# Very long-term outlook of acute coronary syndromes after percutaneous coronary intervention with implantation of polymer-free versus durable-polymer new-generation drug-eluting stents

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## ABSTRACT

**Background**: Detailed long-term follow-up data on patients with acute coronary syndromes (ACS) in general, and those with ST-elevation myocardial infarction (STEMI) in particular, are limited. We aimed to appraise the long-term outlook of patients undergoing percutaneous coronary intervention (PCI) with state-of-the-art coronary stents for STEMI, other types of ACS and stable coronary artery disease (CAD), and also explore the potential beneficial impact of new-generation polymer-free drug-eluting stents (DES) in this setting.

**Methods:** Baseline, procedural and very long-term outcome data on patients undergoing PCI and randomized to implantation of new-generation polymer-free vs durable polymer DES were systematically collected, explicitly distinguishing subjects with admission diagnosis of STEMI, non-ST-elevation ACS (NSTEACS), and stable CAD. Outcomes of interest included death, myocardial infarction, revascularization (ie patient-oriented composite endpoints [POCE]), major adverse cardiac events (MACE), and device-oriented composite endpoints (DOCE).

**Results:** A total of 3002 patients were included, 1770 (59.0%) with stable CAD, 921 (30.7%) with NSTEACS, and 311 (10.4%) with STEMI. At long-term follow-up (7.5±3.1 years), all clinical events were significantly more common in the NSTEACS group and, to a lesser extent, in the stable CAD group (eg POCE occurred in, respectively, 637 [44.7%] vs 964 [37.9%] vs 133 [31.5%], p<0.001). While these differences were largely attributable to adverse coexisting features in patients with NSTEACS (eg advanced age, insulin-dependent diabetes, and extent of CAD), the unfavorable outlook of patients presenting with NSTEACS persisted even after multivariable adjustment including several prognostically relevant factors (hazard ratio [HR] of NSTEACS vs stable CAD 1.19 [95% confidence interval 1.03-1.38], p=0.016). Notably, even after encompassing all prognostically impactful features, no difference between polymer-free and permanent polymer drug-eluting stents appeared (HR=0.96 [0.84-1.10], p=0.560).

**Conclusions:** Unstable coronary artery disease, especially when presenting without ST-elevation, represents an informative marker of adverse long-term prognosis in current state-of-the-art invasive cardiology practice. Even considering admission diagnosis, and despite of using no polymer, polymer-free DES showed similar results with regards to safety and efficacy when compared with DES with permanent polymer.

## INTRODUCTION

The management of coronary artery disease (CAD) has been revolutionized in the last few decades, thanks to momentous developments in prevention, risk-stratification, diagnosis, treatment and rehabilitation, as appropriate.[1,2] Notably, stable CAD has seen a shift toward less invasive treatment and more intensive pharmacologic regimens (eg the polypill concept), whereas timely invasive management has become the standard of care for acute coronary syndromes (ACS), which span from unstable angina (UA) to non-ST-

elevation myocardial infarction (NSTEMI), often considered as a single entity, ie non-ST-elevation ACS (NSTEACS), and, finally, ST-elevation myocardial infarction (STEMI).[3-5]

While STEMI is still a major cause of short-term morbidity and mortality, paradoxically, patients discharged after STEMI may face a better prognosis than other individuals at long-term.[6] This difference may depend on baseline features and thus concomitant risk factors, but also different management strategies. While coronary stenting currently dominates, together with optimal medical therapy, the acute management of ACS, the quest for the optimal coronary stent for such patients continues, and may be seen as overwhelmingly challenging given the plethora of different devices and the need for very long-term follow-up for accurate and poignant decision making.[7,8]

We have previously reported on the early, long-term, and very long-term follow-up of the Intracoronary Stenting and Angiographic Results: Test Efficacy of Sirolimus- and Probucol- and Zotarolimus-Eluting Stents (ISAR-TEST-5) randomized trial, including patients with CAD receiving a novel polymer-free stent capable of eluting both an anti-restenotic agent, sirolimus, and an anti-inflammatory one, probucol (VIVO ISAR, Translumina Therapeutics LLP, Dehradun, India, and Translumina , Hechingen, Germany). Notably, VIVO ISAR is a thin-strut Cobalt-Chromium stent coated with a mixture of sirolimus, probucol and Shellac resin. Its key feature is the combination of sirolimus (an anti-restenotic agent) and probucol (an antioxidant and cholesterol lowering drug), with the latter acting as carrier to control sirolimus drug release kinetics, and therefore replacing the need of polymers, eventually ensuring better safety and efficacy.[9-11] We hereby aimed at exploring the comparative effectiveness and safety of this breakthrough device in comparison to a traditional drug-eluting stent covered with a permanent polymer (Resolute, Medtronic, Santa Clara, CA, USA), and the potential interaction between device features and admission diagnosis, thus explicitly distinguishing patients with STEMI, NSTEACS, and stable CAD.

## MATERIALS AND METHODS

Details of the ISAR-TEST 5 have been previously reported in detail.[9-12] Briefly, between 2008 and 2009, adult patients with symptoms or signs of myocardial ischemia and evidence of significant CAD were randomized 2:1, after appropriate written informed consent, to percutaneous coronary intervention (PCI) with a polymer-free sirolimus- and probucol-eluting stent (PF-DES; Vivo Isar), or a permanent polymer DES (PP-DES; Resolute). The key features of the Vivo Isar device include the combination of an antirestenotic drug (sirolimus) and an antioxidant agent (probucol), which also may have hypolipemic effects, but specifically acts as carrier thus implying that no polymer is needed, to enhance safety, whereas its metallic platform is based on a cobalt chromium alloy, and thin struts.

Notably, patients with left main culprit lesion, cardiogenic shock, malignancies, or other comorbid conditions with life expectancy <12 months or that may result in protocol noncompliance, known allergy to the study medications (probucol, sirolimus, zotarolimus) or pregnancy (present, suspected, or planned) were considered ineligible for enrolment. The study was conducted in keeping with the Declaration of Helsinki and the International Conference on Harmonization of Good Clinical Practices, formally approved by the competent ethics committee, and registered online (ClinicalTrials.gov Identifier: NCT00598533). Analysis of data from 10-year follow-up, which was not prespecified in the trial protocol, was approved by the competent ethics committee, whereas additional written informed consent from patients was waived.

Beside device choice, management recommendations equally applied to both randomization groups, and included aspirin and clopidogrel as peri-procedural and follow-up oral antiplatelet regimens, heparin or bivalirudin as peri-procedural anticoagulants, glycoprotein IIb/IIIa inhibitors as peri-procedural parenteral antiplatelet agents, and angiotensin-converting enzyme inhibitors, beta-blockers, and statins as secondary prevention agents. Notably, clopidogrel was to be continued for at least 6 months after PCI, and aspirin indefinitely. At 6 to 8 months all patients underwent repeat coronary angiography. Clinical follow-up after the first year was based on either telephone calls or office visits.

Originally, the primary study endpoint was the device-oriented composite endpoint (DOCE) (defined as the composite of cardiac death, MI related to the target vessel, or target lesion revascularization [TLR] at

12 months post index intervention), and the trial was designed with a non-inferiority scope and powered for 20% beta, 5% 2-tailed alpha, and a non-inferiority margin of 3% (assuming an event rate of 10%).[12] All other endpoints were adjudicated according to relevant Academic Research Consortium (ARC) definitions.[13]

For the purpose of the present analysis, we distinguished explicitly patients with stable CAD, patients with NSTEACS, including both UA and NSTEMI, and patients with STEMI. Relevant and guideline-sanctioned definitions were used for this classification.[14] On top of the original primary endpoint of DOCE, we also collected details on major adverse cardiac events (MACE, defined as the composite of all-cause death, MI related to the target vessel, or target vessel revascularization [TVR]), and patient-oriented composite outcomes (POCE, defined as the composite of all-cause death, any MI, or any revascularization), as well as death, cardiac death, MI, TLR, TVR, non-TVR, repeat PCI, coronary artery bypass grafting (CABG), definite stent thrombosis, probable stent thrombosis and definite or probable stent thrombosis, and repeat coronary angiography. All events were adjudicated and classified by a committee blinded to treatment allocation.

Descriptive analysis was based computing mean±standard deviation for continuous variables and count (%) for categorical variables. Bivariate analysis was based on analysis of variance for continuous variables and Fisher exact test for categorical variables. Survival analysis was based on the Kaplan-Meier method, and the log-rank test. Several series of multivariable Cox proportional hazard analyses were conducted to explore the potential prognostic role of admission diagnosis, reporting hazard ratios (HR), with 95% confidence intervals. Statistical significance was set at the 2-tailed 0.05 level, without multiplicity adjustment. All computations were performed with Stat 13 (StataCorp, College Station, TX, USA).

## RESULTS

A total of 3002 patients were included, 1770 (59.0%) with stable CAD, 921 (30.7%) with NSTEACS, and 311 (10.4%) with STEMI (Table 1). Several baseline differences were already evident according to admission diagnosis, with individual with stable CAD reporting more frequently a history of hypertension, dyslipidemia, prior MI, prior CABG, and three-vessel disease, STEMI patients being younger, more commonly smokers, with larger body mass index, and worse systolic function, and patients with NSTEACS exhibiting a higher prevalence of female gender, diabetes mellitus (including insulin-dependent diabetes mellitus), and worse renal function (all $p<0.05$).

**Table 1.** Patient features. CAD=coronary artery disease; NSTEACS=non-ST-elevation acute coronary syndromes; STEMI=ST-elevation myocardial infarction.

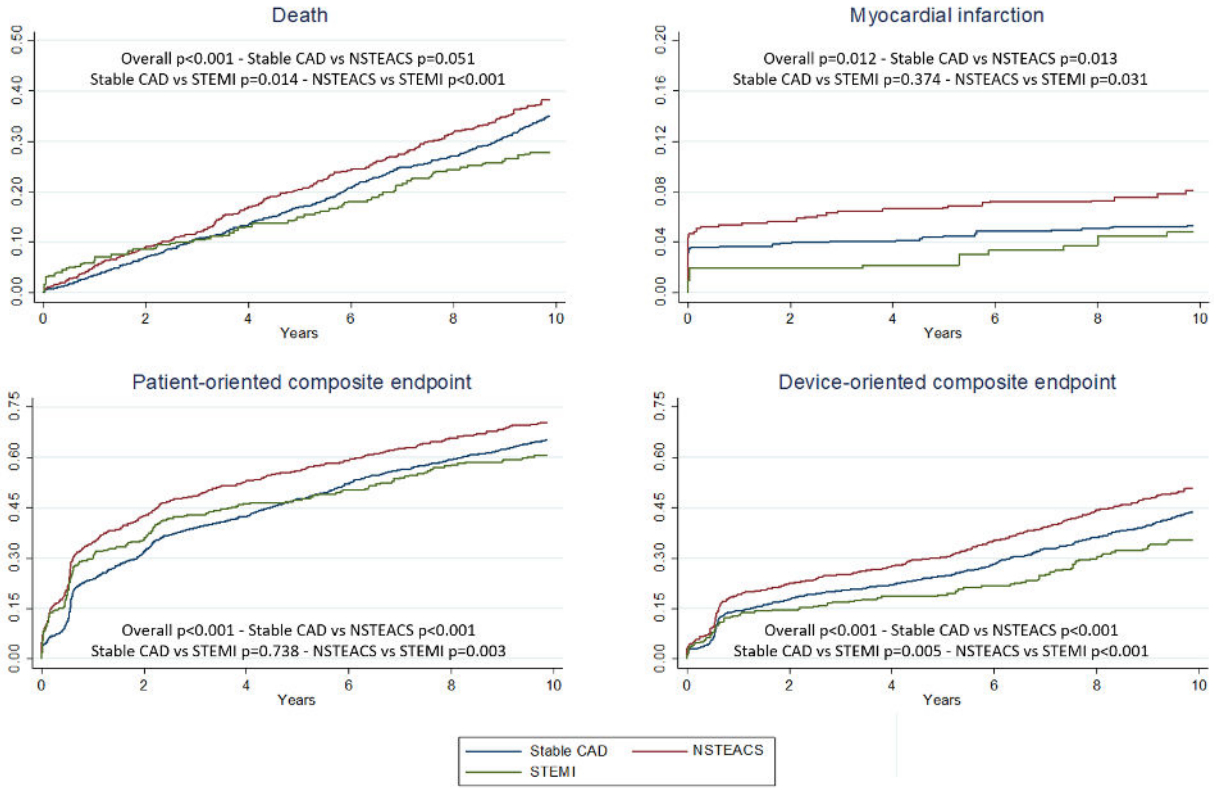
| Feature | Stable CAD | NSTEACS | STEMI | P value |
|---|---|---|---|---|
| Patients | 1770 | 921 | 311 | - |
| Age (years) | 68.1±10.5 | 68.5±11.1 | 64.3±13.3 | <0.001 |
| Female sex | 382 (21.6%) | 251 (27.3%) | 74 (23.8%) | 0.005 |
| Hypertension | 1234 (69.7%) | 630 (68.4%) | 138 (44.4%) | <0.001 |
| Diabetes mellitus | 529 (29.9%) | 277 (30.1%) | 64 (20.6%) | 0.002 |
| Insulin-dependent diabetes mellitus | 173 (9.8%) | 114 (12.4%) | 19 (6.1%) | 0.004 |
| Hypercholesterolemia | 1196 (67.6%) | 577 (62.7%) | 134 (43.1%) | <0.001 |
| Smoking | 236 (13.3%) | 178 (19.3%) | 109 (35.1%) | <0.001 |
| Dyslipidemia | 1196 (67.6%) | 577 (62.7%) | 134 (43.1%) | <0.001 |
| Body mass index ($kg/m^2$) | 27.8±4.5 | 27.4±4.7 | 28.0±4.4 | 0.043 |
| Glomerular filtration rate ($mL/min/1.73\ m^2$) | 74.6±21.7 | 71.9±23.1 | 78.1±3.1 | <0.001 |
| Prior myocardial infarction | 577 (32.6%) | 260 (28.2%) | 48 (15.4%) | <0.001 |
| Prior coronary artery bypass grafting | 190 (10.7%) | 80 (8.7%) | 14 (4.5%) | 0.001 |
| Ejection fraction (%) | 53.6±11.6 | 52.5±12.1 | 46.7±9.6 | <0.001 |
| Coronary artery disease extent | | | | <0.001 |
| 1-vessel disease | 244 (13.8%) | 151 (16.4%) | 94 (30.2%) | |
| 2-vessel disease | 452 (25.5%) | 228 (24.8%) | 91 (29.3%) | |
| 3-vessel disease | 1074 (60.7%) | 542 (58.9%) | 126 (40.5%) | |

Several significant differences were also found in lesion features (Table 2), including more calcified lesions, despite somewhat shorter lesions, in those with stable CAD, higher number of treated lesions per patient and more common involvement of the left anterior descending (LAD) in those with NSTEACS, and less common bifurcation involvement or chronic total occlusions, larger reference vessel diameters, smaller minimum lumen diameters (MLD), and greater diameter stenoses in patients with STEMI (all $p<0.05$). Nonetheless, adverse lesion features according to the historical American College of Cardiology/American Heart Association classification were more frequent in the STEMI group ($p<0.001$).

In terms of procedural features, lesions of those with stable CAD were dilated at higher pressure and received fewer stents, overlap rate was higher in the NSTEACS group, and lesion of STEMI patients received larger balloons and longer total stent length (all $p<0.05$). Acute results were quite favorable, also in terms of peri-procedural complications, despite some significant differences in post-procedural MLD favoring the STEMI group ($p=0.029$ for in-stent MLD, $p=0.031$ for in-segment MLD).

Long-term clinical outcomes are detailed in Table 3 and Figure 1, encompassing an average follow-up of 7.5±3.1 years. Notably, significant differences were found for all relevant outcomes, with the notable exclusion of CABG and stent thrombosis, irrespective of its definition. Indeed, DOCE, MACE, POCE, death, cardiac death, MI, repeat PCI, TLR, TVR, non-TVR, and repeat angiography were most common in the NSTEACS group (all $p<0.05$). Intriguingly, patients with STEMI had numerically lower event rates for all outcomes in comparison to both stable CAD and NSTEACS groups, except for TVR and ST. Notably, PF-DES were associated with similar clinical outcomes at long-term follow-up, overall as well as in patients with stable CAD, NSTEACS, or STEMI (Table 1S; Table 2S; Table 3S; Table 4S; Figure 2)(all $p>0.05$).

**Figure 1.** Failure curve analysis comparing patients with stable coronary artery disease (CAD), non-ST-elevation acute coronary syndromes (NSTEACS) and ST-elevation myocardial infarction (STEMI).




A series of multivariable Cox proportional hazard analysis models (Table 4), including all variables associated at bivariate analysis with POCE, suggested that, on top of established patient prognostic features such as age, diabetic status, renal function, systolic function, and CAD extent, NSTEACS as admission diagnosis still conferred an adverse prognostic effect, when compared to stable CAD (HR=1.20

[1.03-1.38], p=0.016), but not when compared to STEMI. Notably, forcing stent type in the multivariable model confirmed the lack of interaction between this variable and risk of POCE (HR=0.96 for PF-DES [0.84-1.10], p=0.560).

**Table 2.** Lesion features. ACC/AHA=American College of Cardiology/American Heart Association; CAD=coronary artery disease; NSTEACS=non-ST-elevation acute coronary syndromes; STEMI=ST-elevation myocardial infarction.

| Feature | Stable CAD | NSTEACS | STEMI | P value |
|---|---|---|---|---|
| Patients | 1770 | 921 | 311 | - |
| Lesions | 2543 | 1426 | 422 | - |
| Number of lesions per patient | 1.4±0.7 | 1.6±0.7 | 1.4±0.6 | <0.001 |
| Location* | | | | 0.001 |
| Left anterior descending | 1100 (43.3%) | 692 (48.5%) | 189 (44.8%) | |
| Left circumflex | 692 (27.2%) | 315 (22.1%) | 90 (21.3%) | |
| Right coronary artery | 751 (29.5%) | 419 (29.4%) | 143 (33.9%) | |
| Ostial location* | 502 (19.7%) | 305 (21.4%) | 81 (19.2%) | 0.401 |
| Bifurcation* | 733 (28.8%) | 407 (28.5%) | 85 (20.1%) | 0.001 |
| Chronic total occlusion* | 153 (6.0%) | 91 (6.4%) | 6 (1.4%) | <0.001 |
| ACC/AHA lesion type* | | | | <0.001 |
| A | 150 (5.9%) | 41 (2.9%) | 5 (1.2%) | |
| B1 | 648 (25.5%) | 247 (17.3%) | 48 (11.4%) | |
| B2 | 1270 (49.9%) | 763 (53.5%) | 162 (38.4%) | |
| C | 475 (18.7%) | 375 (26.3%) | 207 (49.1%) | |
| Moderate or severe calcification* | 934 (36.7%) | 490 (34.4%) | 107 (25.4%) | <0.001 |
| Lesion length (mm) * | 16.2±9.7 | 17.1±9.7 | 17.1±9.8 | 0.008 |
| Baseline reference vessel diameter (mm) * | 2.79±0.51 | 2.77±0.49 | 2.89±0.50 | <0.001 |
| Baseline minimum lumen diameter (mm) * | 0.98±0.47 | 0.86±0.49 | 0.59±0.57 | <0.001 |
| Baseline diameter stenosis (%)* | 65.1±14.5 | 69.3±15.7 | 79.6±18.9 | <0.001 |
| Balloon diameter (mm) * | 3.07±0.53 | 3.05±0.52 | 3.13±0.52 | 0.032 |
| Stents* | 1.7±0.7 | 1.8±0.6 | 1.8±0.7 | 0.008 |
| Overlapping stents* | 838 (33.0%) | 539 (37.8%) | 137 (32.5%) | 0.006 |
| Total stent length (mm) * | 25.9±12.3 | 26.2±11.9 | 27.5±13.0 | 0.047 |
| Maximum dilation pressure (ATM) * | 15.8±3.2 | 15.3±3.1 | 14.5±2.9 | <0.001 |
| Rotablation* | 12 (0.5%) | 5 (0.4%) | 0 | 0.339 |
| Stent loss* | 4 (0.2%) | 3 (0.2%) | 0 | 0.635 |
| Perforation* | 15 (0.6%) | 13 (0.9%) | 3 (0.7%) | 0.509 |
| Post-procedural in-stent minimum lumen diameter (mm) * | 2.55±0.48 | 2.54±0.47 | 2.61±0.51 | 0.029 |
| Post-procedural in-stent diameter stenosis (%)* | 12.0±7.3 | 11.7±7.4 | 12.6±9.9 | 0.083 |
| Post-procedural in-segment minimum lumen diameter (mm)* | 2.26±0.55 | 2.27±0.54 | 2.34±0.57 | 0.031 |
| Post-procedural in-segment diameter stenosis (%)* | 22.3±12.0 | 21.4±11.9 | 22.1±13.4 | 0.078 |

*per-lesion analysis

Exploratory landmark analysis for death, MI, POCE and DOCE showed the outlook of stable CAD, NSTEACS and STEMI was significantly different both within and after 1 year for death (respectively p=0.012 and p=0.001; Figure 1S), within 1 year for MI (p=0.015; Figure 2S), both within and after 1 year for POCE (respectively p<0.001 and p=0.020); Figure 3S), and both within and after 1 year for DOCE (respectively p=0.003 and p<0001; Figure 4S). Notably, after 1 year STEMI patients always showed a lower rate of adverse events than those with an admission diagnosis of stable CAD or NSTEACS.

**Figure 2:** Failure curve analysis of patient-oriented composite endpoint comparing polymer-free drug-eluting stents (PF-DES) versus durable polymer drug-eluting stents (DP-DES), in the overall population, and distinguishing patients with stable coronary artery disease (CAD), non-ST-elevation acute coronary syndromes (NSTEACS) and ST-elevation myocardial infarction (STEMI.

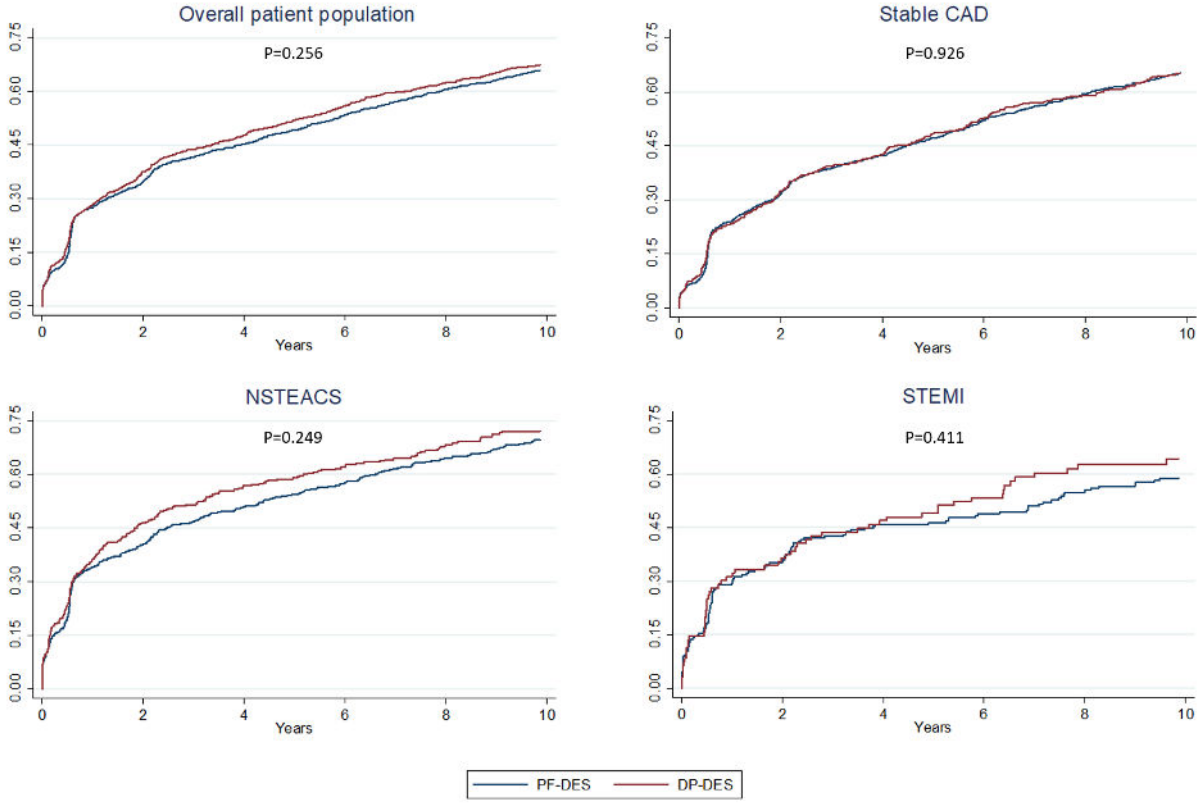
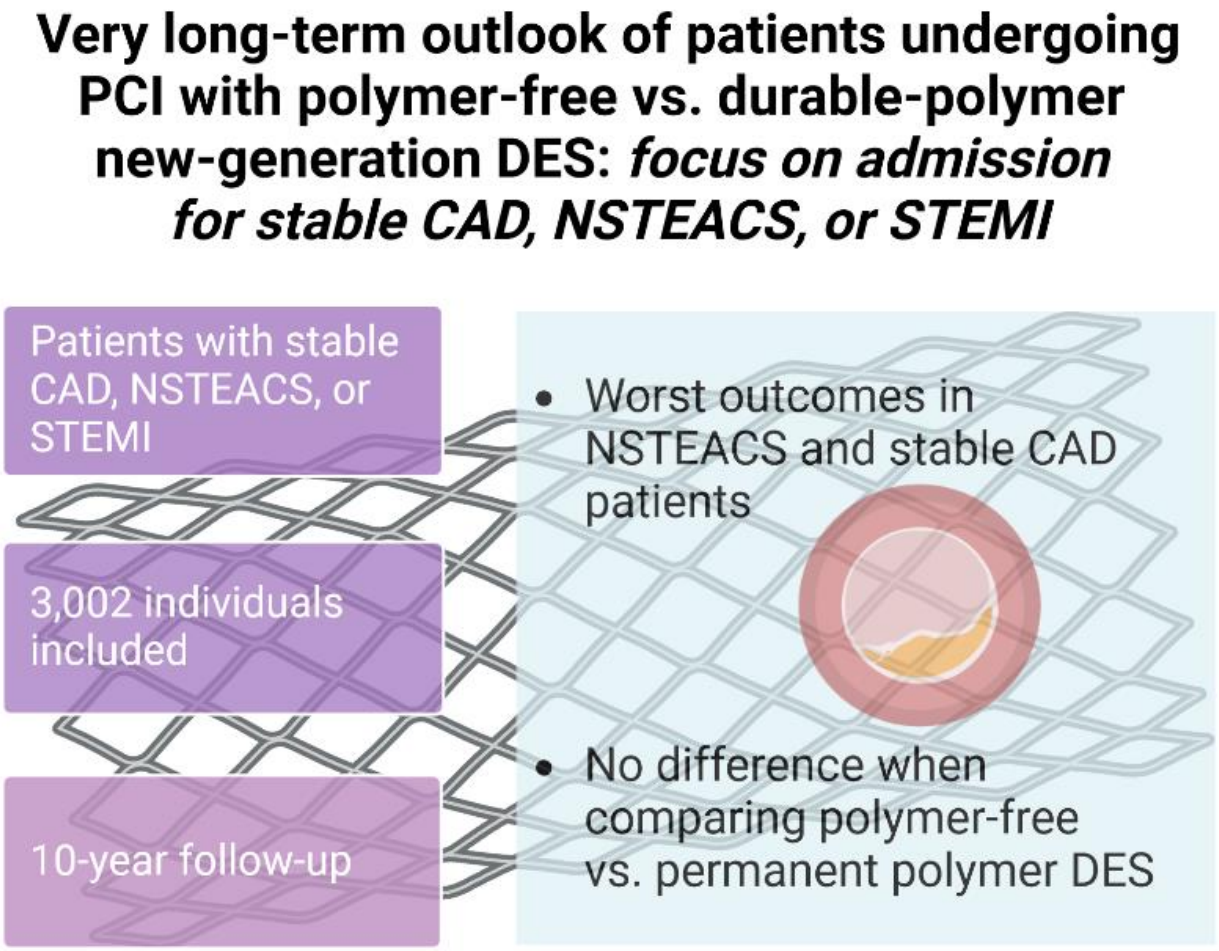



**Table 3.** Clinical outcomes. CAD=coronary artery disease; NSTEACS=non-ST-elevation acute coronary syndromes; STEMI=ST-elevation myocardial infarction.

| Variable | Stable CAD | NSTEACS | STEMI | P value |
|---|---|---|---|---|
| Patients | 1770 | 921 | 311 | - |
| Lesions | 2543 | 1426 | 433 | - |
| Follow-up (years) | 7.5±3.1 | 7.3±3.2 | 7.9±3.0 | 0.010 |
| Device-oriented composite outcome* | 964 (37.9%) | 637 (44.7%) | 133 (31.5%) | <0.001 |
| Major adverse cardiac events | 830 (46.9%) | 476 (51.7%) | 122 (39.2%) | <0.001 |
| Patient-oriented composite outcome | 1098 (62.0%) | 623 (67.6%) | 182 (58.5%) | 0.003 |
| Death | 571 (32.3%) | 330 (35.8%) | 79 (25.4%) | 0.003 |
| Cardiac death | 371 (21.0%) | 232 (25.2%) | 52 (16.7%) | 0.003 |
| Myocardial infarction | 81 (4.6%) | 63 (6.8%) | 11 (3.5%) | 0.016 |
| Coronary artery bypass grafting | 30 (1.7%) | 11 (1.2%) | 1 (0.3%) | 0.136 |
| Repeat percutaneous coronary intervention* | 473 (18.6%) | 313 (22.0%) | 73 (17.3%) | 0.018 |
| Target lesion revascularization* | 501 (19.7%) | 326 (22.9%) | 75 (17.8%) | 0.022 |
| Target vessel revascularization* | 631 (24.8%) | 438 (30.7%) | 108 (25.6%) | <0.001 |
| Non-target vessel revascularization* | 772 (30.4%) | 494 (34.6%) | 109 (25.8%) | 0.001 |
| Repeat coronary angiography | 1382 (78.1%) | 692 (75.1%) | 226 (72.7%) | 0.050 |
| Definite stent thrombosis* | 18 (0.7%) | 14 (1.0%) | 8 (1.9%) | 0.061 |
| Probable stent thrombosis* | 18 (0.7%) | 15 (1.1%) | 2 (0.5%) | 0.414 |
| Definite or probable stent thrombosis* | 36 (1.4%) | 29 (2.0%) | 10 (2.4%) | 0.164 |

*per-lesion analysis

**Figure 3:** Graphical summary of the study results (image generated with BioRender). CAD=coronary artery disease; DES=drug-eluting stent; NSTEACS=non-ST-elevation acute coronary syndromes; PCI=percutaneous coronary intervention; STEMI=ST-elevation myocardial infarction.




## DISCUSSION

This work, originally capitalizing on the long-term follow-up of a pivotal randomized trial on new-generation DES, showcases that unstable coronary artery disease, especially when presenting without ST-elevation, represents an informative marker of adverse long-term prognosis in current state-of-the-art invasive cardiology practice. Notably, NSTEACS was associated with an excess of most types of adverse events up to 10 years of follow-up, and this held true for key outcomes such as death, POCE and DOCE even after discounting events occurring within the first 12 months after the index procedure.

Coronary artery disease is clearly among the most researched after topic in modern medicine, and this depends on a number of factors, ranging from incidence to prevalence, as well as mortality and morbidity burden.[15-17] In addition, CAD has been considered often as a relatively homogenous condition, mainly due to the apparent consistencies in atherosclerotic pathophysiology.[18] However, this paradigm is only superficially true, as even patients and laypersons have recognized the subtleties that enable them to distinguish between ACS and stable CAD.[15,16] Irrespective of the implication on acute management (eg timely reperfusion for STEMI), there is ongoing debate on the importance of using presentation features and admission diagnosis to guide decision making and subsequent care, including advanced age and comorbidities.[19,20] This conundrum is further complicated by the evolution in definitions and appraisal of ACS (eg thanks to the ubiquitous adoption of ultra-sensitive cardiac troponin assays and invasive imaging technique), which tend to be more and more inclusive.[21,22]

**Table 4.** Multivariate Cox proportional hazard analysis for patient-oriented composite outcome. 95%CI=95% confidence interval. CAD=coronary artery disease; DES=drug-eluting stent; NSTEACS=non-ST-elevation acute coronary syndromes; STEMI=ST-elevation myocardial infarction.

| Variable | HR | 95%CI | P value |
|---|---|---|---|
| Model limited to variables with p≤0.10 | | | |
| Age (10-year increments) | 1.12 | 1.04-1.21 | 0.003 |
| Insulin-dependent diabetes mellitus | 1.57 | 1.28-1.92 | <0.001 |
| Smoking | 1.19 | 0.99-1.43 | 0.060 |
| Glomerular filtration rate (10 mL/min/1.73 m2 increments) | 0.96 | 0.92-1.00 | 0.037 |
| Left ventricular ejection fraction (10% increments) | 0.89 | 0.84-0.94 | <0.001 |
| Coronary artery disease extent | 1.46 | 1.33-1.60 | <0.001 |
| 2- vs 1-vessel disease | 1.70 | 1.38-2.11 | <0.001 |
| 3- vs 1-vessel disease | 2.25 | 1.85-2.73 | <0.001 |
| 3- vs 2-vessel disease | 1.32 | 1.13-1.54 | <0.001 |
| Admission diagnosis | | | |
| NSTEACS vs stable CAD | 1.19 | 1.03-1.38 | 0.016 |
| STEMI vs stable CAD | 1.17 | 0.94-1.46 | 0.152 |
| STEMI vs NSTEACS | 0.98 | 0.78-1.23 | 0.865 |
| Model limited to variables with p≤0.10 and stent type | | | |
| Age (10-year increments) | 1.12 | 1.04-1.21 | 0.003 |
| Insulin-dependent diabetes mellitus | 1.57 | 1.28-1.93 | <0.001 |
| Smoking | 1.19 | 0.99-1.43 | 0.063 |
| Glomerular filtration rate (10 mL/min/1.73 m2 increments) | 0.96 | 0.92-1.00 | 0.042 |
| Left ventricular ejection fraction (10% increments) | 0.89 | 0.84-0.94 | <0.001 |
| Coronary artery disease extent | 1.46 | 1.33-1.60 | <0.001 |
| 2- vs 1-vessel disease | 1.70 | 1.38-2.11 | <0.001 |
| 3- vs 1-vessel disease | 2.24 | 1.85-2.73 | <0.001 |
| 3- vs 2-vessel disease | 1.32 | 1.13-1.53 | <0.001 |
| Admission diagnosis | | | |
| NSTEACS vs stable CAD | 1.20 | 1.03-1.38 | 0.016 |
| STEMI vs stable CAD | 1.17 | 0.94-1.46 | 0.151 |
| STEMI vs NSTEACS | 0.98 | 0.78-1.23 | 0.870 |
| Polymer-free DES | 0.96 | 0.84-1.10 | 0.560 |

The ISAR-TEST 5 is a landmark randomized trial which has established the non-inferiority of PF-DES in comparison to DP-DES in a multifaceted patient population, with consistent results at 1, 5, and 10 years.[9,10-12,23] Similarly favorable findings for PF-DES were provided in several ISAR-TEST 5 substudies, including those focused on STEMI at 5 years, diabetes mellitus at 5 years and 10 years, and ACS at 10 years.[10,11,23] Indeed, Coughlan and colleagues provided an interesting comparative effectiveness analysis of PF-DES vs DP-DES in 2042 patients stemming from the ISAR-TEST 4 and 5 studies, with follow-up reaching as many as 10 years.[11] They found that PP-DES were possibly inferior to bioresorbable polymer DES (BP-DES), whereas the performance of PF-DES was reassuring. Indeed, in patients with ACS, BP-DES were associated with fewer POCE compared with new-generation PP-DES at 10 years. The relative frequencies of both device- and patient-related outcomes were comparable and reassuring in patients treated with PF-DES versus BP-DES at 10 years. However, in this report the emphasis was mostly on device-wise comparisons. We hereby expand such findings, by poignantly focusing on presentation-wise comparisons and the interaction between admission diagnosis and DES type. We intriguingly found that, notwithstanding complex background differences in baseline features, lesion characteristics, and procedural features, most clinical outcomes were significantly more frequent over very long-term follow-up in patients who had originally presented with NSTEACS. Such adverse outlook included an excess in DOCE, MACE, POCE, death, cardiac death, MI, and several revascularization subtypes. On a positive note, PF-DES proved similarly safe and effective in all patient subgroups, from stable CAD to NSTEACS and STEMI. However, on a less rosy perspective, the detrimental prognostic impact of NSTEACS, and to a lesser extent of stable

CAD, held true even when discounting events occurring within 1 year. Notably, it has previously been demonstrated that PF-DES are superior to BMS for patients with ACS undergoing PCI. In this analysis, the PF-DES group demonstrated comparable outcomes to the PP-DES group with respect to both the DOCE and POCE at 10 years.

In light of the present findings, and the totality of evidence, it is clear that a simple classification of patients with CAD distinguishing stable CAD, NSTEACS and STEMI still carries a substantial prognostic impact.[18,24] This clearly has to do with several confounding features and comorbidities, but most likely depends, at least partly, on differences in pathophysiology, such that STEMI typically has a more thrombotic (yet thus more sanctionable) mechanistic profile, than NSTEACS and stable CAD.[6,25] Accordingly, these results call for more aggressive and multifaceted interventions to improve long-term prognosis of patients with NSTEACS, including, for instance, potent antiplatelet agents (eg ticagrelor), low-dose novel oral anticoagulants, combination lipid-lowering therapies, and novel anti-diabetic drugs with pleiotropic effects. The favorable results up to 10 years of follow-up for PF-DES, irrespective of admission diagnosis, reinforce the validity of this technological concept, and is a further proof that a metallic platform capable of providing mechanical scaffolding, combined with sirolimus (anti-restenotic) and probucol (anti-inflammatory) drug recipe, is a unique combination to provide favorable clinical results in all patients undergoing PCI, and also optimally engineered for short-term dual antiplatelet therapy regimens.[15,16,26] The polymer free concept appears futuristic and proves a good alternative to PP-DES.

Despite this work strengths, several key limitations can be identified. First, being this a very long-term follow-up study, management strategies (eg antithrombotic therapy) which appeared appropriate 10 years ago would be considered obsolete nowadays.[27] Second, evolution in techniques, lesion appraisal, and imaging support has been momentous, and thus it is likely that current standards of PCI could translate into improved short and long-term clinical outcomes, irrespective of admission diagnosis and DES type.[28] Third, the mandatory angiographic follow-up before 1 year could have increased event rates, leading to repeat revascularization in otherwise asymptomatic or paucisymptomatic patients.[29] Most importantly, this is an very long-term substudy with exploratory and hypothesis-generating scope, and thus its findings should be corroborated in other series.

In conclusion, NSTEACS represents an informative marker of adverse long-term prognosis. Utmost care should be paid to such patients, irrespective of early favorable clinical outlook, ensuring state-of-the-art techniques, devices, and medical management are routinely and proactively adopted. Notably, even considering admission diagnosis, and despite using no polymer, polymer-free DES showed similar results with regards to safety and efficacy when compared with DES with permanent polymer. The role of probucol, as an alternative to polymers, for the optimum drug release stands proven and it may be used to create more polymer free platforms in future. VIVO ISAR represents the future of DES technologies aiming at minimizing risk and maximizing efficacy and effectiveness.

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