Assessing the Safety of Sitagliptin in Older Participants in the Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS)

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OBJECTIVE

Limited data exist regarding safety and efficacy of antihyperglycemic drugs in older patients with type 2 diabetes. The Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) was a randomized, double-blind, placebo-controlled trial assessing the impact of sitagliptin on a primary composite outcome of cardiovascular death, nonfatal stroke, nonfatal myocardial infarction, or unstable angina hospitalizations in patients with type 2 diabetes (HbA_{1c} ≥6.5% [48 mmol/mol] and ≤8.0% [64 mmol/mol]) and cardiovascular disease. We analyzed baseline characteristics and clinical outcomes for TECOS participants aged ≥75 years.

RESEARCH DESIGN AND METHODS

Clinical and safety event summaries are presented for older versus younger participants and for the treatment groups within the older cohort.

RESULTS

Of 14,351 participants with age recorded, 2,004 (14%) were ≥75 years old (mean age 78.3 years [SD 3.1]), with 68% men and type 2 diabetes duration median 12.0 years (IQR 7, 21). During 2.9 years median follow-up, older participants had higher rates of the primary outcome (6.46 vs. 3.67 events per 100 person-years; hazard ratio 1.72 [95% CI 1.52–1.94]), death (2.52 [2.20–2.89]), severe hypoglycemia (1.53 [1.15–2.03]), and fractures (1.84 [1.44–2.35]). In the older cohort, sitagliptin did not significantly impact the primary composite (1.10 [0.89–1.36]), death (1.05 [0.83–1.32]), heart failure hospitalization (0.99 [0.65–1.49]), severe hypoglycemia (1.03 [0.62–1.71]), rates of acute pancreatitis and pancreatic cancer, or serious adverse events.

CONCLUSIONS

Among older patients with well-controlled type 2 diabetes and cardiovascular disease, sitagliptin had neutral effects on cardiovascular risk and raised no significant safety concerns.

Improvements in public health, nutrition, and medical care across many regions of the world have increased life expectancy. During the 20th century, life span increments of up to 2 decades have occurred in the world's wealthiest populations, and recent global estimates indicate that smaller gains of 5–7 years of life expectancy

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occurred worldwide between 1990 and 2013 (1). However, when more people live longer, comorbidities accrue, resulting in a greater burden of chronic disease. An important comorbidity affecting the difference between healthy and total life expectancy is type 2 diabetes (2,3).

Treating type 2 diabetes in older people can be challenging, particularly when concomitant conditions such as kidney dysfunction, heart failure, and cardiovascular disease complicate the choices of antihyperglycemic agents (4). Making prudent, evidence-based choices is hampered further by the lack of data specific to older populations with diabetes. A survey of the clinicaltrials.gov registry found that only 15 of 2,484 (0.6%) interventional trials in diabetes focused on participants over age 65 years, and 54.9% excluded those over 75 years (5). This gap in evidence forces practitioners to extrapolate from data derived from younger, healthier clinical trial populations, possibly leading to erroneous estimates of safety and efficacy effects.

The Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) was a large, pragmatic, double-blind, randomized trial that assessed the cardiovascular safety of adding sitagliptin versus placebo to usual care in patients with type 2 diabetes (HbA_{1c} $\geq$6.5% [48 mmol/mol] and $\leq$8.0% [64 mmol/mol]) and established atherosclerotic cardiovascular disease (6). Here we describe baseline characteristics, clinical outcomes, and the safety profile for sitagliptin for TECOS participants aged 75 years or older.

RESEARCH DESIGN AND METHODS

The design, protocol, and primary results of TECOS (NCT00790205) have been published previously (6,7). The study was designed and run independently by the Duke Clinical Research Institute and the University of Oxford Diabetes Trials Unit in an academic collaboration with the sponsor, Merck Sharp & Dohme. The protocol was approved by the ethics committees associated with all participating trial sites, and all participants provided written informed consent for trial participation.

In brief, 14,671 participants from 38 countries were enrolled between December 2008 and July 2012. Eligible participants were $\geq$50 years old (with no upper age limit) with type 2 diabetes, atherosclerotic cardiovascular disease, and HbA_{1c} values of 6.5–8.0% (48–64 mmol/mol) on stable dose mono- or dual-combination therapy with metformin, pioglitazone, or sulfonylurea, or insulin with or without metformin. Study patients were randomized in a double-blind fashion to either sitagliptin or placebo at doses appropriate for their estimated glomerular filtration rate (eGFR). Patients with an eGFR $<$30 mL/min/1.73 m^2 were not eligible. During follow-up, treatment for type 2 diabetes and its comorbidities was provided by usual care providers based on local guidelines. Because there is a known small but significant contribution to cardiovascular risk from prolonged hyperglycemia, the TECOS design sought to minimize differences in glucose control between treatment groups. After the 4-month visit, the addition of any antihyperglycemic agent was permitted with the exception of glucagon-like peptide-1 (GLP-1) receptor agonists or open-label dipeptidyl peptidase-4 inhibitors. Use of rosiglitazone was discouraged. Data regarding use of concomitant medications, occurrence of severe hypoglycemia (hypoglycemia requiring the assistance of another individual), death, hospitalization, cardiovascular events and interventions, expected clinical events (see Supplementary Appendix A for a listing of expected clinical events), serious adverse events (SAEs), and adverse events (AEs) resulting in study drug discontinuation were recorded at all visits. All reported events of death, myocardial infarction, stroke, hospitalization for unstable angina or heart failure, acute pancreatitis, and cancer (other than nonmelanoma skin cancers) were adjudicated by an independent committee blinded to randomized treatment assignment. Adjudicated event definitions have been published previously (6).

The present analysis cohort includes TECOS participants in the intent-to-treat (ITT) population who had a recorded age. Age data were not available for 320 participants from Lithuania, where recording birth dates for clinical research is not permitted. The 75-year age threshold was selected to be consistent with regulatory guidelines for older populations (8). Events in subsets of patients aged 75 to $<$80 years and 80 years or older were also examined, but clinically significant differences between these subsets were not apparent, and the data presented are pooled. The results first compare older ($\geq$75 years) with younger ($<$75 years) participants, and second compare sitagliptin with placebo within the older cohort. Event summaries are presented for the ITT population, with the exception of treatment-emergent AEs (i.e., SAEs and AEs leading to treatment discontinuation), which are presented for the "all-patients-as-treated" population, defined as all patients from the ITT group who received at least one dose of study drug.

Statistical Analysis

Baseline characteristics are summarized using mean values $\pm$ 1 SD or median and interquartile range (IQR), as appropriate, for continuous variables and number and proportion for categorical variables. Comparisons between older and younger cohorts for continuous variables were carried out by Student *t* tests or Wilcoxon rank-sum tests as appropriate. Categorical variables were compared by χ^2 or exact tests. Although not formally adjusted for multiple comparisons, the chosen threshold for statistical significance for comparisons of baseline characteristics was $<$0.0001. For clinical events, exposure-adjusted rates per 100 patient-years were calculated. Stratified Cox regression models were used to estimate unadjusted hazard ratios (HRs) and 95% CIs when comparing older and younger cohorts or randomized treatment groups within the older cohort. To evaluate whether there were differential treatment effects in the older and younger cohorts, interactions for randomized treatment by age were examined.

AEs were analyzed as binary variables. Counts, proportions of patients with events, and 95% CIs were reported. The CIs for proportions were estimated through the Wilson score method. Differences in proportions between age cohorts were calculated and the CIs were estimated by the Miettinen-Nurminen method. HbA_{1c} data collected longitudinally during the study were analyzed using generalized linear repeated measures models. Least squares mean differences in postrandomization measures between comparison groups were estimated, controlling for the baseline values and region. *P* values were not adjusted for multiple comparisons. A *P* value of $<$0.05 was the threshold for statistical significance when comparing clinical outcomes. All analyses were conducted with the use of SAS software, version 9.0 or higher (SAS Institute, Cary, NC).

RESULTS

Of 14,671 randomized TECOS participants, 14,351 in the ITT population had an age recorded and were included in the present analyses. Of these, 2,004 (14%) participants were ≥75 years old, and 582 (4%) were ≥80 years old. Median durations of follow-up for the primary end point were similar in the older and younger cohorts (2.9 vs. 3.0 years, respectively) and were similar between treatment groups. Median study drug exposure was shorter in the older compared with younger cohorts (2.4 [IQR 1.7, 3.2] vs. 2.7 [2.0, 3.5] years), with a larger proportion of older participants (36.6% vs. 24.1%) discontinuing study drug during follow-up (Supplementary Table 1). AE data are presented for 14,225 participants in the all-patients-as-treated population, of whom 1,979 (14%) were ≥75 years old.

Comparing Older to Younger Participants

Key baseline characteristics according to age are presented in Table 1 (see Supplementary Table 2 for a full list of baseline characteristics). Statistical differences were seen between older and younger cohorts for all baseline characteristics except for sex and utilization of some medications (sulfonylurea, insulin, statin, and other lipid-lowering therapies).

During the study, HbA_{1c} was marginally lower in the older compared with the younger cohorts (least squares mean difference across all visits: −0.11% [95% CI −0.15 to −0.07], $P < 0.0001$) (Fig. 1*A*). The primary composite cardiovascular outcome occurred more often in the older cohort (338 first events [16.9%], 6.46 per 100 person-years) than the younger cohort (1,281 first events [10.4%], 3.67 per 100 person-years) (HR 1.72 [95% CI 1.52–1.94], $P < 0.001$) (Fig. 2). Older participants were also at higher risk for the secondary cardiovascular composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke (HR 1.86 [95% CI 1.63–2.11], $P < 0.001$), hospitalization for heart failure (HR 1.48 [95% CI 1.18–1.87], $P < 0.001$), a composite of heart failure or death (HR 2.02 [95% CI 1.75–2.34], $P < 0.001$), all-cause mortality (HR 2.52 [95% CI 2.20–2.89], $P < 0.001$), malignancy (HR 1.76 [95% CI 1.43–2.15], $P < 0.001$), severe hypoglycemia (HR 1.53 [95% CI 1.15–2.03], $P = 0.004$), and bone fractures (HR 1.84 [95% CI 1.44–2.35], $P < 0.001$). Pancreatitis and pancreatic cancer were uncommon, and rates did not differ significantly between the older and younger cohorts.

Treatment-emergent SAEs for the older and younger cohorts are shown in Supplementary Table 3. The most common system organ class SAE reported in the older cohort was "neoplasms benign, malignant, and unspecified" in 174 individuals vs. 527 in the younger cohort (difference in proportion with event 4.49% [95% CI 3.26–5.86]). All other system organ class SAEs were reported in <5% of the population.

Table 1—Key baseline characteristics for the ITT population

	All participants		≥75 years old	
Characteristic	≥75 years old (*n* = 2,004)	<75 years old (*n* = 12,347)	Sitagliptin (*n* = 970)	Placebo (*n* = 1,034)
Male sex	1,356 (67.7)	8,847 (71.7)	682 (70.3)	674 (65.2)
Age (years)	78.3 ± 3.1	63.4 ± 6.4	78.3 ± 3.0	78.4 ± 3.2
BMI (kg/m^2)*	28.9 ± 4.8	30.3 ± 5.7	29.0 ± 4.9	28.9 ± 4.8
Systolic blood pressure (mmHg)*	137 ± 18	134 ± 17	137 ± 18	137 ± 18
Diastolic blood pressure (mmHg)*	74 ± 11	78 ± 10	74 ± 11	74 ± 11
HbA_{1c} (%)*	7.18 ± 0.46	7.24 ± 0.48	7.19 ± 0.46	7.17 ± 0.46
HbA_{1c} (mmol/mol)*	55.0 ± 5.1	55.7 ± 5.2	55.1 ± 5.1	54.8 ± 5.0
eGFR (mL/min/1.73 m^2)*	65.5 ± 19.2	76.3 ± 21.0	65.3 ± 19.0	65.7 ± 19.3
≥90	205 (10.3)	3,026 (24.8)	95 (9.9)	110 (10.8)
60–89	963 (48.6)	6,761 (55.3)	474 (49.4)	489 (47.8)
30–59	814 (41.0)	2,437 (19.9)	390 (40.6)	424 (41.4)
<30	1 (0.1)	2 (<0.1)	1 (<1.0)	0
LDL cholesterol (mmol/L)*	2.3 ± 2.6	2.4 ± 1.2	2.4 ± 3.7	2.2 ± 0.9
Median duration of diabetes, years (IQR)*	12 (7, 21)	9 (5, 15)	13 (7, 21)	12 (7, 21)
Prior heart failure*	422 (21.1)	1,970 (16.0)	190 (19.6)	232 (22.4)
Medication use				
Metformin*	1,449 (72.3)	10,265 (83.1)	711 (73.3)	738 (71.4)
Sulfonylurea	946 (47.2)	5,569 (45.1)	442 (45.6)	504 (48.7)
Insulin	501 (25.0)	2,844 (23.0)	255 (35.6)	246 (33.8)
Median daily dose, units (IQR)	51.0 (34.0, 80.0)	44.0 (28.0, 67.5)	44.0 (28.0, 72.0)	42.0 (28.5, 64.0)
Monotherapy for type 2 diabetes*	1,066 (53.2)	5,755 (46.6)	514 (53.0)	552 (53.4)
Dual combination therapy for type 2 diabetes*	913 (45.6)	6,477 (52.5)	446 (46.0)	467 (45.2)
Aspirin*	1,473 (73.5)	9,829 (79.6)	702 (72.4)	771 (74.6)
Any antiplatelet*	1,591 (79.4)	10,443 (84.6)	771 (79.5)	820 (79.3)
Statin	1,582 (78.9)	9,998 (81.0)	761 (78.5)	821 (79.4)
Any lipid lowering	1,641 (81.9)	10,340 (83.7)	797 (82.2)	844 (81.6)

Data are *n* (%) or mean ± SD, except where indicated. *P* values comparing sitagliptin and placebo groups were not calculated. See Supplementary Table 2 for full list of baseline characteristics. **P* values <0.0001 comparing older to younger cohorts.

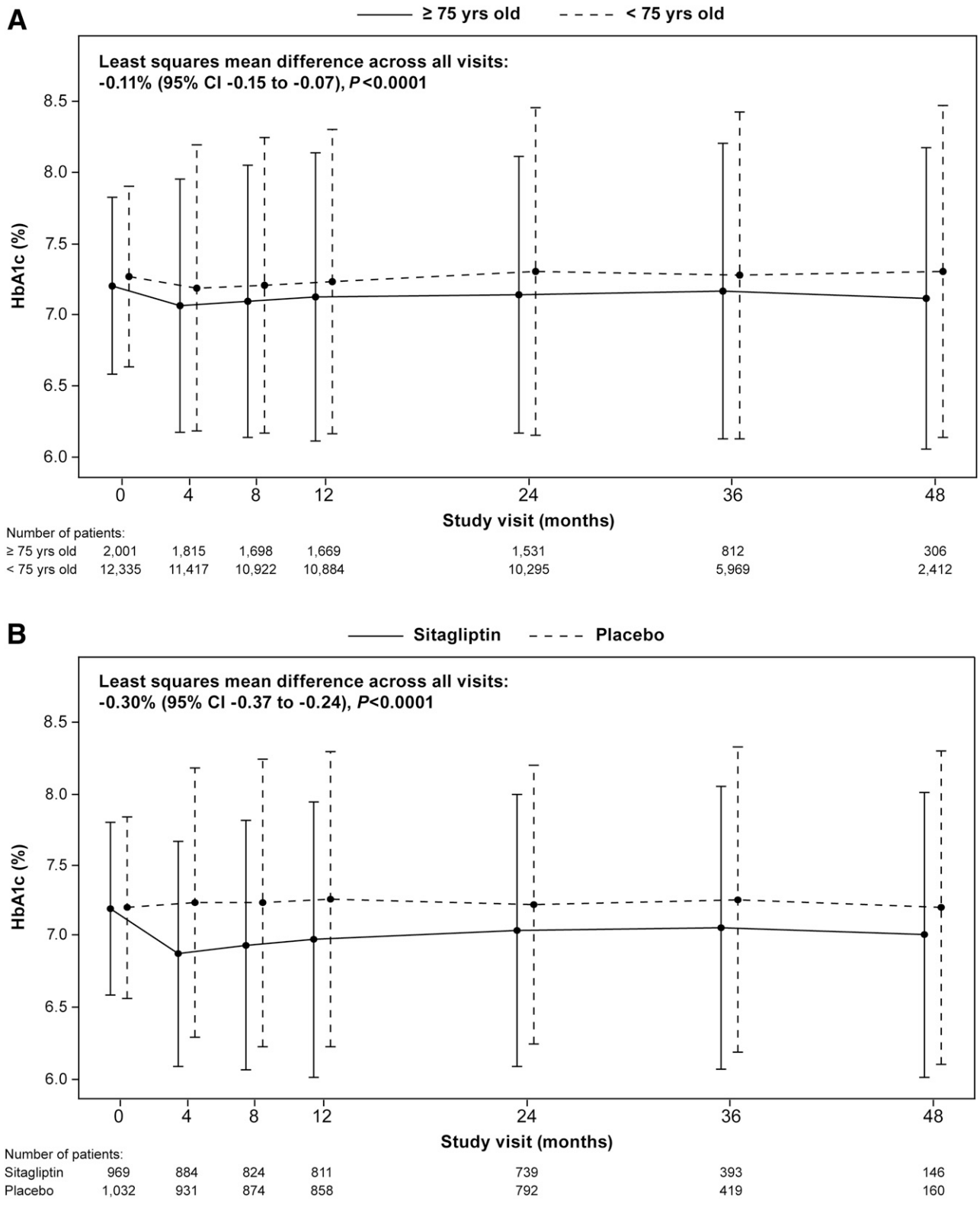

Figure 1—HbA_{1c} over time in older vs. younger cohorts (*A*) and sitagliptin vs. placebo in the older cohort (*B*).

Comparing Sitagliptin to Placebo Within the Older Cohort

The baseline characteristics in the older cohort were generally well balanced between the sitagliptin and placebo groups with regard to their demographic characteristics, including age, ethnicity, race, and region (Table 1 and Supplementary Table 2), although a higher proportion of participants were male in the sitagliptin group (70.3% vs. 65.2%).

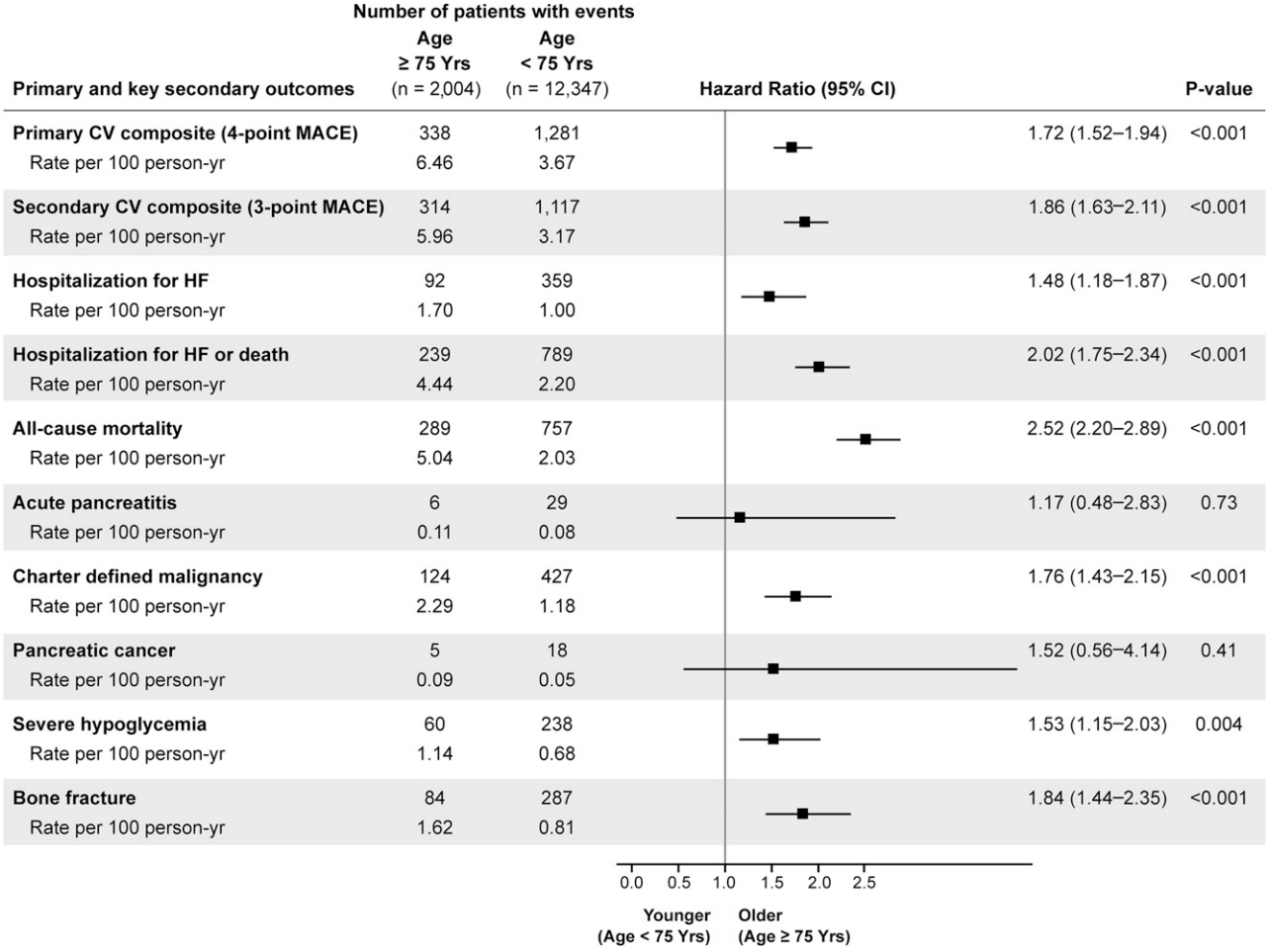

Figure 2—Primary and key secondary outcomes in older vs. younger participants. CV, cardiovascular; HF, heart failure.

After 4 months of study treatment, the mean HbA_{1c} values were 0.4 percentage points lower in the older participants receiving sitagliptin (Fig. 1*B*). This difference narrowed during the study period, with an overall least squares mean difference across all visits of −0.30% (95% CI −0.37 to −0.24, $P < 0.0001$) (Fig. 1*B*). There was no significant heterogeneity of effect for randomized treatment by age for difference in HbA_{1c} between the groups ($P_{interaction} = 0.61$).

Overall in the ITT population, the primary composite cardiovascular outcome occurred in 170 participants in the sitagliptin group (17.5%, 6.75 per 100 person-years) and 168 participants (16.2%, 6.19 per 100 person-years) in the placebo group (HR 1.10 [95% CI 0.89–1.36], $P = 0.39$) (Fig. 3). No differences were seen between treatment groups for the secondary cardiovascular composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke (HR 1.01 [95% CI 0.81–1.26], $P = 0.94$), hospitalization for heart failure (HR 0.99 [95% CI 0.65–1.49], $P = 0.94$), a composite of heart failure or death (HR 1.00 [95% CI 0.77–1.29], $P = 0.99$), all-cause mortality (HR 1.05 [95% CI 0.83–1.32], $P = 0.71$), malignancy (HR 0.95 [95% CI 0.67–1.36], $P = 0.78$), severe hypoglycemia (HR 1.03 [95% CI 0.62–1.71], $P = 0.92$), and bone fractures (HR 1.21 [95% CI 0.78–1.85], $P = 0.40$). Rates of pancreatitis and pancreatic cancer were low and did not differ significantly between treatment groups. Interactions for age and randomized treatment assignment were not statistically significant for any of these reported outcomes ($P > 0.22$ for all).

Proportions of older participants with treatment-emergent SAEs and the 95% CIs for the difference in proportions are shown in Table 2. Overall, SAE numbers were small and generally well balanced between the two treatment groups.

CONCLUSIONS

TECOS, which included >2,000 patients age 75 years or older with well-controlled diabetes, provides the largest clinical trial experience to date with sitagliptin in an older population performed in a usual care setting. The use of sitagliptin versus placebo in this older cohort was not associated with any difference in risk for the primary cardiovascular composite outcome of cardiovascular death, nonfatal stroke, nonfatal myocardial infarction, or hospitalization for unstable angina, a result consistent with the findings reported in the main trial (6). Sitagliptin therapy also did not affect rates for the secondary cardiovascular composite (cardiovascular death, nonfatal stroke, and nonfatal myocardial infarction), death from any cause, or heart failure. Glycemic levels achieved during the study in sitagliptin-treated participants were similar in older and younger cohorts, with the older cohort showing no indication of increased rates

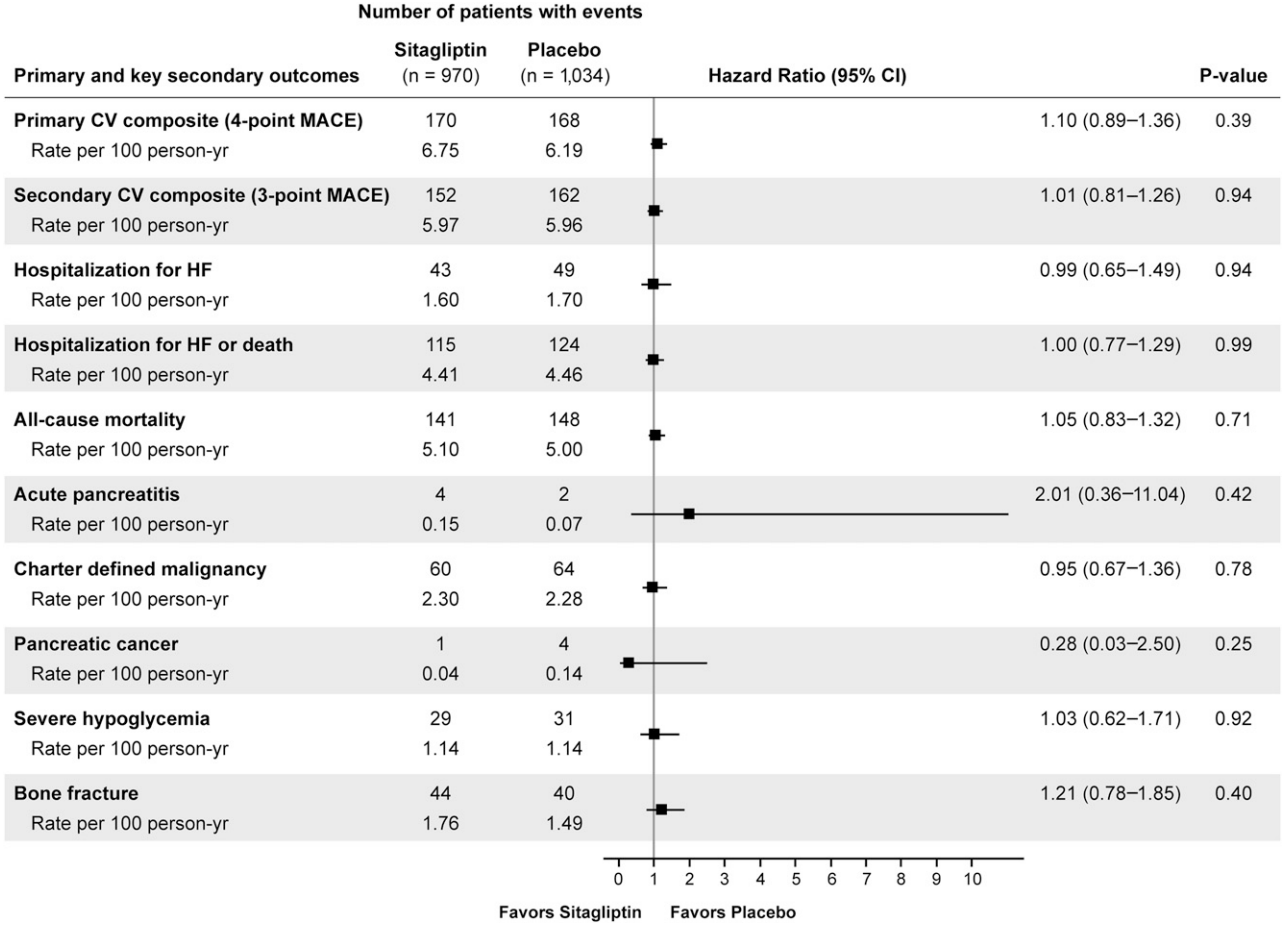

Figure 3—Primary and key secondary outcomes in the older cohort by treatment group. CV, cardiovascular; HF, heart failure.

of hypoglycemia, fractures, or reports of serious falls or other injury identified through safety reporting between the sitagliptin and placebo groups.

Event rates for major adverse cardiovascular events (MACEs) were up to twofold higher in the older TECOS cohort compared with those <75 years of age, with first events of cardiovascular death, nonfatal stroke, and nonfatal myocardial infarction (MACE-3) events occurring in ~16% and 9%, respectively. This seems broadly similar to findings from other cardiovascular outcome trials in patients with type 2 diabetes using dipeptidyl peptidase-4 inhibitors. In the Examination of Cardiovascular Outcomes With Alogliptin Versus Standard of Care (EXAMINE) trial (9), which compared alogliptin versus placebo in an acute coronary syndromes population over 1.5 years of follow-up, the MACE-3 primary outcome occurred in ~15% of those ≥65 years old compared with ~9% in younger participants. The Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction 53 (SAVOR-TIMI-53) trial (10), which compared saxagliptin versus placebo over 2.1 years in a mixed primary/secondary cardiovascular prevention population, showed MACE-3 2-year Kaplan-Meier event rates were 10% for those ≥75 years old vs. 7% in the younger cohort (11). These findings underscore the burden of cardiovascular disease in the elderly and correlate with increasing public health care expenditures (12–15).

The importance of evaluating antihyperglycemic medications to treat type 2 diabetes in older patients should not be underestimated. With increasing longevity, the proportion of older people requiring treatment for type 2 diabetes is rising (16). Older individuals comprise a heterogeneous population, ranging from those living actively and independently to those requiring constant care in nursing homes, but all are subject to increasing age-related risks for complications of type 2 diabetes, cardiovascular disease, and other comorbidities. The overall treatment goals for managing hyperglycemia and risk factors for type 2 diabetes complications are similar for healthy individuals (e.g., those with few coexisting chronic illnesses and little functional disability), but there is increasing recognition that targets for HbA_{1c}, blood pressure, and cholesterol should be individualized to account for fitness, frailty, and functional disability present in older individuals (17–19).

We acknowledge certain limitations in our examination of the impact of sitagliptin in older individuals. First, our observations are limited to effects observed over the median 2.9 years of follow-up, whereas treatment with sitagliptin in routine care may be longer. Second, participants enrolled in TECOS may not be representative of community-based older populations. For example, TECOS eligibility criteria required an entry HbA_{1c} of 6.5–8% (48–64 mmol/mol). Therefore, although the enrolled population has a median type 2 diabetes duration of 12 years, the mean HbA_{1c} of 7.2%

Table 2—Treatment-emergent SAEs by system organ class in the older cohort, by treatment group

System organ class preferred term patients with one or more:	Age ≥75 years old		
	Sitagliptin (*n* = 956)	Placebo (*n* = 1,023)	Difference (95% CI)
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	80 (8.4%)	94 (9.2%)	−0.82 (−3.33 to 1.70)
Basal cell carcinoma	11 (1.2%)	24 (2.3%)	−1.20 (−2.44 to −0.04)
Squamous cell carcinoma	5 (0.5%)	17 (1.7%)	−1.14 (−2.18 to −0.24)
Squamous cell carcinoma of skin	3 (0.3%)	14 (1.4%)	−1.05 (−2.01 to −0.28)
Injury, poisoning, and procedural complications	36 (3.8%)	27 (2.6%)	1.13 (−0.43 to 2.76)
Gastrointestinal disorders	25 (2.6%)	21 (2.1%)	0.56 (−0.79 to 1.98)
Gastroesophageal reflux disease	4 (0.4%)	0 (0.0%)	0.42 (0.04 to 1.07)
Musculoskeletal and connective tissue disorders	18 (1.9%)	11 (1.1%)	0.81 (−0.27 to 1.99)
Osteoarthritis	13 (1.4%)	3 (0.3%)	1.07 (0.31 to 2.05)
Respiratory, thoracic, and mediastinal disorders	15 (1.6%)	12 (1.2%)	0.40 (−0.66 to 1.52)
Metabolism and nutrition disorders	1 (0.1%)	13 (1.3%)	−1.17 (−2.07 to −0.52)
Hyponatremia	1 (0.1%)	7 (0.7%)	−0.58 (−1.31 to −0.03)
Dehydration	0 (0.0%)	5 (0.5%)	−0.49 (−1.14 to −0.09)

Analysis cohort is all older patients as treated. This table includes *1*) sytem organ classes exceeding 1% or where the 95% CI excludes 0; *2*) within the system organ classes that exceed 1%, any preferred term that exceeds 1%; and *3*) any individual preferred term where the 95% CI excludes 0.

(55 mmol/mol) may be lower than that typically seen in older individuals with a long duration of diabetes. Although TECOS did not measure frailty or functional status, it is reasonable to assume that most patients enrolled were ambulatory and reasonably functional since clinic visits every 6 months and the ability to see their usual care doctor at least twice yearly were requirements of the trial design. TECOS also excluded those with severe kidney impairment (eGFR $<$30 mL/min/1.73 m^2), although if renal function declined during follow-up to eGFR $<$30 mL/min/1.73 m^2, participants were permitted to remain on sitagliptin doses adjusted for renal function. Baseline exclusion criteria also included life expectancy of $<$2 years, or any other condition thought to impair the individual's ability to participate fully in the trial.

In conclusion, our study results show that in a large group of older participants with well-controlled diabetes, sitagliptin did not increase the risk of serious hypoglycemia and was neutral with respect to cardiovascular outcomes over ~3 years of follow-up. Although these results cannot exclude the possibility of other benefits or risks emerging over a longer follow-up period, especially in patients with increasingly complex comorbidities, they are reassuring for practitioners managing an aging population with diabetes.

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