

Association of Diabetic Status and Glycemic Control With Ischemic and Bleeding Outcomes in Patients With Stable Coronary Artery Disease: The 5-Year CORONOR Registry

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Background—The relation between diabetes mellitus, glycemic control, and ischemic and bleeding events is poorly described in outpatients with stable coronary artery disease receiving modern secondary prevention.

Methods and Results—The multicenter CORONOR (Suivi d'une cohorte de patients Coronariens stables en région Nord-pas-de-Calais) registry enrolled 4184 outpatients with stable coronary artery disease, including 1297 patients (31%) with diabetes mellitus. A recent glycosylated hemoglobin (HbA1c) was available for 1146 diabetic patients, and 48% had HbA1c $\geq 7\%$. We analyzed 5-year ischemic (cardiovascular death, myocardial infarction, and stroke) and bleeding (Bleeding Academic Research Consortium ≥ 3) outcomes, according to diabetic status and glycemic control. When compared with nondiabetic patients, the ischemic risk was higher in diabetic patients with HbA1c $\geq 7\%$ (hazard ratio [HR], 1.57; 95% confidence interval [CI], 1.25–1.93) but not in diabetic patients with HbA1c $< 7\%$ (HR, 1.06; 95% CI, 0.83–1.36). Diabetic patients with HbA1c $\geq 7\%$ were at higher risk than diabetic patients with HbA1c $< 7\%$ (HR, 1.47; 95% CI, 1.09–1.98). When compared with nondiabetic patients, the bleeding risk was higher in diabetic patients, with HbA1c $< 7\%$ (HR, 1.66; 95% CI, 1.04–2.67) and in those with HbA1c $\geq 7\%$ (HR, 1.75; 95% CI, 1.07–2.86). No difference in bleeding risk was observed between diabetic patients with HbA1c $\geq 7\%$ versus those with HbA1c $< 7\%$. Similar results were obtained when adjusted for baseline characteristics.

Conclusions—The 5-year increased risk of ischemic events in patients with stable coronary artery disease with diabetes mellitus was restricted to those with HbA1c $\geq 7\%$. By contrast, the increase in bleeding risk associated with diabetes mellitus was observed in patients with HbA1c $\geq 7\%$ and in patients with HbA1c $< 7\%$. The level of HbA1c should be taken into account for future research and may help physicians to manage prolonged antithrombotic therapies in this high-risk subgroup. (*J Am Heart Assoc.* 2018;7:e008354. DOI: 10.1161/JAHA.117.008354.)

Key Words: diabetes mellitus • hemoglobin A1c • mortality • prognosis • stable coronary artery disease

Diabetic patients with short- or long-term manifestations of coronary artery disease (CAD) have been shown to be at higher risk of ischemic cardiovascular events than nondiabetic patients.^{1–3} In addition, it has been demonstrated that the cardiovascular prognosis of diabetic patients with CAD

undergoing percutaneous coronary intervention is worse when the level of glycosylated hemoglobin (HbA1c) is high.^{4,5} However, in a context of major improvement in secondary prevention,^{6–9} there is a lack of recent studies evaluating these issues in patients with stable CAD who are known to be at relatively low cardiovascular risk overall.^{10,11} In addition, although patients with CAD with diabetes mellitus (DM) have also been shown to be at higher risk of bleeding,^{12–14} an event with important prognostic consequences,^{14–16} whether this risk may vary according to DM control (HbA1c level) has not been established. Updated knowledge on these issues could be useful because it may allow to better understand the benefit/risk ratio of antithrombotic therapies in patients with CAD who also have DM.

We, thus, designed the present analysis to describe secondary medical prevention, risk factors, and 5-year clinical ischemic and bleeding outcomes according to diabetic status in 4184 outpatients with stable CAD included in the CORONOR (Suivi d'une cohorte de patients Coronariens stables en région

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Accompanying Tables S1 through S3 are available at <http://jaha.ahajournals.org/content/7/10/e008354/DC1/embed/inline-supplementary-material-1.pdf>

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Clinical Perspective

What Is New?

- Observational data are lacking about the relation between diabetes mellitus, glycemic control, and ischemic and bleeding events in patients with stable coronary artery disease receiving modern secondary prevention.
- We demonstrated that the 5-year increased risk of ischemic events in diabetic patients with coronary artery disease was restricted to those with glycosylated hemoglobin $\geq 7\%$.
- By contrast, the increase in bleeding risk associated with diabetes mellitus was observed in patients with glycosylated hemoglobin $\geq 7\%$ and in patients with glycosylated hemoglobin $< 7\%$.

What Are the Clinical Implications?

- Our data suggest that the level of glycosylated hemoglobin should be taken into account for future research and intervention trials in diabetic patients with coronary artery disease.
- Our results may help physicians to manage prolonged antithrombotic therapies in diabetic patients with stable coronary artery disease.

Nord-pas-de-Calais) registry. We also explored the potential refinement to risk stratification that may spring from subdividing DM according to the level of HbA1c.

Methods

This cohort study used prospectively collected data from the CORONOR registry. The study was approved by the French medical data protection committee and authorized by the Commission Nationale de l'Informatique et des Libertés for the treatment of personal health data. All patients consented to the study after being informed through a written document of the objectives of the study and on the treatment of data, as well as on their rights to object, of access and of rectification. Because of data protection principles, the data will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Study Population

The CORONOR registry is a prospective multicenter registry that included 4184 consecutive outpatients with stable CAD. The study population has been previously described in detail.¹¹ The patients were included by 50 cardiologists from the region Nord Pas-de-Calais in France between February 1, 2010 and April 30, 2011. The inclusion criterion was evidence of CAD, defined by at least 1 of the following: previous myocardial

infarction (MI) (> 1 year ago), previous coronary revascularization (> 1 year ago), and/or obstruction of $\geq 50\%$ of the luminal diameter of at least 1 native coronary vessel on coronary angiography. The sole exclusion criterion was hospitalization for MI or coronary revascularization within the past year.

Study Design and Definitions

A case record form, which contained information about demographic and clinical details of the patients, including usual cardiovascular risk factors and treatments, was prospectively completed at initial visit by the investigators (ie, the cardiologist). DM was defined as a patient treated with oral hypoglycemic drugs or insulin or with a history of elevated (> 126 mg/dL) fasting blood glucose on at least 2 separate occasions in conjunction with ongoing dietary measures. In case of DM, the most recent HbA1c value (within 12 months before the inclusion visit) was entered in the case record form. History of hypertension was defined as a patient receiving ≥ 1 antihypertensive treatment. Prior MI included ST-segment-elevation MI and non-ST-segment-elevation MI. Multivessel CAD was defined as ≥ 2 coronary arteries with $\geq 50\%$ stenosis. Left ventricular ejection fraction was the most recent echocardiographic assessment. Estimated glomerular filtration rate was obtained by the MDRD (Modification of Diet in Renal Disease) Study equation.

Clinical follow-up was performed at outpatient visits with treating cardiologists using a standardized case record form to report clinical events.¹⁷ The number of outpatient visits was at the discretion of the treating cardiologists. Protocol-specified follow-up was performed at 2 and at 5 years. When a clinical event was reported, all related documents (reports of outpatient visits and discharge summaries) were collected. Missing information was completed by contacting either general practitioners and/or patients themselves. We collected follow-up data on death, MI, ischemic stroke, and major bleeding. Four investigators participated to the adjudication process (T.M., O.T., N.L., C.B.). All clinical events were adjudicated by 2 investigators blinded to each other. A third investigator joined the adjudication in case of disagreement according to prespecified definitions. For hospitalizations during the follow-up period, hospital records were reviewed for evidence of clinical events. The events reported by the patients were systematically confirmed from the medical reports. The cause of death was determined after a detailed review of the circumstances of death and classified as cardiovascular or noncardiovascular.¹⁸ Deaths from unknown cause were considered as cardiovascular (we also performed a sensitivity analysis after considering unknown deaths as noncardiovascular for the present analysis). MI was defined according to the universal definition.^{17,19} Ischemic stroke was defined as a sudden onset of focal neurological symptoms with the

presence of cerebral infarction in the appropriate territory on brain imaging. To assess ischemic risk, a composite end point was defined as cardiovascular death, MI, or ischemic stroke. Bleeding events were classified using the Bleeding Academic Research Consortium definition.²⁰ Information on Bleeding Academic Research Consortium type 1 and 2 bleeds was not available in our registry. Major bleeding was defined as all Bleeding Academic Research Consortium type ≥ 3 events.

For the present analysis, we compared 3 groups of patients: nondiabetic patients, diabetic patients with an HbA1c at inclusion $<7\%$, and diabetic patients with an HbA1c at inclusion $\geq 7\%$. The choice of the cutoff of 7% was based on recommendations for glycemic control in stable patients with CAD with DM, as summarized by international guidelines.⁷

Statistical Analysis

Continuous variables were described as the mean \pm SD. Categorical variables were presented as absolute numbers and percentages. For comparisons among the 3 patients groups of baseline characteristics, treatments, and risk factor control, we used the χ^2 test for categorical variables and ANOVA for continuous variables. Post hoc comparisons between groups were performed with Bonferroni corrections. Cumulative rates of events were estimated for nondiabetic patients, diabetic patients with an HbA1c at inclusion $<7\%$, and diabetic patients with an HbA1c at inclusion $\geq 7\%$ using the Kaplan-Meier method, and the difference was tested with the log-rank test. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated by the Cox model, with nondiabetic patients as the reference group. The proportional hazard assumption was assessed and satisfied by Schoenfeld residuals and by including an interaction time-dependent term in the Cox regression analysis. HRs were first assessed unadjusted and then adjusted for baseline characteristics. We performed 2 sensitivity analyses: first, after reclassifying unknown deaths as noncardiovascular; and second, assessing separately all-cause death and the nondeath composite of MI or ischemic stroke. In this second sensitivity analysis, the association with the nondeath composite was performed using competitive risk regression, with death as the competing event, according to the method of Fine and Gray²¹; sub-HRs (SHRs) and 95% CIs were calculated. All statistical analyses were performed with the STATA 14.0 software (STATA Corporation, College Station, TX). Statistical significance was assumed at $P<0.05$.

Results

Population

The baseline characteristics of the 4184 patients included in the CORONOR registry have been previously reported.¹¹ This was a

predominantly male cohort (78%), with a mean age of 67 ± 12 years. A history of MI was documented in 62% of the cases, with 86% of the patients having had at least 1 prior coronary revascularization procedure. The cohort overall received a broad range of secondary prevention drugs (antiplatelets in 96%, inhibitors of the renin-angiotensin system in 82%, and statins in 92%). At inclusion into the registry, there were 2887 nondiabetic patients (69%) and 1297 diabetic patients (31%). In the diabetic subgroup, a recent HbA1c measurement was available for 1146 patients: 594 patients (52%) had an HbA1c $<7\%$, whereas 552 patients (48%) had an HbA1c $\geq 7\%$; 151 patients had no recent HbA1c measurement available.

Comparisons in baseline characteristics, medications at inclusion, and risk factor control at inclusion among nondiabetic patients, diabetic patients with HbA1c $<7\%$, and diabetic patients with HbA1c $\geq 7\%$ are shown in Tables 1

Table 1. Baseline Characteristics of the Study Population, According to Diabetic Status and DM Control

Characteristics	Nondiabetic Patients (n=2887)	Diabetic Patients With HbA1c $<7\%$ (n=594)	Diabetic Patients With HbA1c $\geq 7\%$ (n=552)
Age, y	67 \pm 12	67 \pm 9	67 \pm 10
Women	622 (22)	115 (19)	156 (28)* [†]
Persistent angina at inclusion	185 (6)	38 (6)	68 (12)* [†]
History of hypertension	1530 (53)	451 (76)*	421 (76)*
Prior MI	1853 (64)	346 (58)*	330 (60)
Prior coronary angiography	2864 (99)	587 (99)	547 (99)
Multivessel CAD	1574 (55)	355 (60)	373 (68)* [†]
Prior coronary revascularization	2511 (87)	497 (84)	459 (83)*
Prior BMS implantation	1608 (56)	288 (48)*	251 (45)*
Prior DES implantation	654 (23)	159 (27)	193 (35)* [†]
Prior coronary bypass	602 (21)	134 (23)	122 (22)
Prior stroke	188 (7)	63 (11)*	53 (10)*
Prior carotid endarterectomy	72 (2)	26 (4)*	20 (4)
Prior aortic or peripheral intervention	254 (9)	65 (11)	52 (9)
Atrial fibrillation	195 (7)	43 (7)	50 (9)
LVEF, %	58 \pm 11	57 \pm 11	55 \pm 12)* [†]
Estimated GFR, mL/min per 1.73 m ²	80 \pm 23	78 \pm 25	74 \pm 27*

Data are given as mean \pm SD or number (percentage). BMS indicates bare metal coronary stent; CAD, coronary artery disease; DES, drug-eluting coronary stent; DM, diabetes mellitus; GFR, glomerular filtration rate by the MDRD (Modification of Diet in Renal Disease) Study equation; HbA1c, glycosylated hemoglobin; LVEF, left ventricular ejection fraction; MI, myocardial infarction.

* $P<0.05$ vs nondiabetic patients; [†] $P<0.05$ vs diabetic patients with HbA1c $<7\%$.

through 3, respectively. When compared with diabetic patients with HbA1c <7%, diabetic patients with HbA1c ≥7% had slightly lower left ventricular ejection fraction, were more often female, and were more likely to have persistent angina, multivessel CAD, and prior drug-eluting coronary stent implantation. The prescription rate of cardiovascular treatments in diabetic patients did not differ according to HbA1c levels. There were, by contrast, differences in antidiabetic medications with, in particular, a much higher use of insulin in the subgroup with an HbA1c ≥7%. Except for a slightly higher proportion of current smokers and for a higher body mass index in case of HbA1c ≥7%, risk factor control in diabetic patients did not differ according to HbA1c levels.

A comparison of baseline characteristics, medications, and risk factor control in diabetic patients according to availability of HbA1c is provided in Table S1. Except for a lower proportion of antidiabetic medications in patients without HbA1c available at inclusion, no major differences were observed.

Table 2. Baseline Medications at Inclusion, According to Diabetic Status and DM Control

Medications	Nondiabetic Patients (n=2887)	Diabetic Patients With HbA1c <7% (n=594)	Diabetic Patients With HbA1c ≥7% (n=552)
Aspirin	2236 (77)	444 (75)	420 (76)
Clopidogrel	1109 (38)	258 (43)	253 (46)*
Aspirin or clopidogrel	2775 (96)	572 (96)	537 (97)
Aspirin and clopidogrel	570 (20)	130 (22)	136 (25)*
Vitamin K antagonists	309 (11)	65 (11)	75 (14)
ACE inhibitors	1710 (59)	346 (58)	331 (60)
ARBs	606 (21)	187 (31)*	179 (32)*
ACE inhibitors or ARBs	2288 (79)	518 (87)*	492 (89)*
Aldosterone antagonists	175 (6)	46 (8)	49 (9)*
β Blockers	2243 (78)	488 (82)*	465 (84)*
Statins	2679 (93)	542 (91)	496 (90)
Calcium antagonists	664 (23)	174 (29)*	171 (31)*
Diuretics	743 (26)	251 (42)*	263 (48)*
Insulin	...	85 (14)	233 (42)†
Biguanides	...	304 (51)	236 (43)†
Sulfamides	...	157 (26)	172 (31)
Other oral hypoglycemic drugs	...	172 (29)	193 (35)†

Data are given as number (percentage). ACE indicates angiotensin-converting enzyme; ARB, angiotensin-2 receptor blocker; DM, diabetes mellitus; HbA1c, glycosylated hemoglobin.

**P*<0.05 vs nondiabetic patients; †*P*<0.05 vs diabetic patients with HbA1c <7%.

Follow-Up and Outcomes

A 5-year clinical follow-up was achieved in 4094 (98%) of the 4184 patients included in the registry. There were 677 deaths (n=353 noncardiovascular, n=269 cardiovascular, and n=55 unknown cause), 170 MIs, and 96 ischemic strokes. The composite ischemic end point of cardiovascular death, MI, or ischemic stroke occurred in 536 patients. The cumulative rate for the composite ischemic end point was 14% at 5-year follow-up (2.8%/year). There were 123 major bleeding events during the 5-year follow-up (0.7%/year). In most of the cases, the site of bleeding was gastrointestinal (n=56 [45.5%]); there were 35 intracranial bleedings (28.5%).

When compared with nondiabetic patients, the risk of the ischemic end point was higher in diabetic patients with an HbA1c ≥7% (3.9%/year versus 2.6%/year; unadjusted HR, 1.57; 95% CI, 1.25–1.93; *P*<0.0001) (Table 4). By contrast, the risk of the ischemic end point of diabetic patients with an HbA1c <7% was indistinguishable from that of nondiabetic patients (2.8%/year versus 2.6%/year; unadjusted HR, 1.06; 95% CI, 0.83–1.36; *P*=0.623). Similar results were obtained when adjusted for baseline characteristics (age, sex, persistent angina at inclusion, history of hypertension, current smoker, prior MI, multivessel CAD, prior coronary revascularization, prior stroke, atrial fibrillation, and left ventricular ejection fraction [Table 4]); the results were unchanged when the analysis was also adjusted for prior drug-eluting coronary stent implantation, body mass index, systolic blood pressure, and low-density lipoprotein cholesterol (Table S2). The unadjusted HR for the ischemic end point of diabetic patients with an HbA1c ≥7% versus diabetic patients with an HbA1c <7% was 1.47 (95% CI, 1.09–1.98; *P*=0.012). Figure 1 shows unadjusted Kaplan-Meier curves for the ischemic end point for

Table 3. Risk Factor Control at Inclusion, According to Diabetic Status and DM Control

Variable	Nondiabetic Patients (n=2887)	Diabetic Patients With HbA1c <7% (n=594)	Diabetic Patients With HbA1c ≥7% (n=552)
Current smoker	343 (12)	47 (8)*	69 (13)†
Body mass index, kg/m ²	27±4	30±5*	31±6*†
Systolic blood pressure, mm Hg	131±15	135±16*	135±16*
Diastolic blood pressure, mm Hg	75±9	76±9*	76±10
LDL cholesterol, g/L	0.91±0.28	0.84±0.26*	0.84±0.29*

Data are given as mean±SD or number (percentage). DM indicates diabetes mellitus; HbA1c, glycosylated hemoglobin; LDL, low-density lipoprotein.

**P*<0.05 vs nondiabetic patients; †*P*<0.05 vs diabetic patients with HbA1c <7%.

nondiabetic patients, diabetic patients with an HbA1c <7%, and diabetic patients with an HbA1c ≥7%. In a sensitivity analysis reclassifying deaths from unknown causes as non-cardiovascular deaths, similar results were obtained: the unadjusted HR for diabetic patients with an HbA1c ≥7% (versus nondiabetic patients) was 1.63 (95% CI, 1.29–2.06; $P<0.0001$), whereas the unadjusted HR for diabetic patients with an HbA1c <7% (versus nondiabetic patients) was 1.12 (95% CI, 0.86–1.44; $P=0.407$). In another sensitivity analysis (Table S3), we assessed the following separately: (1) all-cause death and (2) the nondeath composite of MI or ischemic stroke (with death as a competing variable). We found similar results, with diabetic patients with an HbA1c ≥7% having worse outcome than nondiabetic patients, and diabetic patients with an HbA1c <7% having similar outcome than nondiabetic patients.

Finally, when compared with nondiabetic patients, the risk of major bleeding was significantly higher in diabetic patients; this was observed for diabetic patients with an HbA1c <7% (0.9%/year versus 0.5%/year; unadjusted HR, 1.66; 95% CI, 1.04–2.67; $P=0.035$) and for diabetic patients

with an HbA1c ≥7% (0.9%/year versus 0.5%/year; unadjusted HR, 1.75; 95% CI, 1.07–2.86; $P=0.025$). Similar results were obtained when adjusted for baseline characteristics (Table 4). No difference in bleeding risk was observed between diabetic patients with an HbA1c ≥7% versus diabetic patients with an HbA1c <7% (HR, 1.05; 95% CI, 0.58–1.90; $P=0.869$). Figure 2 shows unadjusted Kaplan-Meier curves for major bleeding for nondiabetic patients, diabetic patients with an HbA1c <7%, and diabetic patients with an HbA1c ≥7%.

Discussion

It is well established that patients with CAD who also have DM are at higher risk of ischemic events than their nondiabetic counterparts. This has been shown in different settings: after MI/acute coronary syndrome (ACS),¹ after percutaneous coronary interventions,² and in patients with stable CAD.³ There has, however, been tremendous progress within recent years on secondary prevention for stable CAD. In addition, physicians taking care of patients with CAD are likely to identify those with DM as higher-risk individuals and may thus provide more stringent secondary prevention to this subgroup.

The prognosis of diabetic patients with CAD is not uniform. Among indicators that have been the most studied in this subgroup is the level of HbA1c. There are consistent data in the literature indicating a higher risk of cardiovascular events in diabetic patients with CAD with high HbA1c versus low HbA1c. However, this association has been mainly described in cohorts of patients undergoing percutaneous coronary intervention^{4,5} and less frequently in patients with stable CAD (ie, at a chronological distance from any MI and/or coronary revascularization).²² More important, poor glucose control per se might not be the primary reason for the worse outcome in diabetic patients with CAD with high HbA1c. Indeed, strategies of intensive glucose control have failed to decrease major cardiovascular events in diabetic patients.^{23,24} High HbA1c levels may, thus, be linked to other confounders, which are associated with the worse outcome. Diabetic patients with CAD with higher HbA1c may, for example, have more difficulties in treating DM and/or longer duration of DM. No matter what the reason is, a high HbA1c should be considered as a warning sign in diabetic patients with CAD.

Risk stratification is an important part of management for patients with chronic diseases. Our data demonstrate that the association of high HbA1c with more frequent ischemic events when DM coexists with CAD can be extended to patients with very stable CAD. Our results also show that, during a 5-year follow-up period, ischemic event rates in diabetic patients with HbA1c <7% are almost identical to reference rates in nondiabetic patients. It should be

Table 4. Unadjusted and Adjusted HRs for Clinical Outcome, According to Diabetic Status and DM Control

Variable	HR (95% CI)	P Value
Composite end point: cardiovascular death, myocardial infarction, or ischemic stroke		
Unadjusted		
Nondiabetic patients	Reference	...
Diabetic patients with HbA1c <7%	1.06 (0.83–1.36)	0.623
Diabetic patients with HbA1c ≥7%	1.57 (1.25–1.96)	<0.0001
Adjusted*		
Nondiabetic patients	Reference	...
Diabetic patients with HbA1c <7%	1.00 (0.78–1.30)	0.975
Diabetic patients with HbA1c ≥7%	1.41 (1.11–1.78)	0.004
BARC ≥3 bleeding		
Unadjusted		
Nondiabetic patients	Reference	...
Diabetic patients with HbA1c <7%	1.66 (1.04–2.67)	0.035
Diabetic patients with HbA1c ≥7%	1.75 (1.07–2.86)	0.025
Adjusted*		
Nondiabetic patients	Reference	...
Diabetic patients with HbA1c <7%	1.72 (1.06–2.78)	0.029
Diabetic patients with HbA1c ≥7%	1.75 (1.05–2.91)	0.030

BARC indicates Bleeding Academic Research Consortium; CI, confidence interval; DM, diabetes mellitus; HbA1c, glycosylated hemoglobin; HR, hazard ratio.

*Adjusted for age, sex, persistent angina at inclusion, history of hypertension, current smoker, prior myocardial infarction, multivessel coronary artery disease, prior coronary revascularization, prior stroke, atrial fibrillation, and left ventricular ejection fraction.

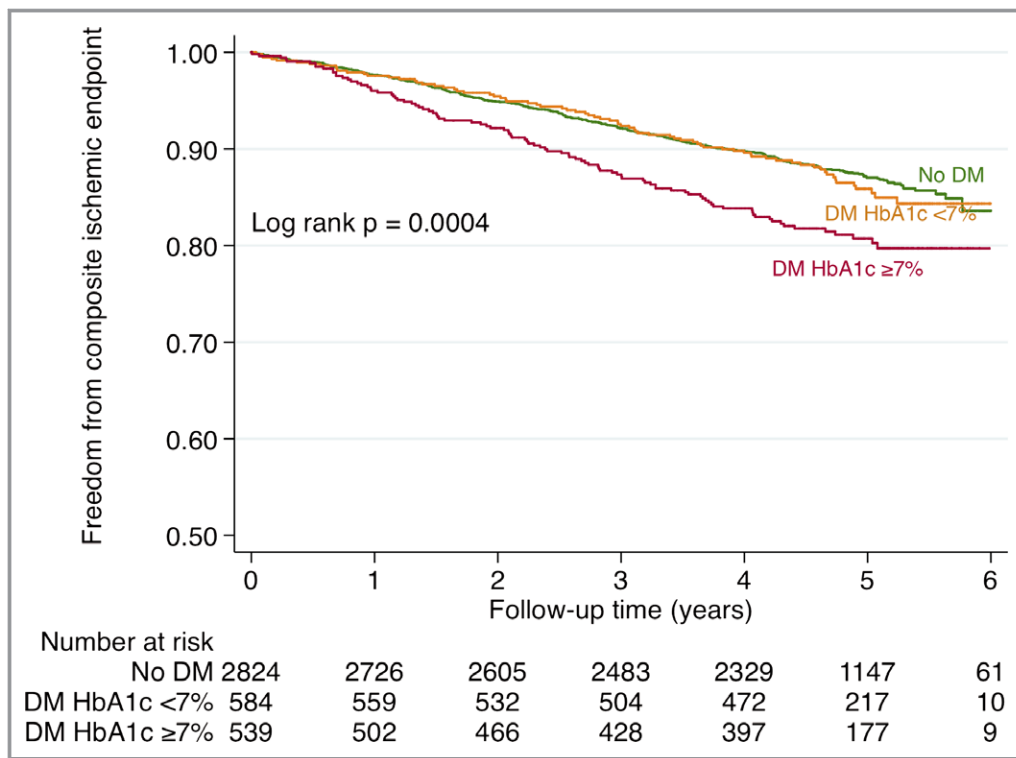


Figure 1. Cardiovascular death, myocardial infarction, or ischemic stroke during 5-year follow-up, according to diabetic status and diabetes mellitus (DM) control. Unadjusted Kaplan-Meier curves are shown. HbA1c indicates glycosylated hemoglobin.

underscored that these findings remain unchanged after adjusting for baseline characteristics. This is important because diabetic patients may have different risk features and/or may have undergone different procedures, such as more frequent use of drug-eluting coronary stent (likely related to the expectation of a higher risk of restenosis²).

These results should be interpreted in the context of a high use of secondary prevention medications. Indeed, the prescription rates of antiplatelets, statins, and angiotensin-converting enzyme inhibitors/angiotensin-2 receptor blockers in diabetic patients with CAD included in our registry are close to the rates achieved after 1 year in diabetic patients with CAD included in recent clinical trials in which optimal medical therapy was prescribed to all patients.²⁵ Effective risk factor control (low-density lipoprotein cholesterol, systolic blood pressure, and smoking cessation) in our cohort was also similar to what was obtained in these clinical trials in which prespecified targets were defined.²⁵

Although the recurrence of ischemic events is a major issue in patients with CAD, recent data have shown that the risk of bleeding events should also be taken into account, especially in a context of modern secondary prevention with a wide use of potent antithrombotic treatments.^{6,7} As a consequence, risk scores have been developed in patients with CAD to predict risks for ischemic and bleeding events and, therefore, to guide

clinical decisions about intensity and duration of antithrombotic therapy.^{12,26,27} The role of DM as a risk factor for bleeding has been well established in patients with ACS.¹² However, in this unstable setting, DM is rather more identified as a risk factor of ischemic events than as a risk factor of bleeding in the physician's mind. Indeed, DM has been associated with a better benefit/risk ratio of more potent P2Y₁₂-ADP receptor antagonists (versus clopidogrel) in ACS.^{13,28} In the past, DM was also a criterion to prescribe upstream glycoprotein IIb to IIIa inhibitors in the context of high-risk non-ST-segment-elevation ACS.²⁹ These results, therefore, suggest that we should be more aggressive on antithrombotics in patients with DM, despite their overall higher risk of bleeding compared with nondiabetic patients. Recently, these results obtained in ACS look to have been extended to the stable CAD situation. Indeed, DM was a targeted variable to enrich the population of the PEGASUS (Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin) and COMPASS (Cardiovascular Outcomes for People Using Anticoagulation Strategies) trials to select higher-risk patients for more aggressive antithrombotic therapy regimens.^{30,31} The relation between DM and bleeding in patients with stable CAD is, however, less clear, and the impact of the HbA1c level is unknown in this context. In

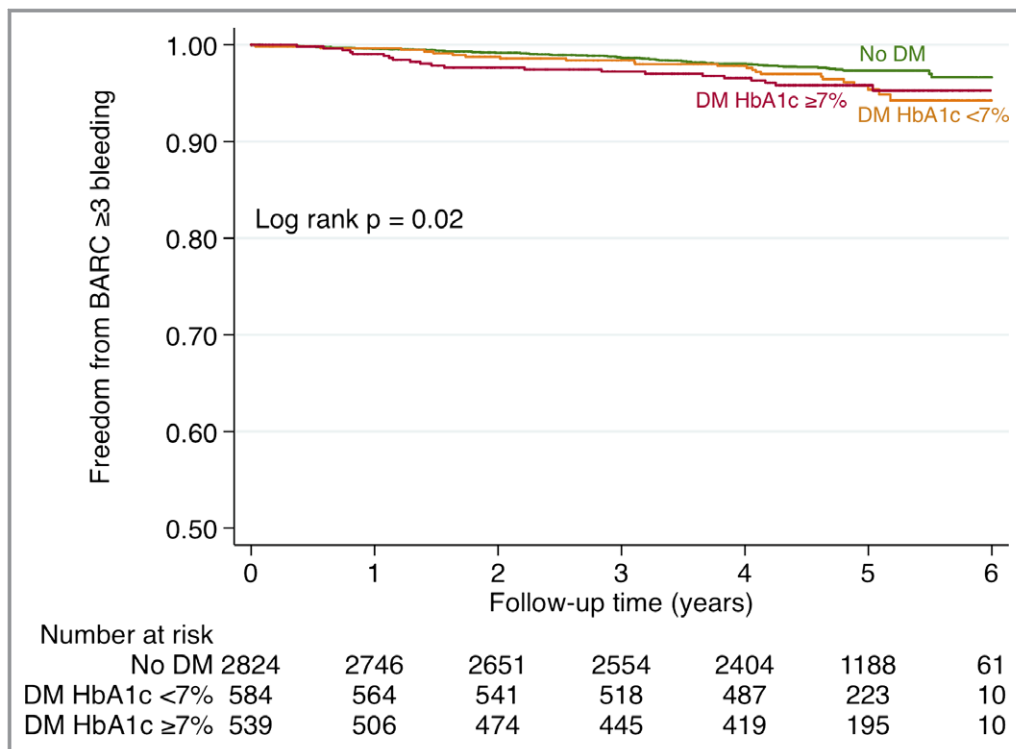


Figure 2. Bleeding Academic Research Consortium (BARC) ≥ 3 bleeding during 5-year follow-up, according to diabetic status and diabetes mellitus (DM) control. Unadjusted Kaplan-Meier curves are shown. HbA1c indicates glycosylated hemoglobin.

selected patients with stabilized CAD included in the randomized DAPT (Dual Antiplatelet Therapy) study, DM was not associated with an increased bleeding risk.²⁶ By contrast, DM was associated with a higher risk of bleeding in the REACH (Reduction of Atherothrombosis for Continued Health) Registry, which included stable patients with or at risk of atherosclerosis and mainly patients with CAD.³² Our data, obtained in patients widely treated by antithrombotic treatments, show that the risk of major (Bleeding Academic Research Consortium ≥ 3) bleeding is significantly higher in diabetic than in nondiabetic patients and are concordant with the results observed in the REACH Registry. At variance to what we observed for ischemic end points, the increase in risk was not solely observed in diabetic patients with an HbA1c $\geq 7\%$ but also in diabetic patients with an HbA1c $< 7\%$. Our results, therefore, suggest that the HbA1c level may help physicians to manage antithrombotic therapies in patients with stable CAD and that more aggressive antithrombotic regimen should be reserved to patients with DM with an HbA1c $\geq 7\%$ who seem to have the best benefit/risk ratio in our analysis.

Study Limitations

First, our data reflect the practice in a regional area, and it will have to be determined whether these findings are

representative of practices in other parts of the world. In France, social coverage and health insurance are uniform over the whole territory, and stable CAD is one of the conditions entitled to full reimbursement of all costs, including medications and diagnostic and therapeutic procedures. Second, the fact that the inclusion was done by cardiologists may overestimate the extent to which these patients are managed in relation to guidelines, and the reality of secondary prevention may be worse. It must also be underscored that the CORONOR population includes individuals with or without prior events and, therefore, the events ascertained in follow-up in this study include incident and recurrent events. Third, HbA1c levels were available only at inclusion in the registry, and the HbA1c level at inclusion may not correspond to a stable HbA1c in subsequent years. The choice of a cutoff of 7% for HbA1c could be debated. As previously stated, this value was derived from international recommendations for the management of DM in stable CAD.⁷ Fourth, to achieve sufficient statistical power, we focused the analysis on a composite ischemic end point (cardiovascular death, MI, or stroke). This combination of events has, however, been extensively used as the primary end point of multiple large randomized controlled trials performed in patients with stable CAD and in patients with DM, including major recent trials.^{30,31,33} Finally, the number of major bleeding events was relatively limited.

In conclusion, our data demonstrate that patients with stable CAD who also have DM achieve a high level of secondary prevention. In this context, the 5-year cardiovascular outcome of diabetic patients with CAD with an HbA1c <7% was similar to that of nondiabetic patients with CAD. By contrast, the increase in bleeding risk associated with DM was observed in patients with HbA1c <7% and in patients with HbA1c ≥7%. The level of HbA1c should be taken into account for future research and intervention trials in diabetic patients with CAD and may help physicians to manage prolonged antithrombotic therapies in this high-risk subgroup.

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Disclosures

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SUPPLEMENTAL MATERIAL

Table S1. Comparison of diabetic patients according to availability of HbA1c.

	Diabetic patients with HbA1c available (n=1146)	Diabetic patients without HbA1c available (n=151)
Age, years	67±10	67±11
Women	271 (24%)	39 (26%)
Persistent angina at inclusion	106 (9%)	12 (8%)
History of hypertension	872 (76%)	117 (77%)
Prior MI	676 (59%)	83 (55%)
Prior coronary angiography	1134 (99%)	149 (99%)
Multivessel CAD	728 (64%)	93 (62%)
Prior coronary revascularization	956 (83%)	128 (85%)
Prior BMS implantation	539 (47%)	66 (44%)
Prior DES implantation	352 (31%)	42 (28%)
Prior coronary bypass	256 (22%)	34 (23%)
Prior stroke	116 (10%)	12 (8%)
Prior carotid endarterectomy	46 (4%)	3 (2%)
Prior aortic or peripheral intervention	117 (10%)	21 (14%)
Atrial fibrillation	93 (8%)	13 (9%)
LVEF, %	56±11	57±10
Estimated GFR, ml/min/1.73m ²	76±26	76±25
Aspirin	864 (75%)	123 (81%)
Clopidogrel	511 (45%)	61 (40%)
Aspirin or clopidogrel	1109 (97%)	149 (99%)
Aspirin and clopidogrel	266 (23%)	35 (23%)
Vitamin K antagonists	140 (12%)	15 (10%)
ACE inhibitors	677 (59%)	94 (62%)
ARB	366 (32%)	34 (23%)*
ACE inhibitors or ARB	1010 (88%)	127 (84%)
Aldosterone antagonists	95 (8%)	9 (6%)
β-blockers	953 (83%)	124 (82%)
Statins	1038 (91%)	140 (93%)
Calcium antagonists	345 (30%)	39 (26%)
Diuretics	514 (45%)	43 (28%)*
Insulin	318 (28%)	21 (14%)*
Biguanides	540 (47%)	51 (34%)*
Sulfamides	329 (29%)	34 (23%)
Other oral hypoglycemic drugs	365 (32%)	30 (20%)*
Current smoker	116 (10%)	18 (12%)
Body mass index, Kg/m ²	30±5	29±5*
Systolic blood pressure, mmHg	135±16	135±15
Diastolic blood pressure, mmHg	75±9	76±9
LDL cholesterol, g/L	0.84±0.27	0.90±0.31

Data are mean ± SD or numbers (percentages).

HbA1c indicates glycosylated hemoglobin; MI, myocardial infarction; CAD, coronary artery disease; BMS, bare metal coronary stent; DES, drug-eluting coronary stent; LVEF, left ventricular ejection fraction; GFR, glomerular filtration rate by the MDRD equation; ACE, angiotensin-converting enzyme; ARB, angiotensin 2 receptor blocker; LDL, low-density lipoprotein.

* p <0.05 vs. diabetic patients with HbA1c available.

Table S2. Adjusted hazard ratios for the composite endpoint of cardiovascular death, myocardial infarction, or ischemic stroke according to diabetic status and diabetes control.

	HR [95% CI]	p value
Non diabetic patients	Reference	-
Diabetic patients with HbA1c <7%	1.02 [0.78-1.34]	0.880
Diabetic patients with HbA1c ≥7%	1.41 [1.10-1.83]	0.008

HbA1c indicates glycosylated hemoglobin.

*Adjusted for age, sex, persistent angina at inclusion, history of hypertension, current smoker, prior MI, multivessel CAD, prior coronary revascularization, prior DES implantation, prior stroke, atrial fibrillation, LVEF, body mass index, systolic blood pressure, LDL cholesterol.

Table S3. Unadjusted risk ratios for clinical outcome according to diabetic status and diabetes control.

	Risk ratios* [95% CI]	p value
All-cause death		
Non diabetic patients	Reference	-
Diabetic patients with HbA1c <7%	1.14 [0.91-1.41]	0.249
Diabetic patients with HbA1c ≥7%	1.63 [1.34-1.99]	< 0.0001
MI or ischemic stroke		
Non diabetic patients	Reference	-
Diabetic patients with HbA1c <7%	1.15 [0.81-1.64]	0.421
Diabetic patients with HbA1c ≥7%	1.50 [1.08-2.08]	0.015

HbA1c indicates glycosylated hemoglobin; MI, myocardial infarction.

*Risk ratios are hazard ratios by Cox regression for all-cause death and subhazard ratios by competitive risk regression (with death as the competing event) for MI or ischemic stroke.