International Journal of Cardiology 275 (2019) 31–35

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Use of prasugrel vs clopidogrel and outcomes in patients with and without diabetes mellitus presenting with acute coronary syndrome undergoing percutaneous coronary intervention

Michela Faggioni [a,b], Usman Baber [a], Jaya Chandrasekhar [a], Samantha Sartori [a], Bimmer E. Claessen [a], Sunil V. Rao [c], Birgit Vogel [a], Mark B. Effron [d,e], Kanhaiya Poddar [i], Serdar Farhan [a], Annapoorna Kini [a], William Weintraub [f], Catalin Toma [g], Sabato Sorrentino [a], Sandra Weiss [f], Clayton Snyder [a], Joseph B. Muhlestein [h], Samir Kapadia [i], Stuart Keller [e], Craig Strauss [j], Melissa Aquino [a], Brian Baker [k], Anthony Defranco [l], Stuart Pocock [m], Timothy Henry [n], Roxana Mehran [a,*]

[a] Icahn School of Medicine at Mount Sinai, New York, NY, United States of America
[b] James J Peters Veterans Affairs Medical Center, Bronx, NY, United States of America
[c] The Duke Clinical Research Institute, Durham, NC, United States of America
[d] John Ochsner Heart and Vascular Institute, Ochsner Medical Center, New Orleans, LA, United States of America
[e] Eli Lilly and Company, Indianapolis, IN, United States of America
[f] Christiana Care Health System, Newark, DE, United States of America
[g] University of Pittsburgh Medical Center, Pittsburgh, PA, United States of America
[h] Intermountain Heart Institute, Salt-Lake city, UT, United States of America
[i] Cleveland Clinic, Cleveland, OH, United States of America
[j] Minneapolis Heart Institute, Minneapolis, MN, United States of America
[k] Daiichi-Sankyo, Inc., Basking Ridge, NJ, United States of America
[l] Aurora Cardiovascular Services, Milwaukee, WI, United States of America
[m] London School of Hygiene and Tropical Medicine, London, United Kingdom
[n] Cedars-Sinai Heart Institute, Los Angeles, CA, United States of America

ARTICLE INFO

Article history:
Received 3 July 2018
Received in revised form 15 October 2018
Accepted 22 October 2018
Available online 25 October 2018

Keywords:
Acute coronary syndrome
Percutaneous coronary intervention
Diabetes mellitus
Prasugrel
Clopidogrel

ABSTRACT

Background: Clinical trial data studies suggest superiority of prasugrel over clopidogrel in patients with diabetes. However, the use, safety and efficacy profile of prasugrel in unselected diabetic patients presenting with acute coronary syndromes (ACS) remain unclear.

Methods: PROMETHEUS was a prospective multicenter observational study of 19,919 ACS PCI patients enrolled 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 7580 (38%) subjects with and 12,329 (62%) without diabetes. Diabetic patients were older and had significantly higher rates of cardiovascular risk factors. However, they were less likely to receive prasugrel (18.2% vs. 21.7%). Use of prasugrel did not increase with the severity of clinical presentation in diabetics, whereas, among non-diabetics, prescription of prasugrel was higher in NSTEMI and STEMI compared to unstable angina. The 90-day and 1-year adjusted risk of MACE was greater in diabetics (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 was also higher in diabetics (4.9% vs. 4.1%, HR 1.19 [1.01–1.39], $p = 0.035$). After multivariable adjustment, use of prasugrel was associated with a lower risk of death in diabetic patients both at 90 days and 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. In diabetics, prasugrel was associated with a lower adjusted risk of 90-day death compared with clopidogrel.

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.

* Corresponding author at: Mount Sinai Hospital, One Gustave L. Levy Place, Box 1030, New York, NY 10029, United States of America.
E-mail address: roxana.mehran@mountsinai.org (R. Mehran).

https://doi.org/10.1016/j.ijcard.2018.10.071
0167-5273/

1. 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.

2. Methods

2.1. 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 as reported by physicians in the participating centers. Patients were followed for 1 year.

2.2. 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.

2.3. 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 χ^2 test. 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 common confounders known in the literature and variables that appeared to be unbalanced between the study groups in the univariate analysis. These included: 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, non-ST elevation MI [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 15.1 (StataCorp, College Station, Texas); p values <0.05 were considered significant.

3. Results

Out of 19,909 patients included in our registry, 7580 (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 2). At discharge, patients with diabetes were more likely to receive ACE inhibitors or angiotensin II receptor inhibitors medications. Statin use was elevated (>90% in both groups) with a higher rate of prescription in non-diabetics (Table 2). 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

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.

	No diabetes 12,329 (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/m^2)	28.95 ± 5.68	31.50 ± 6.62	<0.0001
Weight (kg)	85.4 ± 19.6	90.9 ± 22.3	<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 and discharge medications in patients with and without diabetes mellitus. ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; 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.

	No diabetes 12,329 (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
Prasugrel use at discharge			
Overall, n (%)	2675 (21.7%)	1382 (18.2)	<0.0001
Unstable angina, n (%)	1257 (19.7%)	868 (17.9%)	0.02
NSTEMI, n (%)	790 (22.9%)	369 (18.8%)	<0.0001
STEMI, n (%)	628 (25.0%)	145 (18.6%)	<0.0001
Other discharge medications			
Aspirin	12,114 (98.3%)	7414 (97.8%)	0.09
Clopidogrel	9451 (76.7%)	5986 (79.0%)	<0.0001
ACE-I or ARB	6866 (55.7%)	4952 (65.3%)	<0.0001
Beta blocker	10,380 (84.2%)	6474 (85.4%)	0.18
Statin	11,441 (92.8%)	6853 (90.4%)	<0.0001
Any anticoagulant	2572 (20.9%)	1336 (17.6%)	<0.0001

clinically driven revascularization (Fig. 1A). 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. 1B).

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 in diabetics and non-diabetics by type of P2Y12 used, 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 (Supplementary Fig. 1). 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 (Fig. 2A). 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 (Fig. 2B).

4. 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, patients treated with clopidogrel 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]. In the diabetic subpopulation, lower prescription of prasugrel might be related to the higher prevalence of prior cerebrovascular events, a contraindication to prasugrel use. Furthermore, physicians' perception of a higher bleeding risk in diabetics might also account for the lower use of prasugrel.

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

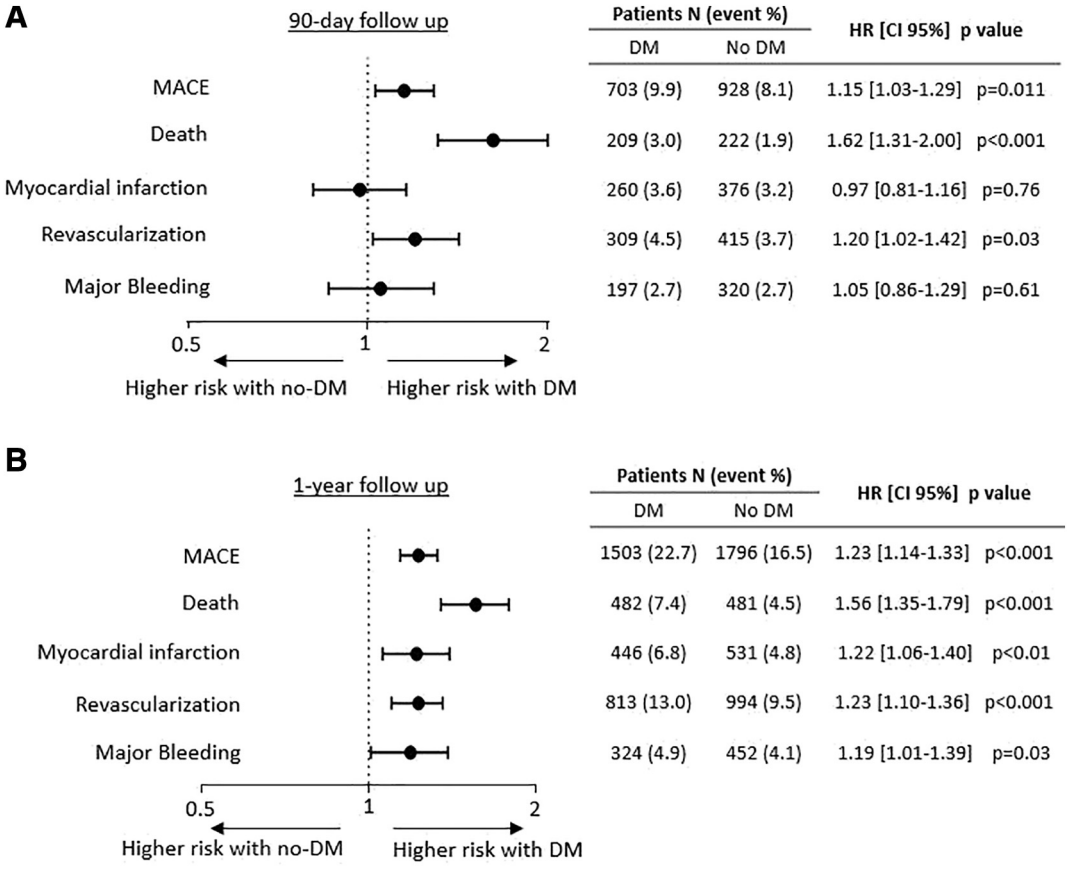

Fig. 1. Adjusted risk of 90-day (A) and 1-year (B) outcomes in patients with and without diabetes. At 90 days, DM was significantly associated with a higher incidence of MACE, death and revascularization. At 1 year the association between DM and the risk of all ischemic and bleeding outcomes became significant.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

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

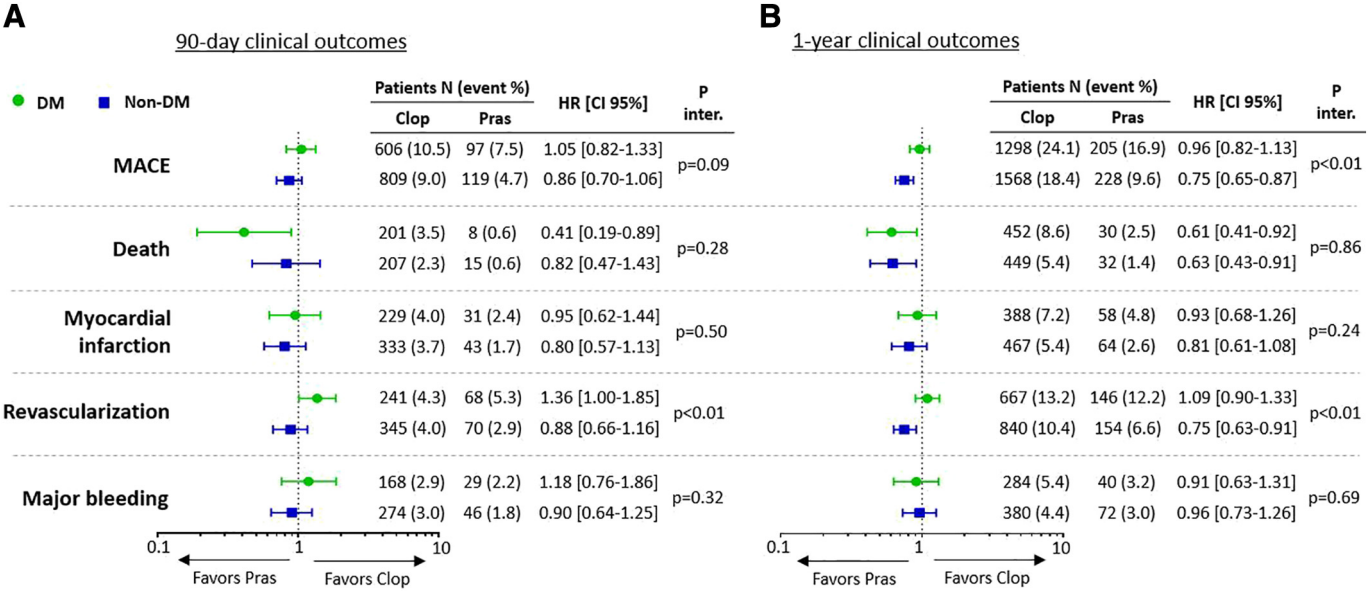

Fig. 2. Ninety-day (A) and one-year (B) clinical outcomes stratified by diabetic status and thienopyridine type. No significant difference in 90-day clinical outcomes was found between clopidogrel- and prasugrel-treated patients regardless of diabetic status except for a lower risk of all cause death associated with the use of prasugrel in diabetics. At 1-year follow-up, use of prasugrel in diabetic patients was associated with a lower risk of all cause death, whereas in non-diabetics use of prasugrel was associated with a reduced risk of MACE, all cause death and revascularization. CI, confidence interval, Clop, clopidogrel; HR, hazard ratio; MACE, major adverse cardiac events; P inter, p for interaction; pras, prasugrel.

major bleeding [17]. Additionally, patients with diabetes might undergo surgeries more frequently than non-diabetics resulting in a higher rate of perioperative bleeding events. Finally, the polypharmacy frequently seen in diabetics, carries a risk of drug-drug interaction which might influence their bleeding profile. 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.

5. Limitations

This study has several limitations. Data were collected between 2010 and 2013: clinical practice might have changed since that time. The rate of bare metal stents used was relatively high and might have influenced the choice of antiplatelet treatment after PCI. 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. Data on the type of bleeding event such as gastrointestinal or cerebral was not recorded. No information was collected regarding the duration of diabetes mellitus. Finally, this study was not randomized, therefore any comparison in outcomes between prasugrel and clopidogrel treated patients should be carefully interpreted.

6. 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. When comparing clinical outcomes by thienopyridine use, the current analysis of contemporary practice data, confirms the findings of randomized clinical trials, and may support a potential benefit of prasugrel use in appropriately selected diabetic patients.

Disclosures

RM has received research grant support from Eli Lilly and Company, Daiichi Sankyo Company, AstraZeneca, The Medicines Co., OrbusNeich, Bayer, and CSL Behring; serves as a consultant for Bayer, CSL Behring, Janssen Pharmaceuticals, Merck & Co, The Medicines Co., and Watermark Consulting; serves on the advisory board of Abbott Laboratories, AstraZeneca, Boston Scientific, Covidien, Janssen Pharmaceuticals, Merck & Co., The Medicines Co., and Sanofi-Aventis; gives industry-sponsored lectures for PlatformQ and Sanofi-Aventis; and has equity in Claret Medical and Elixir Medical Corp. MBE: equity and former employee of Eli Lilly and Company, SK: Employee of Eli Lilly and Co, BB: employee of Daiichi Sankyo.

The PROMETHEUS study was sponsored and funded by Daiichi Sankyo Company, Japan and Eli Lilly and Company, United States.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2018.10.071.

References

[1] L.O. Jensen, M. Maeng, P. Thayssen, H.H. Tilsted, C.J. Terkelsen, A. Kaltoft, 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. 109 (2012) 629–635.
[2] S.M. Donahoe, G.C. Stewart, C.H. McCabe, S. Mohanavelu, S.A. Murphy, C.P. Cannon, et al., Diabetes and mortality following acute coronary syndromes, JAMA 298 (2007) 765–775.
[3] S. Farhan, U. Baber, B. Vogel, M. Aquino, J. Chandrasekhar, M. Faggioni, et al., Impact of diabetes mellitus on ischemic events in men and women after percutaneous coronary intervention, Am. J. Cardiol. 119 (2017) 1166–1172.
[4] S. James, D.J. Angiolillo, J.H. Cornel, D. Erlinge, S. Husted, F. Kontny, et al., Ticagrelor vs. clopidogrel in patients with acute coronary syndromes and diabetes: a substudy from the PLATelet inhibition and patient Outcomes (PLATO) trial, Eur. Heart J. 31 (2010) 3006–3016.
[5] S.D. Wiviott, E. Braunwald, D.J. Angiolillo, S. Meisel, A.J. Dalby, F.W. Verheugt, 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 118 (2008) 1626–1636.
[6] N.P. Dridi, P.I. Johansson, P. Clemmensen, T. Stissing, M.D. Radu, A. Qayyum, 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 25 (2014) 506–512.
[7] S. Sheikh Rezaei, A. Geroldinger, G. Heinze, B. Reichardt, M. Wolzt, 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. 235 (2017) 61–66.
[8] U. Baber, S. Sartori, M. Aquino, A. Kini, S. Kapadia, S. Weiss, 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. 188 (2017) 73–81.
[9] I. Isordia-Salas, M.E. Galvan-Plata, A. Leanos-Miranda, E. Aguilar-Sosa, F. Anaya-Gomez, A. Majluf-Cruz, et al., Proinflammatory and prothrombotic state in subjects with different glucose tolerance status before cardiovascular disease, J. Diabetes Res. 2014 (2014), 631902.
[10] F. Franchi, F. Rollini, N. Aggarwal, J. Hu, M. Kureti, A. Durairaj, 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 134 (2016) 780–792.
[11] M.M.F.G. Benjamin, B.D. Pollock, D.M. Sass, J.M. Schussler, Long term efficacy of prasugrel versus clopidogrel in patients undergoing percutaneous coronary intervention and anticoagulated with bivalirudin, Int. J. Cardiovas. Res. 5 (2016).
[12] T.Y. Wang, TRANSLATE-ACS (treatment with ADP receptor inhibitors: longitudinal assessment of treatment patterns and events after acute coronary syndrome), PT 39 (2014) 790–791.
[13] M.W. Sherwood, S.D. Wiviott, S.A. Peng, M.T. Roe, J. Delemos, E.D. Peterson, 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. 3 (2014), e000849.
[14] A. Sandhu, M. Seth, S. Dixon, D. Share, D. Wohns, T. Lalonde, et al., Contemporary use of prasugrel in clinical practice: insights from the Blue Cross Blue Shield of Michigan Cardiovascular Consortium, Circ. Cardiovasc. Qual. Outcomes 6 (2013) 293–298.
[15] V. Aggarwal, E.J. Armstrong, W. Liu, T.M. Maddox, P.M. Ho, E. Carey, et al., Prasugrel use following PCI and associated patient outcomes: insights from the national VA CART program, Clin. Cardiol. 39 (2016) 578–584.
[16] A. Grodzinsky, S.V. Arnold, T.Y. Wang, P. Sharma, K. Gosch, P.G. Jones, et al., Bleeding risk following percutaneous coronary intervention in patients with diabetes prescribed dual anti-platelet therapy, Am. Heart J. 182 (2016) 111–118.
[17] M. Faggioni, U. Baber, S. Sartori, G. Giustino, D.J. Cohen, T.D. Henry, 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, J. Am. Coll. Cardiol. Intv. 10 (2017) 645–654.