Prevalence and Outcomes of Polyvascular (Coronary, Peripheral, or Cerebrovascular) Disease in Patients With Diabetes Mellitus (From the SAVOR-TIMI 53 Trial)

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We sought to assess the prevalence of polyvascular disease in patients with type 2 diabetes mellitus (T2DM) and its impact on ischemic events. Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (SAVOR)-Thrombolysis in Myocardial Infarction (TIMI) 53, a large contemporary, randomized trial, evaluated the effect of saxagliptin versus placebo in 16,492 patients with T2DM and a history of or at risk for cardiovascular (CV) events. Polyvascular disease was defined as a history of clinical events involving 2 or more vascular beds (coronary, peripheral, or cerebrovascular system) at the time of randomization. The primary composite endpoint of CV death, myocardial infarction, or ischemic stroke was compared according to the number of diseased arterial beds. At the time of randomization, 3,667 (22.2%) patients had risk factors for CV events; 11,423 (69.3%) had established 1 arterial bed disease; 1,298 (7.9%) had 2 bed disease; and 104 (0.6%) had 3 bed disease. Compared with diabetic patients with no established atherosclerosis, the adjusted hazard ratio for the composite primary end point in 1, 2, or 3 diseased beds was 1.95, 3.54, and 4.64, respectively (trend $p < 0.0001$). The adjusted risk for overall mortality increased in a similar stepwise fashion from 1.47 to 2.33 to 3.12, respectively (trend $p = 0.0001$) with each additional diseased arterial territory. In conclusion, in patients with confirmed atherosclerosis enrolled in SAVOR-TIMI 53, 11% had polyvascular disease; and compared with diabetic patients with single bed disease, the risk of ischemic events and overall mortality was substantially higher in patients with T2DM and polyvascular disease. Published by Elsevier Inc. (Am J Cardiol 2019;123:145−152)

Polyvascular disease is defined as the existence of atherosclerosis across 2 or more vascular beds.[1] Patients with atherosclerosis across multiple arterial sites are at heightened risk of cardiovascular (CV) events.[2,3] In particular, observational studies have found this risk to be greatest when polyvascular disease occurs in the setting of diabetes mellitus.[4,5] In the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (SAVOR)-Thrombolysis in Myocardial Infarction (TIMI) 53 study, the addition of saxagliptin, a dipeptidyl peptidase-4 inhibitor, did not affect the rate of ischemic events in patients with type 2 diabetes mellitus (T2DM).[6] The present analysis aims to determine the rates of ischemic events in diabetic patients from the SAVOR-TIMI 53 study according to the number of symptomatic vascular beds. The arterial beds of interest in the present study include coronary (CAD), peripheral (PAD), and cerebral (CVD)

Methods

SAVOR-TIMI 53 was a randomized, double-blind, placebo-control trial of saxagliptin in patients with a history of T2DM. Between May 2010 and December 2011, 16,492 patients with T2DM were randomized to receive 5 mg of saxagliptin (or 2.5 mg daily if estimated glomerular filtration rate was $\leq$50 ml/min) or placebo. The trial design and primary findings of SAVOR-TIMI 53 have been previously published.[6−8] Briefly, study eligibility criteria included a documented history of T2DM in conjunction with a HbA1c of 6.5% to 12.0% in the 6 months before randomization and either multiple risk factors for vascular disease or a history of established CV disease. Multiple risk factors for vascular disease were defined as an age of at least

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55 years in men or 60 years in women in conjunction with 1 of the following: active smoking, dyslipidemia, or hypertension. Established CV disease was characterized as a previous clinical event involving the coronary, peripheral, or cerebrovascular system. Specifically, coronary disease was defined as a previous myocardial infarction (MI) that lead to a hospitalization with a final diagnosis MI, percutaneous coronary intervention, coronary artery bypass graft with revascularization, or objective evidence of CAD (equal or $\geq 50\%$ stenosis) in at least 2 arteries. PAD was defined as intermittent claudication and an ankle brachial index < 0.90 obtained in the previous 12 months, previous peripheral revascularization, or amputation of the legs at any level due to arterial obstructive disease. Patients with amputations secondary to infection and/or peripheral neuropathy were excluded from the PAD cohort. CVD was defined as a previous history of an acute focal neurologic deficit > 24 hours secondary to a cerebral lesion of vascular origin. Patients with a history of cardio-embolic events were excluded from the CVD cohort.[6] For the present study, outcomes were stratified according to total number of symptomatic arterial beds (0, 1, 2, or 3). Patients were followed for a median of 2.1 years.

The primary efficacy end point in SAVOR-TIMI 53 was a composite of CV death, MI, or ischemic stroke. The key secondary efficacy endpoint included the primary endpoint and hospitalization for heart failure, coronary revascularization, or unstable angina. The secondary endpoint of overall mortality was also evaluated. All endpoints, including their components, were adjudicated by a clinical events committee of CV specialists.

Baseline characteristics for study groups were compared using the chi-square test for categorical variables and the nonparametric Kruskal-Wallis test for continuous variables. All efficacy analyses were conducted according to the intention-to-treat principle and included all randomized subjects. A Cox-proportional multivariable hazards model was implemented to estimate hazard ratios (HR) and 95% confidence intervals (CI). This model was adjusted for age, gender, previous heart failure, systolic blood pressure, dyslipidemia, current smoking, estimated glomerular filtration rate (fitted as a continuous variable), duration of T2DM, and baseline HbA1c. Proportional hazards assumption for all final models was assessed and confirmed by score tests using scaled Schoenfeld residuals. Event rates were depicted as Kaplan-Meier failure rates at 24 months and compared using the log-rank test. Statistical significance was assessed at a nominal alpha level of 0.05. All reported p values were 2-sided. All statistical analyses were done with SAS System V9.4 (SAS Institute, Cary, North Carolina).

Results

The SAVOR-TIMI 53 trial randomized 16,492 patients with T2DM; of these, for the present analysis 3,667 (22.2%) had no established atherosclerotic disease in any vascular bed; 11,423 (69.3%) had disease in 1 bed; 1,298 (7.9%) had disease in 2 beds; and 104 (0.6%) had disease in all 3 beds. In patients with disease in a single vascular bed, 78.4% (n = 8,955) had CAD only, 10% (n = 1,148) had PAD only, and 11.6% (n = 1,320) had CVD only. In patients with disease in 2 beds, 93.9% (n = 1,219) had CAD, 54.5% (n = 707) had PAD, and 51.6% (n = 670) had CVD.

Patients with polyvascular disease—atherosclerosis in 2 or 3 vascular beds—had a greater duration of T2DM compared with patients with 0 bed and 1 bed disease. Patients with polyvascular disease were older and were more likely to have hyperlipidemia, hypertension, previous MI, previous coronary revascularization, or previous congestive heart failure at randomization. In patients with confirmed atherosclerotic disease, the rates of smoking were greatest in those with disease across 2 beds (Table 1).

Compared with patients with 0 or 1 bed disease, patients with polyvascular disease were less frequently treated with metformin or a sulfonylurea, but more frequently treated with insulin, statin, angiotensin receptor blocker, β blocker, calcium channel blocker, adenosine diphosphate antagonist, or anticoagulant therapies at randomization. Patients with arterial disease in 1 or more beds were more frequently treated with an angiotensin-converting enzyme (ACE) inhibitor than those with no established disease; however, patients with polyvascular disease experienced lower rates of ACE inhibitor use compared with those with single bed disease (Table 1).

At 2.1 years, the rate of the primary composite end point of CV death, MI, or ischemic stroke occurred more frequently in patients with polyvascular disease; with the lowest rates seen in patients with no established disease in any bed (3.3%) or single bed disease (7.5%), followed by those with disease in 2 (15.6%), and 3 beds (23.9%), log-rank $p < 0.0001$. At 2.1 years, the key secondary endpoint of CV death, nonfatal MI, or nonfatal ischemic stroke, hospitalization for UA, coronary revascularization, or heart failure occurred in 4.8% of patients with no established disease in any bed, 13.9% with disease in a single bed, 22.4% with disease in 2 beds, and 35.7% with disease in 3 beds, log-rank $p < 0.0001$ (Table 2). Patients with 0 bed disease experienced the lowest rates of overall mortality (2.6%), followed by those with 1 (4.7%), 2 (8.3%), and 3 bed disease (14.4%), log-rank $p < 0.0001$. The Kaplan-Meier survival plots for the primary composite end point and overall mortality are depicted in Figures 1 and 2.

After adjustment for differences in key baseline variables, compared with diabetic patients with no established disease in any vascular bed, there was a graded stepwise increase in the risk for the primary composite endpoint with the presence of each additional diseased bed: 1 bed (HR_{adj} [95% CI] = 1.95 [1.63 to 2.35], $p < 0.0001$); 2 beds (HR_{adj} [95% CI] = 3.54 [2.84 to 4.43], $p < 0.0001$); and 3 beds (HR_{adj} [95% CI] = 4.64 [2.87 to 7.15], $p < 0.0001$; Figure 3). A similar increase in the adjusted risk of the key secondary composite end point was also observed: 1 bed (HR_{adj} [95% CI] = 2.40 [2.07 to 2.79], $p < 0.0001$); 2 beds HR_{adj} [95% CI] = 3.51 [2.92 to 4.22], $p < 0.0001$); and 3 beds (HR_{adj} [95% CI] = 5.18 [3.53 to 7.37], $p < 0.0001$; Figure 4). Last, the adjusted risk of overall mortality was as follows: 1 bed (HR_{adj} [95% CI] = 1.47 [1.20 to 1.82], $p = 0.0002$); 2 beds HR_{adj} [95% CI] = 2.33 [1.78 to 3.04], $p < 0.0001$); and 3 beds (HR_{adj} [95% CI] = 3.12 [1.66 to 5.35], $p = 0.0001$; Figure 4).

Table 1
Baseline characteristics

Variable	Number of vascular beds involved				p value all groups
	0 (n = 3,667 [22.2%])	1 (n = 11,423 [69.3%])	2 (n = 1,298 [7.9%])	3 (n = 104 [0.6%])	
Age, mean ± SD (Years)	66.1 (6.7)	64.5 (9.0)	66.5 (8.5)	66.1 (8.7)	< 0.0001
Women	1,707 (46.6%)	3,385 (29.6%)	342 (26.3%)	21 (20.2%)	< 0.0001
Men	1,960 (53.4%)	8,038 (70.4%)	956 (73.7%)	83 (79.8%)	< 0.0001
Body mass index mean ± SD (kg/m^2)	31.8 (5.6)	31.0 (5.6)	31.0 (5.2)	30.4 (4.7)	< 0.0001
Type 2 diabetes mellitus duration median interquartile range (Years)	10.8 (8.2)	12.0 (8.9)	14.7 (9.6)	16.3 (10.6)	< 0.0001
Coronary artery disease	0	8,955 (78.4%)	1,219 (93.9%)	104 (100%)	< 0.0001
Peripheral artery disease	0	1,148 (10%)	707 (54.5%)	104 (100%)	< 0.0001
Cerebrovascular disease	0	1,320 (11.6%)	670 (51.6%)	104 (100%)	< 0.0001
Dyslipidemia*	2,511 (68.5%)	8,125 (71.1%)	1,018 (78.4%)	85 (81.7%)	< 0.0001
Hypertension†	3,122 (85.1%)	9,177 (80.3%)	1,108 (85.4%)	85 (81.7%)	< 0.0001
Prior myocardial infarction	0	5,443 (47.6%)	726 (55.9%)	68 (65.4%)	< 0.0001
Prior coronary revascularization	0	6,163 (54%)	884 (68.1%)	76 (73.1%)	< 0.0001
Prior congestive heart failure	197 (5.4%)	1,622 (14.2%)	262 (20.2%)	24 (23.1%)	< 0.0001
Current smoker	3,082 (84.1%)	9,975 (87.3%)	1,132 (87.2%)	82 (78.8%)	< 0.0001
Estimated glomerular filtration rate mean ± SD (mL/min 1.73 m^2)	74.2 (22.1)	72.7 (22.7)	66.8 (22.2)	65.2 (23.9)	< 0.0001
Albumin/creatinine mean ± SD (mg/mmol)	16.8 (75.0)	21.0 (75.3)	24.7 (72.1)	33.5 (61.8)	< 0.0001
Medications					
Aspirin	1,846 (50.3%)	9,436 (82.6%)	1,042 (80.3%)	80 (76.9%)	< 0.0001
Dose ≤ 100 mg	1,666 (45.4%)	7,298 (63.9%)	779 (60%)	61 (58.7%)	< 0.0001
Insulin	1,146 (31.3%)	4,856 (42.5%)	720 (55.5%)	64 (61.5%)	< 0.0001
Metformin	2,753 (75.1%)	7,827 (68.5%)	786 (60.6%)	49 (47.1%)	< 0.0001
Sulfonylurea	1,545 (42.1%)	4,567 (40%)	448 (34.5%)	37 (35.6%)	< 0.0001
Thiazolidinedione	284 (7.7%)	616 (5.4%)	67 (5.2%)	5 (4.8%)	< 0.0001
Statin	2,296 (62.6%)	9,415 (82.4%)	1,119 (86.2%)	87 (83.7%)	< 0.0001
Angiotensin-converting enzyme inhibitor	1,912 (52.1%)	6,264 (54.8%)	708 (54.5%)	56 (53.8%)	0.04
Angiotensin receptor blocker	1,049 (28.6%)	3,116 (27.3%)	402 (31%)	28 (26.9%)	0.03
β-blocker	1,369 (37.3%)	7,768 (68%)	954 (73.5%)	71 (68.3%)	< 0.0001
Calcium channel blocker	1,157 (31.6%)	3,661 (32%)	514 (39.6%)	46 (44.2%)	< 0.0001
Adenosine diphosphate antagonists	81 (2.2%)	2,404 (21%)	351 (27%)	33 (31.7%)	< 0.0001
Other anticoagulants	180 (4.9%)	969 (8.5%)	171 (13.2%)	18 (17.3%)	< 0.0001
Adenosine diphosphate antagonists or other anticoagulants	259 (7.1%)	3,291 (28.8%)	499 (38.4%)	49 (47.1%)	< 0.0001

SD = standard deviation.

* Dyslipidemia was defined as a high level of low-density lipoprotein cholesterol > 130 mg/dL (> 3.36 mmol/L) or low level of high-density lipoprotein cholesterol defined as < 40 mg/dL (< 1.04 mmol/L) for men or < 50 mg/dL (< 1.30 mmol/L) for women;

† hypertension was defined as a blood pressure > 140/90 mm Hg or on a blood pressure-lowering agent with a blood pressure > 130/80 mm Hg.

The rates of the primary and secondary composite endpoints were similar in diabetic patients randomized to saxagliptin compared with the placebo cohort, regardless of the number of diseased vascular beds (Table 3).

Discussion

In this trial of 16,492 patients with T2DM across the risk spectrum of atherosclerotic disease, we found that after adjustment and compared with patients with no established atherosclerosis, the risk of a major CV event increased in a stepwise manner with each additional disease vascular bed. This pattern was consistent for many ischemic end points, as well as hospitalization for heart failure.

The presence of polyvascular disease and T2DM are each independently associated with an increased risk of CV events.[4,5] In a large international registry after outpatients with CAD, PAD, CVD, or multiple risk factors for atherosclerotic disease, the presence of either polyvascular disease or T2DM conferred a respective 99% and 44% increased risk in the composite end point of CV death, MI, or stroke.[4,9] The present study is novel, in that it evaluates the aggregate effect of polyvascular disease and T2DM on long-term outcomes in the setting of a large contemporary randomized clinical trial. Observational studies evaluating CV outcomes in patients with polyvascular disease have demonstrated a stepwise increase in CV events for each additional diseased vascular bed, placing patients with disease in multiple vascular beds at greatest risk.[1,10,11] This

Table 2
Polyvascular disease outcomes: primary and secondary event rates

	Number of vascular beds involved				All groups Log-rank p value
	0 (n = 3,667 [22.2%])	1 (n = 11,423 [69.3%])	2 (n = 1,298 [7.9%])	3 (n = 104 [0.6%])	
Primary endpoint	148 (3.3%)	856 (7.5%)	196 (15.6%)	22 (23.9%)	< 0.0001
Secondary endpoint	213 (4.8%)	1,562 (13.9%)	284 (22.4%)	34 (35.7%)	< 0.0001
Cardiovascular death	71 (1.5%)	364 (3.2%)	84 (6.3%)	10 (11.5%)	< 0.0001
Myocardial infarction	46 (1.0%)	396 (3.5%)	89 (7.4%)	12 (13.0%)	< 0.0001
Stroke	49 (1.1%)	226 (2.0%)	57 (4.6%)	2 (2.1%)	< 0.0001
Ischemic stroke	42 (1.0%)	202 (1.8%)	53 (4.3%)	1 (1.1%)	< 0.0001
Hospitalization for unstable angina pectoris	13 (0.3%)	145 (1.3%)	16 (1.3%)	4 (4.7%)	< 0.0001
Hospitalization for heart failure	50 (1.1%)	380 (3.4%)	72 (6.0%)	15 (13.8%)	< 0.0001
Hospitalization for coronary revascularization	71 (1.6%)	685 (6.2%)	113 (9.1%)	13 (14.3%)	< 0.0001
All-cause mortality	127 (2.6%)	545 (4.7%)	113 (8.3%)	13 (14.4%)	< 0.0001

study extends these findings to stable diabetic patients with polyvascular disease.

The current analysis further highlights 2 key findings. First, the detrimental relation between polyvascular disease and increased CV risk is present, and likely augmented, in the setting of T2DM. The pathophysiology behind this high-risk population likely involves a complex interplay of hyperglycemia-mediated systemic inflammation, endothelial dysfunction, and abnormal platelet function promoting atherosclerosis.[12–14] Second, despite being at increased risk for CV events, diabetic patients with symptomatic polyvascular disease are not

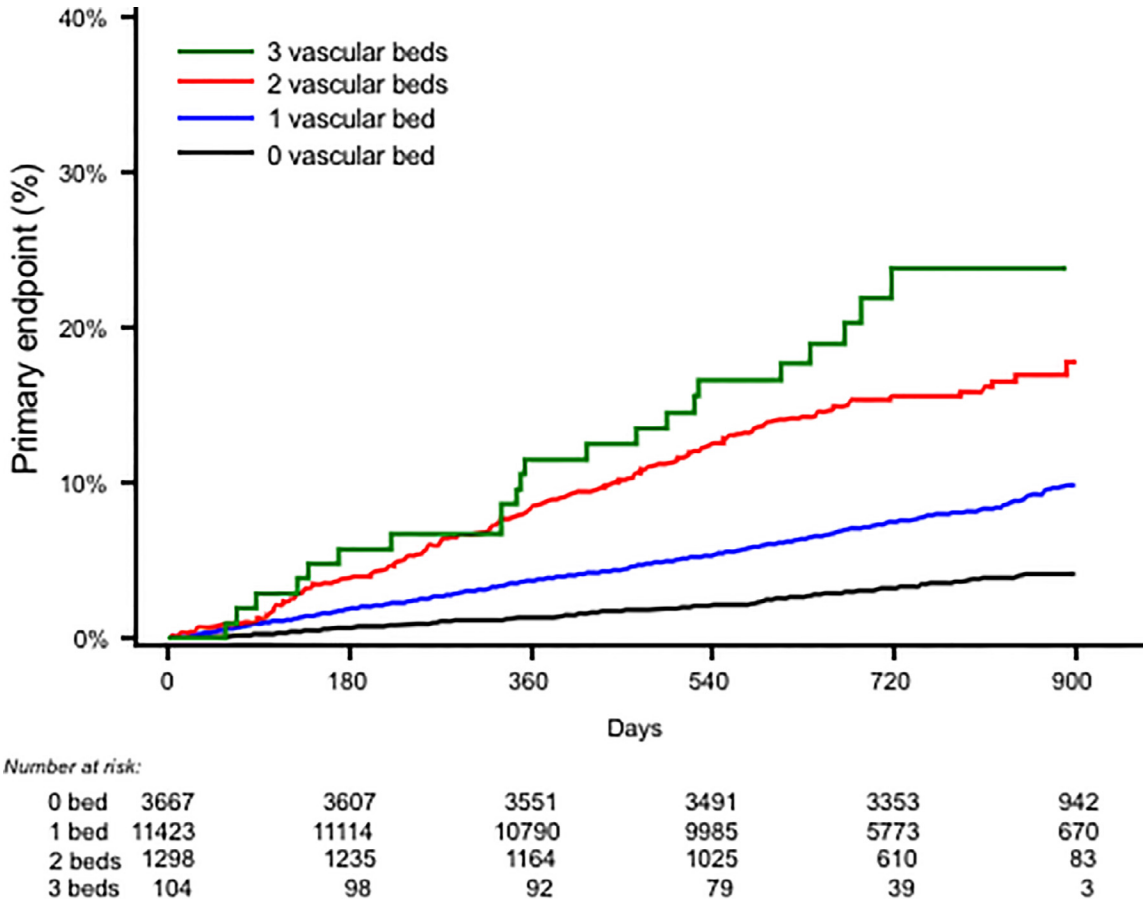

Figure 1. Kaplan-Meier curves for the primary composite end point according to number of diseased vascular beds.

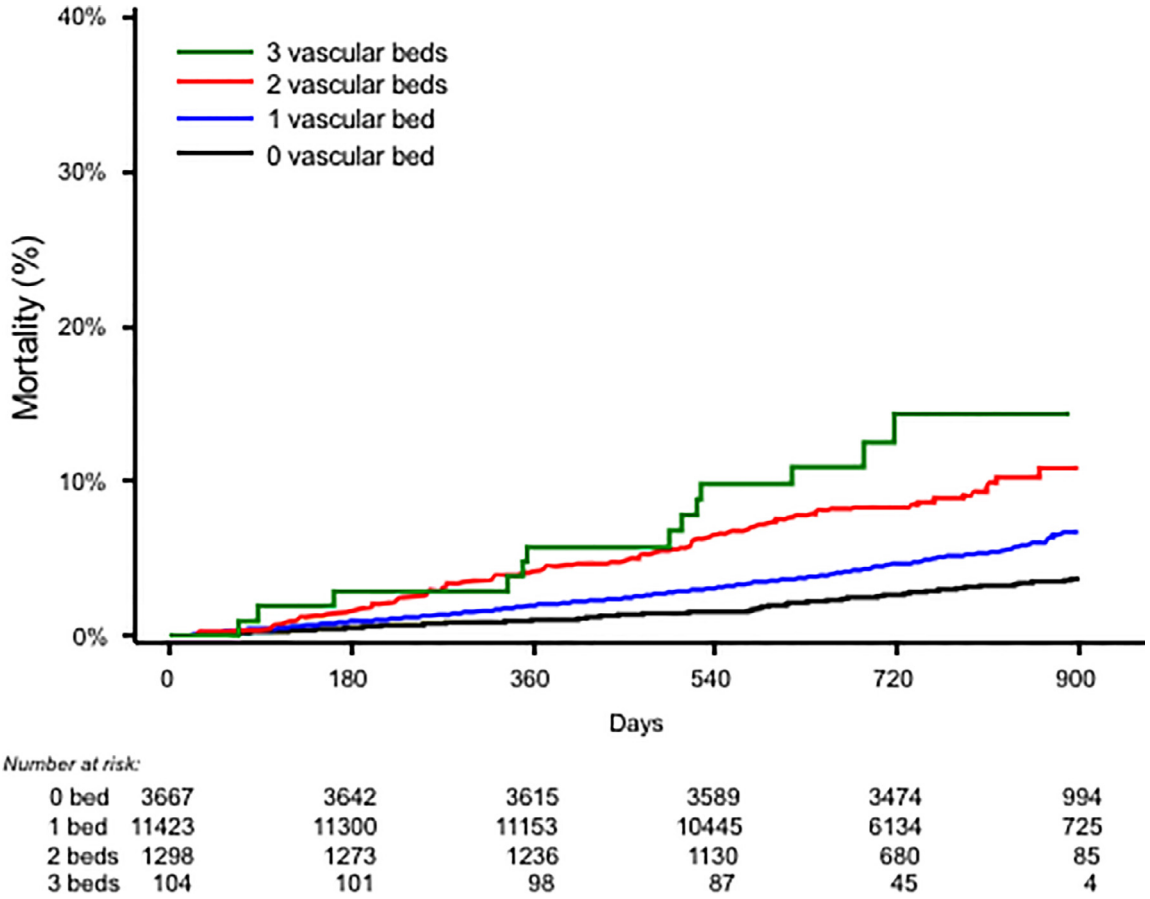

Figure 2. Kaplan-Meier curves for all-cause mortality according to number of diseased vascular beds.

being optimally treated with evidence-based therapies. In the present study, diabetic patients with polyvascular disease, in relation to patients with single bed disease, were found to have substandard rates of aspirin, ACE inhibitor and metformin use in conjunction with increased rates of smoking. The paradox of high-risk CV patients being less likely to receive guideline-recommended medicines, such as aspirin, has been previously described in observational studies.[9,11] The current analysis both confirms and augments these previous findings to include ACE inhibitors and metformin. Studies of diabetic patients have found ACE inhibitors to improve CV disease outcomes independent of blood pressure effects.[15,16] Metformin, an oral glycemic agent, is associated with a mortality benefit in patients with T2DM and established atherosclerosis.[17,18] A possible explanation for the diminished use of both ACE inhibitors and metformin in diabetic patients with polyvascular disease observed in the present study may be due to a heightened prevalence of renal dysfunction. In the case of metformin, an increased use of insulin may also have contributed to its underutilization.

There are limitations to the present analysis. First, this is a post hoc study of subgroups of the overall trial; therefore, all findings should be interpreted with caution. Second, the median patient follow-up was 2.1 years. Therefore, any CV benefit or risk of saxagliptin therapy is uncertain beyond this period of time. Third, the present study limits analyses of secondary end points to individual components of only the primary efficacy endpoint. As such, associations regarding components of the key secondary efficacy endpoint according to number of diseased vascular beds should not be undertaken.

In conclusion, SAVOR-TIMI 53 was a large contemporary, randomized placebo-controlled trial of patients with T2DM in which 11% of patients with atherosclerosis had polyvascular disease. Compared with diabetic patients with single bed atherosclerosis, patients with polyvascular disease experienced 2 to 3 times higher rates of the composite ischemic endpoint of CV death, MI, or stroke, with a stepwise increase in this risk with each additional vascular bed involved. The present study identifies a particularly high-risk population, patients with concomitant T2DM and polyvascular disease, with the potential to benefit greatly from novel therapies aimed at preventing CV events.

Executive Committee

Eugene Braunwald (Study Chair), Deepak L. Bhatt (Co-Principal Investigator), Itamar Raz (Co-Principal Investigator), Jaime A. Davidson, Robert Frederich (nonvoting), Boaz Hirshberg (nonvoting), and Ph. Gabriel Steg.

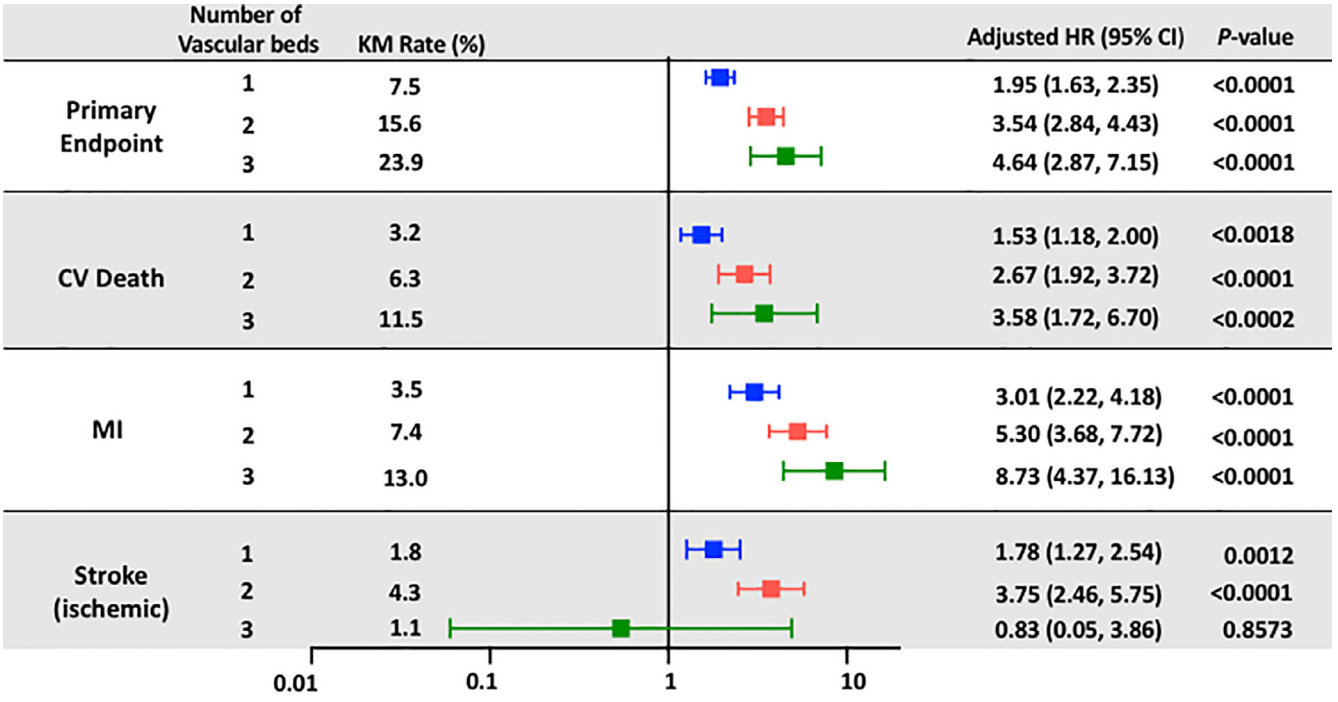

Figure 3. Primary outcomes according to number of diseased vascular beds.
(Adjusted)
Primary end point = composite of cardiovascular death, myocardial infarction, or ischemic stroke.
CI = confidence interval; CV = cardiovascular; HR = hazard ratio; KM = Kaplan-Meier; MI = myocardial infarction.

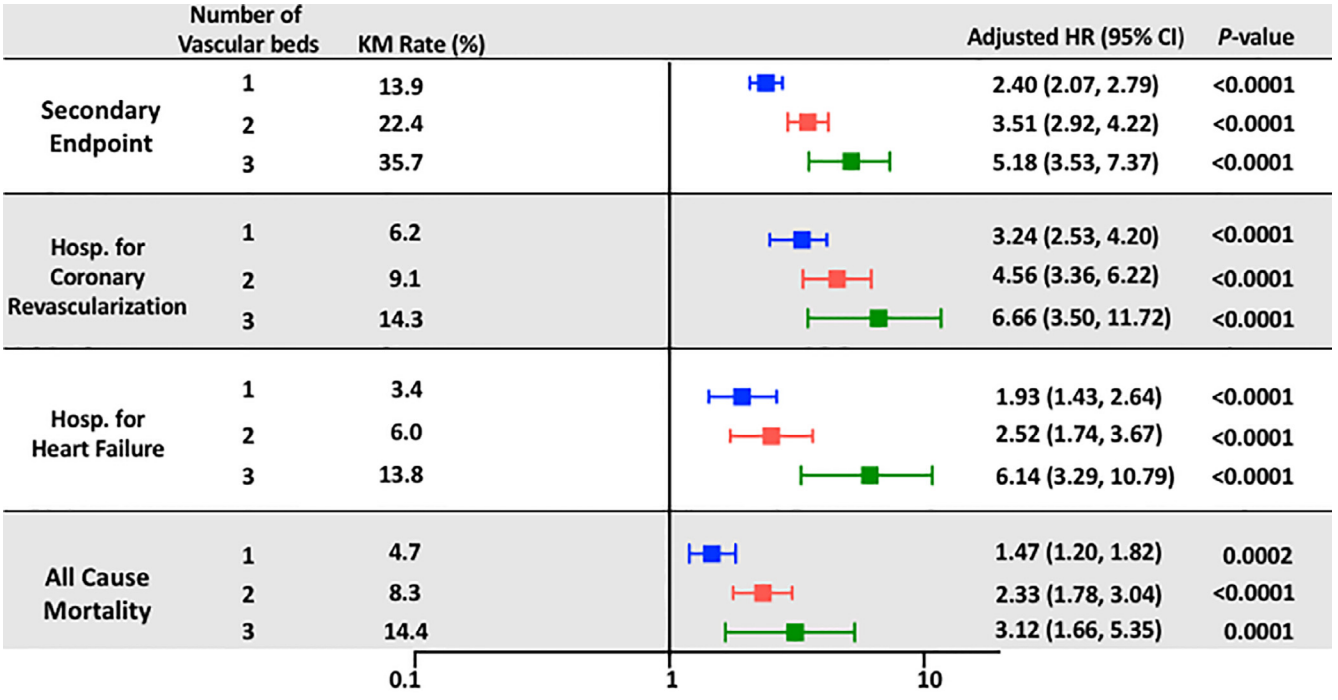

Figure 4. Secondary outcomes according to number of diseased vascular beds.
(Adjusted)
Secondary enpoint = composite of cardiovascular death, myocardial infarction, ischemic stroke, hospitalization for heart failure, coronary revascularization, or unstable angina.
CI = confidence interval; HR = hazard ratio; KM = Kaplan-Meier.

Table 3
Polyvascular disease outcomes: primary and secondary event rate (saxagliptin vs placebo)

End point (%)	Number of vascular beds involved								Interaction p value
	0 (n = 3,667 [22.2%])		1 (n = 11,423 [69.3%])		2 (n = 1,298 [7.9%])		3 (n = 104 [0.6%])		
	Saxagliptin n = 1,858	Placebo n = 1,809	Saxagliptin n = 5,736	Placebo n = 5,687	Saxagliptin n = 635	Placebo n = 663	Saxagliptin n = 51	Placebo n = 53	
Primary endpoint	3.7%	2.9%	7.5%	7.6%	15.8%	15.4%	22.1%	25.6%	0.29
Secondary endpoint	5.2%	4.5%	14.1%	13.8%	23.4%	21.5%	32.1%	39.0%	0.60
Cardiovascular death	1.8%	1.3%	3.2%	3.1%	7.1%	5.6%	11.3%	11.6%	0.54
Myocardial infarction	1.0%	1.1%	3.4%	3.6%	7.2%	7.7%	10.8%	15.2%	0.72
Stroke	1.3%	0.9%	2.0%	2.0%	5.0%	4.3%	2.1%	2.0%	0.67
Ischemic stroke	1.2%	0.7%	1.9%	1.7%	4.7%	4.0%	2.1%	0%	0.68
Hospitalization For UAP	0.3%	0.3%	1.4%	1.2%	1.8%	0.8%	3.2%	6.1%	0.72
Hospitalization for HF	1.3%	0.9%	3.7%	3.1%	7.3%	4.7%	14.6%	13.1%	0.71
Hospitalization for coronary revasc	1.3%	1.9%	6.2%	6.3%	8.9%	9.3%	9.2%	19.6%	0.71
All-cause mortality	3.0%	2.2%	4.9%	4.4%	9.3%	7.3%	15.1%	13.6%	0.70

CV = cardiovascular; HF = heart failure; MI = myocardial infarction; revasc = revascularization; UAP = unstable angina pectoris.

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