Patients With Diabetes Without Significant Angiographic Coronary Artery Disease Have the Same Risk of Myocardial Infarction as Patients Without Diabetes in a Real-World Population Receiving Appropriate Prophylactic Treatment

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OBJECTIVE

The risk of myocardial infarction (MI) in patients with diabetes is greater than for patients without diabetes. Consequently, prophylactic treatment is recommended for patients with diabetes and risk factors for ischemic heart disease. We aimed to estimate the risk of adverse cardiac events in patients with and without diabetes with and without coronary artery disease (CAD) after coronary angiography (CAG).

RESEARCH DESIGN AND METHODS

A population-based cohort of patients registered in the Western Denmark Heart Registry who underwent CAG between 1 January 2003 and 31 December 2012 was stratified according to the presence or absence of obstructive CAD and diabetes. End points were death, cardiac death, and MI. Unadjusted and adjusted rate ratios (RRs) were calculated by using patients without diabetes and without CAD as the reference group.

RESULTS

We included 93,866 patients of whom 12,544 (13.4%) had diabetes at the time of CAG. Median follow-up was 4.1 years. Patients with and without diabetes without obstructive CAD had the same adjusted risk of death (RR 1.03 [95% CI 0.92–1.15]), cardiac death (RR 1.21 [95% CI 0.90–1.64]), and MI (RR 0.88 [95% CI 0.65–1.17]). Patients with diabetes without CAD were more often treated with statins (75.3% vs. 46.0%) and aspirin (65.7% vs. 52.7%) than patients without diabetes and CAD.

CONCLUSIONS

In a real-world population, patients with diabetes with high rates of statin and aspirin treatment had the same risk of cardiovascular events as patients without diabetes in the absence of angiographically significant CAD.

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Patients with diabetes are at high risk for coronary artery disease (CAD) (1). Their risk of myocardial infarction (MI) was initially reported to be equal to that of patients without diabetes with a history of MI (2). However, subsequent studies have suggested that the impact of diabetes on the risk of future CAD is overestimated, although diabetes remains associated with an increased risk of MI (3–10). Adequate risk assessment of patients with diabetes is of great clinical and economic importance (1). Current guidelines suggest that prophylactic treatment (statins, aspirin, and antihypertensive treatment) to reduce the risk of MI is recommended for patients with diabetes and one or more risk factors for ischemic heart disease, including older age, sex, family history of premature cardiovascular disease, hypertension, and hypercholesterolemia (11,12). Can we, however, further distinguish patients with diabetes with a high and a low risk of adverse cardiac events? To provide an expanded understanding of cardiovascular risk assessment in patients with diabetes, we examined long-term clinical outcomes in patients with and without diabetes with and without obstructive CAD by coronary angiography (CAG) by linking CAG results registered in the Western Denmark Heart Registry with outcomes registered in national clinical databases.

RESEARCH DESIGN AND METHODS

Databases

The Western Denmark Heart Registry contains information about all cardiac procedures performed in western Denmark since 1999 and covers a population of 3.5 million people. It has collected data on >120,000 CAGs, including a detailed description of the presence and extent of CAD in patients with and without diabetes (13).

Each hospital that performs cardiac procedures in western Denmark contributes to the registry. Registration is 100% web-based and contains information on patient characteristics, procedural indication and priority, and angiographic findings (13). Patients are registered in the Western Denmark Heart Registry by their 10-digit unique personal identifier, which is issued by the Danish Civil Registration System to each Danish resident upon birth or immigration. This identifier is used by every regional and national registry in Denmark, including the Danish National Patient Registry, which records all hospital-based inpatient and outpatient diagnoses; the Danish Register of Causes of Death, which records the cause of death of all Danish residents; and the Danish National Database of Reimbursed Prescriptions, which contains data on all reimbursed prescriptions at Danish pharmacies (14–16).

Patient Selection

All patients with a CAG procedure registered in the Western Denmark Heart Registry from 1 January 2003 to 31 December 2012 were included in this study (Fig. 1). If a patient underwent multiple CAG examinations during the study period, the first CAG was used as the index procedure. Patients were classified according to presence or absence of diabetes and obstructive CAD. In Denmark, diabetes is diagnosed on the basis of fasting glucose or hemoglobin A_{1c} measurements according to international guidelines. These values, however, are not registered in the Western Denmark Heart Registry, wherein diabetes is entered according to the treatment strategy at the time of intervention. Thus, diabetes was defined as receiving insulin treatment (with or without a supplementary oral glucose-lowering treatment), oral glucose-lowering treatment, or nonpharmacological dietary treatment for diabetes at the time of CAG as recorded in the Western Denmark Heart Registry. Obstructive CAD was defined as one or more epicardial coronary arteries with ≥50% angiographic lumen narrowing, whereas no CAD was defined as no or mild angiographic lumen narrowing (<50%) in a single coronary vessel. Patients with missing coronary or diabetes status (n = 8,593) were excluded. Patients registered with diffuse CAD (n = 7,224) included those with diffuse nonsignificant atherosclerosis in more than one coronary artery or with nonobstructive (<50%) lesions in multiple coronary vessels; these patients were excluded. A small number of additional patients were excluded because of invalid personal identifiers or emigration before their index procedure (n = 99). All patients were >18 years of age.

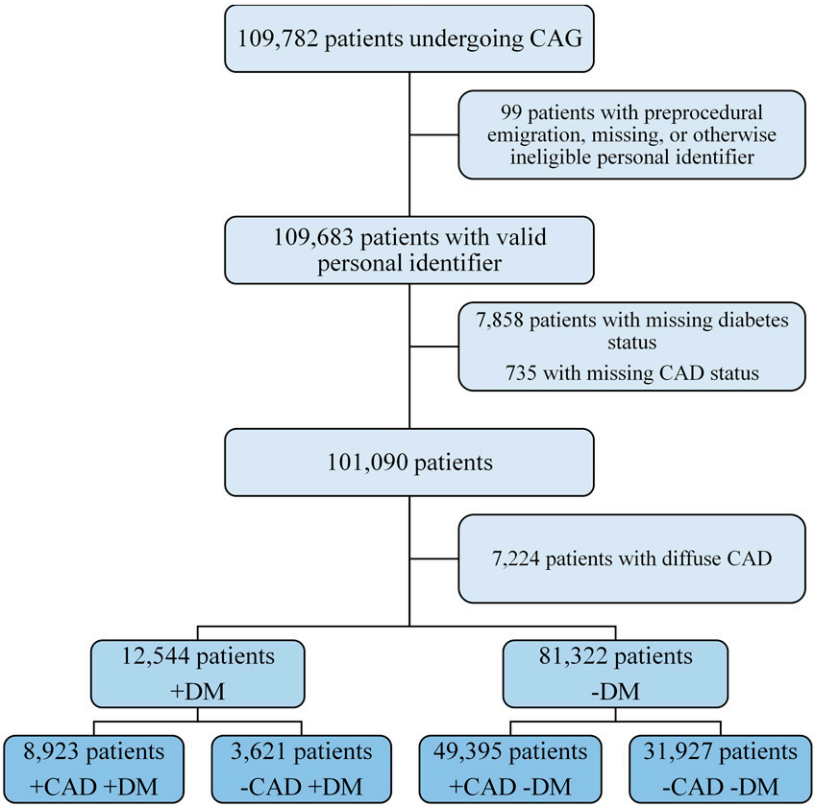

Figure 1—Flowchart of selection of patients who underwent CAG in western Denmark between 1 January 2003 and 31 December 2012. Angiographically determined obstructive CAD was defined as ≥50% lumen narrowing in one or more coronary vessels. +, with; –, without; DM, diabetes.

Comorbidity

The Charlson comorbidity index score was estimated for each patient on the CAG date (17). Comorbidity was ascertained through the Danish National Patient Registry on the basis of ICD-10 codes by using a 5-year look-back period of patient history before inclusion. A Charlson comorbidity index score of 0 in a patient with diabetes was caused by lack of registration of this diagnosis in the Danish National Patient Registry primarily because their general physician treated some patients with diabetes without referring them to the hospital system. This limitation applied only to diabetes diagnoses because the remaining diagnoses included in the Charlson comorbidity index required treatment as a hospital inpatient or in an outpatient setting and thus would be registered in the Danish National Patient Registry.

Medication

Records of treatment with statin (Anatomical Therapeutic Chemical [ATC] codes C10AA01–05, C10AA07), aspirin (ATC codes B01AC06, N02BA01), ACE inhibitor/angiotensin II receptor blocker (ARB) (ATC codes C09AA01–06, C09AA10, C09CA01, C09CA03–04, C09CA06–08), and β-blocker (ATC codes C07AA–AB) were obtained through the Danish National Database of Reimbursed Prescriptions (16). Because of a lack of database coverage before 2004, prescription reimbursement data could only be obtained in patients examined from 2004 to 2012. Treatment was defined as filling one or more prescriptions between 6 months before and 1 month after the index CAG.

MI

MI diagnoses were ascertained through the Danish National Patient Registry by using the ICD-10 code for MI (DI-21) and classified as either a primary (A) or secondary (B) diagnosis during an acute hospital admission. Because of interhospital transfers of patients with acute coronary syndrome, the use of registries to diagnose MI is less valid for the first 30 days after CAG. Beyond 30 days, the sensitivity and specificity of the MI diagnosis was 94% and 98%, respectively (18). Thus, for MI, we initiated follow-up 30 days after CAG.

Cardiac Death

Cardiac death was defined as death resulting from ischemic heart disease (ICD-10 codes I-20–25); sudden cardiac death (I-46); death resulting from ventricular tachycardia (I-47.2); death resulting from heart failure (I-50); or sudden death, unspecified (R-96) as recorded on death certificates from the Danish Register of Causes of Death. Because death certificates completed after 31 December 2011 could not be accessed when we closed to further data entry, cardiac death could only be documented between 1 January 2003 and 31 December 2011.

All-Cause Death

The Danish Civil Registration System provided data on the patients' vital status (dead, alive, or emigrated).

Statistical Analyses

Follow-up began on the hospital discharge date after CAG (except for MI, for which follow-up began 30 days after CAG) and continued until death, emigration, or 7 years after the index intervention, whichever came first. Data on all MIs, cardiac deaths, and all-cause deaths during follow-up were obtained. Cumulative incidence curves were constructed on the basis of cumulative rates of all-cause death, cardiac death, and MI occurring in each patient subgroup during the follow-up period. Because of variable follow-up time, we chose to estimate rate ratios (RRs). In each group, the number of events and combined person-year at risk were calculated to estimate incidence rates of each outcome. RRs were adjusted for age, sex, hypertension, Charlson comorbidity index score, smoking status, and procedural priority (urgency of intervention) (model 1) and further for BMI (model 2) by using modified Poisson regression (19). Finally, we performed additional analyses adjusting for treatment with statins, aspirin, β-blockers, and ACE inhibitors/ARB and treatment in patients without CAD in which event registration started 1 month after CAG (model 3). The χ^2 test was used in significance testing. $P < 0.05$ was considered significant. In case of emigration, patient data were censored. We used SAS 9.2 software (SAS Institute, Cary, NC) for all analyses.

Sensitivity Analysis

In a sensitivity analysis, only patients with no history of MI, percutaneous coronary intervention (PCI), or coronary artery bypass graft recorded in either the Western Denmark Heart Registry or the Danish National Patient Registry were included. The statistical analyses were performed as described above.

Ethics Approval

This study complies with the Declaration of Helsinki and was approved by the Danish Data Protection Agency (Record no. 2012-41-0914; Copenhagen, Denmark).

RESULTS

A total of 93,866 patients were followed after CAG. Of these, 12,544 (13.4%) had diabetes at the time of examination. In the total patient population, 8,923 (9.5%) patients had diabetes and obstructive CAD, 3,621 (3.9%) had diabetes but no obstructive CAD, 49,395 (52.6%) had no diabetes but obstructive CAD, and 31,927 (34.0%) had neither diabetes nor obstructive CAD (Fig. 1). Median follow-up was 4.1 years.

Baseline Characteristics

Patient characteristics are outlined in Table 1. Patients with obstructive CAD were more often men and older, had a history of MI/PCI, and were examined with higher urgency (i.e., acute/subacute vs. elective) than patients without obstructive CAD, irrespective of diabetes status. Patients with obstructive CAD were more frequently associated with acute coronary syndromes as the procedural indication for admission, whereas patients without significant CAD more often underwent CAG because of stable angina pectoris, unspecified angina pectoris, heart valve disease, and cardiomyopathy.

Patients with diabetes were more frequently treated for hypertension, had higher Charlson comorbidity index scores, and were more likely to be obese or overweight than patients without diabetes, regardless of the presence or absence of obstructive CAD. Patients with diabetes but without CAD were more often treated with statins, aspirin, β-blockers, and ACE inhibitors than those without diabetes and CAD. The prevalence of diabetes treatment strategies was similar in patients with diabetes with and without obstructive CAD. Oral glucose-lowering treatment was the most common diabetes treatment strategy.

Clinical End Points

During the follow-up period, 14,424 patients died, 4,085 died as a result of cardiac death, and 4,666 had an MI. The total numbers of adverse events stratified by diabetes and CAD are shown in Table 2.

Table 1—Baseline characteristics

	All patients (*n* = 93,866)	+CAD +DM (*n* = 8,923)	+CAD –DM (*n* = 49,395)	–CAD +DM (*n* = 3,621)	–CAD –DM (*n* = 31,927)
Median follow-up (IQR) (years)	4.1 (1.8–6.5)	3.3 (1.4–5.9)	4.2 (1.9–6.6)	3.3 (1.6–5.7)	4.2 (2.0–6.5)
Male sex	63.7	71.2	72.6	51.1	49.2
Median age (IQR) (years)	65 (56–73)	68 (61–75)	67 (59–75)	62 (54–70)	61 (52–69)
Family history of ischemic heart disease	40.2	38.9	40.8	39.6	39.7
Hypertension	49.4	72.5	47.8	71.3	42.8
Aspirin	71.7	84.5	82.7	65.7	52.7
Statin	71.7	87.6	86.0	75.3	46.0
β-Blocker	68.3	76.0	78.4	57.1	52.5
ACE inhibitor	34.1	50.5	36.0	41.6	26.1
ARB	10.5	18.9	9.5	20.4	8.7
Active smoker	29.3	25.7	33.9	20.7	24.1
Previous smoker	36.1	42.3	36.2	36.2	32.7
Diabetes treatment					
Insulin (± oral glucose lowering)	4.7	36.3	—	31.8	—
Oral glucose lowering	6.9	50.9	—	52.3	—
Dietary	1.8	12.8	—	15.9	—
Charlson comorbidity index score					
0	50.5	28.8	50.1	37.9	58.7
1	24.3	25.2	24.9	28.6	22.7
2	13.5	19.6	13.7	16.8	11.2
≥3	11.7	26.4	11.3	16.7	7.4
BMI (kg/m^2)					
Median (IQR)	26.6 (24.0–29.7)	28.4 (25.5–31.9)	26.3 (24.0–29.1)	29.8 (26.3–34.2)	26.1 (23.4–29.3)
<18.5	1.3	0.5	1.1	0.7	1.7
18.5–25	28.1	17.4	28.4	14.3	32.3
25–30	35.1	33.9	37.1	28.9	33.1
>30	19.4	31.8	16.3	42.1	18.3
Previous MI or PCI					
MI	12.9	23.0	17.4	5.3	4.0
PCI	6.8	11.1	8.9	3.7	2.8
Procedural priority					
Acute	18.0	15.5	26.4	5.1	7.1
Subacute	27.7	31.8	30.5	19.2	23.1
Elective	54.4	52.7	43.1	75.7	69.8
Procedural indication					
STEMI	16.0	13.9	25.0	3.0	4.3
NSTEMI	17.6	23.2	22.7	7.8	9.4
Unstable AP	1.8	1.7	1.6	1.8	2.1
Stable AP	39.9	42.1	35.4	50.0	45.2
Arrhythmia	2.4	2.2	1.7	3.1	3.5
Valvopathy or aortic disease	7.1	5.1	4.5	8.8	11.6
Cardiomyopathy	5.1	4.9	2.8	8.8	8.2
Surveillance	0.2	0.2	0.2	0.4	0.3
Complication	0.0	0.0	0.1	0.1	0.0
Unspecified AP	2.0	1.1	0.7	5.5	4.1
Cardiac arrest	0.1	0.1	0.1	0.1	0.2
Other	4.7	2.9	2.6	7.8	8.3
Missing data	2.8	2.6	2.7	2.8	3.0

Data are % unless otherwise indicated. Baseline characteristics at time of CAG in patients with and without significant CAD and diabetes. Angiographically determined obstructive CAD was defined as at least one coronary vessel with ≥50% lumen narrowing ascertained by CAG. DM was defined as receiving insulin treatment (with or without supplementary oral glucose-lowering treatment), other oral glucose-lowering treatment, or nonpharmacological dietary diabetes treatment at the time of CAG. +, with; −, without; AP, angina pectoris; DM, diabetes; IQR, interquartile range; NSTEMI, non-ST–elevation myocardial infarction; STEMI, ST-elevation myocardial infarction.

Patients without diabetes and CAD had the lowest cumulative risk of all-cause death (14.72% [95% CI 14.2–15.3]), cardiac death (2.20% [95% CI 1.9–2.5]), and MI (2.56% [95% CI 2.3–2.8]) followed by patients with diabetes without CAD, patients without diabetes with CAD, and patients with diabetes and CAD (Table 2). Compared with patients with neither diabetes nor obstructive CAD, patients with diabetes without obstructive CAD had a similar 7-year risk of all-cause death (RR 1.03 [95% CI 0.92–1.15]; *P* = 0.61), cardiac death (RR 1.21 [95% CI 0.90–1.64]; *P* = 0.21), and MI (RR 0.88 [95%

Table 2—Number of events and risk of death, cardiac death, and MI after CAG, with patients without diabetes and without angiographically determined CAD as reference

	Events (*n*)	Cumulative incidence (%)	Unadjusted RR (95% CI)	*P* value‖	Adjusted RR‡ (95% CI)	*P* value	Adjusted RR§ (95% CI)	*P* value
All-cause death								
–CAD –DM (reference)	3,000	14.72	1	—	1	—	1	—
–CAD +DM	455	21.97	1.52 (1.38–1.68)	<0.001	1.03 (0.92–1.15)	0.61	1.14 (1.01–1.28)	0.0311
+CAD –DM	8,673	25.13	1.88 (1.81–1.97)	<0.001	1.06 (1.01–1.11)	0.0166	1.07 (1.01–1.13)	0.0124
+CAD +DM	2,296	37.30	3.12 (2.95–3.30)	<0.001	1.15 (1.08–1.23)	<0.001	1.22 (1.13–1.31)	<0.001
Cardiac death								
–CAD –DM (reference)	354	2.20	1	—	1	—	1	—
–CAD +DM	55	3.75	1.61 (1.21–2.14)	0.001	1.21 (0.90–1.64)	0.21	1.25 (0.90–1.74)	0.19
+CAD –DM	2,901	9.33	5.20 (4.66–5.81)	<0.001	2.51 (2.22–2.83)	<0.001	2.40 (2.09–2.76)	<0.001
+CAD +DM	775	15.33	8.80 (7.75–9.99)	<0.001	2.92 (2.53–3.38)	<0.001	2.79 (2.36–3.30)	<0.001
MI								
–CAD –DM (reference)	473	2.56	1	—	1	—	1	—
–CAD +DM	60	3.60	1.31 (1.00–1.71)	0.0513	0.88 (0.65–1.17)	0.37	0.92 (0.67–1.27)	0.62
+CAD –DM	3,264	10.28	4.71 (4.27–5.19)	<0.001	3.42 (3.08–3.81)	<0.001	3.38 (3.00–3.80)	<0.001
+CAD +DM	869	16.73	8.00 (7.14–8.96)	<0.001	4.15 (3.65–4.71)	<0.001	4.19 (3.63–4.84)	<0.001

Seven-year cumulative incidence and RR of all-cause death, cardiac death, and MI in patients with diabetes and CAD (obstructive CAD defined as at least one coronary vessel with ≥50% lumen narrowing ascertained by CAG), patients without diabetes with CAD, and patients with diabetes without CAD, with patients without diabetes and without CAD as the reference. DM defined as receiving insulin treatment, other oral glucose-lowering treatment, or nonpharmacological dietary diabetes treatment at the time of CAG. +, with; –, without; DM, diabetes. ‖*P* value for comparison with patients without diabetes and obstructive CAD, with $P < 0.05$ considered significant. ‡Model 1: RR adjusted for age, sex, Charlson comorbidity index score, hypertension, smoking, and procedural priority. §Model 2: RR adjusted for age, sex, Charlson comorbidity index score, hypertension, smoking, procedural priority, and BMI.

CI: 0.65–1.17]; $P = 0.37$) after adjustment (Table 2). These results were not significantly affected by additional adjustment for BMI (Table 2). In contrast, patients with obstructive CAD were at higher risk of all-cause death, cardiac death, and MI regardless of diabetes status, although patients with diabetes were at highest risk. Cumulative 7-year incidence curves of all-cause death, cardiac death, and MI are shown in Fig. 2.

With additional adjustment for treatment with statins, aspirin, β-blockers, and ACE inhibitors/ARB, no differences in risk of MI (RR 0.86 [95% CI 0.59–1.24]; $P = 0.41$) and cardiac death (RR 1.08 [95% CI 0.72–1.60]; $P = 0.71$) were seen between patients with and without diabetes without CAD. Only a slightly increased risk of death was seen (RR 1.16 [95% CI: 1.01–1.33]; $P = 0.038$). However, in sensitivity analyses of patients without prior ischemic heart disease (MI, PCI, or coronary artery bypass graft), no differences were seen for any outcome (data not shown).

CONCLUSIONS

In a real-world population, patients with diabetes without angiographically significant CAD had the same low risk of all-cause death, cardiac death, and MI as patients without diabetes and CAD. Some patients with diabetes develop macrovascular CAD, and these patients have a higher risk of cardiac events than those without diabetes but with CAD. However, some patients with diabetes seemed not to develop macrovascular CAD. Patients with diabetes without significant CAD more often received proper prophylactic therapy, such as aspirin, statin, and hypertensive treatment, than their counterparts without diabetes and did not have a greater risk of cardiac events than patients without diabetes and CAD in the 7-year follow-up period. The novel insight from this study is that absence of angiographically significant CAD in patients with diabetes treated with high levels of preventive therapy removes the diabetes-associated increased risk of MI and cardiac death for at least a 7-year period.

That diabetes approximately doubles the risk of MI and death among patients with known CAD is well-known (20,21). Nicholls et al. (22) found that diabetes was among one of the strongest predictors of atherosclerotic burden in patients with established CAD. The patients with diabetes and macrovascular CAD in the current cohort were also those with the highest risk of adverse cardiac events. In a cohort of patients with no knowledge about the presence or absence of CAD except for history of prior MI, Haffner et al. (2) demonstrated that patients with diabetes but without prior MI had a 7-year mortality risk equal to that of patients without diabetes but with previous MI as well as a similar risk of death resulting from CAD (adjusted hazard ratio 1.2 [95% CI 0.6–2.4]). Hence, patients with diabetes were subsequently viewed as a group with a particular need of risk modification targeting hypertension, hypercholesterolemia, and smoking to prevent CAD (11,12). In contrast to the current study, Haffner et al. included patients with diabetes treated with insulin or oral glucose-lowering therapy from 1982 to 1990, an inclusion period likely characterized by a different standard of care than current practice. An increased awareness of prophylactic treatment, including the use of statins, thus may have modified the risk of cardiovascular events in patients with diabetes. Moreover, the study cohort (age 45–64 years, $n = 2,432$) was younger and smaller than the current cohort, and patients were classified on the basis of previous clinical history of MI. Subsequent larger-scale studies, likewise in cohorts without knowledge regarding CAD, modified the results by Haffner et al. by showing that patients with diabetes with no history of MI had a lower risk of future cardiovascular events than patients with previous MI (3–9,23), although diabetes still appeared to be a risk factor, with increased rates of both all-cause and cardiac death (3,7,9,10,23). A meta-analysis of studies comparing patients with diabetes without a history of MI versus patients

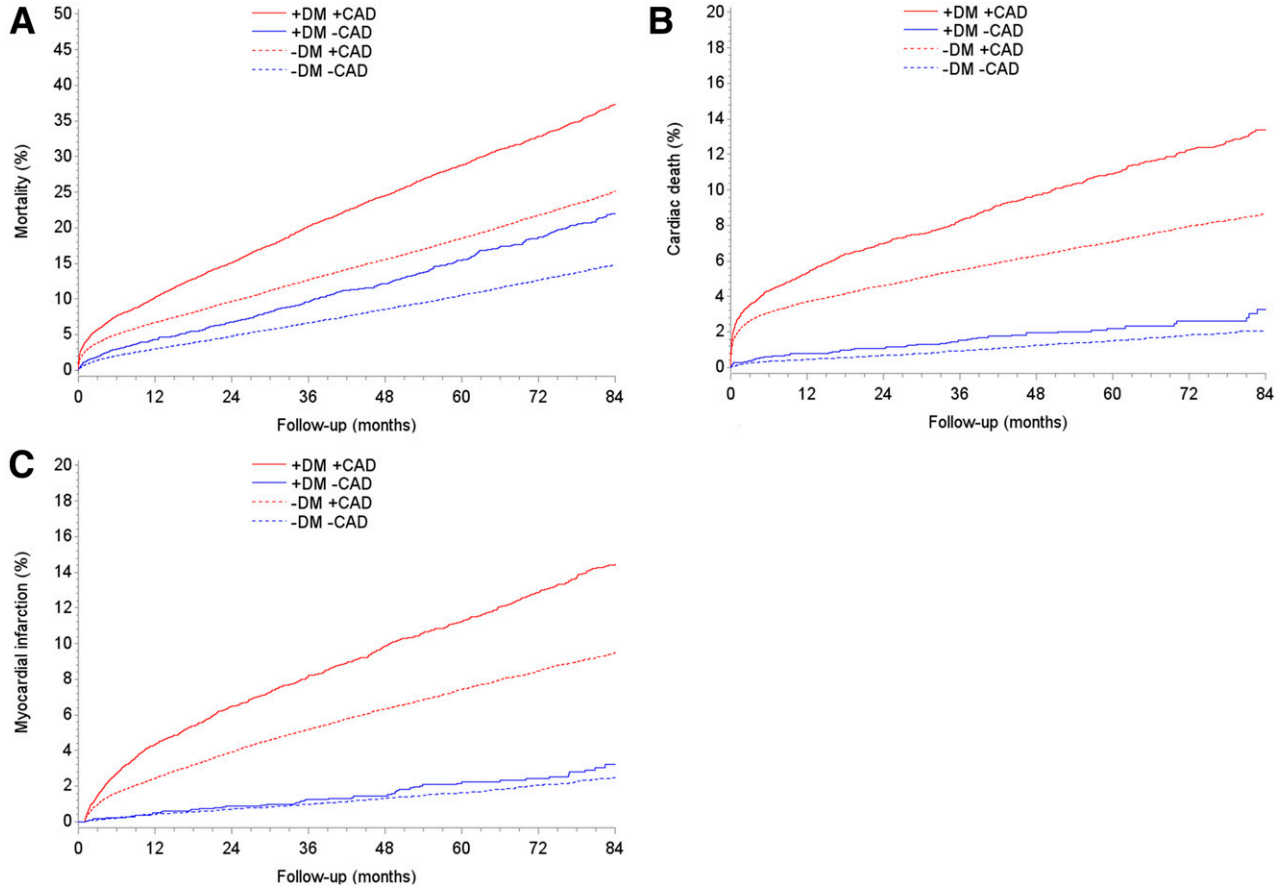

Figure 2—Accumulated rates of all-cause death (*A*), cardiac death (*B*), and myocardial infarction (*C*) over 7 years in patients with diabetes and obstructive CAD, patients with diabetes without obstructive CAD, patients without diabetes with obstructive CAD, and patients without diabetes without obstructive CAD after invasive CAG. +, with; –, without; DM, diabetes.

without diabetes with prior MI yielded a 44% lower risk of MI in the diabetes group (24). None of these studies, however, evaluated the impact of macrovascular angiographic CAD, and the increased awareness of prophylactic treatment, including the use of statins, may have modified the risk of cardiovascular events in patients with diabetes compared with the landmark study by Haffner et al. Only Saely et al. (25) reported data from a small group of patients with (n = 164) and without diabetes (n = 586) after CAG and demonstrated that the risk of cardiovascular events depended more on the coronary status than on the diabetes status and that the risk of cardiovascular events did not differ between patients with and without diabetes without obstructive CAD after 2.2 years of follow-up. In the current study, we used CAG to stratify a large cohort of ~94,000 patients into groups with and without diabetes and CAD and combined this with a registry-based long-term follow-up. We demonstrate that the absence of angiographically significant CAD, even in patients with diabetes, is associated with a very low risk of cardiovascular events over a 7-year period. Why some patients with diabetes developed CAD when others did not is unknown, but genetic factors are likely to be a major influence. Nonetheless, assessment of CAD by CAG seems to be a valid prognostic tool in the risk stratification of patients with diabetes. However, CAG probably is too invasive and has certain limitations in the description of subclinical CAD. The Multi-Ethnic Study of Atherosclerosis showed that increased coronary artery calcium (CAC) score by computed tomography scan is associated with an increased risk of coronary heart disease, and low CAC predicts a low risk of coronary heart disease (26). CAC screening of patients with diabetes may lead to an identification of those with a high likelihood of benefitting from an intensified prophylactic treatment strategy. However, such strategies require further investigation.

The absence of angiographically significant CAD in patients with diabetes in a real-world setting seems to be a valid prognosticator of cardiovascular risk, and to some extent, this is intuitively understandable because atherosclerosis in the majority of patients is a prerequisite for MI. Another explanation is the higher likelihood of prophylactic, or intensified, treatment of comorbidities, such as hypertension and dyslipidemia, in patients with diabetes, which we observed in the current cohort. The contemporary practice of prophylactic aspirin, statin, and antihypertensive treatment may explain the low risk of cardiovascular events among patients with diabetes without CAD. Intensive control and treatment of blood pressure in patients with diabetes has been shown to reduce the risk of MI, death resulting from diabetes, and all-cause death (27,28). Statin treatment has similarly been associated with a significant reduction of coronary events in patients with diabetes (29,30).

Furthermore, fewer active smokers were observed among patients with diabetes, which likely represents another part of the prophylactic effort by the health care system. The current study thus shows that in a real-world, nonselect population where patients with diabetes receive proper prophylactic treatment, patients with diabetes without CAD have a low risk of cardiovascular events comparable with patients without diabetes and without CAD. Patients with diabetes without CAD had high rates of hypertension and smoking, and >80% received medical treatment for diabetes. According to the current guidelines, the majority of these patients should receive prophylactic treatment with aspirin and lipid-lowering medications (11,12). However, the role of aspirin for primary prevention in patients with diabetes without CAD is controversial, and in low-risk patients, the modest benefit in reducing adverse cardiac events can be offset by the increased risk for bleeding, including intracranial and gastrointestinal hemorrhage. Given the very low risk of MI in the current diabetes cohort without CAD, prophylactic aspirin for this group may not be of benefit or may even cause harm, although this remains speculative at this point.

The current data set currently is limited to 7-year follow-up. At this point, we can only state that the lack of angiographic CAD was protective for this period. Within this period, however, there was no indication of a faster development of CAD among patients with diabetes versus those without diabetes and without CAD. Classification of CAD was based on visual angiographic assessment by the treating physician, which also means that gray zones will exist among the various subclassifications of CAD on the individual level. Furthermore, CAG does not describe lesion morphology and vulnerability, and some patients may have had vulnerable plaques that could not be identified by CAG. Nevertheless, the results from ~94,000 CAGs show that the risk of MI was very low for the diabetes cohort when the CAG was judged as not showing significant disease. A risk exists for underestimating MI events in patients with diabetes because of a higher risk of asymptomatic MI in this population and may have led to a lower MI rate in patients with diabetes without CAD. Finally, we were unable to distinguish between patients with type 1 and type 2 diabetes.

In conclusion, in the absence of angiographically significant CAD, patients with diabetes treated with contemporary prophylactic therapy have the same risk of cardiovascular events as patients without diabetes.

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