Secondary Prevention of Cardiovascular Disease in Patients With Type 2 Diabetes Mellitus

International Insights From the TECOS Trial (Trial Evaluating Cardiovascular Outcomes With Sitagliptin)

Editorial, see p 1204

BACKGROUND: Intensive risk factor modification significantly improves outcomes for patients with diabetes mellitus and cardiovascular disease. However, the degree to which secondary prevention treatment goals are achieved in international clinical practice is unknown.

METHODS: Attainment of 5 secondary prevention parameters—aspirin use, lipid control (low-density lipoprotein cholesterol <70 mg/dL or statin therapy), blood pressure control (<140 mm Hg systolic, <90 mm Hg diastolic), angiotensin-converting enzyme inhibitor or angiotensin receptor blocker use, and nonsmoking status—was evaluated among 13 616 patients from 38 countries with diabetes mellitus and known cardiovascular disease at entry into TECOS (Trial Evaluating Cardiovascular Outcomes With Sitagliptin). Logistic regression was used to evaluate the association between individual and regional factors and secondary prevention achievement at baseline. Cox proportional hazards regression analysis was used to determine the association between baseline secondary prevention achievement and cardiovascular death, myocardial infarction, or stroke.

RESULTS: Overall, 29.9% of patients with diabetes mellitus and cardiovascular disease achieved all 5 secondary prevention parameters at baseline, although 71.8% achieved at least 4 parameters. North America had the highest proportion (41.2%), whereas Western Europe, Eastern Europe, and Latin America had proportions of ≈25%. Individually, blood pressure control (57.9%) had the lowest overall attainment, whereas nonsmoking status had the highest (89%). Over a median 3.0 years of follow-up, a higher baseline secondary prevention score was associated with improved outcomes in a step-wise graded relationship (adjusted hazard ratio, 0.60; 95% confidence interval, 0.47–0.77 for those patients achieving all 5 measures versus those achieving ≤2).

CONCLUSIONS: In an international trial population, significant opportunities exist to improve the quality of cardiovascular secondary prevention care among patients with diabetes mellitus and cardiovascular disease, which in turn could lead to reduced risk of downstream cardiovascular events.

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Clinical Perspective

What Is New?

- Minimal data exist about the degree to which secondary prevention goals are met globally in patients with diabetes mellitus and cardiovascular disease (CVD).
- Using data from TECOS (Trial Evaluating Cardiovascular Outcomes With Sitagliptin), we found that only 30% of patients with diabetes mellitus and cardiovascular disease met all 5 secondary parameters of aspirin use, lipid control (low-density lipoprotein cholesterol <70 mg/dL or statin therapy), blood pressure control (<140 mm Hg systolic, <90 mm Hg diastolic), angiotensin-converting enzyme inhibitor or angiotensin receptor blocker use, and nonsmoking status.
- Only 58% of individuals with diabetes mellitus and cardiovascular disease attained blood pressure control.
- The degree to which secondary prevention goals were met in this trial varied by world region and country.

What Are the Clinical Implications?

- Patients with diabetes mellitus and cardiovascular disease are still being undertreated globally with respect to secondary prevention, especially with regard to blood pressure control.
- These gaps in care provide clear opportunities for improvement in this high-risk population.

Patients with type 2 diabetes mellitus are at increased risk for cardiovascular disease (CVD) and worse outcomes when CVD is present. Cardiovascular mortality is increased by 2-fold in adults with diabetes mellitus compared with those without.[1,2] Appropriate secondary prevention can improve CVD outcomes in adults with diabetes mellitus.[3–6] Intensive combined modification of multiple risk factors has been demonstrated to significantly improve long-term outcomes among patients with diabetes mellitus and CVD.[7]

To date, relatively little has been published on the implementation of secondary prevention measures in patients with type 2 diabetes mellitus and their relationship with cardiovascular outcomes.[8,9] In addition, although diabetes mellitus is a global epidemic, there is a lack of information on global variation in secondary prevention in this high-risk population. We sought to address these gaps in knowledge using data from the recent TECOS (Trial Evaluating Cardiovascular Outcomes With Sitagliptin).[10] TECOS was an international, randomized, placebo-controlled trial in patients with type 2 diabetes mellitus and CVD that examined the long-term cardiovascular safety of sitagliptin, a dipeptidyl peptidase 4 inhibitor. TECOS provides high-quality clinical data with longitudinal follow-up information on a global patient population, thus providing a setting in which to study the international attainment of cardiovascular secondary prevention goals. Our primary objective was to assess the overall patterns of secondary prevention therapy in patients with diabetes mellitus. Secondarily, we aimed to investigate patient-level factors associated with optimal uptake of secondary prevention measures, variation of secondary prevention treatment by region and by country, and association of prevention measures with cardiovascular outcomes.

METHODS

Study Cohort and Design

TECOS was a multinational, double-blind, randomized, placebo-controlled study of sitagliptin versus placebo in addition to existing therapy in adults with type 2 diabetes mellitus and CVD.[10] Details of the trial design have been previously described.[11] Briefly, individuals ≥50 years old from 38 countries were included if they had type 2 diabetes mellitus with relatively well-controlled hyperglycemia (glycohemoglobin level, 6.5%–8.0%) and prior CVD (history of major coronary artery disease [CAD], ischemic cerebrovascular disease, or atherosclerotic peripheral artery disease [PAD]). Open-label use of antihyperglycemic therapy other than dipeptidyl peptidase 4 agents and glucagon-like peptide 1 receptor agonists was encouraged to achieve an individually appropriate glycemic target in all patients independently of randomized treatment group. Patients were followed up for the primary composite outcome of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for unstable angina, each of which was centrally adjudicated. The study protocol was approved by the ethics committee at each of the 673 participating trial sites, and all patients provided written informed consent.

This secondary analysis included all patients in the TECOS intention-to-treat cohort with nonmissing data at baseline for the 5 secondary prevention measures that we selected on the basis of clinical guidelines in place during the conduct of the TECOS trial (2008–2012)[12]—namely aspirin use, lipid control (low-density lipoprotein [LDL] cholesterol [LDL-C] <70 mg/dL or statin therapy), blood pressure control (<140 mm Hg systolic and <90 mm Hg diastolic), angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) use, and not currently smoking (ie, never smokers or prior smokers). Given that achieving an LDL-C <70 mg/dL alone (regardless of therapy) was also a guideline recommendation during the TECOS time frame, we examined this alternative, more stringent measure of lipid control as a secondary analysis. Secondary prevention assessments were based on the patients' baseline evaluation. A composite score of optimal secondary prevention measures consisted of the sum of the above 5 parameters. Because few patients achieved only 0 or 1 secondary prevention measures, the categories of 0, 1, and 2 were combined, with final categories stratifying patients into 4 groups by number of secondary prevention parameters reached: 0 to 2, 3, 4, or 5 of 5 measures. The primary outcome used in our analyses was time to

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the first event of a composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke. Hospitalization for unstable angina was not included in this analysis.[10]

Statistical Analyses

Baseline characteristics are displayed with number of patients plus percent within each secondary prevention level for categorical factors and median with 25th and 75th percentiles for continuous measures. A predefined list of covariables was specified as potential confounders related to both the prevalence of secondary prevention measures and CVD events. These included sex, age, history of CAD, history of cerebrovascular disease, history of PAD, history of heart failure, heart rate, body mass index, race, ethnicity, estimated glomerular filtration rate, glycohemoglobin, high-density lipoprotein cholesterol, and world region. Multivariable logistic regression was used to estimate the association between the proportion of each prevention measure and the covariables listed above.

Next, the association between the composite score of the number of secondary prevention measures and the outcome of cardiovascular death, myocardial infarction, or stroke was evaluated with Cox proportional hazards models as done by Lin et al.[13] Kaplan-Meier curves were generated to display the unadjusted relationship of each factor with outcome over time. Multivariable modeling was performed to evaluate the association between each prevention parameter and CVD events and then the composite score of the number of risk factors (values of 0–2 up to 5) and CVD events unadjusted for confounders and then adjusted. In the adjusted models, we included an interaction term to test for effect modification of world region on the relationship between secondary prevention measures and primary outcome. A landmark analysis at 12 and 24 months, including only individuals with complete data at those 2 time points (except for the smoking variable, which was not updated over time), was performed to assess the relationship between secondary prevention measures over time and the primary outcome.

To assess regional variation, the percentage of patients with each of the 5 secondary prevention measures was calculated for each country. These were plotted by region and by prevention measure with a jitter function[14] for similar values.

RESULTS

Among the 14671 patients randomized in TECOS, 13616 (92.8%) had complete baseline data on the 5 secondary prevention measures of interest. The average age of included patients was 65.0 years; 71.6% were male, and 67.6% were white. The most common type of CVD in the population (not mutually exclusive) was CAD (75.9%), followed by cerebrovascular disease (23.5%) and PAD (16.2%; Table 1).

Overall Frequency of Secondary Prevention Measures

Among patients who had complete data, fewer than one third of patients had all 5 secondary prevention measures at baseline (n=4077 [29.9%]). However, nearly three fourths had at least 4 secondary prevention measures at baseline (n=9773 [71.8%]). In this cohort, the individual prevention metric least frequently achieved at baseline was blood pressure, with only 57.9% of the cohort reaching systolic blood pressure <140 mm Hg and diastolic blood pressure <90 mm Hg. Conversely, the metric most frequently achieved at baseline was nonsmoking status (88.6%). Although statin use was relatively high (85.8%), the proportion of patients at the LDL-C target of <70 mg/dL was only 45.4%.

Patient-Level Characteristics Associated With the Frequency of Secondary Prevention Measures

For the secondary prevention score, men more frequently had all 5 secondary prevention measures (31.5% versus 26.1%; Table 1). The age at randomization was similar between all secondary prevention score groups. Of note, compared with those with a history of cerebrovascular disease or PAD, those with a history of CAD more frequently had all 5 prevention measures (33.8% of patients with CAD versus 23.6% of patients with cerebrovascular disease and 20.2% of patients with PAD), whereas they less frequently had 0 to 2 prevention measures (4.4% of patients with CAD versus 9.0% of patients with cerebrovascular disease and 14.6% of patients with PAD; $P<0.0001$ for differences in prevention measures for PAD versus CVD and PAD versus CAD).

The relationships between various baseline characteristics and individual secondary prevention components are shown in Table 2. Those with a history of CAD were significantly more likely to be on aspirin therapy (odds ratio [OR], 2.35; 95% confidence interval [CI], 2.02–2.73), to have lipid control (OR, 2.66; 95% CI, 2.20–3.22), to be on ACEI/ARB therapy (OR, 1.35; 95% CI, 1.15–1.57), and to have blood pressure control (OR, 1.21; 95% CI, 1.07–1.38) than those without CAD. On the other hand, those with a history of PAD were less likely than those without PAD to be on aspirin therapy or to have blood pressure control, and they were less likely to be nonsmokers (OR, 0.63; 95% CI, 0.53–0.76).

Geographical Differences in Achievement of Secondary Prevention Measures

On a regional level, there was wide variation in the secondary prevention score in this trial. North America had the highest proportion of patients with a secondary prevention score of 5 (41.2%), whereas Eastern Europe and Latin America had the lowest proportions

Table 1. Baseline Characteristics of Patient Cohort by Secondary Prevention Score (0–5)

Characteristic	Overall (n=13 616)	Score=0–2 (n=946, 6.9%)	Score=3 (n=2897, 21.3%)	Score=4 (n=5696, 41.8%)	Score=5 (n=4077, 29.9%)
Age at randomization, y*	65 (60, 71)	64 (59, 71)	65 (60, 71)	65 (60, 71)	65 (60, 71)
Female, n (%)	3871 (28.4)	380 (40.2)	878 (30.3)	1604 (28.2)	1009 (24.7)
Hispanic or Latino, n (%)	1627 (11.9)	147 (15.5)	338 (11.7)	686 (12.0)	456 (11.2)
Race					
White	9199 (67.6)	699 (73.9)	1945 (67.1)	3798 (66.7)	2757 (67.6)
Black	417 (3.1)	43 (4.5)	94 (3.2)	164 (2.9)	116 (2.8)
Asian	3086 (22.7)	158 (16.7)	673 (23.2)	1322 (23.2)	933 (22.9)
Other	914 (6.7)	46 (4.9)	185 (6.4)	412 (7.2)	271 (6.6)
Region, n (%)					
North America	2537 (18.6)	105 (11.1)	391 (13.5)	996 (17.5)	1045 (25.6)
Asia Pacific and other	4325 (31.8)	188 (19.9)	907 (31.3)	1909 (33.5)	1321 (32.4)
Western Europe	2005 (14.7)	139 (14.7)	466 (16.1)	871 (15.3)	529 (13.0)
Eastern Europe	3463 (25.4)	383 (40.5)	836 (28.9)	1388 (24.4)	856 (21.0)
Latin America	1286 (9.4)	131 (13.8)	297 (10.3)	532 (9.3)	326 (8.0)
Coronary artery disease, n (%)	10 328 (75.9)	451 (47.7)	1898 (65.5)	4483 (78.7)	3496 (85.7)
Prior myocardial infarction, n (%)	5915 (43.4)	277 (29.3)	1084 (37.4)	2559 (44.9)	1995 (48.9)
Cerebrovascular disease, n (%)	3195 (23.5)	289 (30.5)	840 (29.0)	1312 (23.0)	754 (18.5)
Peripheral artery disease, n (%)	2199 (16.2)	322 (34.0)	618 (21.3)	815 (14.3)	444 (10.9)
Baseline glycohemoglobin, %	7.2 (6.8, 7.7)	7.2 (6.7, 7.7)	7.2 (6.8, 7.7)	7.2 (6.8, 7.7)	7.2 (6.8, 7.6)
Estimated glomerular filtration rate, $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$†	73.0 (60.0, 88.0)	75.0 (61.4, 90.0)	73.0 (60.0, 88.0)	72.0 (60.0, 87.9)	73.0 (60.0, 88.0)
Heart rate, bpm	72.0 (64.0, 79.0)	73.0 (67.0, 80.0)	72.0 (66.0, 80.0)	72.0 (64.0, 78.0)	70.0 (64.0, 78.0)
Body mass index, kg/m^2	29.6 (26.3, 33.3)	29.8 (26.6, 33.5)	29.4 (26.2, 33.2)	29.6 (26.3, 33.2)	29.5 (26.3, 33.3)
Cigarette smoking status, n (%)					
Current	1552 (11.4)	340 (35.9)	675 (23.3)	537 (9.4)	0 (0.0)
Former	5549 (40.8)	222 (23.5)	923 (31.9)	2401 (42.2)	2,003 (49.1)
Never	6515 (47.8)	384 (40.6)	1299 (44.8)	2758 (48.4)	2,074 (50.9)
SBP, mm Hg	133.0 (123.0, 145.0)	142.0 (140.0, 150.0)	141.0 (130.0, 150.0)	138.0 (126.0, 149.0)	126.0 (119.0, 130.0)
DBP, mm Hg	79.0 (70.0, 84.0)	81.0 (76.0, 90.0)	80.0 (73.0, 88.0)	80.0 (70.0, 85.0)	72.0 (67.0, 80.0)
SBP <140 mm Hg and DBP <90 mm Hg, n (%)	7877 (57.9)	174 (18.4)	865 (29.9)	2761 (48.5)	4077 (100)
Blood pressure by treatment for hypertension, n (%)‡					
Untreated with SBP ≥140 mm Hg or DBP ≥90 mm Hg	218 (1.6)	112 (11.8)	106 (3.7)	0 (0.0)	0 (0.0)
Untreated with SBP <140 mm Hg and DBP <90 mm Hg	484 (3.6)	74 (7.8)	170 (5.9)	240 (4.2)	0 (0.0)
Treated with SBP ≥140 mm Hg or DBP ≥90 mm Hg	5521 (40.5)	660 (69.8)	1926 (66.5)	2935 (51.5)	0 (0.0)
Treated with SBP <140 mm Hg and DBP <90 mm Hg	7393 (54.3)	100 (10.6)	695 (24.0)	2521 (44.3)	4077 (100.0)
Low-density lipoprotein cholesterol, mg/dL, n (%)	84.0 (65.0, 108.6)	111.0 (88.8, 139.0)	92.7 (71.6, 121.0)	82.0 (64.0, 105.0)	75.0 (59.4, 95.0)
<70	6183 (45.4)	162 (17.1)	1068 (36.9)	2731 (47.9)	2222 (54.5)
<100	10 054 (73.8)	405 (42.8)	1876 (64.8)	4365 (76.6)	3408 (83.6)
<70 or on statin	11 962 (87.9)	348 (36.8)	2175 (75.1)	5362 (94.1)	4077 (100.0)

(*Continued*)

Table 1. Continued

Characteristic	Overall (n=13 616)	Score=0–2 (n=946, 6.9%)	Score=3 (n=2897, 21.3%)	Score=4 (n=5696, 41.8%)	Score=5 (n=4077, 29.9%)
Medications taken at time of randomization, n (%)					
Statin	11 686 (85.8)	339 (35.8)	2111 (72.9)	5238 (92.0)	3998 (98.1)
ACEI or ARB	10 824 (79.5)	361 (38.2)	1742 (60.1)	4644 (81.5)	4077 (100.0)
Diuretic	5607 (41.2)	320 (33.8)	1147 (39.6)	2373 (41.7)	1767 (43.3)
Calcium channel blocker	4612 (33.9)	295 (31.2)	1036 (35.8)	2005 (35.2)	1276 (31.3)
β-Blocker	8800 (64.6)	458 (48.4)	1721 (59.4)	3756 (65.9)	2865 (70.3)
Aspirin	10 869 (79.8)	247 (26.1)	1687 (58.2)	4858 (85.3)	4077 (100.0)

Score is defined by the sum of the baseline measures: aspirin use, nonsmoking, statin use or low-density lipoprotein cholesterol <70 mg/dL, ACEI/ARB use, and SBP <140 mm Hg and DBP <90. Continuous variables are presented as median (interquartile range), and binary variables are presented as number (column percent). ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; DBP, diastolic blood pressure; and SBP, systolic blood pressure.

*Age is missing among patients enrolled in Lithuania because the entire birth date, including year, was not available.

†The Modification of Diet in Renal Disease Study formula was used to calculate the eGFR. Site-reported values are presented in the table.

‡Treatment for hypertension is defined as use of ACEI, ARB, calcium channel blocker, β-blocker, or diuretic.

(24.7% and 25.3%, respectively; Table 1). More than twice as many patients in Eastern Europe and Latin America had a score of 0 to 2 compared with those in North America (11.1% and 10.2% versus 4.1%, respectively). Achievement of individual prevention components also varied by region in this trial. Compared with North America, those in the Asia Pacific/other region were more likely to be on aspirin therapy (OR, 1.24; 95% CI, 1.01–1.52) and to be nonsmokers (OR, 1.32; 95% CI, 1.04–1.66) at baseline (Figure 1 and Table 2). Lipid control and ACEI/ARB use were not significantly different between these regions, but lower rates of blood pressure control were seen in the Asia Pacific/other region (OR, 0.49; 95% CI, 0.42–0.57). Individuals in the 3 other regions were less likely to achieve blood pressure control than those in North America. Those in Eastern Europe and Latin America were also less likely to achieve LDL-C <70 mg/dL than those in North America.

The variation in secondary prevention measures across individual countries was also substantial in this trial (Figure 2). For example, lipid control varied from 53.7% to 97.8%, and blood pressure control varied from 28.4% to 78.0%.

Table 2. Multivariable Association Between Set of Relevant Covariables and Frequency of Each Secondary Prevention Measure

Baseline Factor	Aspirin Use	Blood Pressure Control	ACEI/ARB Use	Not Smoking	Lipid Control*
Age	0.93 (0.9, 0.96)	0.9 (0.88, 0.93)	1.01 (0.97, 1.04)	1.37 (1.31, 1.44)	0.9 (0.86, 0.94)
Women vs men	0.87 (0.77, 0.97)	0.93 (0.85, 1.03)	1.01 (0.9, 1.14)	1.23 (1.05, 1.44)	0.87 (0.76, 1)
Asian vs white	0.89 (0.73, 1.1)	1.09 (0.94, 1.27)	0.6 (0.5, 0.72)	2.13 (1.66, 2.73)	0.84 (0.65, 1.1)
Black vs white	0.73 (0.55, 0.95)	0.71 (0.56, 0.9)	1.09 (0.81, 1.48)	0.75 (0.54, 1.05)	1.29 (0.9, 1.86)
Other vs white	1.81 (1.36, 2.4)	1.01 (0.81, 1.27)	1.01 (0.77, 1.33)	0.94 (0.64, 1.39)	1.8 (1.33, 2.44)
Hispanic vs non-Hispanic	0.85 (0.64, 1.14)	1.22 (0.96, 1.55)	1.08 (0.8, 1.45)	1.93 (1.27, 2.93)	0.73 (0.51, 1.04)
Coronary artery disease	2.35 (2.02, 2.73)	1.21 (1.07, 1.38)	1.34 (1.15, 1.57)	0.79 (0.65, 0.96)	2.66 (2.2, 3.21)
Cerebrovascular disease	0.95 (0.83, 1.1)	0.96 (0.85, 1.08)	1.1 (0.95, 1.27)	0.81 (0.68, 0.97)	1.1 (0.92, 1.32)
Peripheral artery disease	0.67 (0.58, 0.78)	0.79 (0.7, 0.9)	1 (0.85, 1.16)	0.63 (0.53, 0.76)	1.04 (0.86, 1.26)
Heart failure	0.87 (0.76, 1)	1.17 (1.04, 1.31)	1.41 (1.2, 1.65)	0.97 (0.81, 1.17)	1.08 (0.91, 1.28)
Heart rate	0.97 (0.95, 0.99)	0.97 (0.95, 0.99)	1 (0.97, 1.02)	0.93 (0.9, 0.96)	0.96 (0.93, 0.99)
Body mass index	1 (0.95, 1.05)	0.86 (0.83, 0.9)	1.17 (1.11, 1.23)	1.21 (1.13, 1.29)	0.98 (0.92, 1.04)
Estimated glomerular filtration rate	1.03 (1.01, 1.04)	1 (0.99, 1.01)	0.99 (0.97, 1)	0.95 (0.93, 0.96)	0.99 (0.97, 1)
Glycohemoglobin	1 (0.96, 1.03)	0.94 (0.91, 0.97)	1.02 (0.99, 1.06)	1.01 (0.96, 1.06)	1.01 (0.97, 1.06)
High-density lipoprotein cholesterol	0.99 (0.96, 1.01)	0.98 (0.96, 0.99)	0.99 (0.97, 1.01)	1.06 (1.03, 1.09)	1.01 (0.98, 1.04)

Individuals with complete data for all 5 secondary prevention measures were included in this analyses. The adjustment variables included all of the factors listed above, with the addition of world region. Data shown are odds ratio (95% confidence interval) for 5-U change. ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; and eGFR, estimated glomerular filtration rate.

*Lipid control refers to low-density lipoprotein cholesterol <70 mg/dL or statin use.

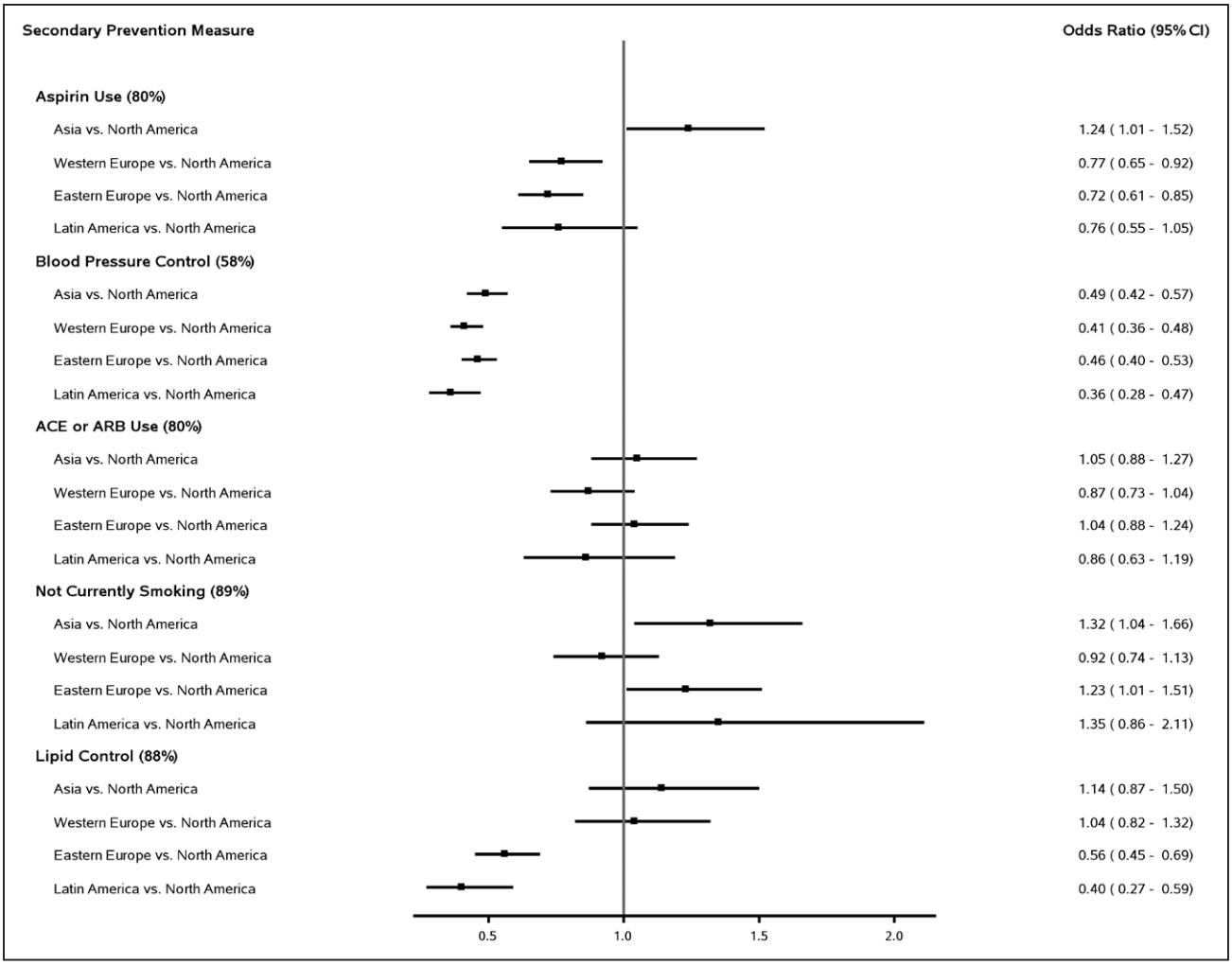

Figure 1. Forest plot with adjusted associations between region and each secondary prevention component. Individuals with complete data for the variable of interest were included in the analyses for each secondary prevention component. Percent represents proportion of the total study population for whom that secondary prevention measure was at goal. Adjustment factors included sex, age, history of coronary artery disease, history of cerebrovascular disease, history of peripheral arterial disease, history of heart failure, heart rate, body mass index, race, ethnicity, estimated glomerular filtration rate, glycohemoglobin level, and high-density lipoprotein cholesterol. Countries and sample size included in each world region were as follows: North America: United States (n=2045) and Canada (n=549). Asia Pacific and other: Australia (n=427), China (n=31), Hong Kong (n=360), India (n=1817), Israel (n=362), Korea (n=330), Malaysia (n=257), New Zealand (n=274), Singapore (n=91), Taiwan (n=210), and South Africa (n=406). Western Europe: Belgium (n=94), Germany (n=503), Spain (n=202), Finland (n=50), France (n=86), United Kingdom (n=516), Italy (n=192), Netherlands (n=309), Norway (n=43), and Sweden (n=81). Eastern Europe: Bulgaria (n=504), Czech Republic (n=462), Estonia (n=88), Hungary (n=565), Lithuania (n=320), Latvia (n=401), Poland (n=605), Romania (n=345), Russia (n=465), Slovakia (n=110), and Turkey (n=100). Latin America: Argentina (n=542), Brazil (n=406), Chile (n=293), and Colombia (n=230). ACE indicates angiotensin-converting enzyme inhibitor; and ARB, angiotensin receptor blocker.

Association Between Secondary Prevention Score and Components With Outcomes

The 3-year Kaplan-Meier event rate for the primary outcome was 10.3% in the TECOS population (4.9% for cardiovascular deaths, 4.3% for myocardial infarctions, and 2.6% for strokes). In Kaplan-Meier analysis, a dose-response relationship was seen, with lower CVD event rates seen with increasing secondary prevention scores (P=0.01; Figure 3). After adjustment for clinical factors, this relationship persisted; with each additional secondary prevention component, individuals were less likely to experience the primary outcome compared with those who had a score of 0 to 2 (adjusted hazard ratio [HR], 0.76; 95% CI, 0.60–0.97 for score of 3; adjusted HR, 0.63; 95% CI, 0.50–0.79 for score of 4; adjusted HR, 0.60; 95% CI, 0.47–0.77 for score of 5; overall P<0.001; Table 3). For individual secondary prevention com-

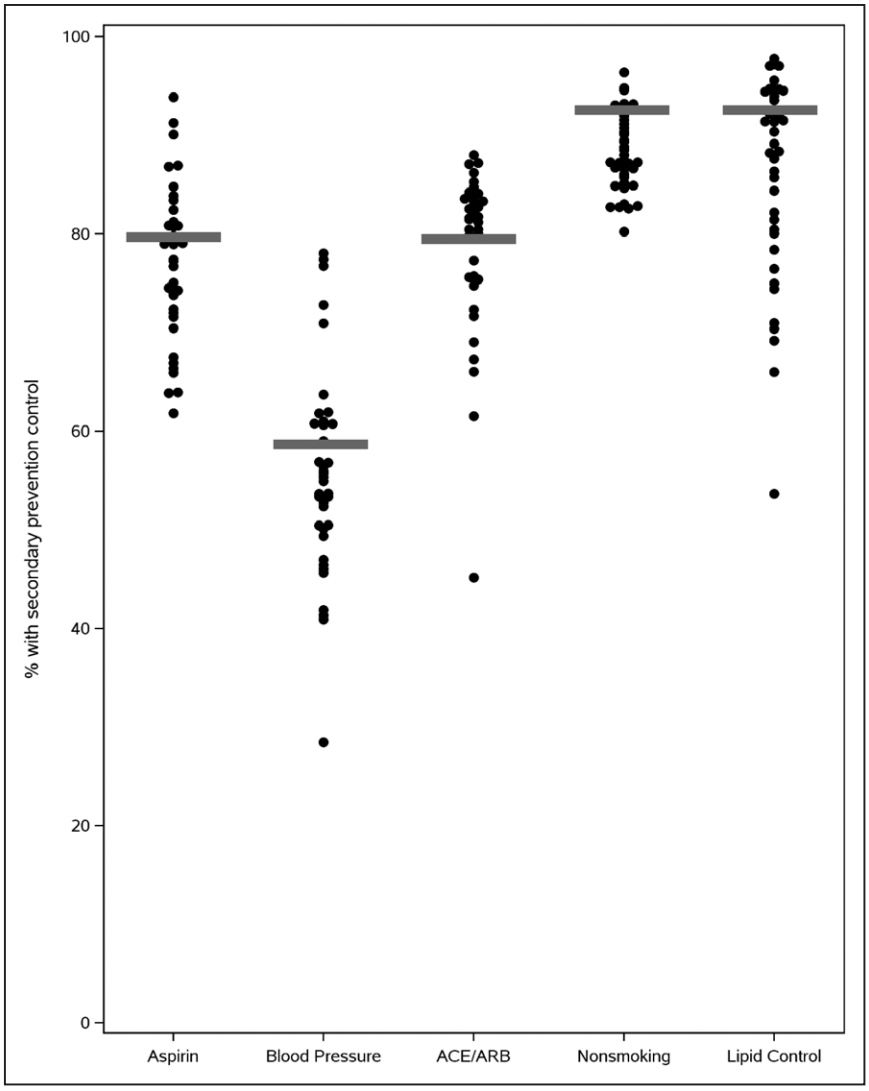

Figure 2. Prevalence of secondary prevention measures.
Each black circle represents the proportion of individuals with the secondary prevention measure within a given country. Red bars represent the mean proportion of individuals with the secondary prevention measures across all countries. Individuals with complete data for the variable of interest were included in the analyses for each secondary prevention component. ACE indicates angiotensin-converting enzyme inhibitor; and ARB, angiotensin receptor blocker.

ponents, aspirin therapy (adjusted HR, 0.79; 95% CI, 0.69–0.92), lipid control (LDL-C <70 mg/dL or statin use; adjusted HR, 0.75; 95% CI, 0.63–0.90), and nonsmoker status (adjusted HR, 0.72; 95% CI, 0.60–0.87) were associated with improved outcomes (Table 3). However, ACEI/ARB therapy (adjusted HR, 1.08; 95% CI, 0.92–1.27) and blood pressure control (adjusted HR, 0.94; 95% CI, 0.83–1.06) were not associated with the primary outcome. There was no evidence of an interaction between secondary prevention measures and world region on the primary outcome (all interaction *P* values for components and score were >0.20).

The relationship between secondary prevention measures at follow-up (12 and 24 months) and the primary outcome was similar to that of secondary prevention measures at baseline, although with the smaller sample size, many of the relationships became nonsignificant (Tables I and II in the online-only Data Supplement).

DISCUSSION

Achievement of guideline-recommended prevention measures can reduce CVD risk in adults with diabetes mellitus and CVD, yet the degree to which these high-risk adults are achieving guideline-indicated secondary prevention interventions has been understudied globally. Our analysis of patients in TECOS suggests that on a global scale, fewer than one third of patients with diabetes mellitus and CVD are receiving optimal CVD secondary preventive care. However, nearly three fourths had at least 4 secondary prevention measures at baseline (n=9773 [71.8%]). Blood pressure and LDL-C control were the 2 most commonly uncontrolled risk factors. Blood pressure control was at target in only 58% of individuals, and only 33% of subjects had an LDL-C <70 mg/dL. More consistent use of composite secondary prevention interventions was associated with a lower likelihood of cardiovascular events over a median of 3 years of follow-up.

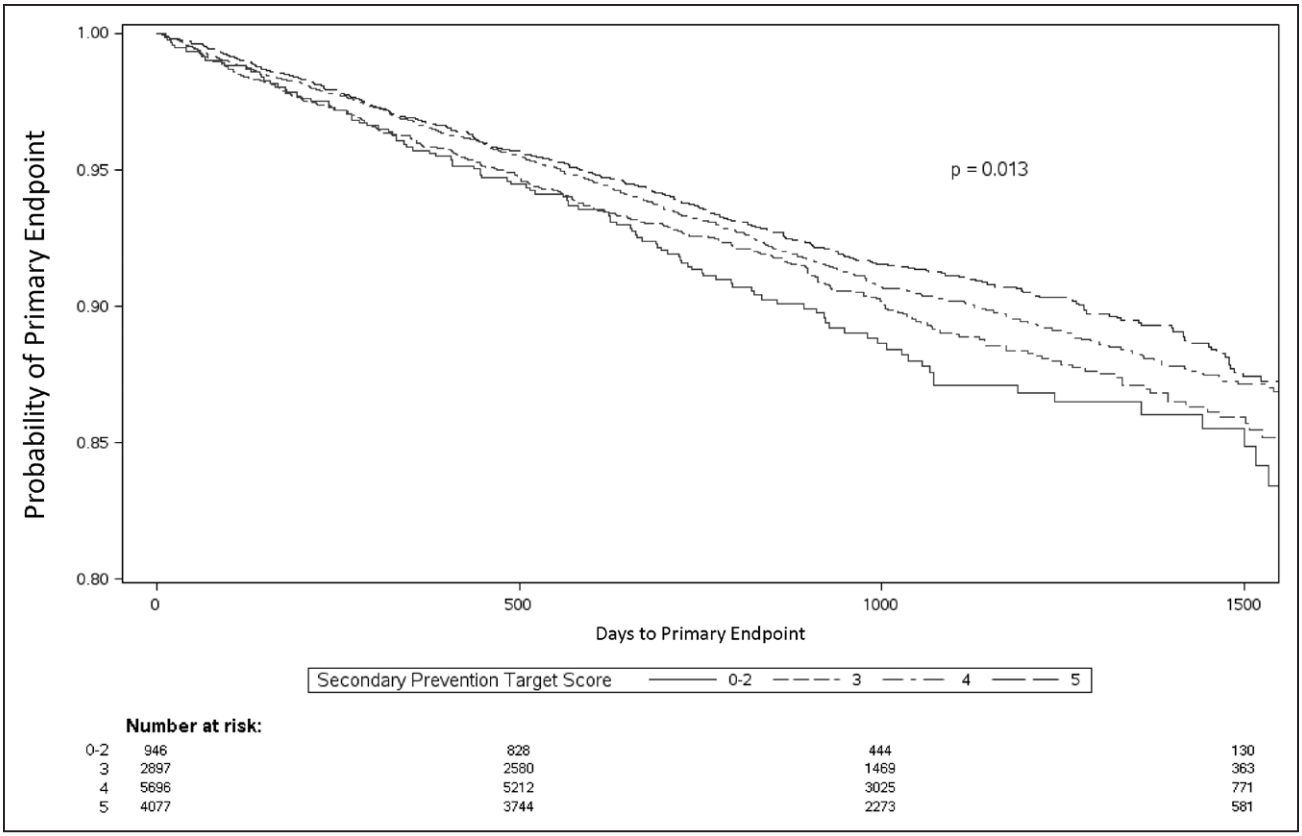

Figure 3. Kaplan-Meier curves of secondary prevention scores for the primary outcome of cardiovascular death, myocardial infarction, or stroke.

Secondary prevention score is the sum of any of the following 5 parameters that are present: aspirin use, lipid control (low-density lipoprotein cholesterol <70 mg/dL or statin therapy), blood pressure control (<140 mm Hg systolic and <90 mm Hg diastolic), angiotensin-converting enzyme inhibitor or angiotensin receptor blocker use, and not currently smoking (ie, never smokers or prior smokers).

Previous studies have specifically examined use of prevention interventions among patients with diabetes mellitus. EUROASPIRE IV (European Action on Secondary and Primary Prevention by Intervention to Reduce Events IV) was a cross-sectional survey of patients with CAD across Europe between 2012 and 2013.[8] Although considerably smaller (n=2183) and representing only care in Europe, the EUROASPIRE IV study found overall results that mirrored ours. Specifically, rates of blood pressure <140/90 mm Hg were achieved in 54% of EUROASPIRE IV survey patients compared with 58% in our group. Similarly, LDL-C <70 mg/dL was achieved in 28% in the EUROASPIRE IV study versus 33% in our study. An examination of the Euro Heart Survey on Diabetes and the Heart revealed that only 30% of patients achieved blood pressure control of <140/90 mm Hg compared with 52.3% in Western Europe and 51.5% in Eastern Europe in our cohort.[9] This difference might be due to improvement in therapy over time because the above study was performed in 2003 to 2004 or to differences in the patient population enrolled in the registry compared with TECOS.

Our data also reveal variation in the frequency of secondary prevention levels at target by geographic region in patients with prior CVD and diabetes mellitus in this trial. Although prior studies indicate that overall smoking prevalence is higher in Asia and Eastern Europe than in North America,[15] North American patients in our trial population were more likely to be currently smoking. The REACH (Reduction of Atherothrombosis for Continued Health) registry conducted in 2003 to 2004 included 67 888 patients with established arterial disease or at high risk for atherothrombosis.[16] In our cohort, individuals in the Asia Pacific/other region had the highest likelihood of being on aspirin therapy, whereas in REACH, those in Asia were among the lowest. Similarly, in our study, Asian Pacific/other patients were as likely as North Americans to have their lipids controlled, whereas in REACH, Asians were less likely to be on statin therapy. The patients enrolled in specialized Asian centers in our trial may be less representative than those from a registry or from the general population. In addition, these apparent improvements in secondary prevention in Asia may be related to the improving economic situation of many countries in this region of the world.[17]

Previous studies have demonstrated that, similar to patients with coronary heart disease, patients with

Table 3. Association Between Secondary Prevention Score, Its Components, and Cardiovascular Death, Myocardial Infarction, or Stroke Outcomes

Parameter	Unadjusted Results		Adjusted Results*	
	HR	95% CI	HR	95% CI
Components				
Aspirin therapy	0.82	0.72–0.93	0.79	0.69–0.92
LDL-C <70 mg/dL or statin use	0.82	0.70–0.96	0.75	0.63–0.90
ACEI or ARB therapy	1.23	1.07–1.42	1.08	0.92–1.27
SBP <140 mm Hg and DBP <90 mm Hg	0.90	0.81–1.01	0.94	0.83–1.06
Not currently smoking	0.85	0.72–0.99	0.72	0.60–0.87
Score (vs 0–2)	1.0 (Referent)		1.0 (Referent)	
3	0.89	0.71–1.10	0.76	0.60–0.97
4	0.80	0.65–0.98	0.63	0.50–0.79
5	0.74	0.60–0.91	0.60	0.47–0.77

Individuals with complete data for all 5 variables of interest were included in the analyses (n=13616); the unadjusted and adjusted component models included all 5 factors simultaneously. ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CI, confidence interval; DBP, diastolic blood pressure; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; and SBP, systolic blood pressure.

*Adjusted for world region, sex, age, history of coronary artery disease, cerebrovascular disease, peripheral artery disease and/or congestive heart failure, pulse, body mass index, Hispanic race, glycohemoglobin, estimated glomerular filtration rate, and high-density lipoprotein cholesterol.

diabetes mellitus and PAD and cerebrovascular disease also benefit from aggressive risk factor modification,[18–22] and these findings are reflected in both the US and European guidelines.[12,23] However, the lower level of secondary prevention achieved in individuals with cerebrovascular disease and PAD compared with those with CAD suggests that patients with cerebrovascular disease and PAD are being undertreated. This finding is in line with previous data on the topic. In the REACH registry, which included patients both with and without diabetes mellitus, those with cerebrovascular disease and PAD were less likely to be on aspirin or statin therapy compared with their CAD counterparts.[16] The PARTNERS study (PAD Awareness, Risk, and Treatment: New Resources for Survival) of 6979 US patients with risk factors for PAD found that those with PAD were treated less intensively for hyperlipidemia and hypertension than those with coronary, cerebral, and abdominal aortic aneurysmal disease.[24] Our data indicate that in patients with diabetes mellitus, the undertreatment of PAD and cerebrovascular disease has persisted since it was recognized in the above studies over a decade ago and presents a clear opportunity for improvement.

We know that multiple risk factors, including hypertension, dyslipidemia, and smoking, increase the risk of poor outcomes in patients with diabetes mellitus and CVD.[25] Thus, the strong association we see between an increasing number of secondary prevention measures and improved outcomes is expected and consistent with prior data on this issue. For example, the STENO-2 trial (Intensified Multifactorial Intervention in Patients With Type 2 Diabetes and Microalbuminuria) found that a multifactorial intervention to modify multiple risk factors in patients with type 2 diabetes mellitus and microalbuminuria was associated with a 50% decrease in long-term clinical events.[7] Our observational data showed a lower risk for CVD events in patients with LDL-C control, aspirin use, and nonsmoking status. We did not observe an independent association in our data between ACEI/ARB therapy and outcomes or between blood pressure control and outcomes, both of which would have been expected to lower CVD event rates.[3,26] It is possible that the relationship between ACEI/ARB therapy and outcomes was confounded by indication for heart failure, although we attempted to correct for this potential bias via adjustment in the model and by performing the analyses in patients without heart failure, which resulted in very similar point estimates. Another potential explanation for our results is that our sample size was too small to detect a difference in outcomes although one exists after adjustment for potential confounders. Alternatively, it is possible that the benefit of lipid control heavily outweighs the benefit of blood pressure control such that it becomes nonsignificant when lipid control is taken into account. A secondary analysis of the STENO-2 trial indicated that although blood pressure control accounted for 11% of the lowering in outcomes, lipid control accounted for 73% of the observed decrease in events.[27]

This study was performed in the context of a large clinical trial, which serves as a strength because collection of clinical characteristics was standardized, and event data were prospectively collected and adjudicated. However, several caveats should be considered in the interpretation of our results. This is a retrospective study of a randomized trial; therefore, the modeling results may be subject to residual confounding. Thus, differences seen between countries and regions may not be generalizable and should be considered exploratory. However, we adjusted for a large number of potential confounders, and our consistency with prior data is reassuring. Furthermore, these data from clinical trial sites, although they were collected before the trial began, may not be representative of all patients in any given country or region. However, care provided at clinical trial sites is likely to have been at least as aggressive as that provided in the general community, and thus, our overall results likely provide a conservative estimate of the global gaps in secondary prevention care. Although this study was more geographically diverse than previous examinations of secondary prevention in patients with diabetes mellitus, certain regions of the world were not included (such as Africa), and low-

income countries were underrepresented, hampering analysis by country economic status. The large number of individuals with missing LDL-C data may have biased our analyses. In addition, LDL-C may not be the optimal parameter to define lipid control in patients with diabetes mellitus. Individuals with diabetes mellitus tend to have small, dense LDL particles, which can lead to a normal or low LDL-C count but a relatively high particle number.[28] LDL particle number or apolipoprotein B may be a better lipid parameter to target in patients with diabetes mellitus, but unfortunately, these levels were not available in our data set. Last, we applied a single standard of secondary prevention care across the globe, but we realize that there are slight differences between existing standards in each country and that these standards vary over time.

CONCLUSIONS

Patients with diabetes mellitus and a history of CVD are at an increased risk of subsequent cardiovascular events and require aggressive risk factor modification. Our analysis of TECOS reveals that this population is still being undertreated globally, especially with regard to blood pressure control. In addition, individuals with PAD and cerebrovascular disease are less likely to have appropriate secondary prevention therapy than their CAD counterparts. These gaps in care provide clear opportunities for improvement in this high-risk population, and recognition of the need for greater secondary preventive care in patients with diabetes mellitus and known CVD is critical to improve outcomes going forward.

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FOOTNOTES

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