortality among patients with CLTI, treated with and without drug eluting methods in subgroups without (panel at left) or with (panel at right) diabetes mellitus. Table showing limbs at risk at different points as numbers and (% ± SE). DE = Drug Eluting, CLTI = chronic limb threatening ischemia.

Picture XXXVI. Cumulative incidence of amputation or mortality in Trial III.





Year	0	1	2	3
DE methods	168	119 (71±3.0%)	33 (20±3.4%)	0 (0)
No DE methods	1508	929 (62±1.1%)	372 (25±1.2%)	13 (1±1.5%)

Year	0	1	2	3
DE methods	201	138 (69±3.0%)	44 (22±3.2%)	4 (2±3.2)
No DE methods	1476	887 (60±1.2%)	377 (26±1.3%)	16 (1±1.3%)

Figure from Trial III showing incidence of reintervention in diabetic and nondiabetic subjects with CLTI . Crude rates of reinterventions for peripheral arterial disease among patients with CLTI, treated with and without drug eluting methods in the subgroups without (panel at left) or with (panel at left) diabetes mellitus. Table showing limbs at risk at different points as numbers and % ± SE. DE = Drug Eluting, CLTI = chronic limb threatening ischemia.

Picture XXXVII. Cumulative incidence of reintervention in Trial III

Specific results of Trial IV

Endpoints
Primary endpoints
Primary limb patency at 12 months
Secondary endpoints
Clinical success at 12 months
Amputation free survival at 12 months
TLR at 12 months
Primary lesion patency at 12 months
SAE at 12 months
Technical success

Picture XXXVIII. Endpoints in Trial IV.

Primary endpoints

Regarding the predetermined primary outcome variable, primary patency, no significant differences were shown at 12 months. All but four available limbs underwent MRA at 12 months. Two of these had DUS performed instead due to poor renal function. The other two patients declined any further investigations. The lesions available for MRA, i.e. subjects alive without major amputation, reached 71% and 59% in the DCB and PTA groups, respectively. Demonstrable rates of target lesion occlusion at available MRAs were 55% and 49% in the respective groups. Primary patency calculated for both limb (at least one treated vessel patent) and lesion did not differ between groups. Limb-orientated patency reached 46% (OR 0.94, [CI 0.43-2.08], p=0.88) in the DCB and PTA group, respectively. See Pictures XXXIX-XL.

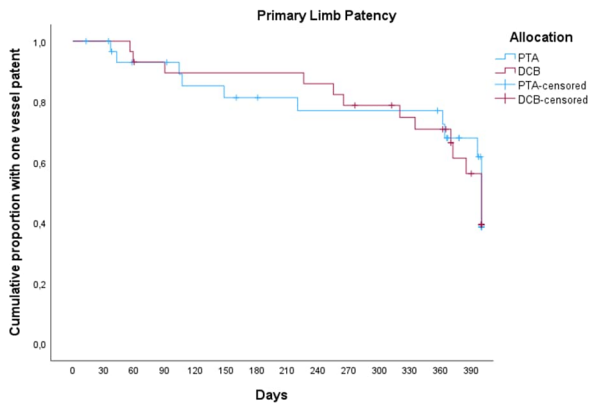
Secondary endpoints

The rate of clinical driven TLR was 11% in both groups. At 12 months, six limbs were amputated in the PTA group compared to two limbs in the DCB group. Six subjects had died in the PTA group compared to three in the DCB group. Recalculating AFS, comparable figures were 88% versus 68% (OR 0.31 [CI 0.10-0.96], p=0.042) in the DCB and PTA groups. The rate of relevant cumulative complications, i.e. SAE up to 12 months, was high but did not differ significantly between groups, 29% in the DCB group and 40% in the PTA group. Rehospitalisation from all causes was common in both groups, 66% after DCB and 60% after PTA. Clinical improvement was monitored, such as pain, healing of ulcers, walking capabilities, well-being, and overall functional status. At 6 and 12 months, no significant differences between groups were detected regarding ulcer

healing, pain, or walking capacity. Overall functional status, defined as generally improved daily activities, was significantly better in the DCB group at six months (70% and 44%, p=0.037), a difference which was no longer significant at 12 months. See Pictures XXXIX-LX.

	PTA	DCB	P value
Available lesions with MRA @ 12m	37 (59)	42 (71)	.15
Target Vessel Occlusion on MRA @ 12m	18 (49)	23 (55)	.59
Amputations @12m	6 (17)	2 (6)	.13
Mortality @12m	6 (18)	3 (9)	.28
Alive without amputation @12m	23 (68)	30 (88)	**.042**
Primary Limb Patency @12m	12 (48)	13 (48)	.99
Primary Lesion Patency @12m	19 (51)	19 (45)	.59
Clinical Driven TLR @12m	4 (11)	4 (11)	1.00
Serious adverse events (SAE) up to 12m	14 (40)	10 (29)	.31
Rehospitalization up to 12m	21 (60)	23 (66)	.62

Picture XXXIX. Figure from Trial IV showing major outcomes at 12 months. Comparison between drug coated balloon (DCB) and conventional balloon angioplasty (PTA). All variables are presented as numbers and percentages, n (%). MRA = magnetic resonance angiography. Limb patency means a limb with at least one treated vessel open. Lesion patency refers to individual treated lesion/vessel. TLR= target lesion revascularisation.



Days	30	90	180	270	360	390
PTA (n=31)	30 (100)	25 (93±5)	20 (82±7)	18 (77±8)	17 (77±8)	11 (67±10)
DCB (n=29)	29 (100)	26 (93±5)	25 (90±6)	22 (79±8)	18 (71±9)	11 (58±10)

Picture XL. Figure from Trial IV showing cumulative limb primary patency comparing drug coated balloon (DCB) and conventional percutaneous transluminal angioplasty (PTA), showing no significant difference up to 12 months. (OR 1.02, p=0.96, CI 0.47-2.21). Table showing limbs at risk at different points as numbers, n and (% ± SE). Limb primary patency means that at least one treated vessel is entirely patent without any assisted treatments.

Discussion

Overall discussion

The benefits of deposition of antiproliferative drugs (in this case, paclitaxel) in specific angioplasty settings have been discussed for some time. There is a considerable amount of scientific proof regarding possible anti-restenotic effects in various vascular territories [362 367 369 370 373 379 400 520 524-528 531 532 536 538 577 583-594]Still, these procedures have not been completely adopted as the standard of care in PAD and malfunctional haemodialysis.

In general, all three RCTs included in this thesis are relatively well-defined, and the groups in each study are, in important aspects, highly comparable without essential differences, limiting demographic bias. Looking at treatment or lesion characteristics, we saw some minor discrepancies, foremost in trials I and IV, showing that even though we had rather highly specified inclusion criteria, there was still some heterogenicity at a sublevel, making comparisons more unreliable when there were problems with limited number of enrolled participants. In the literature overall, there are still too few randomised studies or direct comparisons involving treatments using drug eluting technology, and trials present non-convergent results and are also often heterogeneous regarding outcome variables and lesion characteristics. These issues counteract the ability to make clear conclusions regarding the best treatment strategy in all clinical situations.

Another general finding was the inferior institutional technical success rate in all three trials, a problem that was unexpected and also impacted the interpretation and validity of the trials as cases were functionally lost from the start. This is also an important matter to consider in daily real-world practices as it puts the patients at risk for worse outcomes.

Regarding the two RCTs studying PAD, a high incidence of adverse events and hospitalisations in the follow-up period were consistently observed, reflecting the severity of a CLTI diagnosis and its effect on the overall well-being of the included subjects.

Another essential overall issue is the earlier mentioned discussion regarding the safety of Paclitaxel use regarding mortality and risk for limb amputation. This has been discussed in depth earlier in this thesis. It started in 2018 after the publication of the famous meta-analysis by Katsanos et al[376]. Finally, sufficient data became

available and analysed to firmly oppose this statement and support the continuous use of DET[377 595 596]. Later papers have also been published by the same group regarding the amputation rate after treatment with paclitaxel, foremost a discussion in the IP region[378 405]. This debate is still ongoing, with no other high-quality data supporting this statement[394 407 408 410]. The debate is still important, and we still must consider how to deal with this issue. The amputation rate seems to be mainly driven by high-dose products on the market, but it has not yet been concluded that this is the case, but as randomised studies[387 597] show that low-dose balloons are equally effective as are other immunomodulating compounds[386], there are already today alternative solutions. Our experience regarding amputations in all trials does not support an increased risk for limb loss despite the non-significant finding that all amputations in trial II appeared in the DES group.

The world's most extensive randomised study of drug eluting therapy in PAD, SwedePAD, could not show a mortality risk at a four-year follow-up but has not yet presented outcomes on amputations[377]. Data from SwedePAD will hopefully guide the vascular community in these matters soon. In our retrospective cohort trial (III) and our IP RCT (IV), we had results pointing in the other direction, but in our stent trial (II), all four amputations occurred in the DES group, but this finding was not significant (p=0.060). Conclusions are, therefore, yet to be considered.

All three RCTs were planned, performed, and analysed in an intention-to-treat setting to minimise bias and make the results more generalisable.

Intention-to-treat analysis (ITT)	Per-protocol analysis (PP)
Preserves randomisation.	No preservation of randomisation.
Higher generalisability, reflecting the clinical setting by considering non-compliance.	Ideal setting if non-compliance is not an issue.
Maintains sample size.	Less generalisability and more challenging to show if differences between intervention and control groups are genuinely due to treatment or other factors.
Eliminates bias	May create bias by only including people who follow the protocol.

An important matter is the risks of type I and type II statistical errors, which is a crucial problem when facing a limited number of participants. Since p values are not at a three-star level, there is still a risk of a type I error reaching a few percent. Type II error is important because it is highly correlated to sample size, as well as the size of effect measure, systematic or random errors in the acquired data, and the decided level of significance. Type I and type II errors are also linked as an increased power of a test decreases the risk of a type II error but increases the risk of a type I problem. It is the same problem with lowering the significance level to lower the risk for type I errors. In all RCTs of this thesis, there is a clear risk of type II errors.

It is considered more important to avoid type I errors. The discussion regarding errors is also connected to the earlier discussion regarding which type of analysis you need to consider. ITT leads to an analysis of the entire cohort, including those who are non-compliant, who often are associated with adverse outcomes[598]. The effect is dilutional, but if a difference can still be proven, you have minimised the risk of type I errors.

Type I and Type II errors		
Null Hypothesis	**True**	**False**
Rejected	Type I error False positive Probability = α	Correct decision True positive Probability = 1-β *(statistical power)*
Not rejected	Correct decision True negative Probability = 1-α	Type II error False negative Probability = β

The abovementioned problems are not that problematic in the more extensive retrospective study. Instead, we are dealing with other shortcomings, such as an unfulfilled proportional hazards assumption in some analyses. This is an essential general limitation as the Cox regression statistical analysis depends on the hazards for two subjects having the same proportions over time. Also, the inclusion of too many additional adjustment variables will increase the risk of overfitting and multicollinearity. Multicollinearity is a situation when two or more variables in a regression equation are dependent on each other in such a way that one can be linearly predicted from another with a high degree of accuracy. These phenomena give rise to a low generalisability and increased risks for inaccurate estimates.

An interesting factor to discuss in RCTs is the Hawthorne effect, also called the observer bias effect, which might bias final conclusions[599]. It occurs when the subject or, in this example, the physician alters the behaviour when becoming aware of being enrolled or being part of a study. The randomisation in our three RCTs is blinded for the subjects but not for the staff. However, as our randomisation procedure occurs at the time of device selection during the intervention, the risk of observer bias in this context is minimised. In the follow-up period, treatment is not blinded for the interpreters, and there may be theoretical concerns for observer bias. As authors of all these trials, however, we have not noticed any concerns regarding this problem. In an optimal setting, you should have blinded core lab adjudicated processes in place to eliminate the problems regarding image interpretation. For the clinical follow-up, you must have a fully double blinded postinterventional process to limit this risk to a minimum level. In our real-world context, we did not conclude an actual risk for observer bias in our three RCTs.

Trial specific discussions

Paper I

This study showed no significant differences between drug eluting or standard angioplasty balloons in the treatment of dysfunctional haemodialysis circuits. Drug eluting technology could not demonstrate superior primary patency, longer retreatment intervals, or a higher degree of freedom from TLR.

Regarding the local anti-re-stenotic effects after endovascular treatment of haemodialysis access, publications have so far shown conflicting results. For a long time, no definite signs of superior efficacy were shown. The recent large IN. PACT AV access multicentre RCT showed significantly better target lesion primary patency at six months when subjects were treated with drug eluting balloon angioplasty [600]. These results represent a significant advance in the field of endovascular treatment of dysfunctional AV-fistulas. Analysing subgroups at two years in the LUTONIX randomised trial, there was an observed positive effect with significantly longer retreatment intervals when using DEB. Despite this, the trial failed to reach its primary endpoint of a superior target lesion primary patency at 6 and 24 months for DEB, although superiority could be shown at 9 and 12 months [538]. Also, important reading is the recently published, multicentre prospective randomised PAVE study, enrolling 212 subjects, which did not show any difference between standard treatment (POBA) and DEB angioplasty in the treatment of dysfunctional AV-access [522].

Concerning our study population, there were no essential demographic differences between the groups. The DEB group enrolled significantly more patients with AV fistulas on the left arm. There is no theoretical explanation for this finding, and it is presumably a result of pure chance.

There is a slight imbalance, although not significant, regarding lesion location, with more proximal vein lesions in the DEB group. According to this imbalance, in conjunction with the limited number of patients enrolled, one could argue for worse outcomes in the DEB group, as shown by Manninen et al [601]. They showed that the location of the main treated lesion close to the arteriovenous anastomosis may predict poorer long-term patency.

There is also a slight overweight regarding the frequency of lower arm fistulas in the DEB group, although not significant (p=0.069), which may impact our interpretation of the data due to the limited number of subjects.

There are similar, small, published randomised studies regarding AV-fistulas treated with DEB or POBA that did not show any differences in target lesion revascularisation or patency[523 531 602], as in our study. With this said, you can also

find similar small studies that, on the other hand, reached significant differences between the two groups [526 527 603].

In a retrospective study from our institution in 2014, Bountouris et al. reported primary patency rates after standard PTA reaching 61% at six months and 42% at 12 months when analysing 159 patients treated with PTA in 2008 and 2009[604].

Compared to this, the overall effect of PTA in the current study was inferior at 12 months, with an overall primary patency of 14%. These results are in the lower wide range of results in similar studies presenting POBA primary patency figures in a wide span between 5-55% at 12 months [520 524 528 531 586 591 592 605].

Paper II

In this RCT, which compared outcomes after treatment with DES and BMS in a well-defined patient group with CLTI and FP lesions, we were unable to demonstrate any clinically relevant differences between the groups.

In the literature, there are few direct comparisons between DES and BMS in the treatment of FP lesions. Furthermore, most of the available comparisons are between groups with mixed categories regarding ischemic severity and complexity [443 449 450 563].

Our study groups are comparable, with the only significant difference being pre-treatment ABI measurements, which were 0.45 and 0.58, respectively, in the BMS and DES groups. The reason for this is unclear. There is simultaneously a trend towards more subjects with chronic kidney disease (CKD) as well as subjects with DM in the DES group 0 % vs 15 % (p=0.117) and 41% vs 59% (p=0.256) in the BMS and DES groups, respectively. This, in conjunction with the limited number of study subjects, may impact the results. It is well known that patients with both DM and CKD have a higher incidence of media sclerosis.

The median number of stents used in the treatment arms differed significantly, two in the BMS group and three in the DES group. This may also explain the disparity in the net difference between the stented length and the sum of stent lengths, i.e., the total length of stent overlaps. This finding is due to the differences in available stent lengths on the market.

Overall primary patencies at 12 and 24 months were 43% and 37%, respectively, with no difference between study groups. This is not entirely in line with results in studies of nitinol stenting in the FP region [414 445 447-450 563 574 606-613]. A possible reason for the low primary patency is a high percentage of total occlusions, long lesions with an overall median length of 240 (163-285) mm, and overall Rutherford class 5 (4-5), indicating a high incidence of complex lesions and subjects in our study population.

Freedom from TLR at 12 and 24 months was acceptable and close to findings in earlier publications on stenting of complex FP lesions [414 443 445 447-449 563 574 609 610 612], reaching 73% and 64% in the BMS group and 63% and 59% in the DES group. All patients who lost lesion patency did not necessarily have a clinical indication for TLR.

There was an unexpectedly high incidence of early, pre-discharge patency loss, reaching 12% overall, corresponding to 4.5% in the BMS group and 19% in the DES group (p=0.138). This significantly affects the rates of primary patency, making secondary patency an important efficacy endpoint, as these early occlusions will probably affect later actual drug eluting effects. Secondary patency reached 55% and 50 % at 12 and 24 months in the BMS group compared to 59% and 44% in the DES group. Secondary patency rates were comparable to other studies [443 448 449 613-617].

Looking at the survival tables, an incongruence can be noticed regarding the first six months of follow-up. In this intention-to-treat analysis, the difference was almost significant at six months regarding freedom from TLR, with a tendency for BMS to perform slightly better, 95% ± 5 vs 74% ± 8 in the DES group. The theoretical reason for a BMS to perform better than a DES during the first six months is unclear, as the stent platforms are similar, and apparent drug-related effects are missing. With the limited number of subjects in the study, these tendencies should be interpreted with care. There is numerically a large, non-significant difference between the two groups regarding prestudy treatment of the index leg. That, in conjunction with the limited number of subjects, may have implications.

Survival rates were higher than expected in comparison with other publications [81 84 414 443 609 610 616-625], and the overall rate of survival in our study reaches almost 78% at five years. The reason for this finding is not fully understood, as our study population does not seem healthier regarding baseline characteristics. Improved cardiovascular medication can affect mortality, and this might theoretically be a part of the explanation [304 626], but data to confirm this in our study cannot be extracted.

An important efficacy endpoint is clinical improvement, which is most reliantly monitored as improvement in Rutherford class at 12 and 24 months. Our study noticed no significant differences between the BMS and DES groups regarding clinical effects during follow-up.

There was a relatively high incidence of adverse events during this 24-month trial. Regarding MALE, including amputation, conversion to open surgery, and thrombolysis, there were no significant differences between groups, with an overall rate of 27% at two years. SAE rates, including death, were similar and overall reached 39%. It is expected that subjects with CLTI have a higher incidence of vascular complications and mortality compared to an average population or a population with primarily IC [10 29 86 617 627].

All amputations during the 24-month follow-up period were performed in the DES group. This finding was not significant (p=0.060) but is an interesting tendency in the context of the ongoing discussion regarding the risk of amputation in patients treated with drug eluting technology. A recent meta-analysis suggests that there may be a significantly higher risk for amputations after use of paclitaxel-eluting devices in the lower extremities [378].

Finally, when discussing the polymer-free paclitaxel-eluting stent used in this trial, the choice of DES may also have an impact on overall DES results in a real-world scenario. Although Zilver PTX® DES, studied in this trial, has documented efficacy in treating FP lesions, a recent head-to-head comparison with another DES showed that Zilver PTX® performed worse regarding TLR rates at 24 months [445].

Paper III

In this study, we found that CLTI patients with DM who were treated with drug eluting methods had a lower risk for amputation or death than patients treated without drug eluting methods, whereas we were not able to demonstrate any benefit among CLTI patients without DM or among IC patients.

The most effective type of endovascular treatment for lower extremity PAD in patients with diabetes still remains to be determined[19 256 407 617 628 629]. The use of drug eluting technology might be an attractive adjunct to improve outcomes, in particular, as DM has an adverse effect on the prognosis after endovascular intervention[33-35 38 39 42 43 45 55 630 631]. Drug eluting technologies might potentially offer extra benefits to this subpopulation.

Diabetic patients have constituted 60-100% of the material in previous studies of drug eluting therapy in CLTI[407], and their rate of cardiovascular events after revascularisation is higher than in CTLI patients without DM[632]. Furthermore, their PAD lesions are more often more complex[55]. Even if the role of DM as a predictor of restenosis is not clear[633], the presence of diabetic foot ulcers negatively affects both amputation rates as well as overall survival in this patient cohort, and thus, improved therapies are of paramount importance. The presence of vascular inflammation, as well as increased smooth muscle migration and proliferation, can perhaps be targeted by paclitaxel, and this is a possible mechanism to account for the improved outcomes in diabetic CLTI patients[298].

It is clearly of paramount importance to separately analyse patients with IC and CLTI due to the profound differences in general outcome effects and relevant outcome variables between these two groups.

The fact that the study was nationwide constitutes an important strength. Swedish national registries are reliable in reporting hospitalisation, death, and reinterventions. Although SWEDVASC collects and reports data in accordance with

current reporting guidelines[634 635], some performance data is not collected. For example, detailed information regarding ulcers, healing, and functional performance status is unavailable, limiting the interpretation of detailed outcome efficacy, especially among subjects with diabetes. Our choice of endpoint variables seems relevant, however, also when compared with recently published trial protocols for CLTI[377 636]. The accuracy of SWEDVASC has been systematically evaluated regarding procedures for carotid artery disease and abdominal aortic aneurysm[637], but not regarding endovascular treatment of IC and CLTI. Misclassification of these two entities in the registry has been reported[638], and might have also occurred in our study. We also adjusted for several important confounders, such as age, sex, smoking, previous cardiovascular disease, lipid lowering treatment, aspirin, and oral anticoagulants. On the other hand, potential actual group differences in lipid and blood pressure levels were not accounted for.

Subjects undergoing solitary treatment in the aortoiliac region usually suffer from IC and not CLTI, and patency rates at this level outperform patency rates compared to treatment at lower levels[639 640]. We have chosen *not* to exclude this group as the number of subjects receiving DET at this level was extremely few, only two with CLTI and seven with IC. These numbers will not affect the outcomes in favour of DET, instead, potential dilutional statistical effects might make the performance in the non-DET group look somewhat better. As the primary outcomes in our study for all regions favoured DET, the exclusion of this group did not seem relevant.

The duration of follow-up is comparably long in this study. Most similar studies have follow-up periods of 12 months or less, although there are published randomised studies regarding CLTI patients with longer follow-up[366 374 381 401 641-645].

Furthermore, it is essential to note that the potential benefits of drug eluting technology are only a possible adjunct to the multidisciplinary approach, including blood glucose and risk factor control, appropriate wound care, offloading of foot ulcers, and necessary control of leg oedema to improve limb salvage and mortality in PAD patients with diabetes[646].

Paper IV

In this RCT comparing outcomes after treatment with DCB and PTA in a well-defined patient group with CLTI and complex infragenicular arterial lesions, we were unable to demonstrate any clinically relevant benefits of DCB regarding the primary endpoint. Among the secondary endpoints, however, AFS was significantly higher in the DCB group at 12 months.

The two groups in our study cohort were comparable, except that the PTA group had a higher rate of inflow lesion treatments and more treatments performed in the fibular artery. The reason for the discrepancy in inflow treatments is unclear, and no systematic reason can be given. Neither can this asymmetry be explained by other

demographic or pretreatment characteristics nor does it explain the higher mortality and amputation rate in this group. The higher proportion of PTA treatments of the fibular artery in the PTA group has no systematic explanation and seemingly did not have any demonstrable effects on the results.

Lesion and treatment complexity was high, which is not unexpected in this type of patients[29 647-649], but without any group differences. As expected in a real-life study, many different operators with different levels of experience performed the angioplasties.

There were high rates of complications and rehospitalisations in the 12-month follow-up period in both groups. This was not unexpected due to the fragility and comorbidities in these CLTI subjects[29 579 647-651].

Unexpectedly, few subjects were retreated during follow-up, with no differences between the groups. TLR was, as stipulated, only indicated when the clinical situation necessitated this manoeuvre, and except for the 12-month MRA examination, no regular planned examinations of patency were performed. Most of the subjects in this study (78%) had DM and were accordingly routinely followed at a specialised diabetic foot clinic. Reintervention was not judged as necessary in many study subjects. Many subjects, in reality, had a slow improvement regarding ulcer healing but could not be registered as fully healed. Due to this, the situation was not interpreted as necessitating TLR. However, some TLR procedures were performed early after the 12-month MRA. Most of the amputations were primarily performed due to clinical deterioration, and TLR was then not considered due to age, comorbidities, and clinical situation. However, the rate of amputations was threefold in the group treated with PTA, a difference which was not significant. The total amputation rate in all 70 limbs reached 11% at 12 months, which is comparable to other similar studies[651 652].

Few lesions were objectively patent after 12 months, and the primary limb-based patency, defined as at least one treated vessel patent, was only 36% in the entire cohort, a figure comparable to those reported in many other relevant patient materials[335 337 340 403 577-581], but worse than the often referred DEBATE-BTK and AcoART II studies[403 577].

The choice of MRA as postinterventional follow-up may be rare, but it has constituted the clinical routine at our institution for decades. It allows direct comparison against the pre-interventional MRA. The methodology is complex and requires an MRA service providing high quality images. The most crucial drawback of MRI is its tendency to overestimate stenoses, and you need to be aware of this to allow evaluation of all images with the correct settings and templates. High-quality examinations and highly skilled and experienced interpreters can minimise this problem. In our study, most lesions were, in fact, both pre- and post-interventionally, long occlusions, with a corresponding total signal loss for extended

parts of the crural region. A supplementary duplex ultrasound was sometimes performed in the very few cases with difficulties in interpretation.

Mortality was numerically higher in the PTA group at 12 months, although not reaching significance. The mortality for the whole study cohort at 12 months was 13%, a figure similar to other studies[406]. Subjects with CLTI are expected to have a higher incidence of vascular complications and mortality compared to an average population or patients with IC.

Recalculation of the rate of amputation and/or mortality as AFS showed a significantly better outcome in the group treated with DCB at 12 months. Unfortunately, we cannot prove causality between the rate of amputations or mortality and postoperatively early improved patency due to the unmonitored early patency. This lack of objective information hampers the interpretation of a potential benefit from drug coated balloon treatment. As other studies have shown similar results[653], there is a need for larger randomised studies to help us understand the potential benefits of drug eluting technology.

An important efficacy endpoint is clinical improvement, which is most reliably objectively monitored as improvement in RC. This study was not able to prove a higher efficacy in complete wound healing or improved RC with DCBs, and there were no group differences regarding time to ulcer healing or abolishment of rest pain. Considering general daily activities and well-being, which can be seen as a composite endpoint including other single endpoints such as ulcers, pain, and walking ability, we found that subjects treated with DCBs were significantly more overall satisfied at six months but not at 12 months. An essential limitation regarding this finding is that this information was obtained from our staff interviewing the subjects without validated vascular questionnaires. As discussed earlier, causality between vessel patency and these clinical effects cannot be proven.

Summary

This thesis includes manuscripts from trials performed in an effort to detect any superior treatment effects with drug eluting technology in different clinical scenarios and also to show that the procedures are safe in comparison with standard care.

With limited numbers of participants in trials I and II, these trials could not contribute to the detection of any treatment differences. No safety issues were recorded. The role of DCB in malfunctional haemodialysis access is still unclear, as earlier randomised studies show conflicting results. The aggregation of earlier trials, including this one in a recent meta-analysis, favours DCB treatment to reduce TLR and the restenosis rate[541].

Neither the second trial contributed evidence of DES superiority for the same reason, and no safety issues were recorded. Earlier RCTs are, however, more uniformly in favour of DES use compared to standard PTA ±BMS in the treatment of FP arterial lesions, which is also concluded in recent meta-analyses[392 421 454].

Regarding the observational cohort trial, we observed that AFS was significantly improved in the subjects with DM and CLTI who were treated with drug eluting technology compared to subjects without DM. This finding needs to be explored further.

The last trial could not detect any differences regarding the primary outcome. In the analysis, however, AFS was significantly superior in subjects treated with DCB. This finding also mandates further exploration.

The trials could not uniformly detect a superior efficacy of DET against standard treatment, but no safety issues were detected. Two trials signal that positive treatment effects may be worthy of further exploration.

Conclusion

The overall interpretation of the findings in this thesis is that drug eluting therapy in endovascular treatment of different vascular domains and settings may have a practical impact on efficacy and safety outcome variables in a short and medium-term timeframe. Two trials could not defer the null hypothesis, while two other trials had efficacy signals in a direction speaking for superiority for drug adjunctive angioplasty or stenting procedures. These findings need to be explored further.

I. A superiority of DCB over PTA in treating malfunctional haemodialysis access could not be shown, but validity is limited due to a low number of enrolled subjects.

II. A superiority of DES over BMS in treating FP arterial lesions in subjects with CLTI could not be shown, but validity is limited due to a low number of enrolled subjects.

III. Regarding the primary outcome variable, amputation-free survival (AFS), DET could be shown to be superior to non-DET in treating subjects suffering from diabetes mellitus and CLTI.

IV. DCB superiority over PTA in treating IP arterial lesions in subjects with CLTI could not be shown regarding primary outcome variables, but the secondary outcome variable, amputation-free survival (AFS), was superior in the DCB group.

Scientific limitations

Limitations of the four studies in the thesis at a glance

	Study I	Study II	Study III	Study IV
Selection bias	No	No	Yes	No
Information bias	No, Prospective	No, Prospective	Yes, Retrospective	No, Prospective
Confounding	No, RCT	No, RCT	Yes, Retrospective	No, RCT
Ethical limitations	No	No	No	No
Observational bias	No	No	No	No
Other limitations	Non-consecutive enrolment Low inclusion rate Not core lab adjudicated	Non-consecutive enrolment Low inclusion rate Not core lab adjudicated	Suboptimal categorisation of the level of treatment Numerically unbalanced cohorts External validity	Non-consecutive enrolment Low inclusion rate Not core lab adjudicated

Scientific limitations in a general perspective

Starting with general considerations regarding performing scientific research, you will undoubtedly run into circumstances limiting the possibilities for an optimal final interpretation. Sometimes, these issues will be on the table at the planning stadium, and compromises will need to be made when formulating the study plan.

Running randomised trials comparing different treatments is mostly considered high qualitative research, minimising the risks for confounding. Differences in treatment efficacy will also be compared in a more robust manner. Essential problems with RCTs are the practical difficulties[654], and also that the subjects included often are highly categorised and selected, sometimes making a generalisation of the results to the general vascular population difficult.

Often, you need a large number of subjects to be able to show any relevant therapeutic differences, and although the risk of minor proportional or stochastic effects of uncategorised bias will be at a minimum in single centre trials, this is mostly not an option due to a limited number of recruitable subjects, and you will

have to run more complicated multi centre trials often across the whole world if you consider answering the more important scientific questions in your field.

Running studies in a cluster of centres will probably better represent a "real world" overall scenario considering treatment effects, but many subjects are not eligible for trials[308 655]. Individual centre results will, though, differ from centre to centre due to resources, indications, and treatment volumes. Also, the individual caseload per surgeon will have an impact on the overall quality and results. This means that individual centres in daily practice can have both better and worse results than shown in trials, which will affect the generalisation of trial results[655 656].

Another common theoretical and also practical issue is the choice and interpretation of inclusion, treatment, and follow-up variables. In clinical trials, when using different data obtained from records considered objective, this is not always, in a strictly scientific way, the case. There may be a large variability coupled to where, whom, and in which circumstances the supposed objective finding that could be a measurement or a judgement is documented. It is also common for data that should have been registered to be missing for varied reasons when many departments and staff members participate in projects. It is similar to the problem with all the other prospective healthcare registries that consistently, to some extent, will contain false information due to the fact that there is a lot of data contributors, all with different mindsets and aims. With this said, you must keep in mind that treatment results come in a context, and even though we theoretically could fully optimise study performances, this would probably not reflect the "real world" treatment scenarios. Data supports that the outcome is superior for subjects treated in a trial compared to treatments in a "real world" context[657].

Equally important is the issue with semi-quantitative or semi-categorical data. This happens when certain clinical circumstances sometimes involve slightly subjective judgements of parameters that will give rise to a new seemingly objective variable, sometimes categorical or dichotomous. This is an important issue when constructing a study protocol. The more fully objective parameters that are put into a final analysis, the easier the interpretation and less problematic bias will be.

Moving towards more specific limitations considered during this research project, it must be highlighted how practically difficult it is to run an RCT, and you must send appreciations to those vascular departments that manage to perform high-quality RCTs.

An essential limitation of our three RCTs is the limited number of subjects. Only the third RCT managed to enrol subjects according to the pretrial power calculations. Nevertheless, the trial became formally underpowered due to the unexpected frequency of deaths and amputations. The first two didn´t manage to enrol according to the trial definitions in a reasonable timeframe, and they were finalised beforehand, limiting the possibilities for relevant outcome analyses. It is problematic, both at our institution and at others, that only a fraction of potential

patients will get included in a running trial, and this happens in most cases without good reason other than malfunctioning clinical environments. The three RCTs included only 48/301, 49/111, and 70/228 subjects in the respective study's timeframe. Not only is there a limitation regarding numbers and possibilities for relevant calculations, but it also means that the inclusions are highly non-consecutive, introducing potential bias. This is an important take-home message for future planning of studies, and experienced researchers in the field stipulate that only 10% of potential subjects will be included in a general research environment.

Another issue we encountered was the paucity of complete clinical data for all study subjects. This leads to missing data problems when analysing the trial results. The reason for this phenomenon is primarily a malfunctioning clinical environment, as there are plenty of thoroughly written instructions everywhere in the healthcare services. This situation is probably at risk for further deterioration due to the enormous financial problems that have impacted healthcare services in general.

When including subjects with specified clinical problems, you also sometimes run into limitations, mainly at the posttrial analysis, when recognising different levels of anatomical lesion heterogenicity, making it challenging to perform optimal direct comparisons between the study cohorts. In part, this issue can be minimised with clearly structured and thoroughly planned study protocols.

Lastly, it is important to discuss another important limitation, which became apparent during this research project, namely that surgeons perform at different levels of quality. This goes together with the insight that while performing prospective trials at a department, you will finally receive relevant results regarding overall performance from a quality perspective. The quality was not entirely acceptable in any of the trials when comparing objective performance goals with results published from other departments[380 402 563 658-660]. Most importantly, this circumstance brought awareness regarding the technical success rate, which highly affected and complicated the interpretation of all the trials. Treatments were not acceptably performed in all instances by all interventionists. A problematic technical success rate will have several effects. First, it will deplete the trial from subjects due to censoring in certain aspects, leaving the study with less power for relevant calculations. Second, it will question the overall clinical competence of an institution. Most important, though, is that the subjects eventually will suffer from worse outcomes.

One of the studies performed was a large nationwide observational and comparative cohort study, which also had limitations. With non-randomised data, you will introduce bias and confounding when striving to compare different cohorts. Today, however, with various statistical methods and computer power, complex calculations can be performed to compensate for confounding factors or variable imbalances. With high-level subject matching and fitting of statistical functions, you can almost reach a situation similar to pseudorandomisation. However, when fitting

complex statistical functions to your datasets, you must always be aware of the risk of a situation called “overfitting”, leading to multicollinearity or other statistical problems. This may lead to non-useful data interpretation and a risk of non-justified conclusions. It is an excellent rule to keep studies as clean and straightforward as possible to get relevant and generalisable output.

As previously mentioned, an essential limitation in registries when performing retrospective comparisons is the problem with heterogenicity in aspects of each individual, clinically and anatomically, as well as each centre regarding performance or caseload. Bad performance or low caseload will sometimes act in a contagious way regarding the quality of output and results.

Overall limitations in the thesis

Regarding the three RCTs (I, II, IV), theoretical selection bias can be discussed in the sense of selection for treatment or not and for open or endovascular surgery. In the trial settings, with a comparison of two different treatments that are due for randomisation, this is not an issue. The complete subject workflow data are routinely available in official charts, examinations, and images. It is also complemented by data collection that is transferred directly to research files. In this way, information bias should not be a relevant issue, and there should not be any systematically targeted risk for information bias. Risks for information or data bias are increased at image interpretation and validations of clinical information, but as a single operator performed image interpretation, this eliminates the risk for interobserver variations. The optimal solution for handling part of the data collecting issues is validated core lab analyses, which have not been performed in any of these studies. Still, there is an essential advantage of an RCT, which is minimising the risk of confounding.

The national retrospective observational cohort trial is based on data imputation from two large registries. The external validity of the data has been examined on several occasions and has been considered acceptable[121 637]. Per definition, there is a selection bias regarding the choice of treatment, as this is not fully controlled, and many different vascular centres (~30) are involved. The selection and grouping of subjects depended on correct labelling and other interpretations done at the time of data filing. So, selection bias must be accounted for. The same counts for information bias regarding incorrect or missing filing and labelling. Also, the statistical characteristics in retrospective cohort studies have a lot of concerns with different forms of confounding that must be adjusted for if reliable, useful conclusions should be produced.

All the RCTs functionally have problems with the fact that they all suffer from an insufficient number of subjects, although the last RCT enrolled the precalculated

number of participants. The reason for an inadequate number of subjects is multifactorial. Besides health-related and other factors among the subjects, there are also concerns regarding individual physician and institutional factors that are in play. One reason is that the treatment of CLTI lesions is usually complex in terms of experience, material, and time, making enrolment less appealing. This numerical factor regarding enrolled subjects, highly limits the possibility of contributing with knowledge regarding drug eluting treatment, a knowledge that is highly wished [574].

Trial specific limitations

Paper I

The radiological success, as shown in this study, is not optimal, although similar in both groups. The reason is that the postinterventional analysis, with detailed measurements, was sometimes not performed in line with the procedure. When viewing all the images in the posttrial analysis, some of the treated stenoses, judged correctly treated at the intervention, still had low-grade residual stenoses (>30%). The median values of inflow and outflow diameters are 4.7mm (3.6-6.7) and 6.3mm (4.8-8.0), respectively. The figures, based on the more relevant inflow reference diameters, show median residual stenosis values of 30% (8-42) in POBA vs 17% (0-25) in DEB (p=0.107). There were insufficient subjects to perform a relevant subgroup analysis regarding this issue.

The non-significant heterogenicity regarding lesion location might also have caused potential bias, but this could not be significantly shown with the limited number of study subjects.

The technical procedural protocol with direct angioplasty might be a possible mechanism for suboptimal DEB results. The standard procedure currently implements a strategy with predilatation and vessel preparation, with frequent use of high-pressure balloons, before drug delivery. The reasons for treatment with direct angioplasty in the trial were the limited scientific knowledge concerning DEB performance at the time of the study initiation and the intent to simplify treatment as much as possible. This study was planned in the early era of drug eluting angioplasty for dysfunctional haemodialysis access, and at that time, complete knowledge regarding the technical performance of these new balloons was not established. In this situation, we opted for a strategy with direct PTA, as study protocols with similar features were used in ongoing studies at the time [524 527 589 661 662]. In the end, most subjects in the study received posttreatment angioplasty due to suboptimal primary PTA, with another standard PTA balloon or high-pressure PTA balloon, at the discretion of the performing interventionalist, in 65% vs 59 % (p=0.694), in the two groups, to finally reach a good angioplasty result.

A considerable number of AV fistula treatments were performed outside of the study protocol during the trial´s extended timeframe. This introduces potential bias, although apparent signs of such systemic bias could not be detected in the posttrial analysis.

The trial became underpowered as it was stopped before the planned inclusions were achieved, making the investigation of the pretrial hypothesis suboptimal. The reason for stopping the trial was a slow inclusion rate and a company initiated withdrawal of the product from the market from financial and company related structural perspectives. There were no safety or efficacy issues behind this decision. There are, however, other similar studies that have shown significant differences in treatment efficacy with a similar number of randomised participants[571].

Although the study product was withdrawn, the active substance (paclitaxel) is still widely used for treating dysfunctional haemodialysis fistulas and lesions in other vascular territories.

Paper II

The procedural technical success shown in the study was not optimal in comparison with similar studies [607 608 615 663 664], although there were no differences between groups. The reason is that postinterventional analysis with detailed measurements was sometimes not performed in line with the procedure as recommended. Also, the per protocol DUS at discharge showed stenosis (PSVR >2.0) in only four of the 14 subjects deemed as technical failures. When viewing all the images in the post-trial analysis, some of the treated stenoses, judged as correctly treated at the intervention, still had low grade residual stenoses (>30%). There was also an unexpectedly high incidence of predischarge retreatments of the index FP lesion; one case was in the BMS group, and four cases were in the DES group. The reason for this is unclear, and no common cause could be identified in these five patients, but all five had three open crural outflow vessels. Six study patients did not fully comply with the post-treatment antithrombotic regime, but non-compliance was evenly distributed in groups, and no association with early occlusions was found.

The study became underpowered and did not meet the calculated number of planned enrolments. The reason was that the study was prematurely stopped due to a very slow inclusion rate. The limited number of subjects makes all forms of subgroup analysis unrealistic. Ultimately, according to the pretrial statistical calculations, the study was not at this phase powered to prove a superiority regarding DES vs BMS. However, some other publications on BMS and DES report on a similar limited number of participants [309 574 606 610 665].

During the enrolment period, subjects were treated at our institution without being included in the study, which means that it is a non-consecutive randomisation. We

have not interpreted any potential systemic bias regarding the enrolment in the posttrial analysis.

The treatment of CLTI lesions is usually also complex, regarding time, material, and experience, and results may be impacted by the treating surgeon's experience and caseload. This might certainly also have affected the actual performance of both drug and non-drug eluting nitinol stenting in the FP lesions overall, statistically diluting a potential drug eluting effect.

Paper III

This is a non-randomised comparative cohort study to elucidate a research question requiring a randomised study to be conclusively answered. Such a study, the Swedepad[377], is ongoing and will offer new valuable information in the near future.

The DET group was smaller than the group receiving standard treatment, and confounding might have been caused by differences in treatment region and treatment complexity, even though the calculations were adjusted for other demographic factors. However, in an observational, non-randomised study, selection bias might always result in an imbalance between groups regarding factors affecting the outcome, whether group sizes are balanced or not.

Adjusting the data for anatomical location or modality was not feasible due to limited numbers. We primarily wanted to evaluate patients with and without DM as well as subjects with IC and CLTI patients separately. Too many additional adjustment variables would have introduced a high risk of an overfitted statistical model with a higher risk of multicollinearity, resulting in low generalizability and risk of inaccurate estimates, confidence intervals, and p-values. Therefore, only the adjustment variables that were considered the most important were selected as covariates.

Furthermore, as patients have been treated at different Swedish vascular centres, there are highly varying institution and operator caseloads, and several different types of balloons and stents have been used. This constitutes a theoretical reason for different technical results and treatment efficacies. The small number of patients in some subgroups also limited our ability to perform reliable statistical analyses, especially regarding secondary outcomes. This might also explain the fact that we were not able to demonstrate any benefits among CLTI patients without DM or among IC patients.

The endovascular technology regarding drug coated balloons and drug eluting stents has evolved significantly since 2013-2015, and the operators today probably have more knowledge regarding feasibility and better operational skills.

Paper IV

A significant limitation is the overall sparse number of subjects. Although the study was powered to prove a 50% reduction in the restenosis rate, all attempts to perform a subgroup analysis are unrealistic. We had calculated with a 10% loss of follow-up availability, but the fact that there were more deaths and amputations than expected with a limited number of objective timely evaluations of patency, this rendered us short of subjects for analysis and made the study formally underpowered. This limitation is undoubtedly also relevant regarding the interpretation of secondary endpoint variables.

There are, on the other hand, other publications on DCB and PTA reporting on a similarly limited number of participants[380 400 402 577].

It is important to highlight that during the enrolment period, a total of 158 patients were treated at our institution with crural angioplasty without being included in the study, which means that randomisation was non-consecutive. Only three patients were treated with crural DCB angioplasty outside the study protocol. We did not identify any potential systemic bias regarding the enrolment in the posttrial analysis when records of non-included patients were briefly compared with the study population.

Finally, this is a reminder that treatment of CLTI lesions is usually complex in terms of time, material, and experience, and the expertise and caseload of the treating surgeon and institution may heavily impact results. Remembering that our results are specific to the investigated device is also essential.

Scientific strength

Overall scientific strength of the thesis

Three papers report RCTs, minimising confounding and other statistical shortcomings. RCTs are the gold standard for clinical research concerning treatment methods. A single centre setting should also be considered a strength from an idealistic statistical perspective.

One trial is based on data from two well validated national quality registries, and this should be considered a strength, in the case of analyses of observational retrospective cohort studies, well known for statistical issues that must be handled in compensatory ways.

Reproducibility of the included trials

The lack of systematic labelling of the preinterventional, interventional, and postinterventional clinical or vascular status in all three RCTs is an important restriction for optimal reproducibility. On the other hand, there is an abundant amount of objective raw data regarding measurements and other gradings in all three studies that an external validator can interpret for reliable reproducibility.

Regarding the retrospective cohort study, certain aspects of these national registries have good availability of semi-objective labelling, grading, and categorisation, which may account for good reproducibility. However, relevant patient data can be missing for both systemic and stochastic reasons. There is international consensus regarding data registration in national vascular registries.

Points of perspectives

What about the future of drug eluting therapy in vascular surgery? The evolution will probably continue. If we follow cardiovascular services closely, we may get a glimpse of what lies ahead. Although CAD is a slightly different form of atherosclerotic disease, DES has taken over as the primary method in PCI, and their products also have newer immunomodulating substances in their coatings.

As ideas and principles for endovascular treatments are often imported from cardiac therapies, we will probably see further developments in pharmacomechanical products in the future, even for treating vessel stenoses and occlusions in PAD and malfunctioning haemodialysis access.

Results from the large Swedish national RCT[377](*ClinicalTrials.gov Identifier: NCT02051088*), monitoring drug eluting technology and relevant treatment outcomes are soon expected, hopefully helping the vascular community to achieve clarity regarding the efficacy of drug eluting treatment.

In certain situations, the issue of mechanics in lower limb arteriosclerosis and the concept of debulking or vessel preparation procedures are essential. We will probably see further technical development regarding the mechanical ability to counteract the calcium burden in the future to enable even better treatment effects in the long term. Easier handled and lower-profiled debulking gear will improve the technical results further, and the future role of drug adjunctive angioplasty will evolve into a drug deposition procedure to restrain the development of intimal hyperplasia.

With the improvement of endovascular techniques using DET, there will be a continuous reciprocal effect in the future for open revascularisation in general, but foremost regarding more complex open surgery in PAD, such as distal and pedal bypasses. This may also be true in AV fistula surgery as new methods with endovascular thermally assisted constructions increase and endovascular reinterventions become more efficient.

The complicated nature of these open procedures and the decreasing caseload will make it hard for the majority of future vascular surgeons to perform these with acceptable technical results. This is unfortunate, as open surgery in some very specific settings may still be superior, at least for the moment. The evolving situation described above will further affect the efficacy gap between these two

principal strategies with a simultaneous refinement of the DET results and a general deterioration of open surgical results. To counteract this phenomenon, already seen in some aspects, some form of centralisation of open vascular surgery needs to be discussed, otherwise, we will lose the opportunity in the future to perform these operations in a highly professional way in those highly selected cases that may have an indication for surgery, and still matching the results of endovascular treatment.

The future of endovascular therapy in PAD and haemodialysis access is probably bright, and as discussed, further improvements are expected. Locally delivered drugs on balloons or scaffolds will probably be a major part of these interventional technologies.

Conflict of interests

All papers are submitted for publication with approval from all authors. Manuscripts accepted for publication have gone through a peer-review process.

Project I: Limited financial support from COOK Medical. *(Treatment cost-neutral)*

Project II: Limited financial support from COOK Medical. *(Treatment cost-neutral)*

Project III: Nothing to disclose.

Project IV: Limited financial support from Boston Scientific. *(Treatment cost-neutral)*

Popular science summary of the thesis (English)

This doctoral thesis studies different aspects of improving treatment outcomes in minimally invasive vascular treatment in two predominant areas of vascular surgery, peripheral circulatory disorders to the lower extremities and poorly functioning blood vessel access for haemodialysis.

The treatment usually involves balloon bursting in some form, possibly supplemented with the insertion of a metal stent if the result looks unsatisfactory. These treatments give rise to an inflammatory reaction due to the trauma that occurs when the blood vessel opens up under high pressure. The inflammation leads to cell growth, which further risks cutting off blood flow. One way to counteract this inflammation and cell growth is to provide balloons and stents with a layer of chemotherapy that is secreted to the artery wall and slows down the inflammation. These chemotherapy drugs only have a local effect at the site of the treatment in the blood vessel and are given in small doses that do not affect the rest of the body.

The thesis investigates the effects of these drug balloons and drug stents in the treatment of blood vessel stenoses or occlusions in the femoral artery, lower leg arteries, and upper extremity haemodialysis access. These three studies have been conducted as direct comparisons between a drug product and standard treatment. The choice of treatment is made by lottery to be able to make the most accurate comparisons. No difference was seen in the first two studies, but the number of patients treated was probably too few to allow us to conclude with enough certainty. In the third study, which investigated the treatment of the lower leg arteries, we saw a possible benefit for the group treated with drug balloons, as this group had better composite results for survival and fewer amputations.

One sub-study consisted of a large registry study in which the Swedish Vascular Surgery Registry was coordinated with the Swedish National Diabetes Register. This study showed better results for patients with diabetes who suffered from amputation threatening circulatory impairment in the legs and were treated with the new drug eluting technique. They had better survival rates and fewer amputations.

The thesis cannot show an unambiguous superiority for the more modern drug-secreting balloon bursting technique, but individual results suggest a possible appealing balancing effect that needs to be more clearly evaluated in larger studies.

Popular science summary of the thesis (Swedish)

I denna doktorsavhandling studeras olika aspekter på förbättring av behandlingsresultaten vid minimalinvasiv vaskulär behandling inom två dominerande områden av kärlkirurgin, perifer cirkulationsrubbning till nedre extremiteter och dåligt fungerande blodkärlsaccess vid hemodialys.

Behandlingen innebär oftast ballongsprängning i någon form, eventuellt kompletterat med inläggning av metallstent om resultatet ser otillfredsställande ut. Dessa behandlingar ger upphov till en inflammatorisk reaktion pga. det trauma som sker när blodkärlet öppnas upp under högt tryck. Inflammationen leder till celltillväxt som riskerar att strypa blodflödet. Ett sätt att motverka denna inflammation och celltillväxt är att förse ballonger och stentar med ett lager av cellgifter som utsöndras till kärlväggen och bromsar inflammationen. Dessa cellgifter har bara lokal effekt på platsen för behandlingen i blodkärlet och ges i små doser som inte påverkar kroppen i övrigt.

Avhandlingen har undersökt effekterna av dessa drogballonger och drogstentar vid behandling av blodkärlsförändringar i lårartären, underbensartärerna och i konstgjord blodkärlsaccess på överarmar. Dessa tre undersökningar har genomförts som direkta jämförelser mellan drogbehandlad produkt och standardbehandling. Valet av behandling sker med lottdragning för att kunna göra de mest korrekta jämförelserna. I de två första studierna sågs ingen skillnad, men antalet behandlade patienter var för få för att kunna uttala sig med säkerhet beträffande behandlingsresultaten. Den tredje studien, som undersökte behandling av underbensartärerna såg en möjlig fördel för gruppen som behandlades med drogballong, eftersom denna grupp hade sammantaget bättre överlevnad och mindre antal amputationer.

En delstudie utgjordes av en stor registerstudie där det svenska kärlkirurgiska registret samkördes med det svenska diabetesregistret. Här sågs bättre resultat för patienter med diabetes som led av amputationshotande cirkulationsnedsättning i benen och som behandlades med den moderna drog utsöndrande tekniken. De hade också sammantaget bättre överlevnad och mindre antal amputationer.

Avhandlingen kan inte visa en entydig överlägsenhet för den mer moderna drogutsöndrande ballongsprängningstekniken, men enstaka resultat talar för en möjlig tilltalande behandlingseffekt som behöver värderas tydligare i större studier.

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Other relevant publications

The following publications[287 377] have been authored or coauthored by the author of this thesis and are scientifically relevant to the scientific field of this thesis regarding PAD and DM but are not part of the thesis.

Fransson T, Thörne J. In situ saphenous vein bypass grafting - still first line treatment? A prospective study comparing surgical results between diabetic and non-diabetic populations. Vasa. 2010 Feb;39(1):59-65. doi: 10.1024/0301-1526/a000006. PMID: 20186677.

Nordanstig J, James S, Andersson M, Andersson M, Danielsson P, Gillgren P, Delle M, Engström J, Fransson T, Hamoud M, Hilbertson A, Johansson P, Karlsson L, Kragsterman B, Lindgren H, Ludwigs K, Mellander S, Nyman N, Renlund H, Sigvant B, Skoog P, Starck J, Tegler G, Toivola A, Truedson M, Wahlgren CM, Wallinder J, Öjersjö A, Falkenberg M. Mortality with Paclitaxel-Coated Devices in Peripheral Artery Disease. N Engl J Med. 2020 Dec 24;383(26):2538-2546. doi: 10.1056/NEJMoa2005206. Epub 2020 Dec 9. PMID: 33296560.

References

1. Nikulainen V, Helmio P, Hakovirta H. Changes in rates of vascular procedure types and lower extremity amputations in Finland for 2007-2017 inclusive, a population cohort study of 69,523 revascularizations. *Int J Surg* 2019;72:118-25. doi: 10.1016/j.ijsu.2019.10.039 [published Online First: 20191105]
2. Ratnam L, Karunanithy N, Mailli L, et al. Dialysis Access Maintenance: Plain Balloon Angioplasty. *CardioVascular and Interventional Radiology* 2023;46(9):1136-43. doi: 10.1007/s00270-023-03441-x
3. Song P, Rudan D, Zhu Y, et al. Global, regional, and national prevalence and risk factors for peripheral artery disease in 2015: an updated systematic review and analysis. *Lancet Glob Health* 2019;7(8):e1020-e30. doi: 10.1016/S2214-109X(19)30255-4
4. Collaborators GBDPAD. Global burden of peripheral artery disease and its risk factors, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet Glob Health* 2023;11(10):e1553-e65. doi: 10.1016/S2214-109X(23)00355-8
5. Fowkes FG, Rudan D, Rudan I, et al. Comparison of global estimates of prevalence and risk factors for peripheral artery disease in 2000 and 2010: a systematic review and analysis. *Lancet* 2013;382(9901):1329-40. doi: 10.1016/S0140-6736(13)61249-0 [published Online First: 2013/08/07]
6. Primary P, Abramson BL, Al-Omran M, et al. Canadian Cardiovascular Society 2022 Guidelines for Peripheral Arterial Disease. *Can J Cardiol* 2022;38(5):560-87. doi: 10.1016/j.cjca.2022.02.029
7. Nordanstig J, Behrendt CA, Baumgartner I, et al. Editor's Choice -- European Society for Vascular Surgery (ESVS) 2024 Clinical Practice Guidelines on the Management of Asymptomatic Lower Limb Peripheral Arterial Disease and Intermittent Claudication. *Eur J Vasc Endovasc Surg* 2024;67(1):9-96. doi: 10.1016/j.ejvs.2023.08.067 [published Online First: 20231110]
8. Frank U, Nikol S, Belch J, et al. ESVM Guideline on peripheral arterial disease. *Vasa* 2019;48(Suppl 102):1-79. doi: 10.1024/0301-1526/a000834
9. Mahe G, Boge G, Bura-Riviere A, et al. Disparities Between International Guidelines (AHA/ESC/ESVS/ESVM/SVS) Concerning Lower Extremity Arterial Disease: Consensus of the French Society of Vascular Medicine (SFMV) and the French Society for Vascular and Endovascular Surgery (SCVE). *Ann Vasc Surg* 2021;72:1-56. doi: 10.1016/j.avsg.2020.11.011 [published Online First: 2020/12/29]
10. Aboyans V, Ricco JB, Bartelink MEL, et al. Editor's Choice - 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS). *Eur J Vasc Endovasc Surg*

2018;55(3):305-68. doi: 10.1016/j.ejvs.2017.07.018 [published Online First: 2017/08/31]
11. Fowkes FG, Aboyans V, Fowkes FJ, et al. Peripheral artery disease: epidemiology and global perspectives. *Nat Rev Cardiol* 2017;14(3):156-70. doi: 10.1038/nrcardio.2016.179 [published Online First: 20161117]
12. Criqui MH, Matsushita K, Aboyans V, et al. Lower Extremity Peripheral Artery Disease: Contemporary Epidemiology, Management Gaps, and Future Directions: A Scientific Statement From the American Heart Association. *Circulation* 2021;144(9):e171-e91. doi: 10.1161/CIR.0000000000001005 [published Online First: 20210728]
13. Bonaca MP, Nault P, Giugliano RP, et al. Low-Density Lipoprotein Cholesterol Lowering With Evolocumab and Outcomes in Patients With Peripheral Artery Disease: Insights From the FOURIER Trial (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk). *Circulation* 2018;137(4):338-50. doi: 10.1161/CIRCULATIONAHA.117.032235 [published Online First: 20171113]
14. Cacoub PP, Abola MT, Baumgartner I, et al. Cardiovascular risk factor control and outcomes in peripheral artery disease patients in the Reduction of Atherothrombosis for Continued Health (REACH) Registry. *Atherosclerosis* 2009;204(2):e86-92. doi: 10.1016/j.atherosclerosis.2008.10.023 [published Online First: 20081031]
15. Kochar A, Mulder H, Rockhold FW, et al. Cause of Death Among Patients With Peripheral Artery Disease: Insights From the EUCLID Trial. *Circ Cardiovasc Qual Outcomes* 2020;13(11):e006550. doi: 10.1161/CIRCOUTCOMES.120.006550 [published Online First: 20201112]
16. Anand SS, Bosch J, Eikelboom JW, et al. Rivaroxaban with or without aspirin in patients with stable peripheral or carotid artery disease: an international, randomised, double-blind, placebo-controlled trial. *Lancet* 2018;391(10117):219-29. doi: 10.1016/S0140-6736(17)32409-1 [published Online First: 20171110]
17. Bonaca MP, Scirica BM, Creager MA, et al. Vorapaxar in patients with peripheral artery disease: results from TRA2degreesP-TIMI 50. *Circulation* 2013;127(14):1522-9, 29e1-6. doi: 10.1161/CIRCULATIONAHA.112.000679 [published Online First: 20130315]
18. Creager MA, Matsushita K, Arya S, et al. Reducing Nontraumatic Lower-Extremity Amputations by 20% by 2030: Time to Get to Our Feet: A Policy Statement From the American Heart Association. *Circulation* 2021;143(17):e875-e91. doi: 10.1161/CIR.0000000000000967 [published Online First: 2021/03/26]
19. van Reijen NS, Hensing T, Santema TKB, et al. Outcomes of Conservative Treatment in Patients with Chronic Limb Threatening Ischaemia: A Systematic Review and Meta-Analysis. *Eur J Vasc Endovasc Surg* 2021;62(2):214-24. doi: 10.1016/j.ejvs.2021.01.005 [published Online First: 2021/03/07]
20. Libby P, Buring JE, Badimon L, et al. Atherosclerosis. *Nat Rev Dis Primers* 2019;5(1):56. doi: 10.1038/s41572-019-0106-z [published Online First: 20190816]
21. Behrooz L, Abumoawad A, Rizvi SHM, Hamburg NM. A modern day perspective on smoking in peripheral artery disease. *Front Cardiovasc Med* 2023;10:1154708. doi: 10.3389/fcvm.2023.1154708 [published Online First: 20230428]

22. Reitz KM, Althouse AD, Meyer J, et al. Association of Smoking With Postprocedural Complications Following Open and Endovascular Interventions for Intermittent Claudication. *JAMA Cardiol* 2022;7(1):45-54. doi: 10.1001/jamacardio.2021.3979 [published Online First: 2021/10/07]
23. Boyle JP, Honeycutt AA, Narayan KM, et al. Projection of diabetes burden through 2050: impact of changing demography and disease prevalence in the U.S. *Diabetes Care* 2001;24(11):1936-40. doi: 10.2337/diacare.24.11.1936 [published Online First: 2001/10/27]
24. Singh MV, Dokun AO. Diabetes mellitus in peripheral artery disease: Beyond a risk factor. *Frontiers in Cardiovascular Medicine* 2023;10 doi: 10.3389/fcvm.2023.1148040
25. An J, Nichols GA, Qian L, et al. Prevalence and incidence of microvascular and macrovascular complications over 15 years among patients with incident type 2 diabetes. *BMJ Open Diabetes Res Care* 2021;9(1) doi: 10.1136/bmjdrc-2020-001847 [published Online First: 2021/01/06]
26. Huang D, Refaat M, Mohammedi K, et al. Macrovascular Complications in Patients with Diabetes and Prediabetes. *Biomed Res Int* 2017;2017:7839101. doi: 10.1155/2017/7839101 [published Online First: 2017/12/15]
27. Viigimaa M, Sachinidis A, Toumpourleka M, et al. Macrovascular Complications of Type 2 Diabetes Mellitus. *Curr Vasc Pharmacol* 2020;18(2):110-16. doi: 10.2174/1570161117666190405165151 [published Online First: 2019/04/10]
28. Emerging Risk Factors C, Sarwar N, Gao P, et al. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. *Lancet* 2010;375(9733):2215-22. doi: 10.1016/S0140-6736(10)60484-9 [published Online First: 2010/07/09]
29. Conte MS, Bradbury AW, Kolh P, et al. Global Vascular Guidelines on the Management of Chronic Limb-Threatening Ischemia. *Eur J Vasc Endovasc Surg* 2019;58(1S):S1-S109 e33. doi: 10.1016/j.ejvs.2019.05.006 [published Online First: 2019/06/12]
30. McDermott MM. Lower extremity manifestations of peripheral artery disease: the pathophysiologic and functional implications of leg ischemia. *Circ Res* 2015;116(9):1540-50. doi: 10.1161/CIRCRESAHA.114.303517 [published Online First: 2015/04/25]
31. Broich EM, Reinecke H, Malyar NM, et al. Long-term mortality after invasive diagnostic and endovascular revascularization in PAD patients. *Int Angiol* 2016;35(5):516-25. [published Online First: 2015/09/26]
32. Baubeta Fridh E, Andersson M, Thuresson M, et al. Amputation Rates, Mortality, and Pre-operative Comorbidities in Patients Revascularised for Intermittent Claudication or Critical Limb Ischaemia: A Population Based Study. *Eur J Vasc Endovasc Surg* 2017;54(4):480-86. doi: 10.1016/j.ejvs.2017.07.005 [published Online First: 2017/08/12]
33. Dakhel A, Zarrouk M, Ekelund J, et al. Higher long-term cardiovascular morbidity after open surgery for intermittent claudication caused by infrainguinal atherosclerotic disease in patients with diabetes - a nationwide observational cohort study. *Vasa* 2021;50(3):224-30. doi: 10.1024/0301-1526/a000929 [published Online First: 2020/12/19]

34. Dakhel A, Zarrouk M, Ekelund J, et al. Worse cardiovascular prognosis after endovascular surgery for intermittent claudication caused by infrainguinal atherosclerotic disease in patients with diabetes. *Ther Adv Endocrinol Metab* 2020;11:2042018820960294. doi: 10.1177/2042018820960294 [published Online First: 2020/11/06]
35. Lilja E, Gottsater A, Miftaraj M, et al. The impact of diabetes mellitus on major amputation among patients with chronic limb threatening ischemia undergoing elective endovascular therapy- a nationwide propensity score adjusted analysis. *J Diabetes Complications* 2021;35(2):107675. doi: 10.1016/j.jdiacomp.2020.107675 [published Online First: 2020/08/24]
36. Bakken AM, Palchik E, Hart JP, et al. Impact of diabetes mellitus on outcomes of superficial femoral artery endoluminal interventions. *J Vasc Surg* 2007;46(5):946-58; discussion 58. doi: 10.1016/j.jvs.2007.06.047
37. Abularrage CJ, Conrad MF, Hackney LA, et al. Long-term outcomes of diabetic patients undergoing endovascular infrainguinal interventions. *J Vasc Surg* 2010;52(2):314-22.e1-4. doi: 10.1016/j.jvs.2010.03.015 [published Online First: 20100629]
38. Shammas AN, Jeon-Slaughter H, Tsai S, et al. Major Limb Outcomes Following Lower Extremity Endovascular Revascularization in Patients With and Without Diabetes Mellitus. *J Endovasc Ther* 2017;24(3):376-82. doi: 10.1177/1526602817705135 [published Online First: 20170425]
39. Yap T, Silickas J, Weerakkody R, et al. Predictors of outcome in diabetic patients undergoing infrapopliteal endovascular revascularization for chronic limb-threatening ischemia. *Journal of Vascular Surgery* 2022;75(2):618-24. doi: 10.1016/j.jvs.2021.09.040
40. Faglia E, Clerici G, Clerissi J, et al. Early and Five-year Amputation and Survival Rate of Diabetic Patients with Critical Limb Ischemia: Data of a Cohort Study of 564 Patients. *European Journal of Vascular and Endovascular Surgery* 2006;32(5):484-90. doi: 10.1016/j.ejvs.2006.03.006
41. Faglia E, Clerici G, Clerissi J, et al. Long-term prognosis of diabetic patients with critical limb ischemia: a population-based cohort study. *Diabetes Care* 2009;32(5):822-7. doi: 10.2337/dc08-1223 [published Online First: 2009/02/19]
42. Suzuki K, Iida O, Yamauchi Y, et al. Impact of Diabetes Mellitus on Critical Limb Ischemia With Below the Knee Disease: Japan Below-the-Knee Artery Treatment Subanalysis. *Angiology* 2020;71(5):444-51. doi: 10.1177/0003319713499606 [published Online First: 2013/08/24]
43. Spreen MI, Gremmels H, Teraa M, et al. Diabetes is associated with decreased limb survival in patients with critical limb ischemia: Pooled data from two randomized controlled trials. *Diabetes Care* 2016;39(11):2058-64. doi: 10.2337/dc16-0850
44. Neupane S, Edla S, Maidona E, et al. Long-term outcomes of patients with diabetes mellitus undergoing percutaneous intervention for popliteal and infrapopliteal peripheral arterial disease. *Catheterization and Cardiovascular Interventions* 2018;92(1):117-23. doi: 10.1002/ccd.27571
45. Faglia E, Clerici G, Losa S, et al. Limb revascularization feasibility in diabetic patients with critical limb ischemia: Results from a cohort of 344 consecutive unselected diabetic patients evaluated in 2009. *Diabetes Research and Clinical Practice* 2012;95(3):364-71. doi: 10.1016/j.diabres.2011.10.033

46. Fitridge R, Chuter V, Mills J, et al. Editor's Choice – The Intersocietal IWGDF, ESVS, SVS Guidelines on Peripheral Artery Disease in People With Diabetes Mellitus and a Foot Ulcer. *European Journal of Vascular and Endovascular Surgery* 2023;66(4):454-83. doi: 10.1016/j.ejvs.2023.07.020
47. Lee MS, Rha SW, Han SK, et al. Comparison of diabetic and non-diabetic patients undergoing endovascular revascularization for peripheral arterial disease. *Journal of Invasive Cardiology* 2015;27(3):167-71.
48. Witso E, Ronningen H. Lower limb amputations: registration of all lower limb amputations performed at the University Hospital of Trondheim, Norway, 1994-1997. *Prosthet Orthot Int* 2001;25(3):181-5.
49. Siitonen OI, Niskanen LK, Laakso M, et al. Lower-extremity amputations in diabetic and nondiabetic patients. A population-based study in eastern Finland. *Diabetes Care* 1993;16(1):16-20.
50. Holstein P, Ellitsgaard N, Olsen BB, Ellitsgaard V. Decreasing incidence of major amputations in people with diabetes. *Diabetologia* 2000;43(7):844-7.
51. Zimmet P, Alberti KG, Magliano DJ, Bennett PH. Diabetes mellitus statistics on prevalence and mortality: facts and fallacies. *Nat Rev Endocrinol* 2016;12(10):616-22. doi: 10.1038/nrendo.2016.105 [published Online First: 20160708]
52. Luan J, Xu J, Zhong W, et al. Adverse Prognosis of Peripheral Artery Disease Treatments Associated With Diabetes: A Comprehensive Meta-Analysis. *Angiology* 2022;73(4):318-30. doi: 10.1177/00033197211042494
53. American Diabetes A. Peripheral arterial disease in people with diabetes. *Diabetes Care* 2003;26(12):3333-41. doi: 10.2337/diacare.26.12.3333
54. Kamil S, Sehested TSG, Carlson N, et al. Diabetes and risk of peripheral artery disease in patients undergoing first-time coronary angiography between 2000 and 2012 - a nationwide study. *BMC Cardiovasc Disord* 2019;19(1):234. doi: 10.1186/s12872-019-1213-1 [published Online First: 20191024]
55. Ciavarella A, Silletti A, Mustacchio A, et al. Angiographic evaluation of the anatomic pattern of arterial obstructions in diabetic patients with critical limb ischaemia. *Diabete Metab* 1993;19(6):586-9.
56. Chuter V, Schaper N, Mills J, et al. Effectiveness of revascularisation for the ulcerated foot in patients with diabetes and peripheral artery disease: A systematic review. *Diabetes/Metabolism Research and Reviews* 2023 doi: 10.1002/dmrr.3700
57. Baubeta Fridh E, Andersson M, Thuresson M, et al. Editor's Choice - Impact of Comorbidity, Medication, and Gender on Amputation Rate Following Revascularisation for Chronic Limb Threatening Ischaemia. *Eur J Vasc Endovasc Surg* 2018;56(5):681-88. doi: 10.1016/j.ejvs.2018.06.003 [published Online First: 2018/08/11]
58. Kotov A, Heidemann F, Kuchenbecker J, et al. Sex Disparities in Long Term Outcomes After Open Surgery for Chronic Limb Threatening Ischaemia: A Propensity Score Matched Analysis of Health Insurance Claims. *Eur J Vasc Endovasc Surg* 2021;61(3):423-29. doi: 10.1016/j.ejvs.2020.11.006 [published Online First: 2020/12/19]
59. DeRubertis BG, Vouyouka A, Rhee SJ, et al. Percutaneous intervention for infrainguinal occlusive disease in women: equivalent outcomes despite increased

severity of disease compared with men. *J Vasc Surg* 2008;48(1):150-7; discussion 57-8.
60. Belkin M, Conte MS, Donaldson MC, et al. The impact of gender on the results of arterial bypass with in situ greater saphenous vein. *Am J Surg* 1995;170(2):97-102.
61. Sigvant B, Wiberg-Hedman K, Bergqvist D, et al. A population-based study of peripheral arterial disease prevalence with special focus on critical limb ischemia and sex differences. *J Vasc Surg* 2007;45(6):1185-91. doi: 10.1016/j.jvs.2007.02.004 [published Online First: 2007/06/05]
62. Stavroulakis K, Donas KP, Torsello G, et al. Gender-related long-term outcome of primary femoropopliteal stent placement for peripheral artery disease. *Journal of Endovascular Therapy* 2015;22(1):31-37. doi: 10.1177/1526602814564382
63. Lindgren H, Gottsäter A, Hermansson K, et al. Gender differences in outcome after stent treatment of lesions in the femoropopliteal segment. *Scand J Surg* 2012;101(3):177-83. doi: 10.1177/145749691210100307
64. Porras CP, Bots ML, Teraa M, et al. Differences in Symptom Presentation in Women and Men with Confirmed Lower Limb Peripheral Artery Disease: A Systematic Review and Meta-Analysis. *European Journal of Vascular and Endovascular Surgery* 2022;63(4):602-12. doi: 10.1016/j.ejvs.2021.12.039
65. Lee MH, Li PY, Li B, et al. A systematic review and meta-analysis of sex- and gender-based differences in presentation severity and outcomes in adults undergoing major vascular surgery. *J Vasc Surg* 2022;76(2):581-94 e25. doi: 10.1016/j.jvs.2022.02.030 [published Online First: 20220305]
66. Gallagher KA, Meltzer AJ, Ravin RA, et al. Gender differences in outcomes of endovascular treatment of infrainguinal peripheral artery disease. *Vasc Endovascular Surg* 2011;45(8):703-11. doi: 10.1177/1538574411418008 [published Online First: 20110913]
67. Mazari FA, Khan JA, Samuel N, et al. Long-term outcomes of a randomized clinical trial of supervised exercise, percutaneous transluminal angioplasty or combined treatment for patients with intermittent claudication due to femoropopliteal disease. *Br J Surg* 2017;104(1):76-83. doi: 10.1002/bjs.10324 [published Online First: 20161020]
68. Fakhry F, Rouwet EV, Den Hoed PT, et al. Long-term clinical effectiveness of supervised exercise therapy versus endovascular revascularization for intermittent claudication from a randomized clinical trial. *British Journal of Surgery* 2013;100(9):1164-71. doi: 10.1002/bjs.9207
69. Spronk S, Bosch JL, den Hoed PT, et al. Intermittent claudication: clinical effectiveness of endovascular revascularization versus supervised hospital-based exercise training--randomized controlled trial. *Radiology* 2009;250(2):586-95. doi: 10.1148/radiol.2501080607
70. Whyman MR, Fowkes FGR, Kerracher EMG, et al. Is intermittent claudication improved by percutaneous transluminal angioplasty? A randomized controlled trial. *Journal of Vascular Surgery* 1997;26(4):551-57. doi: 10.1016/S0741-5214(97)70052-1
71. Perkins JMT, Collin J, Creasy TS, et al. Exercise training versus angioplasty for stable claudication. Long and medium term results of a prospective, randomised trial.

European Journal of Vascular and Endovascular Surgery 1996;11(4):409-13. doi: 10.1016/S1078-5884(96)80171-7
72. Klaphake S, Fakhry F, Rouwet EV, et al. Long-term Follow-up of a Randomized Clinical Trial Comparing Endovascular Revascularization Plus Supervised Exercise With Supervised Exercise Only for Intermittent Claudication. *Ann Surg* 2022;276(6):e1035-e43. doi: 10.1097/SLA.0000000000004712 [published Online First: 20201223]
73. Jacobsen A, Houlind KC, Rai A. Life-style counseling program and supervised exercise improves walking distance and quality of life in patients with intermittent claudication. *Physiother Theory Pract* 2022;38(13):2629-39. doi: 10.1080/09593985.2021.1970866 [published Online First: 20210830]
74. Hageman D, Fokkenrood HJP, Gommans LNM, et al. Supervised exercise therapy versus home-based exercise therapy versus walking advice for intermittent claudication. *Cochrane Database of Systematic Reviews* 2018;2018(4) doi: 10.1002/14651858.CD005263.pub4
75. Watson L, Ellis B, Leng GC. Exercise for intermittent claudication. *Cochrane Database of Systematic Reviews* 2008(4) doi: 10.1002/14651858.CD000990.pub2
76. Fowkes FG, Gillespie IN. Angioplasty (versus non surgical management) for intermittent claudication. *Cochrane Database Syst Rev* 2000(2):CD000017. doi: 10.1002/14651858.CD000017
77. Lindgren HIV, Qvarfordt P, Bergman S, et al. Primary Stenting of the Superficial Femoral Artery in Patients with Intermittent Claudication Has Durable Effects on Health-Related Quality of Life at 24 Months: Results of a Randomized Controlled Trial. *Cardiovasc Intervent Radiol* 2018;41(6):872-81. doi: 10.1007/s00270-018-1925-0 [published Online First: 2018/03/10]
78. Lindgren H, Qvarfordt P, Akesson M, et al. Primary Stenting of the Superficial Femoral Artery in Intermittent Claudication Improves Health Related Quality of Life, ABI and Walking Distance: 12 Month Results of a Controlled Randomised Multicentre Trial. *Eur J Vasc Endovasc Surg* 2017;53(5):686-94. doi: 10.1016/j.ejvs.2017.01.026 [published Online First: 2017/04/05]
79. Agnelli G, Belch JJF, Baumgartner I, et al. Morbidity and mortality associated with atherosclerotic peripheral artery disease: A systematic review. *Atherosclerosis* 2020;293:94-100. doi: 10.1016/j.atherosclerosis.2019.09.012 [published Online First: 2019/10/14]
80. Duff S, Mafilios MS, Bhounsule P, Hasegawa JT. The burden of critical limb ischemia: a review of recent literature. *Vasc Health Risk Manag* 2019;15:187-208. doi: 10.2147/VHRM.S209241 [published Online First: 2019/07/17]
81. Rollins KE, Jackson D, Coughlin PA. Meta-analysis of contemporary short- and long-term mortality rates in patients diagnosed with critical leg ischaemia. *Br J Surg* 2013;100(8):1002-8. doi: 10.1002/bjs.9127 [published Online First: 2013/05/08]
82. Soga Y, Iida O, Takahara M, et al. Two-year life expectancy in patients with critical limb ischemia. *JACC Cardiovasc Interv* 2014;7(12):1444-9. doi: 10.1016/j.jcin.2014.06.018 [published Online First: 2014/12/20]
83. Sigvant B, Hasvold P, Kragsterman B, et al. Cardiovascular outcomes in patients with peripheral arterial disease as an initial or subsequent manifestation of atherosclerotic disease: Results from a Swedish nationwide study. *J Vasc Surg*

2017;66(2):507-14 e1. doi: 10.1016/j.jvs.2017.01.067 [published Online First: 2017/04/24]
84. Sigvant B, Lundin F, Wahlberg E. The Risk of Disease Progression in Peripheral Arterial Disease is Higher than Expected: A Meta-Analysis of Mortality and Disease Progression in Peripheral Arterial Disease. *Eur J Vasc Endovasc Surg* 2016;51(3):395-403. doi: 10.1016/j.ejvs.2015.10.022 [published Online First: 2016/01/19]
85. Abu Dabrh AM, Steffen MW, Undavalli C, et al. The natural history of untreated severe or critical limb ischemia. *J Vasc Surg* 2015;62(6):1642-51 e3. doi: 10.1016/j.jvs.2015.07.065 [published Online First: 2015/09/24]
86. Patel K, Liu Y, Etaee F, et al. Differences Between Patients With Intermittent Claudication and Critical Limb Ischemia Undergoing Endovascular Intervention: Insights From the Excellence in Peripheral Artery Disease Registry. *Circ Cardiovasc Interv* 2021;14(11):e010635. doi: 10.1161/circinterventions.121.010635 [published Online First: 20211027]
87. Rueda CA, Nehler MR, Perry DJ, et al. Patterns of artery disease in 450 patients undergoing revascularization for critical limb ischemia: implications for clinical trial design. *J Vasc Surg* 2008;47(5):995-9; discussion 99-1000.
88. Hardman RL, Jazaeri O, Yi J, et al. Overview of classification systems in peripheral artery disease. *Semin Intervent Radiol* 2014;31(4):378-88. doi: 10.1055/s-0034-1393976
89. Fontaine R, Kim M, Kieny R. [Surgical treatment of peripheral circulation disorders]. *Helv Chir Acta* 1954;21(5-6):499-533.
90. Rutherford RB, Baker JD, Ernst C, et al. Recommended standards for reports dealing with lower extremity ischemia: revised version. *J Vasc Surg* 1997;26(3):517-38. doi: 10.1016/s0741-5214(97)70045-4 [published Online First: 1997/10/06]
91. Norgren L, Hiatt WR, Dormandy JA, et al. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). *Eur J Vasc Endovasc Surg* 2007;33 Suppl 1:S1-75. doi: 10.1016/j.ejvs.2006.09.024 [published Online First: 2006/12/05]
92. Jaff MR, White CJ, Hiatt WR, et al. An update on methods for revascularization and expansion of the TASC lesion classification to include below-the-knee arteries: A supplement to the inter-society consensus for the management of peripheral arterial disease (TASC II): The TASC steering committee. *Catheter Cardiovasc Interv* 2015;86(4):611-25. doi: 10.1002/ccd.26122 [published Online First: 20150810]
93. Mills JL, Sr. Update and validation of the Society for Vascular Surgery wound, ischemia, and foot infection threatened limb classification system. *Semin Vasc Surg* 2014;27(1):16-22. doi: 10.1053/j.semvascsurg.2014.12.002 [published Online First: 20141210]
94. . Smoking Cessation: A Report of the Surgeon General. Washington (DC)2020.
95. Balletshofer B, Böckler D, Diener H, et al. Position Paper on the Diagnosis and Treatment of Peripheral Arterial Disease (PAD) in People with Diabetes Mellitus. *Experimental and Clinical Endocrinology and Diabetes* 2022;130:S127-S36. doi: 10.1055/a-1624-3631
96. Twine CP, Kakkos SK, Aboyans V, et al. Editor's Choice - European Society for Vascular Surgery (ESVS) 2023 Clinical Practice Guidelines on Antithrombotic

Therapy for Vascular Diseases. *Eur J Vasc Endovasc Surg* 2023;65(5):627-89. doi: 10.1016/j.ejvs.2023.03.042 [published Online First: 2023/04/06]
97. Antithrombotic Trialists C. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 2002;324(7329):71-86. doi: 10.1136/bmj.324.7329.71
98. Committee CS. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). CAPRIE Steering Committee. *Lancet* 1996;348(9038):1329-39. doi: 10.1016/s0140-6736(96)09457-3
99. Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J* 2020;41(1):111-88. doi: 10.1093/eurheartj/ehz455
100. Masson W, Lobo M, Barbagelata L, et al. Effects of lipid-lowering therapy on major adverse limb events in patients with peripheral arterial disease: A meta-analysis of randomized clinical trials. *Vascular* 2022;30(6):1134-41. doi: 10.1177/17085381211043952
101. Kumbhani DJ, Steg PG, Cannon CP, et al. Statin therapy and long-term adverse limb outcomes in patients with peripheral artery disease: insights from the REACH registry. *Eur Heart J* 2014;35(41):2864-72. doi: 10.1093/eurheartj/ehu080 [published Online First: 20140228]
102. Mancia G, Kreutz R, Brunstrom M, et al. 2023 ESH Guidelines for the management of arterial hypertension The Task Force for the management of arterial hypertension of the European Society of Hypertension: Endorsed by the International Society of Hypertension (ISH) and the European Renal Association (ERA). *J Hypertens* 2023;41(12):1874-2071. doi: 10.1097/HJH.0000000000003480 [published Online First: 20230926]
103. Nordanstig J, Behrendt CA, Bradbury AW, et al. Peripheral arterial disease (PAD) - A challenging manifestation of atherosclerosis. *Prev Med* 2023;171:107489. doi: 10.1016/j.ypmed.2023.107489 [published Online First: 20230407]
104. Heart Outcomes Prevention Evaluation Study I, Yusuf S, Sleight P, et al. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *N Engl J Med* 2000;342(3):145-53. doi: 10.1056/NEJM200001203420301
105. Jansen SCP, Hoorweg BBN, Hoeks SE, et al. A systematic review and meta-analysis of the effects of supervised exercise therapy on modifiable cardiovascular risk factors in intermittent claudication. *J Vasc Surg* 2019;69(4):1293-308 e2. doi: 10.1016/j.jvs.2018.10.069 [published Online First: 20190215]
106. Bonaca MP, Bauersachs RM, Anand SS, et al. Rivaroxaban in Peripheral Artery Disease after Revascularization. *N Engl J Med* 2020;382(21):1994-2004. doi: 10.1056/NEJMoa2000052 [published Online First: 2020/03/30]
107. Eikelboom JW, Connolly SJ, Bosch J, et al. Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease. *N Engl J Med* 2017;377(14):1319-30. doi: 10.1056/NEJMoa1709118 [published Online First: 20170827]
108. National Kidney F. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis* 2002;39(2 Suppl 1):S1-266.

109. National Kidney F. KDOQI Clinical Practice Guideline for Hemodialysis Adequacy: 2015 update. *Am J Kidney Dis* 2015;66(5):884-930. doi: 10.1053/j.ajkd.2015.07.015
110. Lok CE, Huber TS, Orchanian-Cheff A, Rajan DK. Arteriovenous Access for Hemodialysis: A Review. *JAMA* 2024 doi: 10.1001/jama.2024.0535 [published Online First: 20240318]
111. Sheaffer WW, Hangge PT, Chau AH, et al. Minimally Invasive Limited Ligation Endoluminal-Assisted Revision (MILLER): A Review of the Available Literature and Brief Overview of Alternate Therapies in Dialysis Associated Steal Syndrome. *J Clin Med* 2018;7(6) doi: 10.3390/jcm7060128 [published Online First: 20180529]
112. Yu SH, Cook PR, Canty TG, et al. Hemodialysis-related steal syndrome: predictive factors and response to treatment with the distal revascularization-interval ligation procedure. *Ann Vasc Surg* 2008;22(2):210-4. doi: 10.1016/j.avsg.2007.12.005
113. Lok CE, Rajan DK. KDOQI 2019 Vascular Access Guidelines: What Is New. *Seminars in Interventional Radiology* 2022;39(1):3-8. doi: 10.1055/s-0041-1740937
114. Putra G, Soebroto H, Sembiring YE, et al. The longevity of temporary hemodialysis catheters by insertion site in patients undergoing hemodialysis: systematic review. *Italian Journal of Vascular and Endovascular Surgery* 2023;30(3):100-06. doi: 10.23736/S1824-4777.23.01600-5
115. Ravani P, Palmer SC, Oliver MJ, et al. Associations between hemodialysis access type and clinical outcomes: a systematic review. *J Am Soc Nephrol* 2013;24(3):465-73. doi: 10.1681/ASN.2012070643 [published Online First: 2013/02/23]
116. Schmidli J, Widmer MK, Basile C, et al. Editor's Choice – Vascular Access: 2018 Clinical Practice Guidelines of the European Society for Vascular Surgery (ESVS). *European Journal of Vascular and Endovascular Surgery* 2018;55(6):757-818. doi: 10.1016/j.ejvs.2018.02.001
117. Wasse H. Catheter-related mortality among ESRD patients. *Semin Dial* 2008;21(6):547-9. doi: 10.1111/j.1525-139X.2008.00500.x [published Online First: 2008/11/13]
118. Lok CE, Moist L. KDOQI 2019 Vascular Access Guidelines: What Is New? *Adv Chronic Kidney Dis* 2020;27(3):171-76. doi: 10.1053/j.ackd.2020.02.003 [published Online First: 2020/09/07]
119. Roy-Chaudhury P, Sukhatme VP, Cheung AK. Hemodialysis vascular access dysfunction: a cellular and molecular viewpoint. *J Am Soc Nephrol* 2006;17(4):1112-27. doi: 10.1681/ASN.2005050615 [published Online First: 2006/03/28]
120. Lee T, Roy-Chaudhury P. Advances and new frontiers in the pathophysiology of venous neointimal hyperplasia and dialysis access stenosis. *Adv Chronic Kidney Dis* 2009;16(5):329-38. doi: 10.1053/j.ackd.2009.06.009 [published Online First: 2009/08/22]
121. Troeng T, Malmstedt J, Bjorck M. External validation of the Swedvasc registry: a first-time individual cross-matching with the unique personal identity number. *Eur J Vasc Endovasc Surg* 2008;36(6):705-12. doi: 10.1016/j.ejvs.2008.08.017 [published Online First: 2008/10/15]

122. Eliasson B, Gudbjornsdottir S. Diabetes care--improvement through measurement. *Diabetes Res Clin Pract* 2014;106 Suppl 2:S291-4. doi: 10.1016/S0168-8227(14)70732-6 [published Online First: 2015/01/01]
123. Hedin U, Welander G. Upper-arm hemodialysis access in Sweden. *J Vasc Access* 2017;18(Suppl. 1):110-13. doi: 10.5301/jva.5000679 [published Online First: 20170305]
124. Matas R. I. An Operation for the Radical Cure of Aneurism based upon Arteriorrhaphy. *Ann Surg* 1903;37(2):161-96.
125. Matas R. Ligation of the Abdominal Aorta: Report of the Ultimate Result, One Year, Five Months and Nine Days after Ligation of the Abdominal Aorta for Aneurism at the Bifurcation. *Ann Surg* 1925;81(2):457-64. doi: 10.1097/00000658-192502010-00004
126. Carrel A, Guthrie CC. Anastomosis of blood vessels by the patching method and transplantation of the kidney. 1906 [classical article]. *Yale J Biol Med* 2001;74(4):243-7.
127. Leriche R, Morel A. The Syndrome of Thrombotic Obliteration of the Aortic Bifurcation. *Ann Surg* 1948;127(2):193-206. doi: 10.1097/00000658-194802000-00001
128. Murray DW, Jaques LB, Perrett TS, Best CH. Heparin and Vascular Occlusion. *Can Med Assoc J* 1936;35(6):621-2.
129. Murray GD, Best CH. The Use of Heparin in Thrombosis. *Ann Surg* 1938;108(2):163-77. doi: 10.1097/00000658-193808000-00002
130. Best CH. Heparin and Thrombosis. *Br Med J* 1938;2(4062):977-1004 1. doi: 10.1136/bmj.2.4062.977
131. Best CH, Cowan C, Maclean DL. Heparin and the formation of white thrombi. *J Physiol* 1938;92(1):20-31. doi: 10.1113/jphysiol.1938.sp003580
132. Testart J. Jean Kunlin (1904-1991). *Ann Vasc Surg* 1995;9 Suppl:S1-6.
133. Menzoian JO, Koshar AL, Rodrigues N. Alexis Carrel, Rene Leriche, Jean Kunlin, and the history of bypass surgery. *J Vasc Surg* 2011;54(2):571-4. doi: 10.1016/j.jvs.2011.04.028 [published Online First: 20110612]
134. Hall KV. The great saphenous vein used in situ as an arterial shunt after extirpation of the vein valves. A preliminary report. *Surgery* 1962;51:492-5.
135. Leather RP, Powers SR, Karmody AM. A reappraisal of the in situ saphenous vein arterial bypass: its use in limb salvage. *Surgery* 1979;86(3):453-61.
136. Shah DM, Darling RC, 3rd, Chang BB, et al. Long-term results of in situ saphenous vein bypass. Analysis of 2058 cases. *Ann Surg* 1995;222(4):438-46; discussion 46-8. doi: 10.1097/00000658-199510000-00003
137. Watelet J, Cheysson E, Poels D, et al. In situ versus reversed saphenous vein for femoropopliteal bypass: a prospective randomized study of 100 cases. *Ann Vasc Surg* 1987;1(4):441-52. doi: 10.1016/S0890-5096(06)60729-2
138. Watelet J, Soury P, Menard JF, et al. Femoropopliteal bypass: in situ or reversed vein grafts? Ten-year results of a randomized prospective study. *Ann Vasc Surg* 1997;11(5):510-9. doi: 10.1007/s100169900083
139. Harris PL, Veith FJ, Shanik GD, et al. Prospective randomized comparison of in situ and reversed infrapopliteal vein grafts. *Br J Surg* 1993;80(2):173-6. doi: 10.1002/bjs.1800800213

140. Moody AP, Edwards PR, Harris PL. In situ versus reversed femoropopliteal vein grafts: long-term follow-up of a prospective, randomized trial. *Br J Surg* 1992;79(8):750-2. doi: 10.1002/bjs.1800790809
141. Wengerter KR, Veith FJ, Gupta SK, et al. Prospective randomized multicenter comparison of in situ and reversed vein infrapopliteal bypasses. *J Vasc Surg* 1991;13(2):189-97; discussion 97-9.
142. Oudot J, Beaconsfield P. Thrombosis of the aortic bifurcation treated by resection and homograft replacement; report of five cases. *AMA Arch Surg* 1953;66(3):365-74. doi: 10.1001/archsurg.1953.01260030380012
143. Oudot J. [A new case of graft of the aortic bifurcation]. *Mem Acad Chir (Paris)* 1951;77(33-34):1035-6.
144. Oudot J. [A second case of graft of the aortic bifurcation for thrombosis]. *Mem Acad Chir (Paris)* 1951;77(20-21):644-5.
145. Oudot J. [Graft of the aortic bifurcation from the renal arteries to external iliac arteries for thromboarteritis]. *Mem Acad Chir (Paris)* 1951;77(20-21):642-4.
146. Freeman NE, Leeds FH. Operations on large arteries; application of recent advances. *Calif Med* 1952;77(4):229-33.
147. Carrea R, Molins M, Murphy G. [Surgery of spontaneous thrombosis of the internal carotid in the neck; carotido-carotid anastomosis; case report and analysis of the literature on surgical cases]. *Medicina (B Aires)* 1955;15(1):20-9.
148. DeBakey ME. Successful carotid endarterectomy for cerebrovascular insufficiency. Nineteen-year follow-up. *JAMA* 1975;233(10):1083-5.
149. Eastcott HH, Pickering GW, Rob CG. Reconstruction of internal carotid artery in a patient with intermittent attacks of hemiplegia. *Lancet* 1954;267(6846):994-6. doi: 10.1016/s0140-6736(54)90544-9
150. Dubost C, Allary M, Oeconomos N. Resection of an aneurysm of the abdominal aorta: reestablishment of the continuity by a preserved human arterial graft, with result after five months. *AMA Arch Surg* 1952;64(3):405-8.
151. Dubost C. First successful resection of an aneurysm of the abdominal aorta with restoration of the continuity by a human arterial graft. *World J Surg* 1982;6(2):256-7. doi: 10.1007/BF01654704
152. Voorhees AB, Jr., Jaretzki A, 3rd, Blakemore AH. The use of tubes constructed from vinyon "N" cloth in bridging arterial defects. *Ann Surg* 1952;135(3):332-6. doi: 10.1097/00000658-195203000-00006
153. Crawford ES, Bomberger RA, Glaeser DH, et al. Aortoiliac occlusive disease: factors influencing survival and function following reconstructive operation over a twenty-five-year period. *Surgery* 1981;90(6):1055-67.
154. Szilagyi DE, Elliott JP, Jr., Smith RF, et al. A thirty-year survey of the reconstructive surgical treatment of aortoiliac occlusive disease. *J Vasc Surg* 1986;3(3):421-36. doi: 10.1067/mva.1986.avs0030421
155. Scali ST, Arnaoutakis DJ, Neal D, et al. Association between surgeon case volume and years of practice experience with open abdominal aortic aneurysm repair outcomes. *J Vasc Surg* 2021;73(4):1213-26 e2. doi: 10.1016/j.jvs.2020.07.065 [published Online First: 20200722]
156. Scali ST, Suckow BD, Goodney PP, et al. A significant proportion of current endovascular aortic aneurysm repair practice fails to meet Society for Vascular Surgery clinical practice guideline recommended abdominal aortic aneurysm

diameter treatment thresholds in the Vascular Quality Initiative. *J Vasc Surg* 2022;75(4):1234-41 e1. doi: 10.1016/j.jvs.2021.08.109 [published Online First: 20220125]
157. Decker JA, Helmer M, Bette S, et al. Comparison and Trends of Endovascular, Surgical and Hybrid Revascularizations and the Influence of Comorbidity in 1 Million Hospitalizations Due to Peripheral Artery Disease in Germany Between 2009 and 2018. *Cardiovasc Intervent Radiol* 2022;45(10):1472-82. doi: 10.1007/s00270-022-03136-9 [published Online First: 20220415]
158. Fogarty TJ, Cranley JJ, Krause RJ, et al. A method for extraction of arterial emboli and thrombi. *Surg Gynecol Obstet* 1963;116:241-4.
159. Dr. Thomas J Fogarty Awarded Presidential National Medal of Technology and Innovation. PR Newswire, 2014.
160. Rontgen WC. On a New Kind of Rays. *Science* 1896;3(59):227-31. doi: 10.1126/science.3.59.227
161. Rontgen WK. A New Form of Radiation. *Science* 1896;3(72):726-9. doi: 10.1126/science.3.72.726
162. Ferro JM. Egas Moniz (1874-1955). *J Neurol* 2003;250(3):376-7. doi: 10.1007/s00415-003-0901-y
163. Duarte G, Goulao A. Editorial. Egas moniz, the pioneer of cerebral angiography. *Interv Neuroradiol* 1997;3(2):107-11. doi: 10.1177/159101999700300201 [published Online First: 20010515]
164. Seldinger SI. Catheter replacement of the needle in percutaneous arteriography; a new technique. *Acta radiol* 1953;39(5):368-76. doi: 10.3109/00016925309136722
165. Valji K. "A Severe Attack of Common Sense": Sven Ivar Seldinger (1921-1998) and the Birth of Interventional Medicine. *J Vasc Interv Radiol* 2021;32(9):1255-57. doi: 10.1016/j.jvir.2021.05.033
166. Dotter CT, Judkins MP. Transluminal Treatment of Arteriosclerotic Obstruction. Description of a New Technic and a Preliminary Report of Its Application. *Circulation* 1964;30:654-70. doi: 10.1161/01.cir.30.5.654
167. Dotter CT, Frische LH, Judkins MP, Mueller R. The "nonsurgical" treatment of iliofemoral arteriosclerotic obstruction. *Radiology* 1966;86(5):871-5. doi: 10.1148/86.5.871
168. Dotter CT, Judkins MP, Rosch J. Nonoperative treatment of arterial occlusive disease: a radiologically facilitated technique. *Radiol Clin North Am* 1967;5(3):531-42.
169. Dotter CT, Judkins MP. Transluminal recanalization in occlusive disease of the leg arteries. *GP* 1968;37(1):98-106.
170. Dotter CT, Rosch J, Judkins MP. Transluminal dilatation of atherosclerotic stenosis. *Surg Gynecol Obstet* 1968;127(4):794-804.
171. Dotter CT, Rosch J, Anderson JM, et al. Transluminal iliac artery dilatation. Nonsurgical catheter treatment of atheromatous narrowing. *JAMA* 1974;230(1):117-24.
172. Dotter CT. Transluminally-placed coilspring endarterial tube grafts. Long-term patency in canine popliteal artery. *Invest Radiol* 1969;4(5):329-32. doi: 10.1097/00004424-196909000-00008
173. Almen T. Contrast agent design. Some aspects on the synthesis of water soluble contrast agents of low osmolality. *J Theor Biol* 1969;24(2):216-26. doi: 10.1016/s0022-5193(69)80047-0

174. Almen T. Development of nonionic contrast media. *Invest Radiol* 1985;20(1 Suppl):S2-9. doi: 10.1097/00004424-198501002-00003
175. Almen T. Visipaque--a step forward. A historical review. *Acta Radiol Suppl* 1995;399:2-18.
176. Almen T, Boijsen E, Lindell SE. Metrizamide in angiography I. Femoral angiography. *Acta Radiol Diagn (Stockh)* 1977;18(1):33-8. doi: 10.1177/028418517701800104
177. Porstmann W, Wierny L, Warnke H. Closure of persistent ductus arteriosus without thoracotomy. *Ger Med Mon* 1967;12(6):259-61.
178. Porstmann W. [A new corset balloon catheter for Dotter's transluminal recanilization with special reference to obliterations of the pelvic arteries]. *Radiol Diagn (Berl)* 1973;14(2):239-44.
179. Gruntzig A, Kumpe DA. Technique of percutaneous transluminal angioplasty with the Gruntzig ballon catheter. *AJR Am J Roentgenol* 1979;132(4):547-52. doi: 10.2214/ajr.132.4.547
180. Barton M, Gruntzig J, Husmann M, Rosch J. Balloon Angioplasty - The Legacy of Andreas Gruntzig, M.D. (1939-1985). *Front Cardiovasc Med* 2014;1:15. doi: 10.3389/fcvm.2014.00015 [published Online First: 20141229]
181. Gruntzig A. Transluminal dilatation of coronary-artery stenosis. *Lancet* 1978;1(8058):263. doi: 10.1016/s0140-6736(78)90500-7
182. Sigwart U, Puel J, Mirkovitch V, et al. Intravascular stents to prevent occlusion and restenosis after transluminal angioplasty. *N Engl J Med* 1987;316(12):701-6. doi: 10.1056/NEJM198703193161201
183. Puel J, Joffre F, Rousseau H, et al. [Self-expanding coronary endoprosthesis in the prevention of restenosis following transluminal angioplasty. Preliminary clinical study]. *Arch Mal Coeur Vaiss* 1987;80(8):1311-2.
184. Palmaz JC, Kopp DT, Hayashi H, et al. Normal and stenotic renal arteries: experimental balloon-expandable intraluminal stenting. *Radiology* 1987;164(3):705-8. doi: 10.1148/radiology.164.3.2956628
185. Wright KC, Wallace S, Charnsangavej C, et al. Percutaneous endovascular stents: an experimental evaluation. *Radiology* 1985;156(1):69-72. doi: 10.1148/radiology.156.1.4001423
186. Serruys PW, de Jaegere P, Kiemeneij F, et al. A comparison of balloon-expandable-stent implantation with balloon angioplasty in patients with coronary artery disease. Benestent Study Group. *N Engl J Med* 1994;331(8):489-95. doi: 10.1056/NEJM199408253310801
187. Fischman DL, Leon MB, Baim DS, et al. A randomized comparison of coronary-stent placement and balloon angioplasty in the treatment of coronary artery disease. Stent Restenosis Study Investigators. *N Engl J Med* 1994;331(8):496-501. doi: 10.1056/NEJM199408253310802
188. Vroegindeweij D, Vos LD, Tielbeek AV, et al. Balloon angioplasty combined with primary stenting versus balloon angioplasty alone in femoropopliteal obstructions: A comparative randomized study. *Cardiovasc Intervent Radiol* 1997;20(6):420-5. doi: 10.1007/s002709900186
189. Zdanowski Z, Albrechtsson U, Lundin A, et al. Percutaneous transluminal angioplasty with or without stenting for femoropopliteal occlusions? A randomized controlled study. *Int Angiol* 1999;18(4):251-5.

190. Cejna M, Thurnher S, Illiasch H, et al. PTA versus Palmaz stent placement in femoropopliteal artery obstructions: a multicenter prospective randomized study. *J Vasc Interv Radiol* 2001;12(1):23-31. doi: 10.1016/s1051-0443(07)61397-9
191. Grimm J, Müller-Hülsbeck S, Jahnke T, et al. Randomized study to compare PTA alone versus PTA with Palmaz stent placement for femoropopliteal lesions. *Journal of Vascular and Interventional Radiology* 2001;12(8):935-41. doi: 10.1016/S1051-0443(07)61572-3
192. Becquemin JP, Favre JP, Marzelle J, et al. Systematic versus selective stent placement after superficial femoral artery balloon angioplasty: a multicenter prospective randomized study. *J Vasc Surg* 2003;37(3):487-94. doi: 10.1067/mva.2003.155
193. Tomberli B, Mattesini A, Baldereschi GI, Di Mario C. A Brief History of Coronary Artery Stents. *Rev Esp Cardiol (Engl Ed)* 2018;71(5):312-19. doi: 10.1016/j.rec.2017.11.022 [published Online First: 20180201]
194. Suvash Shrestha JP, Gerald Hollander, Jacob Shani. Coronary Artery Stents: From the Beginning to the Present. *Consultant 360* 2020;60(6)
195. Hoffmann R, Mintz GS, Dussaillant GR, et al. Patterns and mechanisms of in-stent restenosis. A serial intravascular ultrasound study. *Circulation* 1996;94(6):1247-54. doi: 10.1161/01.cir.94.6.1247
196. Hoffmann R, Mintz GS, Kent KM, et al. Serial intravascular ultrasound predictors of restenosis at the margins of Palmaz-Schatz stents. *Am J Cardiol* 1997;79(7):951-3. doi: 10.1016/s0002-9149(97)00016-7
197. Lincoff AM, Topol EJ, Ellis SG. Local drug delivery for the prevention of restenosis. Fact, fancy, and future. *Circulation* 1994;90(4):2070-84. doi: 10.1161/01.cir.90.4.2070
198. Moses JW, Leon MB, Popma JJ, et al. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. *N Engl J Med* 2003;349(14):1315-23. doi: 10.1056/NEJMoa035071
199. Stone GW, Ellis SG, Cannon L, et al. Comparison of a polymer-based paclitaxel-eluting stent with a bare metal stent in patients with complex coronary artery disease: a randomized controlled trial. *JAMA* 2005;294(10):1215-23. doi: 10.1001/jama.294.10.1215
200. Camenzind E, Steg PG, Wijns W. Stent thrombosis late after implantation of first-generation drug-eluting stents: a cause for concern. *Circulation* 2007;115(11):1440-55; discussion 55. doi: 10.1161/CIRCULATIONAHA.106.666800 [published Online First: 20070307]
201. Borhani S, Hassanajili S, Ahmadi Tafti SH, Rabbani S. Cardiovascular stents: overview, evolution, and next generation. *Prog Biomater* 2018;7(3):175-205. doi: 10.1007/s40204-018-0097-y [published Online First: 20180910]
202. Bonaa KH, Mannsverk J, Wiseth R, et al. Drug-Eluting or Bare-Metal Stents for Coronary Artery Disease. *N Engl J Med* 2016;375(13):1242-52. doi: 10.1056/NEJMoa1607991 [published Online First: 20160829]
203. Bangalore S, Kumar S, Fusaro M, et al. Short- and long-term outcomes with drug-eluting and bare-metal coronary stents: a mixed-treatment comparison analysis of 117 762 patient-years of follow-up from randomized trials. *Circulation* 2012;125(23):2873-91. doi: 10.1161/CIRCULATIONAHA.112.097014 [published Online First: 20120514]

204. Axel DI, Kunert W, Goggelmann C, et al. Paclitaxel inhibits arterial smooth muscle cell proliferation and migration in vitro and in vivo using local drug delivery. *Circulation* 1997;96(2):636-45. doi: 10.1161/01.cir.96.2.636
205. Herdeg C, Oberhoff M, Baumbach A, et al. Local paclitaxel delivery for the prevention of restenosis: biological effects and efficacy in vivo. *J Am Coll Cardiol* 2000;35(7):1969-76. doi: 10.1016/s0735-1097(00)00614-8
206. Oberhoff M, Herdeg C, Al Ghobainy R, et al. Local delivery of paclitaxel using the double-balloon perfusion catheter before stenting in the porcine coronary artery. *Catheter Cardiovasc Interv* 2001;53(4):562-8. doi: 10.1002/ccd.1223
207. Creel CJ, Lovich MA, Edelman ER. Arterial paclitaxel distribution and deposition. *Circ Res* 2000;86(8):879-84. doi: 10.1161/01.res.86.8.879
208. Hwang CW, Wu D, Edelman ER. Physiological transport forces govern drug distribution for stent-based delivery. *Circulation* 2001;104(5):600-5. doi: 10.1161/hc3101.092214
209. Hwang CW, Wu D, Edelman ER. Impact of transport and drug properties on the local pharmacology of drug-eluting stents. *Int J Cardiovasc Intervent* 2003;5(1):7-12. doi: 10.1080/14628840304614
210. Lovich MA, Creel C, Hong K, et al. Carrier proteins determine local pharmacokinetics and arterial distribution of paclitaxel. *J Pharm Sci* 2001;90(9):1324-35. doi: 10.1002/jps.1085
211. Scheller B, Speck U, Schmitt A, et al. Acute cardiac tolerance of current contrast media and the new taxane protaxel using iopromide as carrier during porcine coronary angiography and stenting. *Invest Radiol* 2002;37(1):29-34. doi: 10.1097/00004424-200201000-00006
212. Scheller B, Speck U, Romeike B, et al. Contrast media as carriers for local drug delivery. Successful inhibition of neointimal proliferation in the porcine coronary stent model. *Eur Heart J* 2003;24(15):1462-7. doi: 10.1016/s0195-668x(03)00317-8
213. Scheller B, Speck U, Schmitt A, et al. Addition of paclitaxel to contrast media prevents restenosis after coronary stent implantation. *J Am Coll Cardiol* 2003;42(8):1415-20. doi: 10.1016/s0735-1097(03)01056-8
214. Morice MC, Serruys PW, Sousa JE, et al. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. *N Engl J Med* 2002;346(23):1773-80. doi: 10.1056/NEJMoa012843
215. Scheller B, Speck U, Abramjuk C, et al. Paclitaxel balloon coating, a novel method for prevention and therapy of restenosis. *Circulation* 2004;110(7):810-4. doi: 10.1161/01.CIR.0000138929.71660.E0 [published Online First: 20040809]
216. Scheller B, Hehrlein C, Bocksch W, et al. Treatment of coronary in-stent restenosis with a paclitaxel-coated balloon catheter. *N Engl J Med* 2006;355(20):2113-24. doi: 10.1056/NEJMoa061254 [published Online First: 20061113]
217. Scheller B, Hehrlein C, Bocksch W, et al. Two year follow-up after treatment of coronary in-stent restenosis with a paclitaxel-coated balloon catheter. *Clin Res Cardiol* 2008;97(10):773-81. doi: 10.1007/s00392-008-0682-5 [published Online First: 20080605]
218. Tepe G, Zeller T, Albrecht T, et al. Local delivery of paclitaxel to inhibit restenosis during angioplasty of the leg. *N Engl J Med* 2008;358(7):689-99. doi: 10.1056/NEJMoa0706356

219. Werk M, Langner S, Reinkensmeier B, et al. Inhibition of restenosis in femoropopliteal arteries. Paclitaxel-coated versus uncoated balloon: Femoral paclitaxel randomized pilot trial. *Circulation* 2008;118(13):1358-65. doi: 10.1161/CIRCULATIONAHA.107.735985
220. Speck U, Scheller B, Abramjuk C, et al. Neointima inhibition: comparison of effectiveness of non-stent-based local drug delivery and a drug-eluting stent in porcine coronary arteries. *Radiology* 2006;240(2):411-8. doi: 10.1148/radiol.2402051248
221. Albrecht T, Speck U, Baier C, et al. Reduction of stenosis due to intimal hyperplasia after stent supported angioplasty of peripheral arteries by local administration of paclitaxel in swine. *Invest Radiol* 2007;42(8):579-85. doi: 10.1097/RLI.0b013e31804f5a60
222. Cremers B, Speck U, Kaufels N, et al. Drug-eluting balloon: very short-term exposure and overlapping. *Thromb Haemost* 2009;101(1):201-6.
223. Kolff WJ. First Clinical Experience with the Artificial Kidney. *Ann Intern Med* 1965;62:608-19. doi: 10.7326/0003-4819-62-3-608
224. Alwall N. On the artificial kidney; apparatus for dialysis of the blood in vivo. *Acta Med Scand* 1947;128(4):317-25.
225. Quinton W, Dillard D, Scribner BH. Cannulation of blood vessels for prolonged hemodialysis. *Trans Am Soc Artif Intern Organs* 1960;6:104-13.
226. Scribner BH, Buri R, Caner JE, et al. The treatment of chronic uremia by means of intermittent hemodialysis: a preliminary report. *Trans Am Soc Artif Intern Organs* 1960;6:114-22.
227. Brescia MJ, Cimino JE, Appel K, Hurwich BJ. Chronic hemodialysis using venipuncture and a surgically created arteriovenous fistula. *N Engl J Med* 1966;275(20):1089-92. doi: 10.1056/NEJM196611172752002
228. Rohl L, Franz HE, Mohring K, et al. Direct arteriovenous fistula for hemodialysis. *Scand J Urol Nephrol* 1968;2(3):191-5. doi: 10.3109/00365596809135366
229. Erben J, Kvasnicka J, Bastecky J, et al. Long-term experience with the technique of subclavian and femoral vein cannulation in hemodialysis. *Artif Organs* 1979;3(3):241-4. doi: 10.1111/j.1525-1594.1979.tb01056.x
230. Heindel P, Fitzgibbon JJ, Feliz JD, et al. Evaluating national guideline concordance of recurrent interventions after radiocephalic arteriovenous fistula creation. *Journal of Vascular Surgery* 2023;77(4):1206-15.e2. doi: 10.1016/j.jvs.2022.12.017
231. Shahverdyan R, Beathard G, Mushtaq N, et al. Comparison of Outcomes of Percutaneous Arteriovenous Fistulae Creation by Ellipsys and WavelinQ Devices. *J Vasc Interv Radiol* 2020;31(9):1365-72. doi: 10.1016/j.jvir.2020.06.008 [published Online First: 20200811]
232. Mallios A, Malik J, Jennings WC. Endovascular Arteriovenous Fistula Creation-Review of Current Experience. *Diagnostics (Basel)* 2022;12(10) doi: 10.3390/diagnostics12102447 [published Online First: 20221010]
233. Berland T, Clement J, Inston N, et al. Percutaneous arteriovenous fistula creation with the 4F WavelinQ EndoAVF System. *J Vasc Surg* 2022;75(3):1038-46 e3. doi: 10.1016/j.jvs.2021.09.025 [published Online First: 20211001]
234. Dua A, Lee CJ. Epidemiology of Peripheral Arterial Disease and Critical Limb Ischemia. *Tech Vasc Interv Radiol* 2016;19(2):91-5. doi: 10.1053/j.tvir.2016.04.001 [published Online First: 2016/07/18]

235. Fereydooni A, Gorecka J, Dardik A. Using the epidemiology of critical limb ischemia to estimate the number of patients amenable to endovascular therapy. *Vascular Medicine (United Kingdom)* 2020;25(1):78-87. doi: 10.1177/1358863X19878271
236. Beckman JA, Creager MA, Libby P. Diabetes and atherosclerosis: epidemiology, pathophysiology, and management. *Jama* 2002;287(19):2570-81.
237. Ankle Brachial Index C, Fowkes FG, Murray GD, et al. Ankle brachial index combined with Framingham Risk Score to predict cardiovascular events and mortality: a meta-analysis. *JAMA* 2008;300(2):197-208. doi: 10.1001/jama.300.2.197
238. Barnes JA, Eid MA, Creager MA, Goodney PP. Epidemiology and Risk of Amputation in Patients With Diabetes Mellitus and Peripheral Artery Disease. *Arterioscler Thromb Vasc Biol* 2020;40(8):1808-17. doi: 10.1161/ATVBAHA.120.314595 [published Online First: 20200625]
239. Chuter VH, Searle A, Barwick A, et al. Estimating the diagnostic accuracy of the ankle–brachial pressure index for detecting peripheral arterial disease in people with diabetes: A systematic review and meta-analysis. *Diabetic Medicine* 2021;38(2) doi: 10.1111/dme.14379
240. Lowry D, Saeed M, Narendran P, Tiwari A. A Review of Distribution of Atherosclerosis in the Lower Limb Arteries of Patients With Diabetes Mellitus and Peripheral Vascular Disease. *Vascular and Endovascular Surgery* 2018;52(7):535-42. doi: 10.1177/1538574418791622
241. Menzoian JO, LaMorte WW, Paniszyn CC, et al. Symptomatology and anatomic patterns of peripheral vascular disease: differing impact of smoking and diabetes. *Ann Vasc Surg* 1989;3(3):224-8.
242. Armstrong DG, Tan TW, Boulton AJM, Bus SA. Diabetic Foot Ulcers: A Review. *JAMA* 2023;330(1):62-75. doi: 10.1001/jama.2023.10578
243. Officers A, Coordinators for the ACRGTA, Lipid-Lowering Treatment to Prevent Heart Attack T. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 2002;288(23):2981-97. doi: 10.1001/jama.288.23.2981
244. Julius S, Kjeldsen SE, Weber M, et al. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. *Lancet* 2004;363(9426):2022-31. doi: 10.1016/S0140-6736(04)16451-9
245. Investigators O, Yusuf S, Teo KK, et al. Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med* 2008;358(15):1547-59. doi: 10.1056/NEJMoa0801317 [published Online First: 20080331]
246. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2009;361(11):1045-57. doi: 10.1056/NEJMoa0904327 [published Online First: 20090830]
247. Hiatt WR, Fowkes FG, Heizer G, et al. Ticagrelor versus Clopidogrel in Symptomatic Peripheral Artery Disease. *N Engl J Med* 2017;376(1):32-40. doi: 10.1056/NEJMoa1611688 [published Online First: 20161113]
248. Mohr JP, Thompson JL, Lazar RM, et al. A comparison of warfarin and aspirin for the prevention of recurrent ischemic stroke. *N Engl J Med* 2001;345(20):1444-51. doi: 10.1056/NEJMoa011258

249. Hurlen M, Abdelnoor M, Smith P, et al. Warfarin, aspirin, or both after myocardial infarction. *N Engl J Med* 2002;347(13):969-74. doi: 10.1056/NEJMoa020496
250. Warfarin Antiplatelet Vascular Evaluation Trial I, Anand S, Yusuf S, et al. Oral anticoagulant and antiplatelet therapy and peripheral arterial disease. *N Engl J Med* 2007;357(3):217-27. doi: 10.1056/NEJMoa065959
251. Efficacy of oral anticoagulants compared with aspirin after infrainguinal bypass surgery (The Dutch Bypass Oral Anticoagulants or Aspirin Study): a randomised trial. *Lancet* 2000;355(9201):346-51.
252. Bhatt DL, Fox KA, Hacke W, et al. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. *N Engl J Med* 2006;354(16):1706-17. doi: 10.1056/NEJMoa060989 [published Online First: 20060312]
253. Belch JJ, Dormandy J, Committee CW, et al. Results of the randomized, placebo-controlled clopidogrel and acetylsalicylic acid in bypass surgery for peripheral arterial disease (CASPAR) trial. *J Vasc Surg* 2010;52(4):825-33, 33 e1-2. doi: 10.1016/j.jvs.2010.04.027 [published Online First: 20100801]
254. Cosentino F, Grant PJ, Aboyans V, et al. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. *Eur Heart J* 2020;41(2):255-323. doi: 10.1093/eurheartj/ehz486
255. Santema TB, Stoekenbroek RM, van Loon J, et al. Not All Patients with Critical Limb Ischaemia Require Revascularisation. *Eur J Vasc Endovasc Surg* 2017;53(3):371-79. doi: 10.1016/j.ejvs.2016.10.018 [published Online First: 20161202]
256. Sibona A, Bianchi C, Leong B, et al. A single center's 15-year experience with palliative limb care for chronic limb threatening ischemia in frail patients. *J Vasc Surg* 2022;75(3):1014-20 e1. doi: 10.1016/j.jvs.2021.09.032 [published Online First: 2021/10/11]
257. Wubbeke LF, Naves C, Daemen JHC, et al. Editor's Choice - Mortality and Major Amputation after Revascularisation in Octogenarians Versus Non-Octogenarians with Chronic Limb Threatening Ischaemia: A Systematic Review and Meta-Analysis. *Eur J Vasc Endovasc Surg* 2020;60(2):231-41. doi: 10.1016/j.ejvs.2020.04.027 [published Online First: 2020/07/28]
258. Elgzyri T, Larsson J, Thorne J, et al. Outcome of ischemic foot ulcer in diabetic patients who had no invasive vascular intervention. *Eur J Vasc Endovasc Surg* 2013;46(1):110-7. doi: 10.1016/j.ejvs.2013.04.013 [published Online First: 20130501]
259. Andersen CA. Noninvasive assessment of lower extremity hemodynamics in individuals with diabetes mellitus. *J Vasc Surg* 2010;52(3 Suppl):76S-80S. doi: 10.1016/j.jvs.2010.06.012
260. Taylor GI, Palmer JH. 'Angiosome theory'. *Br J Plast Surg* 1992;45(4):327-8. doi: 10.1016/0007-1226(92)90063-4
261. Ji D, Zhang T, Li C, et al. Evaluation of angiosome-targeted infrapopliteal endovascular revascularization in critical diabetic limb ischemia. *J Interv Med* 2018;1(3):176-81. doi: 10.19779/j.cnki.2096-3602.2018.03.08 [published Online First: 20190430]
262. Biancari F, Juvonen T. Angiosome-targeted lower limb revascularization for ischemic foot wounds: systematic review and meta-analysis. *Eur J Vasc Endovasc Surg* 2014;47(5):517-22. doi: 10.1016/j.ejvs.2013.12.010 [published Online First: 20140131]

263. Elbadawy A, Ali H, Saleh M, Hasaballah A. Editor's Choice - A Prospective Study to Evaluate Complete Wound Healing and Limb Salvage Rates After Angiosome Targeted Infrapopliteal Balloon Angioplasty in Patients with Critical Limb Ischaemia. *Eur J Vasc Endovasc Surg* 2018;55(3):392-97. doi: 10.1016/j.ejvs.2017.12.003 [published Online First: 20180117]
264. Chae KJ, Shin JY. Is angiosome-targeted angioplasty effective for limb salvage and wound healing in diabetic foot?: A meta-analysis. *PLoS ONE* 2016;11(7) doi: 10.1371/journal.pone.0159523
265. Spillerova K, Biancari F, Leppäniemi A, et al. Differential impact of bypass surgery and angioplasty on angiosome-targeted infrapopliteal revascularization. *European Journal of Vascular and Endovascular Surgery* 2015;49(4):412-19. doi: 10.1016/j.ejvs.2014.12.023
266. Iida O, Takahara M, Soga Y, et al. Impact of angiosome-oriented revascularization on clinical outcomes in critical limb ischemia patients without concurrent wound infection and diabetes. *Journal of Endovascular Therapy* 2014;21(5):607-15. doi: 10.1583/14-4692R.1
267. Iida O, Takahara M, Soga Y, et al. Worse limb prognosis for indirect versus direct endovascular revascularization only in patients with critical limb ischemia complicated with wound infection and diabetes mellitus. *Eur J Vasc Endovasc Surg* 2013;46(5):575-82. doi: 10.1016/j.ejvs.2013.08.002 [published Online First: 2013/09/17]
268. Iida O, Soga Y, Hirano K, et al. Long-term results of direct and indirect endovascular revascularization based on the angiosome concept in patients with critical limb ischemia presenting with isolated below-the-knee lesions. *J Vasc Surg* 2012;55(2):363-70 e5. doi: 10.1016/j.jvs.2011.08.014 [published Online First: 2011/11/05]
269. Alexandrescu VA, Hubermont G, Philips Y, et al. Selective primary angioplasty following an angiosome model of reperfusion in the treatment of Wagner 1-4 diabetic foot lesions: practice in a multidisciplinary diabetic limb service. *J Endovasc Ther* 2008;15(5):580-93. doi: 10.1583/08-2460.1 [published Online First: 2008/10/09]
270. Špillerová K, Settembre N, Biancari F, et al. Angiosome Targeted PTA is More Important in Endovascular Revascularisation than in Surgical Revascularisation: Analysis of 545 Patients with Ischaemic Tissue Lesions. *Eur J Vasc Endovasc Surg* 2017;53(4):567-75. doi: 10.1016/j.ejvs.2017.01.008 [published Online First: 20170216]
271. Shishehbor MH, White CJ, Gray BH, et al. Critical Limb Ischemia: An Expert Statement. *Journal of the American College of Cardiology* 2016;68(18):2002-15. doi: 10.1016/j.jacc.2016.04.071
272. Mills JL. Lower limb ischaemia in patients with diabetic foot ulcers and gangrene: Recognition, anatomic patterns and revascularization strategies. *Diabetes/Metabolism Research and Reviews* 2016;32:239-45. doi: 10.1002/dmrr.2753
273. Faglia E, Clerici G, Mantero M, et al. Incidence of critical limb ischemia and amputation outcome in contralateral limb in diabetic patients hospitalized for unilateral critical limb ischemia during 1999-2003 and followed-up until 2005.

Diabetes Res Clin Pract 2007;77(3):445-50. doi: 10.1016/j.diabres.2007.01.010 [published Online First: 2007/02/24]
274. Malmstedt J, Leander K, Wahlberg E, et al. Outcome after leg bypass surgery for critical limb ischemia is poor in patients with diabetes: a population-based cohort study. *Diabetes Care* 2008;31(5):887-92.
275. Calle-Pascual AL, Duran A, Diaz A, et al. Comparison of peripheral arterial reconstruction in diabetic and non-diabetic patients: a prospective clinic-based study. *Diabetes Res Clin Pract* 2001;53(2):129-36.
276. Danielsson G, Albrechtsson U, Norgren L, et al. Percutaneous transluminal angioplasty of crural arteries: diabetes and other factors influencing outcome. *Eur J Vasc Endovasc Surg* 2001;21(5):432-6.
277. West NEJ, Ruygrok PN, Disco CMC, et al. Clinical and Angiographic Predictors of Restenosis after Stent Deployment in Diabetic Patients. *Circulation* 2004;109(7):867-73. doi: 10.1161/01.CIR.0000116750.63158.94
278. DeRubertis BG, Pierce M, Ryer EJ, et al. Reduced primary patency rate in diabetic patients after percutaneous intervention results from more frequent presentation with limb-threatening ischemia. *J Vasc Surg* 2008;47(1):101-8.
279. Lilja E, Gottsater A, Miftaraj M, et al. Diabetes mellitus was not associated with lower amputation-free survival after open revascularization for chronic limb-threatening ischemia - A nationwide propensity score adjusted analysis. *Vasc Med* 2021;26(5):507-14. doi: 10.1177/1358863X211008249 [published Online First: 2021/05/19]
280. Aronson D. Potential role of advanced glycosylation end products in promoting restenosis in diabetes and renal failure. *Med Hypotheses* 2002;59(3):297-301.
281. Wahlberg E, Jorneskog G. Patients with diabetes and critical limb ischemia have a high peripheral vascular resistance. *Ann Vasc Surg* 1997;11(3):224-9.
282. Hicks RC, Moss J, Higman DJ, et al. The influence of diabetes on the vasomotor responses of saphenous vein and the development of infra-inguinal vein graft stenosis. *Diabetes* 1997;46(1):113-8.
283. Williams SB, Cusco JA, Roddy MA, et al. Impaired nitric oxide-mediated vasodilation in patients with non-insulin-dependent diabetes mellitus. *J Am Coll Cardiol* 1996;27(3):567-74.
284. Davies MG, Kim JH, Klyachkin ML, et al. Diabetes mellitus and experimental vein graft structure and function. *J Vasc Surg* 1994;19(6):1031-43.
285. Brunkwall JS, Bergqvist D. Prostacyclin release from the human saphenous vein in diabetics in lower than in nondiabetics. *World J Surg* 1992;16(6):1141-5; discussion 46.
286. Cardwell RJ, Webb RC. Diabetes and reactivity of isolated human saphenous vein. *Clin Physiol* 1984;4(6):509-17.
287. Fransson T, Thorne J. In situ saphenous vein bypass grafting - still first line treatment? A prospective study comparing surgical results between diabetic and non-diabetic populations. *Vasa* 2010;39(1):59-65. doi: 10.1024/0301-1526/a000006
288. Gahtan V, Harpavat M, Roberts AB, Kerstein MD. Impact of diabetes mellitus on infrainguinal bypass grafting. *J Diabetes Complications* 1998;12(4):197-200.

289. Karacagil S, Almgren B, Bowald S, Bergqvist D. Comparative analysis of patency, limb salvage and survival in diabetic and non-diabetic patients undergoing infrainguinal bypass surgery. *Diabet Med* 1995;12(6):537-41.
290. Jensen LP, Schroeder TV, Lorentzen JE. In situ saphenous vein bypass surgery in diabetic patients. *Eur J Vasc Surg* 1992;6(5):533-9.
291. Shah DM, Chang BB, Fitzgerald KM, et al. Durability of the tibial artery bypass in diabetic patients. *Am J Surg* 1988;156(2):133-5.
292. Panneton JM, Gloviczki P, Bower TC, et al. Pedal bypass for limb salvage: impact of diabetes on long-term outcome. *Ann Vasc Surg* 2000;14(6):640-7.
293. Akbari CM, Pomposelli FB, Jr., Gibbons GW, et al. Lower extremity revascularization in diabetes: late observations. *Arch Surg* 2000;135(4):452-6.
294. Hamdan AD, Saltzberg SS, Sheahan M, et al. Lack of association of diabetes with increased postoperative mortality and cardiac morbidity: results of 6565 major vascular operations. *Arch Surg* 2002;137(4):417-21.
295. Wolfle KD, Bruijnen H, Loeprecht H, et al. Graft patency and clinical outcome of femorodistal arterial reconstruction in diabetic and non-diabetic patients: results of a multicentre comparative analysis. *Eur J Vasc Endovasc Surg* 2003;25(3):229-34.
296. Lazaris AM, Tsiamis AC, Fishwick G, et al. Clinical outcome of primary infrainguinal subintimal angioplasty in diabetic patients with critical lower limb ischemia. *J Endovasc Ther* 2004;11(4):447-53.
297. Awad S, Karkos CD, Serrachino-Inglott F, et al. The impact of diabetes on current revascularisation practice and clinical outcome in patients with critical lower limb ischaemia. *Eur J Vasc Endovasc Surg* 2006;32(1):51-9.
298. Cafasso D, Schneider P. How paclitaxel can improve results in diabetics. *Journal of Cardiovascular Surgery* 2012;53(1):13-21.
299. Butt T, Lilja E, Orneholm H, et al. Amputation-Free Survival in Patients With Diabetes Mellitus and Peripheral Arterial Disease With Heel Ulcer: Open Versus Endovascular Surgery. *Vasc Endovascular Surg* 2019;53(2):118-25. doi: 10.1177/1538574418813746 [published Online First: 2018/11/24]
300. Darling JD, Bodewes TCF, Deery SE, et al. Outcomes after first-time lower extremity revascularization for chronic limb-threatening ischemia between patients with and without diabetes. *J Vasc Surg* 2018;67(4):1159-69. doi: 10.1016/j.jvs.2017.06.119 [published Online First: 20170922]
301. Darling JD, O'Donnell TFX, Deery SE, et al. Outcomes after first-time lower extremity revascularization for chronic limb-threatening ischemia in insulin-dependent diabetic patients. *J Vasc Surg* 2018;68(5):1455-64.e1. doi: 10.1016/j.jvs.2018.01.055
302. Scatena A, Apicella M, Mantuano M, et al. Bypass surgery versus endovascular revascularization for occlusive infrainguinal peripheral artery disease: a meta-analysis of randomized controlled trials for the development of the Italian Guidelines for the treatment of diabetic foot syndrome. *Acta Diabetologica* 2023 doi: 10.1007/s00592-023-02185-x
303. Barani J, Mattiasson I, Lindblad B, Gottsater A. Suboptimal treatment of risk factor for atherosclerosis in critical limb ischemia. *Int Angiol* 2005;24(1):59-63.

304. Alhadad A, Wictorsson C, Alhadad H, et al. Medical risk factor treatment in peripheral arterial disease. Need for further improvement. *Int Angiol* 2013;32(3):332-8. [published Online First: 2013/05/29]
305. Goodney PP, Beck AW, Nagle J, et al. National trends in lower extremity bypass surgery, endovascular interventions, and major amputations. *J Vasc Surg* 2009;50(1):54-60. doi: 10.1016/j.jvs.2009.01.035 [published Online First: 2009/06/02]
306. Bradbury AW, Moakes CA, Popplewell M, et al. A vein bypass first versus a best endovascular treatment first revascularisation strategy for patients with chronic limb threatening ischaemia who required an infra-popliteal, with or without an additional more proximal infra-inguinal revascularisation procedure to restore limb perfusion (BASIL-2): an open-label, randomised, multicentre, phase 3 trial. *Lancet* 2023;401(10390):1798-809. doi: 10.1016/S0140-6736(23)00462-2 [published Online First: 20230425]
307. Farber A, Menard MT, Conte MS, et al. Surgery or Endovascular Therapy for Chronic Limb-Threatening Ischemia. *N Engl J Med* 2022;387(25):2305-16. doi: 10.1056/NEJMoa2207899 [published Online First: 2022/11/08]
308. Stavroulakis K, Katsogridakis E, Torsello G, et al. Editor's Choice - RANDOMisation Screening for Drug coated or Drug Eluting Device Randomised Trials Among Patients Undergoing Endovascular FemorOPopliteal Procedures (RANDOM-STOP study). *Eur J Vasc Endovasc Surg* 2023;66(3):362-68. doi: 10.1016/j.ejvs.2023.06.038 [published Online First: 20230703]
309. Bjorkman P, Auvinen T, Hakovirta H, et al. Drug-Eluting Stent Shows Similar Patency Results as Prosthetic Bypass in Patients with Femoropopliteal Occlusion in a Randomized Trial. *Ann Vasc Surg* 2018;53:165-70. doi: 10.1016/j.avsg.2018.04.014 [published Online First: 20180607]
310. Bosiers MJ, De Donato G, Torsello G, et al. ZILVERPASS Study: ZILVER PTX Stent versus Prosthetic Above-the-Knee Bypass Surgery in Femoropopliteal Lesions, 5-year Results. *Cardiovasc Intervent Radiol* 2023;46(10):1348-58. doi: 10.1007/s00270-023-03549-0 [published Online First: 20230905]
311. Eleissawy MI, Elbarbary AH, Elwagih MM, et al. Ipsilateral Antegrade Angioplasty for Flush Superficial Femoral Artery Occlusion versus Open Bypass Surgery. *Ann Vasc Surg* 2019;61:55-64. doi: 10.1016/j.avsg.2019.05.062 [published Online First: 20190805]
312. Holm J, Arfvidsson B, Jivegard L, et al. Chronic lower limb ischaemia. A prospective randomised controlled study comparing the 1-year results of vascular surgery and percutaneous transluminal angioplasty (PTA). *Eur J Vasc Surg* 1991;5(5):517-22. doi: 10.1016/s0950-821x(05)80338-x
313. McQuade K, Gable D, Pearl G, et al. Four-year randomized prospective comparison of percutaneous ePTFE/nitinol self-expanding stent graft versus prosthetic femoral-popliteal bypass in the treatment of superficial femoral artery occlusive disease. *J Vasc Surg* 2010;52(3):584-90; discussion 90-1, 91 e1-91 e7. doi: 10.1016/j.jvs.2010.03.071
314. Popplewell MA, Davies HOB, Narayanswami J, et al. A Comparison of Outcomes in Patients with Infrapopliteal Disease Randomised to Vein Bypass or Plain Balloon Angioplasty in the Bypass vs. Angioplasty in Severe Ischaemia of the Leg

(BASIL) Trial. *Eur J Vasc Endovasc Surg* 2017;54(2):195-201. doi: 10.1016/j.ejvs.2017.04.020 [published Online First: 20170608]
315. van Walraven LA, van Wijck IPS, Holewijn S, et al. Five-Year Outcomes of the SuperB Trial: A Multicenter Randomized Controlled Trial Comparing Heparin-Bonded Endograft to Surgical Femoropopliteal Bypass. *J Endovasc Ther* 2024:15266028241231520. doi: 10.1177/15266028241231520 [published Online First: 20240213]
316. Wolf GL, Wilson SE, Cross AP, et al. Surgery or balloon angioplasty for peripheral vascular disease: a randomized clinical trial. Principal investigators and their Associates of Veterans Administration Cooperative Study Number 199. *J Vasc Interv Radiol* 1993;4(5):639-48. doi: 10.1016/s1051-0443(93)71939-9
317. Bradbury AW, Adam DJ, Bell J, et al. Multicentre randomised controlled trial of the clinical and cost-effectiveness of a bypass-surgery-first versus a balloon-angioplasty-first revascularisation strategy for severe limb ischaemia due to infrainguinal disease. The Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial. *Health Technol Assess* 2010;14(14):1-210, iii-iv. doi: 10.3310/hta14140
318. Kluckner M, Gruber L, Wippel D, et al. Long-Term Outcome of Bypass Surgery versus Endovascular Revascularization in Long Femoropopliteal Lesions. *J Clin Med* 2023;12(10) doi: 10.3390/jcm12103507 [published Online First: 20230517]
319. Morisaki K, Matsubara Y, Kurose S, et al. Bypass Surgery Provides Better Outcomes Compared with Endovascular Therapy in the Composite Endpoint Comprising Relief from Rest Pain, Wound Healing, Limb Salvage, and Survival after Infra-inguinal Revascularisation in Patients with Chronic Limb Threatening Ischaemia. *European Journal of Vascular and Endovascular Surgery* 2022;63(4):588-93. doi: 10.1016/j.ejvs.2021.12.043
320. Nguyen BN, Conrad MF, Guest JM, et al. Late outcomes of balloon angioplasty and angioplasty with selective stenting for superficial femoral-popliteal disease are equivalent. *J Vasc Surg* 2011;54(4):1051-57.e1. doi: 10.1016/j.jvs.2011.03.283 [published Online First: 20110602]
321. Jia S, Liu J, Sun G, et al. Drug-Coated Balloon Angioplasty Versus Standard Uncoated Balloon Angioplasty for Long Femoropopliteal Lesions: Post Hoc Analysis of the 24-Month Results of the AcoArt I Study. *Annals of Vascular Surgery* 2022;82:70-80. doi: 10.1016/j.avsg.2021.10.066
322. Shammas NW, Jones-Miller S, Lemke J. Meta-Analysis-Derived Benchmarks of Patency and Target Lesion Revascularization of Percutaneous Balloon Angioplasty from Prospective Clinical Trials of Symptomatic Femoropopliteal In-Stent Restenosis. *J Vasc Interv Radiol* 2016;27(8):1195-203. doi: 10.1016/j.jvir.2016.05.003 [published Online First: 20160624]
323. Kamioka N, Soga Y, Kuramitsu S, et al. Clinical outcomes of balloon angioplasty alone versus nitinol stent implantation in patients with small femoropopliteal artery disease: Observations from the Retrospective Multicenter Analysis for Femoropopliteal Stenting (REAL-FP). *Catheter Cardiovasc Interv* 2017;90(5):790-97. doi: 10.1002/ccd.27192 [published Online First: 2017/07/20]
324. Elens M, Colle A, Verhelst R, Astarci P. Comparison of different inflation times on the angiographic image after balloon angioplasty in the femoropopliteal segment: a prospective randomized clinical trial. *J Cardiovasc Surg (Torino)*

2021;62(4):364-68. doi: 10.23736/S0021-9509.21.11633-7 [published Online First: 20210408]
325. Zorger N, Manke C, Lenhart M, et al. Peripheral arterial balloon angioplasty: effect of short versus long balloon inflation times on the morphologic results. *J Vasc Interv Radiol* 2002;13(4):355-9. doi: 10.1016/s1051-0443(07)61736-9
326. Diaz ML, Urtasun F, Barberena J, et al. Cryoplasty versus conventional angioplasty in femoropopliteal arterial recanalization: 3-year analysis of reintervention-free survival by treatment received. *Cardiovasc Intervent Radiol* 2011;34(5):911-7. doi: 10.1007/s00270-010-0032-7 [published Online First: 20101118]
327. Fossaceca R, Guzzardi G, Di Terlizzi M, et al. Comparison of cryoplasty and conventional angioplasty for treating stenotic-occlusive lesions of the femoropopliteal arteries in diabetic patients: immediate, mid-term and long-term results. *Radiol Med* 2012;117(7):1176-89. doi: 10.1007/s11547-012-0793-7 [published Online First: 20120210]
328. Shammas NW, Coiner D, Shammas G, et al. Percutaneous lower extremity arterial interventions using primary balloon angioplasty versus cryoplasty: a randomized pilot trial. *Cardiovasc Revasc Med* 2012;13(3):172-6. doi: 10.1016/j.carrev.2011.12.007
329. Spiliopoulos S, Katsanos K, Karnabatidis D, et al. Cryoplasty versus conventional balloon angioplasty of the femoropopliteal artery in diabetic patients: long-term results from a prospective randomized single-center controlled trial. *Cardiovasc Intervent Radiol* 2010;33(5):929-38. doi: 10.1007/s00270-010-9915-x [published Online First: 20100624]
330. Amighi J, Schillinger M, Dick P, et al. De novo superficial femoropopliteal artery lesions: peripheral cutting balloon angioplasty and restenosis rates--randomized controlled trial. *Radiology* 2008;247(1):267-72. doi: 10.1148/radiol.2471070749 [published Online First: 20080212]
331. Poncyljusz W, Falkowski A, Safranow K, et al. Cutting-balloon angioplasty versus balloon angioplasty as treatment for short atherosclerotic lesions in the superficial femoral artery: Randomized controlled trial. *CardioVascular and Interventional Radiology* 2013;36(6):1500-07. doi: 10.1007/s00270-013-0603-5
332. Holden A, Hill A, Walker A, et al. PRELUDE Prospective Study of the Serranator Device in the Treatment of Atherosclerotic Lesions in the Superficial Femoral and Popliteal Arteries. *J Endovasc Ther* 2019;26(1):18-25. doi: 10.1177/1526602818820787 [published Online First: 20181224]
333. Lugenbiel I, Grebner M, Zhou Q, et al. Treatment of femoropopliteal lesions with the AngioSculpt scoring balloon - results from the Heidelberg PANTHER registry. *Vasa* 2018;47(1):49-55. doi: 10.1024/0301-1526/a000671 [published Online First: 2017/11/09]
334. Brodmann M, Werner M, Holden A, et al. Primary outcomes and mechanism of action of intravascular lithotripsy in calcified, femoropopliteal lesions: Results of Disrupt PAD II. *Catheter Cardiovasc Interv* 2019;93(2):335-42. doi: 10.1002/ccd.27943 [published Online First: 20181125]
335. Mustapha JA, Finton SM, Diaz-Sandoval LJ, et al. Percutaneous transluminal angioplasty in patients with infrapopliteal arterial disease. *Circulation: Cardiovascular Interventions* 2016;9(5) doi: 10.1161/CIRCINTERVENTIONS.115.003468

336. Soder HK, Manninen HI, Jaakkola P, et al. Prospective trial of infrapopliteal artery balloon angioplasty for critical limb ischemia: Angiographic and clinical results. *Journal of Vascular and Interventional Radiology* 2000;11(8):1021-31. doi: 10.1016/S1051-0443(07)61332-3
337. Romiti M, Albers M, Brochado-Neto FC, et al. Meta-analysis of infrapopliteal angioplasty for chronic critical limb ischemia. *J Vasc Surg* 2008;47(5):975-81. doi: 10.1016/j.jvs.2008.01.005 [published Online First: 20080418]
338. Kudo T, Chandra FA, Ahn SS. The effectiveness of percutaneous transluminal angioplasty for the treatment of critical limb ischemia: a 10-year experience. *J Vasc Surg* 2005;41(3):423-35; discussion 35. doi: 10.1016/j.jvs.2004.11.041 [published Online First: 2005/04/20]
339. Conrad MF, Kang J, Cambria RP, et al. Infrapopliteal balloon angioplasty for the treatment of chronic occlusive disease. *Journal of Vascular Surgery* 2009;50(4):799-805.e4. doi: 10.1016/j.jvs.2009.05.026
340. Schmidt A, Ulrich M, Winkler B, et al. Angiographic patency and clinical outcome after balloon-angioplasty for extensive infrapopliteal arterial disease. *Catheterization and Cardiovascular Interventions* 2010;76(7):1047-54. doi: 10.1002/ccd.22658
341. Snyder DJ, Zilinyi RS, Pruthi S, et al. Percutaneous Transluminal Angioplasty for Infrapopliteal Chronic Limb-Threatening Ischemia: A Systematic Review and Meta-analysis of Primary Patency and Binary Restenosis Rates. *Journal of Endovascular Therapy* 2023 doi: 10.1177/15266028231212133
342. Dorros G, Jaff MR, Dorros AM, et al. Tibioperoneal (outflow lesion) angioplasty can be used as primary treatment in 235 patients with critical limb ischemia: five-year follow-up. *Circulation* 2001;104(17):2057-62. doi: 10.1161/hc4201.097943 [published Online First: 2001/10/24]
343. Richards CN, Schneider PA. Explaining the discrepancy between lower patency and higher limb salvage rates after revascularization for critical limb ischemia. *Vascular Disease Management* 2016;13(11):245-51.
344. Tokuda T, Hirano K, Sakamoto Y, et al. Incidence and clinical outcomes of the slow-flow phenomenon after infrapopliteal balloon angioplasty. *Journal of Vascular Surgery* 2017;65(4):1047-54. doi: 10.1016/j.jvs.2016.08.118
345. Losurdo F, Ferraresi R, Ucci A, et al. Association of infrapopliteal medial arterial calcification with lower-limb amputations in high-risk patients: A systematic review and meta-analysis. *Vasc Med* 2021;26(2):164-73. doi: 10.1177/1358863X20979738 [published Online First: 20201229]
346. Spreen MI, Gremmels H, Teraa M, et al. High and immeasurable ankle-brachial index as predictor of poor amputation-free survival in critical limb ischemia. *J Vasc Surg* 2018;67(6):1864-71.e3. doi: 10.1016/j.jvs.2017.10.061 [published Online First: 20171228]
347. Soga Y, Takahara M, Iida O, et al. Efficacy of CilostAzol for Below-the-Knee Artery Disease after Balloon AnGioplasty in PatiEnts with Severe Limb Ischemia (CABBAGE Trial). *Ann Vasc Surg* 2017;45:22-28. doi: 10.1016/j.avsg.2017.05.029 [published Online First: 20170606]
348. Shammas NW, Lam R, Mustapha J, et al. Comparison of orbital atherectomy plus balloon angioplasty vs. balloon angioplasty alone in patients with critical limb

ischemia: results of the CALCIUM 360 randomized pilot trial. *J Endovasc Ther* 2012;19(4):480-8. doi: 10.1583/JEVT-12-3815MR.1
349. Holden A, Lichtenberg M, Nowakowski P, et al. Prospective Study of Serration Angioplasty in the Infrapopliteal Arteries Using the Serranator Device: PRELUDE BTK Study. *J Endovasc Ther* 2022;29(4):586-93. doi: 10.1177/15266028211059917 [published Online First: 20211120]
350. Adams G, Soukas PA, Mehrle A, et al. Intravascular Lithotripsy for Treatment of Calcified Infrapopliteal Lesions: Results from the Disrupt PAD III Observational Study. *Journal of Endovascular Therapy* 2022;29(1):76-83. doi: 10.1177/15266028211032953
351. Biagioni RB, Biagioni LC, Nasser F, et al. Infrapopliteal Angioplasty of One or More than One Artery for Critical Limb Ischaemia: A Randomised Clinical Trial. *Eur J Vasc Endovasc Surg* 2018;55(4):518-27. doi: 10.1016/j.ejvs.2017.12.022
352. Teichgraber U, Lehmann T, Ingwersen M, et al. Long-Term Effectiveness and Safety of Femoropopliteal Drug-Coated Balloon Angioplasty : 5-Year Results of the Randomized Controlled EffPac Trial. *Cardiovasc Intervent Radiol* 2022;45(12):1774-83. doi: 10.1007/s00270-022-03265-1 [published Online First: 20220911]
353. Liao CJ, Song SH, Li T, Zhang Y. Orchid drug-coated balloon versus standard percutaneous transluminal angioplasty for the treatment of femoropopliteal artery disease: 12-month result of the randomized controlled trial. *Vascular* 2022;30(3):448-54. doi: 10.1177/17085381211013968 [published Online First: 20210522]
354. Ni L, Ye W, Zhang L, et al. A Multicenter Randomized Trial Assessing ZENFlow Carrier-Free Drug-Coated Balloon for the Treatment of Femoropopliteal Artery Lesions. *Front Cardiovasc Med* 2022;9:821672. doi: 10.3389/fcvm.2022.821672 [published Online First: 20220315]
355. Shishehbor MH, Zeller T, Werner M, et al. Randomized Trial of Chocolate Touch Compared with Lutonix Drug-Coated Balloon in Femoropopliteal Lesions (Chocolate Touch Study). *Circulation* 2022;145(22):1645-54. doi: 10.1161/CIRCULATIONAHA.122.059646
356. Nowakowski P, Uchto W, Hrycek E, et al. Microcrystalline paclitaxel-coated balloon for revascularization of femoropopliteal artery disease: Three-year outcomes of the randomized BIOPAC trial. *Vascular Medicine (United Kingdom)* 2021;26(4):401-08. doi: 10.1177/1358863X20988360
357. Zhang B, Yang M, He T, et al. Twelve-Month Results From the First-in-China Prospective, Multi-Center, Randomized, Controlled Study of the FREEWAY Paclitaxel-Coated Balloon for Femoropopliteal Treatment. *Front Cardiovasc Med* 2021;8:686267. doi: 10.3389/fcvm.2021.686267 [published Online First: 20210910]
358. Sachar R, Soga Y, Ansari MM, et al. 1-Year Results From the RANGER II SFA Randomized Trial of the Ranger Drug-Coated Balloon. *JACC Cardiovasc Interv* 2021;14(10):1123-33. doi: 10.1016/j.jcin.2021.03.021
359. Ye W, Zhang X, Dai X, et al. Reewarm™ PTX drug-coated balloon in the treatment of femoropopliteal artery disease: A multi-center, randomized controlled trial in China. *International Journal of Cardiology* 2021;326:164-69. doi: 10.1016/j.ijcard.2020.10.060

360. Tacke J, Muller-Hulsbeck S, Schroder H, et al. The Randomized Freeway Stent Study: Drug-Eluting Balloons Outperform Standard Balloon Angioplasty for Postdilatation of Nitinol Stents in the SFA and PI Segment. *Cardiovasc Intervent Radiol* 2019;42(11):1513-21. doi: 10.1007/s00270-019-02309-3 [published Online First: 20190820]
361. Du X, Wang F, Wu DM, et al. Comparison between paclitaxel-coated balloon and standard uncoated balloon in the treatment of femoropopliteal long lesions in diabetics. *Medicine (Baltimore)* 2019;98(13):e14840. doi: 10.1097/MD.0000000000014840
362. Brodmann M, Werner M, Meyer DR, et al. Sustainable Antirestenosis Effect With a Low-Dose Drug-Coated Balloon: The ILLUMENATE European Randomized Clinical Trial 2-Year Results. *JACC Cardiovasc Interv* 2018;11(23):2357-64. doi: 10.1016/j.jcin.2018.08.034 [published Online First: 2018/12/14]
363. Albrecht T, Waliszewski M, Roca C, et al. Two-Year Clinical Outcomes of the CONSEQUENT Trial: Can Femoropopliteal Lesions be Treated with Sustainable Clinical Results that are Economically Sound? *CardioVascular and Interventional Radiology* 2018;41(7):1008-14. doi: 10.1007/s00270-018-1940-1
364. Steiner S, Willfort-Ehringer A, Sievert H, et al. 12-Month Results From the First-in-Human Randomized Study of the Ranger Paclitaxel-Coated Balloon for Femoropopliteal Treatment. *JACC Cardiovasc Interv* 2018;11(10):934-41. doi: 10.1016/j.jcin.2018.01.276 [published Online First: 20180502]
365. Xu Y, Jia X, Zhang J, et al. Drug-Coated Balloon Angioplasty Compared With Uncoated Balloons in the Treatment of 200 Chinese Patients With Severe Femoropopliteal Lesions: 24-Month Results of AcoArt I. *JACC: Cardiovascular Interventions* 2018;11(23):2347-53. doi: 10.1016/j.jcin.2018.07.041
366. Schneider PA, Laird JR, Tepe G, et al. Treatment Effect of Drug-Coated Balloons Is Durable to 3 Years in the Femoropopliteal Arteries: Long-Term Results of the IN.PACT SFA Randomized Trial. *Circ Cardiovasc Interv* 2018;11(1):e005891. doi: 10.1161/CIRCINTERVENTIONS.117.005891
367. Krishnan P, Faries P, Niazi K, et al. Stellarex Drug-Coated Balloon for Treatment of Femoropopliteal Disease: Twelve-Month Outcomes From the Randomized ILLUMENATE Pivotal and Pharmacokinetic Studies. *Circulation* 2017;136(12):1102-13. doi: 10.1161/CIRCULATIONAHA.117.028893 [published Online First: 20170720]
368. Rosenfield K, Jaff MR, White CJ, et al. Trial of a Paclitaxel-Coated Balloon for Femoropopliteal Artery Disease. *N Engl J Med* 2015;373(2):145-53. doi: 10.1056/NEJMoa1406235 [published Online First: 2015/06/25]
369. Scheinert D, Schulte KL, Zeller T, et al. Paclitaxel-releasing balloon in femoropopliteal lesions using a BTHC excipient: Twelve-month results from the BIOLUX P-I randomized trial. *Journal of Endovascular Therapy* 2015;22(1):14-21. doi: 10.1177/1526602814564383
370. Tepe G, Schnorr B, Albrecht T, et al. Angioplasty of femoral-popliteal arteries with drug-coated balloons: 5-year follow-up of the THUNDER trial. *JACC Cardiovasc Interv* 2015;8(1 Pt A):102-8. doi: 10.1016/j.jcin.2014.07.023
371. Scheinert D, Duda S, Zeller T, et al. The LEVANT i (lutonix paclitaxel-coated balloon for the prevention of femoropopliteal restenosis) trial for femoropopliteal revascularization: First-in-human randomized trial of low-dose drug-coated

balloon versus uncoated balloon angioplasty. *JACC: Cardiovascular Interventions* 2014;7(1):10-19. doi: 10.1016/j.jcin.2013.05.022
372. Liistro F, Grotti S, Porto I, et al. Drug-eluting balloon in peripheral intervention for the superficial femoral artery: the DEBATE-SFA randomized trial (drug eluting balloon in peripheral intervention for the superficial femoral artery). *JACC Cardiovasc Interv* 2013;6(12):1295-302. doi: 10.1016/j.jcin.2013.07.010 [published Online First: 20131113]
373. Werk M, Albrecht T, Meyer DR, et al. Paclitaxel-coated balloons reduce restenosis after femoro-popliteal angioplasty: evidence from the randomized PACIFIER trial. *Circ Cardiovasc Interv* 2012;5(6):831-40. doi: 10.1161/CIRCINTERVENTIONS.112.971630 [published Online First: 20121127]
374. Iida O, Soga Y, Urasawa K, et al. Drug-coated balloon versus uncoated percutaneous transluminal angioplasty for the treatment of atherosclerotic lesions in the superficial femoral and proximal popliteal artery: 2-year results of the MDT-2113 SFA Japan randomized trial. *Catheter Cardiovasc Interv* 2019;93(4):664-72. doi: 10.1002/ccd.28048 [published Online First: 20190212]
375. de Boer SW, de Vries JPPM, Werson DA, et al. Drug coated balloon supported Supera stent versus Supera stent in intermediate and long-segment lesions of the superficial femoral artery: 2-year results of the RAPID Trial. *Journal of Cardiovascular Surgery* 2019;60(6):679-85. doi: 10.23736/S0021-9509.19.11109-3
376. Katsanos K, Spiliopoulos S, Kitrou P, et al. Risk of Death Following Application of Paclitaxel-Coated Balloons and Stents in the Femoropopliteal Artery of the Leg: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *J Am Heart Assoc* 2018;7(24):e011245. doi: 10.1161/JAHA.118.011245 [published Online First: 2018/12/19]
377. Nordanstig J, James S, Andersson M, et al. Mortality with Paclitaxel-Coated Devices in Peripheral Artery Disease. *N Engl J Med* 2020;383(26):2538-46. doi: 10.1056/NEJMoa2005206 [published Online First: 20201209]
378. Katsanos K, Spiliopoulos S, Teichgraber U, et al. Editor's Choice - Risk of Major Amputation Following Application of Paclitaxel Coated Balloons in the Lower Limb Arteries: A Systematic Review and Meta-Analysis of Randomised Controlled Trials. *Eur J Vasc Endovasc Surg* 2022;63(1):60-71. doi: 10.1016/j.ejvs.2021.05.027 [published Online First: 20210727]
379. Zeller T, Baumgartner I, Scheinert D, et al. Drug-eluting balloon versus standard balloon angioplasty for infrapopliteal arterial revascularization in critical limb ischemia: 12-month results from the IN.PACT DEEP randomized trial. *J Am Coll Cardiol* 2014;64(15):1568-76. doi: 10.1016/j.jacc.2014.06.1198
380. Patel A, Irani FG, Pua U, et al. Randomized Controlled Trial Comparing Drug-coated Balloon Angioplasty versus Conventional Balloon Angioplasty for Treating Below-the-Knee Arteries in Critical Limb Ischemia: The SINGA-PACLI Trial. *Radiology* 2021;300(3):715-24. doi: 10.1148/radiol.2021204294 [published Online First: 20210706]
381. Zeller T, Micari A, Scheinert D, et al. The IN.PACT DEEP Clinical Drug-Coated Balloon Trial: 5-Year Outcomes. *JACC Cardiovasc Interv* 2020;13(4):431-43. doi: 10.1016/j.jcin.2019.10.059

382. Hata Y, Iida O, Ito N, et al. Roles of Angioplasty With Drug-Coated Balloon for Chronic Ischemia in Wound Healing. *J Endovasc Ther* 2021;28(5):778-87. doi: 10.1177/15266028211025023 [published Online First: 20210621]
383. Yoshikawa M, Torii S, Aihara K, et al. Differences in Biologic Drug Effects and Distal Particulate Embolization in Three Paclitaxel-Coated Balloons for Femoropopliteal Lesions in a Rabbit Model. *Journal of Endovascular Therapy* 2023 doi: 10.1177/15266028231161215
384. Torii S, Jinnouchi H, Sakamoto A, et al. Comparison of Biologic Effect and Particulate Embolization after Femoral Artery Treatment with Three Drug-Coated Balloons in Healthy Swine Model. *J Vasc Interv Radiol* 2019;30(1):103-09. doi: 10.1016/j.jvir.2018.07.025 [published Online First: 20181207]
385. Kolodgie FD, Pacheco E, Yahagi K, et al. Comparison of Particulate Embolization after Femoral Artery Treatment with IN.PACT Admiral versus Lutonix 035 Paclitaxel-Coated Balloons in Healthy Swine. *J Vasc Interv Radiol* 2016;27(11):1676-85 e2. doi: 10.1016/j.jvir.2016.06.036 [published Online First: 20160915]
386. Taneva GT, Pitoulias GA, Abu Bakr N, et al. assessment of sirolimus- vs. paClitaxel-coated balloon angioPlasty in atherosclerotic femoropopliteal lesions (asClePios study): preliminary results. *Journal of Cardiovascular Surgery* 2022;63(1):8-12. doi: 10.23736/S0021-9509.21.12169-X
387. Nakama T, Takahara M, Iwata Y, et al. Low-Dose vs High-Dose Drug-Coated Balloon for Symptomatic Femoropopliteal Artery Disease: The PROSPECT MONSTER Study Outcomes. *JACC Cardiovasc Interv* 2023;16(21):2655-65. doi: 10.1016/j.jcin.2023.08.022 [published Online First: 20231004]
388. Steiner S, Schmidt A, Zeller T, et al. Low-Dose vs High-Dose Paclitaxel-Coated Balloons for Femoropopliteal Lesions: 2-Year Results From the COMPARE Trial. *JACC Cardiovasc Interv* 2022;15(20):2093-102. doi: 10.1016/j.jcin.2022.08.004 [published Online First: 2022/10/21]
389. Shishehbor MH, Scheinert D, Jain A, et al. Comparison of Drug-Coated Balloons vs Bare-Metal Stents in Patients With Femoropopliteal Arterial Disease. *J Am Coll Cardiol* 2023;81(3):237-49. doi: 10.1016/j.jacc.2022.10.016 [published Online First: 20221101]
390. Cassese S, Ndrepepa G, Fusaro M, et al. Paclitaxel density and clinical efficacy of drug-coated balloon angioplasty for femoropopliteal artery disease: meta-analysis and adjusted indirect comparison of 20 randomised trials. *EuroIntervention : journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology* 2019;15(6):e560-e62. doi: 10.4244/EIJ-D-18-00550
391. Albrecht T, Ukrow A, Werk M, et al. Impact of Patient and Lesion Characteristics on Drug-Coated Balloon Angioplasty in the Femoropopliteal Artery: A Pooled Analysis of Four Randomized Controlled Multicenter Trials. *Cardiovasc Intervent Radiol* 2019;42(4):495-504. doi: 10.1007/s00270-018-2137-3 [published Online First: 20181211]
392. Lukacs RA, Weisshaar LI, Tornyos D, Komocsi A. Comparing Endovascular Approaches in Lower Extremity Artery Disease: Insights from a Network Meta-Analysis. *J Clin Med* 2024;13(4) doi: 10.3390/jcm13041024 [published Online First: 20240210]

393. Koeckerling D, Raguindin PF, Kastrati L, et al. Endovascular revascularization strategies for aortoiliac and femoropopliteal artery disease: a meta-analysis. *Eur Heart J* 2023;44(11):935-50. doi: 10.1093/eurheartj/ehac722
394. Ullah W, Zghouzi M, Sattar Z, et al. Safety and efficacy of drug-coated balloon for peripheral artery revascularization—A systematic review and meta-analysis. *Catheterization and Cardiovascular Interventions* 2022;99(4):1319-26. doi: 10.1002/ccd.30074
395. Abdoli S, Mert M, Lee WM, et al. Network meta-analysis of drug-coated balloon angioplasty versus primary nitinol stenting for femoropopliteal atherosclerotic disease. *J Vasc Surg* 2021;73(5):1802-10 e4. doi: 10.1016/j.jvs.2020.10.075 [published Online First: 20201126]
396. Khan MS, Zou F, Khan AR, et al. Meta-Analysis Comparing Endovascular Treatment Modalities for Femoropopliteal Peripheral Artery Disease. *Am J Cardiol* 2020;128:181-88. doi: 10.1016/j.amjcard.2020.05.015 [published Online First: 20200516]
397. Feng H, Chen X, Guo X, et al. Comparison of efficacy and safety of drug-eluting versus uncoated balloon angioplasty for femoropopliteal arterial occlusive disease: a meta-analysis. *BMC Cardiovasc Disord* 2020;20(1):395. doi: 10.1186/s12872-020-01667-y [published Online First: 20200831]
398. Liistro F, Weinberg I, Almonacid Popma A, et al. Paclitaxel-coated balloons versus percutaneous transluminal angioplasty for infrapopliteal chronic total occlusions: the IN.PACT BTK randomised trial. *EuroIntervention* 2022;17(17):e1445-e54. doi: 10.4244/EIJ-D-21-00444 [published Online First: 20220401]
399. Mustapha JA, Brodmann M, Geraghty PJ, et al. Drug-Coated vs Uncoated Percutaneous Transluminal Angioplasty in Infrapopliteal Arteries: Six-Month Results of the Lutonix BTK Trial. *J Invasive Cardiol* 2019;31(8):205-11. [published Online First: 2019/08/02]
400. Zeller T, Beschorner U, Pilger E, et al. Paclitaxel-Coated Balloon in Infrapopliteal Arteries: 12-Month Results From the BIOLUX P-II Randomized Trial (BIOTRONIK'S-First in Man study of the Passeo-18 LUX drug releasing PTA Balloon Catheter vs. the uncoated Passeo-18 PTA balloon catheter in subjects requiring revascularization of infrapopliteal arteries). *JACC Cardiovasc Interv* 2015;8(12):1614-22. doi: 10.1016/j.jcin.2015.07.011
401. Liistro F, Reccia MR, Angioli P, et al. Drug-Eluting Balloon for Below the Knee Angioplasty: Five-Year Outcome of the DEBATE-BTK Randomized Clinical Trial. *Cardiovasc Intervent Radiol* 2022;45(6):761-69. doi: 10.1007/s00270-022-03104-3 [published Online First: 20220321]
402. Liistro F, Angioli P, Ventoruzzo G, et al. Randomized Controlled Trial of Acotec Drug-Eluting Balloon Versus Plain Balloon for Below-the-Knee Angioplasty. *JACC Cardiovasc Interv* 2020;13(19):2277-86. doi: 10.1016/j.jcin.2020.06.045 [published Online First: 20200916]
403. Jia X, Zhuang B, Wang F, et al. Drug-Coated Balloon Angioplasty Compared With Uncoated Balloons in the Treatment of Infrapopliteal Artery Lesions (AcoArt II-BTK). *J Endovasc Ther* 2020:1526602820969681. doi: 10.1177/1526602820969681 [published Online First: 2020/10/30]
404. Haddad SE, Shishani JM, Qtaish I, et al. One Year Primary Patency of Infrapopliteal Angioplasty Using Drug- Eluting Balloons: Single Center Experience at King

Hussein Medical Center. *J Clin Imaging Sci* 2017;7:31. doi: 10.4103/jcis.JCIS_34_17 [published Online First: 20170803]
405. Katsanos K, Spiliopoulos S, Kitrou P, et al. Risk of Death and Amputation with Use of Paclitaxel-Coated Balloons in the Infrapopliteal Arteries for Treatment of Critical Limb Ischemia: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *J Vasc Interv Radiol* 2020;31(2):202-12. doi: 10.1016/j.jvir.2019.11.015 [published Online First: 20200115]
406. Ipema J, Huizing E, Schreve MA, et al. Editor's Choice - Drug Coated Balloon Angioplasty vs. Standard Percutaneous Transluminal Angioplasty in Below the Knee Peripheral Arterial Disease: A Systematic Review and Meta-Analysis. *Eur J Vasc Endovasc Surg* 2020;59(2):265-75. doi: 10.1016/j.ejvs.2019.10.002 [published Online First: 20191227]
407. Barbarawi M, Qazi AH, Lee J, et al. Meta-Analysis Comparing Drug-Coated Balloons and Percutaneous Transluminal Angioplasty for Infrapopliteal Artery Disease. *Am J Cardiol* 2022;183:115-21. doi: 10.1016/j.amjcard.2022.08.007 [published Online First: 20220916]
408. Cui HJ, Wu YF. The Efficacy of Drug-Coated Balloons and Drug-Eluting Stents in Infrapopliteal Revascularization: A Meta-analysis. *J Endovasc Ther* 2024:15266028231222385. doi: 10.1177/15266028231222385 [published Online First: 20240106]
409. Guo J, Ning Y, Wang H, et al. The efficacy and safety of different endovascular modalities for infrapopliteal arteries lesions: A network meta-analysis of randomized controlled trials. *Front Cardiovasc Med* 2022;9:993290. doi: 10.3389/fcvm.2022.993290 [published Online First: 20221109]
410. Giannopoulos S, Ghanian S, Parikh SA, et al. Safety and Efficacy of Drug-Coated Balloon Angioplasty for the Treatment of Chronic Limb-Threatening Ischemia: A Systematic Review and Meta-Analysis. *J Endovasc Ther* 2020;27(4):647-57. doi: 10.1177/1526602820931559 [published Online First: 20200607]
411. Schillinger M, Sabeti S, Dick P, et al. Sustained benefit at 2 years of primary femoropopliteal stenting compared with balloon angioplasty with optional stenting. *Circulation* 2007;115(21):2745-9. doi: 10.1161/CIRCULATIONAHA.107.688341 [published Online First: 20070514]
412. Chalmers N, Walker PT, Belli AM, et al. Randomized trial of the SMART stent versus balloon angioplasty in long superficial femoral artery lesions: the SUPER study. *Cardiovasc Intervent Radiol* 2013;36(2):353-61. doi: 10.1007/s00270-012-0492-z [published Online First: 20121016]
413. Dick P, Wallner H, Sabeti S, et al. Balloon angioplasty versus stenting with nitinol stents in intermediate length superficial femoral artery lesions. *Catheter Cardiovasc Interv* 2009;74(7):1090-5. doi: 10.1002/ccd.22128
414. Laird JR, Katzen BT, Scheinert D, et al. Nitinol stent implantation vs. balloon angioplasty for lesions in the superficial femoral and proximal popliteal arteries of patients with claudication: three-year follow-up from the RESILIENT randomized trial. *J Endovasc Ther* 2012;19(1):1-9. doi: 10.1583/11-3627.1 [published Online First: 2012/02/09]
415. Rastan A, Krankenberg H, Baumgartner I, et al. Stent placement vs. balloon angioplasty for popliteal artery treatment: Two-year results of a prospective,

multicenter, randomized trial. *Journal of Endovascular Therapy* 2015;22(1):22-27. doi: 10.1177/1526602814564386
416. Saxon RR, Coffman JM, Gooding JM, et al. Long-term results of ePTFE stent-graft versus angioplasty in the femoropopliteal artery: single center experience from a prospective, randomized trial. *J Vasc Interv Radiol* 2003;14(3):303-11. doi: 10.1097/01.rvi.0000058425.01661.d0
417. Saxon RR, Dake MD, Volgelzang RL, et al. Randomized, multicenter study comparing expanded polytetrafluoroethylene-covered endoprosthesis placement with percutaneous transluminal angioplasty in the treatment of superficial femoral artery occlusive disease. *J Vasc Interv Radiol* 2008;19(6):823-32. doi: 10.1016/j.jvir.2008.02.008 [published Online First: 20080410]
418. Geraghty PJ, Mewissen MW, Jaff MR, Ansel GM. Three-year results of the VIBRANT trial of VIABAHN endoprosthesis versus bare nitinol stent implantation for complex superficial femoral artery occlusive disease. *Journal of Vascular Surgery* 2013;58(2):386-95. doi: 10.1016/j.jvs.2013.01.050
419. Lammer J, Zeller T, Hausegger KA, et al. Sustained benefit at 2 years for covered stents versus bare-metal stents in long SFA lesions: the VIASTAR trial. *Cardiovasc Intervent Radiol* 2015;38(1):25-32. doi: 10.1007/s00270-014-1024-9 [published Online First: 20141205]
420. Ott I, Cassese S, Groha P, et al. Randomized Comparison of Paclitaxel-Eluting Balloon and Stenting Versus Plain Balloon Plus Stenting Versus Directional Atherectomy for Femoral Artery Disease (ISAR-STATH). *Circulation* 2017;135(23):2218-26. doi: 10.1161/CIRCULATIONAHA.116.025329
421. Zhao S, Li L, Cui K. Network Analysis of Endovascular Treatment Strategies for Femoropopliteal Arterial Occlusive Disease. *J Endovasc Ther* 2023;30(4):487-98. doi: 10.1177/15266028221090434 [published Online First: 20220408]
422. Dubosq-Lebaz M, Fels A, Chatellier G, Gouëffic Y. Systematic Review and Meta-analysis of Clinical Outcomes After Endovascular Treatment in Patients With Femoropopliteal Lesions Greater Than 50 mm. *Journal of Endovascular Therapy* 2023 doi: 10.1177/15266028231202709
423. Kinstner CM, Lammer J, Willfort-Ehringer A, et al. Paclitaxel-Eluting Balloon Versus Standard Balloon Angioplasty in In-Stent Restenosis of the Superficial Femoral and Proximal Popliteal Artery: 1-Year Results of the PACUBA Trial. *JACC: Cardiovascular Interventions* 2016;9(13):1386-92. doi: 10.1016/j.jcin.2016.04.012
424. Krankenberg H, Tubler T, Ingwersen M, et al. Drug-Coated Balloon Versus Standard Balloon for Superficial Femoral Artery In-Stent Restenosis: The Randomized Femoral Artery In-Stent Restenosis (FAIR) Trial. *Circulation* 2015;132(23):2230-6. doi: 10.1161/CIRCULATIONAHA.115.017364 [published Online First: 20151007]
425. Liao CJ, Song SH, Li T, et al. Randomized controlled trial of orchid drug-coated balloon versus standard percutaneous transluminal angioplasty for treatment of femoropopliteal artery in-stent restenosis. *Int Angiol* 2019;38(5):365-71. doi: 10.23736/S0392-9590.19.04243-3 [published Online First: 20190927]
426. Liistro F, Angioli P, Porto I, et al. Paclitaxel-eluting balloon vs. standard angioplasty to reduce recurrent restenosis in diabetic patients with in-stent restenosis of the superficial femoral and proximal popliteal arteries: the DEBATE-ISR study. *J*

Endovasc Ther 2014;21(1):1-8. doi: 10.1583/13-4420R.1 [published Online First: 2014/02/08]
427. Tepe G, Schroeder H, Albrecht T, et al. Paclitaxel-Coated Balloon vs Uncoated Balloon Angioplasty for Treatment of In-Stent Restenosis in the Superficial Femoral and Popliteal Arteries: The COPA CABANA Trial. *J Endovasc Ther* 2020;27(2):276-86. doi: 10.1177/1526602820907917 [published Online First: 20200225]
428. Bosiers M, Deloose K, Callaert J, et al. Stent-grafts are the best way to treat complex in-stent restenosis lesions in the superficial femoral artery: 24-month results from a multicenter randomized trial. *Journal of Cardiovascular Surgery* 2020;61(5):617-25. doi: 10.23736/S0021-9509.20.11382-X
429. Gandini R, Del Giudice C, Merolla S, et al. Treatment of chronic SFA in-stent occlusion with combined laser atherectomy and drug-eluting balloon angioplasty in patients with critical limb ischemia: a single-center, prospective, randomized study. *J Endovasc Ther* 2013;20(6):805-14. doi: 10.1583/13-4308MR.1
430. Dippel EJ, Makam P, Kovach R, et al. Randomized controlled study of excimer laser atherectomy for treatment of femoropopliteal in-stent restenosis: initial results from the EXCITE ISR trial (EXCImer Laser Randomized Controlled Study for Treatment of FemoropopliTEal In-Stent Restenosis). *JACC Cardiovasc Interv* 2015;8(1 Pt A):92-101. doi: 10.1016/j.jcin.2014.09.009 [published Online First: 20141210]
431. Brodmann M, Rief P, Froehlich H, et al. Neointimal hyperplasia after silverhawk atherectomy versus percutaneous transluminal angioplasty (PTA) in femoropopliteal stent reobstructions: a controlled, randomized pilot trial. *Cardiovasc Intervent Radiol* 2013;36(1):69-74. doi: 10.1007/s00270-012-0479-9 [published Online First: 20120925]
432. Bohme T, Noory E, Beschorner U, et al. Photoablative atherectomy followed by a paclitaxel-coated balloon to inhibit restenosis in instent femoro-popliteal obstructions (PHOTOPAC). *Vasa* 2021;50(5):387-93. doi: 10.1024/0301-1526/a000959 [published Online First: 20210610]
433. Dick P, Sabeti S, Mlekusch W, et al. Conventional balloon angioplasty versus peripheral cutting balloon angioplasty for treatment of femoropopliteal artery in-stent restenosis: initial experience. *Radiology* 2008;248(1):297-302. doi: 10.1148/radiol.2481071159
434. Ahn J, Yu H, Rha SW, et al. Randomized clinical trial to compare the efficacy of self-expanding bare metal nitinol stent and balloon angioplasty alone for below-the-knee lesions following successful balloon angioplasty: 1-year clinical outcomes. *PLoS One* 2023;18(11):e0294132. doi: 10.1371/journal.pone.0294132 [published Online First: 20231113]
435. Schulte KL, Pilger E, Schellong S, et al. Primary Self-EXPANDing Nitinol Stenting vs Balloon Angioplasty With Optional Bailout Stenting for the Treatment of Infrapopliteal Artery Disease in Patients With Severe Intermittent Claudication or Critical Limb Ischemia (EXPAND Study). *J Endovasc Ther* 2015;22(5):690-7. doi: 10.1177/1526602815598955 [published Online First: 20150805]
436. Rand T, Lammer J, Rabbia C, et al. Percutaneous transluminal angioplasty versus turbostatic carbon-coated stents in infrapopliteal arteries: InPeria II trial. *Radiology* 2011;261(2):634-42. doi: 10.1148/radiol.11101357

437. Brodmann M, Froehlich H, Dorr A, et al. Percutaneous transluminal angioplasty versus primary stenting in infrapopliteal arteries in critical limb ischemia. *Vasa* 2011;40(6):482-90. doi: 10.1024/0301-1526/a000152
438. Randon C, Jacobs B, De Ryck F, Vermassen F. Angioplasty or primary stenting for infrapopliteal lesions: results of a prospective randomized trial. *Cardiovasc Intervent Radiol* 2010;33(2):260-9. doi: 10.1007/s00270-009-9765-6 [published Online First: 20091203]
439. Bosiers M, Peeters P, D'Archambeau O, et al. AMS INSIGHT--absorbable metal stent implantation for treatment of below-the-knee critical limb ischemia: 6-month analysis. *Cardiovasc Intervent Radiol* 2009;32(3):424-35. doi: 10.1007/s00270-008-9472-8 [published Online First: 20081218]
440. Rand T, Basile A, Cejna M, et al. PTA versus carbofilm-coated stents in infrapopliteal arteries: pilot study. *Cardiovasc Intervent Radiol* 2006;29(1):29-38. doi: 10.1007/s00270-005-0276-9
441. Biondi-Zoccai GG, Sangiorgi G, Lotrionte M, et al. Infragenicular stent implantation for below-the-knee atherosclerotic disease: clinical evidence from an international collaborative meta-analysis on 640 patients. *J Endovasc Ther* 2009;16(3):251-60. doi: 10.1583/09-2691.1
442. Gouëffic Y, Torsello G, Zeller T, et al. Efficacy of a Drug-Eluting Stent Versus Bare Metal Stents for Symptomatic Femoropopliteal Peripheral Artery Disease: Primary Results of the EMINENT Randomized Trial. *Circulation* 2022;146(21):1564-76. doi: 10.1161/CIRCULATIONAHA.122.059606
443. Dake MD, Ansel GM, Jaff MR, et al. Durable Clinical Effectiveness With Paclitaxel-Eluting Stents in the Femoropopliteal Artery: 5-Year Results of the Zilver PTX Randomized Trial. *Circulation* 2016;133(15):1472-83; discussion 83. doi: 10.1161/CIRCULATIONAHA.115.016900 [published Online First: 20160311]
444. Fransson T, Gottsater A, Abdulrasak M, et al. Randomized clinical Trial Comparing drug Eluting Stent Zilver PTX(R) Versus Bare Metal Stent Zilver Flex(R) for Treatment of Lesions in Femoral and Popliteal Arteries in Chronic Limb Threatening Ischemia. *Vasc Endovascular Surg* 2023;57(7):706-16. doi: 10.1177/15385744231171746 [published Online First: 20230421]
445. Muller-Hulsbeck S, Benko A, Soga Y, et al. Two-Year Efficacy and Safety Results from the IMPERIAL Randomized Study of the Eluvia Polymer-Coated Drug-Eluting Stent and the Zilver PTX Polymer-free Drug-Coated Stent. *Cardiovasc Intervent Radiol* 2021;44(3):368-75. doi: 10.1007/s00270-020-02693-1 [published Online First: 20201122]
446. Falkowski A, Bogacki H, Szemitko M. Assessment of Mortality and Factors Affecting Outcome of Use of Paclitaxel-Coated Stents and Bare Metal Stents in Femoropopliteal PAD. *J Clin Med* 2020;9(7) doi: 10.3390/jcm9072221 [published Online First: 20200713]
447. Liistro F, Angioli P, Porto I, et al. Drug-Eluting Balloon Versus Drug-Eluting Stent for Complex Femoropopliteal Arterial Lesions: The DRASTICO Study. *J Am Coll Cardiol* 2019;74(2):205-15. doi: 10.1016/j.jacc.2019.04.057
448. Bausback Y, Wittig T, Schmidt A, et al. Drug-Eluting Stent Versus Drug-Coated Balloon Revascularization in Patients With Femoropopliteal Arterial Disease. *Journal of the American College of Cardiology* 2019;73(6):667-79. doi: 10.1016/j.jacc.2018.11.039

449. Miura T, Miyashita Y, Soga Y, et al. Drug-Eluting Versus Bare-Metal Stent Implantation With or Without Cilostazol in the Treatment of the Superficial Femoral Artery. *Circ Cardiovasc Interv* 2018;11(8):e006564. doi: 10.1161/CIRCINTERVENTIONS.118.006564 [published Online First: 2018/10/26]
450. Duda SH, Bosiers M, Lammer J, et al. Drug-eluting and bare nitinol stents for the treatment of atherosclerotic lesions in the superficial femoral artery: long-term results from the SIROCCO trial. *J Endovasc Ther* 2006;13(6):701-10. doi: 10.1583/05-1704.1
451. Park JI, Ko YG, Lee YJ, et al. Long coverage with drug-eluting stents is superior to spot coverage for long femoropopliteal artery disease: PARADE II study. *Front Cardiovasc Med* 2022;9:1022071. doi: 10.3389/fcvm.2022.1022071 [published Online First: 20221019]
452. Zhou Y, Zhang Z, Lin S, et al. Comparative Effectiveness of Endovascular Treatment Modalities for De Novo Femoropopliteal Lesions: A Network Meta-analysis of Randomized Controlled Trials. *J Endovasc Ther* 2020;27(1):42-59. doi: 10.1177/1526602819895996 [published Online First: 2020/01/18]
453. Li M, Tu H, Yan Y, et al. Meta-analysis of outcomes from drug-eluting stent implantation in femoropopliteal arteries. *PLoS One* 2023;18(9):e0291466. doi: 10.1371/journal.pone.0291466 [published Online First: 20230921]
454. Zenunaj G, Traina L, Acciarri P, et al. Primary Drug-Coated Balloon Versus Drug-Eluting Stent for Native Atherosclerotic Femoropopliteal Lesions: A Systematic Review and Meta-Analysis. *Ann Vasc Surg* 2023;92:294-303. doi: 10.1016/j.avsg.2023.01.043 [published Online First: 20230204]
455. Miki K, Tanaka T, Yanaka K, et al. Influence of self-expanding paclitaxel-eluting stent sizing on neointimal hyperplasia in superficial femoral artery lesions. *Circulation Journal* 2020;84(10):1854-61. doi: 10.1253/circj.CJ-20-0470
456. Feiring AJ, Krahn M, Nelson L, et al. Preventing leg amputations in critical limb ischemia with below-the-knee drug-eluting stents: the PaRADISE (PReventing Amputations using Drug eluting StEnts) trial. *J Am Coll Cardiol* 2010;55(15):1580-9. doi: 10.1016/j.jacc.2009.11.072
457. Varcoe RL, DeRubertis BG, Kolluri R, et al. Drug-Eluting Resorbable Scaffold versus Angioplasty for Infrapopliteal Artery Disease. *N Engl J Med* 2024;390(1):9-19. doi: 10.1056/NEJMoa2305637 [published Online First: 20231025]
458. van Overhagen H, Nakamura M, Geraghty PJ, et al. Primary results of the SAVAL randomized trial of a paclitaxel-eluting nitinol stent versus percutaneous transluminal angioplasty in infrapopliteal arteries. *Vasc Med* 2023;28(6):571-80. doi: 10.1177/1358863X231199489 [published Online First: 20231016]
459. Spreen MI, Martens JM, Knippenberg B, et al. Long-Term Follow-up of the PADI Trial: Percutaneous Transluminal Angioplasty Versus Drug-Eluting Stents for Infrapopliteal Lesions in Critical Limb Ischemia. *J Am Heart Assoc* 2017;6(4) doi: 10.1161/JAHA.116.004877 [published Online First: 20170414]
460. Siablis D, Kitrou PM, Spiliopoulos S, et al. Paclitaxel-coated balloon angioplasty versus drug-eluting stenting for the treatment of infrapopliteal long-segment arterial occlusive disease: The IDEAS randomized controlled trial. *JACC: Cardiovascular Interventions* 2014;7(9):1048-56. doi: 10.1016/j.jcin.2014.04.015

461. Scheinert D, Katsanos K, Zeller T, et al. A prospective randomized multicenter comparison of balloon angioplasty and infrapopliteal stenting with the sirolimus-eluting stent in patients with ischemic peripheral arterial disease: 1-year results from the ACHILLES trial. *J Am Coll Cardiol* 2012;60(22):2290-5. doi: 10.1016/j.jacc.2012.08.989
462. Rastan A, Brechtel K, Krankenberg H, et al. Sirolimus-eluting stents for treatment of infrapopliteal arteries reduce clinical event rate compared to bare-metal stents: long-term results from a randomized trial. *J Am Coll Cardiol* 2012;60(7):587-91. doi: 10.1016/j.jacc.2012.04.035
463. Bosiers M, Scheinert D, Peeters P, et al. Randomized comparison of everolimus-eluting versus bare-metal stents in patients with critical limb ischemia and infrapopliteal arterial occlusive disease. *J Vasc Surg* 2012;55(2):390-8. doi: 10.1016/j.jvs.2011.07.099 [published Online First: 20111214]
464. Falkowski A, Poncyljusz W, Wilk G, Szczerbo-Trojanowska M. The evaluation of primary stenting of sirolimus-eluting versus bare-metal stents in the treatment of atherosclerotic lesions of crural arteries. *Eur Radiol* 2009;19(4):966-74. doi: 10.1007/s00330-008-1225-1 [published Online First: 20081126]
465. Li Y, Shen X, Zhuang H. Comparation of drug-eluting stents and control therapy for the treatment of infrapopliteal artery disease: a Bayesian analysis. *Int J Surg* 2023;109(12):4286-97. doi: 10.1097/JS9.0000000000000736 [published Online First: 20231201]
466. Li MX, Tu HX, Yin MC. Meta-analysis of outcomes from drug-eluting stent implantation in infrapopliteal arteries. *World J Clin Cases* 2023;11(22):5273-87. doi: 10.12998/wjcc.v11.i22.5273
467. Fong KY, Xin L, Ng J, et al. A systematic review and meta-analysis of sirolimus-eluting stents for treatment of below-the-knee arterial disease. *Journal of Vascular Surgery* 2023;77(4):1264-73.e3. doi: 10.1016/j.jvs.2022.09.022
468. Wang J, Chen X, Zhao J, Zhang WW. Systematic Review and Meta-analysis of the Outcomes of Drug-Eluting Stent Versus Drug-Coated Balloon Angioplasty for Lower Extremity Peripheral Artery Diseases. *Ann Vasc Surg* 2022;85:1-8 e5. doi: 10.1016/j.avsg.2022.04.039 [published Online First: 20220511]
469. Shammas NW, Shammas G, Christensen L, et al. Jetstream Atherectomy with Paclitaxel-Coated Balloons: Two-Year Outcome of the Prospective Randomized JET-RANGER Study. *Vasc Health Risk Manag* 2023;19:133-37. doi: 10.2147/VHRM.S403177 [published Online First: 20230311]
470. Cai Z, Guo L, Qi L, et al. Midterm Outcome of Directional Atherectomy Combined with Drug-Coated Balloon Angioplasty Versus Drug-Coated Balloon Angioplasty Alone for Femoropopliteal Arteriosclerosis Obliterans. *Ann Vasc Surg* 2020;64:181-87. doi: 10.1016/j.avsg.2019.06.014 [published Online First: 20190823]
471. Zeller T, Langhoff R, Rocha-Singh KJ, et al. Directional Atherectomy Followed by a Paclitaxel-Coated Balloon to Inhibit Restenosis and Maintain Vessel Patency: Twelve-Month Results of the DEFINITIVE AR Study. *Circ Cardiovasc Interv* 2017;10(9):e004848. doi: 10.1161/CIRCINTERVENTIONS.116.004848
472. Dattilo R, Himmelstein SI, Cuff RF. The COMPLIANCE 360° trial: A randomized, prospective, multicenter, pilot study comparing acute and long-term results of

orbital atherectomy to balloon angioplasty for calcified femoropopliteal disease. *Journal of Invasive Cardiology* 2014;26(8):355-60.
473. Shammas NW, Coiner D, Shammas GA, et al. Percutaneous lower-extremity arterial interventions with primary balloon angioplasty versus SilverHawk atherectomy and adjunctive balloon angioplasty: Randomized trial. *Journal of Vascular and Interventional Radiology* 2011;22(9):1223-28. doi: 10.1016/j.jvir.2011.05.013
474. Tielbeek AV, Vroegindeweij D, Buth J, Landman GH. Comparison of balloon angioplasty and Simpson atherectomy for lesions in the femoropopliteal artery: angiographic and clinical results of a prospective randomized trial. *Journal of vascular and interventional radiology : JVIR* 1996;7(6):837-44.
475. Vroegindeweij D, Kemper FJ, Tielbeek AV, et al. Recurrence of stenoses following balloon angioplasty and Simpson atherectomy of the femoro-popliteal segment. A randomised comparative 1-year follow-up study using colour flow duplex. *Eur J Vasc Surg* 1992;6(2):164-71. doi: 10.1016/s0950-821x(05)80235-x
476. Lammer J, Pilger E, Decrinis M, et al. Pulsed excimer laser versus continuous-wave Nd:YAG laser versus conventional angioplasty of peripheral arterial occlusions: prospective, controlled, randomised trial. *Lancet* 1992;340(8829):1183-8. doi: 10.1016/0140-6736(92)92891-i
477. Huppert PE, Duda SH, Helber U, et al. Comparison of pulsed laser-assisted angioplasty and balloon angioplasty in femoropopliteal artery occlusions. *Radiology* 1992;184(2):363-7. doi: 10.1148/radiology.184.2.1535716
478. Belli AM, Cumberland DC, Procter AE, Welsh CL. Follow-up of conventional angioplasty versus laser thermal angioplasty for total femoropopliteal artery occlusions: results of a randomized trial. *Journal of vascular and interventional radiology : JVIR* 1991;2(4):485-88. doi: 10.1016/S1051-0443(91)72229-X
479. Pan D, Guo J, Su Z, et al. Efficacy and Safety of Atherectomy Combined With Balloon Angioplasty vs Balloon Angioplasty Alone in Patients With Femoro-Popliteal Lesions: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *J Endovasc Ther* 2023:15266028231215354. doi: 10.1177/15266028231215354 [published Online First: 20231204]
480. Wu Z, Huang Q, Pu H, et al. Atherectomy Combined with Balloon Angioplasty versus Balloon Angioplasty Alone for de Novo Femoropopliteal Arterial Diseases: A Systematic Review and Meta-analysis of Randomised Controlled Trials. *Eur J Vasc Endovasc Surg* 2021;62(1):65-73. doi: 10.1016/j.ejvs.2021.02.012 [published Online First: 20210608]
481. Lin F, Wang H, Ding W, et al. Atherectomy plus drug-coated balloon versus drug-coated balloon only for treatment of femoropopliteal artery lesions: A systematic review and meta-analysis. *Vascular* 2021;29(6):883-96. doi: 10.1177/1708538120985732 [published Online First: 20210121]
482. Babaev A, Halista M, Bakirova Z, et al. Directional versus orbital atherectomy of femoropopliteal artery lesions: Angiographic and intravascular ultrasound outcomes. *Catheter Cardiovasc Interv* 2022;100(4):687-95. doi: 10.1002/ccd.30339 [published Online First: 20220716]
483. Zeller T, Giannopoulos S, Brodmann M, et al. Orbital Atherectomy Prior to Drug-Coated Balloon Angioplasty in Calcified Infrapopliteal Lesions: A Randomized, Multicenter Pilot Study. *J Endovasc Ther* 2022;29(6):874-84. doi: 10.1177/15266028211070968 [published Online First: 20220127]

484. Rastan A, Brodmann M, Böhme T, et al. Atherectomy and Drug-Coated Balloon Angioplasty for the Treatment of Long Infrapopliteal Lesions: A Randomized Controlled Trial. *Circulation: Cardiovascular Interventions* 2021;14(6):E010280. doi: 10.1161/CIRCINTERVENTIONS.120.010280
485. Wu H, Zheng D, Zhou L, et al. A Systematic Review and Meta-analysis of Atherectomy Plus Balloon Angioplasty Versus Balloon Angioplasty Alone for Infrapopliteal Arterial Disease. *J Endovasc Ther* 2023:15266028231209236. doi: 10.1177/15266028231209236 [published Online First: 20231107]
486. Nugteren MJ, Welling RHA, Bakker OJ, et al. Vessel Preparation in Infrapopliteal Arterial Disease: A Systematic Review and Meta-Analysis. *J Endovasc Ther* 2022:15266028221120752. doi: 10.1177/15266028221120752 [published Online First: 20220904]
487. Argyriou C, Schoretsanitis N, Georgakarakos EI, et al. Preemptive open surgical vs. endovascular repair for juxta-anastomotic stenoses of autogenous AV fistulae: a meta-analysis. *J Vasc Access* 2015;16(6):454-8. doi: 10.5301/jva.5000444 [published Online First: 20150629]
488. Kwon H, Choi JY, Ko HK, et al. Comparison of surgical and endovascular salvage procedures for juxta-anastomotic stenosis in autogenous wrist radiocephalic arteriovenous fistula. *Ann Vasc Surg* 2014;28(8):1840-6. doi: 10.1016/j.avsg.2014.06.060 [published Online First: 20140707]
489. Long B, Brichart N, Lermusiaux P, et al. Management of perianastomotic stenosis of direct wrist autogenous radial-cephalic arteriovenous accesses for dialysis. *J Vasc Surg* 2011;53(1):108-14. doi: 10.1016/j.jvs.2010.08.007 [published Online First: 20100922]
490. Napoli M, Prudenzano R, Russo F, et al. Juxta-anastomotic stenosis of native arteriovenous fistulas: surgical treatment versus percutaneous transluminal angioplasty. *J Vasc Access* 2010;11(4):346-51. doi: 10.5301/jva.2010.5968
491. Tessitore N, Mansueto G, Lipari G, et al. Endovascular versus surgical preemptive repair of forearm arteriovenous fistula juxta-anastomotic stenosis: analysis of data collected prospectively from 1999 to 2004. *Clin J Am Soc Nephrol* 2006;1(3):448-54. doi: 10.2215/CJN.01351005 [published Online First: 20060301]
492. Brooks JL, Sigley RD, May KJ, Jr., Mack RM. Transluminal angioplasty versus surgical repair for stenosis of hemodialysis grafts. A randomized study. *Am J Surg* 1987;153(6):530-1. doi: 10.1016/0002-9610(87)90148-6
493. Hoffer EK, Sultan S, Herskowitz MM, et al. Prospective randomized trial of a metallic intravascular stent in hemodialysis graft maintenance. *J Vasc Interv Radiol* 1997;8(6):965-73. doi: 10.1016/s1051-0443(97)70695-x
494. Quinn SF, Schuman ES, Demlow TA, et al. Percutaneous transluminal angioplasty versus endovascular stent placement in the treatment of venous stenoses in patients undergoing hemodialysis: intermediate results. *J Vasc Interv Radiol* 1995;6(6):851-5. doi: 10.1016/s1051-0443(95)71200-3
495. Beathard GA. Gianturco self-expanding stent in the treatment of stenosis in dialysis access grafts. *Kidney Int* 1993;43(4):872-7. doi: 10.1038/ki.1993.122
496. Kakisis JD, Avgerinos E, Giannakopoulos T, et al. Balloon angioplasty vs nitinol stent placement in the treatment of venous anastomotic stenoses of hemodialysis grafts after surgical thrombectomy. *J Vasc Surg* 2012;55(2):472-8. doi: 10.1016/j.jvs.2011.08.043 [published Online First: 20111216]

497. Chan MR, Bedi S, Sanchez RJ, et al. Stent placement versus angioplasty improves patency of arteriovenous grafts and blood flow of arteriovenous fistulae. *Clin J Am Soc Nephrol* 2008;3(3):699-705. doi: 10.2215/CJN.04831107 [published Online First: 20080206]
498. Vogel PM, Parise C. Comparison of SMART stent placement for arteriovenous graft salvage versus successful graft PTA. *J Vasc Interv Radiol* 2005;16(12):1619-26. doi: 10.1097/01.RVI.0000179792.23867.01
499. Dolmatch B, Cabrera T, Pergola P, et al. Prospective, randomized, multicenter clinical study comparing a self-expanding covered stent to percutaneous transluminal angioplasty for treatment of upper extremity hemodialysis arteriovenous fistula stenosis. *Kidney International* 2023;104(1):189-200. doi: 10.1016/j.kint.2023.03.015
500. Falk A, Maya ID, Yevzlin AS, Investigators R. A Prospective, Randomized Study of an Expanded Polytetrafluoroethylene Stent Graft versus Balloon Angioplasty for In-Stent Restenosis in Arteriovenous Grafts and Fistulae: Two-Year Results of the RESCUE Study. *J Vasc Interv Radiol* 2016;27(10):1465-76. doi: 10.1016/j.jvir.2016.06.014 [published Online First: 2016/08/16]
501. Haskal ZJ, Saad TF, Hoggard JG, et al. Prospective, Randomized, Concurrently-Controlled Study of a Stent Graft versus Balloon Angioplasty for Treatment of Arteriovenous Access Graft Stenosis: 2-Year Results of the RENOVA Study. *J Vasc Interv Radiol* 2016;27(8):1105-14.e3. doi: 10.1016/j.jvir.2016.05.019 [published Online First: 20160704]
502. Haskal ZJ, Trerotola S, Dolmatch B, et al. Stent graft versus balloon angioplasty for failing dialysis-access grafts. *New England Journal of Medicine* 2010;362(6):494-503. doi: 10.1056/NEJMoa0902045
503. Kavan J, Kudlicka J, Malik J, et al. Treatment of failing arterio-venous dialysis graft by angioplasty, stent, and stent graft: Two-years analysis of patency rates and cost-effectiveness. *Experimental and Therapeutic Medicine* 2019;18(5):4144-50. doi: 10.3892/etm.2019.8050
504. Mohr BA, Sheen AL, Roy-Chaudhury P, et al. Clinical and Economic Benefits of Stent Grafts in Dysfunctional and Thrombosed Hemodialysis Access Graft Circuits in the REVISE Randomized Trial. *Journal of Vascular and Interventional Radiology* 2019;30(2):203-11.e4. doi: 10.1016/j.jvir.2018.12.006
505. Rajan DK, Falk A. A Randomized Prospective Study Comparing Outcomes of Angioplasty versus VIABAHN Stent-Graft Placement for Cephalic Arch Stenosis in Dysfunctional Hemodialysis Accesses. *Journal of Vascular and Interventional Radiology* 2015;26(9):1355-61. doi: 10.1016/j.jvir.2015.05.001
506. Vesely T, DaVanzo W, Behrend T, et al. Balloon angioplasty versus Viabahn stent graft for treatment of failing or thrombosed prosthetic hemodialysis grafts. *Journal of Vascular Surgery* 2016;64(5):1400-10.e1. doi: 10.1016/j.jvs.2016.04.035
507. Yang HT, Yu SY, Su TW, et al. A prospective randomized study of stent graft placement after balloon angioplasty versus balloon angioplasty alone for the treatment of hemodialysis patients with prosthetic graft outflow stenosis. *Journal of Vascular Surgery* 2018;68(2):546-53. doi: 10.1016/j.jvs.2017.12.062
508. Shemesh D, Goldin I, Zaghal I, et al. Angioplasty with stent graft versus bare stent for recurrent cephalic arch stenosis in autogenous arteriovenous access for

hemodialysis: A prospective randomized clinical trial. *Journal of Vascular Surgery* 2008;48(6):1524-31.e2. doi: 10.1016/j.jvs.2008.07.071
509. Aftab SA, Tay KH, Irani FG, et al. Randomized clinical trial of cutting balloon angioplasty versus high-pressure balloon angioplasty in hemodialysis arteriovenous fistula stenoses resistant to conventional balloon angioplasty. *Journal of Vascular and Interventional Radiology* 2014;25(2):190-98. doi: 10.1016/j.jvir.2013.10.020
510. Murakami M, Furushima D, Hamamoto S, et al. Comparison of peripheral cutting balloon angioplasty with conventional balloon angioplasty for recurrent hemodialysis vascular access stenosis: A prospective randomized controlled trial. *Journal of Vascular Access* 2023 doi: 10.1177/11297298231209489
511. Rasuli P, Chennur VS, Connolly MJ, et al. Randomized trial comparing the primary patency following cutting versus high-pressure balloon angioplasty for treatment of de novo venous stenoses in hemodialysis arteriovenous fistulae. *Journal of Vascular and Interventional Radiology* 2015;26(12):1840-46e1. doi: 10.1016/j.jvir.2015.08.024
512. Saleh HM, Gabr AK, Tawfik MM, Abouellail H. Prospective, randomized study of cutting balloon angioplasty versus conventional balloon angioplasty for the treatment of hemodialysis access stenoses. *Journal of Vascular Surgery* 2014;60(3):735-40. doi: 10.1016/j.jvs.2014.04.002
513. Vesely TM, Siegel JB. Use of the peripheral cutting balloon to treat hemodialysis-related stenoses. *J Vasc Interv Radiol* 2005;16(12):1593-603. doi: 10.1097/01.RVI.0000190928.19701.DD
514. Pinelo A, Almeida P, Loureiro L, et al. Use of a Paclitaxel Drug-Eluting Stent for the Treatment of Hemodialysis Access Outflow Stenosis. *J Vasc Interv Radiol* 2024;35(3):384-89. doi: 10.1016/j.jvir.2023.11.010 [published Online First: 20231122]
515. Shaikh A, Albalas A, Desiraju B, et al. The role of stents in hemodialysis vascular access. *J Vasc Access* 2023;24(1):107-16. doi: 10.1177/11297298211015069 [published Online First: 20210517]
516. Katsanos K, Ho P, Tang TY, et al. Polymer-coated paclitaxel-eluting stents for the treatment of stenosed native arteriovenous fistulas: Long-term results from the ELUDIA study. *J Vasc Access* 2023:11297298231174263. doi: 10.1177/11297298231174263 [published Online First: 20230621]
517. Hongsakul K, Akkakrisee S, Bannangkoon K, et al. Results of drug-eluting stent in significant restenosis of the hemodialysis access: An initial study. *Semin Dial* 2022;35(2):165-70. doi: 10.1111/sdi.12993 [published Online First: 20210616]
518. Bjorkman P, Weselius EM, Kokkonen T, et al. Drug-Coated Versus Plain Balloon Angioplasty In Arteriovenous Fistulas: A Randomized, Controlled Study With 1-Year Follow-Up (The Drecorest Ii-Study). *Scand J Surg* 2019;108(1):61-66. doi: 10.1177/1457496918798206 [published Online First: 2018/09/06]
519. Fransson T, Gottsater A, Abdulrasak M, et al. Drug-eluting balloon (DEB) versus plain old balloon angioplasty (POBA) in the treatment of failing dialysis access: A prospective randomized trial. *J Int Med Res* 2022;50(3):3000605221081662. doi: 10.1177/03000605221081662 [published Online First: 2022/04/01]
520. Irani FG, Teo TKB, Tay KH, et al. Hemodialysis arteriovenous fistula and graft stenoses: Randomized trial comparing drug-eluting balloon angioplasty with

conventional angioplasty. *Radiology* 2018;289(1):238-47. doi: 10.1148/radiol.2018170806
521. Karmota AG. Paclitaxel coated-balloon (PCB) versus standard plain old balloon (POB) fistuloplasty for failing dialysis access. *Ann R Coll Surg Engl* 2020;102(8):601-05. doi: 10.1308/rcsann.2020.0121 [published Online First: 20200615]
522. Karunanithy N, Robinson EJ, Ahmad F, et al. A multicenter randomized controlled trial indicates that paclitaxel-coated balloons provide no benefit for arteriovenous fistulas. *Kidney International* 2021;100(2):447-56. doi: 10.1016/j.kint.2021.02.040
523. Kim JW, Kim JH, Byun SS, et al. Paclitaxel-coated balloon versus plain balloon angioplasty for dysfunctional autogenous radiocephalic arteriovenous fistulas: A prospective randomized controlled trial. *Korean Journal of Radiology* 2020;21(11):1239-47. doi: 10.3348/kjr.2020.0067
524. Kitrou PM, Katsanos K, Spiliopoulos S, et al. Drug-eluting versus plain balloon angioplasty for the treatment of failing dialysis access: final results and cost-effectiveness analysis from a prospective randomized controlled trial (NCT01174472). *Eur J Radiol* 2015;84(3):418-23. doi: 10.1016/j.ejrad.2014.11.037 [published Online First: 20141215]
525. Kitrou PM, Papadimatos P, Spiliopoulos S, et al. Paclitaxel-Coated Balloons for the Treatment of Symptomatic Central Venous Stenosis in Dialysis Access: Results from a Randomized Controlled Trial. *Journal of Vascular and Interventional Radiology* 2017;28(6):811-17. doi: 10.1016/j.jvir.2017.03.007
526. Kitrou PM, Spiliopoulos S, Katsanos K, et al. Paclitaxel-coated versus plain balloon angioplasty for dysfunctional arteriovenous fistulae: one-year results of a prospective randomized controlled trial. *J Vasc Interv Radiol* 2015;26(3):348-54. doi: 10.1016/j.jvir.2014.11.003 [published Online First: 2014/12/30]
527. Lai CC, Fang HC, Tseng CJ, et al. Percutaneous angioplasty using a paclitaxel-coated balloon improves target lesion restenosis on inflow lesions of autogenous radiocephalic fistulas: a pilot study. *J Vasc Interv Radiol* 2014;25(4):535-41. doi: 10.1016/j.jvir.2013.12.014 [published Online First: 2014/02/18]
528. Liao MT, Lee CP, Lin TT, et al. A randomized controlled trial of drug-coated balloon angioplasty in venous anastomotic stenosis of dialysis arteriovenous grafts. *Journal of Vascular Surgery* 2020;71(6):1994-2003. doi: 10.1016/j.jvs.2019.07.090
529. Lookstein R, Haruguchi H, Suemitsu K, et al. IN.PACT AV Access Randomized Trial of Drug-Coated Balloons for Dysfunctional Arteriovenous Fistulae: Clinical Outcomes through 36 Months. *J Vasc Interv Radiol* 2023;34(12):2093-102 e7. doi: 10.1016/j.jvir.2023.07.007 [published Online First: 20230717]
530. Maleux G, van der Linden E, Heijboer RJJ, et al. Multicenter Randomized Controlled Trial of APERTO-Paclitaxel Drug-Eluting Balloon Angioplasty Versus Standard Percutaneous Transluminal Angioplasty in Dysfunctional Hemodialysis Grafts and Native Fistulae. *Journal of Endovascular Therapy* 2023 doi: 10.1177/15266028231215212
531. Maleux G, Vander Mijnsbrugge W, Henroteaux D, et al. Multicenter, Randomized Trial of Conventional Balloon Angioplasty versus Paclitaxel-Coated Balloon Angioplasty for the Treatment of Dysfunctioning Autologous Dialysis Fistulae.

Journal of Vascular and Interventional Radiology 2018;29(4):470-75.e3. doi: 10.1016/j.jvir.2017.10.023
532. Moreno-Sánchez T, Moreno-Ramírez M, Machancoses FH, et al. Efficacy of Paclitaxel Balloon for Hemodialysis Stenosis Fistulae After One Year Compared to High-Pressure Balloons: A Controlled, Multicenter, Randomized Trial. *CardioVascular and Interventional Radiology* 2020;43(3):382-90. doi: 10.1007/s00270-019-02372-w
533. Novak M, Matras P, Kavan J, et al. Angioplasty of Dysfunctional Dialysis Fistula or Graft with Resveratrol-Excipient and Paclitaxel-Coated Balloon Improves Primary Patency Rates Compared to Plain Angioplasty Alone. *Journal of Clinical Medicine* 2022;11(24) doi: 10.3390/jcm11247405
534. Pang SYC, Au-Yeung KCL, Liu GYL, et al. Randomized Controlled Trial for Paclitaxel-coated Balloon versus Plain Balloon Angioplasty in Dysfunctional Hemodialysis Vascular Access: 12-month Outcome from a Nonsponsored Trial. *Annals of Vascular Surgery* 2021;72:299-306. doi: 10.1016/j.avsg.2020.10.005
535. Roosen LJ, Karamermer Y, Vos JA, et al. Paclitaxel-coated balloons do not prevent recurrent stenosis in hemodialysis access fistulae: Results of a randomized clinical trial. *Italian Journal of Vascular and Endovascular Surgery* 2017;24(2):35-40. doi: 10.23736/S1824-4777.17.01282-7
536. Swinnen JJ, Hitos K, Kairaitis L, et al. Multicentre, randomised, blinded, control trial of drug-eluting balloon vs Sham in recurrent native dialysis fistula stenoses. *J Vasc Access* 2019;20(3):260-69. doi: 10.1177/1129729818801556 [published Online First: 20180918]
537. Therasse E, Caty V, Gilbert P, et al. Safety and Efficacy of Paclitaxel-Eluting Balloon Angioplasty for Dysfunctional Hemodialysis Access: A randomized trial Comparing with Angioplasty Alone. *Journal of Vascular and Interventional Radiology* 2021;32(3):350-59.e2. doi: 10.1016/j.jvir.2020.10.030
538. Trerotola SO, Saad TF, Roy-Chaudhury P, Lutonix AVCTI. The Lutonix AV Randomized Trial of Paclitaxel-Coated Balloons in Arteriovenous Fistula Stenosis: 2-Year Results and Subgroup Analysis. *J Vasc Interv Radiol* 2020;31(1):1-14 e5. doi: 10.1016/j.jvir.2019.08.035 [published Online First: 2019/11/11]
539. Yin Y, Shi Y, Cui T, et al. Efficacy and Safety of Paclitaxel-Coated Balloon Angioplasty for Dysfunctional Arteriovenous Fistulas: A Multicenter Randomized Controlled Trial. *American Journal of Kidney Diseases* 2021;78(1):19-27.e1. doi: 10.1053/j.ajkd.2020.11.022
540. Zhao Y, Wang P, Wang Y, et al. Drug-Coated Balloon Angioplasty for Dysfunctional Arteriovenous Hemodialysis Fistulae: A Randomized Controlled Trial. *Clinical journal of the American Society of Nephrology : CJASN* 2023 doi: 10.2215/CJN.0000000000000359
541. Zhang Y, Yuan FL, Hu XY, et al. Comparison of drug-coated balloon angioplasty versus common balloon angioplasty for arteriovenous fistula stenosis: A systematic review and meta-analysis. *Clinical Cardiology* 2023;46(8):877-85. doi: 10.1002/clc.24078
542. Yang Q, Xia C. Angioplasty for dysfunctional arteriovenous fistulas: A meta-analysis of recent randomized controlled trials compared paclitaxel-coated balloon versus

conventional balloon angioplasty. *Journal of Vascular Access* 2023 doi: 10.1177/11297298231213724
543. Li Y, Shi Z, Zhao Y, et al. Long-term mortality and patency after drug-coated balloon angioplasty in the hemodialysis circuit: A systematic review and meta-analysis of randomized controlled trials. *Journal of Vascular Access* 2023;24(5):1104-13. doi: 10.1177/11297298211070125
544. Enzmann FK, Nierlich P, Holzenbein T, et al. Vein Bypass Versus Nitinol Stent in Long Femoropopliteal Lesions: 4-Year Results of a Randomized Controlled Trial. *Ann Surg* 2023;277(6):e1208-e14. doi: 10.1097/SLA.0000000000005413 [published Online First: 20220217]
545. Meecham L, Bate G, Patel S, Bradbury AW. A Comparison of Clinical Outcomes Following Femoropopliteal Bypass or Plain Balloon Angioplasty with Selective Bare Metal Stenting in the Bypass Versus Angioplasty in Severe Ischaemia of the Limb (BASIL) Trial. *Eur J Vasc Endovasc Surg* 2019;58(1):52-59. doi: 10.1016/j.ejvs.2019.01.006 [published Online First: 20190218]
546. Meecham L, Patel S, Bate GR, Bradbury AW. Editor's Choice - A Comparison of Clinical Outcomes Between Primary Bypass and Secondary Bypass After Failed Plain Balloon Angioplasty in the Bypass versus Angioplasty for Severe Ischaemia of the Limb (BASIL) Trial. *Eur J Vasc Endovasc Surg* 2018;55(5):666-71. doi: 10.1016/j.ejvs.2018.02.015 [published Online First: 20180327]
547. Bradbury AW, Adam DJ, Bell J, et al. Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial: An intention-to-treat analysis of amputation-free and overall survival in patients randomized to a bypass surgery-first or a balloon angioplasty-first revascularization strategy. *J Vasc Surg* 2010;51(5 Suppl):5S-17S. doi: 10.1016/j.jvs.2010.01.073
548. Bradbury AW, Adam DJ, Bell J, et al. Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial: Analysis of amputation free and overall survival by treatment received. *J Vasc Surg* 2010;51(5 Suppl):18S-31S. doi: 10.1016/j.jvs.2010.01.074
549. Lepantalo M, Laurila K, Roth WD, et al. PTFE bypass or thrupass for superficial femoral artery occlusion? A randomised controlled trial. *Eur J Vasc Endovasc Surg* 2009;37(5):578-84. doi: 10.1016/j.ejvs.2009.01.003 [published Online First: 20090220]
550. Adam DJ, Beard JD, Cleveland T, et al. Bypass versus angioplasty in severe ischaemia of the leg (BASIL): multicentre, randomised controlled trial. *Lancet* 2005;366(9501):1925-34. doi: 10.1016/S0140-6736(05)67704-5
551. van der Zaag ES, Legemate DA, Prins MH, et al. Angioplasty or bypass for superficial femoral artery disease? A randomised controlled trial. *European Journal of Vascular and Endovascular Surgery* 2004;28(2):132-37. doi: 10.1016/j.ejvs.2004.04.003
552. Tepe G. Intravascular Lithotripsy for Peripheral Artery calcification. Mid-term Outcomes From the Randomized Disrupt PAD III Trial. 2022
553. Banerjee S, Das TS, Abu-Fadel MS, et al. Pilot trial of cryoplasty or conventional balloon post-dilation of nitinol stents for revascularization of peripheral arterial segments: The COBRA trial. *Journal of the American College of Cardiology* 2012;60(15):1352-59. doi: 10.1016/j.jacc.2012.05.042

554. Jahnke T, Mueller-Huelsbeck S, Charalambous N, et al. Prospective, Randomized Single-center Trial to Compare Cryoplasty versus Conventional Angioplasty in the Popliteal Artery: Midterm Results of the COLD Study. *Journal of Vascular and Interventional Radiology* 2010;21(2):186-94. doi: 10.1016/j.jvir.2009.10.021
555. Teichgraber U, Lehmann T, Aschenbach R, et al. Femoropopliteal Drug-coated Balloon Angioplasty: Long-term Results of the Randomized EffPac Trial. *Radiology* 2022;304(1):225-27. doi: 10.1148/radiol.212622 [published Online First: 2022/03/23]
556. Ko YG, Ahn CM, Rha SW, et al. Comparison of Spot versus Long Stenting for Femoropopliteal Artery Disease. *Ann Vasc Surg* 2019;58:101-07. doi: 10.1016/j.avsg.2018.11.023 [published Online First: 2019/02/16]
557. Iida O, Urasawa K, Komura Y, et al. Self-Expanding Nitinol Stent vs Percutaneous Transluminal Angioplasty in the Treatment of Femoropopliteal Lesions: 3-Year Data From the SM-01 Trial. *J Endovasc Ther* 2019;26(2):158-67. doi: 10.1177/1526602819826591 [published Online First: 2019/02/01]
558. Laird JR, Zeller T, Loewe C, et al. Novel Nitinol Stent for Lesions up to 24 cm in the Superficial Femoral and Proximal Popliteal Arteries: 24-Month Results From the TIGRIS Randomized Trial. *J Endovasc Ther* 2018;25(1):68-78. doi: 10.1177/1526602817749242 [published Online First: 20171229]
559. Zeller T, Gaines PA, Ansel GM, Caro CG. Helical centerline stent improves patency: Two-year results from the randomized mimics trial. *Circulation: Cardiovascular Interventions* 2016;9(6) doi: 10.1161/CIRCINTERVENTIONS.115.002930
560. Brancaccio G, Lombardi R, Stefanini T, et al. Comparison of embolic load in femoropopliteal interventions: percutaneous transluminal angioplasty versus stenting. *Vasc Endovascular Surg* 2012;46(3):229-35. doi: 10.1177/1538574411422276 [published Online First: 20120412]
561. Krankenberg H, Schluter M, Steinkamp HJ, et al. Nitinol stent implantation versus percutaneous transluminal angioplasty in superficial femoral artery lesions up to 10 cm in length: the femoral artery stenting trial (FAST). *Circulation* 2007;116(3):285-92. doi: 10.1161/CIRCULATIONAHA.107.689141 [published Online First: 20070625]
562. Grenacher L, Saam T, Geier A, et al. PTA versus palmaz stent placement in femoropopliteal artery stenoses: Results of a multicenter prospective randomized study (REFSA). *RoFo Fortschritte auf dem Gebiet der Rontgenstrahlen und der Bildgebenden Verfahren* 2004;176(9):1302-10. doi: 10.1055/s-2004-813377
563. Goueffic Y, Sauguet A, Desgranges P, et al. A Polymer-Free Paclitaxel-Eluting Stent Versus a Bare-Metal Stent for De Novo Femoropopliteal Lesions: The BATTLE Trial. *JACC Cardiovasc Interv* 2020;13(4):447-57. doi: 10.1016/j.jcin.2019.12.028 [published Online First: 2020/02/23]
564. Shammas NW, Purushottam B, Shammas WJ, et al. Jetstream Atherectomy Followed by Paclitaxel-Coated Balloons versus Balloon Angioplasty Followed by Paclitaxel-Coated Balloons: Twelve-Month Exploratory Results of the Prospective Randomized JET-RANGER Study. *Vasc Health Risk Manag* 2022;18:603-15. doi: 10.2147/VHRM.S371177 [published Online First: 20220802]
565. Goo DE, Kim YJ, Park SW, et al. A Prospective Multicenter Randomized Controlled Trial for Comparing Drug-Coated and Conventional Balloon Angioplasty in

Venous Anastomotic Stenosis of Hemodialysis Arteriovenous Grafts. *CardioVascular and Interventional Radiology* 2024;47(1):36-44. doi: 10.1007/s00270-023-03536-5
566. Hsieh MY, Lin PS, Liao MT, et al. A Randomised Trial Comparing Drug Coated Balloons and Conventional Balloons for the Treatment of Stent Graft Stenosis in Dialysis Vascular Access. *European Journal of Vascular and Endovascular Surgery* 2023;66(2):253-60. doi: 10.1016/j.ejvs.2023.05.028
567. Walczak IM. Diabetes technology news. FDA approves CYPHER Stent. *Diabetes Technol Ther* 2003;5(3):509-10.
568. Dvir D, Torguson R, Waksman R. Overview of the 2011 food and drug administration's circulatory system devices panel of the medical devices advisory committee meeting on the Zilver(R) PTX(R) drug-eluting peripheral stent. *Cardiovasc Revasc Med* 2012;13(5):281-5. doi: 10.1016/j.carrev.2012.05.003 [published Online First: 2012/08/18]
569. WMA DECLARATION OF HELSINKI – ETHICAL PRINCIPLES FOR MEDICAL RESEARCH INVOLVING HUMAN SUBJECTS. In: WMA, ed., 2013.
570. Schulz KF, Altman DG, Moher D, Group C. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *BMJ* 2010;340:c332. doi: 10.1136/bmj.c332 [published Online First: 2010/03/25]
571. Katsanos K, Karnabatidis D, Kitrou P, et al. Paclitaxel-coated balloon angioplasty vs. plain balloon dilation for the treatment of failing dialysis access: 6-month interim results from a prospective randomized controlled trial. *J Endovasc Ther* 2012;19(2):263-72. doi: 10.1583/11-3690.1
572. Laird JR, Katzen BT, Scheinert D, et al. Nitinol stent implantation versus balloon angioplasty for lesions in the superficial femoral artery and proximal popliteal artery: twelve-month results from the RESILIENT randomized trial. *Circ Cardiovasc Interv* 2010;3(3):267-76. doi: 10.1161/CIRCINTERVENTIONS.109.903468 [published Online First: 2010/05/21]
573. Dake MD, Ansel GM, Jaff MR, et al. Sustained safety and effectiveness of paclitaxel-eluting stents for femoropopliteal lesions: 2-year follow-up from the Zilver PTX randomized and single-arm clinical studies. *J Am Coll Cardiol* 2013;61(24):2417-27. doi: 10.1016/j.jacc.2013.03.034 [published Online First: 2013/04/16]
574. Bosiers M, Deloose K, Callaert J, et al. Results of the Protégé EverFlex 200-mm-long nitinol stent (ev3) in TASC C and D femoropopliteal lesions. *Journal of Vascular Surgery* 2011;54(4):1042-50. doi: 10.1016/j.jvs.2011.03.272
575. Bosiers M, Peeters P, Tessarek J, et al. The Zilver(R) PTX(R) Single Arm Study: 12-month results from the TASC C/D lesion subgroup. *J Cardiovasc Surg (Torino)* 2013;54(1):115-22. [published Online First: 2013/01/09]
576. Dake MD, Ansel GM, Jaff MR, et al. Paclitaxel-eluting stents show superiority to balloon angioplasty and bare metal stents in femoropopliteal disease: twelve-month Zilver PTX randomized study results. *Circ Cardiovasc Interv* 2011;4(5):495-504. doi: 10.1161/CIRCINTERVENTIONS.111.962324 [published Online First: 2011/09/29]
577. Liistro F, Porto I, Angioli P, et al. Drug-eluting balloon in peripheral intervention for below the knee angioplasty evaluation (DEBATE-BTK): a randomized trial in

diabetic patients with critical limb ischemia. *Circulation* 2013;128(6):615-21. doi: 10.1161/CIRCULATIONAHA.113.001811
578. Bosiers M, Hart JP, Deloose K, et al. Endovascular therapy as the primary approach for limb salvage in patients with critical limb ischemia: experience with 443 infrapopliteal procedures. *Vascular* 2006;14(2):63-9. doi: 10.2310/6670.2006.00014
579. Giles KA, Pomposelli FB, Spence TL, et al. Infrapopliteal angioplasty for critical limb ischemia: relation of TransAtlantic InterSociety Consensus class to outcome in 176 limbs. *J Vasc Surg* 2008;48(1):128-36. doi: 10.1016/j.jvs.2008.02.027 [published Online First: 20080523]
580. Lo RC, Darling J, Bensley RP, et al. Outcomes following infrapopliteal angioplasty for critical limb ischemia. *Journal of Vascular Surgery* 2013;57(6):1455-63. doi: 10.1016/j.jvs.2012.10.109
581. Balzer JO, Khan V, Thalhammer A, et al. Below the knee PTA in critical limb ischemia results after 12 months: Single center experience. *European Journal of Radiology* 2010;75(1):37-42. doi: 10.1016/j.ejrad.2010.04.014
582. Dake MD, Van Alstine WG, Zhou Q, Ragheb AO. Polymer-free paclitaxel-coated Zilver PTX Stents--evaluation of pharmacokinetics and comparative safety in porcine arteries. *J Vasc Interv Radiol* 2011;22(5):603-10. doi: 10.1016/j.jvir.2010.12.027 [published Online First: 20110317]
583. Patanè D, Giuffrida S, Morale W, et al. Drug-eluting balloon for the treatment of failing hemodialytic radiocephalic arteriovenous fistulas: our experience in the treatment of juxta-anastomotic stenoses. *J Vasc Access* 2014;15(5):338-43. doi: 10.5301/jva.5000211 [published Online First: 20140210]
584. Massmann A, Fries P, Obst-Gleditsch K, et al. Paclitaxel-coated balloon angioplasty for symptomatic central vein restenosis in patients with hemodialysis fistulas. *J Endovasc Ther* 2015;22(1):74-9. doi: 10.1177/1526602814566907
585. Hongsakul K, Bannangkoon K, Rookkapan S, et al. Paclitaxel-Coated Balloon Angioplasty for Early Restenosis of Central Veins in Hemodialysis Patients: A Single Center Initial Experience. *Korean J Radiol* 2018;19(3):410-16. doi: 10.3348/kjr.2018.19.3.410 [published Online First: 2018/05/02]
586. Kocaaslan C, Oztekin A, Bademci MS, et al. A retrospective comparison analysis of results of drug-coated balloon versus plain balloon angioplasty in treatment of juxta-anastomotic de novo stenosis of radiocephalic arteriovenous fistulas. *J Vasc Access* 2020;21(5):596-601. doi: 10.1177/1129729819893205 [published Online First: 2019/12/12]
587. Fanelli F, Cannavale A, Corona M, et al. The "DEBELLUM"--lower limb multilevel treatment with drug eluting balloon--randomized trial: 1-year results. *J Cardiovasc Surg (Torino)* 2014;55(2):207-16.
588. Micari A, Brodmann M, Keirse K, et al. Drug-Coated Balloon Treatment of Femoropopliteal Lesions for Patients With Intermittent Claudication and Ischemic Rest Pain: 2-Year Results From the IN.PACT Global Study. *JACC Cardiovasc Interv* 2018;11(10):945-53. doi: 10.1016/j.jcin.2018.02.019
589. Schroeder H, Meyer DR, Lux B, et al. Two-year results of a low-dose drug-coated balloon for revascularization of the femoropopliteal artery: Outcomes from the ILLUMENATE first-in-human study. *Catheterization and Cardiovascular Interventions* 2015;86(2):278-86. doi: 10.1002/ccd.25900

590. Massara M, Finocchiaro P, Volpe A, et al. Percutaneous drug-eluting balloon angioplasty to treat dialysis access stenosis. *Seminars in Vascular Surgery* 2017;30(2-3):67-69. doi: 10.1053/j.semvascsurg.2017.10.001
591. Lučev J, Breznik S, Dinevski D, et al. Endovascular Treatment of Haemodialysis Arteriovenous Fistula with Drug-Coated Balloon Angioplasty: A Single-Centre Study. *CardioVascular and Interventional Radiology* 2018;41(6):882-89. doi: 10.1007/s00270-018-1942-z
592. Patanè D, Failla G, Coniglio G, et al. Treatment of juxta-anastomotic stenoses for failing distal radiocephalic arteriovenous fistulas: Drug-coated balloons versus angioplasty. *Journal of Vascular Access* 2019;20(2):209-16. doi: 10.1177/1129729818793102
593. Tozzi M, Franchin M, Savio D, et al. Drug-coated balloon angioplasty in failing haemodialysis arteriovenous shunts: 12-month outcomes in 200 patients from the Aperto Italian registry. *Journal of Vascular Access* 2019;20(6):733-39. doi: 10.1177/1129729819848609
594. Scheinert D, Schmidt A, Zeller T, et al. German center subanalysis of the LEVANT 2 global randomized study of the Lutonix drug-coated balloon in the treatment of femoropopliteal occlusive disease. *Journal of Endovascular Therapy* 2016;23(3):409-16. doi: 10.1177/1526602816644592
595. Bair EC, McCarver BC, Cooper NT, et al. The Use of Paclitaxel-Coated Devices in the Treatment of Peripheral Arterial Disease is Not Associated With Increased Mortality or Amputations. *Annals of Vascular Surgery* 2022;87:64-70. doi: 10.1016/j.avsg.2022.04.047
596. Secemsky EA, Shen C, Schermerhorn M, Yeh RW. Longitudinal assessment of safety of femoropopliteal endovascular treatment with paclitaxel-coated devices among Medicare beneficiaries the SAFE-PAD study. *JAMA Internal Medicine* 2021;181(8):1071-80. doi: 10.1001/jamainternmed.2021.2738
597. Steiner S, Schmidt A, Zeller T, et al. COMPARE: prospective, randomized, non-inferiority trial of high- vs. low-dose paclitaxel drug-coated balloons for femoropopliteal interventions. *Eur Heart J* 2020;41(27):2541-52. doi: 10.1093/eurheartj/ehaa049
598. Sabate E, De Geest S. Adherence to long-term therapies management: a call for cardiovascular nursing managers and policymakers. *Prog Cardiovasc Nurs* 2004;19(1):28-9. doi: 10.1111/j.0889-7204.2004.02896.x
599. McCambridge J, Witton J, Elbourne DR. Systematic review of the Hawthorne effect: new concepts are needed to study research participation effects. *J Clin Epidemiol* 2014;67(3):267-77. doi: 10.1016/j.jclinepi.2013.08.015 [published Online First: 20131122]
600. Lookstein RA, Haruguchi H, Ouriel K, et al. Drug-Coated Balloons for Dysfunctional Dialysis Arteriovenous Fistulas. *N Engl J Med* 2020;383(8):733-42. doi: 10.1056/NEJMoa1914617 [published Online First: 2020/08/20]
601. Manninen HI, Kaukanen ET, Ikaheimo R, et al. Brachial arterial access: endovascular treatment of failing Brescia-Cimino hemodialysis fistulas--initial success and long-term results. *Radiology* 2001;218(3):711-8. doi: 10.1148/radiology.218.3.r01mr38711 [published Online First: 2001/03/07]

602. Bjorkman P, Weselius EM, Venermo M. No difference in mid- to long-term mortality after vascular paclitaxel exposure. *Ann Vasc Surg* 2020 doi: 10.1016/j.avsg.2020.08.147 [published Online First: 2020/09/27]
603. Cildag MB, Koseoglu OF, Akdam H, Yenicerioglu Y. The primary patency of drug-eluting balloon versus conventional balloon angioplasty in hemodialysis patients with arteriovenous fistula stenoses. *Jpn J Radiol* 2016;34(10):700-04. doi: 10.1007/s11604-016-0577-8 [published Online First: 2016/08/28]
604. Bountouris I, Kristmundsson T, Dias N, et al. Is Repeat PTA of a Failing Hemodialysis Fistula Durable? *Int J Vasc Med* 2014;2014:369687. doi: 10.1155/2014/369687 [published Online First: 20140122]
605. Kim WS, Pyun WB, Kang BC. The primary patency of percutaneous transluminal angioplasty in hemodialysis patients with vascular access failure. *Korean Circ J* 2011;41(9):512-7. doi: 10.4070/kcj.2011.41.9.512 [published Online First: 2011/10/25]
606. AbuRahma AF, Beasley M, AbuRahma ZT, et al. Clinical Outcome of Drug-Eluted Stenting (Zilver PTX) in Patients With Femoropopliteal Occlusive Disease a Single Center Experience. *J Endovasc Ther* 2021:15266028211049339. doi: 10.1177/15266028211049339 [published Online First: 2021/10/09]
607. Phair J, Carnevale M, Lipsitz EC, et al. Primary Patency of Long-Segment Femoropopliteal Artery Lesions in Patients with Peripheral Arterial Occlusive Disease Treated with Paclitaxel-Eluting Technology. *Annals of Vascular Surgery* 2020;66:595-600. doi: 10.1016/j.avsg.2019.11.044
608. Phillips JA, Falls A, Kolluri R, et al. Full Drug-Eluting Stent Jacket: Two-Year Results of a Single-Center Experience With Zilver PTX Stenting for Long Lesions in the Femoropopliteal Arteries. *J Endovasc Ther* 2018;25(3):295-301. doi: 10.1177/1526602818762805 [published Online First: 2018/03/17]
609. Vent PA, Kaladji A, Davaine JM, et al. Bare Metal Versus Paclitaxel-Eluting Stents for Long Femoropopliteal Lesions: Prospective Cohorts Comparison Using a Propensity Score-Matched Analysis. *Ann Vasc Surg* 2017;43:166-75. doi: 10.1016/j.avsg.2016.10.058 [published Online First: 2017/03/17]
610. Kang WY, Campia U, Didier RJ, et al. A single center experience of Zilver PTX for femoro-popliteal lesions. *Cardiovasc Revasc Med* 2016;17(6):399-403. doi: 10.1016/j.carrev.2016.02.004 [published Online First: 20160209]
611. Lammer J, Bosiers M, Zeller T, et al. First clinical trial of nitinol self-expanding everolimus-eluting stent implantation for peripheral arterial occlusive disease. *J Vasc Surg* 2011;54(2):394-401. doi: 10.1016/j.jvs.2011.01.047 [published Online First: 20110612]
612. Labed P, Gonzalez F, Jayet J, et al. Endovascular Treatment of Long Femoropopliteal Lesions with Contiguous Bare Metal Stents. *Annals of Vascular Surgery* 2021;76:276-84. doi: 10.1016/j.avsg.2021.04.033
613. Davaine JM, Querat J, Kaladji A, et al. Treatment of TASC C and D femoropoliteal lesions with paclitaxel eluting stents: 12 month results of the STELLA-PTX registry. *European Journal of Vascular and Endovascular Surgery* 2015;50(5):631-37. doi: 10.1016/j.ejvs.2015.07.018
614. Zamani N, Sharath SE, Browder RC, et al. Outcomes after Endovascular Stent Placement for Long-Segment Superficial Femoral Artery Lesions. *Ann Vasc Surg*

2021;71:298-307. doi: 10.1016/j.avsg.2020.08.124 [published Online First: 20200903]
615. Giannopoulos S, Lyden SP, Bisdas T, et al. Endovascular Intervention for the Treatment of Trans-Atlantic Inter-Society Consensus (TASC) D Femoropopliteal Lesions: A Systematic Review and Meta-Analysis. *Cardiovasc Revasc Med* 2021;22:52-65. doi: 10.1016/j.carrev.2020.06.014 [published Online First: 20200612]
616. Perlander A, Jivegard L, Nordanstig J, et al. Amputation-free survival, limb symptom alleviation, and reintervention rates after open and endovascular revascularization of femoropopliteal lesions in patients with chronic limb-threatening ischemia. *J Vasc Surg* 2020;72(6):1987-95. doi: 10.1016/j.jvs.2020.03.029 [published Online First: 2020/04/11]
617. Almasri J, Adusumalli J, Asi N, et al. A systematic review and meta-analysis of revascularization outcomes of infrainguinal chronic limb-threatening ischemia. *Eur J Vasc Endovasc Surg* 2019;58(1S):S110-S19. doi: 10.1016/j.ejvs.2019.04.013 [published Online First: 20190617]
618. Phair J, Carnevale M, Lipsitz EC, et al. Amputation-free Survival in Patients with Critical Limb Ischemia Treated with Paclitaxel-eluting Stents and Paclitaxel-coated Balloons. *Ann Vasc Surg* 2020;62:8-14. doi: 10.1016/j.avsg.2019.05.013 [published Online First: 20190615]
619. Biagioni RB, Brandão GD, Biagioni LC, et al. Endovascular treatment of TransAtlantic Inter-Society Consensus II D femoropopliteal lesions in patients with critical limb ischemia. *J Vasc Surg* 2019;69(5):1510-18. doi: 10.1016/j.jvs.2018.08.176 [published Online First: 20190102]
620. Dake MD, Ansel GM, Bosiers M, et al. Paclitaxel-Coated Zilver PTX Drug-Eluting Stent Treatment Does Not Result in Increased Long-Term All-Cause Mortality Compared to Uncoated Devices. *Cardiovasc Intervent Radiol* 2020;43(1):8-19. doi: 10.1007/s00270-019-02324-4 [published Online First: 2019/09/11]
621. Behrendt CA, Sedrakyan A, Peters F, et al. Editor's Choice - Long Term Survival after Femoropopliteal Artery Revascularisation with Paclitaxel Coated Devices: A Propensity Score Matched Cohort Analysis. *Eur J Vasc Endovasc Surg* 2020;59(4):587-96. doi: 10.1016/j.ejvs.2019.12.034 [published Online First: 20200108]
622. Baril DT, Chaer RA, Rhee RY, et al. Endovascular interventions for TASC II D femoropopliteal lesions. *J Vasc Surg* 2010;51(6):1406-12. doi: 10.1016/j.jvs.2010.01.062 [published Online First: 20100410]
623. Sugimoto M, Komori K, Yokoi H, et al. Long-Term Effectiveness of a Drug-Eluting Stent for Femoropopliteal In-Stent Restenosis: Subanalysis of the Zilver PTX Japan Post-Market Surveillance Study. *J Endovasc Ther* 2021;28(2):229-35. doi: 10.1177/1526602820966708 [published Online First: 2020/10/22]
624. Stern JR, Tran K, Chandra V, et al. Paclitaxel exposure and long-term mortality of patients treated with the Zilver PTX drug-eluting stent. *Vascular* 2021;29(4):567-73. doi: 10.1177/1708538120964371 [published Online First: 2020/10/16]
625. Heidemann F, Peters F, Kuchenbecker J, et al. Long Term Outcomes After Revascularisations Below the Knee with Paclitaxel Coated Devices: A Propensity Score Matched Cohort Analysis. *European Journal of Vascular and Endovascular Surgery* 2020;60(4):549-58. doi: 10.1016/j.ejvs.2020.06.033

626. Sigvant B, Kragsterman B, Falkenberg M, et al. Contemporary cardiovascular risk and secondary preventive drug treatment patterns in peripheral artery disease patients undergoing revascularization. *J Vasc Surg* 2016;64(4):1009-17 e3. doi: 10.1016/j.jvs.2016.03.429 [published Online First: 2016/05/23]
627. Kithcart AP, Beckman JA. ACC/AHA Versus ESC Guidelines for Diagnosis and Management of Peripheral Artery Disease: JACC Guideline Comparison. *J Am Coll Cardiol* 2018;72(22):2789-801. doi: 10.1016/j.jacc.2018.09.041 [published Online First: 2018/12/01]
628. Cassese S, Ndrepepa G, Liistro F, et al. Drug-Coated Balloons for Revascularization of Infrapopliteal Arteries: A Meta-Analysis of Randomized Trials. *JACC Cardiovasc Interv* 2016;9(10):1072-80. doi: 10.1016/j.jcin.2016.02.011 [published Online First: 2016/05/02]
629. Reijnen M, van Wijck I, Brodmann M, et al. Five-Year Outcomes after Paclitaxel Drug-Coated Balloon Treatment of Femoropopliteal Lesions in Diabetic and Chronic Limb-Threatening Ischemia Cohorts: IN.PACT Global Study Post Hoc Analysis. *Cardiovasc Intervent Radiol* 2023;46(10):1329-45. doi: 10.1007/s00270-023-03478-y [published Online First: 20230801]
630. Richter L, Freisinger E, Luders F, et al. Impact of diabetes type on treatment and outcome of patients with peripheral artery disease. *Diab Vasc Dis Res* 2018;15(6):504-10. doi: 10.1177/1479164118793986 [published Online First: 2018/09/25]
631. Graziani L, Silvestro A, Bertone V, et al. Vascular Involvement in Diabetic Subjects with Ischemic Foot Ulcer: A New Morphologic Categorization of Disease Severity. *European Journal of Vascular and Endovascular Surgery* 2007;33(4):453-60. doi: 10.1016/j.ejvs.2006.11.022
632. Mwipatayi BP, Barry IP, Brodmann M, et al. Twenty-Four-Month Outcomes of Drug-Coated Balloon in Diabetic Patients in the BIOLUX P-III Registry: A Subgroup Analysis. *Ann Vasc Surg* 2021;75:237-52. doi: 10.1016/j.avsg.2021.02.050 [published Online First: 2021/04/09]
633. Iida O, Takahara M, Soga Y, et al. 1-Year Outcomes of Fluoropolymer-Based Drug-Eluting Stent in Femoropopliteal Practice: Predictors of Restenosis and Aneurysmal Degeneration. *JACC Cardiovasc Interv* 2022;15(6):630-38. doi: 10.1016/j.jcin.2022.01.019 [published Online First: 2022/03/26]
634. Behrendt CA, Bertges D, Eldrup N, et al. International Consortium of Vascular Registries Consensus Recommendations for Peripheral Revascularisation Registry Data Collection. *Eur J Vasc Endovasc Surg* 2018;56(2):217-37. doi: 10.1016/j.ejvs.2018.04.006 [published Online First: 20180530]
635. Stoner MC, Calligaro KD, Chaer RA, et al. Reporting standards of the Society for Vascular Surgery for endovascular treatment of chronic lower extremity peripheral artery disease. *J Vasc Surg* 2016;64(1):e1-e21. doi: 10.1016/j.jvs.2016.03.420 [published Online First: 2016/06/28]
636. Nugteren MJ, Hazenberg C, Akkersdijk GP, et al. The Dutch chronic lower limb-threatening ischemia registry (THRILLER): A study protocol for popliteal and infrapopliteal endovascular interventions. *PLoS One* 2023;18(7):e0288912. doi: 10.1371/journal.pone.0288912 [published Online First: 20230720]

637. Venermo M, Lees T. International Vascunet Validation of the Swedvasc Registry. *Eur J Vasc Endovasc Surg* 2015;50(6):802-8. doi: 10.1016/j.ejvs.2015.07.021 [published Online First: 2015/09/05]
638. Djerf H, Hellman J, Baubeta Fridh E, et al. Low Risk of Procedure Related Major Amputation Following Revascularisation for Intermittent Claudication: A Population Based Study. *Eur J Vasc Endovasc Surg* 2020;59(5):817-22. doi: 10.1016/j.ejvs.2019.11.023 [published Online First: 2019/12/24]
639. Salem M, Hosny MS, Francia F, et al. Management of Extensive Aorto-Iliac Disease: A Systematic Review and Meta-Analysis of 9319 Patients. *Cardiovasc Intervent Radiol* 2021;44(10):1518-35. doi: 10.1007/s00270-021-02785-6 [published Online First: 20210303]
640. Mallory A, Giannopoulos S, Lee P, et al. Covered Stents for Endovascular Treatment of Aortoiliac Occlusive Disease: A Systematic Review and Meta-Analysis. *Vascular and Endovascular Surgery* 2021;55(6):560-70. doi: 10.1177/15385744211010381
641. Iida O, Nakamura M, Yamauchi Y, et al. 3-Year Outcomes of the OLIVE Registry, a Prospective Multicenter Study of Patients With Critical Limb Ischemia: A Prospective, Multi-Center, Three-Year Follow-Up Study on Endovascular Treatment for Infra-Inguinal Vessel in Patients With Critical Limb Ischemia. *JACC Cardiovasc Interv* 2015;8(11):1493-502. doi: 10.1016/j.jcin.2015.07.005 [published Online First: 2015/09/26]
642. Grotti S, Liistro F, Angioli P, et al. Paclitaxel-Eluting Balloon vs Standard Angioplasty to Reduce Restenosis in Diabetic Patients With In-Stent Restenosis of the Superficial Femoral and Proximal Popliteal Arteries: Three-Year Results of the DEBATE-ISR Study. *J Endovasc Ther* 2016;23(1):52-7. doi: 10.1177/1526602815614555 [published Online First: 20151028]
643. Iida O, Takahara M, Soga Y, et al. Three-Year Outcomes of Surgical Versus Endovascular Revascularization for Critical Limb Ischemia: The SPINACH Study (Surgical Reconstruction Versus Peripheral Intervention in Patients With Critical Limb Ischemia). *Circ Cardiovasc Interv* 2017;10(12):e005531. doi: 10.1161/CIRCINTERVENTIONS.117.005531 [published Online First: 2017/12/17]
644. Soga Y, Iida O, Urasawa K, et al. Three-Year Results of the IN.PACT SFA Japan Trial Comparing Drug-Coated Balloons With Percutaneous Transluminal Angioplasty. *J Endovasc Ther* 2020;27(6):946-55. doi: 10.1177/1526602820948240 [published Online First: 2020/09/01]
645. Torsello G, Stavroulakis K, Brodmann M, et al. Three-Year Sustained Clinical Efficacy of Drug-Coated Balloon Angioplasty in a Real-World Femoropopliteal Cohort. *J Endovasc Ther* 2020;27(5):693-705. doi: 10.1177/1526602820931477 [published Online First: 2020/06/26]
646. Malyar NM, Freisinger E, Meyborg M, et al. Amputations and mortality in in-hospital treated patients with peripheral artery disease and diabetic foot syndrome. *J Diabetes Complications* 2016;30(6):1117-22. doi: 10.1016/j.jdiacomp.2016.03.033 [published Online First: 2016/04/28]
647. Ferraresi R, Ucci A, Casini A, et al. GLASS(Global Limb Anatomic Staging System): A critical appraisal. *Journal of Cardiovascular Surgery* 2021;62(2):98-103. doi: 10.23736/S0021-9509.20.11696-3

648. Haga M, Shindo S, Motohashi S, et al. Early evaluation of the infrainguinal revascularization strategy selection tool of the Global Vascular Guidelines for chronic limb-threatening ischemia patients. *Journal of Vascular Surgery* 2021;74(4):1253-60.e2. doi: 10.1016/j.jvs.2021.04.034
649. Giannopoulos S, Varcoe RL, Lichtenberg M, et al. Balloon Angioplasty of Infrapopliteal Arteries: A Systematic Review and Proposed Algorithm for Optimal Endovascular Therapy. *Journal of Endovascular Therapy* 2020;27(4):547-64. doi: 10.1177/1526602820931488
650. Gentile F, Lundberg G, Hultgren R. Outcome for Endovascular and Open Procedures in Infrapopliteal Lesions for Critical Limb Ischemia: Registry Based Single Center Study. *Eur J Vasc Endovasc Surg* 2016;52(5):643-49. doi: 10.1016/j.ejvs.2016.07.013 [published Online First: 20160902]
651. Strøm M, Konge L, Lönn L, et al. Amputation-Free Survival after Crural Percutaneous Transluminal Angioplasty for Critical Limb Ischemia. *Scandinavian journal of surgery : SJS : official organ for the Finnish Surgical Society and the Scandinavian Surgical Society* 2016;105(1):42-48. doi: 10.1177/1457496915571403
652. Utsunomiya M, Iida O, Yamauchi Y, et al. Influence of Repeat Intervention on the Risk of Major Amputation after Infrapopliteal Angioplasty for Critical Limb Ischemia. *Journal of Endovascular Therapy* 2016;23(5):710-16. doi: 10.1177/1526602816656831
653. Ribeiro TF, Ferreira RS, Correia R, et al. Paclitaxel in real-life data is not associated with reduced survival but has limited benefit in preventing amputation. *International Angiology* 2022;41(3):205-11. doi: 10.23736/S0392-9590.22.04763-0
654. Blazeby JM. Recruiting patients into randomized clinical trials in surgery. *Br J Surg* 2012;99(3):307-8. doi: 10.1002/bjs.7818 [published Online First: 20120111]
655. Patel MR, Jones WS. Peripheral Artery Disease Therapies May Perform Differently in Practice Than in Randomized Trials the Need for Learning Health Systems. *JACC: Cardiovascular Interventions* 2016;9(7):725-27. doi: 10.1016/j.jcin.2016.01.021
656. Tokuda T, Takahara M, Iida O, et al. Institutional Volume and Initial Results for Endovascular Treatment for Chronic Occlusive Lower-Extremity Artery Disease: A Report From the Japanese Nationwide Registry. *J Endovasc Ther* 2023:15266028231161242. doi: 10.1177/15266028231161242 [published Online First: 2023/03/21]
657. Siracuse JJ, Goodney PP, Menard MT, et al. Participation in a Chronic Limb Threatening Ischemia Randomized Trial Is Inversely Correlated with Regional Amputation Rate in Limb Threatening Ischemia Patients. *Annals of Surgery* 2021;274(4):621-26. doi: 10.1097/SLA.0000000000005058
658. Latz CA, Wang LJ, Boitano L, et al. Contemporary Endovascular Outcomes for Critical Limb Ischemia Are Still Failing to Meet Society for Vascular Surgery Objective Performance Goals. *Vasc Endovascular Surg* 2021;55(1):33-38. doi: 10.1177/1538574420964623 [published Online First: 2020/10/09]
659. Bertges DJ, White R, Cheng YC, et al. Registry Assessment of Peripheral Interventional Devices objective performance goals for superficial femoral and

popliteal artery peripheral vascular interventions. *J Vasc Surg* 2021;73(5):1702-14.e11. doi: 10.1016/j.jvs.2020.09.030 [published Online First: 20201017]
660. Steiner S, Honton B, Langhoff R, et al. 2-Year Results With a Sirolimus-Eluting Self-Expanding Stent for Femoropopliteal Lesions: The First-in-Human ILLUMINA Study. *JACC Cardiovasc Interv* 2022;15(6):618-26. doi: 10.1016/j.jcin.2021.12.034 [published Online First: 20220223]
661. Schroeder H, Meyer DR, Lux B, et al. A Pilot Study of Femoropopliteal Artery Revascularisation with a Low Dose Paclitaxel Coated Balloon: Is Predilatation Necessary? *Eur J Vasc Endovasc Surg* 2017;54(3):348-55. doi: 10.1016/j.ejvs.2017.06.020 [published Online First: 2017/08/06]
662. Rajan DK, Sidhu A, Noel-Lamy M, et al. Elastic Recoil after Balloon Angioplasty in Hemodialysis Accesses: Does It Actually Occur and Is It Clinically Relevant? *Radiology* 2016;279(3):961-7. doi: 10.1148/radiol.2015150991 [published Online First: 2015/12/24]
663. Fujihara M, Utsunomiya M, Higashimori A, et al. Outcomes of Zilver PTX stent implantation for the treatment of complex femoropopliteal artery disease. *Heart Vessels* 2016;31(2):152-7. doi: 10.1007/s00380-014-0596-2 [published Online First: 2014/10/30]
664. Tran K, Ullery BW, Kret MR, Lee JT. Real-World Performance of Paclitaxel Drug-Eluting Bare Metal Stenting (Zilver PTX) for the Treatment of Femoropopliteal Occlusive Disease. *Ann Vasc Surg* 2017;38:90-98. doi: 10.1016/j.avsg.2016.08.006 [published Online First: 20160820]
665. Garriboli L, Miccoli T, Pruner G, Jannello AM. PTA and Stenting of Femoropopliteal Trunk With Cordis Smartflex Stent System: A Single-Center Experience. *Vasc Endovascular Surg* 2020;54(1):17-24. doi: 10.1177/1538574419875551 [published Online First: 20190916]

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