# Use of prasugrel vs clopidogrel and outcomes in diabetic patients presenting with acute coronary syndrome undergoing percutaneous coronary intervention

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ABBREVIATIONS

ACS acute coronary syndrome

CABG coronary artery bypass graft

CKD chronic kidney disease

DM diabetes mellitus

MACE major adverse cardiac events

MI myocardial infarction

PCI percutaneous coronary intervention

ABSTRACT

BACKGROUND

Patients with diabetes mellitus (DM) have a higher risk of thrombotic events after PCI. Clinical trial data and observational studies suggest superiority of prasugrel over clopidogrel in patients with DM. However, the use, safety and efficacy profile of prasugrel in unselected patients with DM presenting with acute coronary syndromes (ACS) remains unclear.

METHODS

The PROMETHEUS study was a retrospective multicenter observational study of 19,919 ACS PCI patients enrolled from 8 US centers between 2010 and 2013. The primary endpoint was 90-day major adverse cardiovascular events (MACE), comprising all-cause death, myocardial infarction, stroke or unplanned revascularization. The safety endpoint was bleeding requiring hospitalization**.**

RESULTS

We identified 7,580 (38%) subjects with and 12,329 (62%) without diabetes mellitus. Patient with diabetes were older, had significantly higher rates of hypertension, dyslipidemia and prior history of myocardial infarction and were more likely to have complex coronary artery disease. They more frequently were treated with second generation drug eluting stents (70.3% vs 66.7% in non-diabetics). However, the use of prasugrel was lower in diabetic patients compared to non-diabetics (18.2% vs 21.7 %). In addition, the use of prasugrel did not increase with the severity of the clinical presentation in diabetics as opposed to the non-diabetic population where prescription of prasugrel was higher in NSTEMI and STEMI respectively compared to unstable angina. At 90 days and 1 year after PCI the risk of major adverse cardiac events was greater in those with diabetes (at 1 year: 22.7% vs. 16.5%; HR 1.22 [1.14-1.33], p<0.001). At 1 year, the risk of bleeding events was also higher in diabetics than non-diabetics (4.9% vs. 4.1%, HR 1.19 [1.01-1.39], p=0.035). Prasugrel use was associated with lower unadjusted rates of MACE and bleeding events in both diabetics and non-diabetics. After multivariable adjustment, use of prasugrel was associated with a lower risk of death in diabetic patients both at 90 days and 1 year and with a lower risk of MACE, death and revascularization in non-diabetics at 1 year.

CONCLUSIONS

Use of prasugrel in diabetic patients with PCI-treated ACS was lower than in non-diabetics despite their high- risk profile and the severity of their clinical presentation. After multivariable adjustment, use of prasugrel was associated with a lower risk of 90-day death in diabetic patients.

INTRODUCTION

Patients with diabetes mellitus presenting with acute coronary syndromes have a higher risk of short and long-term outcomes compared with non-diabetics(1-3). This can be in part attributed to the several comorbidities often associated with diabetes such as obesity, hypertension, hypercholesterolemia and chronic kidney disease that increase the risk of cardiovascular events in these patients. In addition, diabetes has been associated with a proinflammatory and prothrombotic environment with greater platelet reactivity than in non-diabetics (7,8). Therefore, patients with diabetes can benefit from a strict control of cardiovascular risk factors and treatment with potent P2Y12 inhibitors for the secondary prevention of cardiovascular events(4).

A subanalysis of the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction 38 (TRITON-TIMI 38) showed that prasugrel significantly reduces the rate of the primary composite endpoint of cardiovascular mortality, myocardial infarction, and stroke at 15 months compared with clopidogrel in patients with diabetes(5). In part, the higher efficacy of prasugrel can be explained by the results of in vitro studies which showed a greater platelet inhibition with prasugrel compared to double dose of clopidogrel(6).

Despite the increasing evidence from randomized trials and observational studies on novel P2Y12 inhibitors, in the general population clopidogrel remains the most commonly prescribed antiplatelet agent together with aspirin because of its cost, widespread availability and its safe bleeding profile(7).

Here, we use an all-comer multicenter prospective registry of patients presenting with acute coronary syndrome to describe the use of prasugrel and clopidogrel in diabetic and non-diabetic patients after percutaneous coronary intervention (PCI). In addition, we investigate the short and long term clinical outcomes by diabetic status and by the use of clopidogrel vs prasugrel.

Methods

Study population

Prometheus is a multicenter prospective registry comprising 19,914 patients who presented with acute coronary syndrome and were treated with PCI between January 2010 and June 2013 in the 8 enrolling centers. The study was approved by the ethics committees of all centers. The primary endpoint of this study was major adverse cardiac events at 90 days(8). The choice of P2Y12 inhibitor was at the discretion of the treating physicians, but all patients were discharged on either prasugrel or clopidogrel. Data management, quality checks, statistical analyses, and results reporting were the responsibility of the data coordinating center at the Icahn School of Medicine at Mount Sinai (New York, New York). Study sponsors (Daiichi Sankyo and Eli Lilly) did not have access to data. For the purpose of this analysis, the study population was divided into 2 groups based on diabetic status and was followed for 1 year.

Endpoint definitions

The primary clinical endpoint was a composite of major adverse cardiac events (MACE), including all-cause death, non-fatal myocardial infarction (MI), stroke or unplanned coronary revascularization at 90 days from index hospital PCI. The secondary endpoints included individual components of MACE and major bleeding events. The primary safety endpoint was major bleeding, defined as any clinically overt hemorrhage requiring hospitalization or blood transfusion. The rate of clinical endpoints was assessed at 90 days and 1 year after index PCI using data obtained from electronic medical records.

Statistical analysis

Continuous variables are reported as mean ± SD and were compared between the study groups using Student’s t-test. Categorical variables were reported as percentages and compared with the χ2test. The cumulative incidence of adverse events was calculated as a Kaplan-Meier estimate of time to first event and groups were compared using log-rank test. To evaluate the adjusted associations between diabetes and clinical outcomes, hazard ratios were calculated using Cox proportional hazards regression. The variables used in the model include: age, gender, body mass index, race, hypertension, hypercholesterolemia, smoking habit, chronic kidney disease, prior MI, prior percutaneous coronary intervention, congestive heart failure, stent type used (bare metal stent vs drug-eluting stent), multivessel disease, clinical presentation (unstable angina, NSTEMI and ST elevation MI[STEMI]), and participating center. The 1-year rates of MACE and bleeding events were presented using Kaplan Meier curves and were compared by means of log-rank test.

To evaluate the association between treatment groups (clopidogrel vs prasugrel) and clinical outcomes in both DM and non-DM patients we used multivariable Cox regression models with the dependent outcome as treatment with prasugrel (vs clopidogrel). The model included the following covariates: age, gender, race, body mass index, hypertension, hypercholesterolemia, smoking habit, chronic kidney disease, prior MI, prior percutaneous coronary intervention, congestive heart failure, stent type used (bare metal stent vs drug eluting stent), multivessel disease, clinical presentation and participating center. All data were analyzed using Stata version 14.0 (StataCorp, College Station, Texas) or SAS version 9.4 (SAS Institute, Cary, North Carolina); p values < 0.05 were considered significant.

Results

Out of 19,909 patients included in our registry, 7,580 (38%) subjects had DM while 12,329 (62%) did not. Baseline characteristics of the study population are presented in table 1. Patients with DM were older, more often male, and had higher rates of cardiovascular risk factors such as hypercholesterolemia, obesity, hypertension and chronic kidney disease. They more frequently had a history of myocardial infarction, coronary revascularization, heart failure and cerebrovascular disease. Unstable angina was the most common clinical presentation in diabetics. Angiographically, patients with diabetes were more likely to present with multivessel disease, complex B2/C lesions and required significantly longer stents. Diabetic patients were treated with second generation DES in 70.3% of cases vs only 66.7% in their non-diabetic counterparts (Table 2). The use of prasugrel was overall 18.2% in patients with diabetes vs 21.7 in non-diabetics. Use of prasugrel progressively increased with the severity of the clinical presentation in non-diabetics, being the lowest in unstable angina and the highest in STEMI. In contrast, in patients with diabetes use of prasugrel did not change with presentation (Table 3). In-hospital events were rare. Nevertheless, the rate of in hospital death (0.5% vs 0.3%, p=0.03) renal insufficiency requiring dialysis (0.4% vs 0.1%, p>0.001) and blood transfusion (3.4% vs 2.1%, p>0.001) was higher in diabetics than non-diabetics. At 90 days, presence of diabetes was associated with a higher adjusted risk of MACE, all cause death and clinically driven revascularization (Fig 1 A). Similarly, at 1 year, diabetes was associated with a higher risk of all ischemic outcomes, including MI and a higher risk of major bleeding events (Fig 1 B).

Irrespective of the presence or absence of diabetes, patients treated with clopidogrel were older, more often female and had higher rates of hypertension, prior MI, prior PCI and CABG compared to those treated with prasugrel. They were also more likely to receive a bare metal stent or a first-generation drug eluting stent (supplementary tables 1-2). When looking at unadjusted rates of MACE and bleeding events based on antiplatelet use, patients with diabetes on clopidogrel had the most episodes followed by non-diabetics on clopidogrel. Among patients treated with prasugrel, those without diabetes had lower unadjusted rates of bleeding and ischemic events throughout the 1 year follow up (Figure 2). After multivariate adjustment, use of prasugrel was associated with a similar risk of 90-day ischemic and bleeding events as clopidogrel in non-diabetics. There was a significant association between prasugrel use and lower adjusted risk of 90-day death in diabetic patients (Table 4). At 1 year follow up, use of prasugrel was associated with a significantly lower risk of MACE, death and revascularization in patients without diabetes. In diabetics, at 1 year, prasugrel use was only associated with lower risk of death. A significant interaction was found for 1-year MACE and both 90 day and 1-year revascularization: use of prasugrel was significantly associated with a reduced risk of MACE and revascularization in non-diabetics but not in diabetic patients (Table 5).

Discussion

We describe the patterns of prasugrel use after PCI in a contemporary all comer population of acute coronary syndrome patients with and without DM. Key findings are the following: 1) patients with diabetes were older and had significantly more cardiovascular risk factors and comorbidities compared to non-diabetics; 2) diabetic patients had more complex coronary artery disease and were more frequently treated with second generation drug eluting stents, 3) however, diabetics were significantly less likely to receive prasugrel compared to non-diabetics; 4) while in non-diabetics the use of prasugrel increased with the severity of the clinical presentation, from unstable angina to NSTEMI and STEMI, the rate of prasugrel prescription remained constant in the diabetic population regardless of the clinical presentation; 5) at 90 days and 1 year after PCI, diabetes was associated with a higher risk of ischemic events while the association with increased risk of major bleeding events became apparent only at 1 year follow up; 6) the unadjusted incidence of both MACE and major bleeding events was higher in diabetic patients on clopidogrel compared to those treated with prasugrel; 7) irrespective of the presence of diabetes, patient treated with prasugrel were older and had higher rates of cardiovascular risk factors than patients treated with prasugrel; 8) after adjusting for confounding factors, the use of prasugrel as compared to clopidogrel was associated with reduced rates of 90-day and one-year death in diabetics and with reduced rates of one-year MACE, death, and revascularization in non-diabetics.

It is well known that diabetes generates a systemic proinflammatory and prothrombotic state that predisposes to ischemic events(9). Several studies have reported a higher incidence of both primary and secondary cardiovascular events in diabetic patients. Current treatment strategies for the secondary prevention of cardiac events might be less efficacious in these patients than in non-diabetics. For instance, the Optimizing Antiplatelet Therapy in Diabetes Mellitus (OPTIMUS) trial, showed that almost two thirds of diabetic patients with stable coronary artery disease on chronic treatment with aspirin and clopidogrel were hyporesponders to clopidogrel(10). Conversely, prasugrel was shown to provide greater platelet inhibition in vitro compared to high dose clopidogrel. A subanalysis of the TRITON-TIMI 38 trial reported a significantly lower rate of ischemic adverse events in diabetic patients treated with prasugrel than in clopidogrel treated subjects in the absence of an excess of major bleeding events(5). Importantly, the benefit margin conferred by prasugrel with regards to ischemic events was greater in diabetic patients than in nondiabetics. Still, real world data from prospective registries do not consistently show a significant difference in outcomes between clopidogrel and prasugrel treated patients(11,12).

The discrepancy between clinical trial and real-world data might be explained with the lower and selected use of prasugrel outside clinical trials (7). Our data, for instance, show a lower use of prasugrel in ACS patients with diabetes regardless of the severity of the clinical presentation. Data from Blue Cross/Blue Shield database and from the National Cardiovascular Data Registry (NCDR) ACTION Registry have shown a progressive increase in prasugrel use from 2009 when the drug was first approved by the FDA for use in patients with ACS(13,14). For example, data from the NCDR ACTION Registry reported an increase in prasugrel prescription from 3% in 2009 to 18% in 2012(13). This slow but progressive change might reflect an increasing familiarity with prasugrel use among physicians. Some of the barriers to the uptake of prasugrel include the increased risk of bleeding events and its contraindication in patients with prior cerebrovascular events. In addition, the higher cost of novel P2Y12 inhibitors contributes to their lower use outside clinical trials. Nevertheless, a recent study conducted among Veterans Administration hospitals confirmed a lower utilization of prasugrel despite the substantially uniform coverage in the veteran population(15).

Our data confirm a higher rate of ischemic events in diabetic patients after PCI, with the risk increasing over time from 90 days to 1 year. Importantly, we also described a higher rate of major bleeding events in diabetics. This finding is in contrast with prior reports which showed comparable 1-year rates of bleeding events in patients with and without diabetes(16). The increased risk of bleeding in our study population became evident at 1 year follow up. That might reflect a greater compliance to DAPT after PCI in diabetic patients or a longer physician directed DAPT duration in diabetics compared to non-diabetics which would put diabetic patients at higher risk of long term major bleeding(17). The observation of a comparable risk of bleeding with a greater risk of ischemic events at 90 days would warrant increased use of prasugrel in diabetic patients at least in the first months after PCI. When looking at outcomes by thienopyridine type we observed an association between prasugrel use and lower risk of death in diabetics at 90 days. A 1 year follow up the association became significant for a lower risk of MACE, death and revascularization in non-diabetics. Interestingly, the risk of bleeding events was unchanged regardless of the thienopyridine used. These data should be interpreted with caution due to the small sample size of prasugrel treated patients. However, they also suggest that when prescribing prasugrel, physicians might be selecting the patients with higher ischemic risk and lower bleeding risk.

This study has several limitations. The use of P2Y12 inhibitors after discharge was not recorded and compliance to treatment was not verified. No data were obtained on insurance and socioeconomic status. The choice of p2Y12 inhibitor was at the discretion of the treating physician but the reasons for the choice were not collected. This study was not randomized, therefore any comparison in outcomes between prasugrel and clopidogrel treated patients should be carefully interpreted.

Conclusions

Patients with diabetes more frequently present with comorbidities and complex coronary artery disease which translates to a greater risk of ischemic clinical outcomes compared to non-diabetics at both 90 days and 1 year after PCI. Nevertheless, prasugrel is less frequently prescribed in diabetic patients regardless of their clinical presentation. Use of prasugrel was associated with a lower risk of death in diabetics at 90 days. The association extended to non-diabetics at 1 year follow-up. No significant difference was found in the risk of bleeding regardless of the thienopyridine used.

References

1. Jensen LO, Maeng M, Thayssen P et al. Influence of diabetes mellitus on clinical outcomes following primary percutaneous coronary intervention in patients with ST-segment elevation myocardial infarction. Am J Cardiol 2012;109:629-35.

2. Donahoe SM, Stewart GC, McCabe CH et al. Diabetes and mortality following acute coronary syndromes. JAMA 2007;298:765-75.

3. Farhan S, Baber U, Vogel B et al. Impact of Diabetes Mellitus on Ischemic Events in Men and Women After Percutaneous Coronary Intervention. Am J Cardiol 2017;119:1166-1172.

4. James S, Angiolillo DJ, Cornel JH et al. Ticagrelor vs. clopidogrel in patients with acute coronary syndromes and diabetes: a substudy from the PLATelet inhibition and patient Outcomes (PLATO) trial. European heart journal 2010;31:3006-16.

5. Wiviott SD, Braunwald E, Angiolillo DJ et al. Greater clinical benefit of more intensive oral antiplatelet therapy with prasugrel in patients with diabetes mellitus in the trial to assess improvement in therapeutic outcomes by optimizing platelet inhibition with prasugrel-Thrombolysis in Myocardial Infarction 38. Circulation 2008;118:1626-36.

6. Dridi NP, Johansson PI, Clemmensen P et al. Prasugrel or double-dose clopidogrel to overcome clopidogrel low-response--the TAILOR (Thrombocytes And IndividuaLization of ORal antiplatelet therapy in percutaneous coronary intervention) randomized trial. Platelets 2014;25:506-12.

7. Sheikh Rezaei S, Geroldinger A, Heinze G, Reichardt B, Wolzt M. Clopidogrel, prasugrel, or ticagrelor use and clinical outcome in patients with acute coronary syndrome: A nationwide long-term registry analysis from 2009 to 2014. Int J Cardiol 2017;235:61-66.

8. Baber U, Sartori S, Aquino M et al. Use of prasugrel vs clopidogrel and outcomes in patients with acute coronary syndrome undergoing percutaneous coronary intervention in contemporary clinical practice: Results from the PROMETHEUS study. Am Heart J 2017;188:73-81.

9. Isordia-Salas I, Galvan-Plata ME, Leanos-Miranda A et al. Proinflammatory and prothrombotic state in subjects with different glucose tolerance status before cardiovascular disease. J Diabetes Res 2014;2014:631902.

10. Franchi F, Rollini F, Aggarwal N et al. Pharmacodynamic Comparison of Prasugrel Versus Ticagrelor in Patients With Type 2 Diabetes Mellitus and Coronary Artery Disease: The OPTIMUS (Optimizing Antiplatelet Therapy in Diabetes Mellitus)-4 Study. Circulation 2016;134:780-92.

11. Benjamin MM FG, Pollock BD, Sass DM and Schussler JM. Long Term Efficacy of Prasugrel versus Clopidogrel in Patients undergoing Percutaneous Coronary Intervention and Anticoagulated with Bivalirudin. Int J Cardiovas Res 2016;5.

12. Wang TY. TRANSLATE-ACS (Treatment With ADP Receptor Inhibitors: Longitudinal Assessment Of Treatment Patterns and Events After Acute Coronary Syndrome). PT 2014;39:790-791.

13. Sherwood MW, Wiviott SD, Peng SA et al. Early clopidogrel versus prasugrel use among contemporary STEMI and NSTEMI patients in the US: insights from the National Cardiovascular Data Registry. J Am Heart Assoc 2014;3:e000849.

14. Sandhu A, Seth M, Dixon S et al. Contemporary use of prasugrel in clinical practice: insights from the Blue Cross Blue Shield of Michigan Cardiovascular Consortium. Circ Cardiovasc Qual Outcomes 2013;6:293-8.

15. Aggarwal V, Armstrong EJ, Liu W et al. Prasugrel Use Following PCI and Associated Patient Outcomes: Insights From the National VA CART Program. Clin Cardiol 2016;39:578-584.

16. Grodzinsky A, Arnold SV, Wang TY et al. Bleeding risk following percutaneous coronary intervention in patients with diabetes prescribed dual anti-platelet therapy. Am Heart J 2016;182:111-118.

17. Faggioni M, Baber U, Sartori S et al. Incidence, Patterns, and Associations Between Dual-Antiplatelet Therapy Cessation and Risk for Adverse Events Among Patients With and Without Diabetes Mellitus Receiving Drug-Eluting Stents: Results From the PARIS Registry. JACC Cardiovasc Interv 2017;10:645-654.

Figure legends

Figure 1. **Adjusted risk of 90-day (A) and 1-year (B) outcomes in patients with and without diabetes.** At 90 days, DM was significantly associated with a higher incidence of MACE, death and revascularization. At 1 year the association between DM and the risk of all ischemic and bleeding outcomes became significant. Non-diabetics are used as reference. DM, diabetes mellitus; MACE, major adverse cardiac events. HR, Hazard ratio; CI, confidence interval

Figure 2. **Unadjusted rate of 1-year MACE (A) and bleeding events (B) in patients with and without diabetes based on the use of either prasugrel or clopidogrel.** Presence of diabetes was associatedwith a higher unadjusted rate of MACE and major bleeding events in both clopidogrel and prasugrel treated patients. Clop, clopidogrel; DM, diabetes mellitus; Pras, prasugrel; MACE, major adverse cardiac events.

Table 1. Baseline characteristics in patients with and without diabetes mellitus. BMI, body mass index; CABG, coronary artery bypass graft; CAD, coronary artery disease; NSTEMI, non-ST elevation myocardial infarction; PAD, peripheral artery disease; STEMI, ST segment elevation myocardial infarction.

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|  | **No Diabetes  12329 (62.0%)** | **Diabetes  7580 (38.0%)** | **P value** |
| Age, years | 64.03 ± 12.80 | 65.00 ± 11.33 | <0.0001 |
| Sex (female), n (%) | 3498 (28.4%) | 2804 (37.0%) | <0.0001 |
| BMI (kg/m2) | 28.95 ± 5.68 | 31.50 ± 6.62 | <0.0001 |
| Diabetes on insulin | n/a | 2534 (33.4%) | n/a |
| Hypertension, n (%) | 9337 (75.7%) | 7044 (92.9%) | <0.0001 |
| Hypercholesterolemia, n (%) | 9690 (78.6%) | 6999 (92.3%) | <0.0001 |
| Baseline creatinine, mg/dl | 1.08 ± 0.77 | 1.38 ± 1.41 | <0.0001 |
| Smoking, n (%) | 3526 (28.6%) | 1480 (19.5%) | <0.0001 |
| Family history of CAD, n (%) | 3841 (31.2%) | 2351 (31.0%) | 0.83 |
| Previous myocardial infarction, n (%) | 3337 (27.1%) | 2626 (34.6%) | <0.0001 |
| Previous PCI, n (%) | 2835 (23.0%) | 2203 (29.1%) | <0.0001 |
| Previous CABG, n (%) | 1696 (13.8%) | 1737 (22.9%) | <0.0001 |
| Prior PAD, n (%) | 1208 (9.8%) | 1223 (16.1%) | <0.0001 |
| Prior Cerebrovascular Disease, n (%) | 1203 (9.8%) | 1182 (15.6%) | <0.0001 |
| CAD Presentation |  |  | <0.0001 |
| Unstable Angina, n (%) | 6374 (51.7%) | 4838 (63.8%) |  |
| NSTEMI, n (%) | 3448 (28.0%) | 1963 (25.9%) |  |
| STEMI, n (%) | 2507 (20.3%) | 778 (10.3%) |  |

Table 2. Procedural characteristics in patients with and without diabetes mellitus. BMS, bare metal stent; DES, drug eluting stent; GPIIb/IIIa, glycoprotein IIb/IIIa; LAD, Left anterior descending artery; LMWH, low molecular weight heparin; PCI, percutaneous coronary intervention; RCA, right coronary artery.

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|  | **No Diabetes  12329 (62.0%)** | **Diabetes  7580 (38.0%)** | **P value** |
| Multivessel disease, n (%) | 4645 (37.7%) | 3751 (49.5%) | <0.0001 |
| PCI vessel |  |  |  |
| Left main, n (%) | 348 (2.8%) | 319 (4.2%) | <0.0001 |
| LAD, n (%) | 5624 (45.6%) | 3269 (43.1%) | <0.001 |
| Circumflex, n (%) | 3387 (27.5%) | 2505 (33.0%) | <0.0001 |
| RCA, n (%) | 4319 (35.0%) | 2477 (32.7%) | <0.001 |
| At least 1 type B2/C lesion, n (%) | 8253 (66.9%) | 5349 (70.6%) | <0.0001 |
| Bifurcation lesion, n (%) | 1306 (10.6%) | 816 (10.8%) | 0.80 |
| Moderate/severe calcifications, n (%) | 1599 (13.0%) | 1172 (15.5%) | <0.0001 |
| Total stent length, mm | 29.81 ± 19.97 | 32.11 ± 21.99 | <0.0001 |
| Minimum stent diameter, mm | 2.99 ± 0.50 | 2.92 ± 0.49 | <0.0001 |
| At least one BMS, n (%) | 2984 (24.2%) | 1511 (19.9%) | <0.0001 |
| At least one DES (1st gen), n (%) | 1696 (13.8%) | 1096 (14.5%) | 0.16 |
| At least one DES (2nd gen), n (%) | 8228 (66.7%) | 5328 (70.3%) | <0.0001 |
| Procedural anticoagulation |  |  |  |
| Bivalirudin, n (%) | 8667 (70.3%) | 5798 (76.5%) | <0.0001 |
| GPIIb/IIIa inhibitor, n (%) | 3147 (25.5%) | 1416 (18.7%) | <0.0001 |
| LMWH, n (%) | 149 (1.2%) | 58 (0.8%) | 0.001 |

Table 3. Use of prasugrel in patients with and without diabetes based on clinical presentation, (unstable angina, NSTEMI and STEMI). NSTEMI, non-ST elevation myocardial infarction; STEMI, ST elevation myocardial infarction

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|  | **Patients treated with prasugrel, n (%)** | | |  |
| Clinical presentation | **Diabetes** | **No diabetes** | **P value** | |
| Unstable angina, n (%) | 868 (17.9 %) | 1257 (19.7%) | 0.02 | |
| NSTEMI, n (%) | 369 (18.8%) | 790 (22.9%) | <0.0001 | |
| STEMI, n (%) | 145 (18.6%) | 628 (25.0%) | <0.0001 | |

Table 4. Ninety-day clinical outcomes stratified by diabetic status and thienopyridine type. Clop, clopidogrel; HR, hazard ratios; MACE, major adverse cardiac events; pras, prasugrel, P inter, p for interaction; HR, Hazard ratio; CI, confidence interval

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| --- | --- | --- | --- | --- | --- | --- | --- |
|  | **No Diabetes** | | **HR [CI 95%]** | **Diabetes** | | **HR [CI 95%]** | **P inter.** |
|  | **Clop** | **Pras** | **Clop** | **Pras** |
| MACE | 809 (9.0) | 119 (4.7) | 0.86 [0.70-1.06] | 606 (10.5) | 97 (7.5) | 1.05 [0.82-1.33] | p=0.09 |
| Death | 207 (2.3) | 15 (0.6) | 0.82 [0.47-1.43] | 201 (3.5) | 8 (0.6) | 0.41 [0.19-0.89] | p=0.28 |
| Myocardial infarction | 333 (3.7) | 43 (1.7) | 0.80 [0.57-1.13] | 229 (4.0) | 31 (2.4) | 0.95 [0.62-1.44] | p=0.50 |
| Revascularization | 345 (4.0) | 70 (2.9) | 0.88 [0.66-1.16] | 241 (4.3) | 68 (5.3) | 1.36 [1.00-1.85] | P<0.01 |
| Major bleeding | 274 (3.0) | 46 (1.8) | 0.90 [0.64-1.25] | 168 (2.9) | 29 (2.2) | 1.18 [0.76-1.86] | p=0.32 |

Table 5. One-year clinical outcomes stratified by diabetic status and thienopyridine type. Clop, clopidogrel; HR, hazard ratios; MACE, major adverse cardiac events; pras, prasugrel, P inter, p for interaction; HR, Hazard ratio; CI, confidence interval

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|  | **No Diabetes** | | **HR [CI 95%]** | **Diabetes** | | **HR [CI 95%]** | **P inter.** |
|  | **Clop** | **Pras** | **Clop** | **Pras** |
| MACE | 1568 (18.4) | 228 (9.6) | 0.75 [0.65-0.87] | 1298 (24.1) | 205 (16.9) | 0.96 [0.82-1.13] | p<0.01 |
| Death | 449 (5.4) | 32 (1.4) | 0.63 [0.43-0.91] | 452 (8.6) | 30 (2.5) | 0.61 [0.41-0.92] | p=0.86 |
| Myocardial infarction | 467 (5.4) | 64 (2.6) | 0.81 [0.61-1.08] | 388 (7.2) | 58 (4.8) | 0.93 [0.68-1.26] | p=0.24 |
| Revascularization | 840 (10.4) | 154 (6.6) | 0.75 [0.63-0.91] | 667 (13.2) | 146 (12.2) | 1.09 [0.90-1.3] | P<0.01 |
| Major bleeding | 380 (4.4) | 72 (3.0) | 0.96 [0.73-1.26] | 284 (5.4) | 40 (3.2) | 0.91 [0.63-1.31] | p=0.69 |

Figure 1. **Adjusted risk of 90-day (A) and 1-year (B) outcomes in patients with and without diabetes.** At 90 days, DM was significantly associated with a higher incidence of MACE, death and revascularization. At 1 year the association between DM and the risk of all ischemic and bleeding outcomes became significant. Non-diabetics are used as reference. DM, diabetes mellitus; MACE, major adverse cardiac events. HR, Hazard ratio; CI, confidence interval

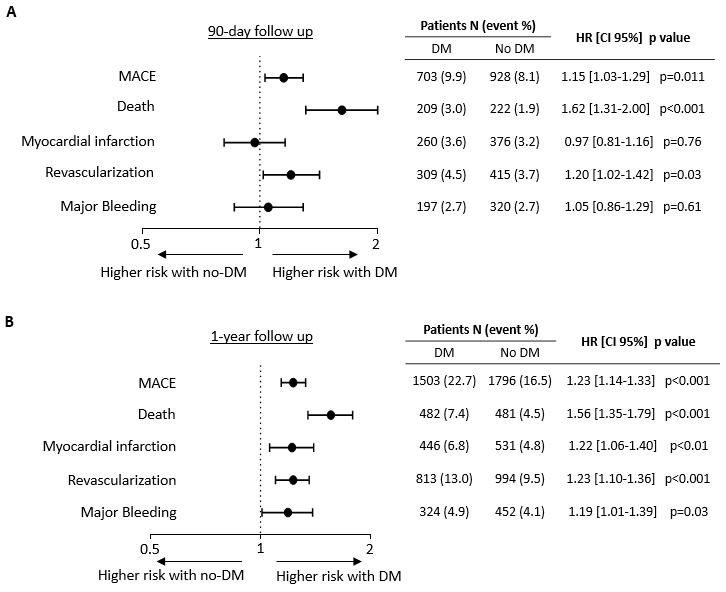
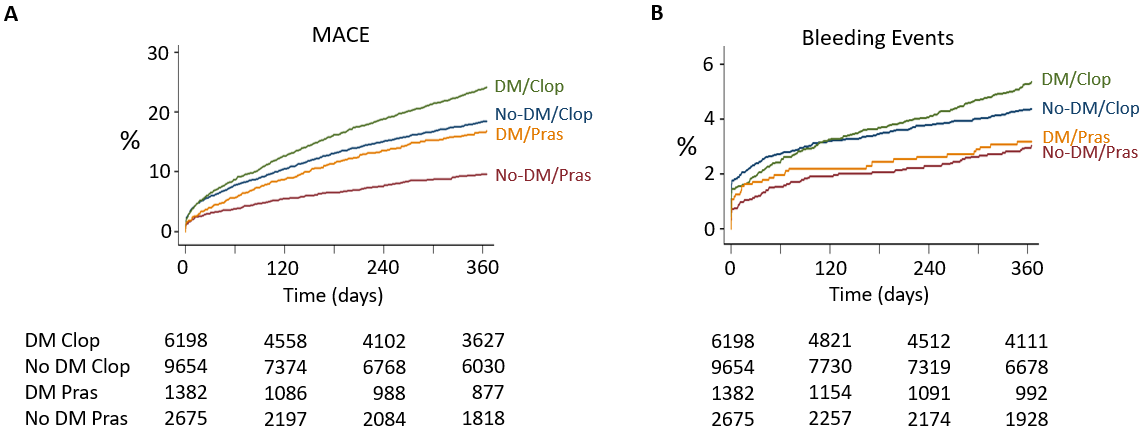


Figure 2. **Unadjusted rate of 1-year MACE (A) and bleeding events (B) in patients with and without diabetes based on the use of either prasugrel or clopidogrel.** Presence of diabetes was associatedwith a higher unadjusted rate of MACE and major bleeding events in both clopidogrel and prasugrel treated patients. Clop, clopidogrel; DM, diabetes mellitus; Pras, prasugrel; MACE, major adverse cardiac events.



SUPPLEMENTARY MATERIAL

Supplementary table 1. Baseline and procedural characteristic in diabetic patients by thienopyridine use. BMI, body mass index; BMS, bare metal stents; CABG, coronary artery bypass graft; CAD, coronary artery disease; DES, drug eluting stent; NSTEMI, non-ST elevation myocardial infarction; PCI, percutaneous coronary interventions; STEMI, ST elevation myocardial infarction.

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|  | **Patients with Diabetes** | |  |
|  | **Clopidogrel**  **5983 (80.0%)** | **Prasugrel**  **1480 (20.0%)** | **P value** |
| Age, years | 66.3 ± 11.3 | 59.5 ± 9.7 | <0.0001 |
| Sex (female), n (%) | 2290 (38.3%) | 465 (31.4%) | <0.0001 |
| BMI, (kg/m2) | 31.2 ± 6.6 | 32.8 ± 6.6 | <0.0001 |
| Diabetes on insulin | 2057 (34.4%) | 429 (29.0%) | <0.0001 |
| Hypertension, n (%) | 5611 (93.8%) | 1326 (89.6%) | <0.0001 |
| Hypercholesterolemia, n (%) | 5522 (92.3%) | 1374 (92.8%) | 0.54 |
| Baseline creatinine, mg/dl | 1.4 ± 1.5 | 1.2 ± 1.1 | <0.0001 |
| Smoking, n (%) | 1121 (18.7%) | 333 (22.5%) | <0.01 |
| Family history of CAD, n (%) | 1808 (30.2%) | 526 (35.5%) | <0.0001 |
| Previous myocardial infarction, n (%) | 2156 (36.0%) | 416 (28.1%) | <0.0001 |
| Previous PCI, n (%) | 1808 (30.2%) | 364 (24.6%) | <0.0001 |
| Previous CABG, n (%) | 1487 (24.9%) | 224 (15.1%) | <0.0001 |
| Multivessel disease, n (%) | 2933 (49.0%) | 760 (51.4%) | 0.11 |
| At least one BMS, n (%) | 1284 (21.5%) | 174 (11.8%) | <0.0001 |
| At least one DES (1st gen), n (%) | 944 (15.8%) | 128 (8.6%) | <0.0001 |
| At least one DES (2nd gen), n (%) | 4060 (67.9%) | 1220 (82.4%) | <0.0001 |

Supplementary table 2. Baseline and procedural characteristic in non-diabetic patients by thienopyridine use. BMI, body mass index; BMS, bare metal stents; CABG, coronary artery bypass graft; CAD, coronary artery disease; DES, drug eluting stent; NSTEMI, non-ST elevation myocardial infarction; PCI, percutaneous coronary interventions; STEMI, ST elevation myocardial infarction.

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|  | **Patients without Diabetes** | |  |
|  | **Clopidogrel**  **9445(78.0%)** | **Prasugrel**  **2734(22.0%)** | **P value** |
| Age, years | 65.9 ± 12.9 | 57.4 ± 10.0 | <0.0001 |
| Sex (female), n (%) | 2881 (30.5%) | 565 (20.7%) | <0.0001 |
| BMI, (kg/m2) | 28.7 ± 5.6 | 29.9 ± 5.8 | <0.0001 |
| Hypertension, n (%) | 7495 (79.4%) | 1738 (63.6%) | <0.0001 |
| Hypercholesterolemia, n (%) | 7573 (80.2%) | 2006 (73.4%) | <0.0001 |
| Baseline creatinine, mg/dl | 1.1 ± 0.8 | 1.0 ± 0.4 | <0.0001 |
| Smoking, n (%) | 2579 (27.3%) | 913 (33.4%) | <0.0001 |
| Family history of CAD, n (%) | 2908 (30.8%) | 899 (32.9%) | 0.04 |
| Previous myocardial infarction, n (%) | 2761 (29.2%) | 526 (19.2%) | <0.0001 |
| Previous PCI, n (%) | 2287 (24.2%) | 523 (19.1%) | <0.0001 |
| Previous CABG, n (%) | 1481 (15.7%) | 188 (6.9%) | <0.0001 |
| Multivessel disease, n (%) | 3592 (38.0%) | 1006 (36.8%) | 0.24 |
| At least one BMS, n (%) | 2498 (26.4%) | 417 (15.3%) | <0.0001 |
| At least one DES (1st gen), n (%) | 1396 (14.8%) | 266 (9.7%) | <0.0001 |
| At least one DES (2nd gen), n (%) | 6034 (63.9%) | 2128 (77.8%) | <0.0001 |