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Comparative Effectiveness of Aspirin Dosing in Cardiovascular Disease and Diabetes Mellitus: A Subgroup Analysis of the ADAPTABLE Trial

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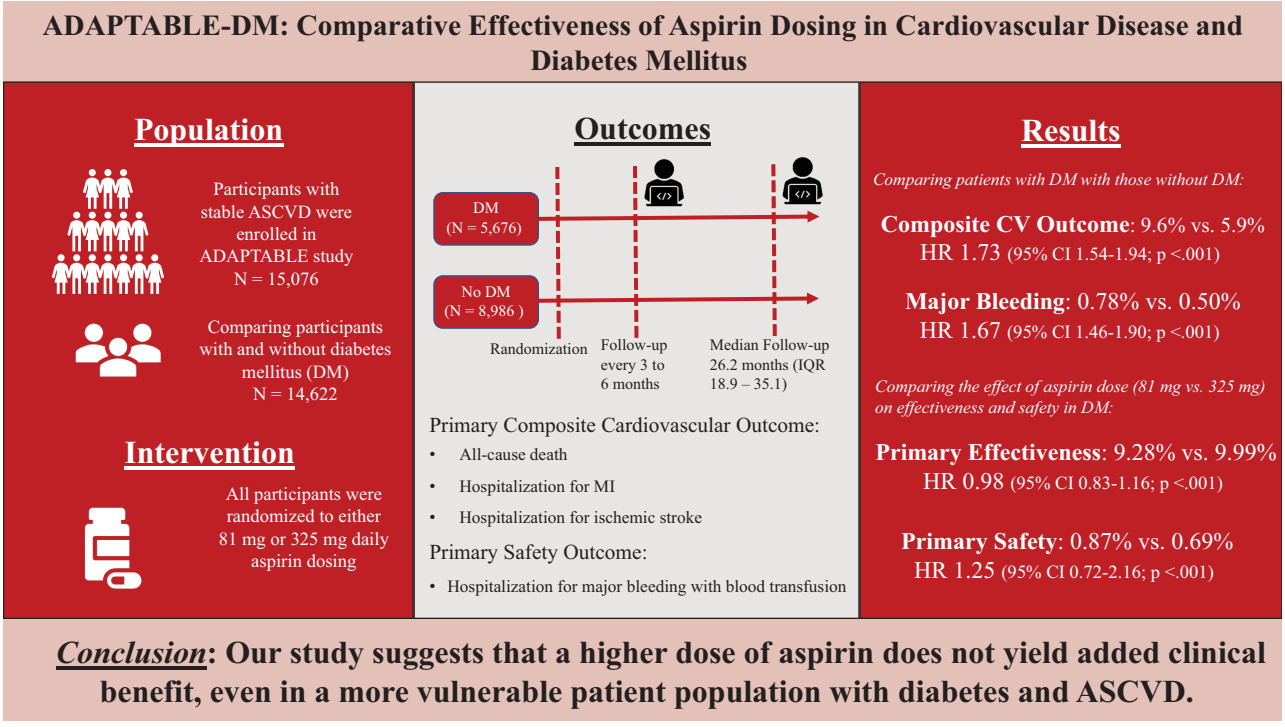

ADAPTABLE, Aspirin Dosing: A Patient-Centric Trial Assessing Benefits and Long-Term Effectiveness; ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; HR, hazard ratio; IQR, interquartile range; MI, myocardial infarction.

ARTICLE HIGHLIGHTS

- Patients with diabetes mellitus (DM) have a high clinical burden of atherosclerotic cardiovascular disease (ASCVD), with evidence supporting aspirin dosing in secondary prevention being limited.
- We compared patients with and without DM and whether 81 mg vs. 325 mg of aspirin affects effectiveness and/or safety in patients with stable ASCVD.
- Patients with DM had heavier comorbidity burden and more cardiovascular and bleeding events; aspirin 325 mg was not more effective at reducing cardiovascular risk and did not increase bleeding rates.
- Our findings support that 81 mg of aspirin is a safe and effective dosing strategy in patients with DM and ASCVD for secondary prevention.

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ORIGINAL ARTICLE

OBJECTIVE

Patients with diabetes mellitus (DM) and concomitant atherosclerotic cardiovascular disease (ASCVD) must be on the most effective dose of aspirin to mitigate risk of future adverse cardiovascular events.

RESEARCH DESIGN AND METHODS

ADAPTABLE, an open-label, pragmatic study, randomized patients with stable, chronic ASCVD to 81 mg or 325 mg of daily aspirin. The effects of aspirin dosing was assessed on the primary effectiveness outcome, a composite of all-cause death, hospitalization for myocardial infarction, or hospitalization for stroke, and the primary safety outcome of hospitalization for major bleeding. In this prespecified analysis, we used Cox proportional hazards models to compare aspirin dosing in patients with and without DM for the primary effectiveness and safety outcome.

RESULTS

Of 15,076 patients, 5,676 (39%) had DM of whom 2,820 (49.7%) were assigned to 81 mg aspirin and 2,856 (50.3%) to 325 mg aspirin. Patients with versus without DM had higher rates of the composite cardiovascular outcome (9.6% vs. 5.9%; $P < 0.001$) and bleeding events (0.78% vs. 0.50%; $P < 0.001$). When comparing 81 mg vs. 325 mg of aspirin, patients with DM had no difference in the primary effectiveness outcome (9.3% vs. 10.0%; hazard ratio [HR] 0.98 [95% CI 0.83–1.16]; $P = 0.265$) or safety outcome (0.87% vs. 0.69%; subdistribution HR 1.25 [95% CI 0.72–2.16]; $P = 0.772$).

CONCLUSIONS

This study confirms the inherently higher risk of patients with DM irrespective of aspirin dosing. Our findings suggest that a higher dose of aspirin yields no added clinical benefit, even in a more vulnerable population.

Approximately 34 million people in the U.S. have a diagnosis of diabetes mellitus (DM), which comprises almost 10.5% of the U.S. population and is steadily increasing (1,2). Atherosclerotic cardiovascular disease (ASCVD), which includes coronary heart disease, is nearly twice as prevalent in patients with DM and conveys a greater attributable morbidity and mortality (3). Given the clinical burden of ASCVD

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and macrovascular complications in patients with DM, it is important that these patients are treated using the most effective therapies to mitigate risk of future cardiovascular events.

Based on evidence from prior randomized trials and clinical investigations, the efficacy of aspirin is proven in patients with established ASCVD for secondary prevention of cardiovascular events (4,5). However, it is not clear what the optimal long-term aspirin dose is for secondary prevention. Although the most recent European guidelines give a class 1A recommendation for daily low-dose (81 mg) aspirin, the American College of Cardiology and American Heart Association guidelines have not taken a definitive stance on dosing strategies (81 mg vs. 325 mg) (6,7). Patients with DM have been shown to have altered platelet function, but it remains unknown whether this has any effect on the required dose of aspirin for secondary prevention of cardiovascular events (8,9). The American Diabetes Association recommends the lowest possible daily aspirin dose in patients with DM and ASCVD to help minimize adverse effects, particularly gastrointestinal (GI) bleeding. This recommendation comes with the acknowledgment of little evidence to support either dosing strategy (10).

The Aspirin Dosing: A Patient-Centric Trial Assessing Benefits and Long-Term Effectiveness (ADAPTABLE) study was an open-label, pragmatic, randomized controlled trial that reported no significant differences in effectiveness or safety outcomes between 81 mg and 325 mg of daily aspirin in patients with ASCVD (11). The aim of this subgroup analysis of the ADAPTABLE study is to compare effectiveness and safety of 81 mg vs. 325 mg in patients with concomitant ASCVD and DM.

RESEARCH DESIGN AND METHODS

Data Source

The design, methods, and main results of the ADAPTABLE study (ClinicalTrials.gov identifier NCT02697916) have been previously published (11,12). In brief, ADAPTABLE was an open-label, pragmatic trial that randomized 15,076 patients with stable, chronic ASCVD from 40 centers and 1 private health insurance plan participating in the Patient-Centered Outcomes Research Network (PCORnet) to self-administer 81 mg or 325 mg of daily aspirin to assess the effects on the composite of all-cause death, hospitalization for myocardial infarction (MI), or hospitalization for stroke. An independent data and safety monitoring committee approved the study protocol and monitored participant safety throughout the course of the study. All participants provided informed consent prior to enrollment. The institutional review board at each participating center approved the protocol and study conduct.

Study Population

The study population comprised patients $\geq$18 years of age with established ASCVD as defined by any of the following *1*) prior MI, *2*) prior coronary revascularization procedure (percutaneous coronary intervention [PCI] or coronary artery bypass grafting [CABG] surgery), *3*) prior coronary angiography demonstrating $\geq$75% stenosis of at least one epicardial coronary artery, or *4*) history of chronic ischemic heart disease, coronary artery disease, or ASCVD. Exclusion criteria included a history of significant allergy to aspirin, history of GI bleeding within 12 months, bleeding disorder that precluded aspirin use, current or planned use of an oral anticoagulant or ticagrelor, and women who were pregnant or nursing (11). In addition, patients were excluded from the current analysis if their medical history (and therefore DM status) was not available within the electronic health record data at the enrolling center (Fig. 1). The remaining patients were grouped based on DM status, which was defined by occurrence of a relevant ICD-9-CM and ICD-10-CM code (DX09 250* diabetes mellitus, DX10 E11. *type 2 diabetes mellitus. *type 1 diabetes mellitus) within a look-back period of 5 years from the date of enrollment. Patients in the DM group were then classified as controlled (hemoglobin A_{1c} [HbA_{1c}] $\leq$8%) and uncontrolled (HbA_{1c} >8%) based on the most recent HbA_{1c} value measured prior to randomization. These classifications were chosen in reference to American Diabetes Association guidelines for glycemic targets in patients with DM, which suggest targeting <7% as a goal and considering a less stringent target of <8% for certain patients (13).

Clinical Outcomes

Outcomes were ascertained from multiple data sources, including patient report at scheduled study encounters, queries of electronic health record data organized according to the PCORnet Common Data Model format, linkage with data sources from PCORnet private health plan partners (Aetna, Anthem, and Humana), and linkage with fee-for-service Centers for Medicare & Medicaid Services claims data (11). This ascertainment process was validated using traditional blinded adjudication as the gold standard (14). The primary effectiveness outcome for this analysis was the time to first occurrence of all-cause death, hospitalization for MI, or hospitalization for ischemic stroke. Secondary outcomes included coronary revascularization (PCI or CABG surgery), the individual components of the primary composite end point, and hospitalization for transient ischemic attack. The primary safety outcome was hospitalization for major bleeding with an associated blood product transfusion.

Statistical Analysis

Descriptive summaries of baseline demographic and clinical variables were presented for each cohort (patients with DM and patients without DM). Continuous variables are presented as means with SDs and medians with 25th and 75th percentiles (interquartile range [IQR]). Categorical variables are presented as counts and proportions. *P* values are reported from the χ^2 test for discrete measures and the *t* test for continuous variables.

Cumulative incidence rates for the primary effectiveness outcome, secondary outcomes, and primary safety outcome were estimated at median follow-up from initial randomization (26.2 months) using the Kalbfleisch and Prentice cumulative incidence function estimator by DM status at baseline. The primary effectiveness end point and all-cause death were modeled using Cox proportional hazards regression. The Fine and Gray method was used to model the primary safety end point, hospitalization for MI, and hospitalization for stroke outcomes to account for the competing risk of death. For each clinical outcome, DM status at baseline was included in the models as the primary exposure, with and without covariate adjustment, and hazard ratios (HRs) (or subdistribution hazard ratios [sHRs]) with 95% CIs are presented. This analysis was repeated to include the interaction between DM group and randomized aspirin dose (81 mg and 325 mg). Cumulative incidence rates

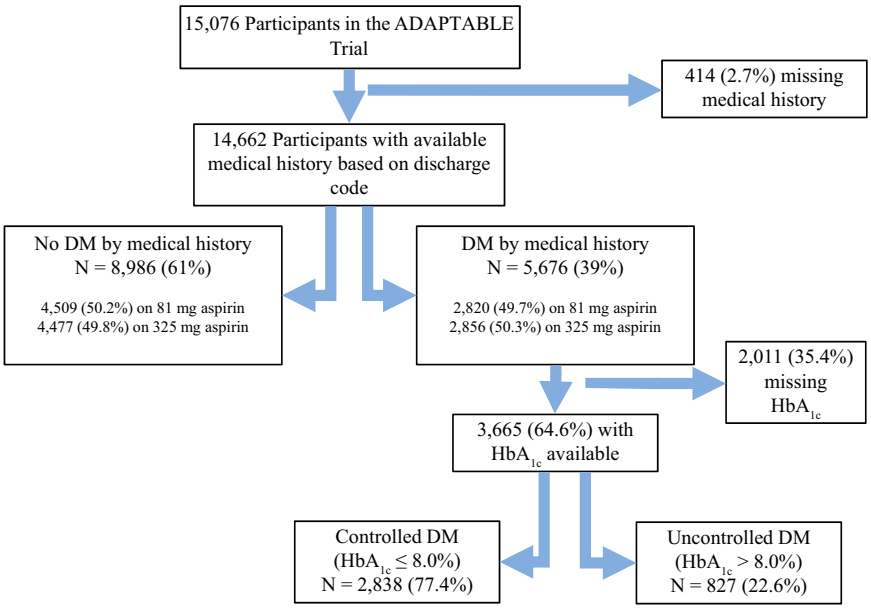

Figure 1—Flow diagram of patient population.

and HRs (or sHRs) with 95% CIs are presented in forest plots comparing 81-mg with 325-mg aspirin doses within each DM subgroup. Both sets of models were adjusted for baseline covariates prespecified as potential confounders, including age, sex, current smoking status, randomization follow-up strata, internet access at randomization, race, ethnicity, history of coronary artery disease, MI, CABG surgery, PCI, cerebrovascular disease, hypertension, hyperlipidemia, atrial fibrillation, congestive heart failure, peripheral artery disease (PAD), bleeding, prior aspirin use, baseline P2Y12 inhibitor use, and BMI.

The analysis was repeated in the subgroup of patients with DM at baseline to compare the 81-mg with 325-mg aspirin dose by level of DM control for the primary effectiveness end point and primary safety end point. Models included randomized aspirin dose, DM control group, and an interaction term, with and without covariate adjustment. Event counts, cumulative incidence rates, and unadjusted and adjusted HRs with 95% CIs are presented by DM control group. *P* values for tests of the interaction are also presented.

As a sensitivity analysis, self-reported aspirin dose was included in the model as a time-dependent exposure to account for nonadherence to randomized aspirin dose for the primary effectiveness end point, the primary safety end point, and all-cause death. Models were fit with DM at baseline, time-varying self-reported aspirin dose, and an interaction term between self-reported aspirin dose and DM at baseline. Adjustment measures were age, sex, race, ethnicity, prior aspirin dose, prior MI, prior PCI, history of atrial fibrillation, no internet use at randomization, baseline P2Y12 inhibitor use, and history of bleeds. This methodology assumes that the decision to switch doses is made for reasons unrelated to the outcome of interest, beyond the baseline adjustment measures.

All hypothesis tests were two-sided, and $P < 0.05$ was interpreted as statistically significant without adjustment for multiple comparisons in this prespecified subgroup analysis. Modeling assumptions of linearity were checked using natural cubic splines, and proportional hazards were tested using weighted Schoenfeld residuals. Transformations were included when necessary. Missing covariates were handled using multiple imputation. All analyses were performed by the Duke Clinical Research Institute using SAS 9.4 statistical software (SAS Institute, Cary, NC).

RESULTS

Of the 15,076 ADAPTABLE participants with chronic, stable ASCVD, 414 (2.7%) did not have documentation sufficient to determine a history of DM, leaving 14,662 (97.3%) patients for this subgroup analysis. Of these patients, 5,676 (39%) had a history of DM, of whom 2,820 (49.7%) were assigned to the 81-mg group (Fig. 1). There was a median follow-up of 26.2 months (IQR 18.9–35.1).

HbA_{1c} values were available for 3,665 patients (64.6%) in the DM group, and 827 (22.6%) had HbA_{1c} values >8.0%, while the remaining 2,838 (77.4%) had HbA_{1c} values ≤8.0%. When compared with patients without DM, patients with DM were younger (65.8 vs. 67.3 years), more likely to be women (34.6% vs. 29.3%), more likely to be African American (13.2% vs. 6.0%), and more likely to have a higher BMI (mean 32.8 vs. 29.7 kg/m^2; all $P < 0.05$). Overall, the patients with DM had a higher burden of cardiovascular comorbidities, such as hypertension, hyperlipidemia, chronic kidney disease, chronic obstructive pulmonary disease, PAD, prior PCI or CABG surgery, and prior MI compared with patients without DM ($P < 0.05$). The patients with DM also had a higher likelihood of prior bleeding, baseline P2Y12 inhibitor use, peptic ulcer disease, and significant GI bleeding ($P < 0.05$) (Table 1). The baseline characteristics of patients with DM stratified by aspirin dosing strategy are shown in Supplementary Table 1.

The composite cardiovascular outcome was confirmed in 583 patients with DM (cumulative incidence rate at median follow-up 9.6%) and in 541 patients without DM (5.9%; unadjusted HR 1.73 [95% CI 1.54–1.94]; $P < 0.001$) (Table 2). All-cause mortality occurred in 337 patients with DM (5.3%) and 320 (3.4%) without DM. After adjustment for baseline characteristics and randomized aspirin dose, the cumulative incidence of hospitalization for stroke remained higher in patients with DM compared with those without DM (adjusted sHR 1.70 [95% CI 1.23–2.33]; $P = 0.001$) (Table 2).

The effect of aspirin dose (81 mg vs. 325 mg) on the primary effectiveness outcome and key secondary outcomes was assessed in patients with and without DM (Fig. 2). Cumulative incidence curves are shown in Supplementary Fig. 1. There was no statistically significant difference in the primary effectiveness outcome between the 81-mg and 325-mg dose of aspirin in patients with DM (9.3% vs. 10.0%; adjusted HR 0.98 [95% CI 0.83–1.16]) or without DM (6.0% vs. 5.8%; adjusted HR 1.12 [95% CI 0.95–1.33]) (Fig. 2), and the effect did not differ by DM group (adjusted interaction $P = 0.265$) (Fig. 2). When evaluating the primary effectiveness outcome in the DM group by glycemic control, patients with controlled DM (HbA_{1c} ≤8% at baseline) had a rate of 11.9% in

Table 1—Demographic and presenting characteristics, medical history, and medications by DM subgroup

Characteristic	All patients (*N* = 14,662)	No DM (*n* = 8,986)	DM (*n* = 5,676)	*P**
Age, median (IQR), years	67.5 (60.7–73.5)	68.1 (61.3–73.9)	66.4 (59.7–72.6)	<0.0001
Randomized dose				0.5591
81 mg	7,329 (50.0)	4,509 (50.2)	2,820 (49.7)	
325 mg	7,333 (50.0)	4,477 (49.8)	2,856 (50.3)	
Women, *n* (%)	4,594 (31.3)	2,632 (29.3)	1,962 (34.6)	<0.0001
Race, *n* (%)				<0.0001
White	11,712 (79.9)	7,559 (84.1)	4,153 (73.2)	
Black or African American	1,295 (8.8)	543 (6.0)	752 (13.2)	
Hispanic ethnicity	472 (3.3)	204 (2.3)	268 (4.8)	<0.0001
Current smoker	1,356 (9.8)	861 (10.2)	495 (9.3)	0.0667
Baseline P2Y12 inhibitor use†	2,990 (22.2)	1,630 (19.7)	1,360 (26.0)	<0.0001
BMI, median (IQR), kg/m^2	30.0 (26.7–34.4)	28.9 (25.9–32.7)	32.1 (28.1–36.6)	<0.0001
Medical history,‡ *n* (%)				
Atrial fibrillation/flutter	1,233 (8.4)	736 (8.2)	497 (8.8)	0.2293
History of bleeding§	1,267 (8.6)	660 (7.3)	607 (10.7)	<0.0001
Significant GI bleed	950 (6.5)	492 (5.5)	458 (8.1)	<0.0001
History of ICH	208 (1.4)	113 (1.3)	95 (1.7)	0.0379
History of bleeding disorder	176 (1.2)	87 (1.0)	89 (1.6)	0.0012
Prior CABG surgery	3,527 (24.1)	1,860 (20.7)	1,667 (29.4)	<0.0001
Coronary artery disease	13,714 (93.5)	8,295 (92.3)	5,419 (95.5)	<0.0001
Congestive heart failure	3,504 (23.9)	1,706 (19.0)	1,798 (31.7)	<0.0001
PAD	3,493 (23.8)	1,496 (16.6)	1,997 (35.2)	<0.0001
COPD	2,778 (18.9)	1,456 (16.2)	1,322 (23.3)	<0.0001
Cardiovascular disease	2,624 (17.9)	1,424 (15.8)	1,200 (21.1)	<0.0001
Chronic kidney disease	2,648 (18.1)	982 (10.9)	1,666 (29.4)	<0.0001
Hypertension	12,512 (85.3)	7,153 (79.6)	5,359 (94.4)	<0.0001
Hyperlipidemia	12,946 (88.3)	7,660 (85.2)	5,286 (93.1)	<0.0001
Prior MI	5,305 (36.2)	3,016 (33.6)	2,289 (40.3)	<0.0001
Peptic ulcer disease	445 (3.0)	229 (2.5)	216 (3.8)	<0.0001
PCI/CABG surgery	7,977 (54.4)	4,573 (50.9)	3,404 (60.0)	<0.0001
Number of health encounters in CDM, median (IQR)	28.0 (10.0–66.0)	23.0 (8.0–54.0)	39.0 (14.5–86.0)	<0.0001
Medication at the time of randomization				
Prior aspirin use	13,232 (96.0)	8,062 (95.6)	5,170 (96.7)	0.0018
Prior aspirin dose‖				0.6606
81 mg	11,293 (85.4)	6,882 (85.4)	4,411 (85.3)	
162 mg	303 (2.3)	192 (2.4)	111 (2.2)	
325 mg	1,614 (12.2)	978 (12.1)	636 (12.3)	
Other dose‡	22 (0.2)	10 (0.1)	12 (0.2)	
Laboratory				
HbA_{1c} (%)				<0.0001
n	5,535	1,870	3,665	
Mean ± SD	6.7 ± 1.5	5.7 ± 0.5	7.3 ± 1.5	
Median (IQR)	6.3 (5.7–7.3)	5.7 (5.4–5.9)	6.9 (6.2–7.9)	
Adherence after randomization¶				
Adherence outcome: dose switching or aspirin discontinuation				
81 mg: event (estimated %)		724 (10.74)	468 (11.45)	
325 mg: event (estimated %)		2,178 (44.32)	1,402 (44.86)	
Aspirin discontinuation				
81 mg: event (estimated %)		450 (6.38)	290 (6.79)	
325 mg: event (estimated %)		693 (10.60)	429 (10.13)	
Dose switching				
81 mg: event (estimated %)		284 (4.21)	187 (4.57)	
325 mg: event (estimated %)		1,591 (32.38)	1,044 (33.41)	

CDM, Common Data Model; COPD, chronic obstructive pulmonary disease; ICH, intracranial hemorrhage. **P* values are reported for tests comparing DM vs. no DM groups (χ^2 test for discrete measures and *t* test for continuous variables). †Percentages are based on 13,500 participants with available medications data (8,274 no DM and 5,226 DM). ‡Percentages are based on 14,661 participants with available medical history data (8,985 no DM and 5,676 DM). §History of bleeding includes GI bleed, ICH, and bleeding disorder. ‖Percentages are based on 13,210 participants with available aspirin history data (8,052 no DM and 5,158 DM). ¶Composite adherence outcome is defined as dose switching or discontinuation that occurred when a participant reported a dose different from the randomized dose, reported discontinuation of aspirin (permanent or temporary), or never reported aspirin information during follow-up (missing visits after randomization). Switching dose or discontinuing prior to withdrawal of consent was counted as a dose switch or discontinuation event. The end-of-study visit was excluded from defining dose switching and discontinuation because an observed spike in reports of dose switching at the end-of-study visit seemed to reflect participants' intended dose after trial participation.

Table 2—Primary composite cardiovascular outcome, key secondary outcomes, and major bleeding rates by DM subgroup

	No history of DM	History of DM	Unadjusted Cox model		Adjusted Cox model	
	Event (cumulative incidence rate, %)*	Event (cumulative incidence rate, %)*	HR (95% CI)†	*P*†	HR (95% CI)‡	*P*†
Death, MI, or stroke	541 (5.9)	583 (9.6)	1.73 (1.54–1.94)	<0.001	1.37 (1.20–1.56)	<0.001
All-cause mortality	320 (3.4)	337 (5.3)	1.66 (1.42–1.93)	<0.001	1.43 (1.21–1.70)	<0.001
MI	206 (2.4)	219 (3.8)	1.68 (1.39–2.03)	<0.001	1.24 (1.01–1.52)	0.042
Stroke	75 (0.8)	109 (1.8)	2.29 (1.70–3.07)	<0.001	1.70 (1.23–2.33)	0.001
Major bleeding	42 (0.5)	52 (0.8)	1.93 (1.29–2.90)	0.001	1.78 (1.18–2.69)	0.006
PCI or CABG surgery	440 (4.7)	460 (8.2)	1.67 (1.46–1.90)	<0.001	1.43 (1.24–1.65)	<0.001

*Cumulative incidence rates were calculated at median follow-up (26.2 months) using the Kalbfleisch and Prentice cumulative incidence function estimator. Events include data from electronic health record data, Centers for Medicare & Medicaid Services claims, private insurance claims, and confirmed participant-reported outcomes. †HRs compare history of DM with no history of DM. The primary end point and all-cause mortality are modeled using Cox proportional hazards regression. For all other outcomes, the competing risk of death is taken into account using the Fine and Gray method, and sHRs are reported. ‡Adjustment measures for death, MI, or stroke included randomized treatment, age, sex, current smoking status, randomization follow-up strata, internet access at randomization, race, ethnicity, history of coronary artery disease, MI, CABG surgery, PCI, cerebrovascular disease, hypertension, hyperlipidemia, atrial fibrillation, congestive heart failure, PAD, bleeding, baseline P2Y12 inhibitor use, and BMI; adjustment measures for all-cause death, MI, and revascularization (PCI or CABG surgery) included randomized treatment, age, sex, current smoking status, randomization follow-up strata, internet access at randomization, race, ethnicity, history of coronary artery disease, MI, CABG, PCI, cerebrovascular disease, hypertension, hyperlipidemia, atrial fibrillation, congestive heart failure, PAD, and BMI; adjustment measures for stroke included randomized treatment, age, sex, current smoking status, race, ethnicity, history of coronary artery disease, cerebrovascular disease, hypertension, hyperlipidemia, atrial fibrillation, congestive heart failure, PAD, P2Y12 inhibitor use, and BMI; and adjustment measures for major bleeding included randomized treatment, age, sex, hypertension, P2Y12 inhibitor use, and BMI.

the 81-mg group and 14.5% in the 325-mg group, but no significant difference after adjustment (adjusted HR 1.11 [95% CI 0.90–1.36]) (Supplementary Table 2). Patients with uncontrolled DM (HbA_{1c} >8 at baseline) had similar rates of the primary effectiveness outcome by aspirin dose (7.7% in the 81-mg group and 7.3% in the 325-mg group; adjusted HR 0.98 [95% CI 0.67–1.42]) (Supplementary Table 2). The effect did not differ by DM control group (*P* = 0.558).

Hospitalization for major bleeding with an associated blood transfusion occurred in 52 patients with DM (0.8%) (Supplementary Fig. 2) and 42 patients without DM (0.5%) (Table 2). After adjustment, patients with DM remained at a higher risk of major bleeding compared with patients without DM (sHR 1.78 [95% CI 1.18–2.69]; *P* = 0.006) (Table 2). There was no statistically significant difference in the primary safety outcomes between the 81-mg and 325-mg groups in patients with DM (0.87% vs. 0.69%; adjusted sHR 1.25 [95% CI 0.72–2.16]) or patients without DM (0.45% vs. 0.54%; adjusted sHR 1.11 [95% CI 0.60–2.03]) (Fig. 2), and the effect did not differ by DM group (adjusted interaction *P* = 0.772) (Fig. 2). The rates of primary safety outcome were low in patients with controlled DM, with no difference between aspirin dose (0.68% vs. 0.86%; adjusted sHR 4.94 [95% CI 0.58–42.4]) (Supplementary Table 2). Similarly, rates of the primary safety outcome were low in patients with uncontrolled DM, with no statistically significant difference between aspirin dosing (1.20% vs. 0.25; adjusted sHR 0.98 [95% CI 0.54–1.77]) (Supplementary Table 2). The effect did not differ by DM control group (*P* = 0.153).

Of patients randomized to the 81-mg group, 11.5% with DM and 10.7% without DM switched or discontinued the dose after randomization. Of patients randomized to the 325-mg group, 44.9% with DM and 44.3% without DM switched or discontinued the dose after randomization (Table 1). Rates of the primary effectiveness outcome were higher in participants with DM who self-reported aspirin doses of 81 mg vs. 325 mg but did not reach statistical significance (5.21 vs. 4.01 events per 100 patient-years; adjusted HR 1.21 [95% CI 1.00–1.48]) (Supplementary Table 3). In patients without DM, there was no significant difference between self-reported aspirin dose of 81 mg vs. 325 mg (2.90 vs. 2.42 events per 100 patient-years; adjusted HR 1.16 [95% CI 0.95–1.42]). The effect did not differ by DM at baseline (adjusted interaction *P* = 0.669).

CONCLUSIONS

The ADAPTABLE study, a large open-label, pragmatic, multicenter trial, enrolled 15,076 total patients with established ASCVD of whom 5,676 had a documented history of DM. Patients with DM had heavier comorbidity burden and experienced higher rates of adverse cardiovascular events while also having a higher risk for major bleeding irrespective of aspirin dosing compared with patients without DM. After adjustment for baseline characteristics, patients with DM had no difference in the primary composite effectiveness outcome of death, MI, or stroke or safety outcomes when comparing the 81-mg vs. 325-mg daily dosing strategies of aspirin. Patients with uncontrolled DM, defined as hemoglobin HbA_{1c} >8%, had higher rates of adverse cardiovascular events and all-cause death compared with patients with controlled DM, but there was no impact of aspirin dosing on risk of future events in either group.

Among its numerous prognostic consequences, DM has a known substantial impact on ASCVD risk and its related complications, including MI, cerebrovascular events, and cardiovascular mortality (15). Our analysis is consistent with prior reports. ADAPTABLE participants with stable ASCVD and DM had higher rates of adverse cardiovascular outcomes regardless of aspirin dosing compared with patients without DM. However, after adjustment for baseline characteristics and treatment, this risk was attenuated and only

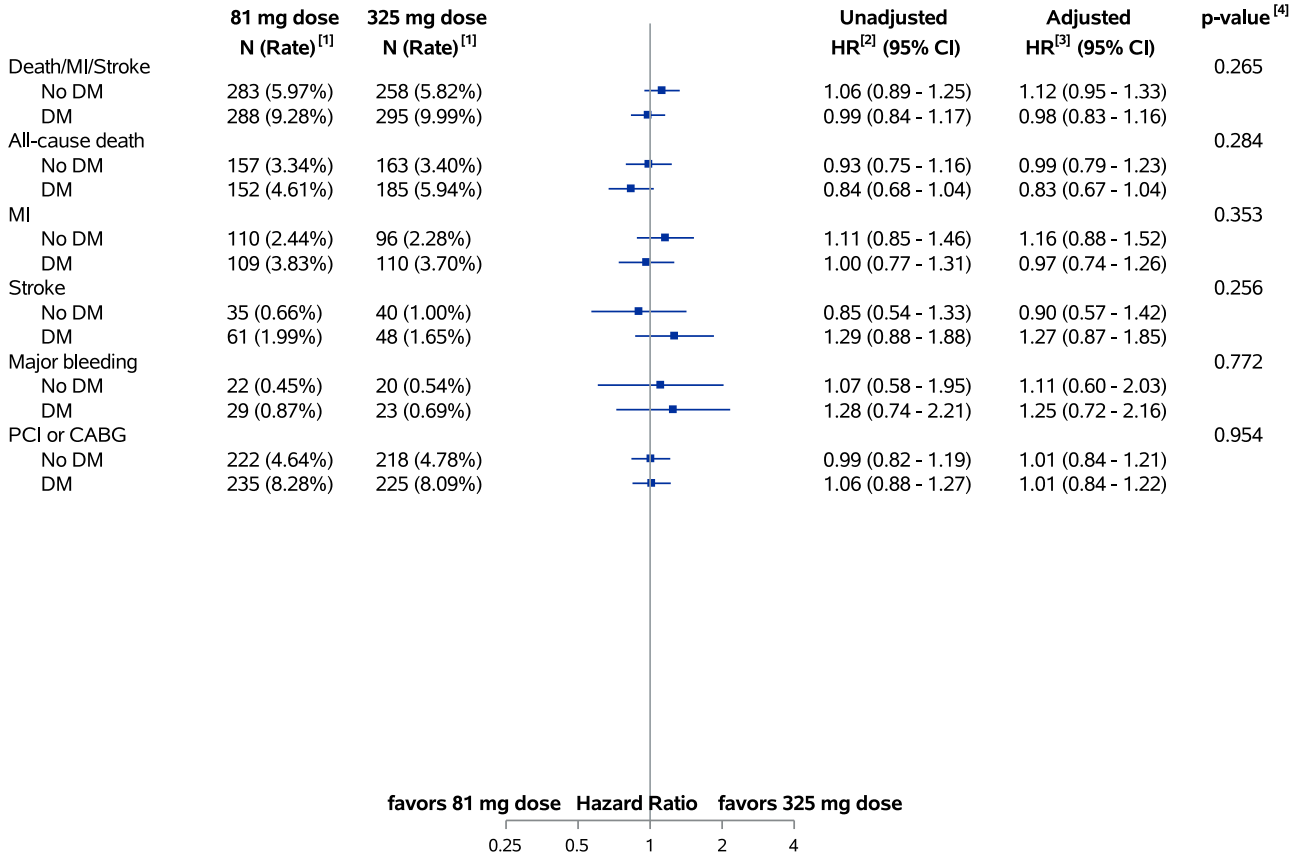

Figure 2—Primary effectiveness outcome, key secondary effectiveness outcomes and primary safety outcome in participants randomized to an 81 mg or a 325 mg aspirin dose by DM subgroup of the ADAPTABLE study (*N* = 14,662). [1] *N* represents the total number of events over follow-up. Cumulative incidence rates are calculated at median follow-up (26.2 months) using the Kalbfleisch and Prentice cumulative incidence function estimator. Events include data from electronic health records, Centers for Medicare & Medicaid Services claims, private insurance claims, and confirmed participant reported outcomes. [2] HRs are comparing 81 mg with 325 mg. The primary end point and all-cause death are modeled using Cox proportional hazards regression. For all other outcomes, the competing risk of death is taken into account using the Fine and Gray method. [3] Adjustment measures for death/MI/stroke included age, sex, current smoking status, randomization follow-up strata, internet access at randomization, race, ethnicity, history of coronary artery disease, MI, CABG surgery, PCI, cerebrovascular disease, hypertension, hyperlipidemia, atrial fibrillation, congestive heart failure, PAD, bleeding, baseline P2Y12 inhibitor use, and BMI; adjustment measures for all-cause death, MI, and revascularization (PCI or CABG) included age, sex, current smoking status, randomization follow-up strata, internet access at randomization, race, ethnicity, history of coronary artery disease, MI, CABG surgery, PCI, cerebrovascular disease, hypertension, hyperlipidemia, atrial fibrillation, congestive heart failure, PAD, P2Y12 inhibitor use, and BMI; adjustment measures for stroke included age, sex, current smoking status, race, ethnicity, history of coronary artery disease, cerebrovascular disease, hypertension, hyperlipidemia, atrial fibrillation, congestive heart failure, PAD, and BMI; and adjustment measures for major bleeding included age, sex, hypertension, P2Y12 inhibitor use, and BMI by treatment and covariates. [4] Statistical comparison is interaction of randomized treatment dose and DM.

remained significant for hospitalization for stroke and revascularization likely because patients with stable ASCVD and DM had a heavier baseline burden of comorbidities that attributed to a heightened risk of cardiovascular events, such as hypertension, hyperlipidemia, prior MI, PAD, and chronic kidney disease. DM is often a component of a cardiometabolic disease state, or the metabolic syndrome, in which patients not only experience obesity but also have concomitant elevated blood pressures, cholesterol levels, and blood glucose levels. All of these are modifiable risk factors, and patients with poorly controlled DM often have higher blood pressures and cholesterol levels, compounding their risk and potentially contributing to their higher adverse event rates (16). Our exploratory analysis comparing a low versus high aspirin dosing strategy in poorly controlled and controlled DM also did not demonstrate any significant interaction in the primary effectiveness outcome. However, our population of patients with uncontrolled DM by our definition was small, and controlling glucose levels is only part of the challenge in cardiometabolic disease states.

The role of antiplatelet therapy as secondary prevention after an ASCVD event is well established. However, the intensity of antithrombotic therapy in terms of number of drugs, doses, frequency, and duration remains unclear. Patients with DM are known to have a higher risk of ASCVD, which can be accounted for in part from their prothrombotic risk profile. This prothrombotic milieu is complex and multifactorial, driven mainly by hyperreactive or immature platelets that are more prone to adhesion, activation, aggregation, and eventually thrombus formation (17). In our study, patients with DM experienced more ischemic and thrombotic events compared with patients without DM. Yet, there was no differential effect by intensifying aspirin dosing. There was also a high number of patients who switched dosing strategies from high-dose to low-dose daily aspirin during the study, which could have impacted dosing effects on the primary

effectiveness and safety outcome and skewed the findings toward no difference. There is a suggestion, however with less substantial evidence, that staying on the assigned aspirin dose may have resulted in lower outcomes with higher dose treatment strategy. Overall, there is a known proven protective effect of aspirin in secondary prevention, and our study suggests that there is no differential effect in low or high daily dosing in patients with DM and established ASCVD.

It remains unclear how the pharmacodynamic response to aspirin may be altered by the platelet physiology in patients with DM (18). There are data that twice-daily dosing can help improve platelet inhibition in patients with DM (19). Aspirin Twice a Day in Patients With Diabetes and Acute Coronary Syndrome (ANDAMAN; ClinicalTrials.gov identifier NCT02520921) is an ongoing randomized clinical trial to compare twice-daily low-dose aspirin with once-daily low-dose aspirin in patients after acute coronary syndrome. Other ongoing trials are exploring dose time and formulations in patients with DM in efforts to improve the overall efficacy of aspirin therapy for secondary prevention (20).

Aspirin therapy carries a known and unavoidable increased risk of bleeding complications, especially in higher risk individuals (21). Our study showed no difference in the primary safety outcome of major bleeding requiring transfusion in patients with or without DM irrespective of aspirin dose. However, DM was independently associated with a heightened risk of major bleeding compared with no DM. The increased risk of bleeding in patients with DM, even on low-dose aspirin, has been shown (22). The more surprising finding was no difference in bleeding risk between the low- and high-dose treatment arms, even in patients with DM. While this finding could suggest that any dose of aspirin conveys similar bleeding risk, it is more likely that the results were impacted by low overall rates of major bleeding events in the study period.

The current study has some limitations. It is a prespecified secondary analysis of a subgroup of the overall ADAPTABLE trial; as such, results are considered hypothesis generating, and multiple tests should be interpreted with caution. The ADAPTABLE trial was an open-label design and had a high crossover rate from 325 mg daily aspirin to 81 mg daily aspirin during the study period. Given that 85% of the overall population were on 81 mg of aspirin at baseline, it is possible that this high crossover rate was driven by patient or clinician bias toward a lower dose aspirin strategy. The switching of doses may have had an impact on the effectiveness and safety outcomes and could have biased the results toward the null. Our safety outcome was limited to just bleeding events requiring transfusions, so nonmajor bleeding events were not captured in this study. There was a lower number of traditionally underrepresented racial and ethnic groups who are often more burdened by DM and its complications, and this limits the overall generalizability of the results. Finally, our DM population was derived based on chart history, limiting our ability to reliably differentiate between type 1 and type 2 DM, and our overall DM population was relatively well controlled with a mean HbA_{1c} of 7.3%. There was a high number of patients without measured HbA_{1c} levels in our system; however, our rate of missing HbA_{1c} was consistent with reports of electronic health record in prior literature (23). DM medications (particularly insulin), variability in control, or duration of disease were not collected and would have helped with understanding the disease burden in this population.

In ADAPTABLE, an open-label, pragmatic, randomized controlled trial of 81 mg vs. 325 mg daily aspirin in secondary prevention of patients with chronic stable ASCVD, patients with DM had a higher risk of adverse cardiovascular events and major bleeding irrespective of aspirin dose. There was no difference in the primary effectiveness outcome or major bleeding safety outcome when comparing 81 mg vs. 325 mg daily aspirin in patients with DM. This study highlights the increased risk of patients with DM and concomitant ASCVD and the need to find the most potent preventive therapies while balancing their risk profile in order to mitigate their inherently high cardiovascular risk. With an ongoing change in practice patterns toward use of 81 mg daily aspirin as seen in our study, more evidence is needed to support this important decision. Our findings suggest that an increased daily dose of aspirin yields no extra clinical benefit, even in a vulnerable patient population with DM and established ASCVD.

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