

Characteristics and Prognosis in Women and Men With Type 1 Diabetes Undergoing Coronary Angiography: A Nationwide Registry Report

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OBJECTIVE

To describe sex aspects on extent of coronary artery disease (CAD) and prognosis in a contemporary population with type 1 diabetes.

RESEARCH DESIGN AND METHODS

All patients undergoing coronary angiography, 2001–2013, included in the Swedish Coronary Angiography and Angioplasty Registry and the Swedish National Diabetes Register as type 1 diabetes were followed for mortality until 31 December 2013. The coronary angiogram was classified into normal, one-vessel disease, two-vessel disease, three-vessel disease, and left main stem disease.

RESULTS

In all, 2,776 patients (42% women) with mean age 58 years (SD 11) were followed for 7.2 years (SD 2.2). Diabetes duration was longer in women (37 \pm 14 vs. 34 \pm 14 years in men; *P* < 0.001), who also had more retinopathy (68% vs. 65%; *P* = 0.050), whereas microalbuminuria was less common (41% vs. 51%; *P* < 0.001). Indications for coronary angiography did not substantially differ in women and men. The extent of CAD was somewhat less severe in women (normal angiogram 23.5% vs. 19.1%, three-vessel and left main stem disease 34.5% vs. 40.4%; *P* = 0.002), whereas mortality did not differ (adjusted hazard ratio 1.03 [95% CI 0.88–1.20]; *P* = 0.754). The standard mortality ratio for women the first year was 7.49 (5.73–9.62) and for men was 4.58 (3.60–5.74).

CONCLUSIONS

In patients with type 1 diabetes admitted for coronary angiography, the extent of CAD was almost similar in women and men, and total long-term mortality did not differ. Type 1 diabetes was associated with higher mortality risk in women than in men when compared with the general population. These data support that type 1 diabetes attenuates the cardiovascular risk difference seen in men and women in the general population.

The prevalence of type 1 diabetes is increasing globally (1). In Sweden, 39.5 new cases of type 1 diabetes per 100,000 children and adolescents (0–19 years old) per year (2017) are diagnosed (1). Despite improvements in management and treatment, type 1 diabetes remains associated with increased mortality rates compared with the general population (2–4). An increased risk for cardiovascular (CV) disease in women compared

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with men with type 1 diabetes has been proposed (5), and a 40% excess mortality risk in women compared with men with type 1 diabetes was demonstrated in a meta-analysis by Huxley et al. (6). In the general population, women suffer from acute coronary syndrome (ACS) \sim 10 years later (7) than men; a protective role of estrogen has been suggested (8). Furthermore, the extent of coronary artery disease (CAD) in ACS is less severe in women than in men when diabetes is not present (9). However, sex-related protection seems to be abolished in women with diabetes as they suffer from ACS at about the same age as men (10). In type 2 diabetes, this has partly been explained by a more extensive risk factor burden (10-12) as well as a suboptimal management (13), with a lower proportion of women than men achieving the recommended treatment targets for CV risk factors (14). We recently demonstrated that in patients with type 1 diabetes undergoing coronary angiography, death due to ischemic heart disease was related to the number of affected coronary artery vessels (4). However, little is known about the sex-related differences in type 1 diabetes when it comes to features of CAD and prognosis. The aim of the current study was to investigate CAD and mortality in women and men in a contemporary unselected cohort of patients with type 1 diabetes. We hypothesized an equal burden of CAD and similar mortality rates in women and men with type 1 diabetes.

RESEARCH DESIGN AND METHODS Patients

All patients (n = 2,844) with type 1 diabetes undergoing coronary angiography during 2001-2013 registered in the Swedish Coronary Angiography and Angioplasty Registry (SCAAR) and in the Swedish National Diabetes Register (NDR) were identified. Due to incomplete information regarding angiographic results, 68 individuals (2%) were excluded, leaving 2,766 patients as the final study cohort that was followed for mortality until 31 December 2013 (mean follow-up time 7.1 years [SD 3.2]). Only the information from the first coronary angiography was collected. The national quality registry SCAAR has collected data on patients undergoing coronary angiography since the start of the registry in 1998 and includes all 29 centers performing these procedures. The collected data have

been monitored and validated annually since 2001 by comparing 50 entered variables in 20 randomly selected interventions per hospital and year with the patient's hospital records. The overall correspondence rate in data was 95% during the study period (15). The NDR comprises risk factors, diabetic complications, and medications and includes >95% of all individuals \geq 18 years of age with type 1 diabetes where patients were informed about registry entry with permission to opt out (16). Baseline characteristics are derived from the SCAAR at the first angiography during the study period and from the NDR based on data obtained at the visit closest to the coronary angiography, allowing 365 days before or after the coronary angiogram. The long-term follow-up was obtained by merging the SCAAR and the NDR database with the Swedish National Patient Register and the Swedish National Cause of Death Registry, which contains information on underlying causes of death.

Outcome Measures and Definitions

Type 1 diabetes was defined both with an epidemiological definition (onset age before 30 years and insulin treatment alone) and using the clinicians' diagnosis of type 1 diabetes and onset age before 50 years. HbA_{1c} is reported as % (National Glycohemoglobin Standardization Program [NGSP]) and mmol/mol (International Federation of Clinical Chemistry [IFCC]). Estimated glomerular filtration rate (eGFR) was calculated with the MDRD equation (17). CAD was visually judged by the local coronary interventionist and categorized into normal (atheromatosis/stenosis <50%), one-vessel disease, two-vessel disease, three-vessel disease, and left main stem disease. Complete revascularization was a clinical judgement and was defined as any nontreated significant (at least 60%) stenosis in a coronary artery supplying \leq 10% of the myocardium. Causes of mortality were classified according to the ICD-10 and categorized into 13 main causes of mortality (further specified in Supplementary Fig. 3). Standard mortality ratio (SMR) was the comparison of the mortality in our cohort to the expected mortality in the general Swedish population of the same age.

Statistical Analysis

Baseline characteristics are presented as mean and SD for continuous variables and numbers and percentages for categorical variables. Automatic multiple imputation was used to handle missing data in some of the clinical variables (indication, BMI, smoking, eGFR, microalbuminuria, and HbA_{1c}). Missing data were imputed 10 times using fully conditional specification in the SPSS statistical package, based on an iterative Markov Chain Monte Carlo procedure. All imputed variables were considered as being at least missing at random. The comparison between sexes was performed by group (all women vs. all men) and not by pairwise comparison (one matched woman to one matched man). The χ^2 or, when appropriate, Fisher exact test was used to compare baseline characteristics between the different groups. Cox proportional hazards regression analyses were performed to study the association between the number of affected coronary vessels and mortality. The multivariate models included age, sex, hospital, admission year, indication, treated hypertension, treated hyperlipidemia, previous myocardial infarction (MI), previous heart failure (HF), previous coronary artery bypass grafting (CABG), previous stroke, previous renal failure, peripheral artery disease, retinopathy, albuminuria, diabetes duration, HbA_{1c}, BMI, and eGFR. SMR was calculated for women and men, respectively, for each year up to 5 years after the coronary angiography. Mortality estimates for the general Swedish population were obtained from the Swedish Statistical responsible for official statistics and for other government statistics in Sweden (18). Kaplan-Meier curves were computed to illustrate time to mortality by affected coronary vessels on the angiogram. A two-sided P value of <0.05 was accepted as statistically significant. All analyses were conducted using the SPSS statistical program software (version 23; SPSS Inc., Chicago, IL).

Ethical Consideration

The local ethical board at the University of Gothenburg approved the study (DNR 612-08).

RESULTS

Patients

The baseline characteristics of the patients with type 1 diabetes (men n = 1,621; women n = 1,155) are presented in Table 1. The mean age for all patients was 58 years, BMI 26.4 kg/m², and HbA_{1c} 8.3% (67 mmol/mol). Smoking was more common in women compared with men

	n	All patients (<i>n</i> = 2,776)	Men (<i>n</i> = 1,621)	Women (<i>n</i> = 1,155)	P valu
Clinical characteristics	2 770	57.5 (19–88) ± 10.9	(7, 0, 10, 00) + 10, 0	F7 F (22, 9C) + 11 O	0.005
Age (years)	2,776		57.6 (19–88) \pm 10.8	57.5 (23–86) ± 11.0	0.995
BMI (kg/m ²)	2,360	26.4 (15.4–74.5) ± 4.5	26.4 (16.9–52.8) ± 3.9	26.4 (15.4–74.5) ± 5.1	0.742
Smoker (current)	2,744	14.6 (400)	12.6 (202) 127 (84, 210) + 17	17.3 (198)	0.001
Systolic blood pressure (mmHg)	2,575	136 (84–220) ± 18	137 (84–210) ± 17	136 (85–220) ± 18	0.409
Diastolic blood pressure (mmHg) Hypertension (treated)	2,575	73 (40–115) ± 10	74 (40–110) ± 10	71 (40–115) ± 10	< 0.00
	2,763	78.7 (2,175)	79.5 (1,278)	77.7 (897)	0.250
Hyperlipidemia (treated) Atrial fibrillation	2,698	79.4 (2,143)	80.3 (1,262)	78.2 (881)	0.262
	2,776	5.2 (144)	5.7 (93)	4.4 (51)	0.140
Previous disease	2 700	20 5 (1.000)	20.0 (C20)	20.0 (420)	0.04
MI Description DCI	2,766	38.5 (1,069)	38.9 (630)	38.0 (439)	0.64
Previous PCI	2,617	5.8 (153)	5.9 (90)	5.8 (63)	0.96
Previous CABG	2,776	10.5 (291)	11.5 (186)	9.1 (105)	0.04
HF (hospitalization)	2,766	14.9 (414)	15.0 (243)	14.8 (171)	0.89
Stroke (hospitalization)	2,776	8.3 (231)	8.6 (140)	7.9 (91)	0.47
Renal insufficiency (hospitalization) Peripheral artery disease (hospitalization)	2,766	11.0 (306) 16.3 (452)	11.2 (182)	10.7 (124)	0.68
1 , (1 ,	2,766	10.5 (452)	17.0 (275)	15.3 (177)	0.249
Diabetes-related variables	2.000				0.40
HbA _{1c} (mmol/mol)	2,638	$66.7 (26-145) \pm 14.0$	$66.4 (26-145) \pm 13.8$	67.1 (29–136) ± 14.4	0.18
HbA_{1c} (%)	2,638	8.3 (4.5–15.4) ± 3.4	8.2 (4.5–15.4) ± 3.4	8.3 (4.8–14.6) \pm 3.5	0.18
Diabetes duration (years)	2,776	35.0 (0–76) ± 14.1	33.6 (0-73) ± 14.0	37.0 (0–76) ± 14.2	< 0.0
Debut age (years)	2,776	22.6 (0–50) ± 13.3	24.1 (0–50) ± 13.2	20.6 (0–50) ± 13.0	<0.0
Creatinine (μmol/L)	2,524	121 (24–1,013) ± 128	129 (42–1,013) ± 138	110 (24–859) ± 111	< 0.00
LDL (mg/dL)	1,840	2.66 (0.37–7.34) ± 0.89	2.65 (0.48–7.34) ± 0.88	2.66 (0.37–7.29) ± 0.91	0.78
HDL (mg/dL)	1,861	$1.52(0.43-4.0) \pm 0.49$	$1.43(0.43-3.90) \pm 0.47$	$1.65(0.60-3.97) \pm 0.49$	< 0.00
Triglycerides (mg/dL)	1,880	$1.39(0.3-14.1) \pm 1.0$	$1.39(0.3-14.1) \pm 1.0$	$1.39(0.3-13.0) \pm 1.0$	0.96
Retinopathy	2,766	66.1 (1,836)	64.7 (1,048)	68.2 (788)	0.05
Never severe hypoglycemia in the last year	596	89.8 (535)	88.4 (290)	91.4 (245)	0.50
Pump	2,033	12.2 (248)	11.1 (131)	13.7 (117)	0.08
Never physical activity	1,376	15.2 (209)	15.3 (122)	15.0 (87)	0.33
Microalbuminuria	2,276	46.8 (1,065)	50.6 (676)	41.3 (389)	< 0.00
Macroalbuminuria	2,318	23.5 (544)	26.1 (356)	19.7 (188)	< 0.00
Angio indication	2,752		20.2 (425)	22 7 (270)	0.00
Stable		31.3 (862)	30.3 (486)	32.7 (376)	
NSTE-ACS		37.5 (1,032)	36.6 (586)	38.8 (446)	
STEMI		10.2 (280)	11.2 (180)	8.7 (100)	
Chest pain		4.9 (135)	4.1 (65)	6.1 (70)	
Silent ischemic heart disease		2.9 (81)	3.0 (48)	2.9 (33)	
Arrhythmia		1.3 (36)	1.3 (21)	1.3 (15)	
Valvular		3.6 (98)	4.0 (64)	3.0 (34)	
HF A subia su sum una		3.6 (100)	4.5 (72)	2.4 (28)	
Aortic aneurysm		0.0 (1)	0.0 (0)	0.1 (1)	
Cardiac arrest		0.4 (10)	0.2 (4)	0.5 (6)	
Angiographic findings	2,776				0.00
Normal		20.9 (580)	19.1 (309)	23.5 (271)	
One-vessel disease		23.1 (641)	23.1 (375)	23.0 (266)	
Two-vessel disease		18.1 (503)	17.5 (283)	19.0 (220)	
Three-vessel disease		29.3 (815)	30.4 (493)	27.9 (322)	
Left main stem disease		8.5 (237)	10.0 (161)	6.6 (76)	
Stent					
Numbers	993	1.2 (0–5) \pm 0.9	1.2 (0–5) \pm 0.9	1.2 (0–4) \pm 0.9	0.81
Drug-eluting stent	803	58.0 (466)	53.9 (257)	64.1 (209)	0.004
Complete revascularization after PCI	876	58.8 (515)	58.7 (304)	58.9 (211)	0.45
Primary decision after angiography	2,698				0.18
No therapy		9.7 (263)	9.2 (144)	10.5 (119)	
Medical		19.5 (525)	18.0 (281)	21.5 (244)	
CABG		19.8 (535)	21.0 (328)	18.2 (207)	
PCI		36.2 (976)	36.7 (573)	35.5 (403)	

Data are % (n) or mean (range) \pm SD unless otherwise indicated.

(17% vs. 13%; P = 0.001). Treated hypertension and hyperlipidemia were extensive and did not differ between the sexes. Diabetes duration was longer in women $(37 \pm 14 \text{ vs. } 34 \pm 14 \text{ years}; P < 0.001),$ who also had more retinopathy (68% vs. 65%; P = 0.050), whereas microalbuminuria was less common (41% vs. 51%; P <0.001). The indications for coronary angiography in women and men, respectively, were stable CAD 33% vs. 30%, non-STelevation ACS (NSTE-ACS) 39% vs. 37%, ST-elevation MI (STEMI) 9% vs. 11%, HF 2% vs. 5%, atypical chest pain 6% vs. 4%, silent ischemia 2.9% vs. 3.0%, and other rare reasons.

Coronary Angiography Findings and Decision

Supplementary Fig. 1 depicts the extent of CAD, which differed between women and men (P < 0.001). Coronary angiography revealed no significant stenosis in 23% of the women and 19% of the men, and 23% of both women and men had one-vessel disease, 19% vs. 18% had two-vessel disease, and 28% vs. 30% had three-vessel disease. Left main stem disease was present in 7% vs. 10% in

women and men, respectively. There was no difference in judged complete revascularization after percutaneous coronary intervention (PCI) between the sexes (59%; P = 0.45). In patients with threevessel disease, CABG was the primary decision in 48.6% of the women and 43.9% of the men. The corresponding figures for PCI were 27.0% for women vs. 30.7% for men. Figure 1 illustrates the findings on coronary angiograms in women (Fig. 1A) and men (Fig. 1B) by indication. In stable CAD and NSTE-ACS, women more often had normal coronary angiograms than men, whereas in STEMI, women rarely had a normal angiogram (4% normal).

Background Population Admitted for Coronary Angiography but Without Diabetes

During the same years, 2001–2013, 163,608 patients without diabetes performed a coronary angiography in Sweden (49,951 women and 113,657 men). In this background population, mean age for women was 68.1 years (SD 10.5, range 3–97) and for men 65.8 years (SD 10.0, range 16–96). Coronary angiography revealed no significant stenosis in

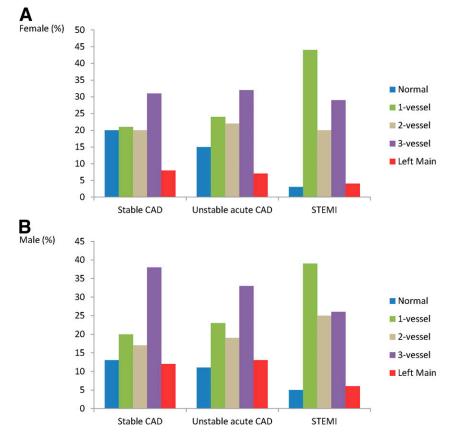


Figure 1—Percentage with CAD by indication in women (A) and men (B).

22% of the women and 12% of the men, and 27% vs. 25% had one-vessel disease, 23% vs. 26% had two-vessel disease, and 21% vs. 28% had three-vessel disease. Left main stem disease was present in 7% vs. 9% in women and men, respectively. Supplementary Table 1 shows the distribution of coronary vessel disease in those with and without diabetes.

Long-term Follow-up

During follow-up, 640 patients died, 23% of both women and men, with no difference in mortality risk between sexes (adjusted hazard ratio [HR] 1.03 [95% CI 0.88-1.20; P = 0.754) (Supplementary Fig. 2). Kaplan-Meier curves for time to mortality by affected coronary vessels (Fig. 2) demonstrate lower rates in those with normal and one-vessel disease in both sexes and substantially higher if multivessel disease is present. The estimated 8-year crude mortality rate derived from the Kaplan-Meier curves was in normal angiogram 15% vs. 20% in women and men, respectively, for one-vessel disease 25% vs. 20%, for two-vessel disease 29% vs. 30%, for three-vessel disease 45% vs. 35%, and for left main stem disease 43% vs. 44%. The adjusted HR for mortality in women compared with men by affected coronary vessels did not differ significantly between men and women (HR for one-vessel 0.87 [95% CI 0.55-1.38], HR for two-vessel 1.05 [0.69-1.61], and HR for three-vessel 1.21 [0.93-1.58]). Variables associated with mortality are presented in Supplementary Table 2, where the strongest were renal failure (1.89 [1.25-2.85] in women vs. 2.61 [1.89-3.60] in men) and NSTE-ACS (2.22 [1.33-3.71] in women vs. 1.87 [1.26-2.77] in men). Causes of death are described in Supplementary Fig. 3. CV disease was the most common cause of death and was evenly distributed between sexes (49.1% vs. 47.5%). Death due to ischemic heart disease (38.0% vs. 38.2%) was increased by the number of affected coronary artery vessels in both sexes. Cancer mortality was more common among men (11.0% vs. 6.8%), whereas death due to urinary tract disease was more common among women (2.3% vs. 0.3%). SMR is depicted in Fig. 3. SMR for women the first year was 7.49 (5.73-9.62) and decreased to 5.38 (3.89-7.24) after 5 years. Corresponding figures for men were SMR 4.58 (3.60-5.74) the first year and decreased to 2.53 (1.83-3.41) after 5 years.

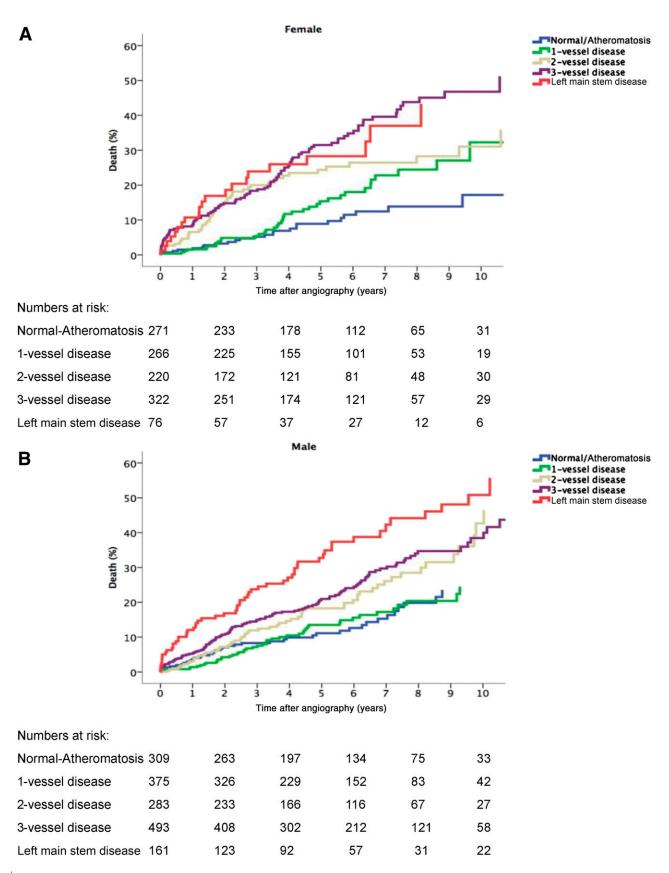


Figure 2—Time to mortality by affected coronary artery vessels at the index coronary angiography (unadjusted) in women (A) and men (B).

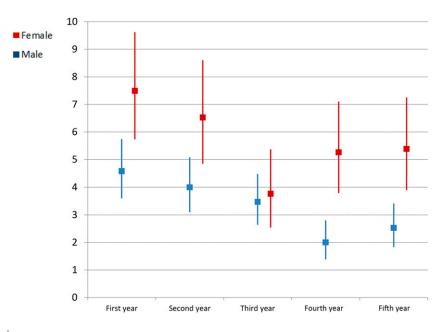


Figure 3—The SMR for the first 5 years after the index coronary angiography in women (red) and men (blue) with type 1 diabetes compared with the general population.

When constructing an SMR ratio between women and men, the women-to-men ratio of SMR was 1.64 the first year (7.49/ 4.58) and 2.13 the fifth year (5.38/2.53).

CONCLUSIONS

In this nationwide study including all patients with type 1 diabetes who underwent coronary angiography in Sweden during 2001-2013, we report the extent of CAD in women and men with type 1 diabetes in a contemporary population exposed to modern diabetes treatment during a long period, including a careful risk factor and glucose control. To the best of our knowledge, this is one of the largest updated examinations of coronary angiography in type 1 diabetes of its kind. There are two important messages from the current study. First, although women had somewhat less extensive coronary vessel disease than men, there was no substantial difference of numbers of affected coronary vessels between men and women with type 1 diabetes. This is in contrast to women and men without diabetes, where women are described to more often have nonobstructive CAD or only one vessel affected (18,19). Second, there was no mortality difference between men and women with type 1 diabetes, as described after ACS in the general population where age-adjusted mortality advantages are seen in the female population (10,20,21). The advantage

related to female sex in the general population has previously been described to be attenuated, although primarily for type 2 diabetes (10,22). In the current study, the mortality risk the first year in women with type 1 diabetes was increased by seven to eight times compared with women in the general population and by four to five times in men with type 1 diabetes compared with men without diabetes. The higher SMR in women may partly be attributed to the low risk of mortality in women without diabetes in this age-group. Huxley et al. (6) also found an excess mortality risk in women with type 1 diabetes (SMR 5.80 [4.89-6.89]) compared with women without diabetes. This is lower than the increased risk in the present population the first year and illustrates the higher mortality risk in women with type 1 diabetes when CAD is present. Previous reports on coronary angiography findings from a sex perspective in the population with diabetes are sparse. Data from the Euro Heart Survey demonstrated a considerably lower proportion of normal angiograms in women with diabetes (diabetes type not specified) compared with women without diabetes, with no major difference between men with or without diabetes (normal angiography 3% in women with diabetes vs. 11% in those without; corresponding figures for men were 2% vs. 4%). This is in accordance with the current study where the extent of CAD did not substantially differ between sexes when type 1 diabetes was present. Further, when compared with the population without diabetes, despite being 10 years younger, women with type 1 diabetes more often had extensive three-vessel disease than women without diabetes (28% vs. 21% and mean age 58 vs. 68 years) (Supplementary Table 1). The mechanisms behind the attenuation of the female-related advantage seen when type 1 diabetes is present are not exactly known. Suggested mechanisms are that women with diabetes compared with women without diabetes more often have multiple CV risk factors, such as dysglycemia, dyslipidemia, hypertension, and renal disease. A higher burden of insulin resistance in women with type 1 diabetes associated with a high calcium score has been proposed as a contributing factor (23). Furthermore, hormonal mechanisms, with disturbed monthly hormonal variations and early menopause (24) resulting in the early loss of the potentially beneficial impact of estrogen on for instance endothelial function (25), are more common when diabetes is present (10).

Our data further show that in accordance with the situation in the general population, the number of affected coronary vessels influences mortality risk even when type 1 diabetes is present. Thus, diabetes itself is not the only reason for the excess mortality risk, but the extent of CAD also matters. This strengthens the need to include aggressive CV preventive strategies early after diabetes diagnosis, especially in women with type 1 diabetes where one cannot assume a protection of just being a woman. Indeed, prevention in this respect is effective. In earlier reports from the 1990s, including a highly selected group of patients with type 1 diabetes and a more severe comorbidity, a much higher proportion of CAD was reported, with as much as 84% having three-vessel disease (26,27). Surprisingly to us, we found that as many as 44% of the population had no or only one vessel affected despite 35 years of diabetes duration, indicating that CAD is not inevitable. Furthermore, extensive preventive therapy, including glucose control by means of insulin pump therapy and lipidlowering treatment with statins, has in registry reports been associated with lower CV mortality, although not further analyzed for women and men separately (28,29).

CV disease was the primary cause of death in \sim 45% in both sexes, much lower than the previously often reported figure of 75-80%. There was no significant difference in mortality causes between the sexes, with CV disease in 45% and ischemic heart disease in 35%, which is similar to that in the general population, although CV mortality seems to occur at an earlier age if diabetes is present. This is in accordance with recent reports showing a decline in death due to CV disease in the population with diabetes in the last decades, from \sim 80% in the 1990s (30) to today's level, with a parallel increase in other mortality causes such as cancer, due to improved longevity in the diabetes population (31,32).

Strengths and Limitations

The major strength of the current study is the use of the unique national registries during a long follow-up time, implying an unselected population from an everyday clinical setting, enabling our results to be generalizable to other populations than the study cohort. During the current study period, almost all patients with type 1 diabetes in Sweden were included, considering the high coverage of the NDR (>95% of all individuals ≥ 18 years of age with type 1 diabetes), resulting in a unique large population with type 1 diabetes with coronary angiography findings. Previous data are mostly related to type 2 diabetes or an unspecified type of diabetes (33,34). The major limitation of this study is the observational study design where there is always a possibility of unknown residual confounders that are not possible to control for. Baseline variables such as lipids, HbA_{1c}, and medication have been collected adjacent to the coronary angiogram and not from the total diabetes duration time. Furthermore, apart from extensive antihyperlipidemic and antihypertensive treatment at the time for the procedure (almost 80%, with no difference between sexes) (Table 1), we lack information about other cardioprotective medications during the follow-up period. However, it is our conviction that patients have been handled according to guidelines, receiving optimal cardioprotective treatment if indicated. Another limitation in our cohort is the lack of information on treatment or residual ischemia during follow-up. Furthermore, there is a possibility that a normal angiogram (classified as atheromatosis/ stenosis <50%) may comprise undiagnosed microvascular disease; however, our data showed the best survival in those classified as normal angiography findings. We did not analyze if the impact of the revascularization strategy, CABG or PCI, affected the outcome, which was chosen according to the physician in charge. There may be a risk of remaining ischemia, and that lack of complete revascularization may have affected the prognosis. However, revascularization was completed if possible, and patients were handled according to guidelines where CABG was performed, if clinically indicated. The goal is always to achieve complete revascularization; however, if ischemic burden is still present, it is not routinely clinically evaluated and therefore not reported in the SCAAR registry. Finally, we did not statistically compare our coronary angiography findings with CAD patients without diabetes and adjusted for other risk factors, because we found a substantial age difference with much higher mean age (almost 10 years older) in patients without diabetes admitted for coronary angiography, making such comparison difficult.

Conclusion

In this nationwide population-based study of individuals with type 1 diabetes referred for coronary angiography, women and men had almost similar coronary angiography findings and long-term mortality rate. However, type 1 diabetes was associated with higher mortality risk in women than in men when compared with the general population. These data support that type 1 diabetes attenuates the CV risk difference seen in men and women in the general population and highlights the need for preventive strategies early after the diabetes diagnosis.

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Duality of Interest. V.R. has received honoraria from AstraZeneca, Novo Nordisk, and Boehringer Ingelheim on expert group participation. K.E.-O. has received lecture honoraria from Novo Nordisk, Sanofi, and Abbott. A.N. has received honoraria on expert group participation from AstraZeneca, Merck Sharp & Dohme, Eli Lilly and Company, Novo Nordisk, and Boehringer Ingelheim. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. V.R. and A.N. developed the study design and finalized the manuscript after adjustments by all authors. C.H., A.-M.S., N.S., and K.E.-O. developed the study design. B.L. developed the study design, managed the database, and performed the statistical analyses. All authors made substantial contributions to the manuscript and took part in the interpretation of the results. V.R. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. International Diabetes Federation. *Diabetes Atlas*. 8th ed. Brussels, Belgium, International Diabetes Federation, 2017

2. Matteucci E, Giampietro O. Epidemiology of cardiovascular disease in patients with type 1 diabetes: European perspective. Exp Clin Endocrinol Diabetes 2014;122:208–214

3. Soedamah-Muthu SS, Fuller JH, Mulnier HE, Raleigh VS, Lawrenson RA, Colhoun HM. All-cause mortality rates in patients with type 1 diabetes mellitus compared with a non-diabetic population from the UK general practice research database, 1992-1999. Diabetologia 2006;49:660–666

4. Ritsinger V, Hero C, Svensson AM, et al. Mortality and extent of coronary artery disease in 2776 patients with type 1 diabetes undergoing coronary angiography: a nationwide study. Eur J Prev Cardiol 2017;24:848–857 DOI:10.1177/ 2047487316687860

5. Soedamah-Muthu SS, Fuller JH, Mulnier HE, Raleigh VS, Lawrenson RA, Colhoun HM. High risk of cardiovascular disease in patients with type 1 diabetes in the U.K.: a cohort study using the general practice research database. Diabetes Care 2006;29:798–804

6. Huxley RR, Peters SA, Mishra GD, Woodward M. Risk of all-cause mortality and vascular events in women versus men with type 1 diabetes: a systematic review and meta-analysis. Lancet Diabetes Endocrinol 2015;3:198–206

7. Pencina MJ, D'Agostino RB Sr, Larson MG, Massaro JM, Vasan RS. Predicting the 30-year risk of cardiovascular disease: the Framingham Heart Study. Circulation 2009;119:3078–3084

 Lagranha CJ, Deschamps A, Aponte A, Steenbergen C, Murphy E. Sex differences in the phosphorylation of mitochondrial proteins result in reduced production of reactive oxygen species and cardioprotection in females. Circ Res 2010; 106:1681–1691

9. al-Khalili F, Svane B, Di Mario C, et al. Intracoronary ultrasound measurements in women with myocardial infarction without significant coronary lesions. Coron Artery Dis 2000;11:579–584 10. Norhammar A, Schenck-Gustafsson K. Type 2 diabetes and cardiovascular disease in women. Diabetologia 2013;56:1–9

11. Juutilainen A, Kortelainen S, Lehto S, Rönnemaa T, Pyörälä K, Laakso M. Gender difference in the impact of type 2 diabetes on coronary heart disease risk. Diabetes Care 2004;27:2898– 2904

12. Paul S, Thomas G, Majeed A, Khunti K, Klein K. Women develop type 2 diabetes at a higher body mass index than men. Diabetologia 2012;55: 1556–1557

13. Gouni-Berthold I, Berthold HK, Mantzoros CS, Böhm M, Krone W. Sex disparities in the treatment and control of cardiovascular risk factors in type 2 diabetes. Diabetes Care 2008;31:1389– 1391 14. Franzini L, Ardigò D, Cavalot F, et al. Women show worse control of type 2 diabetes and cardiovascular disease risk factors than men: results from the MIND.IT Study Group of the Italian Society of Diabetology. Nutr Metab Cardiovasc Dis 2013;23:235–241

15. Uppsala Clinical Research Center, Uppsala, Sweden, 2017. Available from http://www.ucr .uu.se/swedeheart/om-swedeheart/organisation. Accessed 15 September 2017

16. Eeg-Olofsson K, Cederholm J, Nilsson PM, Gudbjörnsdóttir S, Eliasson B; Steering Committee of the Swedish National Diabetes Register. Glycemic and risk factor control in type 1 diabetes: results from 13,612 patients in a national diabetes register. Diabetes Care 2007;30:496–502 17. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease study group. Ann Intern Med 1999; 130:461–470

18. Johnston N, Jönelid B, Christersson C, et al. Effect of gender on patients with ST-elevation and non-ST-elevation myocardial infarction without obstructive coronary artery disease. Am J Cardiol 2015;115:1661–1666

19. Collste O, Sörensson P, Frick M, et al. Myocardial infarction with normal coronary arteries is common and associated with normal findings on cardiovascular magnetic resonance imaging: results from the Stockholm Myocardial Infarction with Normal Coronaries study. J Intern Med 2013;273:189–196

20. Lawesson SS, Alfredsson J, Fredrikson M, Swahn E. A gender perspective on short- and long-term mortality in ST-elevation myocardial infarction—a report from the SWEDEHEART register. Int J Cardiol 2013;168:1041–1047

21. Norhammar A, Stenestrand U, Lindbäck J, Wallentin L; Register of Information and Knowledge about Swedish Heart Intensive Care Admission (RIKS-HIA). Women younger than 65 years with diabetes mellitus are a high-risk group after myocardial infarction: a report from the Swedish Register of Information and Knowledge about Swedish Heart Intensive Care Admission (RIKS-HIA). Heart 2008;94:1565–1570

22. Huxley R, Barzi F, Woodward M. Excess risk of fatal coronary heart disease associated with diabetes in men and women: meta-analysis of 37 prospective cohort studies. BMJ 2006;332:73–78

23. Dabelea D, Kinney G, Snell-Bergeon JK, et al.; Coronary Artery Calcification in Type 1 Diabetes Study. Effect of type 1 diabetes on the gender difference in coronary artery calcification: a role for insulin resistance? The Coronary Artery Calcification in Type 1 Diabetes (CACTI) Study. Diabetes 2003;52:2833–2839

24. Dorman JS, Steenkiste AR, Foley TP, et al.; Familial Autoimmune and Diabetes (FAD) Study. Menopause in type 1 diabetic women: is it premature? Diabetes 2001;50:1857–1862

25. Ross RL, Serock MR, Khalil RA. Experimental benefits of sex hormones on vascular function and the outcome of hormone therapy in cardiovascular disease. Curr Cardiol Rev 2008;4:309–322

26. Valsania P, Zarich SW, Kowalchuk GJ, Kosinski E, Warram JH, Krolewski AS. Severity of coronary artery disease in young patients with insulindependent diabetes mellitus. Am Heart J 1991; 122:695–700

27. Pajunen P, Taskinen MR, Nieminen MS, Syvänne M. Angiographic severity and extent of

coronary artery disease in patients with type 1 diabetes mellitus. Am J Cardiol 2000;86:1080–1085 28. Steineck I, Cederholm J, Eliasson B, et al.; Swedish National Diabetes Register. Insulin pump therapy, multiple daily injections, and cardiovascular mortality in 18,168 people with type 1 diabetes: observational study. BMJ 2015;350:h3234 29. Hero C, Rawshani A, Svensson AM, et al. Association between use of lipid-lowering therapy and cardiovascular diseases and death in individuals with type 1 diabetes. Diabetes Care 2016;39: 996–1003

 Ritsinger V, Malmberg K, Mårtensson A, Rydén L, Wedel H, Norhammar A. Intensified insulin-based glycaemic control after myocardial infarction: mortality during 20 year follow-up of the randomised Diabetes Mellitus Insulin Glucose Infusion in Acute Myocardial Infarction (DIGAMI 1) trial. Lancet Diabetes Endocrinol 2014;2:627–633
Harding JL, Shaw JE, Peeters A, Guiver T, Davidson S, Magliano DJ. Mortality trends among people with type 1 and type 2 diabetes in Australia: 1997-2010. Diabetes Care 2014;37:2579–2586

32. Gregg EW, Sattar N, Ali MK. The changing face of diabetes complications. Lancet Diabetes Endocrinol 2016;4:537–547

33. Ritsinger V, Saleh N, Lagerqvist B, Norhammar A. High event rate after a first percutaneous coronary intervention in patients with diabetes mellitus: results from the Swedish coronary angiography and angioplasty registry. Circ Cardiovasc Interv 2015;8:e002328

34. Saleh N, Petursson P, Lagerqvist B, et al. Longterm mortality in patients with type 2 diabetes undergoing coronary angiography: the impact of glucose-lowering treatment. Diabetologia 2012; 55:2109–2117