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Incident Myocardial Infarction and Very Late Stent Thrombosis in Outpatients With Stable Coronary Artery Disease

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ABSTRACT

BACKGROUND Current data are lacking for incidence, correlates, and prognosis associated with incident myocardial infarction (MI) in patients with stable coronary artery disease (CAD). Furthermore, the contribution of very late stent thrombosis (VLST) to these events remains poorly understood.

OBJECTIVES This study aimed to analyze the residual risk of MI, together with relevant associated factors, and related mortality in stable CAD outpatients.

METHODS The multicenter CORONOR (Suivi d'une cohorte de patients COROnariens stables en region NORd-Pas-de-Calais) study enrolled 4,184 unselected outpatients with stable CAD (i.e., MI or coronary revascularization >1 year previously). Five-year follow-up was achieved for 4,094 patients (98%).

RESULTS We identified a linear risk of incident MI (0.8% annually), with ST-segment elevation MI constituting one-third of all cases. Current smoking, low-density lipoprotein cholesterol, multivessel CAD, diabetes with glycosylated hemoglobin >7%, and persistent angina were all associated with increased risk, and prior bypass surgery was associated with decreased risk. When used as a time-dependent variable, incident MI was associated with an increased risk of death (hazard ratio: 2.05; $p < 0.0001$). Among patients with prior stent implantation, VLST was causal in 20% of MI cases and presented more often as ST-segment elevation MI versus MI not related to a stented site (59% vs. 26%, $p = 0.001$). Adjusted mortality was 4 times higher in patients with VLST than in MI not related to a stented site.

CONCLUSIONS In stable CAD outpatients, incident MI occurs at a stable rate of 0.8% annually, is related to VLST in one-fifth of cases, and is associated with an increased mortality risk, especially for VLST. Multivessel CAD and residual uncontrolled risk factors are strongly associated with MI. (J Am Coll Cardiol 2017;69:2149–56)

Secondary prevention is a key issue for outpatients with stable coronary artery disease (CAD) (1,2). The goal of any physician is to protect this patient group from recurrent ischemic events and their related mortality, especially incident myocardial infarction (MI). The identification of those patients at risk of incident MI is an integral part of managing stable CAD and would enable such patients to be targeted with more aggressive therapy or closer follow-up.

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ABBREVIATIONS AND ACRONYMS

BMS = bare-metal stent

CAD = coronary artery disease

DES = drug-eluting stent

LDL = low-density lipoprotein

MI = myocardial infarction

NSTEMI = non-ST-segment elevation myocardial infarction

PCI = percutaneous coronary intervention

STEMI = ST-segment elevation myocardial infarction

VLST = very late stent thrombosis

Much of the historic literature on CAD has concerned unstable patients and events that occurred within the first year after an acute coronary event. Patient cohorts and studies focusing on stable CAD are rare (3–7). A high risk of cardiovascular events has been associated with age, sex, uncontrolled risk factors, and the absence of coronary revascularization (3,4,6); however, information on the residual risk of incident MI in stable CAD patients (i.e., several years after the last event) and its determinants in a more contemporary dataset is lacking. In addition, since the widespread use of first-generation drug-eluting stents (DES), very late stent thrombosis (VLST) has been shown to be a concern in stabilized patients after percutaneous coronary interventions (PCI) (8–12).

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The CORONOR (Suivi d'une cohorte de patients COROnariens stables en region NORd-Pas-de-Calais) registry includes a large contemporary (inclusion period 2010 to 2011) population of unselected outpatients with stable CAD in whom all events were adjudicated during follow-up (7,13). This study presents an opportunity to better comprehend the residual risk of incident MI in stable CAD outpatients, as well as the contribution played by VLST. The present analysis aimed to assess the residual risk of MI, the factors associated with incident MI during follow-up, and related mortality in the 5-year CORONOR registry. We also explored the relative contribution of VLST in this setting.

METHODS

POPULATION. The CORONOR study is a multicenter registry that enrolled 4,184 consecutive outpatients with stable CAD between February 2010 and April 2011 (7,13). Patients were included by 50 cardiologists from the French Region of Nord-Pas-de-Calais during outpatient visits. Patients were eligible if they had evidence of CAD, defined by at least 1 of the following criteria: previous MI (>1 year ago), previous coronary revascularization (>1 year ago), or obstruction of ≥50% of the luminal diameter of at least 1 native vessel on coronary angiography. The sole exclusion criterion was hospitalization for MI or coronary revascularization within the year. To present the real-life spectrum of stable CAD, patients with other cardiovascular or noncardiovascular illnesses or comorbidities were not excluded.

A case record form, which contained information regarding demographic and clinical patient details, inclusive of the usual cardiovascular risk factors and treatments, was completed at the initial visit. Clinical follow-up was performed at outpatient visits or by contacting either general practitioners or the patients themselves. This study was approved by the French medical data protection authority and authorized by the Commission nationale de l'informatique et des libertés for the treatment of personal health data. All patients consented to this study after being informed in writing of its objectives and the treatment of their data, together with their right to object, rights of access, and mechanisms for redress. Detailed descriptions of the study population have been published previously (7,13).

STUDY DESIGN. For the present analysis, we focused on the 4,094 patients (98%) for whom follow-up was available. Incident MI, coronary revascularization, and the cause of death were adjudicated by 2 investigators, with a third opinion in cases of disagreement. 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 records. MI was defined according to the universal definition (14) and categorized as either ST-segment elevation myocardial infarction (STEMI) or non-ST-segment elevation myocardial infarction (NSTEMI). Only type 1, 3, 4, and 5 MIs were considered as endpoints for the present analysis. Adjudication was performed primarily on the basis of cardiac troponin I values (ADVIA Centaur TnI-Ultra, Siemens, Malvern, Pennsylvania) (62% of cases) or high-sensitivity cardiac troponin T values (Elecsys TnT-hs, Roche, Rotkreuz, Switzerland) (29% of cases).

We first compared patients with incident MI to patients without MI in the overall CORONOR population. In order to not underestimate the impact of some undiagnosed MIs, we also performed an analysis for the combined endpoint of MI or sudden death. Then, to assess the contribution of VLST to incident MI, we focused on patients who underwent at least 1 stent implantation before their inclusion (n = 2,816 with follow-up available). In this subset of patients, all MIs were systematically categorized as MIs not related to a stented site or to a definite stent thrombosis according to the definition of the Academic Research Consortium (15). In 95.5% of the cases, the allocation was angiographically confirmed; in 4.5% of the cases, coronary angiography was not performed but there was no electrocardiographic evidence of acute ischemia in the territory of a previously implanted stent, and these events were categorized as MIs not related to a stented site. We

then compared patients with confirmed VLST to those with an MI not related to a stented site. In the group with VLST, information on time since stent implantation, type of stent, and antithrombotic treatment at the time of VLST, including any recent (within 3 months) modifications, was collected retrospectively.

STATISTICAL ANALYSIS. Continuous variables are described as the mean ± SD except for delays, which are described as medians with 25th and 75th percentiles. Categorical variables are presented as absolute numbers and percentages. When focusing on incident MI as individual endpoint, we analyzed death as a competing event. Cumulative incidence functions are shown. Univariate and multivariate assessments of baseline variables associated with incident MI were performed with competitive risk regression, with death as a competing event, according to the method of Fine and Gray (16). Subhazard ratios and 95% confidence intervals (CIs) were calculated. The proportional hazards assumption was tested and satisfied by the inclusion of interaction time-dependent terms in the multivariable regression analysis. Variables with a p value <0.05 in univariate analysis were entered into the final model. Collinearity was excluded by means of a correlation matrix between candidate predictors. Similar analyses were performed for the composite endpoint of MI or sudden death, with other causes of death (except those that were sudden) used as a competing event. The association of incident MI with subsequent all-cause mortality was assessed by Cox analysis with incident MI as a time-dependent variable. Hazard ratios (HRs) and 95% CIs were calculated. The comparison of baseline variables between patients with VLST and those with MI at a nonstented site was performed with the chi-square test, the Fisher exact test for categorical variables, and the Student unpaired *t* test for continuous variables. The impact of VLST (vs. MI not related to a stented site) on all-cause mortality was assessed by Cox analysis. All statistical analyses were performed with STATA version 14.1 software (Stata Corp., College Station, Texas). Statistical significance was assumed at a p value <0.05.

RESULTS

STUDY POPULATION. The baseline characteristics of the 4,184 patients included in the CORONOR study have been described (7). Clinical follow-up was completed in 4,094 patients (98%) at a median of 4.9 years. As shown in Table 1, this was a predominantly male cohort (78%), with a mean age of 67 ± 12 years. Most patients were asymptomatic at inclusion (persistent angina in 7.3% of the cases). A history of

TABLE 1 Baseline Characteristics of the Study Population

	All Patients (N = 4,094)	No MI (n = 3,924)	MI (n = 170)	p Value
Age, yrs	67 ± 12	67 ± 11	65 ± 13	0.129
Males	78.0	77.8	82.4	0.169
Persistent angina at inclusion	7.3	6.9	15.3	<0.0001
History of hypertension	60.1	60.2	57.7	0.516
Diabetes mellitus	31	30.9	34.1	0.363
Diabetes mellitus with HbA_{1c} >7%	13.2	12.9	20.0	0.007
Body mass index, kg/m^2	28 ± 5	28 ± 5	28 ± 5	0.554
LDL cholesterol, mg/dl	89 ± 28	89 ± 28	95 ± 32	0.007
Current smoker	11.3	10.9	20.0	<0.0001
Prior MI	62.4	62.2	67.7	0.153
Multivessel CAD	57.8	57.4	65.3	0.047
Prior stent implantation	68.8	68.7	71.2	0.518
Prior coronary bypass	21.4	21.7	12.4	0.004
Left ventricular ejection fraction,%*	58 ± 11	57 ± 11	58 ± 9	0.285
Treatment at inclusion				
Single-antiplatelet therapy	75.7	75.9	71.2	0.163
Dual-antiplatelet therapy	20.7	20.4	28.2	0.014
Beta-blockers	79.2	79	83.5	0.156
ACE inhibitor or ARB	81.8	81.8	81.8	0.975
Statins	92.2	92.3	90.0	0.288
Ezetimibe	15.4	15.5	12.9	0.387

Values are mean ± SD or %. *Most recent echocardiographic assessment, available in 4,037 patients.
ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CAD = coronary artery disease; HbA_{1c} = glycosylated hemoglobin; LDL = low-density lipoprotein; MI = myocardial infarction.

MI was documented in 62.4% of cases, with 85.9% of the patients having had at least 1 prior coronary revascularization procedure. Our cohort was prescribed a broad range of secondary preventative medications (antiplatelet drugs [96.4%], statins [92.2%], inhibitors of the renin-angiotensin system [81.8%], and beta-blockers [79.2%]).

RISK OF MI. Of the 4,094 patients, 170 were hospitalized for MI during the follow-up period (5-year cumulative incidence of 4% [0.8% per year]). In total, 187 MIs occurred in the 170 patients during the follow-up. There were 19 periprocedural MIs (10%). During the same period, there were 677 deaths (91 of which were sudden), and 481 patients underwent coronary revascularization. Thirty-two percent of the MIs were categorized as STEMI and the remainder as NSTEMI. Univariate and multivariate assessments of baseline variables associated with incident MI are shown in Tables 1 and 2. By multivariate analysis, current smoking (p = 0.002), low-density lipoprotein (LDL) cholesterol (p = 0.007), multivessel CAD (p = 0.015), diabetes mellitus with glycosylated hemoglobin >7% (p = 0.016), and persistent angina at inclusion (p = 0.028) were all associated with increased risk, whereas prior coronary bypass was associated with a decreased risk (p = 0.011). An analysis of variables associated with the combined

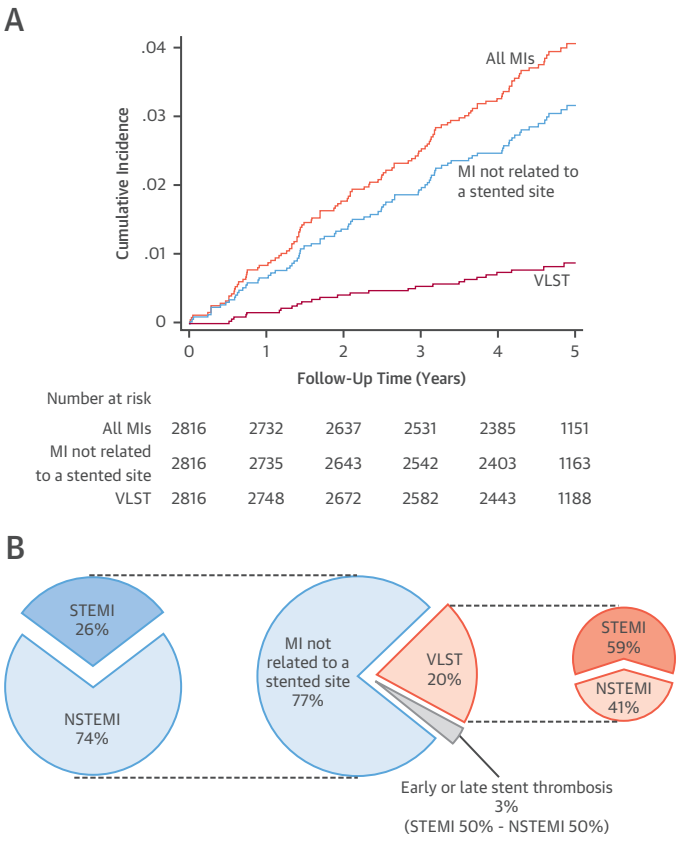
TABLE 2 Multivariate Analysis: Independent Predictors of MI During 5-Yr Follow-Up

	SHR	95% CI	p Value
Current smoker	1.87	1.27–2.77	0.002
LDL cholesterol (per 10 mg/dl)	1.06	1.02–1.11	0.007
Prior coronary bypass	0.53	0.32–0.86	0.011
Multivessel CAD	1.53	1.08–2.15	0.015
Diabetes mellitus with HbA_{1c} >7%	1.62	1.09–2.40	0.016
Persistent angina at inclusion	1.70	1.06–2.73	0.028

CI = confidence interval; SHR = subhazard ratios by competitive risk regression; other abbreviations as in Table 1.

endpoint of MI or sudden death is provided in Online Tables 1 and 2. Similarly, uncontrolled risk factors and persistent angina at inclusion were associated with a higher risk of events.

FIGURE 1 Contribution of VLST to Incident MI in Subgroup of 2,816 Patients With Prior Stent Implantation



(A) Cumulative incidence of all MIs, MI not related to a stented site, and VLST during 5-year follow-up. **(B)** Relative proportion of STEMI and NSTEMI events according to type of MI; n = 132 MIs in 121 patients. MI = myocardial infarction; NSTEMI = non-ST-segment elevation myocardial infarction; STEMI = ST-segment elevation myocardial infarction; VLST = very late stent thrombosis.

The mortality rate of the 170 patients with incident MI was 20% (n = 34) at the end of the follow-up (median = 821 [261 to 1,214] days after MI). When used as a time-dependent variable, incident MI during follow-up was associated with a significant increase in mortality (age and sex-adjusted HR: 2.05; 95% CI: 1.39 to 3.02; p < 0.0001). Unadjusted mortality rates were 3.5% per year for patients without MI and 7% per year for patients with incident MI.

RELATIVE CONTRIBUTION OF VLST. When we reviewed the 2,816 patients with a history of prior stent implantation at inclusion, 121 were hospitalized for MI during follow-up (Figure 1). In total, 132 MIs occurred in the 121 patients during the follow-up period. MI was related to VLST in 27 cases (20%), whereas it was not related to a stented site in 101 cases. Only 2 patients had both types of MI during follow-up. Twenty-two VLSTs occurred in stents implanted before inclusion in the study, whereas 5 occurred in stents implanted during the follow-up period. In addition, there were 3 cases of early stent thrombosis and 1 case of late stent thrombosis that occurred in stents implanted during the follow-up period. As shown in Table 3, cases of VLST occurred up to 17 years after stent implantation (median 5.2 years). First-generation DES were involved in 52% of cases, second-generation DES in 11%, and bare-metal stents (BMS) in the remainder (37%). In the great majority of cases (88%), there was no change in antithrombotic treatment within 3 months of VLST. A status of no antiplatelet therapy at the time of stent thrombosis was documented in only 3 cases, including 1 patient who received oral anticoagulation alone and 2 patients with no antithrombotic drug treatment. As shown in Figure 1, the clinical presentation of VLST was different from that of MI not related to a stented site (p = 0.001), with a majority of STEMI events (59%) in the VLST group and a majority of NSTEMI (74%) in the group of MIs not related to a stented site. The risk of VLST appeared constant over time, at 0.15% annually (Figure 1). When we considered the first event during follow-up, no statistically significant differences in baseline characteristics were observed between patients with VLST and patients with MI not related to a stented site (data not shown). Finally, the prognosis of patients with VLST was compared with that of patients with MI not related to a stented site. The unadjusted mortality rates were 7% per year after MI not related to a stented site and 18% per year after MI related to VLST. Adjusted mortality at the 5-year follow-up was 4 times greater after MI related to VLST (age- and sex-adjusted HR: 4.16; 95% CI: 1.50 to 11.50; p = 0.006),

TABLE 3 Details of the 27 Cases of Very Late Stent Thrombosis

Time since stent implantation, yrs	
Median	5.2
Range, minimum–maximum	1–17
Type of stent, n (%)	
Bare-metal stent	10 (37)
First-generation drug-eluting stent	14 (51.9)
Second-generation drug-eluting stent	3 (11.1)
Antithrombotic treatment at the time of very late stent thrombosis, n (%)	
Single-antiplatelet therapy	14 (51.9)
Dual-antiplatelet therapy	7 (25.9)
Anticoagulant and antiplatelet therapy	3 (11.1)
Anticoagulant alone	1 (3.7)
None	2 (7.4)
Change in antithrombotic treatment during past 3 months, n (%)	3 (11.1)

and this difference remained statistically significant when adjusted for age, sex, and clinical presentation (STEMI vs. NSTEMI; HR: 4.02; 95% CI: 1.42 to 11.38; p = 0.009).

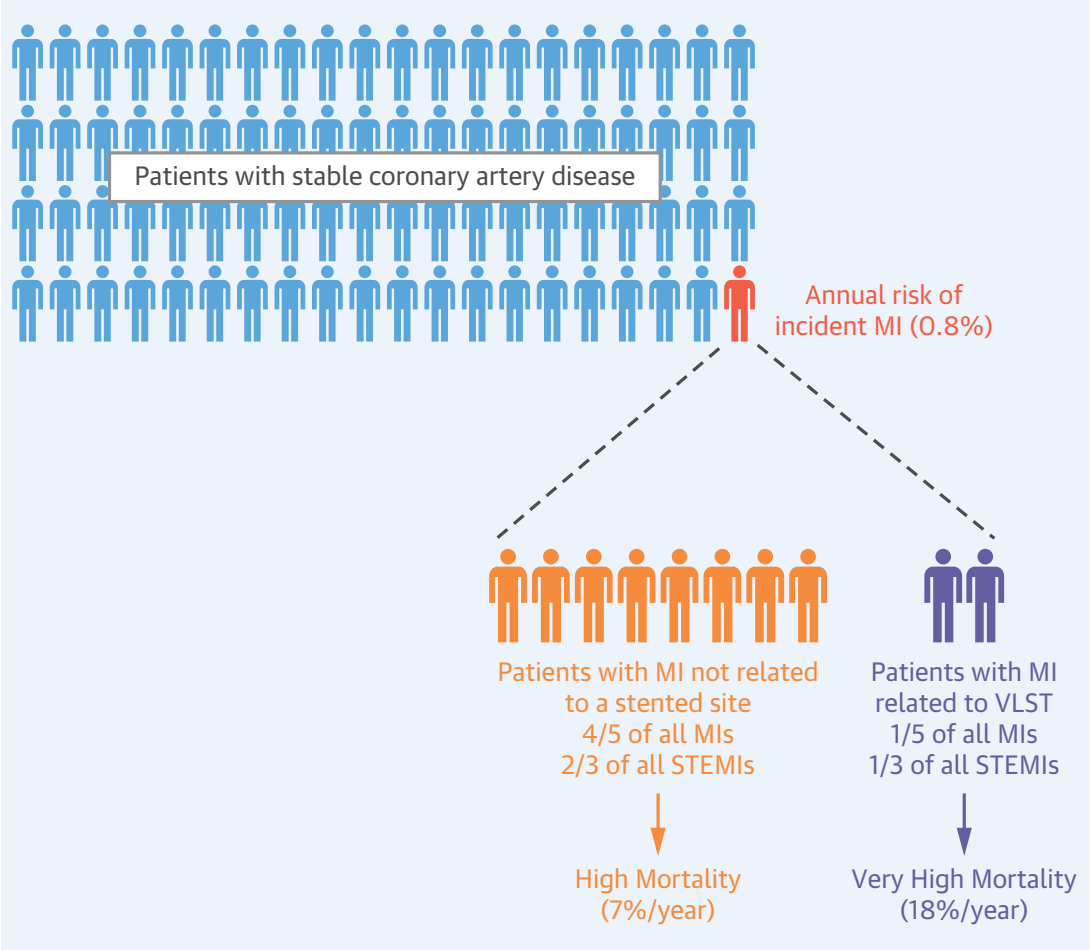
DISCUSSION

Our study demonstrates that patients with stable CAD have a linear risk of MI of 0.8% per year in contemporary practice, confirms the findings from previous studies (3,4,6) on the risk associated with uncontrolled risk factors after MI and on the protective effect of previous coronary bypass surgery, and shows that a significant proportion of MI is related to VLST, with important prognostic implications (**Central Illustration**).

MI is the most commonly feared event in patients with established CAD; however, there is limited information on the incidence, risk factors, and prognostic impact of MI when it occurs in outpatients with stable CAD (i.e., at a chronological distance from any acute event). Previous data were often obtained from randomized studies that included patients according to specific inclusion and exclusion criteria (3,17–19). Cohorts and registries of CAD patients often failed to exclude patients with a recent hospitalization or were performed at a time when secondary prevention was not as stringent as in contemporary practice (4,20–23). To the best of our knowledge, CORONOR is the first registry entirely dedicated to contemporary and unselected CAD outpatients in a very stable setting (at least 1 year since their last coronary event, with a median of 5 years) for whom long-term (5-year) follow-up is available. We reported a risk of MI of 4% after 5 years (0.8% per year). Although this could still be an underestimate (some cases of sudden death might be due to undiagnosed fatal MI), this result emphasizes that in a real-life setting, MI is now a relatively rare event in stabilized CAD patients. This rate is less than half that reported in the placebo arm of the recent PEGASUS-TIMI 54 (Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin-Thrombolysis In Myocardial Infarction 54) trial (5.25% at 3 years), a difference that might be attributed to the selection of post-MI patients with enrichment criteria for a high risk of ischemic events in that study (19). Our result is more in line with the rate of 1% at 1-year follow-up reported in the CLARIFY (Prospective Observational Longitudinal Registry of Patients With Stable Coronary Artery Disease) registry (5). The explanation for the low risk of an event seen in the present study is likely to be multifactorial. First, most patients had a history of myocardial revascularization, including previous coronary bypass surgery in more than 20% of the cases. Second, the proportion of patients receiving medication for secondary prevention was very high for an unselected study population. Third, although not optimal, risk factor control was good compared with that reported in the previous literature. For example, a mean systolic blood pressure of 132 mm Hg, mean LDL cholesterol of 89 mg/dl, and a rate of current smoking of 11.3% all compare favorably with the identical metrics (at least 6 months after a coronary event) recorded in the EUROASPIRE III (European Action on Secondary Prevention through Intervention to Reduce Events) study (mean systolic pressure = 140 mm Hg; mean LDL cholesterol = 107 mg/dl; 17.2% rate of current smoking) (24).

Although infrequent, incident MI remains an important prognostic indicator for patients with stable CAD. In the present study, all-cause mortality was doubled in those patients who had an MI during follow-up versus those who avoided MI. This highlights the importance of trying to prevent these events. The identification of factors associated with incident MI could shed light on relevant implicated mechanisms. Besides the unfavorable impact of multivessel disease and persistent angina and the protective effect of prior coronary bypass surgery (25), the results of the present study highlight the importance of residual uncontrolled risk factors. This suggests that additional efforts to help patients quit smoking and more intensive lipid-lowering therapy might be of potential benefit in further decreasing the rate of MI in this population. Although we reported statin prescriptions for >90% of patients, some might still benefit from switching to more potent statins or increasing their dose (17).

CENTRAL ILLUSTRATION **MI and VLST in Stable CAD**



Lemesle, G. et al. J Am Coll Cardiol. 2017;69(17):2149–56.

In patients with stable coronary artery disease (CAD), incident myocardial infarction (MI) is a relatively rare event that is related to very late stent thrombosis (VLST) a substantial proportion of the time. Incident MI has important prognostic implications, especially when the cause is VLST. STEMI = ST-segment elevation myocardial infarction.

Ezetimibe (prescription rate of 15% at inclusion in our registry) might have an effect on incident MI (26). Large randomized trials with PCSK-9 (proprotein convertase subtilisin kexin-9) inhibitors will be reported in the near future. Our results also support an increased effort in terms of secondary prevention for patients with diabetes mellitus. Finally, other strategies could also be of value for risk reduction in stable CAD, such as more intensive antithrombotic treatment for higher-risk patients. Indeed, prolonged dual-antiplatelet therapy has shown efficacy in the prevention of incident MI in certain CAD patients (18,19). Although in our registry, the rate of dual-antiplatelet therapy at baseline was relatively high for a stable CAD population (27), some patients might still benefit from an intensified treatment. Our study, highlighting multivessel CAD and other uncontrolled risk factors as variables associated with recurrent events, agrees with recently published data (28) and could help physicians stratify their patients in terms of risk.

Previous studies have shown that VLST (i.e., occurring >1 year after stent implantation) is still a possible although rare complication of PCI (8-12). To the best of our knowledge, there has been no prior attempt to analyze VLST in an unselected cohort of

patients with stable CAD. Indeed, the current literature on VLST is primarily from the follow-up of prospective cohorts/registries of patients undergoing stent implantation in academic or expert centers (9,10). Although these studies are extremely useful in deriving yearly rates of stent thrombosis and their correlates with stent type, they might be of limited value in extrapolating the importance of VLST to a real-life setting (i.e., unselected patients and centers; different stent types and indications). The annual rate of 0.15% approximates (or is even less than) the rates observed in academic/expert centers (0.2% to 0.5% annually) (9-11,29). In our study, the time interval between PCI and VLST was long (median 5.2 years; maximum 17 years), with the risk of VLST constant over time. Importantly, VLST is not limited to DES and has also been reported in patients with BMS (30). In agreement with these data, more than one-third of the cases of VLST in the present study population arose in patients with a BMS. A few cases of VLST were preceded by a change in antithrombotic treatment, although in most cases, the patients had ongoing antiplatelet therapy at the time of VLST. Our results show that although a rare event, VLST is the cause of incident MI in one-fifth of cases. In addition, adjusted mortality was 4 times higher after VLST than after MI not related to a stented site in the present study, which is, to the best of our knowledge, the first to compare mortality data for VLST versus MI at a nonstented site within the same cohort. Therefore, VLST is still an important event to consider in stable CAD outpatients.

STUDY LIMITATIONS. We lack longitudinal information on patient medication, compliance, and risk factor control over the 5-year follow-up; however, major changes during the follow-up period are unlikely given that all patients had been stable for at least 1 year at inclusion, with their cardiologists confirming continued treatment. Nonetheless, this remains a limitation of our study.

In this study, no differences in baseline characteristics were observed between patients with VLST and those with MI not related to a stented site; however, this comparison has limited statistical power because of the low number of VLST events. In addition, we do not have detailed data on PCI procedures before inclusion for the stented population. This is a limitation when considering parameters that might differentiate patients with VLST versus those with MI not related to a stented site.

CONCLUSIONS

Our study shows that incident MI occurs at a constant annual rate of 0.8% and is related to a VLST in one-fifth of the cases that arise in unselected outpatients with stable CAD (**Central Illustration**). We found that incident MI was associated with an increase in all-cause mortality. VLST was frequently associated with STEMI and predicted a higher risk of death. Multivessel CAD and residual uncontrolled risk factors appeared to be strongly associated with incident MI. The intensity of secondary prevention, including the use of new lipid-lowering drugs and prolonged dual-antiplatelet therapy, should be adjusted to the patient's risk profile.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Even with modern therapeutic management, patients with stable CAD face a risk of MI, and these events are associated with considerable mortality, especially when related to very late stent thrombosis.

TRANSLATIONAL OUTLOOK: Additional studies are needed to develop ways to prevent very late stent thrombosis in stable patients with ischemic heart disease and to assess the impact of these interventions on rates of MI and mortality.

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APPENDIX For supplemental tables, please see the online version of this paper.