JACC: CARDIOVASCULAR INTERVENTIONS VOL. 13, NO. 19, 2020

Ticagrelor or Prasugrel in Patients With Acute Coronary Syndromes and Diabetes Mellitus

Gjin Ndrepepa, MD,[a,b] Adnan Kastrati, MD,[a,b,c] Maurizio Menichelli, MD,[d] Franz-Josef Neumann, MD,[e] Jochen Wöhrle, MD,[f] Isabell Bernlochner, MD,[c,g] Gert Richardt, MD,[h] Bernhard Witzenbichler, MD,[i] Dirk Sibbing, MD,[c,j] Senta Gewalt, MD,[a,b] Dominick J. Angiolillo, MD, PhD,[k] Christian W. Hamm, MD,[l,m] Alexander Hapfelmeier, MSc,[n] Dietmar Trenk, PhD,[e] Karl-Ludwig Laugwitz, MD,[c,g] Heribert Schunkert, MD,[a,b,c] Stefanie Schüpke, MD,[a,b,c] Katharina Mayer, MD[a,b]

ABSTRACT

OBJECTIVES The aim of this study was to assess the efficacy and safety of ticagrelor versus prasugrel in patients with diabetes mellitus (DM) presenting with acute coronary syndromes (ACS) in whom invasive therapy was planned.

BACKGROUND The efficacy and safety of ticagrelor versus prasugrel in patients with ACS with DM undergoing invasive treatment remain unknown.

METHODS This pre-specified analysis of the ISAR-REACT (Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment) 5 trial included 892 patients with ACS with DM and 3,124 patients with ACS without DM randomized to prasugrel or ticagrelor. The primary endpoint was a composite of death, myocardial infarction, or stroke; the safety endpoint was Bleeding Academic Research Consortium types 3 to 5 bleeding (both assessed 12 months after randomization).

RESULTS The primary endpoint occurred in 51 patients (11.2%) in the ticagrelor group and 55 patients (13.0%) in the prasugrel group in the DM cohort (hazard ratio: 0.84; 95% confidence interval: 0.58 to 1.24; $p = 0.383$) and in 132 patients (8.6%) in the ticagrelor group and 81 patients (5.2%) in the prasugrel group in the non-DM cohort (hazard ratio: 1.70; 95% confidence interval: 1.29 to 2.24; $p < 0.001$). There was a significant treatment arm-by-diabetic status interaction ($p_{int} = 0.0035$). Bleeding Academic Research Consortium types 3 to 5 bleeding occurred in 27 patients (6.9%) in the ticagrelor group and 19 patients (5.5%) in the prasugrel group ($p = 0.425$) in the DM cohort and in 68 patients (5.2%) in the ticagrelor group and 60 patients (4.6%) in the prasugrel group in the non-DM cohort ($p = 0.500$).

CONCLUSIONS DM seems to affect the efficacy of ticagrelor and prasugrel in patients with ACS. In patients with DM, the efficacy of ticagrelor was comparable with that of prasugrel. (Prospective, Randomized Trial of Ticagrelor Versus Prasugrel in Patients With Acute Coronary Syndrome [ISAR-REACT 5]; NCT01944800)
(J Am Coll Cardiol Intv 2020;13:2238–47) © 2020 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

From the [a]Department of Cardiology, Deutsches Herzzentrum München, Munich, Germany; [b]Technische Universität München, Munich, Germany; [c]German Center for Cardiovascular Research, Partner Site Munich Heart Alliance, Munich, Germany; [d]Department of Cardiology, Ospedale Fabrizio Spaziani, Frosinone, Italy; [e]Department of Cardiology and Angiology II, University Heart Center Freiburg - Bad Krozingen, Bad Krozingen, Germany; [f]Department of Cardiology, Medical Campus Lake Constance, Friedrichshafen, Germany; [g]Medizinische Klinik und Poliklinik Innere Medizin I (Kardiologie, Angiologie, Pneumologie), Klinikum rechts der Isar, Munich, Germany; [h]Heart Center Bad Segeberg, Bad Segeberg, Germany; [i]Departments of Cardiology and Pneumology, Helios Amper-Klinikum Dachau, Dachau, Germany; [j]Department of Cardiology, Klinik der Universität München, Ludwig-Maximilians-University, Munich, Germany; [k]Division of Cardiology, University of Florida College of Medicine, Jacksonville, Florida; [l]Heart Center, Campus Kerckhoff of Justus-Liebig-University, Giessen, Germany; [m]German Center for Cardiovascular Research, Partner Site Rhine-Main, Frankfurt, Germany; and the [n]Technical University of Munich, School of Medicine, Institute of General Practice and Health Services Research, Munich, Germany. This research was supported by grant FKZ 81X1600501 from the German Center for Cardiovascular Research and Deutsches Herzzentrum München. Dr. Neumann has received personal fees from

ISSN 1936-8798 https://doi.org/10.1016/j.jcin.2020.07.032

Patients with diabetes mellitus (DM) presenting with acute coronary syndromes (ACS) undergoing percutaneous coronary intervention (PCI) have increased platelet reactivity (1), reduced response to antiplatelet drugs (2), and a higher risk for subsequent thrombotic events and mortality compared with patients without DM (3–5). Patients with DM are more commonly found to be poor responders to clopidogrel (2), and they are at increased risk for ischemic events such as myocardial infarction and stent thrombosis after PCI (6). In the OPTIMUS (Optimizing Antiplatelet Therapy in Diabetes Mellitus) study, 60% of patients remained suboptimal responders after doubling of clopidogrel maintenance dose (7), emphasizing the need for alternative platelet inhibition strategies in patients with DM. Prasugrel and ticagrelor are newer antiplatelet drugs that

SEE PAGE 2248

have shown superiority over clopidogrel in terms of degree and stability of platelet inhibition (8,9) in patients with DM and a reduction of ischemic events in patients with ACS and DM after PCI (6,10). The TRITON-TIMI (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis In Myocardial Infarction) 38 trial showed that patients with DM tended to have a greater reduction in ischemic events without an increase in TIMI (Thrombolysis In Myocardial Infarction) major bleeding with prasugrel compared with clopidogrel (6). The PLATO (Platelet Inhibition and Clinical Outcomes) trial showed that ticagrelor compared with clopidogrel reduced ischemic events without an increase in major bleeding events irrespective of diabetic status (10). However, considering substantial differences in patient populations across the trials and the lack of head-to-head comparisons of ticagrelor versus prasugrel in patients with DM in previous studies, it remains unclear as to which drug should be preferred in patients with ACS and DM in whom invasive therapy is planned.

The ISAR-REACT (Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment) 5 trial showed that prasugrel was superior to ticagrelor in reducing the composite endpoint of death, myocardial infarction, or stroke without increasing the risk for major bleeding in patients with ACS undergoing PCI (11). In the ISAR-REACT 5 trial, an analysis of ticagrelor versus prasugrel efficacy according to diabetic status was prespecified. In the primary publication, only the treatment effect regarding the composite efficacy endpoint in patients with and without DM was shown. Herein, we present the detailed results of this pre-specified analysis assessing the efficacy and safety of ticagrelor versus prasugrel according to diabetic status in patients with ACS in whom an invasive treatment strategy was planned.

ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome(s)

BARC = Bleeding Academic Research Consortium

CI = confidence interval

DM = diabetes mellitus

HR = hazard ratio

IQR = interquartile range

PCI = percutaneous coronary intervention

STEMI = ST-segment elevation myocardial infarction

METHODS

PATIENTS AND DESIGN. This study represents a prespecified analysis of the ISAR-REACT 5 trial in which the efficacy and safety of prasugrel versus ticagrelor in ACS patients in whom an invasive treatment strategy was planned were assessed according to diabetic

Amgen, Boehringer Ingelheim, Daiichi-Sankyo, Novartis, and Ferrer; has received grants and personal fees from Pfizer, Biotronik, Edwards Lifesciences, Bayer Healthcare, and Boston Scientific; and has received grants from Medtronic and GlaxoSmithKline outside the submitted work. Dr. Sibbing has received personal fees from Bayer, Sanofi, AstraZeneca, Pfizer, Ferrer, and Daiichi-Sankyo; and has received grants and personal fees from Roche Diagnostics outside the submitted work. Dr. Angiolillo has received grants and personal fees from Amgen, Aralez, Bayer, Biosensors, Boehringer Ingelheim, Bristol Myers Squibb, Chiesi, Daiichi-Sankyo, Eli Lilly, Janssen, Merck, Sanofi, CeloNova, and AstraZeneca; has received personal fees from Haemonetics, PhaseBio, PLx Pharma, Pfizer, The Medicines Company, and St. Jude Medical; and has received grants from CSL Behring, Eisai, Gilead, Idorsia Pharmaceuticals, Matsutani Chemical Industry, Novartis, Osprey Medical, Renal Guard Solutions, and the Scott R. MacKenzie Foundation outside the submitted work. Dr. Hamm has received personal fees from AstraZeneca outside the submitted work. Dr. Trenk received grants from Deutsches Herzzentrum Munich during the conduct of the study; and has received personal fees from Amgen, AstraZeneca, Bayer, Berlin Chemie, Boehringer Ingelheim, Bristol Myers Squibb, Daiichi-Sankyo, Ferrer, Pfizer, and Sanofi outside the submitted work. Dr. Schunkert has received personal fees from Merck Sharp & Dohme, Amgen, Bayer Vital, Boehringer Ingelheim, Daiichi-Sankyo, Novartis, Servier, Brahms, Bristol Myers Squibb, Medtronic, Sanofi, Synlab, Pfizer, and Vifor; and has received grants and personal fees from AstraZeneca outside the submitted work. Dr. Schüpke received grants from the German Center for Cardiovascular Research during the conduct of the study; has received personal fees from Bayer Vital; has received grants from Else Kröner-Fresenius-Stiftung; and has received lecture fees from Daiichi-Sankyo outside the submitted work. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC: Cardiovascular Interventions* author instructions page.

Manuscript received June 11, 2020; revised manuscript received July 10, 2020, accepted July 20, 2020.

status. The design and results of the ISAR-REACT 5 trial have previously been published (11). In brief, patients hospitalized for ACS (unstable angina pectoris, non-ST-segment elevation myocardial infarction, or ST-segment elevation myocardial infarction [STEMI]) in whom invasive treatment was planned were included. The inclusion and exclusion criteria are reported in the primary publication (11). Patients were randomized to receive ticagrelor (a loading dose of 180 mg as soon as possible after randomization and continued at a maintenance dose of 90 mg twice daily) or prasugrel (a loading dose of 60 mg after coronary anatomy was known [i.e., with no pre-treatment before diagnostic coronary angiography] but before PCI [before the guidewire crossed the lesion] and continued at a maintenance dose of 10 mg once daily). In patients with STEMI, prasugrel was given as soon as possible after randomization. In patients ≥75 years of age or those with body weight <60 kg (irrespective of age), a reduced maintenance dose of prasugrel (5 mg) was recommended. Aspirin therapy included a loading dose of 150 to 300 mg intravenous or chewed aspirin and a maintenance dose of 75 to 100 mg daily in the ticagrelor and prasugrel arms. The study protocol was approved by the local ethics committee at each participating center. The study conformed to the Declaration of Helsinki.

DM was diagnosed if the patient was receiving active treatment with insulin or an oral hypoglycemic agent on admission to the hospital. For patients diagnosed with DM who were on dietary therapy alone, documentation of abnormal fasting blood glucose or an abnormal result on a glucose tolerance test according to World Health Organization criteria was required. Of the 4,018 patients recruited in the ISAR-REACT 5 trial, information on DM was available in 4,016 patients. On the basis of the presence of DM, patients were categorized in 2 groups: those with DM (n = 892) and those without DM (n = 3,124).

OUTCOMES AND DEFINITIONS. The efficacy endpoint was a composite of death, myocardial infarction, or stroke at 12 months after randomization. The safety endpoint was the incidence of bleeding types 3 to 5 as defined by the Bleeding Academic Research Consortium (BARC) (12) at 12 months after randomization. Other endpoints analyzed were the individual components of the primary endpoint, the incidence of cardiovascular death, and stent thrombosis (definite or probable) (13) at 12 months after randomization. Detailed definitions of the study endpoints are provided in the primary publication (11).

FOLLOW-UP. Clinical follow-up was scheduled at 30 ± 10 days, 6 ± 1 month, and 12 ± 1 month. Patients were contacted by telephone, hospital or outpatient visit, or structured follow-up letter. In case of potential endpoint-related adverse events, source data were solicited. All serious adverse events and efficacy and safety endpoints in this trial were monitored on site. In addition, 100% of source data were checked in at least 10% of patients at all centers.

STATISTICAL ANALYSIS. The analysis of outcomes in patients according to diabetic status was prespecified in the study protocol (11). Continuous data are presented as mean ± SD or median (interquartile range [IQR]) and were compared using either Student's *t*-test or the nonparametric Wilcoxon rank sum test. Categorical variables are presented as counts and proportions and were compared using the chi-square test. The cumulative incidence of the efficacy and safety endpoints according to the study drug (prasugrel or ticagrelor) in patients with or without DM was computed using the Kaplan-Meier method. The participating center and stratification according to clinical presentation (ACS with or without ST-segment elevation) were entered into the Cox proportional hazards model as covariates along with study treatment group. For all endpoints except the primary endpoint and all-cause death, the cumulative incidence functions were computed to account for competing risk. To estimate the interaction between the treatment arm and DM for the study endpoints as well as between treatment arm and pre-specified subgroups in patients with and without DM, an interaction term was entered into the Cox proportional hazards models. Treatment effect estimates are presented as hazard ratios (HRs) along with corresponding 95% confidence intervals (CIs). The efficacy endpoint was analyzed according to the intention-to-treat principle including all patients as initially assigned irrespective of the actual treatment received. The safety endpoint of bleeding was analyzed in a modified intention-to-treat population. It included all patients with at least 1 application of the study drug with bleeding assessed for up to 7 days after discontinuation of the study drug. Patients were analyzed from randomization until death, withdrawal of consent, or last contact date. Statistical analysis was performed using R version 3.6.0 (R Foundation for Statistical Computing, Vienna, Austria). A 2-sided p value <0.05 was considered to indicate statistical significance.

TABLE 1 Baseline Characteristics

	Diabetes (n = 892)			No Diabetes (n = 3,124)		
	Ticagrelor (n = 463)	Prasugrel (n = 429)	p Value	Ticagrelor (n = 1,548)	Prasugrel (n = 1,576)	p Value
Age (yrs)	66.8 ± 11.0	67.5 ± 11.5	0.364	63.8 ± 12.2	63.9 ± 12.1	0.928
Age ≥75 yrs	131 (28.3)	139 (32.4)	0.182	359 (23.2)	353 (22.4)	0.597
Women	121 (26.1)	97 (22.6)	0.252	357 (23.1)	381 (24.2)	0.490
On insulin therapy	143 (30.9)	137 (31.9)	0.791	–	–	–
Current smoker	117/459 (25.5)	95/425 (22.4)	0.311	565/1,543 (36.6)	572/1,574 (36.3)	0.902
Arterial hypertension	399/462 (86.4)	361/428 (84.3)	0.449	1,033/1,546 (66.8)	1,023/1,575 (65.0)	0.289
Hypercholesterolemia	318/461 (69.0)	298 (69.5)	0.934	860/1,546 (55.6)	865/1,574 (55.0)	0.733
Prior myocardial infarction	102/462 (22.1)	81/428 (18.9)	0.280	209/1,547 (13.5)	239 (15.2)	0.205
Previous PCI	152/462 (32.9)	140/428 (32.7)	0.999	301 (19.4)	323/1,575 (20.5)	0.485
Previous CABG	35/462 (7.6)	51/428 (11.9)	0.038	80 (5.2)	79 (5.0)	0.908
Cardiogenic shock	7/462 (1.5)	9/428 (2.1)	0.684	23 (1.5)	24 (1.5)	0.999
Systolic blood pressure (mm Hg)	145 ± 24.7	143 ± 24.8	0.348	143 ± 25.2	143 ± 24.4	0.640
Diastolic blood pressure (mm Hg)	81.0 ± 13.9	80.1 ± 13.8	0.358	82.3 ± 14.8	82.3 ± 13.8	0.926
Heart rate (beats/min)	79.0 ± 16.9	77.8 ± 14.4	0.288	76.4 ± 15.6	75.5 ± 15.8	0.125
Weight <60 kg	14/460 (3.0)	12/423 (2.8)	0.999	94/1,542 (6.1)	82/1,564 (5.2)	0.342
Body mass index (kg/m^2)	29.5 ± 5.1	29.2 ± 4.6	0.397	27.3 ± 4.3	27.4 ± 4.3	0.301
Creatinine (μmol/l)	93.0 ± 34.9	94.2 ± 35.3	0.608	86.1 ± 24.5	86.5 ± 28.8	0.622
Diagnosis at admission			0.705			0.953
Unstable angina	64 (13.8)	67 (15.6)		185 (12.0)	194 (12.3)	
NSTEMI	233 (50.3)	216 (50.3)		697 (45.0)	708 (44.9)	
STEMI	166 (35.9)	146 (34.1)		666 (43.0)	674 (42.8)	
Coronary angiography	460 (99.4)	428 (99.8)	0.625	1,542 (99.6)	1,572 (99.7)	0.545
Treatment strategy			0.237			0.738
PCI	376/462 (81.4)	367 (85.5)		1,299/1,545 (84.1)	1,333/1,575 (84.6)	
CABG	17/462 (3.7)	11 (2.6)		30/1,545 (1.9)	25/1,575 (1.6)	
Conservative	69/462 (14.9)	51 (11.9)		216/1,545 (14.0)	217/1,575 (13.8)	

Values are mean ± SD, n (%), or n/N (%). Missing continuous data: patients with diabetes: systolic blood pressure, 1 patient (in the prasugrel group); diastolic blood pressure, 4 patients (2 in each group); body mass index, 10 patients (4 in the ticagrelor group, 6 in the prasugrel group); patients without diabetes: systolic blood pressure, 2 patients (1 in each group); diastolic blood pressure, 12 patients (5 in the ticagrelor group, 7 in the prasugrel group); heart rate, 2 patients (1 in each group); body mass index, 21 patients (8 in the ticagrelor group, 13 in the prasugrel group); creatinine, 6 patients (5 patients in the ticagrelor group, 1 patient in the prasugrel group). The remaining continuous data were complete.

CABG = coronary artery bypass grafting; NSTEMI = non-ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

RESULTS

BASELINE DATA. This analysis included 4,016 patients from the ISAR-REACT 5 trial cohort. Of this group, 892 patients (22.2%) had DM and 3,124 patients did not have DM. In the group with DM, 463 patients were assigned to ticagrelor and 429 patients to prasugrel. In the group without DM, 1,548 patients were assigned to ticagrelor and 1,576 patients to prasugrel. Baseline data are shown in **Table 1**. In the group with DM, baseline characteristics did not differ significantly according to study drug (prasugrel or ticagrelor), with the exception of the proportions of patients with previous coronary artery bypass surgery (a higher proportion of prasugrel-assigned patients had previous coronary artery bypass surgery). In patients without DM, baseline characteristics were well balanced, with no statistically significant differences according to study drug.

ANGIOGRAPHIC AND PROCEDURAL DATA. Diagnostic coronary angiography was performed in 4,002 patients (99.7%), with no difference in patients with or without DM (99.6% vs. 99.7%; p = 0.566). Angiographic data are shown in Supplemental Table S1. There were no significant differences according to study drug with respect to vascular access route, number of narrowed coronary arteries, or left ventricular ejection fraction in patients with or without DM. Procedural data are shown in Supplemental Table S2. There were no significant differences according to study drug with respect to treated vessel, complexity or number of lesions per patient treated, baseline or post-procedural TIMI flow grade, type of intervention, size and length of implanted stents, proportions of successful PCI, and periprocedural antithrombotic medications in the groups with and without DM. Data on final diagnosis and drug therapy at discharge are shown in

TABLE 2 Clinical Outcomes

Endpoint	Diabetes (n = 892)				No Diabetes (n = 3,124)				
	Ticagrelor (n = 463)	Prasugrel (n = 429)	Hazard Ratio (95% CI)	p Value	Ticagrelor (n = 1,548)	Prasugrel (n = 1,576)	Hazard Ratio (95% CI)	p Value	p_{int}
Primary endpoint (death, myocardial infarction, or stroke)*	51 (11.2)	55 (13.0)	0.84 (0.58–1.24)	0.383	132 (8.6)	81 (5.2)	1.70 (1.29–2.24)	<0.001	0.0035
Death*	26 (5.7)	26 (6.2)	0.91 (0.53–1.56)	0.723	63 (4.1)	46 (3.0)	1.41 (0.96–2.06)	0.077	0.194
Cardiovascular	23	19			39	39			
Noncardiovascular	3	7			24	7			
Myocardial infarction†	26 (5.9)	28 (6.8)	0.85 (0.50–1.45)	0.551	70 (4.6)	32 (2.1)	2.30 (1.51–3.49)	<0.001	0.004
Type 1	15	15			37	20			
Type 2	3	1			1	2			
Type 4a	3	6			16	5			
Type 4b	5	6			15	5			
Type 5	0	0			1	0			
STEMI	9	9			22	5			
Stroke†	8 (1.7)	6 (1.4)	1.26 (0.43–3.63)	0.672	14 (0.9)	13 (0.8)	1.10 (0.52–2.35)	0.797	0.845
Ischemic	5	6			11	11			
Hemorrhagic	3	0			3	2			
Definite or probable stent thrombosis†	6 (1.3)	9 (2.1)	0.60 (0.21–1.68)	0.330	20 (1.3)	11 (0.7)	1.87 (0.90–3.90)	0.096	0.079
Definite stent thrombosis†	6 (1.3)	7 (1.6)	0.78 (0.26–2.33)	0.658	16 (1.0)	5 (0.3)	3.29 (1.20–8.90)	0.020	0.058
BARC types 3–5 bleeding†	27/455 (6.9)	19/383 (5.5)	1.27 (0.70–2.29)	0.425	68/1,534 (5.2)	60/1,389 (4.6)	1.13 (0.80–1.60)	0.500	0.732
BARC type 3a	13	10			34	31			
BARC type 3b	9	6			23	25			
BARC type 3c	1	1			3	1			
BARC type 4	2	1			6	1			
BARC type 5a	0	0			1	0			
BARC type 5b	2	1			1	2			

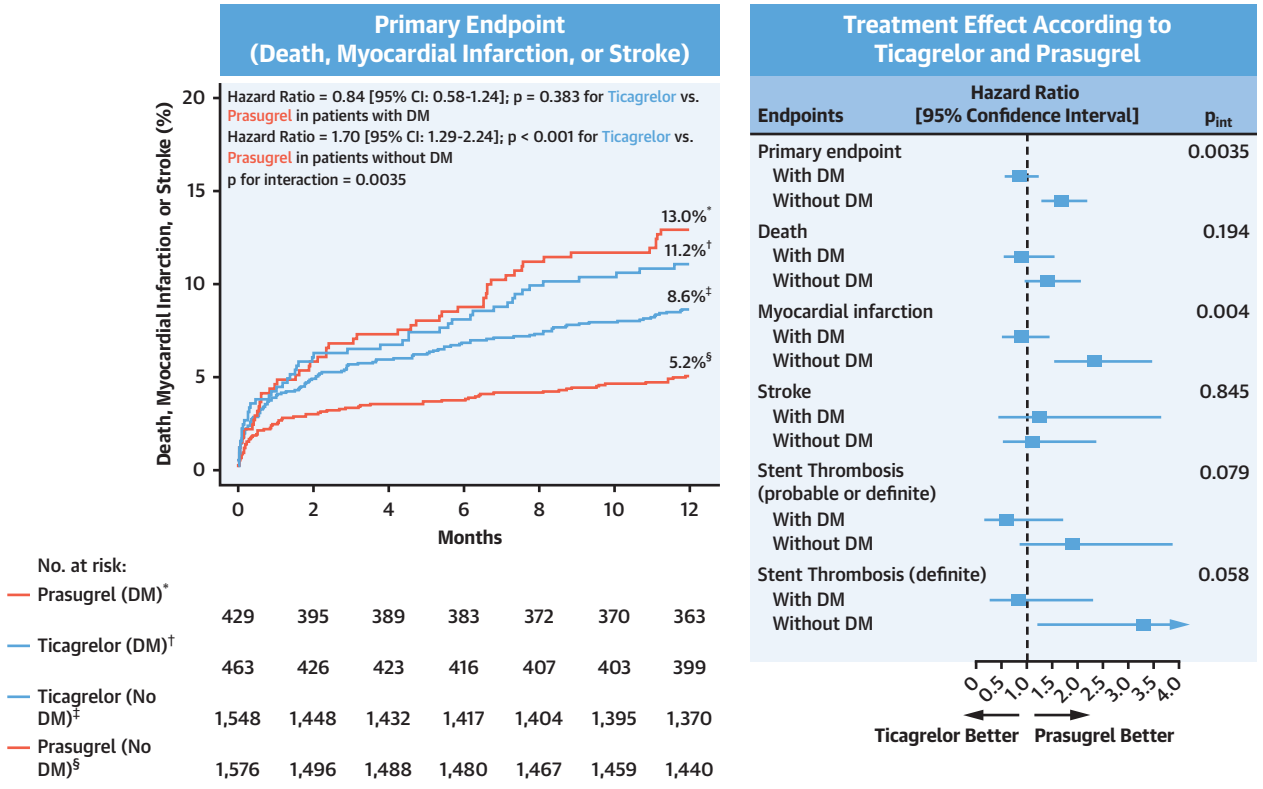
Values are numbers of events with Kaplan-Meier estimates (%) for the primary endpoint and death or cumulative incidence (%) after accounting for competing risk for the remaining endpoints. Bleeding was analyzed in a modified intention-to-treat population, which included all patients with at least 1 application of the study drug; they were assessed for up to 1 week following drug discontinuation. The risk estimates (hazard ratios with 95% CIs) were obtained from the Cox proportional hazards model after adjustment for participating center and stratification according to clinical presentation (acute coronary syndrome with or without ST-segment elevation) and with the interaction term entered into the model. *1-year cumulative incidence (%). †1-year cumulative incidence accounting for competing risks (%).

BARC = Bleeding Academic Research Consortium; CI = confidence interval; STEMI = ST-segment elevation myocardial infarction.

Supplemental Table S3. Data did not differ significantly between the prasugrel and ticagrelor arms (except for study drug per se) in patients with or without DM.

CLINICAL OUTCOMES. The median follow-up duration was 365.2 days (IQR: 365.2 to 365.2 days) in patients with DM and 365.2 days (IQR: 365.2 to 365.2 days) in patients without DM (p = 0.548). One-year follow-up was complete in all but 22 patients (2.5%) with DM and 68 patients (2.2%) without DM (p = 0.606). Clinical outcomes are shown in **Table 2**. In patients with DM, the primary endpoint (death of any cause, myocardial infarction, or stroke at 1 year after randomization) occurred in 51 patients in the ticagrelor group and 55 patients in the prasugrel group (cumulative incidence of the primary endpoint 11.2% and 13.0%, respectively; HR: 0.84; 95% CI: 0.58 to 1.24; p = 0.383) (**Central Illustration**). In patients without DM, the primary endpoint occurred in 132 patients in the ticagrelor group and 81 patients in the prasugrel group (cumulative incidence of the primary endpoint 8.6% and 5.2%, respectively; HR: 1.70; 95% CI: 1.29 to 2.24; p < 0.001) (**Central Illustration**) There was a significant interaction between treatment arm and diabetic status, showing similar efficacy of prasugrel and ticagrelor in patients with DM and worse results with ticagrelor compared with prasugrel in patients without DM (p for interaction = 0.0035). In patients with DM, there were no differences according to study drug for any of the individual components of the efficacy endpoint (death, myocardial infarction, or stroke) or incidence of stent thrombosis (definite or probable). In patients without DM, there were numerically fewer deaths (3.0% vs. 4.1%; p = 0.077) and a significantly lower

CENTRAL ILLUSTRATION **Efficacy Endpoints With Ticagrelor and Prasugrel in Patients With and Without Diabetes**



Ndrepepa, G. et al. J Am Coll Cardiol Intv. 2020;13(19):2238–47.

(Left) One-year cumulative incidence of the primary endpoint (1-year incidence of death, myocardial infarction, or stroke) in patients with or without diabetes mellitus (DM) assigned to prasugrel or ticagrelor. **(Right)** Treatment effect and interaction associated with ticagrelor or prasugrel in patients with and without DM. Hazard ratios along with 95% confidence intervals (CIs) for the individual endpoints **(right)** are shown in **Table 2**.

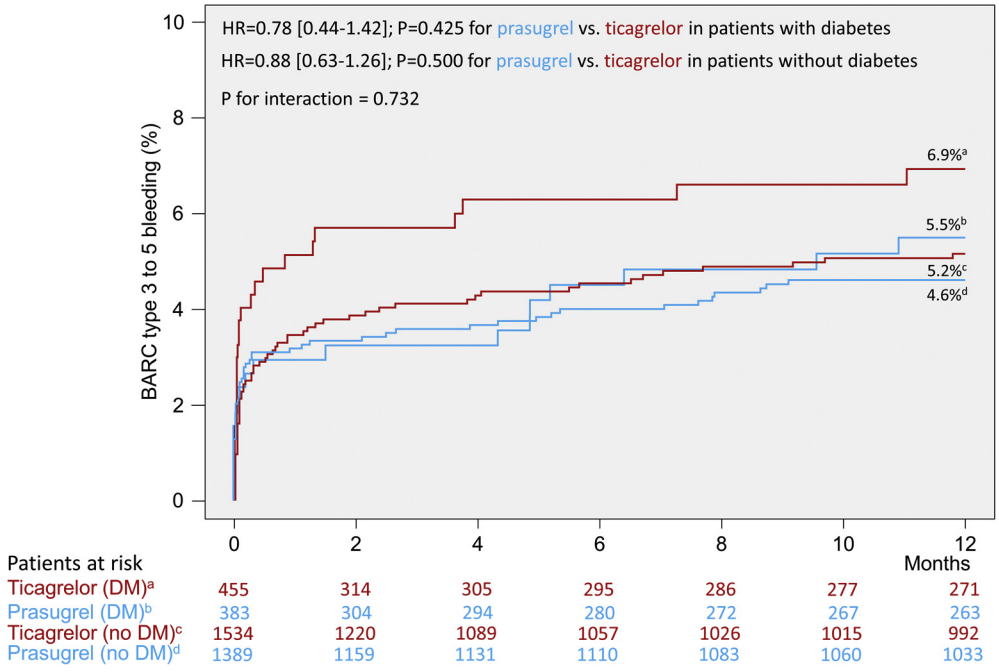
incidence of myocardial infarction (2.1% vs. 4.6%; p < 0.001) and definite stent thrombosis (0.3% vs. 1.0%; p = 0.020) in the prasugrel group compared with the ticagrelor group (**Table 2, Central Illustration**). Timing of the occurrence of stent thrombosis and myocardial infarction is shown in Supplemental Table S4.

The analysis of the primary endpoint was performed in subgroups according to age (≥75 years vs. <75 years), sex (female vs. male), smoking status (active vs. not active smoker), body weight (<60 kg vs. ≥60 kg), serum creatinine (median or higher vs. less than the median), insulin therapy (yes vs. no), cardiogenic shock (yes vs. no), clinical presentation (STEMI, non-ST-segment elevation myocardial infarction, or unstable angina) and treatment strategy (PCI, coronary artery bypass surgery, or conservative therapy). In patients with DM, ticagrelor and prasugrel showed similar efficacy across all subgroups (Supplemental Figure 1). In patients without DM, prasugrel reduced ischemic events in patients <75 years of age, male patients, nonsmokers, patients with body weight ≥60 kg, patients with serum creatinine ≥83.1 μmol/l, patients without cardiogenic shock, patients with STEMI, and those treated with PCI compared with ticagrelor (Supplemental Figure 2). However, there was no significant interaction between treatment arm and any of the variables in terms of efficacy.

Study drug discontinuation rates and antithrombotic medication after discontinuation of study drug during follow-up are shown in Supplemental Table S5.

BLEEDING EVENTS. Bleeding events are shown in **Table 2**. In patients with DM, the safety endpoint (BARC types 3 to 5 bleeding) occurred in 27 patients in the ticagrelor group and 19 patients in the prasugrel

FIGURE 1 **1-Year Cumulative Incidence Accounting for Competing Risks for the Safety Endpoint (1-Year Incidence of BARC Types 3 to 5 Bleeding) in Patients With or Without DM Assigned to Prasugrel or Ticagrelor**



Bleeding was evaluated in the modified intention-to-treat population. BARC = Bleeding Academic Research Consortium; DM = diabetes mellitus; HR = hazard ratio.

group (cumulative incidence accounting for competing risks for BARC types 3 to 5 bleeding 6.9% vs. 5.5%; respectively; HR: 1.27; 95% CI: 0.70 to 2.29; p = 0.425) (Figure 1). In patients without DM, the safety endpoint occurred in 68 patients in the ticagrelor group and 60 patients in the prasugrel group (cumulative incidence accounting for competing risks 5.2% vs. 4.6%, respectively; HR: 1.13; 95% CI: 0.80 to 1.60; p = 0.500) (Figure 1). Individual classes of bleeding according to prasugrel or ticagrelor in patients with and without DM are shown in Table 2.

DISCUSSION

The main findings of this study can be summarized as follows. 1) In patients with ACS with DM in whom an invasive treatment strategy was planned, ticagrelor and prasugrel showed comparable efficacy in terms of reduction of ischemic events (a composite of death, myocardial infarction, or stroke) up to 1 year after randomization. 2) In patients without DM, prasugrel was superior to ticagrelor in terms of reduction of the risk for ischemic events up to 1 year after randomization. Thus, there was a significant treatment effect-by-diabetic status interaction demonstrating no statistically significant difference between ticagrelor and prasugrel in reducing ischemic events in patients with DM and superior efficacy of prasugrel over ticagrelor in reducing ischemic events in patients without DM. 3) Therapy with ticagrelor or prasugrel appears to be associated with a similar risk for bleeding irrespective of diabetic status.

The evidence on the efficacy and safety of prasugrel or ticagrelor in patients with ACS with DM undergoing PCI remains controversial. In the TRITON-TIMI 38 trial, prasugrel reduced the risk for ischemic events in patients with and without DM compared with clopidogrel. Of note, net clinical benefit (a composite of ischemic and bleeding events) was greater in patients with DM compared with those without DM (p for interaction = 0.05) (6). In the PLATO trial, the reduction in the incidence of ischemic events by ticagrelor in patients with DM was consistent with the results in the overall trial (10). However, the magnitude of ischemic benefit of ticagrelor was enhanced in patients with levels of glycated hemoglobin or glucose higher than the median, albeit without an interaction between treatment

effect and glycated hemoglobin or glucose level (10). In a recent large observational study of patients with ACS and DM undergoing PCI, prasugrel reduced the risk for death at 90 days and 1 year compared with clopidogrel. Other studies evidenced the efficacy of ticagrelor in patients with DM undergoing high-risk PCI (14) and those with previous myocardial infarction (15) or stable coronary artery disease (16). A comparison of absolute reductions by prasugrel over clopidogrel in the TRITON-TIMI 38 and PLATO trials (6,10) has led to the suggestion that prasugrel might be better than ticagrelor in patients with ACS with DM (17). However, these observations should be interpreted with great caution, given the marked differences between the trials. The PRAGUE-18 (Comparison of Prasugrel and Ticagrelor in the Treatment of Acute Myocardial Infarction) trial did not demonstrate a difference between ticagrelor and prasugrel in terms of anti-ischemic efficacy or risk for bleeding in the overall group of patients with ACS or patients with DM (18). In a propensity-matched analysis (386 pairs treated with prasugrel or ticagrelor) of a registry-based data, the rate of net adverse cardiovascular events (death, stroke, myocardial infarction, or BARC types 3 to 5 bleeding) did not differ significantly in prasugrel- or ticagrelor-treated patients after 19 ± 5 months of follow-up. Nevertheless, patients treated with ticagrelor had a lower incidence of death and BARC types 2 to 5 bleeding compared with prasugrel (19). Although it is unanimously agreed that patients with ACS and DM require strong platelet inhibition, no conclusion from these observations can be drawn yet as to whether prasugrel or ticagrelor should be the preferred antiplatelet strategy in these patients.

Our study showed that ticagrelor and prasugrel exerted similar efficacy in terms of ischemic events, with no significant difference in the risk for bleeding between the drugs in patients with ACS with DM in whom invasive treatment (mostly PCI) was planned. The reasons why prasugrel did not show superior efficacy (compared with ticagrelor) in the diabetic subset of patients with ACS as in the overall cohort of patients with ACS (11,20) remain poorly understood. From a mechanistic standpoint, irreversibility of platelet inhibition by prasugrel may be seen as favorable in the context of DM. However, there is evidence suggesting that the efficacy of prasugrel in patients with DM may be attenuated. A pharmacodynamic study by Erlinge et al. (21) showed lower plasma levels of the active metabolites of prasugrel and clopidogrel in patients with DM treated with aspirin. In addition, the low chronic inflammatory state associated with DM may reduce the metabolic activity of major cytochrome P450 isoforms involved in the biotransformation of prasugrel to its active compound (22).

Available evidence suggests that ticagrelor may be particularly advantageous in patients with DM undergoing PCI. Pharmacodynamic studies have shown a similar (23,24) or greater (25–27) platelet inhibition by ticagrelor compared with prasugrel in patients with ACS with DM. In the OPTIMUS 4 trial, which included aspirin-treated patients with ACS and DM, ticagrelor exerted a similar or greater inhibition of adenosine diphosphate–induced platelet reactivity in acute (30 min to 2 h) and maintenance (1 week) phases of treatment compared with prasugrel (23). Another randomized trial of patients with STEMI and DM showed a rapid onset of action after loading doses of ticagrelor and prasugrel in decreasing platelet reactivity and a similar degree of platelet inhibition up to 12 h, with only a trend toward stronger inhibition by ticagrelor at 2 h (24). Besides platelet inhibition, ticagrelor may exert other salutary vascular effects via its pleiotropic effects, such as increased circulation levels of adenosine (via reduced cellular uptake) (28) leading to vasodilatation (29), improved endothelial function (29,30), and modulation (suppression) of inflammation (31). A recent randomized study of ticagrelor versus prasugrel in patients with DM presenting with non-ST-segment elevation ACS showed significant reductions of inflammatory cytokines such as interleukin-6 and tumor necrosis factor-alpha and increased circulating endothelial progenitor cells by ticagrelor, leading to improved endothelial function in these patients (31). Ticagrelor was also shown to improve microvascular function compared with clopidogrel in patients with DM presenting with STEMI (32). It is also important to note that patients with DM are characterized by increased platelet turnover rates, with newly generated platelets, typically hyperreactive, being more frequently released into the systemic circulation (33,34). This may explain why drugs with twice-daily administration, such as ticagrelor, may be beneficial, as they would allow more efficacious platelet inhibition over the 24-h time period compared with drugs administered once daily (33,35).

STUDY LIMITATIONS. First, although the analysis according to diabetic status was pre-specified in the setting of the ISAR-REACT 5 trial, it carries the known limitations of subgroup analyses in general, and its results should be considered as exploratory or hypothesis generating.

Second, the DM cohort was not powered to show a difference in the primary endpoint according to study drug. Thus, an absolute difference of 1.8% in the primary endpoint favoring ticagrelor remained statistically insignificant.

Third, although baseline characteristics were well balanced in patients with DM treated with prasugrel or ticagrelor, randomization was not performed according to diabetic status, and consequently unidentified confounders cannot entirely be ruled out.

Fourth, because data on glycated hemoglobin and other markers of metabolic control were not available, the impact of the quality of metabolic control on drug efficacy could not be assessed.

CONCLUSIONS

The presence or absence of DM seems to affect the relative efficacy of ticagrelor and prasugrel in patients with ACS. In patients with DM, the efficacy of ticagrelor was comparable with that of prasugrel. The efficacy advantage of prasugrel over ticagrelor observed in the entire ISAR-REACT 5 population was confined to patients without DM.

ADDRESS FOR CORRESPONDENCE: Dr. Adnan Kastrati, Deutsches Herzzentrum München, Lazarettstrasse 36, 80636 München, Germany. E-mail: kastrati@dhm.mhn.de.

PERSPECTIVES

WHAT IS KNOWN? Patients with DM presenting with ACS have increased platelet reactivity, reduced response to antiplatelet drugs, and a higher risk for thrombotic and ischemic events and mortality than patients without DM. Patients with DM presenting with ACS and undergoing PCI require potent platelet inhibition.

WHAT IS NEW? This pre-specified analysis of the ISAR-REACT 5 trial provides data on the efficacy and safety of ticagrelor versus prasugrel in patients with and without DM undergoing invasive treatment (mostly PCI). The study showed that ticagrelor and prasugrel have comparable efficacy in terms of reduction of ischemic events (death, myocardial infarction, or stroke) in patients with DM and that therapy with ticagrelor or prasugrel appears to be associated with a similar risk for bleeding irrespective of diabetic status.

WHAT IS NEXT? Although ticagrelor and prasugrel showed comparable efficacy and safety in the present study, specifically designed randomized and powered studies are needed to establish the most optimal antithrombotic therapy in patients with DM presenting with ACS and undergoing invasive therapy.

REFERENCES

1. Angiolillo DJ, Fernandez-Ortiz A, Bernardo E, et al. Platelet function profiles in patients with type 2 diabetes and coronary artery disease on combined aspirin and clopidogrel treatment. Diabetes 2005;54:2430–5.

2. Angiolillo DJ, Jakubowski JA, Ferreiro JL, et al. Impaired responsiveness to the platelet P2Y12 receptor antagonist clopidogrel in patients with type 2 diabetes and coronary artery disease. J Am Coll Cardiol 2014;64:1005–14.

3. Haffner SM, Lehto S, Ronnemaa T, Pyorala K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. N Engl J Med 1998;339:229–34.

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

5. Roffi M, Topol EJ. Percutaneous coronary intervention in diabetic patients with non-ST-segment elevation acute coronary syndromes. Eur Heart J 2004;25:190–8.

6. 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.

7. Angiolillo DJ, Shoemaker SB, Desai B, et al. Randomized comparison of a high clopidogrel maintenance dose in patients with diabetes mellitus and coronary artery disease: results of the Optimizing Antiplatelet Therapy in Diabetes Mellitus (OPTIMUS) study. Circulation 2007;115:708–16.

8. Angiolillo DJ, Badimon JJ, Saucedo JF, et al. A pharmacodynamic comparison of prasugrel vs. high-dose clopidogrel in patients with type 2 diabetes mellitus and coronary artery disease: results of the Optimizing Anti-Platelet Therapy in Diabetes Mellitus (OPTIMUS)-3 trial. Eur Heart J 2011;32:838–46.

9. Sweeny JM, Angiolillo DJ, Franchi F, et al. Impact of diabetes mellitus on the pharmacodynamic effects of ticagrelor versus clopidogrel in troponin-negative acute coronary syndrome patients undergoing ad hoc percutaneous coronary intervention. J Am Heart Assoc 2017;6:e005650.

10. 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. Eur Heart J 2010;31:3006–16.

11. Schupke S, Neumann FJ, Menichelli M, et al. Ticagrelor or prasugrel in patients with acute coronary syndromes. N Engl J Med 2019;381:1524–34.

12. Mehran R, Rao SV, Bhatt DL, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. Circulation 2011;123:2736–47.

13. Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation 2007;115:2344–51.

14. Angiolillo DJ, Baber U, Sartori S, et al. Ticagrelor with or without aspirin in high-risk patients with diabetes mellitus undergoing percutaneous coronary intervention. J Am Coll Cardiol 2020;75:2403–13.

15. Bhatt DL, Bonaca MP, Bansilal S, et al. Reduction in ischemic events with ticagrelor in diabetic patients with prior myocardial infarction in PEGASUS-TIMI 54. J Am Coll Cardiol 2016;67:2732–40.

16. Steg PG, Bhatt DL, Simon T, et al. Ticagrelor in patients with stable coronary disease and diabetes. N Engl J Med 2019;381:1309–20.

17. Saucedo JF. Antiplatelet therapy for patients with diabetes mellitus and acute coronary syndrome. Prim Care Diabetes 2012;6:167–77.

18. Motovska Z, Hlinomaz O, Miklik R, et al. Prasugrel versus ticagrelor in patients with acute myocardial infarction treated with primary percutaneous coronary intervention: multicenter randomized PRAGUE-18 study. Circulation 2016;134:1603–12.

19. Peyracchia M, Saglietto A, Biole C, et al. Efficacy and safety of clopidogrel, prasugrel and ticagrelor in ACS patients treated with PCI: a propensity score analysis of the RENAMI and BleeMACS registries. Am J Cardiovasc Drugs 2020;20:259–69.

20. Baldetti L, Melillo F, Moroni F, et al. Meta-analysis comparing $P2Y_{12}$ inhibitors in acute coronary syndrome. Am J Cardiol 2020;125:1815–22.

21. Erlinge D, Varenhorst C, Braun OO, et al. Patients with poor responsiveness to thienopyridine treatment or with diabetes have lower levels of circulating active metabolite, but their platelets respond normally to active metabolite added ex vivo. J Am Coll Cardiol 2008;52:1968–77.

22. Gravel S, Chiasson JL, Turgeon J, Grangeon A, Michaud V. Modulation of CYP450 activities in patients with type 2 diabetes. Clin Pharmacol Ther 2019;106:1280–9.

23. 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.

24. Sardella G, Mancone M, Stio RE, et al. Prasugrel or ticagrelor in ST-segment-elevation myocardial infarction patients with diabetes mellitus. Circulation 2017;136:602–4.

25. Alexopoulos D, Xanthopoulou I, Mavronasiou E, et al. Randomized assessment of ticagrelor versus prasugrel antiplatelet effects in patients with diabetes. Diabetes Care 2013;36:2211–6.

26. Alexopoulos D, Vogiatzi C, Stavrou K, et al. Diabetes mellitus and platelet reactivity in patients under prasugrel or ticagrelor treatment: an observational study. Cardiovasc Diabetol 2015;14:68.

27. Laine M, Frere C, Toesca R, et al. Ticagrelor versus prasugrel in diabetic patients with an acute coronary syndrome. A pharmacodynamic randomised study. Thromb Haemost 2014;111:273–8.

28. Armstrong D, Summers C, Ewart L, Nylander S, Sidaway JE, van Giezen JJ. Characterization of the adenosine pharmacology of ticagrelor reveals therapeutically relevant inhibition of equilibrative nucleoside transporter 1. J Cardiovasc Pharmacol Ther 2014;19:209–19.

29. Cattaneo M, Schulz R, Nylander S. Adenosine-mediated effects of ticagrelor: evidence and potential clinical relevance. J Am Coll Cardiol 2014;63:2503–9.

30. Mangiacapra F, Panaioli E, Colaiori I, et al. Clopidogrel versus ticagrelor for antiplatelet maintenance in diabetic patients treated with percutaneous coronary intervention: results of the CLOTILDIA study (Clopidogrel High Dose Versus Ticagrelor for Antiplatelet Maintenance in Diabetic Patients). Circulation 2016;134:835–7.

31. Jeong HS, Hong SJ, Cho SA, et al. Comparison of ticagrelor versus prasugrel for inflammation, vascular function, and circulating endothelial progenitor cells in diabetic patients with non-ST-segment elevation acute coronary syndrome requiring coronary stenting: a prospective, randomized, crossover trial. J Am Coll Cardiol Intv 2017;10:1646–58.

32. Liu Y, Ding LY, Li XZ. Therapy with ticagrelor for ST-elevated acute coronary syndrome accompanied by diabetes mellitus. Eur Rev Med Pharmacol Sci 2019;23:312–8.

33. Ferreiro JL, Angiolillo DJ. Diabetes and antiplatelet therapy in acute coronary syndrome. Circulation 2011;123:798–813.

34. Bernlochner I, Goedel A, Plischke C, et al. Impact of immature platelets on platelet response to ticagrelor and prasugrel in patients with acute coronary syndrome. Eur Heart J 2015;36:3202–10.

35. Capodanno D, Patel A, Dharmashankar K, et al. Pharmacodynamic effects of different aspirin dosing regimens in type 2 diabetes mellitus patients with coronary artery disease. Circ Cardiovasc Interv 2011;4:180–7.

KEY WORDS acute coronary syndrome, diabetes, percutaneous coronary intervention, prasugrel, ticagrelor

APPENDIX For supplemental tables and figures, please see the online version of this paper.