# Causes of Death in a Contemporary Cohort of Patients With Type 2 Diabetes and Atherosclerotic Cardiovascular Disease: Insights From the TECOS Trial

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## OBJECTIVE

**We evaluated the specific causes of death and their associated risk factors in a contemporary cohort of patients with type 2 diabetes and atherosclerotic cardiovascular disease (ASCVD).**

## RESEARCH DESIGN AND METHODS

**We used data from the Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) study (*n* = 14,671), a cardiovascular (CV) safety trial adding sitagliptin versus placebo to usual care in patients with type 2 diabetes and ASCVD (median follow-up 3 years). An independent committee blinded to treatment assignment adjudicated each cause of death. Cox proportional hazards models were used to identify risk factors associated with each outcome.**

## RESULTS

**A total of 1,084 deaths were adjudicated as the following: 530 CV (1.2/100 patient-years [PY], 49% of deaths), 338 non-CV (0.77/100 PY, 31% of deaths), and 216 unknown (0.49/100 PY, 20% of deaths). The most common CV death was sudden death (*n* = 145, 27% of CV death) followed by acute myocardial infarction (MI)/stroke (*n* = 113 [MI *n* = 48, stroke *n* = 65], 21% of CV death) and heart failure (HF) (*n* = 63, 12% of CV death). The most common non-CV death was malignancy (*n* = 154, 46% of non-CV death). The risk of specific CV death subcategories was lower among patients with no baseline history of HF, including sudden death (hazard ratio [HR] 0.4; *P* = 0.0036), MI/stroke death (HR 0.47; *P* = 0.049), and HF death (HR 0.29; *P* = 0.0057).**

## CONCLUSIONS

**In this analysis of a contemporary cohort of patients with diabetes and ASCVD, sudden death was the most common subcategory of CV death. HF prevention may represent an avenue to reduce the risk of specific CV death subcategories.**

The global burden of diabetes has risen significantly over the past few decades; by 2030, more than 500 million adults will be affected (1). Diabetes is an established risk factor for cardiovascular (CV) disease (1–3), and myocardial infarction (MI) is believed to be the most common cause of death among these patients (4). However, recognition is growing that diabetes may increase the risk of other causes of CV death, including sudden death (5) and heart failure (HF) (6), and non-CV deaths, such as malignancy (4).

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Among patients with prediabetes and risk factors for CV disease, non-CV deaths, specifically malignancy, contribute to the large burden of all-cause mortality (4,7). Because the use of medical therapy to target modifiable CV risk factors has improved and aggressive risk factor management has become more widespread (8), the distribution of causes of death among a contemporary cohort of patients with diabetes and established atherosclerotic CV disease (ASCVD) should be reexamined. In addition, risk factors associated with specific causes of death should be elucidated to gain an understanding of potentially modifiable risk factors. To achieve these goals, we used data from the Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS). We sought to assess *1*) the distribution of specific causes of death, *2*) patient demographic profiles associated with specific causes of death, and *3*) risk factors associated with causes of death.

## RESEARCH DESIGN AND METHODS

TECOS was a double-blind, multinational, placebo-controlled CV safety study evaluating the long-term effect of adding sitagliptin, a dipeptidyl peptidase 4 inhibitor, to usual care in patients with type 2 diabetes and established ASCVD. The main methods and results have been reported (9,10). Briefly, the TECOS study randomized 14,735 patients to the addition of either sitagliptin or placebo to their existing antihyperglycemic therapy in the context of usual care. Eligible patients were ≥50 years of age with type 2 diabetes and established ASCVD, which included a history of major coronary artery disease (CAD), ischemic cerebrovascular disease, or atherosclerotic peripheral arterial disease (PAD). Eligible patients had glycosylated hemoglobin ($HbA_{1c}$) values of 6.5–8.0% (48–64 mmol/mol) on treatment with stable doses of one or two oral antihyperglycemic agents (metformin, pioglitazone, or sulfonylurea) or stable treatment with insulin with or without metformin. Patients were excluded from enrollment if they had two or more episodes of severe hypoglycemia in the previous year or if their estimated glomerular filtration rate (eGFR) was <30 mL/min/1.73 $m^2$ at baseline. The primary CV outcome was a composite of CV death, nonfatal MI, nonfatal stroke, or hospitalization for unstable angina.

An independent clinical events committee adjudicated causes of death. The committee determinations were used for the purposes of this analysis. Definitions of cause-specific mortality are provided in Supplementary Table 1. In the primary TECOS results article, deaths adjudicated as a result of unknown causes were included as CV deaths, per protocol, in the statistical analysis (9,10); however, for the current analysis, deaths of unknown causes were considered separately from CV death. In addition, deaths as a result of stroke and MI were combined because of the small number of events.

TECOS adjudication was led by the Duke Clinical Research Institute (DCRI) Clinical Events Classification Committee (CECC). Details of the conduct and organization of the DCRI CECC are located in the appendix of the TECOS primary results article (10). In brief, DCRI CECC members adjudicated each suspected event by using the prespecified end point criteria on the basis of the preponderance of the evidence and clinical knowledge and experience. TECOS CECC members adjudicating events were blinded to treatment allocation and did not adjudicate events from their own institutional site.

Cox regression modeling was used to determine risk factors for all-cause death and CV death in the intention-to-treat TECOS patient population ($n$ = 14,671). A combination of backward and regular stepwise selection methods were used to create a multivariable model of independent risk factors for all-cause mortality and CV death. Linearity assumptions for all continuous baseline characteristics were assessed, and transformations, such as logarithms (base 10) and linear splines, were applied as necessary. Proportional hazards assumptions were assessed and transformations or time interactions used as needed. By using a stepwise procedure with a criterion of $P < 0.10$ for inclusion, a list of covariates for the final multivariable model was generated. These candidate baseline characteristics were age, ethnicity, geographic region, sex, duration of diabetes, New York Heart Association (NYHA) functional class, history of hypertension, race, history of MI, history of CAD, history of coronary artery bypass graft surgery, history of cerebrovascular disease, prior CV disease, history of percutaneous coronary intervention (PCI), history of PAD, history of HF, smoking status, weight, BMI, systolic blood pressure, diastolic blood pressure, eGFR, and $HbA_{1c}$. A sensitivity analysis that included unknown causes of death with CV causes of death also was conducted. For CV death, a further sensitivity analysis that used the Fine-Gray method (11) accounted for the competing risk of non-CV and unknown causes of death, with results reported on the basis of subdistributional hazard functions. Multiple imputation through fully conditional specification methods was used for missing baseline covariates; estimates reflect results aggregated over 25 imputations accounting for uncertainty as a result of missingness. Details of the approach to missing data are presented in the Supplementary Data. All analyses were performed with SAS 9.4 statistical software (SAS Institute, Cary, NC).

## RESULTS

### Distribution of Cause-Specific Mortality

Among the 14,671 patients in the TECOS intention-to-treat population, 1,084 died during a median follow-up period of 3.0 years. Of these, adjudication identified 530 CV deaths (49% of all deaths, 1.20/100 patient-years [PY]), 338 non-CV deaths (31% of all deaths, 0.77/100 PY), and 216 deaths of unknown cause (20% of all deaths, 0.49/100 PY) (Fig. 1). Sudden deaths made up the largest defined subcategory of CV death ($n$ = 145, 27% of CV deaths) followed by acute MI/stroke ($n$ = 113 [MI $n$ = 48, stroke $n$ = 65], 21% of CV deaths), and HF ($n$ = 63, 12% of CV deaths). Among non-CV causes of death, malignancy was the most common ($n$ = 154 deaths, 46% of non-CV deaths).

### Baseline Demographics and Causes of Mortality

Differences in baseline demographic variables were found among the various causes of death (Table 1), including age, sex, comorbidities (smoking, obesity, chronic kidney disease, hypertension), and history of CV disease (history of HF, cerebrovascular disease). Of all categories of CV death, patients who died as a result of sudden death had the youngest median age (67 years), were most likely to have an $HbA_{1c}$ ≥7.5% ($n$ = 63 [44%]), and were most likely to use insulin ($n$ = 45 [31%]). Patients who died as a result of acute MI/stroke were most likely to be Hispanic/Latino and had the lowest prevalence of aspirin use at baseline (63%). Patients who died as a result of HF had the oldest

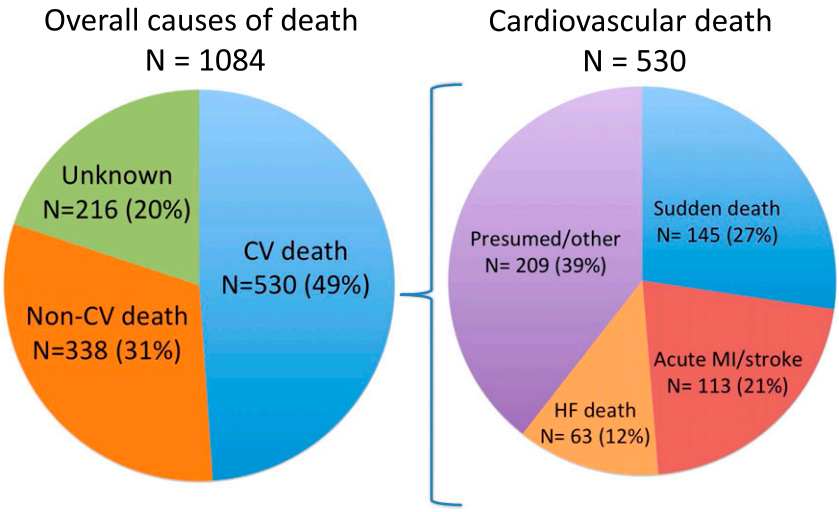


**Figure 1**—Distribution of causes of mortality.

median age (70 years), longest median duration of diabetes (13.0 years), lowest median eGFR (60 mL/min/1.73 $m^2$), and highest prevalence of CAD (89%). Relative to other non-CV deaths, patients who died as a result of malignancy were least likely to be female (20%), were mostly white (88%), were least likely to have an $HbA_{1c}$ ≥7.5% (*n* = 46 [31%]), and had the highest median BMI (29.5 kg/$m^2$).

Patients who died as a result of unknown causes had differences in the following baseline CV risk factors compared with patients who died as a result of CV causes: history of CAD (76.6% for CV death, 69.4% for unknown cause of death), history of PAD (17.2% for CV death, 21.3% for unknown cause of death), prior MI (50.9% for CV death, 44.9% for unknown cause of death), and prior HF (35.3% for CV death, 30.6% for unknown cause of death) (Supplementary Table 2).

### Cumulative Incidence of Causes of Death and Nonfatal Events Before Death

The cumulative incidence of CV mortality (including deaths of unknown cause) was greater than non-CV mortality over the duration of follow-up (Supplementary Fig. 1). When CV deaths and deaths of unknown cause were separated, the cumulative incidence of deaths of unknown cause was less than that of CV deaths (Supplementary Fig. 2). Among those who died as a result of CV causes, 17% (*n* = 90) had experienced a nonfatal CV event (MI, stroke, or unstable angina) versus 13% (*n* = 43) who died as a result of a non-CV death and 9% (*n* = 20) who died as a result of an unknown cause.

### Risk Factors Associated With Specific Causes of Death

Baseline characteristics associated with an increased risk of all-cause death included age (per 5-year increase, hazard ratio [HR] 1.27; $P < 0.0001$), prior MI (HR 1.26; $P = 0.0005$), and $HbA_{1c}$ (per 1% increase, HR 1.23; $P = 0.0014$) (Table 2). Baseline characteristics associated with a reduced risk of all-cause mortality were absence of HF (HR 0.59; $P < 0.0001$), female sex (HR 0.69; $P < 0.0001$), history of PCI (HR 0.74; $P < 0.0001$), and higher eGFR (per $\log_{10}$ higher, HR 0.46; $P < 0.0001$) (Table 2). For CV mortality specifically (Table 3), similar results were seen. The absence of prior HF was consistently associated with a reduced risk of specific CV causes of death, including sudden death (HR 0.40; $P = 0.0036$), HF (HR 0.29; $P = 0.0057$), and acute MI/stroke (HR 0.47; $P = 0.0486$); furthermore, a higher NYHA class was associated with a higher mortality risk (Supplementary Table 3). A higher eGFR was associated with a decreased risk of sudden death (eGFR per $\log_{10}$ higher, HR 0.33; $P = 0.0001$) and HF mortality (eGFR per $\log_{10}$ higher, HR 0.33; $P = 0.0142$) (Supplementary Table 3). A 1% higher $HbA_{1c}$ was associated with an increased risk of sudden death (HR 1.41; $P = 0.0389$), whereas a history of PCI was associated with a decreased risk of sudden death (HR 0.61; $P = 0.0066$). Relatively few significant risk factors were identified for the combined categories of presumed CV and other CV death. Risk of death as a result of unknown causes was similar to that for CV death, including age, history of HF, sex, and renal function (Supplementary Table 3).

A sensitivity analysis that added deaths as a result of unknown causes to the CV death category yielded similar results (Supplementary Table 4). Furthermore, the Fine-Gray method yielded similar results for the association of risk factors with CV death, adjusting for non-CV or unknown deaths as a competing risk (Supplementary Table 5).

## CONCLUSIONS

We evaluated the specific causes of death and associated risk factors in an older population of patients with type 2 diabetes and established ASCVD. The results are notable for the following major findings: *1*) sudden death was the most common cause of CV death; *2*) patients who experienced sudden death had a distinct profile, including being relatively younger and having less-well-controlled glycemia; *3*) non-CV death, specifically as a result of malignancy, contributed to a large burden of overall death; and *4*) the preservation of eGFR and absence of prior HF at baseline were consistently associated with a lower risk of multiple causes of death, including sudden death, HF, and acute MI/stroke.

### Sudden Death in TECOS

Sudden death among patients with established ASCVD is of significant clinical interest given the potential for prevention through the use of devices such as the implantable cardioverter defibrillator (12). Sudden death often is presumed to be arrhythmic in nature; however, in the absence of an autopsy, the true underlying mechanism that leads to sudden death often is unknown. Diabetes independently increases the risk for sudden death (13,14). The mechanisms remain unclear but may reflect a combination of microvascular disease (e.g., cardiac autonomic dysfunction) and macrovascular disease (14). The burden of thrombotic events contributing to sudden death among patients with diabetes also likely is underestimated (15). In the current study, a history of PCI was associated with a significant decrease in the risk of sudden death, suggesting that underlying obstructive coronary atherosclerosis may be a contributor to the mechanism underlying sudden death. Furthermore, the results suggest that poor glycemic control is associated with an increased risk of

**Table 1—Baseline characteristics and specific causes of mortality**

| Characteristic | CV death | | | | Non-CV death | | |
|---|---|---|---|---|---|---|---|
| | Sudden death (*n* = 145) | Acute MI/stroke (*n* = 113) | HF (*n* = 63) | Presumed and other CV cause (*n* = 209) | Malignancy (*n* = 154) | Other (*n* = 184) | Unknown cause (*n* = 216) |
| Demographic | | | | | | | |
| Age (years) | 67 (62, 73) | 69 (63, 75) | 70 (65, 77) | 68 (61, 74) | 69 (65, 74) | 71 (65, 77) | 70 (62, 76) |
| Female sex | 36 (25) | 39 (35) | 16 (25) | 49 (23) | 31 (20) | 49 (27) | 59 (27) |
| Race | | | | | | | |
| White | 88 (61) | 84 (74) | 44 (70) | 127 (61) | 135 (88) | 117 (64) | 141 (65) |
| Black | 5 (3) | 3 (3) | 3 (5) | 1 (0) | 1 (1) | 5 (3) | 6 (3) |
| Asian | 39 (27) | 10 (9) | 9 (14) | 56 (27) | 13 (8) | 34 (18) | 46 (21) |
| Other | 13 (9) | 16 (14) | 7 (11) | 25 (12) | 5 (3) | 28 (15) | 23 (11) |
| Not Hispanic or Latino | 130 (90) | 94 (83) | 55 (87) | 178 (85) | 143 (93) | 142 (77) | 187 (87) |
| Hispanic or Latino | 15 (10) | 19 (17) | 8 (13) | 31 (15) | 11 (7) | 42 (23) | 29 (13) |
| Medical history and baseline laboratory results | | | | | | | |
| Duration of diabetes (years) | 11.0 (6.0, 17.0) | 11.0 (6.0, 18.0) | 13.0 (6.0, 17.0) | 11.0 (5.0, 17.0) | 11.0 (6.0, 20.0) | 12.0 (6.0, 20.0) | 11.0 (6.0, 18.5) |
| Qualifying $HbA_{1c}$ | | | | | | | |
| % | 7.3 (6.9, 7.7) | 7.2 (6.8, 7.7) | 7.1 (6.7, 7.6) | 7.3 (6.8, 7.7) | 7.2 (6.9, 7.5) | 7.3 (6.9, 7.7) | 7.3 (6.8, 7.8) |
| mmol/mol | 56 (52, 61) | 55 (51, 61) | 54 (50, 60) | 56 (51, 61) | 55 (52, 59) | 56 (51, 61) | 56 (51, 61) |
| $HbA_{1c}$ | | | | | | | |
| % | 7.4 (6.8, 7.8) | 7.2 (6.8, 7.8) | 7.2 (6.7, 7.6) | 7.3 (6.9, 7.8) | 7.2 (6.8, 7.6) | 7.2 (6.8, 7.7) | 7.3 (6.8, 7.8) |
| mmol/mol | 57 (51, 62) | 55 (51, 62) | 55 (50, 60) | 56 (52, 62) | 55 (51, 60) | 55 (51, 61) | 56 (51, 62) |
| Qualifying $HbA_{1c}$ categories | | | | | | | |
| <7% | 42 (30) | 38 (34) | 25 (40) | 64 (31) | 47 (32) | 58 (32) | 73 (34) |
| 7–7.5% | 37 (26) | 28 (25) | 17 (27) | 56 (27) | 56 (38) | 48 (27) | 56 (26) |
| ≥7.5% | 63 (44) | 46 (41) | 21 (33) | 85 (41) | 46 (31) | 75 (41) | 84 (39) |
| eGFR (mL/min/1.73 $m^2$) | 63.0 (53.6, 80.0) | 61.0 (51.0, 81.0) | 60.0 (48.0, 78.0) | 68.0 (56.0, 90.0) | 66.0 (57.0, 82.0) | 63.5 (50.0, 79.0) | 65.0 (54.8, 82.0) |
| $Log_{10}$ eGFR (mL/min/1.73 $m^2$) | 4.1 (4.0, 4.4) | 4.1 (4.0, 4.4) | 4.1 (3.9, 4.4) | 4.1 (3.9, 4.4) | 4.2 (4.0, 4.5) | 4.2 (4.0, 4.4) | 4.2 (3.9, 4.4) |
| Serum Cr (mg/dL) | 1.10 (0.90, 1.24) | 1.04 (0.90, 1.24) | 1.12 (0.90, 1.42) | 1.02 (0.85, 1.21) | 1.05 (0.88, 1.26) | 1.10 (0.90, 1.32) | 1.05 (0.85, 1.24) |
| $Log_{10}$ Cr (mg/dL) | 0.10 (−0.11, 0.22) | 0.04 (−0.11, 0.22) | 0.11 (−0.10, 0.35) | 0.02 (−0.16, 0.19) | 0.04 (−0.13, 0.23) | 0.10 (−0.11, 0.28) | 0.05 (−0.16, 0.22) |
| History of vascular disease | 143 (99) | 113 (100) | 62 (98) | 207 (99) | 154 (100) | 182 (99) | 214 (99) |
| History of CAD | 114 (79) | 83 (73) | 56 (89) | 153 (73) | 119 (77) | 134 (73) | 150 (69) |
| Cerebrovascular disease | 35 (24) | 44 (39) | 13 (21) | 69 (33) | 37 (24) | 50 (27) | 66 (31) |
| PAD | 28 (19) | 18 (16) | 8 (13) | 37 (18) | 29 (19) | 48 (26) | 46 (21) |
| Prior MI | 74 (51) | 55 (49) | 42 (67) | 99 (47) | 64 (42) | 85 (46) | 97 (45) |
| Prior CHF | 52 (36) | 42 (37) | 31 (49) | 62 (30) | 31 (20) | 64 (35) | 66 (31) |
| History of hypertension | 127 (88) | 103 (91) | 53 (84) | 189 (90) | 137 (89) | 170 (92) | 194 (90) |
| NYHA classification | | | | | | | |
| I | 11 (21) | 7 (17) | 6 (19) | 8 (13) | 8 (26) | 10 (16) | 8 (12) |
| II | 19 (37) | 16 (38) | 11 (35) | 37 (60) | 16 (52) | 25 (39) | 29 (44) |
| III | 9 (17) | 12 (29) | 7 (23) | 9 (15) | 1 (3) | 11 (17) | 10 (15) |
| IV | 2 (4) | 0 (0) | 1 (3) | 0 (0) | 0 (0) | 0 (0) | 4 (6) |
| Not available | 11 (21) | 7 (17) | 6 (19) | 8 (13) | 6 (19) | 18 (28) | 15 (23) |
| Systolic BP (mmHg) | 132 (122, 146) | 140 (126, 151) | 130 (117, 140) | 130 (120, 146) | 135 (124, 145) | 133 (125, 149) | 135 (123, 145) |
| Diastolic BP (mmHg) | 78 (70, 83) | 80 (70, 82) | 75 (67, 80) | 80 (70, 86) | 75 (67, 81) | 75 (68, 82) | 78 (70, 85) |
| Weight (kg) | 84 (68, 98) | 80 (69, 95) | 85 (72, 95) | 81 (69, 98) | 86 (77, 98) | 80 (67, 91) | 78 (66, 93) |

*Continued on p. 1767*

**Table 1—Continued**

| Characteristic | CV death | | | | Non-CV death | | |
|---|---|---|---|---|---|---|---|
| | Sudden death ($n$ = 145) | Acute MI/stroke ($n$ = 113) | HF ($n$ = 63) | Presumed and other CV cause ($n$ = 209) | Malignancy ($n$ = 154) | Other ($n$ = 184) | Unknown cause ($n$ = 216) |
| BMI (kg/m$^2$) | 29.5 (25.5, 33.5) | 28.5 (25.5, 32.4) | 29.5 (26.6, 33.5) | 28.7 (25.3, 32.9) | 29.5 (26.5, 33.7) | 28.4 (25.3, 32.1) | 28.4 (25.8, 32.5) |
| Smoking history | | | | | | | |
| Never | 82 (57) | 57 (50) | 32 (51) | 98 (47) | 52 (34) | 84 (46) | 110 (51) |
| Current | 16 (11) | 12 (11) | 6 (10) | 31 (15) | 23 (15) | 19 (10) | 21 (10) |
| Former | 47 (32) | 44 (39) | 25 (40) | 80 (38) | 79 (51) | 81 (44) | 85 (39) |
| Antihyperglycemic therapies | | | | | | | |
| Metformin | 117 (81) | 87 (77) | 45 (71) | 159 (76) | 113 (73) | 121 (66) | 150 (69) |
| Sulfonylurea | 71 (49) | 64 (57) | 33 (52) | 100 (48) | 69 (45) | 78 (42) | 105 (49) |
| Pioglitazone/thiazolidinedione | 1 (1) | 4 (4) | 4 (6) | 2 (1) | 5 (3) | 3 (2) | 7 (3) |
| Insulin | 45 (31) | 17 (15) | 16 (25) | 54 (26) | 45 (29) | 66 (36) | 59 (27) |
| CV medications | | | | | | | |
| Statins | 109 (75) | 84 (74) | 46 (73) | 156 (75) | 130 (84) | 129 (70) | 151 (70) |
| Aspirin | 107 (74) | 71 (63) | 45 (71) | 152 (73) | 110 (71) | 139 (76) | 158 (73) |
| ACE inhibitors/ARBs | 126 (87) | 92 (81) | 53 (84) | 158 (76) | 119 (77) | 146 (79) | 167 (77) |
| β-Blockers | 102 (70) | 77 (68) | 41 (65) | 136 (65) | 98 (64) | 115 (63) | 140 (65) |
| Diuretics | 94 (65) | 63 (56) | 40 (63) | 113 (54) | 62 (40) | 89 (48) | 114 (53) |

Data are median (interquartile range) or $n$ (%). ARB, angiotensin receptor blocker; BP, blood pressure; CHF, congestive heart failure; Cr, creatinine.

sudden death. Although prospective studies are needed, these clinical variables may be considered when risk stratifying patients for therapies that prevent arrhythmic death, such as the implantable cardioverter defibrillator. Additional research is needed into the underlying mechanism that drives sudden death as well as strategies to reduce the risk of sudden death (e.g., improved glycemic control).

The current analyses also suggest that within TECOS, patients who had sudden death had a different clinical profile than those who died as a result of other causes. To date, limited information exists from studies that have evaluated various profiles of causes of death among patients with diabetes and established ASCVD (16). Whether differences in clinical profile relate to different underlying mechanisms of disease that lead to sudden death over other causes of death remains to be evaluated in future studies.

Other CV outcome studies evaluating antihyperglycemic therapies also have suggested that the most common cause of CV death is sudden death. In the BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) study (17), sudden death was the most commonly adjudicated cause of CV death (68 of 227 [29.9%]). In the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction 53 (SAVOR-TIMI 53) trial (18), of the patients who died as a result of CV causes ($n$ = 529), 240 (45%) deaths were adjudicated as sudden death. In TECOS, the specific cause of death was not determined in 39% of all-cause deaths (216 adjudicated as unknown and 209 adjudicated as presumed CV deaths of 1,084 all-cause deaths). In the EMPA-REG OUTCOME trial, 28% of events were considered to be in the other category (129 deaths of 463 all-cause deaths). In the SAVOR-TIMI 53 trial, 14.5% of CV deaths were presumed ($n$ = 77 of 529). These deaths included fatal cases that were not assessable because of a lack of information (reflecting unknown causes of death) and were presumed to be CV deaths per conventional definition. These differences in results may reflect specifics of adjudication definitions and processes, patient populations, drug effects, or other issues of trial conduct or organization.

**Table 2—Risk factors associated with all-cause mortality**

| Risk factor | Adjusted HR (95% CI) | *P* value |
|---|---|---|
| Age per 5-year increase | 1.27 (1.22–1.32) | < 0.0001 |
| Asymptomatic (no CHF) vs. NYHA I | 0.59 (0.45–0.76) | < 0.0001 |
| NYHA II vs. NYHA I | 1.17 (0.87–1.58) | 0.3035 |
| NYHA III vs. NYHA I | 1.50 (1.04–2.15) | 0.0288 |
| NYHA IV vs. NYHA I | 3.86 (1.64–9.08) | 0.002 |
| History of PCI | 0.74 (0.65–0.85) | < 0.0001 |
| Female vs. male sex | 0.69 (0.59–0.79) | < 0.0001 |
| eGFR per $\log_{10}$ (mL/min/1.73 $m^2$) higher | 0.46 (0.37–0.58) | < 0.0001 |
| Prior MI | 1.26 (1.10–1.43) | 0.0005 |
| $HbA_{1c}$ (%) per 1% increase | 1.23 (1.08–1.39) | 0.0014 |
| History of PAD | 1.28 (1.09–1.49) | 0.0024 |
| Current vs. never smoker | 1.33 (1.09–1.62) | 0.0057 |
| History of cerebrovascular disease | 1.22 (1.06–1.40) | 0.0064 |

By Cox proportional hazards model, multivariable analysis. Other variables in the model were history of hypertension (HR 1.18 [95% CI 0.97–1.44]; *P* = 0.0968) and former vs. never smoker (HR 0.99 [95% CI 0.87–1.14]; *P* = 0.9). CHF, congestive heart failure.

### Distribution of Causes of Death in TECOS

Emerging evidence suggests an association between dysglycemia and cancer-related death (4,19,20). In trials of antihyperglycemic agent safety, regulatory agencies often expect that deaths attributed to unknown causes will be combined with CV deaths for the purposes of statistical analysis. This has been considered valid given the likelihood that patients with diabetes will die primarily as a result of CV causes and because this assumption creates a putative worst-case scenario in the assessment of CV safety. The current study identified that the rate of cumulative incidence of deaths of unknown cause is less than that of CV causes of death. The risk factors for deaths of unknown cause are similar to those for CV death; however, the demographic profile of patients who died as a result of an unknown cause did not align with that of any specific CV-caused death. Furthermore, the distribution of nonfatal events before death appears to be different in patients who died as a result of an unknown cause compared with those whose death was attributable to a CV cause.

Compared with older trials, contemporary glucose-lowering drug trials are more likely to enroll patients on therapies that target modifiable CV risk factors. In the UK Prospective Diabetes Study, only 0.3% of patients were taking lipid-lowering agents (21), compared with the TECOS study, where >70% of patients were taking statins. As a result, the burden of mortality may be shifting from CV to non-CV. Patients whose deaths were adjudicated as non-CV had similar numbers of nonfatal CV events to patients whose deaths were of CV causes, further highlighting the burden of non-CV death among patients with type 2 diabetes. Similarly, unknown causes of death may not truly represent CV mortality. The current results suggest that the practice of combining CV deaths and deaths of unknown cause in contemporary clinical trial analyses should be conducted with caution. These concerns highlight the need for continued rigorous efforts within trials to collect all available data and accurately adjudicate causes of death to minimize use of the unknown or undetermined categories.

**Table 3—Risk factors associated with cardiovascular death**

| Risk factor | Adjusted HR (95% CI) | *P* value |
|---|---|---|
| Age per 5-year increase | 1.19 (1.12–1.26) | < 0.0001 |
| Prior MI | 1.44 (1.20–1.73) | 0.0001 |
| Asymptomatic (no CHF) vs. NYHA I | 0.53 (0.37–0.76) | 0.0005 |
| NYHA II vs. NYHA I | 1.15 (0.77–1.73) | 0.49 |
| NYHA III vs. NYHA I | 1.64 (1.02–2.63) | 0.0042 |
| NYHA IV vs. NYHA I | 3.13 (0.94–10.4) | 0.064 |
| History of PCI | 0.63 (0.51–0.76) | < 0.0001 |
| Female vs. male sex | 0.68 (0.55–0.83) | 0.0002 |
| eGFR per $\log_{10}$ (mL/min/1.73 $m^2$) higher | 0.48 (0.35–0.66) | < 0.0001 |
| Systolic BP ≤135 mmHg per 5-unit increase | 0.93 (0.88–0.97) | 0.0025 |
| $HbA_{1c}$ (%) per 1% increase | 1.29 (1.08–1.54) | 0.0046 |
| History of cerebrovascular disease | 1.29 (1.06–1.58) | 0.0109 |
| BMI ≤30 kg/$m^2$ per 5-unit increase | 0.70 (0.59–0.83) | 0.0001 |

By Cox proportional hazards model, multivariable analysis. Other variables in the model were Latin America vs. North America (HR 1.83 [95% CI 1.3–2.6]; *P* = 0.0006); Asia Pacific/other vs. North America (HR 1.40 [95% CI 1.04–1.89]; *P* = 0.28); Western Europe vs. North America (HR 1.05 [95% CI 0.73–1.50]; *P* = 0.79); Eastern Europe vs. North America (HR 1.50 [95% CI 1.11–2.03]; *P* = 0.008); BMI >30 kg/$m^2$ (HR 1.13 [95% CI 1.00–1.29]; *P* = 0.049); and systolic BP >135 mmHg (HR 1.04 [95% CI 1.00–1.08]; *P* = 0.06). BP, blood pressure; CHF, congestive heart failure.

### HF and Renal Disease and Risk for Mortality

In the current analysis, a history of HF and worsening renal function appeared to be the most common risk factors for cause-specific death. Similar results have been seen in other disease states at higher risk for CV events, such as atrial fibrillation (22). Although identifying a history of HF and subsequent HF events in clinical trials often is difficult (23), patients with diabetes are at a higher risk of developing HF (6,24,25). Furthermore, as expected, higher eGFR was associated with a decreased risk of all-cause mortality, CV mortality, sudden cardiac death, and HF death. The association of kidney disease, HF, and diabetes and the increased risk of CV mortality has been previously recognized and may be due to an increased risk of thrombotic events, electrolyte-induced arrhythmias, increased myocardial fibrosis, and autonomic dysfunction (26,27). Preserving renal function and optimizing HF care may represent an option to improve outcomes among patients with diabetes and CV disease.

### Strengths and Limitations

The large sample size and independent, blinded adjudication processes are some of the major strengths of this analysis; however, these results are subject to the limitations of a post hoc analysis. In addition, as stated above, an adjudicated cause of death was not obtainable in 20%

of patients. Ejection fraction data were not available for the entire cohort and, thus, were not included in the analyses. No adjustments were made for multiplicity. As with most clinical trials, the population enrolled in TECOS may not completely reflect the overall diabetes population, and the results of these analyses may not be directly generalizable.

In summary, this analysis of data from a contemporary trial of older patients with type 2 diabetes and established ASCVD found that sudden death was the most common cause of CV mortality, and patients with sudden death had a distinct profile of being relatively younger with less-well-controlled glycemia. However, given the substantial burden of deaths as a result of malignancy, deaths attributable to unknown causes may not primarily represent CV causes; thus, caution should be exercised when combining CV and unknown causes of death in clinical trial mortality data. Preservation of renal function and prevention or optimization of HF may represent avenues to improve outcomes among patients with diabetes and CV disease; additional studies to evaluate such preventive strategies are needed.

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