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Atrial fibrillation and its association with type 2 diabetes and hypertension in a Swedish community

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Aim: To explore the prevalence of atrial fibrillation in patients with hypertension and type 2 diabetes and to identify possible mechanisms for the development of atrial fibrillation.

Methods: A community-based, cross-sectional observational study was conducted in the primary health care in Skara, Sweden, and 1739 subjects (798 men, 941 women) were surveyed. Patients were categorized as those with hypertension only (n = 597); those with both hypertension and type 2 diabetes (n = 171), and those with type 2 diabetes only (n = 147). In the reference population, 824 normotensive subjects without diabetes were identified and used as controls. Participants were examined for cardiovascular risk factors including fasting blood glucose, serum insulin, blood pressure, lipids and anthropometric measures. Resting electrocardiogram (ECG) was recorded and Minnesota-coded. Insulin resistance was measured by the homeostasis model assessment (HOMA).

Results: Age-adjusted prevalence of atrial fibrillation was 2% in patients with hypertension only, 6% in patients with both hypertension and type 2 diabetes, 4% in patients with type 2 diabetes only and 2% in controls, respectively. Age and sex adjusted odds ratios (OR) (95% CI) were; hypertension 0.7 (0.30–1.5), combined hypertension and type 2 diabetes 3.3 (1.6–6.7), and type 2 diabetes 2.0 (0.9–4.7). The association with combined hypertension and type 2 diabetes remained significant when adjusted for cardiovascular disease (CVD) risk factors and body mass index (BMI), was attenuated with adjustment for ischemic ECG; 2.4 (1.1–5.0) and lost significance with adjustment for insulin resistance; 1.3 (0.5–3.1).

Conclusions: Atrial fibrillation is associated with the combined occurrence of type 2 diabetes and hypertension. Insulin resistance may be a common underlying mechanism.

Introduction

Atrial fibrillation is a prevalent condition that has been associated with hypertension, ischemic heart disease (IHD), heart failure and valvular heart disease and different metabolic disturbances [1–5]. Furthermore, atrial fibrillation is also a major risk factor for stroke [6–9]. Information on the epidemiology of atrial fibrillation and its determinants is important for how surveillance and secondary prevention in these patients are conducted.

The Skaraborg Hypertension and Diabetes Project comprises a population-based sample of patients with hypertension and type 2 diabetes, and a comprehensive surveillance of cardiovascular disease (CVD) risk factors

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in the reference population [10,11]. The project has revealed significant differences in cardiovascular risk factors, metabolism and lifestyles between categories of hypertension and type 2 diabetes [10,12–14].

The aims of the present study were to explore the prevalence of atrial fibrillation in subgroups of patients with hypertension and type 2 diabetes and, furthermore, to identify possible mechanisms for the development of atrial fibrillation in these patients.

Methods

In Skara, a Swedish town with about 18 thousand residents, the health care centre is the only available outpatient facility. Practically, all residents with hypertension and type 2 diabetes in Skara are, since the 1970s, treated in primary care according to continuously updated medical care programmes including annual checkups [15–18]. In 1992–93, 1149 patients with known hypertension and known diabetes were consecutively seen at the health care centre for an extended annual visit, constituting the baseline survey of the Skaraborg Hypertension and Diabetes Project, described in detail elsewhere [10]. After exclusion of subjects with type 1 diabetes (n = 33), those younger than 40 years (n = 36) or those with missing electrocardiogram (ECG) (n = 160), 915 patients remained for this study.

From the population census register, 1400 subjects aged 40 years or above were randomly selected, stratified by age and gender. These subjects were in 1993–94 invited to the clinic for a health checkup including the same tests as those of the patient survey. In all 1109, subjects (80%) accepted and completed the investigation. With exclusion of those with hypertension (n = 243; 195 cases previously known and 48 cases identified at the survey) or diabetes mellitus (n = 97; 84 cases previously known and 13 cases identified at the survey), and those missing ECG (n = 15), 824 subjects remained as reference for this study.

All subjects were seen in the morning, and samples were drawn after a 10 h overnight fast. Fasting blood glucose was analyzed locally with a method from Hemocue (Hemocue AB, Ängelholm, Sweden). Routine tests were analyzed at the local hospital laboratory (Kärnsjukhuset, Skövde, Sweden). Other samples were immediately frozen at −80 °C and shipped to Wallenberg Laboratory, University hospital in Malmö, Sweden, for analyses of serum insulin [19], and of serum lipids by standard commercial methods (Lipids Laboratory, Lund University, Sweden). Height (to the nearest cm) and weight (to the nearest 0.1 kg) were measured in light indoor clothes and no shoes. Waist and hip circumferences were measured at the umbilical level and at the widest circumference between hip and buttocks, respectively. Body mass index (BMI) was calculated as weight/length^2 (kg m^{-2}), and waist-to-hip ratio as waist circumference/hip circumference (cm/cm). A physical examination was performed, and a 12-lead resting ECG was recorded and Minnesota-coded at the ECG-coding centre at the University Hospital in Gothenburg [20]. The conduction of the investigation has been described in detail previously [10].

In a structured interview, the participants were questioned about medical history, medications and smoking habits. They were categorized as current smokers or non-smokers (never or stopped).

Blood pressure was measured with a sphygmomanometer in the supine position after 5 min rest using Tri-cuff for automatic adjustment of cuff size for arm circumference [21]. Diagnostic criteria for hypertension were three consecutive blood pressure readings at least at 160 mmHg systolic or 90 mmHg diastolic, respectively, or ongoing antihypertensive treatment.

Subjects with previously known diabetes were categorized as such. In other cases, the following procedures were applied. (i) Patients identified with a fasting blood glucose in the range 5.5–6.6 mmol/l had a new appointment within the next weeks for a standard oral glucose tolerance test (OGTT) with a 75 g glucose load, using capillary whole blood glucose tests. Fasting blood glucose exceeding 6.6 mmol/l or a 2 h blood glucose exceeding 11.0 mmol/l was used as diagnostic criteria for diabetes [22]. (ii) Subjects with a fasting blood glucose exceeding 6.6 mmol/l had a new test within the next weeks, and when fasting blood glucose was ≥ 6.6 mmol/l, they were categorized as diabetes mellitus, and when < 6.6 mmol/l they had an appointment for an OGTT. When diabetes type 1 could be excluded based on clinical criteria, the diabetes was categorized as type 2 diabetes.

The participants were categorized into four groups; hypertension only, hypertension and type 2 diabetes combined, type 2 diabetes only and normotensive controls without diabetes.

Atrial fibrillation was identified by its specific Minnesota-code (8.3.1) [20]. The Whitehall criteria were used to categorize an ECG as normal or having changes consistent with IHD [23,24]. Subjects with possible (1.3, 4.1–4.3 or 5.1–5.3) or probable (1.1, 1.2 or 7.1.1) IHD according to these criteria were categorized as having ischemic ECG. Major Q-wave (1.1 and 1.2) and minor Q-wave (1.3) were combined in one category labelled Q-waves. Left ventricular hypertrophy (LVH) ((3.1 or

3.2) and (4.1–4.3 and 5.1–5.3)) and ST-depression (4.1–4.3) were defined accordingly.

Insulin resistance was assessed from fasting glucose and fasting insulin concentrations using the Homeostasis Model Assessment (HOMA) [25,26]. The HOMA model is not applicable to subjects treated with insulin, and 46 patients were excluded from the HOMA analysis for this reason.

Comorbidity was assessed by the structured interview and by examining the medical records at the health care centre [10]. A history of stroke [including transient ischemic attack (TIA)], myocardial infarction or congestive heart failure was defined as previous events of hospitalization for these conditions when confirmed in the medical files. Peripheral arterial disease and angina pectoris were defined as doctor's diagnoses of intermittent claudication and angina pectoris, respectively. Previous myocardial infarction or prevalent angina pectoris was categorized as IHD. Cardiovascular disease (CVD) included IHD, stroke, peripheral arterial disease and heart failure.

Prevalences were age-standardized using the reference population as standard. Associations between categorical data were estimated using logistic regression and expressed as odds ratios (OR) with 95% confidence intervals (CI). In all regressions, age and sex were entered as covariates to control for confounding. When indicated also other covariates were included in the regressions. Means were adjusted for age, and differences in means were analyzed with analysis of covariance (ANCOVA) with age as a covariate. Because of skewed distributions, values of serum insulin, insulin resistance (HOMA IR) and serum triglycerides were log-transformed for analyses. All tests were two-sided, and statistical significance was assumed when $p < 0.05$.

The Skaraborg Hypertension and Diabetes Project has been approved by the Committee on Research Ethics at the Medical Faculty of the University of Göteborg.

Results

This study enrolled 1739 subjects of whom 597 (34%) had hypertension only (234 men and 363 women), 171 (10%) had both hypertension and type 2 diabetes (87 men and 84 women), 147 (9%) had type 2 diabetes only (76 men and 71 women) and 824 (47%) were normotensive population controls without diabetes (401 men and 423 women). Table 1 shows cardiovascular risk factors in these categories for men and women, respectively. Generally, risk factor levels were higher in patients than in controls in both genders, and they were highest in patients with both hypertension and type 2

diabetes. As hypertension in these patients was based on hypertension known at the study visit, the vast majority was treated with blood pressure-lowering medications (87%). Mean age was similar in the three patient categories, but control subjects were younger.

Age-standardized proportions of atrial fibrillation, as shown in Table 2, was 2% both in controls and in subjects with hypertension only, 4% in patients with type 2 diabetes only and 6% in those with both hypertension and type 2 diabetes. In the latter group only, the risk of atrial fibrillation was significantly different from that of controls (OR 3.3, 95% CI 1.6–6.7). For ECG, changes consistent with IHD and LVH proportions and ORs increased correspondingly and significantly.

Some clinical characteristics for subjects with atrial fibrillation among patients and among controls from the population sample are shown in Table 3. In both groups, a majority was more than 70 years old, and most of the cases in both groups were known prior to the survey. Those with atrial fibrillation in the control group seemed to have had less symptoms at presentation while the patients more often presented with palpitation and congestive heart failure. Categories of comorbidity in this table are overlapping. In both groups, a majority had some known CVD as IHD, stroke, heart failure or peripheral arterial disease. In both groups, congestive heart failure was a major problem.

Table 4 shows odds ratios for atrial fibrillation in the different patient categories. The OR was highest in patients with both hypertension and type 2 diabetes being more than three times increased also when adjusted for differences in age and sex (OR 3.3; CI 1.6–6.7). This association between atrial fibrillation and the combined occurrence of hypertension and type 2 diabetes was then challenged by adjusting for different combinations of other variables, as proxies for possible mechanisms for the development of atrial fibrillation, and to account for confounding factors.

First, we adjusted for differences between the patients and the control subjects in BMI, systolic blood pressure, and serum triglycerides, as a proxy for the metabolic syndrome. However, the association remained (OR 3.7; CI 1.6–8.7), Table 4. Next, we adjusted for differences in LDL/HDL-cholesterol ratio, current smoking and systolic blood pressure to account for the most recognized CVD risk factors, and the outcome was virtually unchanged. When instead adjusting for differences in the prevalence of ischemic ECG, the odds ratio for the combined group fell, but the risk was still twofold and statistically significant (OR 2.4; CI 1.1–5.0). Finally, when we adjusted for differences in HOMA IR to account for the possibility that insulin resistance acts

Table 1 Gender-specific characteristics at baseline in subgroups of patients with hypertension and diabetes type 2, and controls, respectively. Skaraborg Hypertension and Diabetes Project 1992–94

	Population controls	Hypertension only		Hypertension and type 2 diabetes		Type 2 diabetes only	
	mean ± SD	mean ± SD	p	mean ± SD	p	mean ± SD	p
Men	(n = 401)	(n = 234)	(n = 87)	(n = 76)			
Age (years)	61 ± 13.1	65 ± 10.3	<0.001	71 ± 9.3	<0.001	68 ± 9.4	<0.001
Systolic blood pressure (mmHg)	136 ± 18.4	154 ± 18.6	<0.001	165 ± 21.1	<0.001	148 ± 21.3	<0.001
Diastolic blood pressure (mmHg)	76 ± 9.2	87 ± 7.5	<0.001	88 ± 8.6	<0.001	83 ± 8.6	<0.001
BMI (kg m^{-2})	25.9 ± 3.2	27.7 ± 3.5	<0.001	28.4 ± 4.4	<0.001	27.6 ± 4.0	<0.001
Waist hip ratio (cm/cm)	0.93 ± 0.06	0.96 ± 0.07	<0.001	0.97 ± 0.07	<0.001	0.96 ± 0.06	<0.001
Serum insulin* (mU l^{-1})	4.9 ± 4.6	6.7 ± 6.3	<0.001	7.7 ± 5.8	<0.001	5.8 ± 5.1	0.083
Fasting blood glucose (mmol l^{-1})	4.8 ± 0.6	5.5 ± 0.7	<0.001	8.2 ± 2.2	<0.001	8.8 ± 2.7	<0.001
Total cholesterol (mmol l^{-1})	5.9 ± 1.0	5.8 ± 1.06	0.309	5.7 ± 1.0	0.082	5.6 ± 1.0	0.016
LDL-cholesterol (mmol l^{-1})	4.3 ± 1.0	4.1 ± 1.0	0.058	3.9 ± 0.8	0.003	3.9 ± 1.0	0.004
HDL-cholesterol (mmol l^{-1})	1.05 ± 0.22	1.00 ± 0.24	0.007	0.96 ± 0.23	0.001	0.97 ± 0.18	0.005
LDL/HDL ratio	4.3 ± 1.5	4.3 ± 1.4	0.934	4.3 ± 1.3	0.928	4.2 ± 1.3	0.669
Triglycerides* (mmol l^{-1})	1.2 ± 0.7	1.5 ± 1.2	<0.001	1.7 ± 1.3	<0.001	1.5 ± 0.7	0.002
HOMA IR*	1.0 ± 2.2	1.7 ± 2.1	<0.001	2.7 ± 2.0	<0.001	2.1 ± 2.2	<0.001
Women	n = 423	n = 363		n = 84		n = 71	
Age (years)	60 ± 12.5	68 ± 10.2	<0.001	71 ± 9.6	<0.001	72 ± 10.0	<0.001
Systolic blood pressure (mmHg)	139 ± 19.8	156 ± 18.9	<0.001	160 ± 19.5	<0.001	154 ± 21.0	<0.001
Diastolic blood pressure (mmHg)	74 ± 9.8	83 ± 9.2	<0.001	85 ± 9.4	<0.001	81 ± 10.0	<0.001
BMI (kg m^{-2})	25.8 ± 4.5	28.1 ± 5.1	<0.001	29.4 ± 4.7	<0.001	27.7 ± 5.5	0.024
Waist hip ratio (cm/cm)	0.81 ± 0.07	0.84 ± 0.07	<0.001	0.89 ± 0.07	<0.001	0.88 ± 0.07	<0.001
Serum insulin* (mU l^{-1})	4.5 ± 4.0	6.7 ± 6.4	<0.001	8.7 ± 6.1	<0.001	7.7 ± 8.5	<0.001
Fasting blood glucose (mmol l^{-1})	4.8 ± 0.52	5.4 ± 0.7	<0.001	8.3 ± 2.5	<0.001	9.2 ± 2.9	<0.001
Total cholesterol (mmol l^{-1})	6.2 ± 1.2	6.4 ± 1.2	0.186	6.1 ± 1.3	0.483	5.9 ± 1.1	0.010
LDL-cholesterol (mmol l^{-1})	4.4 ± 1.1	4.5 ± 1.1	0.570	4.2 ± 1.1	0.068	4.0 ± 1.0	<0.001
HDL-cholesterol (mmol l^{-1})	1.24 ± 0.25	1.18 ± 0.26	0.003	1.05 ± 0.23	<0.001	1.08 ± 0.25	<0.001
LDL/HDL ratio	3.7 ± 1.2	4.0 ± 1.5	0.007	4.2 ± 1.4	0.005	3.8 ± 1.1	0.873
Triglycerides* (mmol l^{-1})	1.1 ± 0.5	1.4 ± 0.7	<0.001	1.7 ± 1.0	<0.001	1.6 ± 1.4	<0.001
HOMA IR*	1.0 ± 2.2	1.6 ± 2.1	<0.001	3.2 ± 1.8	<0.001	3.1 ± 2.2	<0.001

HOMA, homeostasis model assessment; BMI, body mass index; LDL, low-density lipoprotein; HDL, high-density lipoprotein. Differences in means between categories of patients and controls were analyzed with ANCOVA with age as covariate.
*Geometric mean used for analyses.

as a mechanism for development of atrial fibrillation. The OR now fell substantially and was no longer statistically significant (OR 1.3; CI 0.5–3.1).

The difference in insulin resistance (HOMA IR) between subjects with atrial fibrillation and those without, respectively, was further explored in the whole study population and in non-hypertensive subjects without diabetes. In the whole study population, the higher levels of HOMA IR in the 55 subjects with atrial fibrillation (2.6; SD, 2.0), compared to those 1684 subjects with sinus rhythm (1.3; SD, 2.4), was very robust and remained significant (p < 0.001) also when adjusted for differences in age, sex, BMI, systolic blood pressure and serum triglycerides. This was also seen in non-hypertensive subjects without diabetes (16 subjects with atrial fibrillation: 1.6; SD, 2.0 and 808 subjects with sinus rhythm: 0.94; SD, 2,2) in a corresponding analysis (p < 0.014).

Discussion

This study showed a novel association between atrial fibrillation and the combined occurrence of type 2 diabetes and hypertension. IHD and possibly also a combination of insulin resistance and impaired glucose control are plausible mechanisms for the development of atrial fibrillation. However, it should be kept in mind that a cross-sectional study cannot give proof of causality.

In contrast to several other studies, patients with hypertension only did not have an increased prevalence of atrial fibrillation [3–5]. However, one possible explanation could be that in our categorization of the patients, we excluded those with both hypertension and type 2 diabetes from those with hypertension alone, this could else be a confounding factor. In our study, the OR for atrial fibrillation in patients with type 2 diabetes alone was increased twofold and borderline significant with a

Table 2 Prevalences and odds ratios for specific electrocardiogram (ECG) categories in control subjects and in patients with hypertension and/or type 2 diabetes. Skaraborg Hypertension and Diabetes Project 1992–94

Categories	Population controls (n = 824)			Hypertension only (n = 597)				Hypertension and type 2 diabetes (n = 171)				Type 2 diabetes only (n = 147)			
	n	%	OR	n	%	OR	CI	n	%	OR	CI	n	%	OR	CI
Atrial fibrillation	16	2	1.0	11	2	0.7	0.3–1.5	18	6	3.3	1.6–6.7	10	4	2.0	0.9–4.7
Ischemic ECG (Whitehall)	131	17	1.0	157	21	1.4	1.1–1.8	86	33	3.2	2.2–4.7	53	25	1.8	1.2–2.7
Q-wave (major or minor)	40	5	1.0	43	6	1.3	0.8–2.0	23	10	2.0	1.1–3.5	15	9	1.5	0.8–2.9
Left ventricular hypertrophy	18	2	1.0	28	3	1.9	1.0–3.5	20	7	3.4	1.7–6.8	12	5	2.4	1.1–5.3
ST-depression	36	5	1.0	35	4	1.0	0.6–1.7	38	1	3.7	2.2–6.1	18	7	1.8	1.0–3.3

The risk of electrocardiogram (ECG) changes in the patient groups, as compared to controls, was estimated by logistic regression with adjustment for differences in age and sex. Associations are presented as odds ratios (OR) with 95% confidence intervals (CI). Prevalences were age-standardized using the Skara population as standard.

Table 3 Characteristics of patients with hypertension and/or type 2 diabetes and of controls with atrial fibrillation. Skaraborg Hypertension and Diabetes Project 1992–94*

Characteristics	Patients with hypertension and/or type 2 diabetes n (%)	Population controls n (%)
Age ≥70 years	31 (79)	14 (88)
Male gender	12 (31)	11 (69)
Atrial fibrillation	39 (100)	16 (100)
Known	26 (67)	13 (81)
New	7 (18)	2 (12)
Paroxysmal	6 (15)	1 (6)
Duration years		
0–1	14 (36)	4 (25)
2–5	13 (33)	7 (44)
6	12 (31)	5 (31)
Presenting symptoms		
Palpitations	14 (36)	1 (6)
Dyspnea	3 (8)	2 (12)
Heart failure	6 (15)	2 (12)
Symptomless	9 (23)	6 (38)
Comorbidity		
CVD	25 (64)	11 (69)
IHD	10 (26)	3 (19)
Stroke/TIA	5 (13)	4 (25)
Heart failure	16 (41)	8 (50)

CVD, cardiovascular disease; IHD, ischemic heart disease; TIA, transient ischemic attack.

*The total number of patients with atrial fibrillation is 39 and the corresponding figure among population controls is 16.

rather wide CI. Thus, a type 2 error cannot be completely excluded. Other studies often considered hypertension and IHD in relation to atrial fibrillation, whereas type 2 diabetes less often has been explored in these patients and reported results are conflicting [1–5]. However, the prevalence of atrial fibrillation was highest in patients with both hypertension and type 2 diabetes, and this specific category does not seem to have been explored in previous studies on atrial fibrillation.

In both sexes, CVD risk factors clustered in subjects with both hypertension and type 2 diabetes, as previously shown in this project in accordance with other studies [10,27,28] with a pattern resembling the metabolic syndrome [29,30].

When insulin resistance was accounted for (HOMA IR), the association between atrial fibrillation and the combined occurrence of hypertension and type 2 diabetes lost statistical significance. Further analyses were thus confined to HOMA IR. Patients with atrial fibrillation were more insulin-resistant than subjects with sinus rhythm in the whole study population, as well as in normotensive controls without diabetes. In a previous

Table 4 Odds ratios of atrial fibrillation in patients with hypertension and/or type 2 diabetes as compared to non-hypertensive subjects without diabetes. Skaraborg Hypertension and Diabetes Project 1992–94

ECG category	Population controls	Hypertension only		Hypertension and type 2 diabetes		Type 2 diabetes only	
	OR	OR	CI	OR	CI	OR	CI
Atrial fibrillation							
The risk adjusted for differences in age and sex	1.0	0.7	(0.3–1.5)	3.3	(1.6–6.7)	2.0	(0.9–4.7)
The risk adjusted for differences in age, sex, BMI, systolic blood pressure and serum triglycerides*	1.0	0.8	(0.3–1.9)	3.7	(1.6–8.7)	2.2	(0.9–5.4)
The risk adjusted for differences in age, sex, LDL/HDL-cholesterol ratio, current smoking and systolic blood pressure	1.0	0.9	(0.4–2.0)	4.4	(1.9–10.1)	2.0	(0.8–5.0)
The risk adjusted for differences in age, sex and ischemic ECG	1.0	0.6	(0.3–1.4)	2.4	(1.1–5.0)	1.7	(0.7–4.0)
The risk adjusted for differences in age, sex and HOMA IR*	1.0	0.5	(0.2–1.1)	1.3	(0.5–3.1)	0.6	(0.2–1.9)

The risk of atrial fibrillation in the patient groups, as compared to controls, was estimated by logistic regression with adjustment for differences in age and sex. The associations were successively challenged by different sets of covariates to consider different pathways for the development of atrial fibrillation. Associations are presented as odds ratios (OR) with 95% confidence intervals (CI). ECG, electrocardiogram; BMI, body mass index; LDL, low-density lipoprotein; HDL, high-density lipoprotein; HOMA IR, homeostasis model assessment insulin resistance.
*Geometric mean used for analyses.

study on four cases, insulin resistance was associated with sick sinus syndrome [31]. It is, therefore, possible that impaired glucose metabolism can be related to electrophysiological instability in the myocardium. Furthermore, insulin resistance has been shown to be associated with left ventricular hypertrophy [32]. Several potential mechanisms have been suggested to explain this association, such as an altered myocardial protein degradation, an increased sympathetic activation, an increased renal sodium reabsorption or by an insulin-like growth factor [33]. These mechanisms may be relevant also in the context of explaining the association between insulin resistance and atrial fibrillation.

The current antidiabetic treatment at baseline in the study population has been described in detail before [12], the most frequent treatments being recommendations on diet (42%), and treatment with sulphonylurea (31%), metformin (0.5%) and insulin (11%). All patients categorized as hypertensive did receive pharmacological treatment and the most frequently used antihypertensive drugs were β-blockers and diuretics. Insulin resistance (HOMA IR) was more prominent also in control subjects with atrial fibrillation compared to those with sinus

rhythm. As CVD was less prevalent in the controls and as they did not take any antihyperglycemic or antihypertensive medications, this study strongly argues against a significant confounding from these sources. The definitions of hypertension from the early 1990s have changed and do no longer apply today and may be a limitation of the study. However, the association between insulin resistance and atrial fibrillation should be valid as it was found also among controls. Furthermore, one limitation of the method is that subjects treated with insulin cannot be assessed by the HOMA method, as serum levels of insulin are part of the formulas.

In conclusion, this study showed that atrial fibrillation is a common condition in subjects with hypertension and type 2 diabetes and that insulin resistance was a plausible common underlying mechanism. This could be further supported by a recent risk score for predicting stroke or death in individuals with atrial fibrillation, which found increased systolic blood pressure and diabetes mellitus to be two of the most important risk factors [9]. Improved prevention and treatment of type 2 diabetes and other components of the metabolic syndrome may prevent the development of atrial fibrillation.

References

1 Benjamin E, Levy D, Vaziri S, D'Agostino R, Belanger A, Wolf P. Independent risk factors for atrial fibrillation in a population based cohort. The Framingham Heart Study JAMA 1994; **271:** 840–844.

2 Lip GYH, Beevers DG. History, epidemiology, and importance of atrial fibrillation. BMJ 1995; **311:** 1361–1363.

3 Langenberg M, Hellemons BSP, van Ree JW *et al.* Atrial fibrillation in elderly patients: prevalence and comorbidity in general practice. BMJ 1996; **313:** 1534.

4 Lip GYH, Golding DJ, Nazir M, Beevers DG, Child DL, Fletcher RI. A survey of atrial fibrillation in general practice: the West Birmingham Atrial Fibrillation Project. Br J General Pract 1998; **47:** 285–289.

5 Krahn AD, Manfreda J, Tate RB, Mathewson FAL, Cuddy TE. The natural history of atrial fibrillation: incidence, risk factors, and prognosis in the Manitoba follow-up study. Am J Med 1995; **98:** 476–484.

6 Aronow WS, Ahn C, Gutstein H. Prevalence of atrial fibrillation and association of atrial fibrillation with prior and new thromboembolic stroke in older patients. J Am Geriatr Soc 1996; **44:** 521–523.

7 Domanski MJ. The epidemiology of atrial fibrillation. Coronary Artery Dis 1995; **6:** 95–100.

8 Feinberg WM, Blackshear JL, Laupacis A, Kronmal R, Hart RG. Prevalence, age distribution, and gender of patients with atrial fibrillation. Arch Intern Med 1995; **155:** 469–473.

9 Wang T, Massaro J, Levy D *et al.* A risk score for predicting stroke or death in individuals with new-onset atrial fibrillation in the community. JAMA 2003; **290:** 1049–1056.

10 Bøg-Hansen E, Lindblad U, Bengtsson K, Ranstam J, Melander A, Råstam L. Risk factor clustering in patients with hypertension and NIDDM. The Skaraborg Hypertension Project. J Int Med 1998; **243:** 223–232.

11 Östgren CJ, Lindblad U, Ranstam J, Melander A, Råstam L. Associations between smoking and beta-cell function in a non-hypertensive and non-diabetic population. The Skaraborg Hypertension Diabetes Project. Diabetic Med 2000; **17:** 445–450.

12 Östgren CJ, Lindblad U, Bøg-Hansen E, Ranstam J, Melander A, Råstam L. Differences in treatment and metabolic abnormalities between normo- and hypertensive patients with type 2 diabetes: the Skaraborg Hypertension and Diabetes Project. Diabetes, Obesity Metabolism 1999; **1:** 105–112.

13 Bøg-Hansen E, Lindblad U, Ranstam J, Melander A, Råstam L. Impaired glucose metabolism and obesity in Swedish patients with borderline isolated systolic hypertension: Skaraborg Hypertension and Diabetes Project. Diabetes, Obesity Metabolism 2001; **1:** 25–31.

14 Bengtsson AK, Orho M, Lindblad U *et al.* Polymorphisms in the ACE but not in the angiotensinogen gene is associated with increased risk of hypertension and type 2 diabetes. The Skaraborg Hypertension Project. J Hypertens 1999; **17:** 1569–1575.

15 Berglund G, Isacsson S-O, Rydén L. The Skaraborg Project – a controlled trial regarding the effect of structured hypertension care. Acta Med Scand 1979; **205** (Suppl. 626): 64–68.

16 Råstam L, Berglund G, Isacsson S-O, Rydén L. The Skaraborg Hypertension Project. II. Feasibility of a medical care program for hypertension. Acta Med Scand 1986; **219:** 249–260.

17 Råstam L, Berglund G, Isacsson S-O, Rydén L. The Skaraborg Hypertension Project. III. Influence on blood pressure of a medical care program for hyper-tension. Acta Med Scand 1986; **219:** 261–269.

18 Lindblad U. The Prognosis of hypertension. The Skaraborg Hypertension Project. Malmö, Lund University, (PhD Dissertation), 1993.

19 Andersen L, Dinesen B, Jørgensen PN, Poulsen F, Røder ME. Enzyme immunoassay for intact human insulin in serum or plasma. Clin Chem 1993; **38:** 578–582.

20 Rose GA, Blackburn H, Gillum RF *et al.* In: Rose GA ed. Cardiovascular Survey Methods, 2nd edn. Geneva: World Health Organization, 1982; 123–129.

21 Råstam L, Sjönell G. A new device for measuring blood pressure in adults. Lancet 1991; **337:** 249–250.

22 World Health Organization Expert Committee. Diabetes mellitus. Technical Report series no. 742, Geneva, Switzerland 1985.

23 Reid DD, Hamilton PJR, McCartney R, Rose G, Jarrett RJ, Keen H. Smoking and other risk factors for coronary heart disease in British civil servants. Lancet 1976; **2:** 979–984.

24 Diabetes Drafting Group. Prevalence of small vessel and large vessel disease in diabetic patients from 14 centres. Diabetologia 1985; **28** (Suppl.): 615–640.

25 Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and β-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985; **28:** 412–419.

26 Haffner S, Miettinen H, Stern M. The homeostasis model in the San Antonio Heart Study. Diabetes Care 1997; **20:** 1087–1092.

27 Criqui MH, Barrett-Connor E, Holdbrook MJ, Austin M, Turner JD. Clustering of cardiovascular disease risk factors. Prev Med 1980; **9:** 525–533.

28 The Hypertension in Diabetes Study Group. Hypertension in Diabetes Study (HDS) II. Increased risk of

cardiovascular complications in hypertensive type 2 diabetic patients. J Hypertension 1993; **11:** 319–325.

29 Reaven GM. Banting Lecture 1988: role of insulin resistance in human disease. Diabetes 1988; **37:** 1595–1607.

30 DeFronzo RA, Ferrannini E. Insulin resistance: a multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia and atherosclerotic cardiovascular disease. Diabetes Care 1991; **14:** 173–194.

31 Wasada T, Katsumori K, Kasanuki H *et al.* Association of sick sinus syndrome with hyperinsulinemia and insulin resistance in patients with non-insulin-dependent diabetes mellitus: report of four cases. Intern Med 1995; **34:** 1174–1177.

32 Rutter M, Parise H, Benjamin E *et al.* Impact of glucose intolerance and insulin resistance on cardiac structure and function. Circulation 2003; **107:** 448–454.

33 Young ME, McNulty P, Taegtmeyer H. Adaptation and maladaptation of the heart in diabetes: Part 2: potential mechanisms. Circulation 2002; **105:** 1861–1870.