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
LV systolic function				**0.712**
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)
Combined end-points			
Death—MI (%)	840 (13.3)	295 (22.9)	545 (10.9)
Death—MI-any (%) revascularisation*	1213 (24.2)	373 (31.7)	860 (22.4)
Stent thrombosis†			
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

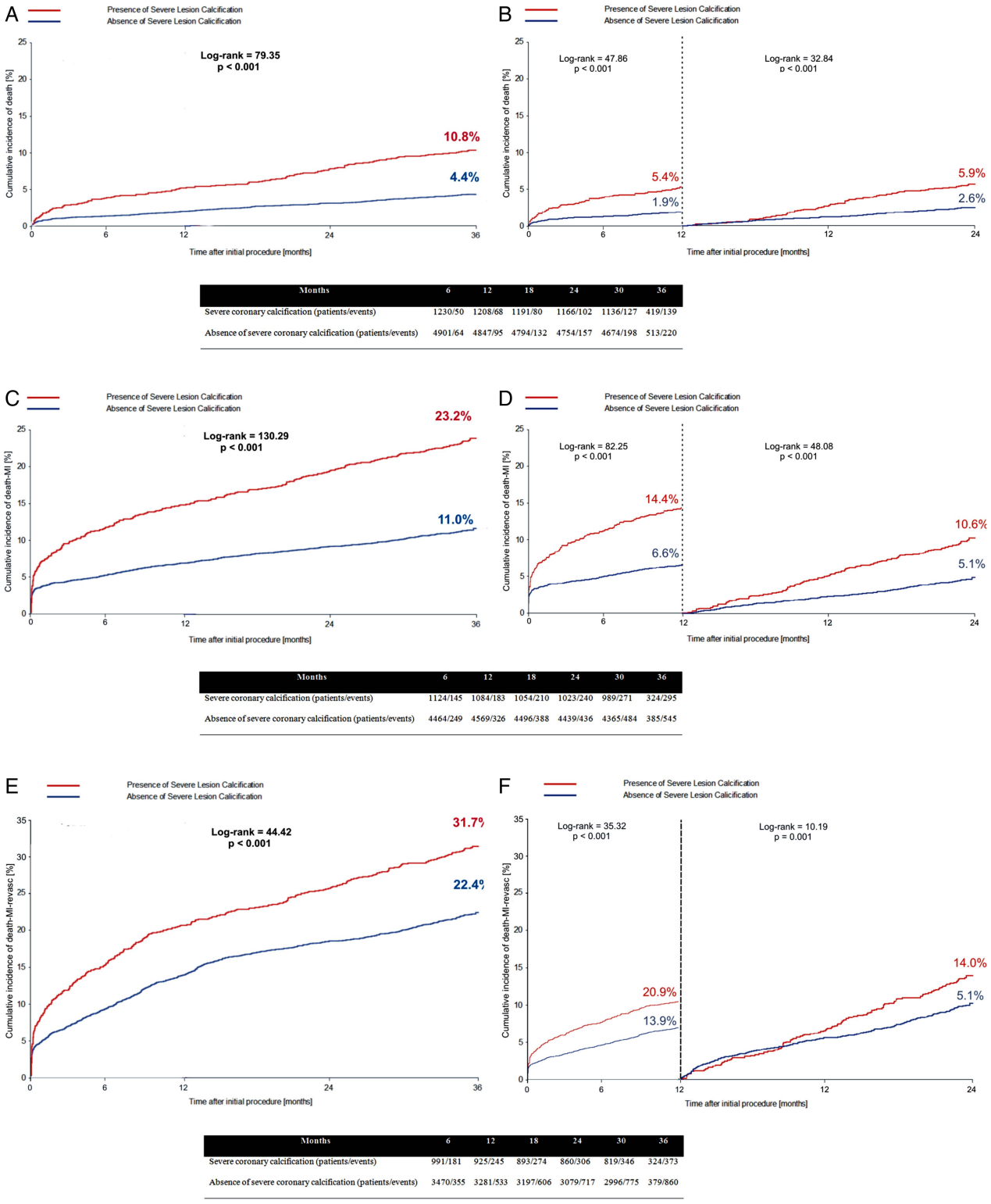

Figure 1 Kaplan–Meier and landmark analysis for the all-cause mortality (A, B), death—myocardial infarction (C, D) and for the combined end-point death—myocardial infarction-any revascularisation (E, F) in patients with and without severe lesion calcification. The landmark analysis was performed for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

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
Comorbidities				
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
Angiographic variables				
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*[3] 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*[7] 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.[6 8] 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
Comorbidities				
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
Angiographic variables				
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
Comorbidity				
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
Angiographic variables				
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.[20 21] 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.[16 22] 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.[23 24]

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,[5 6] 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.[25] 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.[26] 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.[27] 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.[28]

Study limitations

Several intravascular imaging studies have shown that coronary angiography has a limited sensitivity in detecting the presence of calcified plaques.[17 29] 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.[30] Of note, Genereux *et al*[31] 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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