

## ORIGINAL ARTICLE

# Prognostic implications of coronary calcification in patients with obstructive coronary artery disease treated by percutaneous coronary intervention: a patient-level pooled analysis of 7 contemporary stent trials

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## ABSTRACT

**Objective** To investigate the long-term prognostic implications of coronary calcification in patients undergoing percutaneous coronary intervention for obstructive coronary artery disease.

**Methods** Patient-level data from 6296 patients enrolled in seven clinical drug-eluting stents trials were analysed to identify in angiographic images the presence of severe coronary calcification by an independent academic research organisation (Cardialysis, Rotterdam, The Netherlands). Clinical outcomes at 3-years follow-up including all-cause mortality, death—myocardial infarction (MI), and the composite end-point of all-cause death—MI—any revascularisation were compared between patients with and without severe calcification.

**Results** Severe calcification was detected in 20% of the studied population. Patients with severe lesion calcification were less likely to have undergone complete revascularisation (48% vs 55.6%,  $p < 0.001$ ) and had an increased mortality compared with those without severely calcified arteries (10.8% vs 4.4%,  $p < 0.001$ ). The event rate was also high in patients with severely calcified lesions for the combined end-point death—MI (22.9% vs 10.9%;  $p < 0.001$ ) and death—MI—any revascularisation (31.8% vs 22.4%;  $p < 0.001$ ). On multivariate Cox regression analysis, including the Syntax score, the presence of severe coronary calcification was an independent predictor of poor prognosis (HR: 1.33 95% CI 1.00 to 1.77,  $p = 0.047$  for death; 1.23, 95% CI 1.02 to 1.49,  $p = 0.031$  for death—MI, and 1.18, 95% CI 1.01 to 1.39,  $p = 0.042$  for death—MI—any revascularisation), but it was not associated with an increased risk of stent thrombosis.

**Conclusions** Patients with severely calcified lesions have worse clinical outcomes compared to those without severe coronary calcification. Severe coronary calcification appears as an independent predictor of worse prognosis, and should be considered as a marker of advanced atherosclerosis.

presence of severe coronary calcification was a predictor of worse clinical outcomes. In the era of plain old balloon angioplasty, severe coronary calcification was associated with an increased risk of coronary dissection and procedural failure, while in the bare-metal stent era, it was associated with a higher incidence of in-stent restenosis and target lesions revascularisations (TLR).<sup>1–2</sup> The advent of drug-eluting stents (DES) changed the landscape of coronary intervention through the reduced risk of restenosis and TLR, thereby allowing the interventional treatment of complex lesions and high-risk patients. Several studies have examined the efficacy of DES in heavily calcified lesions reporting mixed results. Some have demonstrated a high success rate and a marked reduction in TLR, while others have reported that patients with calcified lesions undergoing PCI with DES have a higher incidence of stent thrombosis (ST) and an increased major adverse event rate, compared to the event rate reported in patients without coronary calcification.<sup>3–8</sup> However, all the previous studies included a small number of patients with few events,<sup>4–7,8</sup> whereas only one has reported the prognostic implications of lesion calcium in patients treated with a second-generation DES.<sup>4</sup>

The aim of the current analysis is to examine the effect of coronary calcification on hard clinical endpoints in patients treated with a first or second-generation DES.

## METHODS

### Studied population

We retrospectively analysed data from patients implanted with a DES who were recruited in the following stent trials: the ARTS II (Arterial Revascularisation Therapies Study II), the LEADERS (Limus Eluted From a Durable vs Erodable Stent Coating) trial, the MULTISTRATEGY (Multicenter Evaluation of Single High-Dose Bolus Tirofiban vs Abciximab With Sirolimus-Eluting Stent or Bare-Metal Stent in Acute Myocardial Infarction (MI)) study, the STRATEGY (Single High-Dose Bolus Tirofiban and Sirolimus-Eluting Stent vs Abciximab



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## INTRODUCTION

From the early days of percutaneous coronary intervention (PCI) it became apparent that the

and Bare-Metal Stent in Myocardial Infarction) trial, the SIRTAX (Sirolimus-Eluting Stent Compared With Paclitaxel-Eluting Stent for Coronary Revascularization), the SYNTAX (Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery) and the RESOLUTE (Resolute All Comers) trial. The aim and inclusion criteria were different between studies: two trials included stable patients with complex coronary artery disease and aimed to compare outcomes between patients treated with PCI or bypass surgery (the SYNTAX and the ARTS II), two evaluated the efficacy of DES treatment combined with different IIb/IIIa inhibitors in patients admitted with an acute MI (the STRATEGY and MYLISTRATEGY trial), the SIRTAX assessed the effectiveness of two first-generation DES devices in patients with obstructive coronary artery disease that was amenable to PCI, the LEADERS compared a DES with a biodegradable polymer to a first-generation DES in patients with coronary artery disease and, finally, the RESOLUTE all-comers compared two second-generation DES with different drug elution in an unselected patient population which was representative of patients treated in everyday clinical practice. A detailed description of each study design has been reported elsewhere.<sup>9–15</sup> All studies complied with the Declaration of Helsinki, and were approved by the ethical review board of the institution involved, whereas, the included patients provided written informed consent for participation in these studies.

### Data processing

The baseline demographic data and the X-ray angiographic data of the patients recruited in these studies were transferred to an independent academic research organisation (Cardialysis, Rotterdam, The Netherlands) for further processing. Two trained analysts reviewed the angiographic films; they calculated the Syntax score using a previously described methodology, and identified the presence of severely calcified lesions defined as: radiopacities noted without cardiac motion before contrast injection, generally compromising both sides of the arterial lumen.<sup>16–17</sup> In case of disagreement, the opinion of a third expert analyst was requested, and the final decision was obtained by consensus. At the time of the angiographic analysis, the reviewers were blinded to the patients' demographic characteristics and clinical outcomes.

### Clinical end-points and definitions

All the studied patients were followed-up for at 3 years. The primary end-point of this analysis was all-cause mortality at 3 years follow-up. Secondary end-points of this analysis were the combined end-points for death—all MIs (ST-elevation and non-ST-elevation MI)—and the composite end-point for—MI—any revascularisation. As it has been previously reported, there was an inconsistency in the definition of ST-elevation and non-ST-elevation MI among the different studies, which can be attributed to the different populations included in each study, the different study designs, and the different periods when the trials were conducted.<sup>18</sup> Considering the fact that the events reported in each trial were reviewed by an independent clinical event committee a decision was taken not to readjudicate MI using a uniform definition and, instead, all MIs are defined as per the individual study protocol definition. Revascularisation follow-up data were available in only 4 (ARTS II, SYNTAX, LEADERS, and RESOLUTE) studies and, thus, the combined end-point all-cause mortality—any MI—any revascularisation was reported only for the patients recruited in these studies.

Additionally, the ST events were recorded and compared in the two groups. ST was classified as definite, probable and

possible, according to the Academic Research Consortium definitions.<sup>19</sup> Definite ST data were available in six studies (ARTS II, SYNTAX, LEADERS, RESOLUTE, MULTISTRATEGY and SIRTAX), probable ST data in 5 (ARTS II, SYNTAX, LEADERS, RESOLUTE, and MULTISTRATEGY), and the possible in 4 (ARTS II, SYNTAX, LEADERS, and RESOLUTE) out of the seven clinical trials.

### Statistics

Numerical variables are presented as median with 25th and 75th percentiles while categorical variables are presented as absolute values and percentages. The studied patients were categorised into those with severely calcified coronary lesions and those without severe lesion calcification. Comparisons between the two groups were performed using the Mann–Whitney U test for the continuous variables, and the  $\chi^2$  test for the categorical variables.

Cox regression analysis was used to identify predictors of adverse events, that is, all-cause mortality,—MI, death—MI—any revascularisation, and ST. The hazard ratio (HR) and the 95% confidence interval (CI) for the continuous variables were estimated per unit increase. The estimates from the univariate analysis predictors of worse prognosis were entered into a multivariable model to identify independent predictors of worse outcomes. In the multivariable models, the 'forced enter' method was deemed appropriate. To address the clustering effect, shared frailty models were used in univariate and multivariate analyses. To exclude collinearity, we identified the variables that were highly correlated ( $r > 0.5$  and  $p < 0.05$ ), and we included in the model only those variables that had a higher level of prognostic significance.

The proportionality of hazards assumption was examined by residual plotting. Graphical plots were made by the Kaplan–Meier method. The log-rank statistic was used to compare prognosis between the two groups. A  $p$  value  $< 0.05$  (two-tailed) was considered statistically significant. Data analysis was performed using the Statistical Package for Social Sciences (SPSS) V.18.0 (SPSS, Chicago, Illinois, USA) and the STATA V.12.0 software (Stata, College Station, Texas, USA).

## RESULTS

### Baseline demographics

The Syntax score, and the clinical and the follow-up data were available for 6296 patients out of the 7639 patients that were enrolled in the seven clinical trials. Most of the studied patients were male with a history of hypertension and hypercholesterolaemia and were admitted because of an acute coronary event. Four out of 10 patients were treated with a first-generation DES (ie, a sirolimus or paclitaxel-eluting stent), and six out of 10 patients with a second-generation device (ie, an everolimus, zotarolimus, or a biolimus-eluting platform).

Twenty per cent of the studied patients had severely calcified lesions on coronary angiography (table 1). These patients were older and were more likely to suffer from hypertension and hypercholesterolaemia compared to the group of patients without severe lesion calcium who were more often diabetic. Patients with severe calcification had a higher Syntax score (12.1 units higher than those without severe calcification, 95% CI 11.5 to 12.7;  $p < 0.001$ ), and were less likely to have undergone complete revascularisation (data with regards complete revascularisation was available only for the ARTS II the STRATEGY, MULTISTRATEGY and the SYNTAX study). No differences were noted between the two groups with regards to the cause of admission, the incidence of LV systolic dysfunction, and the prevalence of peripheral vascular disease (PVD).

## Coronary artery disease

**Table 1** Baseline demographics of the patients with and without severely calcified lesions

	All studied patients (n=6296)	Patients with severely calcified lesions (n=1291)	Patients without severe calcifications (n=5005)	p Value
Age (years)	64 (56–72)	69 (62–75)	63 (55–71)	<0.001
Male (%)	4740 (75.3)	957 (74.1)	3783 (75.6)	0.280
BMI	27.1 (24.7–30.0)	27.0 (24.2–30.0)	27.2 (24.8–30.1)	0.001
Hypertension	4328 (69.4)	969 (75.5)	3359 (67.7)	<0.001
Hypercholesterolaemia (%)	4056 (65.2)	899 (70.2)	3157 (63.9)	<0.001
Diabetes mellitus (%)	1453 (23.2)	1079 (21.7)	374 (29.0)	<0.001
Peripheral vascular disease (%)	1745 (30.7)	397 (32.1)	1348 (30.3)	0.214
Cerebrovascular disease (%)	182 (4.9)	73 (7.2)	109 (4.0)	<0.001
Creatinine > 200 mol/L	61 (1.1)	20 (1.6)	41 (0.9)	0.025
Positive smoking history (%)	3257 (52.1)	648 (50.4)	2609 (52.6)	0.161
<i>LV systolic function</i>				<b>0.712</b>
Normal LV function (%)	3838 (78.4)	833 (77.6)	3005 (78.7)	
Moderate LV dysfunction (%)	865 (17.7)	196 (18.2)	669 (17.5)	
Severe LV dysfunction (%)	191 (3.9)	45 (4.2)	146 (3.8%)	
Unstable presentation (%)	3349 (53.2)	672 (52.1)	2677 (53.5)	0.357
History of previous MI (%)	1745 (30.7)	397 (32.1)	1348 (30.3)	0.214
Syntax score	15 (9–23)	25 (18–34)	13 (7–20)	<0.001
Complete revascularisation (%)	1086 (53)	339 (48)	550 (55.6)	0.001
Treatment with 2nd generation DES (%)	2709 (43.0)	375 (29.0)	2334 (46.5)	<0.001

BMI, Body Mass Index; MI, myocardial infarction; DES, drug-eluting stent.

**Severe lesion calcification and clinical end-points**

All studied patients were followed-up for 3 years. During follow-up, 359 (5.7%) patients died, of whom 139 had severely calcified lesions (table 2). The Kaplan–Meier analysis showed that patients with severely calcified lesions had significantly higher all-cause mortality (10.8% vs 4.4%, log-rank test=79.35;  $p<0.001$ ) compared to those without. Landmark analysis showed an increased mortality in the group of patients with severely calcified lesions at 1 year post-procedure, and also for the period between 1 and 3 years follow-up (figure 1A).

**Table 2** Reported events in the studied patients at a follow-up period of 3 years

	All studied patients (n=6296)	Patients with severely calcified lesions (n=1291)	Patients without severe calcifications (n=5005)
Death (%)	359 (5.7)	139 (10.8)	220 (4.4)
MI (%)	551 (8.8)	183 (14.2)	368 (7.4)
Any revascularisation* (%)	866 (17.3)	241 (20.5)	625 (16.3)
<i>Combined end-points</i>			
Death—MI (%)	840 (13.3)	295 (22.9)	545 (10.9)
Death—MI—any revascularisation*	1213 (24.2)	373 (31.7)	860 (22.4)
<i>Stent thrombosis†</i>			
Definite (%)	129 (2.1)	38 (3.0)	91 (1.8)
Probable (%)	43 (0.8)	16 (1.3)	27 (0.7)
Possible (%)	97 (1.9)	35 (3.0)	62 (1.6)

\*Revascularisation data were available in 5018 patients (1175 with severely calcified lesions and 3843 in patients without severe coronary calcification).

†Definite stent thrombosis data were available in 6222 patients (1279 with severe lesion calcification and 4943 without calcified coronaries), probable stent thrombosis in 5364 (1221 with severely calcified coronaries and 4143 without severe coronary calcification) and possible in 5034 patients (1182 with severe and 3852 without severe coronary calcification). MI, myocardial infarction.

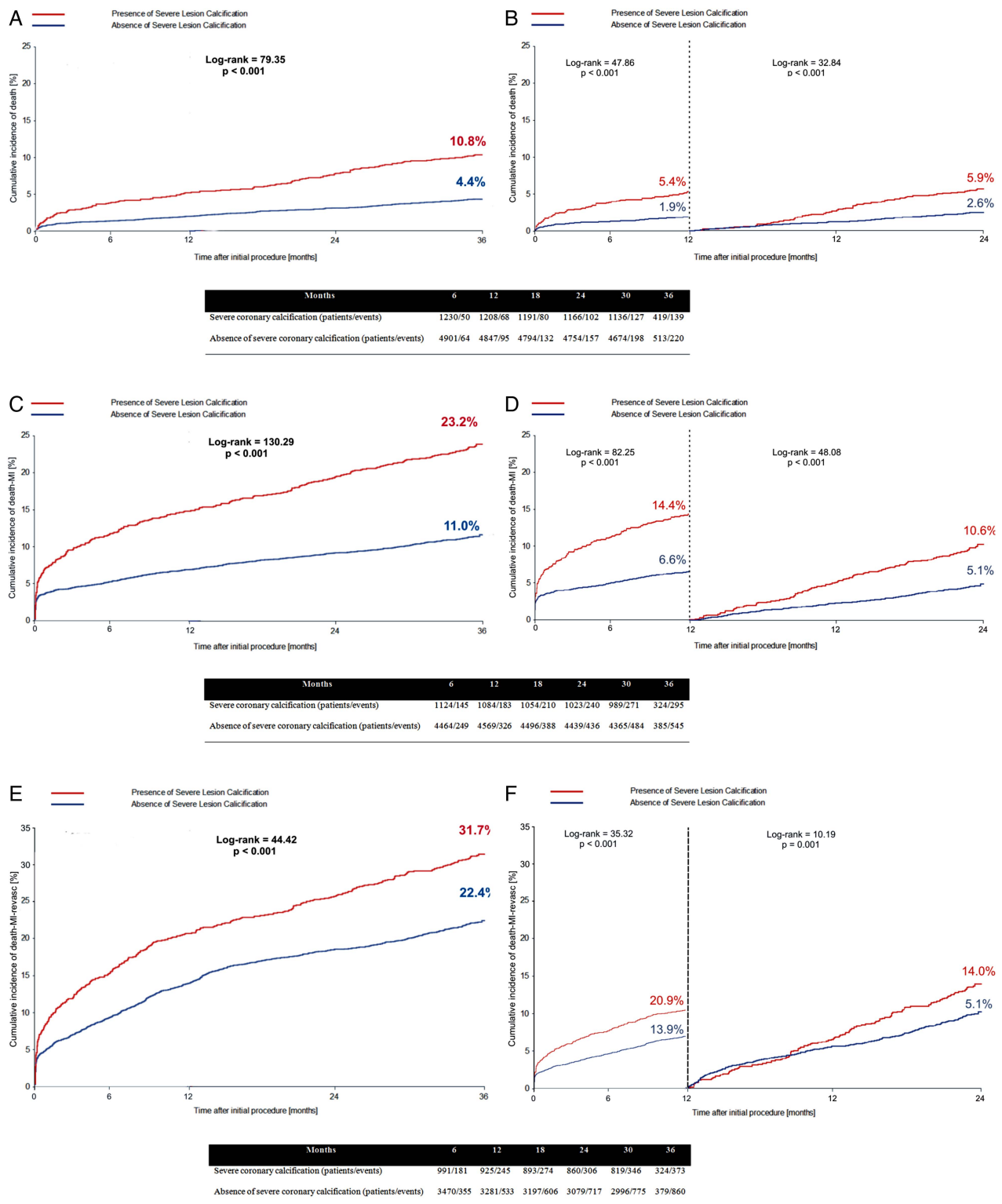
Severe calcification appeared as a predictor of increased mortality in the univariate Cox regression analysis (HR: 2.41, 95% CI 1.92 to 3.00;  $p<0.001$ ). Table 3 shows all the predictors of all-cause mortality identified by univariate Cox regression analysis. In the multivariate model, that included all the independent predictors of worse outcomes, apart from the history of cerebrovascular disease and PVD because of missing data, the presence of calcified lesions was independently associated with an increased all-cause mortality (table 3).

The combined end-point death—MI was reported in 840 patients. Patients with severe lesion calcification were at a higher risk of experiencing an event compared to those without calcified lesions (23.2% vs 11.0%; log-rank=130.29;  $p<0.001$ ). Landmark analysis showed a worse prognosis in the group of patients with severely calcified lesions at the first year post-procedure, but also for the period between 1 and 3 years follow-up (figure 1B).

In univariate Cox regression analysis, severe calcification was a predictor of death—MI (HR: 1.86, 95% CI 1.60 to 2.16;  $p<0.001$ ). In the multivariate model built, excluding the history of cerebrovascular and PVD, severe calcification was a predictor of death—MI (table 4).

Outcome data with regards the combined end-point death—MI—any revascularisation was available in 5018 patients. At 3-year follow-up, 1213 events were reported, of which 860 (22.4%) occurred in patients without severely calcified lesions, and 373 (31.8%) in patients with severe lesion calcification (log-rank=14.55;  $p<0.001$ , figure 1C). Similarly to what has been reported for the other end-points, landmark analysis showed a worse outcome in the group of patients with severely calcified lesions at 1 year post-procedure, and also for the period between 1 and 3 years follow-up (figure 1C). Severe lesion calcification was a predictor of worse outcome in univariate and multivariate Cox regression analysis (table 5).

During follow-up, 269 ST events occurred, of which 129 were definite, 43 probable and 97 possible ST (table 3). Patients with calcified coronaries had an increased incidence of ST



**Figure 1** Kaplan-Meier and landmark analysis for the all-cause mortality (A, B), death—myocardial infarction (C, D) and for the combined end-point death—myocardial infarction—any revascularisation (E, F) in patients with and without severe lesion calcification. The landmark analysis was performed for the first year and for the period 1–3 years follow-up.

compared to those without coronary calcification (definite ST: 3% vs 1.8%, log-rank=6.97; p=0.008; definite/probable ST: 4.3% vs 2.1%, log-rank=17.06, p<0.001). Severe lesion calcification was a predictor of ST in univariate analysis (definite ST: HR: 1.66, 95% CI 1.13 to 2.42; p<0.001; definite/probable ST: HR: 1.95, 95% CI 1.37 to 2.76; p<0.001), but it was not an independent predictor in the multivariate models (definite

ST: HR: 1.41, 95% CI 0.87 to 2.28; p=0.167; definite/probable ST: HR: 1.40, 95% CI 0.91 to 2.15; p=0.124).

## DISCUSSION

This retrospective analysis provides additional evidence about the prognostic implications of lesion calcium in patients undergoing PCI. We found that severe lesion calcification is an



## Coronary artery disease

**Table 3** Univariate and multivariate Cox regression analysis of variables associated with increased all-cause mortality.

	Univariate Cox regression		Multivariate Cox regression*	
	HR (95% CI)	p Value	HR (95% CI)	p Value
Increasing age (per decade)	2.02 (1.81 to 2.25)	<0.001	1.76 (1.54 to 2.01)	<0.001
Female gender	1.33 (1.07 to 1.67)	0.011	1.11 (0.85 to 1.46)	0.438
<i>Comorbidities</i>				
History of diabetes mellitus	1.85 (1.49 to 2.29)	<0.001	1.60 (1.24 to 2.06)	<0.001
History of hypertension	1.30 (1.03 to 1.65)	0.029	1.00 (0.74 to 1.35)	0.991
Absence of history of hypercholesterolaemia	1.41 (1.14 to 1.74)	0.002	1.16 (0.89 to 1.52)	0.258
History of peripheral vascular disease*	2.59 (1.80 to 3.63)	<0.001	–	
History of cerebrovascular disease*	1.96 (1.26 to 3.03)	<0.001	–	
Increased creatinine (>200 mol/L)	7.23 (4.60 to 11.36)	<0.001	3.37 (1.87 to 5.64)	<0.001
LV systolic dysfunction	2.17 (1.83 to 2.59)	<0.001	1.81 (1.50 to 2.19)	<0.001
Previous history of myocardial infarction	1.24 (1.00 to 1.55)	0.052	1.21 (0.93 to 1.56)	0.154
<i>Angiographic variables</i>				
Syntax score (per unit)	1.04 (1.03 to 1.05)	<0.001	1.02 (1.01 to 1.03)	<0.001
Severe lesion calcification	2.41 (1.92 to 3.00)	<0.001	1.33 (1.00 to 1.77)	0.047

\*Because of missing data, the history of cerebrovascular and peripheral vascular diseases were not entered into the multivariate analysis.

independent predictor of worse outcomes, and its presence appears to provide additional prognostic information from the Syntax score which reflects coronary artery disease complexity.

Several studies in the past have examined the prognostic implications of lesion calcification in the DES era. Moussa *et al*<sup>3</sup> were the first to show a significant reduction in TLR with paclitaxel-eluting stents compared to bare-metal stents, and no difference in the incidence of TLR between calcified and non-calcified lesions treated with a DES. Kawaguchi *et al*<sup>7</sup> showed a higher risk of in-stent restenosis in calcified lesions but no difference in the incidence of adverse cardiovascular events; however, the small number of patients included in this analysis (n=380), and the lack of multivariate analysis, does not allow us to draw firm conclusions. More recent studies, however, have shown that lesion calcification is associated with an increased risk of cardiovascular events, and provided robust evidence about its prognostic implications.<sup>6, 8</sup> In all these reports, the patients were mainly treated with a first-generation DES, the prognostic

implications of lesion calcification in these studies has been associated with the complexity of the PCI, while the Syntax score which reflects more accurately the anatomical complexity of the lesion was not available.

In this study, we examined for the first time the prognostic implications of lesion calcification in a large group of patients treated with either a first or a second-generation DES. Importantly, we have a reliable and reproducible assessment of lesion complexity as we included in this analysis only the patients that had Syntax score evaluation. We found that lesion calcification provided additional prognostic information as it was an independent predictor of all-cause mortality, death—MI and death—MI—any revascularisation. The fact that the patients with severely calcified lesions have worse prognosis at short term (ie, within the first year post-procedure), and also at long-term follow-up, indicates that the poor outcome in this group of patients is not only related to periprocedural complications.

**Table 4** Univariate and multivariate Cox regression analysis of variables associated with the combined end-point death—myocardial infarction

	Univariate Cox regression		Multivariate Cox regression*	
	HR (95% CI)	p Value	HR (95% CI)	p Value
Increasing age (per decade)	1.36 (1.28 to 1.45)	<0.001	1.28 (1.18 to 1.39)	<0.001
Female gender	1.24 (1.07 to 1.44)	0.004	1.08 (0.90 to 1.30)	0.402
<i>Comorbidities</i>				
History of diabetes mellitus	1.55 (1.34 to 1.80)	<0.001	1.45 (1.22 to 1.71)	<0.001
History of hypertension	1.20 (1.03 to 1.40)	0.021	1.00 (0.82 to 1.21)	0.994
History of peripheral vascular disease*	1.85 (1.46 to 2.35)	<0.001	–	
History of cerebrovascular disease*	1.70 (1.26 to 2.29)	0.001	–	
Increased creatinine (> 200 mol/L)	4.01 (2.75 to 5.85)	<0.001	2.56 (1.64 to 3.99)	<0.001
LV systolic dysfunction	1.57 (1.38 to 1.78)	<0.001	1.36 (1.18 to 1.56)	<0.001
History of previous myocardial infarction	1.21 (1.04 to 1.40)	0.011	1.15 (0.97 to 1.36)	0.113
<i>Angiographic variables</i>				
Syntax score (per unit)	1.03 (1.02 to 1.04)	<0.001	1.02 (1.01 to 1.03)	<0.001
Severe lesion calcification	1.86 (1.60 to 2.16)	<0.001	1.23 (1.02 to 1.49)	0.031

\*Because of missing data, the history of cerebrovascular and peripheral vascular disease was not entered into the multivariate analysis.

**Table 5** Univariate and multivariate Cox regression analysis of variables associated with death—myocardial infarction—any revascularisation.

	Univariate Cox regression		Multivariate Cox regression*	
	HR (95% CI)	p Value	HR (95% CI)	p Value
Increasing age (per decade)	1.14 (1.08 to 1.20)	<0.001	1.08 (1.02 to 1.16)	0.013
<i>Comorbidity</i>				
History of diabetes mellitus	1.52 (1.35 to 1.72)	<0.001	1.42 (1.23 to 1.64)	<0.001
History of hypertension	1.23 (1.08 to 1.40)	0.002	1.07 (0.91 to 1.25)	0.431
History of peripheral vascular disease*	1.44 (1.15 to 1.82)	0.002	–	
Increased creatinine (>200 mol/L)	2.76 (1.91 to 3.99)	<0.001	2.04 (1.33 to 3.14)	0.001
LV systolic dysfunction	1.25 (1.11 to 1.41)	<0.001	1.15 (1.02 to 1.31)	0.026
Previous history of myocardial infarction	1.17 (1.04 to 1.32)	0.010	1.07 (0.93 to 1.23)	0.335
<i>Angiographic variables</i>				
Syntax score (per unit)	1.03 (1.02 to 1.03)	<0.001	1.03 (1.02 to 1.03)	<0.001
Severe lesion calcification	1.52 (1.34 to 1.72)	<0.001	1.18 (1.01 to 1.39)	0.042
First generation stent	1.15 (0.98 to 1.35)	0.091	1.13 (0.90 to 1.41)	0.289

\*Because of missing data, the history of peripheral vascular disease was not entered into the multivariate analysis.

A potential explanation of this finding is that coronary calcification is a marker of extensive atherosclerotic disease. Indeed, several electron beam-computed tomography-based studies have shown that coronary calcification is a predictor of atherosclerosis progression and is related with increased cardiovascular mortality in the general population.<sup>20 21</sup> However, in patients undergoing PCI, the focus has been towards the development of anatomical scores that would allow accurate assessment of lesion complexity, or the implications of the lesion on myocardial perfusion and the prognostic value of coronary calcification has been ignored.<sup>16 22</sup> The present study convincingly demonstrates that severe lesion calcification provides additional information which, until today, has been neglected and not been taken into consideration in the prognostic models developed for patients undergoing PCI.<sup>23 24</sup>

Severe lesion calcification appeared to be associated with an increased risk of ST in univariate analysis, but it was not an independent predictor of ST. Our results are different from the findings of other reports which showed that lesion calcification is independently associated with an increased risk of ST,<sup>5 6</sup> but are similar to the findings of the SYNTAX study, that included the Syntax score, which can compete with lesion calcification in the multivariate model.<sup>25</sup> Nevertheless, the fact that this study did not include procedural information (ie, number of implanted stents, length and diameter of stents, etc), lesion characteristics (ie, length of the lesion, vessel diameter, the number of the bifurcated lesions), and the type and duration of antiplatelet treatment, does not allow us to draw firm conclusions about the factors related to ST.

We have recently demonstrated that patients suffering from coronary artery disease with severely calcified lesions are more likely to receive suboptimal revascularisation and have a higher residual Syntax score which is a powerful determinant of prognosis.<sup>26</sup> Additionally, in this study, we found that patients with severely calcified lesions are less likely to have undergone complete revascularisation. A decalcification strategy with extensive metallic stent implantation cannot be justified as there is robust evidence that stent length is a predictor of TLR. On the other hand, bioresorbable scaffolds appear to overcome the limitations of the traditional metallic stents and seem to have a role for the treatment of heavily calcified lesions.<sup>27</sup> Whether complete revascularisation—implementing a decalcification strategy of long-calcified lesions with atherectomy, or the recently introduced

orbital atherectomy system followed by bioresorbable scaffold implants—would improve outcomes in this high-risk population, needs to be proven by future studies.<sup>28</sup>

### Study limitations

Several intravascular imaging studies have shown that coronary angiography has a limited sensitivity in detecting the presence of calcified plaques.<sup>17 29</sup> However, it has a high specificity for detecting severe calcification, and has been shown in this study to provide useful prognostic information. By contrast with previous studies which implemented a more thorough classification scheme for characterising lesion calcification, we decided to classify patients in a binary fashion to those who have lesions with none/mild/moderate calcification, and those with severe calcification. Although this may be regarded initially as a limitation of the current analysis, our decision was based on the low intraobserver and interobserver variability reported for the discrimination between none/mild and moderate/severe calcification.<sup>30</sup> Of note, Genereux *et al*<sup>31</sup> have shown that experts can identify and differentiate with a high agreement severely calcified lesions from the other lesions; based on these findings, we decided to use a reproducible metric and divide patients based on the presence of severe calcification.

Finally, a significant limitation of this study is the fact that the medications data, such as the type of medications, the doses and the duration of treatment (especially the duration of dual antiplatelet treatment), as well as procedural data (ie, treatment of bifurcation lesions, length of the lesions, vessel diameter, number of implanted stents, dimensions of the stents, etc) were not available.

### CONCLUSIONS

Patients with severely calcified lesions are at a high risk of experiencing a cardiovascular event. Severe lesion calcification appears to provide additional prognostic information to the Syntax score, which reflects lesion complexity, because it is a marker of extensive atherosclerosis, and because patients with severely calcified lesions do not receive complete revascularisation. Further research is needed to explore whether a decalcification strategy and complete revascularisation of these high-risk patients would have a beneficial effect on their prognosis.

## Key messages

**What is known on this subject?**

There is strong evidence demonstrating that lesion calcium is associated with an increased risk of target vessel revascularisation following bare-metal or drug-eluting stent implantation. However, there are limited data regarding the impact of lesion calcium on hard clinical end-points in the drug-eluting stents era.

**What might this study add?**

This study shows that the patients with severely calcified lesions who undergo percutaneous coronary intervention (PCI) with a first-generation or a second-generation drug-eluting stent often undergo incomplete revascularisation and have worse clinical outcomes compared to those without severe coronary calcification.

**How might this impact on clinical practice?**

All the previous risk models that were designed to predict prognosis in patients undergoing PCI did not take into account lesion calcification. This study is anticipated to trigger the re-evaluation of the existing risk scores and the design of new models that would predict patients' prognosis with a higher accuracy.

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**Heart**

## Prognostic implications of coronary calcification in patients with obstructive coronary artery disease treated by percutaneous coronary intervention: a patient-level pooled analysis of 7 contemporary stent trials

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