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Diabetes-Related Factors and the Effects of Ticagrelor Plus Aspirin in the THEMIS and THEMIS-PCI Trials



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ABSTRACT

BACKGROUND THEMIS (The Effect of Ticagrelor on Health Outcomes in Diabetes Mellitus Patients Intervention Study) (n = 19,220) and its pre-specified THEMIS-PCI (The Effect of Ticagrelor on Health Outcomes in Diabetes Mellitus Patients Intervention Study-Percutaneous Coronary Intervention) (n = 11,154) subanalysis showed, in individuals with type 2 diabetes mellitus (median duration 10.0 years; HbA_{1c} 7.1%) and stable coronary artery disease without prior myocardial infarction (MI) or stroke, that ticagrelor plus aspirin (compared with placebo plus aspirin) produced a favorable net clinical benefit (composite of all-cause mortality, MI, stroke, fatal bleeding, and intracranial bleeding) if the patients had a previous percutaneous coronary intervention.

OBJECTIVES In these post hoc analyses, the authors examined whether the primary efficacy outcome (cardiovascular death, MI, stroke: 3-point major adverse cardiovascular events [MACE]), primary safety outcome (Thrombolysis In Myocardial Infarction-defined major bleeding) and net clinical benefit varied with diabetes-related factors.

METHODS Outcomes were analyzed across baseline diabetes duration, HbA_{1c}, and antihyperglycemic medications.

RESULTS In THEMIS, the incidence of 3-point MACE increased with diabetes duration (6.7% for ≤5 years, 11.1% for >20 years) and HbA_{1c} (6.4% for ≤6.0%, 11.8% for >10.0%). The relative benefits of ticagrelor plus aspirin on 3-point MACE reduction (hazard ratio [HR]: 0.90; p = 0.04) were generally consistent across subgroups. Major bleeding event rate (overall: 1.6%) did not vary by diabetes duration or HbA_{1c} and was increased similarly by ticagrelor across all subgroups (HR: 2.32; p < 0.001). These findings were mirrored in THEMIS-PCI. The efficacy and safety of ticagrelor plus aspirin did not differ by baseline antihyperglycemic therapy. In THEMIS-PCI, but not THEMIS, ticagrelor generally produced favorable net clinical benefit across diabetes duration, HbA_{1c}, and antihyperglycemic medications.

CONCLUSION Ticagrelor plus aspirin yielded generally consistent and favorable net clinical benefit across the diabetes-related factors in THEMIS-PCI but not in the overall THEMIS population. (J Am Coll Cardiol 2021;77:2366-77) © 2021 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).



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Individuals with both type 2 diabetes mellitus and coronary artery disease are at high risk for cardiovascular events (1-5). Among those with acute coronary syndrome (6) or a history of myocardial infarction (MI) (7), the addition of the reversible P2Y₁₂ receptor antagonist ticagrelor to background aspirin therapy can offer enhanced protection against cardiovascular events in patients both with and without diabetes. Before the reporting of THEMIS (The Effect of Ticagrelor on Health Outcomes in Diabetes Mellitus Patients Intervention Study) (8), it was unknown if expanding antiplatelet therapy beyond aspirin would yield additional benefits in individuals who have type 2 diabetes mellitus and

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coronary artery disease but without a prior cardiovascular event. In brief, THEMIS (n = 19,220) and the pre-specified THEMIS-PCI (Effect of Ticagrelor on Health Outcomes in Diabetes Mellitus Patients Intervention Study-Percutaneous Coronary Intervention) (n = 11,154) subgroup analysis (9) suggested that dual antiplatelet therapy (DAPT) with ticagrelor and low-dose aspirin may specifically benefit individuals with type 2 diabetes mellitus and stable atherosclerosis but without a history of MI or stroke and who had previously undergone a PCI. The U.S. Food and Drug Administration has since, based on THEMIS, additionally approved ticagrelor to reduce the risk of a first MI or stroke in patients with coronary artery disease who are at high risk for such events regardless of whether they have diabetes or not (10), and Health Canada, based on THEMIS-PCI, has expanded approval of ticagrelor more specifically in patients with coronary artery disease, type 2 diabetes, and a history of PCI (11).

The ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified Release Controlled Evaluation) investigators showed that duration of diabetes could influence cardiovascular responses to antihyperglycemic agents (12,13). More recently, an analysis from the DECLARE-TIMI 58 (Dapagliflozin Effect on Cardiovascular Events—Thrombolysis In Myocardial Infarction 58) study (14) demonstrated that in a contemporaneous type 2 diabetes mellitus population with well controlled risk factors, diabetes duration was again associated with increasing risk of atherosclerotic cardiovascular disease. Of note, meta-analyses of major trials investigating the potential benefit of glucose control on cardiovascular outcomes have revealed that although intensive glucose control had no overall benefit on major cardiovascular events, there was a modest reduction in MI (15,16). These collective findings led us to consider if diabetes duration and baseline HbA_{1c} levels may have, in some way, driven the outcomes observed with the ticagrelor plus aspirin strategy adopted in THEMIS and its THEMIS-PCI subpopulation. Furthermore, the robust clinical trial evidence demonstrating that sodium-glucose cotransporter 2 (SGLT2) inhibitors and many glucagon-like peptide 1 (GLP-1) receptor agonists can offer clinically significant cardiovascular benefits (17-19) also led us to investigate whether any of the currently available pharmacotherapies for type 2 diabetes mellitus could have influenced the clinical outcomes evoked by the combination of ticagrelor and aspirin.

ABBREVIATIONS AND ACRONYMS

- DAPT** = dual antiplatelet therapy
DPP-4 = dipeptidyl peptidase 4
GLP-1 = glucagon-like peptide 1
HbA_{1c} = glycated hemoglobin
MACE = major adverse cardiovascular events
MI = myocardial infarction
PCI = percutaneous coronary intervention
SGLT2 = sodium-glucose cotransporter-2
THEMIS = The Effect of Ticagrelor on Health Outcomes in Diabetes Mellitus Patients Intervention Study
THEMIS-PCI = THEMIS-Percutaneous Coronary Intervention
TIMI = Thrombolysis In Myocardial Infarction

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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 [Author Center](#).

METHODS

The design, baseline characteristics, and main results of THEMIS and THEMIS-PCI have been reported (8,9,20). Briefly, enrollment for the phase 3b, double-blinded, placebo-controlled THEMIS trial took place at 1,315 sites in 42 countries from February 10, 2014, to May 24, 2016 (8). All of the trial centers obtained ethical approval according to local regulations. A total of 19,220 individuals (31.4% women) with angiographically proven coronary artery disease and type 2 diabetes mellitus (median duration at trial entry: 10.0 years; median baseline HbA_{1c}: 7.1% [54 mmol/mol]), but no history of MI or stroke, were randomized 1:1 to either ticagrelor or placebo in addition to low-dose aspirin (75 to 150 mg) and other evidence-based therapies for a median follow-up of 39.9 months (8). At study initiation, participants allocated to the ticagrelor arm took 90 mg ticagrelor twice daily (orally). Approximately a year later, because the combination of 60 mg ticagrelor twice daily with low-dose aspirin was demonstrated in another trial of participants with stable atherosclerosis to have a better tolerability and similar efficacy profile than that of 90 mg ticagrelor twice daily plus low-dose aspirin (7), the ticagrelor study dose was amended to 60 mg twice daily for all participants.

The primary efficacy outcome was the time to first occurrence of a 3-point major adverse cardiovascular events (MACE) composite of cardiovascular death, MI, or stroke. The primary safety outcome was major bleeding per the TIMI definition. Net clinical benefit was a pre-specified exploratory endpoint consisting of irreversible harm events and was evaluated as time to first event of the composite of all-cause mortality, MI, stroke, fatal bleeding, or intracranial bleeding (8,20).

STATISTICAL ANALYSES. In these nonpre-specified and post hoc analyses, the THEMIS population and THEMIS-PCI subpopulation were examined according to the following baseline characteristics: duration of diabetes, HbA_{1c} level and use of metformin, sulfonylurea, and insulin or any of the newer antihyperglycemic classes, namely, dipeptidyl peptidase-4 (DPP-4) inhibitors, SGLT2 inhibitors, and GLP-1 receptor agonists.

The efficacy analyses were conducted according to the intention-to-treat principle: All participants who underwent randomization were included; all events that occurred before or at the primary analysis censoring date (October 29, 2018) were entered into the analyses. The safety analyses were performed in the safety analysis population, which included all

participants who had been randomized and who had taken at least 1 dose of the assigned study drug; all events that occurred between randomization and through 7 days after the last dose was administered were included in the analyses. Participants randomized at sites closed by the sponsor before unblinding were excluded from all efficacy and safety analyses (20).

For time-to-event analyses, Cox proportional hazards models were used, with the treatment group as the explanatory variable and the Efron method for ties; confidence intervals (CIs) and p values were calculated with the use of Wald statistics. Given that the CIs for net clinical benefit were not adjusted for multiple comparisons, the inferences drawn from these intervals may not be reproducible. Follow-up data for participants without events were censored either on the censoring date for the primary analysis or on the date of the last clinical assessment, whichever came first. The results of Kaplan-Meier analyses are presented at 36 months. The p values for interaction between treatment groups and subgroups were calculated from the Cox proportional hazards model with treatment group, subgroup, and interaction term as explanatory variables. All analyses were conducted with SAS software version 9.4 (SAS Institute, Cary, North Carolina).

ROLE OF THE FUNDER. THEMIS (NCT01991795) was designed and governed by an academic Executive Committee that included nonvoting members who represented the sponsor, AstraZeneca. AstraZeneca funded the trial and was involved in the data collection and analysis. The data presented herein were independently analyzed by the Baim Clinical Research Institute, an academic research organization.

RESULTS

As previously reported, the baseline characteristics of the participants in the ticagrelor plus aspirin and placebo plus aspirin arms of the full THEMIS cohort and THEMIS-PCI subcohort were balanced (8,9). The baseline characteristics of the full THEMIS population stratified by duration of diabetes and baseline HbA_{1c} are summarized in Supplemental Tables 1 and 2. In contrast, there were clinically significant differences between those who had undergone a PCI procedure before study entry and those who had not (9).

The primary efficacy outcome (3-point MACE) was recorded for 8.1% of the overall THEMIS cohort and 7.3% of the THEMIS-PCI subcohort. In THEMIS, the event rates of the 3-point MACE were generally higher

TABLE 1 Primary Efficacy Outcome in the Overall THEMIS Cohort By Baseline Diabetes-Related Factors and Selected Baseline Antihyperglycemic Therapy

	Ticagrelor		Placebo		Hazard Ratio (95% CI)	p Value	Pinteraction	Risk Difference % (95% CI)	p Value	Pinteraction
	N	Patients With Events	N	Patients With Events						
Overall	9,619	736 (7.7)	9,601	818 (8.5)	0.90 (0.81-0.99)	0.0378		-0.9 (-1.6 to -0.1)	0.0281	
Duration of type 2 diabetes mellitus at baseline, yrs							0.8255			0.8169
≤5	2,462	157 (6.4)	2,426	169 (7.0)	0.91 (0.74-1.14)	0.4189		-0.6 (-2.0 to 0.8)	0.4225	
>5 to 10	2,353	146 (6.2)	2,461	182 (7.4)	0.84 (0.68-1.05)	0.1208		-1.2 (-2.6 to 0.2)	0.1091	
>10 to 15	1,944	170 (8.7)	1,949	173 (8.9)	0.99 (0.80-1.23)	0.9477		-0.1 (-1.9 to 1.6)	0.9100	
>15 to 20	1,293	100 (7.7)	1,250	116 (9.3)	0.84 (0.64-1.10)	0.2067		-1.5 (-3.7 to 0.6)	0.1765	
>20	1,561	163 (10.4)	1,511	177 (11.7)	0.88 (0.71-1.09)	0.2371		-1.3 (-3.5 to 0.9)	0.2746	
Baseline HbA _{1c} , %							0.1567			0.1542
≤6	1,263	86 (6.8)	1,285	76 (5.9)	1.16 (0.85-1.57)	0.3549		0.9 (-1.0 to 2.8)	0.3724	
>6 to 7	3,301	209 (6.3)	3,259	241 (7.4)	0.86 (0.71-1.04)	0.1119		-1.1 (-2.3 to 0.2)	0.0967	
>7 to 8	2,334	184 (7.9)	2,449	215 (8.8)	0.90 (0.74-1.10)	0.3177		-0.9 (-2.5 to 0.7)	0.2722	
>8 to 9	1,227	108 (8.8)	1,163	122 (10.5)	0.84 (0.65-1.09)	0.1891		-1.7 (-4.1 to 0.7)	0.1658	
>9 to 10	633	51 (8.1)	615	75 (12.2)	0.64 (0.45-0.92)	0.0144		-4.1 (-7.5 to -0.8)	0.0185	
>10	625	77 (12.3)	596	67 (11.2)	1.10 (0.79-1.52)	0.5748		1.1 (-2.5 to 4.7)	0.5948	
Use of key antihyperglycemic agents										
Metformin							0.0695			0.0854
Yes	7,304	494 (6.8)	7,310	583 (8.0)	0.85 (0.75-0.95)	0.0065		-1.2 (-2.1 to -0.4)	0.0053	
No	2,315	242 (10.5)	2,291	235 (10.3)	1.03 (0.86-1.24)	0.7194		0.2 (-1.6 to 2.0)	0.8467	
Sulfonylurea							0.2290			0.2499
Yes	3,350	267 (8.0)	3,416	281 (8.2)	0.98 (0.83-1.16)	0.7943		-0.3 (-1.6 to 1.0)	0.7215	
No	6,269	469 (7.5)	6,185	537 (8.7)	0.86 (0.76-0.97)	0.0174		-1.2 (-2.2 to -0.2)	0.0149	
Dipeptidyl peptidase 4 inhibitor							0.6870			0.6646
Yes	1,819	124 (6.8)	1,795	130 (7.2)	0.94 (0.74-1.20)	0.6327		-0.4 (-2.1 to 1.2)	0.6489	
No	7,800	612 (7.8)	7,806	688 (8.8)	0.89 (0.80-0.99)	0.0399		-1.0 (-1.8 to -0.1)	0.0298	
Sodium-glucose cotransporter 2 inhibitor							0.7795			0.8611
Yes	189	9 (4.8)	174	10 (5.7)	0.78 (0.31-1.92)	0.5821		-1.0 (-5.6 to 3.6)	0.8144	
No	9,430	727 (7.7)	9,427	808 (8.6)	0.90 (0.82-1.00)	0.0435		-0.9 (-1.6 to -0.1)	0.0310	
Glucagon-like peptide 1 receptor agonist							0.9090			0.8206
Yes	203	15 (7.4)	210	16 (7.6)	0.92 (0.46-1.87)	0.8256		-0.2 (-5.3 to 4.9)	1.0000	
No	9,416	721 (7.7)	9,391	802 (8.5)	0.90 (0.81-0.99)	0.0383		-0.9 (-1.7 to -0.1)	0.0265	
Insulin							0.4562			0.4573
Yes	2,798	286 (10.2)	2,710	323 (11.9)	0.85 (0.73-1.00)	0.0515		-1.7 (-3.4 to -0.0)	0.0480	
No	6,821	450 (6.6)	6,891	495 (7.2)	0.92 (0.81-1.05)	0.2145		-0.6 (-1.4 to 0.3)	0.1776	

Values are n or n (%), unless otherwise indicated.

with increasing duration of diabetes (6.7% for ≤5 years and 11.1% for >20 years; $p = 0.0001$) and baseline HbA_{1c} levels (6.4% for ≤6.0% [42 mmol/mol] and 11.8% for >10.0% [86 mmol/mol]; $p = 0.0001$). Similar observations were observed for THEMIS-PCI. The relative benefits of DAPT with ticagrelor plus low-dose aspirin on 3-point MACE in THEMIS (HR: 0.90; 95% CI: 0.81 to 0.99; $p = 0.04$) and THEMIS-PCI (HR: 0.85; 95% CI: 0.74 to 0.97; $p = 0.013$) did not differ across the duration of diabetes and HbA_{1c} subgroups examined (Table 1 and Supplemental Table 3, respectively).

The primary safety outcome (TIMI-defined major bleeding) occurred in 1.6% of the overall THEMIS population (HR: 2.32; 95% CI: 1.82 to 2.94; for ticagrelor vs. placebo; $p < 0.001$) (Supplemental Figure 1) and 2.0% of the THEMIS-PCI subcohort (HR: 2.03; 95% CI: 1.48 to 2.76; for ticagrelor vs. placebo; $p < 0.0001$). Although the frequencies of major bleeding did not vary by diabetes duration or baseline HbA_{1c} levels, they were consistently higher with ticagrelor plus aspirin across all the strata of diabetes duration and HbA_{1c} evaluated (Table 2, Supplemental Table 4).

TABLE 2 Primary Safety Outcome in the Overall THEMIS Cohort By Baseline Diabetes-Related Factors and Selected Baseline Antihyperglycemic Therapy

	Ticagrelor		Placebo		Hazard Ratio (95% CI)	p Value	P _{interaction}
	N	Patients With Events	N	Patients With Events			
Overall	9,562	206 (2.2)	9,531	100 (1.0)	2.32 (1.82-2.94)	<0.001	
Duration of type 2 diabetes mellitus at baseline, yrs							0.8275
≤5	2,445	47 (1.9)	2,406	25 (1.0)	2.04 (1.26-3.32)	0.0039	
>5 to 10	2,343	49 (2.1)	2,444	21 (0.9)	2.75 (1.65-4.59)	0.0001	
>10 to 15	1,931	43 (2.2)	1,933	18 (0.9)	2.72 (1.57-4.72)	0.0004	
>15 to 20	1,287	32 (2.5)	1,244	19 (1.5)	1.88 (1.07-3.32)	0.0291	
>20	1,550	35 (2.3)	1,501	16 (1.1)	2.39 (1.32-4.32)	0.0039	
Baseline HbA _{1c} , %							0.2227
≤6	1,260	27 (2.1)	1,281	12 (0.9)	2.55 (1.29-5.04)	0.0069	
>6 to 7	3,276	81 (2.5)	3,237	36 (1.1)	2.56 (1.73-3.78)	<0.0001	
>7 to 8	2,324	41 (1.8)	2,437	23 (0.9)	2.13 (1.28-3.55)	0.0037	
>8 to 9	1,221	25 (2.0)	1,152	17 (1.5)	1.56 (0.84-2.89)	0.1561	
>9 to 10	629	20 (3.2)	613	3 (0.5)	6.91 (2.05-23.26)	0.0018	
>10	624	8 (1.3)	593	7 (1.2)	1.15 (0.42-3.16)	0.7920	
Metformin use at baseline							0.6126
Yes	7,258	156 (2.1)	7,257	73 (1.0)	2.40 (1.82-3.17)	<0.0001	
No	2,304	50 (2.2)	2,274	27 (1.2)	2.08 (1.30-3.33)	0.0021	
Sulfonylurea use at baseline							0.4937
Yes	3,333	81 (2.4)	3,394	36 (1.1)	2.59 (1.75-3.83)	<0.0001	
No	6,229	125 (2.0)	6,137	64 (1.0)	2.17 (1.60-2.93)	<0.0001	
Dipeptidyl peptidase 4 inhibitor use at baseline							0.6293
Yes	1,811	46 (2.5)	1,784	20 (1.1)	2.61 (1.55-4.42)	0.0003	
No	7,751	160 (2.1)	7,747	80 (1.0)	2.24 (1.72-2.93)	<0.0001	
Sodium-glucose cotransporter 2 inhibitor use at baseline							0.8877
Yes	189	4 (2.1)	172	2 (1.2)	2.08 (0.38-11.36)	0.3985	
No	9,373	202 (2.2)	9,359	98 (1.0)	2.32 (1.82-2.95)	<0.0001	
Glucagon-like peptide 1 receptor agonist use at baseline							0.2811
Yes	202	6 (3.0)	209	1 (0.5)	7.25 (0.87-60.23)	0.0667	
No	9,360	200 (2.1)	9,322	99 (1.1)	2.27 (1.78-2.89)	<0.0001	
Insulin use at baseline							0.5452
Yes	2,779	56 (2.0)	2,685	23 (0.9)	2.65 (1.63-4.31)	<0.0001	
No	6,783	150 (2.2)	6,846	77 (1.1)	2.22 (1.69-2.92)	<0.0001	

Values are n or n (%), unless otherwise indicated.

Regardless of study drug assignment in THEMIS, insulin-using participants were at a relatively higher risk for 3-point MACE (HR: 1.65; 95% CI: 1.49 to 1.83; $p < 0.0001$) but had similar bleeding risks as those who were not on insulin (HR: 0.92; 95% CI: 0.71 to 1.19; $p = 0.52$) (Tables 1 and 2). In contrast, there was no difference in risk for 3-point MACE (HR: 1.00; 95% CI: 0.91 to 1.11; $p = 0.93$) or TIMI major bleeding (HR: 1.12; 95% CI: 0.89 to 1.41; $p = 0.34$) between those who were treated with a sulfonylurea and those who were not. There also did not appear to be any clinically relevant differences in risk for 3-point MACE or bleeding risk when the participants were classified in a similar fashion according to whether

they were treated or not treated with metformin, a DPP-4 inhibitor, SGLT2 inhibitor, or GLP-1 receptor agonist. We found similar results to those described above when the THEMIS-PCI subpopulation was stratified according to baseline antihyperglycemic regimens.

Using the irreversible harm pre-specified definition of net clinical benefit (composite of all-cause mortality, MI, stroke, fatal bleeding, or intracranial bleeding in the intention-to-treat population), net clinical benefit with ticagrelor add-on in the THEMIS cohort and THEMIS-PCI subcohort was similar across diabetes duration and HbA_{1c} (Tables 3 and 4). Notably, ticagrelor was generally associated

TABLE 3 Net Clinical Benefit in the THEMIS Cohort By Baseline Diabetes-Related Factors and Selected Baseline Antihyperglycemic Therapy

	Ticagrelor		Placebo		Hazard Ratio (95% CI)	p Value	Pinteraction	Risk Difference % (95% CI)	p Value	Pinteraction
	N	Patients With Events	N	Patients With Events						
Overall	9,619	968 (10.1)	9,601	1,039 (10.8)	0.93 (0.86-1.02)	0.1249		-0.8 (-1.6 to -0.1)	0.0894	
Duration of type 2 diabetes mellitus at baseline, yrs							0.5082			0.5109
≤5	2,462	198 (8.0)	2,426	213 (8.8)	0.92 (0.75-1.11)	0.3746		-0.7 (-2.3 to 0.8)	0.3541	
>5 to 10	2,353	187 (7.9)	2,461	234 (9.5)	0.84 (0.69-1.02)	0.0738		-1.6 (-3.2 to 0.0)	0.0590	
>10 to 15	1,944	222 (11.4)	1,949	211 (10.8)	1.07 (0.88-1.29)	0.5109		0.6 (-1.4 to 2.6)	0.5751	
>15 to 20	1,293	147 (11.4)	1,250	152 (12.2)	0.95 (0.76-1.19)	0.6684		-0.8 (-3.3 to 1.7)	0.5388	
>20	1,561	214 (13.7)	1,511	228 (15.1)	0.90 (0.75-1.08)	0.2596		-1.4 (-3.9 to 1.1)	0.2807	
Baseline HbA _{1c} , %							0.3597			0.3572
≤6	1,263	117 (9.3)	1,285	107 (8.3)	1.12 (0.86-1.45)	0.4038		0.9 (-1.3 to 3.1)	0.4416	
>6 to 7	3,301	273 (8.3)	3,259	306 (9.4)	0.89 (0.75-1.05)	0.1533		-1.1 (-2.5 to 0.3)	0.1171	
>7 to 8	2,334	249 (10.7)	2,449	276 (11.3)	0.96 (0.81-1.13)	0.6077		-0.6 (-2.4 to 1.2)	0.5173	
>8 to 9	1,227	142 (11.6)	1,163	145 (12.5)	0.93 (0.74-1.17)	0.5446		-0.9 (-3.5 to 1.7)	0.5292	
>9 to 10	633	73 (11.5)	615	96 (15.6)	0.72 (0.53-0.97)	0.0333		-4.1 (-7.9 to -0.3)	0.0386	
>10	625	88 (14.1)	596	82 (13.8)	1.02 (0.76-1.38)	0.8733		0.3 (-3.6 to 4.2)	0.9341	
Metformin use at baseline							0.0688			0.0843
Yes	7,304	664 (9.1)	7,310	750 (10.3)	0.89 (0.80-0.98)	0.0234		-1.2 (-2.1 to -0.2)	0.0174	
No	2,315	304 (13.1)	2,291	289 (12.6)	1.06 (0.90-1.24)	0.4878		0.5 (-1.4 to 2.5)	0.6285	
Sulfonylurea use at baseline							0.1735			0.1871
Yes	3,350	353 (10.5)	3,416	359 (10.5)	1.01 (0.88-1.17)	0.8516		0.0 (-1.4 to 1.5)	1.0000	
No	6,269	615 (9.8)	6,185	680 (11.0)	0.89 (0.80-1.00)	0.0417		-1.2 (-2.3 to -0.1)	0.0321	
Dipeptidyl peptidase 4 inhibitor use at baseline							0.8726			0.8426
Yes	1,819	166 (9.1)	1,795	173 (9.6)	0.95 (0.77-1.17)	0.6226		-0.5 (-2.4 to 1.4)	0.6080	
No	7,800	802 (10.3)	7,806	866 (11.1)	0.93 (0.85-1.02)	0.1448		-0.8 (-1.8 to 0.2)	0.1027	
Sodium-glucose cotransporter 2 inhibitor use at baseline										0.9862
Yes	189	11 (5.8)	174	11 (6.3)	0.83 (0.36-1.92)	0.6642		-0.5 (-5.4 to 4.4)	1.0000	
No	9,430	957 (10.1)	9,427	1,028 (10.9)	0.94 (0.86-1.02)	0.1363		-0.8 (-1.6 to 0.1)	0.0921	
Glucagon-like peptide 1 receptor agonist use at baseline							0.8186			0.9218
Yes	203	21 (10.3)	210	24 (11.4)	0.85 (0.47-1.53)	0.5964		-1.1 (-7.1 to 4.9)	0.7542	
No	9,416	947 (10.1)	9,391	1,015 (10.8)	0.94 (0.86-1.02)	0.1379		-0.8 (-1.6 to 0.1)	0.0949	
Insulin use at baseline							0.5819			0.5878
Yes	2,798	366 (13.1)	2,710	393 (14.5)	0.90 (0.78-1.04)	0.1492		-1.4 (-3.2 to 0.4)	0.1275	
No	6,821	602 (8.8)	6,891	646 (9.4)	0.95 (0.85-1.06)	0.3380		-0.5 (-1.5 to 0.4)	0.2720	

Values are n or n (%), unless otherwise indicated. Net clinical benefit was pre-specified as irreversible harms and evaluated as time to first event of the composite of all-cause mortality, myocardial infarction, stroke, fatal bleeding, or intracranial bleeding in the intention-to-treat population.

with greater net clinical benefit across the diabetes duration and HbA_{1c} spectra in the THEMIS-PCI subcohort but not in the overall THEMIS cohort.

DISCUSSION

The present analyses from the THEMIS cohort (8,20) revealed that although diabetes duration and HbA_{1c} levels correlated positively with the incidence of MACE (Central Illustration), they did not influence major bleeding event rates. The favorable impact of ticagrelor plus aspirin had on MACE was consistent across the duration and HbA_{1c} subgroups examined

albeit with an increase in major bleeding events and baseline antihyperglycemic therapy had no influence on the efficacy and safety of ticagrelor. Importantly, in the THEMIS-PCI but not the overall THEMIS population, the combination of ticagrelor plus aspirin resulted in generally consistent and favorable net clinical benefit across the various diabetes-related factors examined.

Current clinical guidelines consistently recommend aspirin as a secondary prevention strategy for cardiovascular events in type 2 diabetes mellitus (21-24). Contrary to the assumption that DAPT would provide protection beyond that offered by aspirin, results from DAPT studies with type 2 diabetes

TABLE 4 Net Clinical Benefit in the THEMIS-PCI Cohort By Baseline Diabetes-Related Factors and Selected Baseline Antihyperglycemic Therapy

	Ticagrelor		Placebo		Hazard Ratio (95% CI)	p Value	Pinteraction	Risk Difference % (95% CI)	p Value	Pinteraction
	N	Patients With Events	N	Patients With Events						
Overall	5,588	519 (9.3)	5,596	617 (11.0)	0.85 (0.75-0.95)	0.0052	0.012	-1.7 (-2.8 to -0.6)	0.003	
Duration of type 2 diabetes mellitus at baseline, yrs							0.3450			0.3192
≤5	1,374	107 (7.8)	1,392	125 (9.0)	0.86 (0.67-1.12)	0.2581		-1.2 (-3.3 to 0.9)	0.2727	
>5 to 10	1,383	101 (7.3)	1,446	152 (10.5)	0.70 (0.54-0.89)	0.0047		-3.2 (-5.3 to -1.1)	0.0030	
>10 to 15	1,157	125 (10.8)	1,139	122 (10.7)	1.02 (0.79-1.30)	0.9035		0.1 (-2.4 to 2.6)	0.9464	
>15 to 20	760	77 (10.1)	722	86 (11.9)	0.86 (0.63-1.17)	0.3371		-1.8 (-5.0 to 1.4)	0.2813	
>20	881	109 (12.4)	894	132 (14.8)	0.82 (0.64-1.06)	0.1275		-2.4 (-5.6 to 0.8)	0.1461	
Baseline HbA _{1c} , %							0.3467			0.3262
≤6	702	62 (8.8)	744	72 (9.7)	0.90 (0.64-1.26)	0.5387		-0.8 (-3.8 to 2.1)	0.5876	
>6 to 7	1,940	132 (6.8)	1,929	184 (9.5)	0.71 (0.57-0.89)	0.0031		-2.7 (-4.5 to -1.0)	0.0022	
>7 to 8	1,380	149 (10.8)	1,419	166 (11.7)	0.94 (0.76-1.18)	0.5989		-0.9 (-3.2 to 1.4)	0.4731	
>8 to 9	687	75 (10.9)	675	80 (11.9)	0.91 (0.67-1.25)	0.5758		-0.9 (-4.3 to 2.4)	0.6093	
>9 to 10	363	41 (11.3)	360	55 (15.3)	0.72 (0.48-1.08)	0.1137		-4.0 (-8.9 to 1.0)	0.1254	
>10	348	49 (14.1)	330	42 (12.7)	1.10 (0.73-1.67)	0.6391		1.4 (-3.8 to 6.5)	0.6527	
Metformin use at baseline							0.1835			0.1955
Yes	4,253	364 (8.6)	4,311	457 (10.6)	0.80 (0.70-0.92)	0.0020		2.0 (-3.3 to -0.8)	0.0014	
No	1,305	155 (11.9)	1,285	160 (12.5)	0.96 (0.77-1.20)	0.7174		-0.6 (-3.1 to 1.9)	0.6741	
Sulfonylurea use at baseline							0.5999			0.5823
Yes	1,937	190 (9.8)	1,981	220 (11.1)	0.88 (0.73-1.07)	0.2110		-1.3 (-3.2 to 0.6)	0.1921	
No	3,621	329 (9.1)	3,615	397 (11.0)	0.83 (0.72-0.96)	0.0111		-1.9 (-3.3 to -0.5)	0.0078	
Dipeptidyl peptidase 4 inhibitor use at baseline							0.4293			0.4444
Yes	1,204	96 (8.0)	1,164	120 (10.3)	0.77 (0.59-1.00)	0.0533		-2.3 (-4.7 to -0.0)	0.0538	
No	4,354	423 (9.7)	4,432	497 (11.2)	0.87 (0.76-0.99)	0.0313		-1.5 (-2.8 to -0.2)	0.0235	
Sodium-glucose cotransporter 2 inhibitor use at baseline							0.7177			0.7814
Yes	117	6 (5.1)	99	7 (7.1)	0.63 (0.21-1.89)	0.4078		-1.9 (-8.4 to 4.5)	0.5785	
No	5,441	513 (9.4)	5,497	610 (11.1)	0.85 (0.76-0.96)	0.0066		-1.7 (-2.8 to -0.5)	0.0041	
Glucagon-like peptide 1 receptor agonist use at baseline							0.6596			0.6069
Yes	130	15 (11.5)	123	14 (11.4)	0.97 (0.47-2.02)	0.9435		0.2 (-7.7 to 8.0)	1.0000	
No	5,428	504 (9.3)	5,473	603 (11.0)	0.84 (0.75-0.95)	0.0046		-1.7 (-2.9 to -0.6)	0.0029	
Insulin use at baseline							0.4354			0.4846
Yes	1,541	204 (13.2)	1,495	222 (14.8)	0.89 (0.74-1.08)	0.2476		-1.6 (-4.1 to 0.9)	0.2099	
No	4,017	315 (7.8)	4,101	395 (9.6)	0.81 (0.70-0.94)	0.0059		-1.8 (-3.0 to -0.6)	0.0046	

Values are n or n (%), unless otherwise indicated. Net clinical benefit was pre-specified as irreversible harms and evaluated as time to first event of the composite of all-cause mortality, myocardial infarction, stroke, fatal bleeding, or intracranial bleeding in the intention-to-treat population.

mellitus cohorts that had well controlled traditional risk factors have been somewhat disappointing (7,25-28). Although clopidogrel is the most widely prescribed antithrombotic adjunct to aspirin, ticagrelor affords faster and more favorable antiplatelet outcomes (29,30). Furthermore, head-to-head comparisons have revealed that ticagrelor has superior benefits to clopidogrel in acute coronary syndrome (6,26). The benefits of ticagrelor over clopidogrel in individuals with type 2 diabetes mellitus may be attributed in part to impaired clopidogrel metabolism resulting in less exposure to the active clopidogrel metabolite (31) and the twice daily regimen of

ticagrelor that may be favorable in diabetes mellitus where platelet turnover rates are high (32). Of note, Capodanno et al. (33) found that 81 mg aspirin taken twice daily was more effective than 81 mg aspirin once daily at reducing platelet reactivity.

Unlike earlier outcome trials which evaluated secondary prevention with DAPT, THEMIS enrolled individuals who did not have a history of MI or stroke, resulting in a population that had a lower cardiovascular risk profile even though type 2 diabetes mellitus was a mandatory entry criterion. In addition and similarly to many of the earlier DAPT studies, the THEMIS participants were exceptionally well

managed and in accord with guideline recommendations; specifically, 90% were on a statin, 79% were taking either an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, and 74% were using a β -blocker (8). Accordingly, the observations described herein further emphasize that individuals with type 2 diabetes mellitus and stable coronary artery disease without a history of MI or stroke, but who have undergone a PCI, and who are pharmacologically well managed can benefit significantly from the addition of ticagrelor on an aspirin background.

Like several studies that have previously investigated DAPT strategies with aspirin (34-37), THEMIS reported that decreases in the risk of the primary efficacy outcome occurred simultaneously with increases in bleeding events (8). This has, unsurprisingly, driven much discussion on the risk-benefit balance of applying DAPT approaches. That said, examination of data from the THEMIS-PCI subcohort showed that the rise in bleeding events was accompanied by a net clinical benefit among those who had previously undergone coronary revascularization relative to those without (9). In reviewing the present work, an important take-home message would be that the risk of a THEMIS-PCI participant experiencing a bleeding event with ticagrelor plus aspirin was not influenced by where they were positioned on the diabetes continuum. This is especially relevant given the burgeoning population with diabetes and the growing proportion of these individuals who are anticipated to require a PCI during their lifetime.

Previous studies have suggested that diabetes-related factors, such as diabetes duration, HbA_{1c} levels, and background antihyperglycemic therapies, can influence cardiovascular risk and outcomes in populations with type 2 diabetes mellitus (14-17). Accordingly, the goal of the present nonpre-specified analyses was to examine whether the efficacy, safety, and net clinical benefit observed with the combination of ticagrelor and low-dose aspirin in the THEMIS cohort and THEMIS-PCI subcohort varied across diabetes-related factors including duration of diabetes, baseline HbA_{1c}, and baseline antihyperglycemic medications.

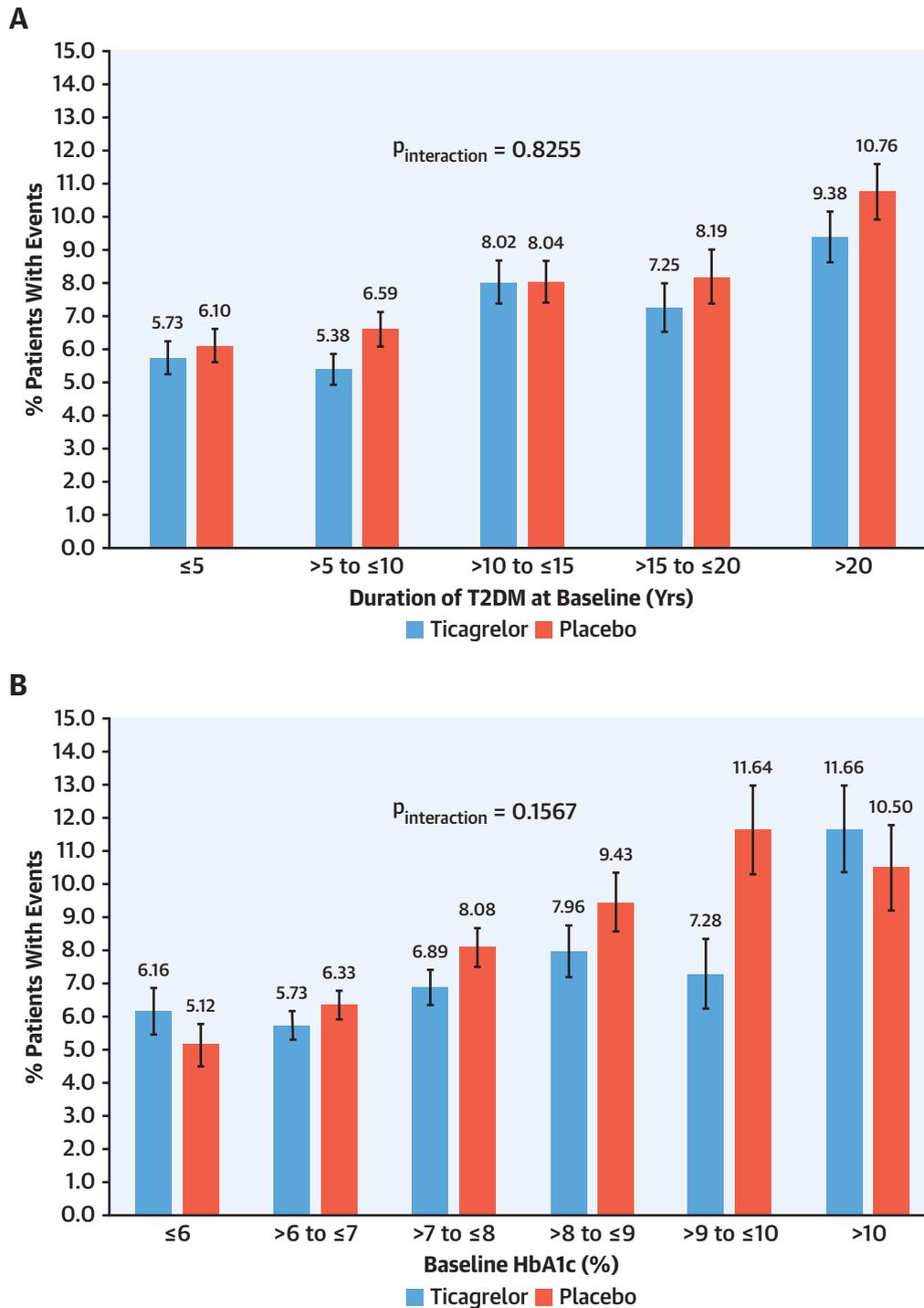
These analyses extend the findings of the overall THEMIS cohort (8) and smaller THEMIS-PCI subpopulation (9). The collective data remind us that type 2 diabetes mellitus is a progressive condition and that those who live with this disorder have a continuum of risk. The results indicate that the combination of ticagrelor and low-dose aspirin merits consideration alongside other guideline-recommended vascular

protective strategies in individuals with type 2 diabetes mellitus who have stable coronary artery disease, a prior PCI, and proven tolerance for DAPT with low bleeding risk. Importantly, these benefits are apparent regardless of diabetes-related factors (diabetes duration and HbA_{1c}) or the baseline antihyperglycemic regimen.

The notion of expanding secondary prevention strategies beyond aspirin monotherapy, in cases of diabetes with stable atherosclerosis and acceptable bleeding risk, is not new and is supported by a recent pre-specified analysis from the COMPASS (Cardiovascular Outcomes for People Using Anti-coagulation Strategies) trial (38). Specifically, COMPASS demonstrated that when DAPT was not indicated, dual pathway inhibition with 2.5 mg rivaroxaban twice daily plus aspirin, compared with placebo plus aspirin, offered greater risk reduction of ischemic harm and all-cause mortality, as well as greater net clinical benefit in those with diabetes compared with those without diabetes. Of note, a pre-specified analysis from the TWILIGHT (Ticagrelor With Aspirin or Alone in High-Risk Patients After Coronary Intervention) trial revealed that ticagrelor monotherapy for 1 year following 3 months of DAPT with ticagrelor plus aspirin after PCI in participants with diabetes lowered the risk of clinically relevant bleeding in the absence of any increases of ischemic events (39). Whether the THEMIS-PCI participants would have experienced similar benefits by switching to a ticagrelor strategy that did not include aspirin is unknown and intriguing.

STUDY LIMITATIONS. It is important to recognize that the results reported herein have some limitations. First, the analyses were based on baseline HbA_{1c} readings and the baseline antihyperglycemic regimens. In view of the median follow-up duration of 39.9 months, it is likely that there were at least some temporal fluctuations in HbA_{1c} levels as well as modifications in glucose-lowering strategies, especially given evolving guideline recommendations during the study period. Second, rates of use of novel classes of antihyperglycemic agents were low and resulted in limited ability to ascertain potential treatment interactions. Third, net clinical benefit, which was a pre-specified exploratory endpoint in THEMIS and THEMIS-PCI, had a relatively restrictive definition of time to first event of the composite of all-cause mortality, MI, stroke, fatal bleeding, or intracranial bleeding.

CENTRAL ILLUSTRATION Primary Efficacy Outcome of 3-Point Major Adverse Cardiovascular Events (Cardiovascular Death, Myocardial Infarction, Stroke)



Leiter, L.A. et al. J Am Coll Cardiol. 2021;77(19):2366-77.

CONCLUSIONS

Despite proactive management of traditional cardiovascular risk factors, ischemic events remain an ongoing concern among individuals with type 2 diabetes mellitus and established coronary artery disease who do not have a history of MI or stroke. The present results indicate that together, ticagrelor plus aspirin reduced the incidence of MACE regardless of baseline duration of diabetes and baseline HbA_{1c} but at the expense of major bleeding events. Notably, the combination of ticagrelor plus aspirin resulted in generally consistent and favorable net clinical benefit across the various diabetes-related factors in THEMIS-PCI, but not in the overall THEMIS population.

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CENTRAL ILLUSTRATION Continued

Outcomes were examined across groups of patients with type 2 diabetes mellitus (T2DM) duration ranging from ≤ 5 years to >20 years and separately by levels of baseline HbA_{1c} ranging from $\leq 6\%$ to $>10\%$. In THEMIS, the incidence of the primary efficacy outcome was positively correlated with (A) increasing duration of type 2 diabetes mellitus and (B) with the level of HbA_{1c} at baseline. Ticagrelor plus aspirin treatment did not have a significant interaction with either parameter. Neither duration of type 2 diabetes mellitus nor baseline HbA_{1c} influenced major bleeding rates (not shown). In THEMIS-PCI, ticagrelor plus aspirin yielded generally consistent and favorable net clinical benefit across the diabetes-related factors. THEMIS = The Effect of Ticagrelor on Health Outcomes in Diabetes Mellitus Patients Intervention Study; THEMIS-PCI = The Effect of Ticagrelor on Health Outcomes in Diabetes Mellitus Patients Intervention Study-Percutaneous Coronary Intervention.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE: In patients with type 2 diabetes mellitus and stable coronary artery disease without prior myocardial infarction or stroke, dual antiplatelet therapy with ticagrelor plus aspirin reduces the risk of ischemic events, independent of diabetes duration, baseline antihyperglycemic therapy or HbA_{1c}, but increases the risk of bleeding.

TRANSLATIONAL OUTLOOK: Future studies should evaluate the safety and efficacy of dual antiplatelet therapy with ticagrelor plus aspirin in patients with diabetes taking new classes of antihyperglycemic agents.

REFERENCES

- Cavender MA, Steg PG, Smith SC Jr., et al. Impact of diabetes mellitus on hospitalization for heart failure, cardiovascular events, and death: outcomes at 4 Years from the Reduction of Atherothrombosis for Continued Health (REACH) registry. *Circulation* 2015;132:923-31.
- Low Wang CC, Hess CN, Hiatt WR, Goldfine AB. Clinical update: cardiovascular disease in diabetes mellitus: atherosclerotic cardiovascular disease and heart failure in type 2 diabetes mellitus—mechanisms, management, and clinical considerations. *Circulation* 2016;133:2459-502.
- Haffner SM, Lehto S, Ronnema 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.
- Krempf M, Parhofer KG, Steg PG, et al. Cardiovascular event rates in diabetic and nondiabetic individuals with and without established atherosclerosis (from the Reduction of Atherothrombosis for Continued Health [REACH] registry). *Am J Cardiol* 2010;105:667-71.
- Gregg EW, Li Y, Wang J, et al. Changes in diabetes-related complications in the United States, 1990-2010. *N Engl J Med* 2014;370:1514-23.
- Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2009;361:1045-57.
- Bonaca MP, Bhatt DL, Cohen M, et al. Long-term use of ticagrelor in patients with prior myocardial infarction. *N Engl J Med* 2015;372:1791-800.
- 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.
- Bhatt DL, Steg PG, Mehta SR, et al. Ticagrelor in patients with diabetes and stable coronary artery disease with a history of previous percutaneous coronary intervention (THEMIS-PCI): a phase 3, placebo-controlled, randomised trial. *Lancet* 2019;394:1169-80.
- AstraZeneca Pharmaceuticals. Brilinta (ticagrelor) tablets: prescribing information. May 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/022433s028lbl.pdf. Accessed June 18, 2020.
- AstraZeneca Canada. Brilinta ticagrelor tablets: consumer information. August 25, 2020. Available at: <https://www.astrazeneca.ca/content/dam/az-ca/downloads/productinformation/brilinta-consumer-information-leaflet-en.pdf>. Accessed December 18, 2020.
- Duckworth WC, Abraira C, Moritz TE, et al. The duration of diabetes affects the response to intensive glucose control in type 2 subjects: the VA Diabetes Trial. *J Diabetes Complications* 2011;25:355-61.
- Zoungas S, Woodward M, Li Q, et al. Impact of age, age at diagnosis and duration of diabetes on the risk of macrovascular and microvascular complications and death in type 2 diabetes. *Diabetologia* 2014;57:2465-74.
- Bajaj HS, Raz I, Mosenson O, et al. Cardiovascular and renal benefits of dapagliflozin in patients with short and long-standing type 2 diabetes: analysis from the DECLARE-TIMI 58 trial. *Diabetes Obes Metab* 2020;22:1122-31.
- Control Group, Turnbull FM, Abraira C, et al. Intensive glucose control and macrovascular outcomes in type 2 diabetes. *Diabetologia* 2009;52:2288-98.
- Emerging Risk Factors Collaboration, Sarwar N, Gao P, et al. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. *Lancet* 2010;375:2215-22.
- Zelniker TA, Wiviott SD, Raz I, et al. Comparison of the effects of glucagon-like peptide receptor agonists and sodium-glucose cotransporter 2 inhibitors for prevention of major adverse cardiovascular and renal outcomes in type 2 diabetes mellitus. *Circulation* 2019;139:2022-31.
- Bhatt DL, Szarek M, Pitt B, et al. Sotagliflozin in patients with diabetes and chronic kidney disease. *N Engl J Med* 2021;384:129-39.
- Bhatt DL, Szarek M, Steg PG, et al. Sotagliflozin in patients with diabetes and recent worsening heart failure. *N Engl J Med* 2021;384:117-28.
- Bhatt DL, Fox K, Harrington RA, et al. Rationale, design and baseline characteristics of the effect of ticagrelor on health outcomes in diabetes mellitus patients intervention study. *Clin Cardiol* 2019;42:498-505.
- Diabetes Canada Clinical Practice Guidelines Expert Committee, Stone JA, Houlden RL, Lin P, Udell JA, Verma S. Cardiovascular protection in people with diabetes. *Can J Diabetes* 2018;42 Suppl 1:S162-9.

22. Stone JA, Houlden RL, Lin P, Udell JA, Verma S. Erratum to "Cardiovascular protection in people with diabetes": Can J Diabetes 2018;42(S1):S162-S169. Can J Diabetes 2019;43:154.
23. Handelsman Y, Bloomgarden ZT, Grunberger G, et al. American Association of Clinical Endocrinologists and American College of Endocrinology—clinical practice guidelines for developing a diabetes mellitus comprehensive care plan—2015. Endocr Pract 2015;21 Suppl 1:1-87.
24. LeRoith D, Biessels GJ, Braithwaite SS, et al. Treatment of diabetes in older adults: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2019;104:1520-74.
25. Bhatt DL, Fox KA, Hacke W, et al. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. N Engl J Med 2006;354:1706-17.
26. 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.
27. Bhatt DL, Flather MD, Hacke W, et al. Patients with prior myocardial infarction, stroke, or symptomatic peripheral arterial disease in the CHARISMA trial. J Am Coll Cardiol 2007;49:1982-8.
28. Bhatt DL, Steg PG. THEMIS and THEMIS-PCI. Eur Heart J 2019;40:3378-81.
29. Mangiacapra F, Panaioli E, Colaioni 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.
30. 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.
31. 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.
32. Ferreiro JL, Angiolillo DJ. Diabetes and antiplatelet therapy in acute coronary syndrome. Circulation 2011;123:798-813.
33. 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.
34. Meredith IT, Tanguay JF, Kereiakes DJ, et al. Diabetes mellitus and prevention of late myocardial infarction after coronary stenting in the randomized Dual Antiplatelet Therapy Study. Circulation 2016;133:1772-82.
35. Elmariah S, Doros G, Benavente OR, et al. Impact of clopidogrel therapy on mortality and cancer in patients with cardiovascular and cerebrovascular disease: a patient-level meta-analysis. Circ Cardiovasc Interv 2018;11:e005795.
36. 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.
37. Bhatt DL. Prasugrel in clinical practice. N Engl J Med 2009;361:940-2.
38. Bhatt DL, Eikelboom JW, Connolly SJ, et al. Role of combination antiplatelet and anticoagulation therapy in diabetes mellitus and cardiovascular disease: insights from the COMPASS trial. Circulation 2020;141:1841-54.
39. 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.

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