Blood pressure control in type 2 diabetes over time - what can we learn from different trajectories?

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Elevated blood pressure in patients with type 2 diabetes is a prevalent condition and a well-documented cardiovascular risk factor in need of treatment, often by use of a tailored drug therapy based on synergistic combinations. In recent European guidelines the blood pressure goal for these patients is set to <140/85 mmHg according to both the ESH-ESC guidelines [1] and the ESC-EASD guidelines [2] of 2013, but lower in patients with macroalbuminuria (<130/80 mmHg). Previously however lower goals were recommended and this has to be taken into account when interpreting epidemiological studies from earlier periods. In general the care of patients with diabetes has improved in recent years as more emphasis has been put on early screening, detection and treatment of type 2 diabetes in the post-UKPDS era since 1998 when evidence was shown for benefits of risk factor control. It is therefore of importance to have access to register-based information in order to follow trends in blood pressure control in populations, sometimes on a local or regional scale, but also on a national scale. Data from the National Diabetes Register (NDR) of Sweden has for example documented favourable trends according to improved blood pressure control over time, both in the untreated normotensive and treated hypertensive patients with type 2 diabetes [3,4], even if still about half of all hypertensive patients do not achieve a systolic blood pressure <140 mmHg. The coverage rate of NDR is currently very high, based on reports from approximately 95 percent of all patients with diabetes in Sweden from both primary health care and the hospital level (NDR Annual Report 2014) why data should be reliable. Similar trends have been noticed also in other populations with diabetes such as in the US [5] and in the UK [6], however based on screening surveys and not patient registers *per se*.

In order to achieve a better understanding of the variation in blood pressure control in risk patients new methods have now been applied to characterize trajectories of blood pressure levels over time by use of so called Latent Class Growth Modeling (LCGM). This statistical method has recently been applied to a cohort of 5711 Dutch patients with type 2 diabetes and a least two measurements of systolic blood pressure during a mean of 5.7 years of follow-up (range 2-9 years) [7]. By use of LCGM four different patterns (trajectories) of blood pressure control were revealed (Adequate SBP control class; Delayed responders class; Insufficient SBP control class; Non-responders class). The authors were able to show that a majority of these patients (85%) were well controlled (SBP $\leq$140 mmHg) during the full observation period (Adequate SBP control class), but that the other three subgroups (15%) were in a poor blood pressure control, either during the early phase (Delayed responders class) or partly (Insufficient SBP control class) during the period, or not at all with a worsening control over time (Non-responders class). The risk of microvascular complications (nephropathy, retinopathy) during follow-up was elevated in all the three subgroups with insufficient blood pressure control. Cardiovascular mortality was increased only in the “Insufficient SBP control class”. Most remarkably,

total mortality was significantly *lower* in the "non-responder class" even following full adjustment for age, sex, diabetes duration, BMI and HbA1c. This finding was indeed contra-intuitive and currently lacks a full explanation. Furthermore, the authors found no significant differences in the proportion of dropouts or smokers between subgroups why these factors could not explain the finding. There was however a lack of data on other lifestyle variables or psychosocial background characteristics that could have contributed to the description of the non-responders. Selection bias and competing mortality risk could eventually have played a role, and other studies are needed to challenge this strange finding in independent analyses based on independent cohorts.

Another lack of information is missing data on treatment intensification or on treatment adherence. Furthermore, the associations of drug class membership with the proportion of medication use might have been underestimated, since this information was obtained by self-report only. More precise information on treatment is hopefully available in other cohorts if the findings should be replicated.

What can we learn from the clinical study from the Netherlands? In my opinion there is a clear motive to study trajectories over time in blood pressure control in patients at elevated risk, for example patients with type 2 diabetes, in order to select patients where increased efforts should be made to reduce both blood pressure and other cardiovascular risk factors as these often tend to cluster in the same patient. This could mean offering a more frequent visit and follow-up programme for selected risk patients with regular visits to both diabetes nurses and physicians. Some of these patients may be non-compliant due to side effects of prescribed drugs, neglect or lack of motivation, or simply unbearable cost of drugs, but various degrees of resistant hypertension could also play a role. For some difficult-to-control patients with these characteristics the addition of an aldosterone antagonist such as spironolactone could benefit the blood pressure control to a substantial degree [8].

Other ways to improve blood pressure control in risk patients could include a wider use of home blood pressure measurements, also allowing for some drug adjustment by the patient himself or herself [9]. Another way is to recommend bedtime intake of antihypertensive drugs as this has been shown to be effective in patients with type 2 diabetes, when either all [10] or some [11] of the daily antihypertensive drugs were taken at bedtime as an example of chronotherapy. This will improve not only night-time blood pressure control based on increased nocturnal natriuresis but also during 24-hour [10], and could be relevant to patients with for example increased night-time blood pressure. In fact, 24-h ambulatory blood pressure monitoring should be used more widely as masked hypertension is a clinical problem in many patients with type 2 diabetes [12].

In conclusion, the study by Walraven *et al.* [7] could show that in 15 percent of all type 2 diabetes patients from a population-based cohort a suboptimal blood pressure control pattern over time was revealed, associated with increased risk of microvascular complications and for one subclass also increased risk of cardiovascular mortality. It is enigmatic that the subgroup with “non-responsive” hypertension was at lower risk of total mortality compared to the well-controlled majority group. This spurious finding has to be further analysed in independent cohorts and should at this moment in time not be taken for granted as it may represent a chance finding.

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