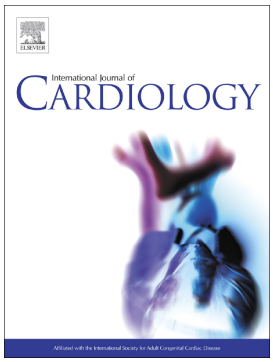
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Type 1 and type 2 diabetes mellitus and incidence of seven cardiovascular diseases

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Abstract

Background: The association between type 1 diabetes mellitus (T1DM) and specific cardiovascular diseases (CVD) is uncertain. Furthermore, data on type 2 diabetes mellitus (T2DM) in relation to risk of aortic valve stenosis, atrial fibrillation, abdominal aortic aneurysm, and intracerebral hemorrhage are scarce and inconclusive. We examined the associations of T1DM and T2DM with incidence of seven CVD outcomes.

Methods: This study comprised 71 483 Swedish adults from two population-based prospective cohorts. T1DM and T2DM diagnosis and incident CVD cases were ascertained through linkage with the population-based registers.

Results: T1DM was associated with myocardial infarction (hazard ratio [HR] 3.26; 95% confidence interval [CI] 2.47–4.30), heart failure (HR 2.68; 95% CI 1.76–4.09), and ischemic stroke (HR 2.61; 95% CI 1.80–3.79). Increased risk of myocardial infarction, ischemic stroke, and heart failure was also observed in T2DM patients and the magnitude of the associations increased with longer T2DM duration. T2DM was also associated with an increased risk of aortic valve stenosis (HR 1.34; 95% CI 1.05–1.71) and with lower risk of abdominal aortic aneurysm (HR 0.57; 95% CI 0.40–0.82) and intracerebral hemorrhage (HR 0.51; 95% CI 0.30-0.88). Only long-term T2DM (≥20 years) was associated with an increased risk of atrial fibrillation (HR 1.44; 95% CI 1.02-2.04).

Conclusion: T1DM and T2DM are associated with increased risk of major CVD outcomes.

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1. Introduction

Abundant evidence from observational [1,2] and genetic studies [3-5] indicates that type 2 diabetes mellitus (T2DM) is associated with an increased risk of major atherosclerosis-related cardiovascular diseases (CVD), including coronary heart disease and ischemic stroke. However, less is known about the relationship of T2DM with other CVD outcomes, such as aortic valve stenosis, abdominal aortic aneurysm, and intracerebral hemorrhage, and studies on T2DM and atrial fibrillation are inconclusive [6,7]. Most data on type 1 diabetes mellitus (T1DM) in relation to risk of CVD derive from retrospective medical record review studies (cohorts of T1DM patients exclusively), with standardized mortality or incidence ratio of any CVD, coronary heart disease, or stroke as the outcome [8]. Such register-based studies are generally limited by the inability to adjust for confounding by adiposity, lifestyle factors (e.g., diet, smoking, and physical activity), and other CVD risk factors.

In this study, data from two population-based prospective cohorts of generally healthy men and women were analyzed to investigate the associations of T1DM and T2DM with incidence of seven CVD outcomes, while adjusting for adiposity, lifestyle, and other potential confounders. Moreover, the association between duration of T2DM and CVD was examined.

2. Methods

2.1. Study population

The source population for these analyses were 48 850 men (born 1918-1952) in the Cohort of Swedish Men and 39 227 women (born 1914-1948) in the Swedish Mammography Cohort. Participants of these two cohorts were residents of the adjacent counties Örebro, Västmanland and Uppsala of central Sweden. They completed a 350-item questionnaire concerning diet, lifestyle, and other risk factors for chronic diseases in the autumn of 1997 and have since then been followed up through linkage with population-based registers, using the unique personal

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identity number assigned to each Swedish resident at birth. The study was approved by the Regional Ethical Review Board at Karolinska Institutet. The completion of the questionnaire was considered to imply informed consent.

2.2. Assessment of Diabetes Mellitus

T1DM and T2DM were defined on the basis of a diagnosis recorded in the Swedish National Patient or Diabetes Registers before start of follow-up (i.e., 1 January 1998). The baseline questionnaire inquired about information on diabetes mellitus (DM) without specification of type. Participants with self-reported DM but without a DM diagnosis verified in the registers were excluded because they could not be classified according to type of DM.

2.3. Assessment of Covariates

Information on education, smoking history, weight, height, physical activity (exercise and walking/bicycling), family history of myocardial infarction before 60 years of age, history of hypertension and hypercholesterolemia, alcohol consumption, and diet was obtained from the baseline (1997) questionnaire. Hypertension and hypercholesterolemia was defined by a self-reported history of these conditions. Body mass index (BMI) was calculated as weight divided by height squared (kg/m^2). Overweight was defined as BMI $\geq$25 kg/m^2. We constructed a modified Dietary Approaches to Stop Hypertension diet score, as a measure of an overall healthy diet, based on seven food groups, as described previously [9].

2.4. Case Ascertainment

CVD cases were identified by linkage of study participants with the national Swedish Patient and Swedish Cause of Death Registers. CVD events that occurred during follow-up were classified according to the International Classification of Diseases 10th Revision codes. The

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outcomes in this study were based on a discharge diagnosis and included acute myocardial infarction (I21), heart failure (I50 and I11.0), aortic valve stenosis (I35.0 and I35.2), atrial fibrillation (I48), abdominal aortic aneurysm (I71.3 and I71.4), ischemic stroke (I63), and intracerebral hemorrhage (I61). The validity of CVD diagnoses in the Swedish National Patient Register is high, with a positive predictive value around 100% for some CVDs, such as myocardial infarction and atrial fibrillation, and >85% for many other diagnoses [10].

2.5. Statistical Analysis

Participants were categorized into three groups according to DM status: no DM (reference group), T1DM, and T2DM. Follow-up time was defined as the time elapsed from 1 January 1998 to the date of diagnosis of CVD, date of death, or 31 December 2014, whichever came first. Hazard ratios (HR) with 95% confidence intervals (CI) by DM status were estimated by Cox proportional hazards regression models with age as the underlying time variable and stratified by sex to allow for different baseline hazards function for men and women. The multivariable model was further adjusted for BMI (in kg/m^2; <22.5, 22.5-24.9, 25.0-27.4, 27.5-29.9, or ≥30.0), education (less than high school, high school, or university), family history of myocardial infarction before 60 years of age (yes/no), smoking status and pack-years of smoking (never smoker; past smoker <20 or ≥20 pack-years; current smoker <20, or ≥20 pack-years), aspirin use (never, 1–6 tablets/week, or ≥7 tablets/week), exercise (in hours/week; <1, 1–2, 3–4, or ≥5), walking/bicycling (almost never, <20 min/day, 20–40 min/day, or >40 min/day), history of hypertension (yes/no), history of hypercholesterolemia (yes/no), alcohol consumption (never drinkers, past drinkers, or current drinkers of <1 drink/week, 1–6 drinks/week, 7–14 drinks/week, 14–21 drinks/week, or >21 drinks/week), total energy intake (kcal/day; continuous), and a modified Dietary Approaches to Stop Hypertension diet score (quartiles). The analyses were performed using SAS (version 9.4,

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SAS Institute, Cary, NC) and Stata (version 14.2; StataCorp, TX, USA). All tests were two-sided and deemed statistically significant at $P < 0.05$.

3. Results

Of the 48 850 men and 39 227 women in the two cohorts, those with a missing or incorrect personal identity number (this number is needed to identify diagnoses of diabetes, CVD, cancer, and deaths), those who died or had a diagnosis of cancer or CVD before start of follow-up (i.e., 1 January 1998), and those with an extreme total energy intake were excluded (Figure S1). Excluded were also 103 participants with DM of unknown type or secondary DM as well as 1138 participants with self-reported diabetes but without a DM diagnosis recorded in the registers. Thus, the analytic cohort consisted of 71 483 participants (37 982 men [mean age 58.9 ± 9.4 years] and 33 501 women [mean age 61.1 ± 9.0 years]).

Baseline characteristics of participants by DM status at baseline are presented in Table 1. Compared with participants without DM, those with T1DM were, on average, younger and less likely to be overweight and to have a family history of myocardial infarction, whereas T2DM patients were older and more likely to be overweight and to have a family history of myocardial infarction. Both T1DM and T2DM patients more frequently used aspirin, were more likely to have a history of hypertension, consumed less alcohol, and had a healthier diet compared with non-diabetics. The median duration of DM was 28.1 years (interquartile range 17.6-38.5 years) for T1D and 5.5 years (interquartile range 2.5-10.5 years) for T2D.

During up to 17 years of follow-up, the number of incident cases of cardiovascular disease ascertained was 6242 for myocardial infarction, 4268 for heart failure, 1242 for aortic valve stenosis, 9421 for atrial fibrillation, 1201 for abdominal aortic aneurysm, 4913 for ischemic stroke, and 680 for intracerebral hemorrhage.

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T1DM was associated with an increased risk of myocardial infarction (HR 3.26; 95% CI 2.47–4.30), heart failure (HR 2.68; 95% CI 1.76–4.09), and ischemic stroke (HR 2.61; 95% CI 1.80–3.79), but not with aortic valve stenosis or atrial fibrillation (Table S1 and Figure 1). Analyses could not be conducted for abdominal aortic aneurysm or intracerebral hemorrhage because of no cases or only one case, respectively, in T1DM patients.

The risk of myocardial infarction, heart failure, and ischemic stroke was also higher in T2DM patients, compared with individuals without DM, after adjustment for age and sex only and further for BMI (Table S1). The associations remained in the multivariable model (Table S1 and Figure 1). T2DM was also associated with an increased risk of aortic valve stenosis (multivariable HR 1.34; 95% CI 1.05–1.71) and with lower risk of abdominal aortic aneurysm (multivariable HR 0.57; 95% CI 0.40–0.82) and intracerebral hemorrhage (multivariable HR 0.51; 95% CI 0.30-0.88) (Table S1 and Figure 1). T2DM was associated with a statistically significant increased risk of atrial fibrillation in the age- and sex-adjusted analysis but the association did not persist after adjustment for BMI (the major confounder) (Table S1) and other risk factors (Table S1 and Figure 1).

The associations of T2DM with risk of myocardial infarction, heart failure, and ischemic stroke were more pronounced with longer duration of T2DM (Table 2). Although there was no overall association between T2DM and risk of atrial fibrillation, long-term T2DM (≥20 years) was associated with an increased risk (HR 1.44; 95% CI 1.02–2.04) compared with no diabetes. The inverse association between T2DM and risk of abdominal aortic aneurysm was stronger with longer T2DM duration but this finding was based on few cases (Table 2).

4. Discussion

In this population-based prospective study, both T1DM and T2DM were associated with an increased risk of myocardial infarction, heart failure, and ischemic stroke after adjustment for

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BMI, diet, lifestyle, and other risk factors. The magnitude of the elevated risk increased with longer duration of T2DM. T2DM was further associated with an increased risk of aortic valve stenosis and with a reduced risk of abdominal aortic aneurysm and intracerebral hemorrhage. Patients with long-term (≥20 years) T2DM also had an increased risk of atrial fibrillation, whereas T1DM was not associated with risk of this CVD outcome.

Results from the present study agree with findings from the CALIBER program, which showed that T2DM was associated with increased risk of myocardial infarction, heart failure, and ischemic stroke [2]. Likewise, our findings of positive associations between T1DM and risk of heart failure and ischemic stroke are consistent with previous studies [11,12]. Most other studies of T1DM in relation to risk of CVD are register-based studies that compared the prevalence, incidence, or mortality rates of CVD in hospitalized T1DM patients with the rates in a nondiabetic population [8]. Those studies have reported higher standardized rates of coronary heart disease and cerebrovascular disease in T1DM patients as compared with the nondiabetic population [8].

Our results extend previous observations by showing an even stronger association of T1DM than of T2DM with CVD outcomes. This finding may partly reflect longer duration of T1DM compared with T2DM. Some support for this is that magnitude of the positive relation between T2DM and risk of myocardial infarction, heart failure, and ischemic stroke increased with longer T2DM duration. Patients with long-term T2DM (≥20 years) had nearly the same relative risk increase of these CVD outcomes as T1DM patients (mean duration of T1DM in this study was about 28 years). Another possible explanation for the different magnitude of association for the two DM types is that treatments may differ for T1DM patients (insulin therapy) and T2DM patients (diet and exercise alone or combined with diabetes medications [e.g., metformin] and/or insulin therapy).

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In contrast to myocardial infarction, heart failure, and ischemic stroke, less is known about the association between DM and other CVD outcomes. DM has been associated with increased prevalence of aortic valve calcification on CT [13] and echocardiography [14], and to predict an accelerated aortic valve stenosis progression [15]. However, prospective data on T2DM in relation to incidence of aortic valve stenosis are limited and inconsistent. Findings from this study are in line with the increased risk of aortic valve stenosis among DM patients observed in a recent study based on data from electronic databases [16]. That study did not adjust for BMI, which was a strong confounder of the association between T2DM and aortic valve stenosis in our study, and a risk factor for aortic valve stenosis [17]. In two smaller prospective studies, DM was associated with an approximately 3-fold increased risk of aortic valve stenosis in a cohort of 5079 Swedish adults (including 69 cases in the whole cohort) [18] but was not associated with risk of aortic valve stenosis in a cohort of 3243 Norwegian adults, possibly because of lack of power with only 6 cases among DM patients [19]. None of the above mentioned reports specified the type of DM. The present study showed that T2DM but not T1DM was associated with a significant increased risk of aortic valve stenosis. However, because of few cases among T1DM patients, we cannot exclude that statistical type II error explains the lack of association between T1DM and risk of aortic valve stenosis.

Studies on T2DM and risk of atrial fibrillation have reported equivocal results [6,7,20]. The disparate findings may partly be due to limited statistical power and residual confounding as few studies adjusted for other major risk factors such as obesity [7], which was a strong confounder in the present study. Similarly, in the Women's Healthy Study, T2DM was not associated with risk of atrial fibrillation after adjustment for changes in other risk factors, including BMI and hypertension, during follow-up [20]. The discrepancies in study findings may also be related to different T2DM durations in different study populations. Results from this study showed that only long-term T2DM (≥20 years) was associated with risk of atrial

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fibrillation. Studies on T1DM in relation to atrial fibrillation risk are rare, but the current study showed that there is no association between the two diseases.

Although the lower risk of abdominal aortic aneurysm observed among T2DM patients in this study may appear counterintuitive, such diabetes-aneurysm paradox has been previously reported [1,21]. T2DM has further been related to a reduction in abdominal aortic aneurysm enlargement [22,23]. The apparent protective effects of DM on abdominal aortic anerysm formation may relate to an increased extracellular matrix and thicker abdominal aortic wall obseved in DM patients [21]. A thicker aortic wall reults in decreased wall stress, which is considered fundamental to abdominal aortic anerysm development and progression [21]. In addition, calcification, which is a primary driver of the development of aortic valve stenosis (and which was increased in T2DM patients in this study), may be protective for the evolution of abdominal aortic aneurysms [24]. However, it cannot be excluded that medications used in T2DM, and not the disease *per se*, may be the protective factor for abdominal aortic aneurysm formation.

Data on T2DM in relation to risk of intracerebral hemorrhage are limited and conflicting [1,22]. Our results corroborate those of the Lausanne Stroke Registry study [22] but were based on few cases and should therefore be interpreted with caution. Further large studies of the association between T2DM and risk of intracerebral hemorrhage are necessary to better understand the relationship.

Major strengths of this study include the objective information on DM and ascertainment of several different CVD outcomes through population-based registers with accurate data on diagnoses. Another important strength, which differs this study from several previous studies, is that the risk estimates could be adjusted for major potential confounders, including body mass index and lifestyle factors.

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This study also has several limitations, such as potential underascertainment of DM via the registers. Another shortcoming is that despite the large sample size, the number of T1DM patients was rather limited, leading to low power in the analyses of T1DM in relation to CVD risk. We may therefore have missed weak associations. A further limitation is that quite many individuals were excluded from the analysis, primarily due to prevalent CVD at baseline, and this reduced the power.

In summary, results from this prospective study representing individuals from the general population showed that T1DM and T2DM were strongly associated with increased risk of atherosclerosis-related CVD outcomes and heart failure. The magnitude of the excess risk was particularly pronounced in T1DM patients and in individuals with long-term T2DM who also had an increased risk of atrial fibrillation. In contrast, T2DM patients were less likely to be diagnosed with abdominal aortic aneurysm and intracerebral hemorrhage. Taken together, these results reinforce both T1DM and T2DM as strong risk factors for major CVD outcomes.

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Conflict of interest statement

The authors have no conflicts of interest to declare.

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Table 1. Characteristics of study participants according to type 1 and type 2 diabetes mellitus status at baseline

Characteristic	No diabetes (n = 69 106)	Type 1 diabetes (n = 247)	Type 2 diabetes (n = 2130)
Age, years, mean (SD)	59.9 (9.3)	57.2 (9.1)	63.2 (8.8)
Postsecondary education, %	18.8	17.0	13.8
Family history of myocardial infarction, %	15.2	11.4	18.3
Current smoker, %	24.3	25.3	23.8
Overweight (BMI ≥25 kg/m^2), %	48.7	47.1	73.4
Walk/bicycle ≥40 min/day, %	34.4	28.6	33.0
Exercise ≥2 hours/week, %	57.7	62.7	59.2
Aspirin use ≥7 tablets/week, %	6.3	9.9	8.7
Hypertension, %	19.2	35.2	41.3
Hypercholesterolemia, %	10.0	8.0	15.8
Energy intake, kcal/day, mean (SD)	2250 (853)	2320 (941)	2250 (846)
Alcohol, drinks/week, mean (SD)*	6.6 (10.1)	5.5 (8.9)	6.3 (8.2)
mDASH diet score, mean (SD)†	21.6 (4.4)	22.5 (4.2)	22.3 (4.3)

Abbreviations: BMI, body mass index; mDASH, modified Dietary Approaches to Stop Hypertension; SD, standard deviation.

*Among current drinkers.

†A measure of a healthy diet; the mDASH diet score ranges from 7 (minimal adherence) to 35 (maximal adherence).

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Table 2. Hazard ratios (95% confidence interval) for the association between duration of type 2 diabetes mellitus and cardiovascular disease

		Duration of type 2 diabetes mellitus			
Cardiovascular disease	**No diabetes**	**<5 years**	**5-9.9 years**	**10-19.9 years**	**≥20 years**
Myocardial infarction					
No. of cases	5797	156	113	89	36
Multivariable HR*	1.00 (ref.)	1.48 (1.26-1.74)	1.96 (1.63-2.37)	1.73 (1.40-2.13)	3.07 (2.21-4.26)
Heart failure					
No. of cases	3945	112	82	80	27
Multivariable HR*	1.00 (ref.)	1.34 (1.14-1.66)	1.80 (1.45-2.25)	2.14 (1.71-2.67)	2.66 (1.82-3.89)
Aortic valve stenosis					
No. of cases	1165	37	20	11	5
Multivariable HR*	1.00 (ref.)	1.52 (1.10-2.12)	1.44 (0.92-2.49)	1.95 (0.52-1.72)	1.74 (0.72-4.19)
Atrial fibrillation					
No. of cases	9007	173	103	84	32
Multivariable HR*	1.00 (ref.)	0.99 (0.85-1.15)	1.05 (0.87-1.28)	1.01 (0.82-1.26)	1.44 (1.02-2.04)
Abdominal aortic aneurysm					
No. of cases	1170	18	11	2	0
Multivariable HR*	1.00 (ref.)	0.79 (0.50-1.26)	0.85 (0.47-1.54)	0.15 (0.04-0.61)	–
Ischemic stroke					
No. of cases	4476	124	82	78	25
Multivariable HR*	1.00 (ref.)	1.48 (1.23-1.77)	1.78 (1.43-2.21)	2.02 (1.61-2.53)	2.30 (1.55-3.41)
Intracerebral hemorrhage					
No. of cases	666	6	3	4	0
Multivariable HR*	1.00 (ref.)	0.52 (0.23-1.16)	0.48 (0.15-1.49)	0.59 (0.22-1.58)	–

*Hazard ratios were estimated by Cox proportional hazards regression models with age as the time scale and stratified by sex and adjusted for BMI, education, family history of myocardial infarction, smoking status and pack-years of smoking, aspirin use, exercise, walking/bicycling, history of hypertension, history of hypercholesterolemia, alcohol consumption, total energy intake, and a modified Dietary Approaches to Stop Hypertension diet score.

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FIGURE LEGEND

Figure 1. Type 1 and type 2 diabetes mellitus and cardiovascular disease. Hazard ratios were estimated by Cox proportional hazards regression models with age as the time scale and stratified by sex and adjusted for BMI, education, family history of myocardial infarction, smoking status and pack-years of smoking, aspirin use, exercise, walking/bicycling, history of hypertension, history of hypercholesterolemia, alcohol consumption, total energy intake, and a modified Dietary Approaches to Stop Hypertension diet score. Analyses could not be conducted for T1DM and risk of abdominal aortic aneurysm and intracerebral hemorrhage because of no cases or only one case among T1DM patients. CI, confidence interval; HR, hazard ratio; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

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Highlights

- This study investigated the associations of type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM) with incidence of seven CVD outcomes in a cohort of 71 483 adults.
- T1DM was strongly associated with increased risk of myocardial infarction, heart failure, and ischemic stroke.
- T2DM was associated with increased risk of myocardial infarction, ischemic stroke, heart failure, and aortic valve stenosis and with lower risk of abdominal aortic aneurysm and intracerebral hemorrhage.

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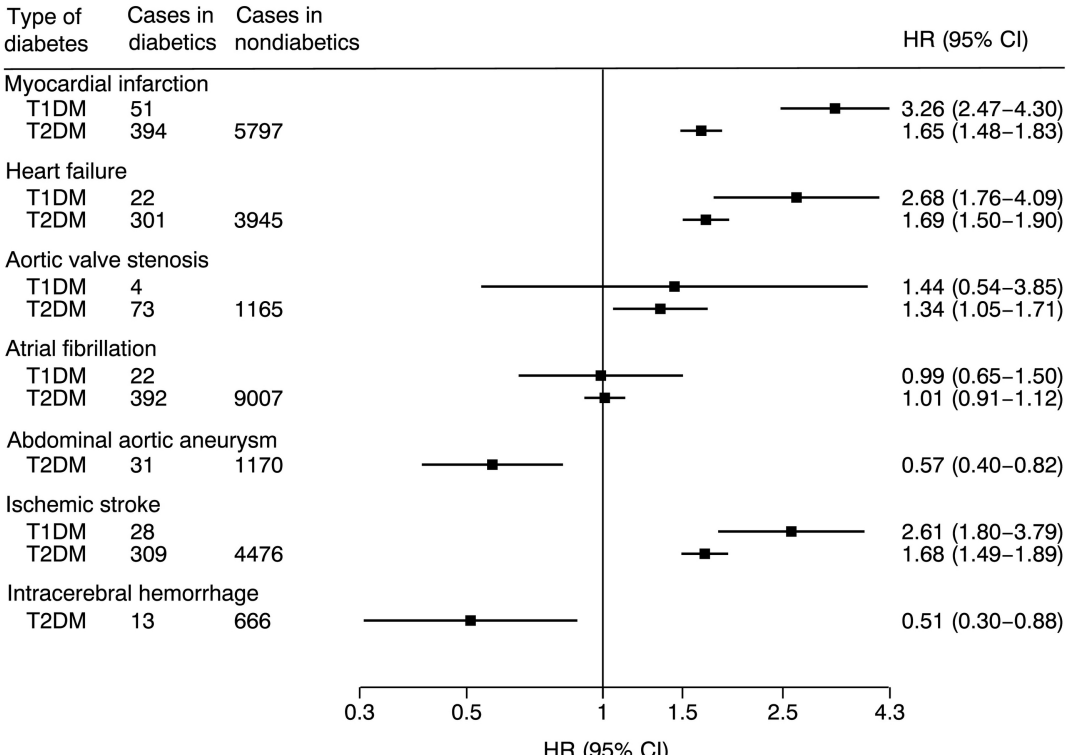

Type of diabetes
Cases in diabetics
Cases in nondiabetics
HR (95% CI)
Myocardial infarction
T1DM 51 3.26 (2.47–4.30)
T2DM 394 5797 1.65 (1.48–1.83)
Heart failure
T1DM 22 2.68 (1.76–4.09)
T2DM 301 3945 1.69 (1.50–1.90)
Aortic valve stenosis
T1DM 4 1.44 (0.54–3.85)
T2DM 73 1165 1.34 (1.05–1.71)
Atrial fibrillation
T1DM 22 0.99 (0.65–1.50)
T2DM 392 9007 1.01 (0.91–1.12)
Abdominal aortic aneurysm
T2DM 31 1170 0.57 (0.40–0.82)
Ischemic stroke
T1DM 28 2.61 (1.80–3.79)
T2DM 309 4476 1.68 (1.49–1.89)
Intracerebral hemorrhage
T2DM 13 666 0.51 (0.30–0.88)
0.3
0.5
1
1.5
2.5
4.3
HR (95% CI)

Figure 1