Efficacy and Safety of Dapagliflozin in the Elderly: Analysis From the DECLARE–TIMI 58 Study

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OBJECTIVE

Data regarding the effects of sodium–glucose cotransporter 2 inhibitors in the elderly (age ≥65 years) and very elderly (age ≥75 years) are limited.

RESEARCH DESIGN AND METHODS

The Dapagliflozin Effect on Cardiovascular Events (DECLARE)–TIMI 58 assessed cardiac and renal outcomes of dapagliflozin versus placebo in patients with type 2 diabetes. Efficacy and safety outcomes were studied within age subgroups for treatment effect and age-based treatment interaction.

RESULTS

Of the 17,160 patients, 9,253 were <65 years of age, 6,811 ≥65 to <75 years, and 1,096 ≥75 years. Dapagliflozin reduced the composite of cardiovascular death or hospitalization for heart failure consistently, with a hazard ratio (HR) of 0.88 (95% CI 0.72, 1.07), 0.77 (0.63, 0.94), and 0.94 (0.65, 1.36) in age-groups <65, ≥65 to <75, and ≥75 years, respectively (interaction *P* value 0.5277). Overall, dapagliflozin did not significantly decrease the rates of major adverse cardiovascular events, with HR 0.93 (95% CI 0.81, 1.08), 0.97 (0.83, 1.13), and 0.84 (0.61, 1.15) in age-groups <65, ≥65 to <75, and ≥75 years, respectively (interaction *P* value 0.7352). The relative risk reduction for the secondary prespecified cardiorenal composite outcome ranged from 18% to 28% in the different age-groups with no heterogeneity. Major hypoglycemia was less frequent with dapagliflozin versus placebo, with HR 0.97 (95% CI 0.58, 1.64), 0.50 (0.29, 0.84), and 0.68 (0.29, 1.57) in age-groups <65, ≥65 to <75, and ≥75 years, respectively (interaction *P* value 0.2107). Safety outcomes, including fractures, volume depletion, cancer, urinary tract infections, and amputations were balanced with dapagliflozin versus placebo, and acute kidney injury was reduced, all regardless of age. Genital infections that were serious or led to discontinuation of the study drug and diabetic ketoacidosis were uncommon, yet more frequent with dapagliflozin versus placebo, without heterogeneity (interaction *P* values 0.1058 and 0.8433, respectively).

CONCLUSIONS

The overall efficacy and safety of dapagliflozin are consistent regardless of age.

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Type 2 diabetes mellitus (T2DM) is a prevalent disorder in the elderly, with approximately one-quarter of people age >65 years with diabetes and an expected increase in rates of diabetes in the upcoming years (1). Diabetes care in the elderly is challenging due to high rates of concomitant comorbidities, functional disability, frailty, cognitive impairment, and polypharmacy. The complexity of treatment, side effects, and drug interactions are important considerations when choosing the appropriate glucose-lowering pharmacotherapy for older patients with diabetes (1,2). However, data regarding the efficacy and safety of glucose-lowering agents are often lacking, particularly in the very elderly, age ≥75 years. The U.S. Food and Drug Administration as well as the European Medicines Agency recommended collecting comprehensive data especially in very elderly patients with diabetes to enable appropriate assessment of their drug responses (2,3).

Sodium–glucose cotransporter 2 (SGLT2) inhibitors have been available for the treatment of diabetes since 2012. Multiple clinical benefits beyond glucose lowering have been established with this drug class. These include reduced hospitalizations for heart failure, renal protection, and improvements in weight and blood pressure (4–8). Furthermore, the drugs are taken orally and at any time of the day and have no known significant drug interactions (8). Considering their multiple favorable effects, minimal incremental risk for hypoglycemia, and simplicity of administration, they appear to be an attractive therapeutic option for older adults addressing the many comorbidities more prevalent in this population. Nevertheless, there has been some hesitance in clinical practice prescribing these agents to the elderly, mostly due to insufficient long-term safety data (1). Older patients are more prone to the development of fractures and acute kidney injury (AKI), and safety alerts regarding these potential risks with some SGLT2 inhibitors have been issued (9). Moreover, due to the limited therapeutic experience in patients age 75 years and older, initiation of SGLT2 inhibitor therapy at this age has so far not been recommended by some authorities (10).

The Dapagliflozin Effect on Cardiovascular Events (DECLARE)–TIMI 58 study is a cardiovascular (CV) outcome study that ascertained the CV and renal effects of dapagliflozin on a large patient population both with and without established cardiovascular disease, including a large cohort of elderly and very elderly patients (4). In the present analysis, we studied the efficacy and safety of dapagliflozin stratified by age.

RESEARCH DESIGN AND METHODS

Study Overview

In the DECLARE–TIMI 58 trial, a total of 17,160 patients, including 7,907 age ≥65 years and 1,096 age ≥75 years, with T2DM and established atherosclerotic cardiovascular disease or risk factors, 41% and 59%, respectively, were randomly assigned to receive dapagliflozin or placebo in addition to standard of care and followed for a median period of 4.2 years. The study enrolled patients at least 40 years old, with HbA_{1c} 6.5%−12.0% and creatinine clearance ≥60 mL/min. Patients who remained eligible after a 4–8-week placebo run-in period were randomized in a 1:1 double-blind fashion to dapagliflozin 10 mg daily or matched placebo. All patients were to be treated according to regional standards of care for CV risk factors: blood pressure, lipids, antithrombotic treatment, and HbA_{1c}. The design, baseline characteristics, and principal results of this study have been published (4,11,12).

Assessment of Outcomes

The dual primary composite efficacy end points were CV death or hospitalization for heart failure (CVD/HHF) and major adverse cardiovascular events (MACE; the composite of CV death, MI, or ischemic stroke). A secondary prespecified cardiorenal composite outcome was a sustained decrease of 40% or more in estimated glomerular filtration rate (eGFR) to <60 mL/min/1.73 m^2, new end-stage renal disease (ESRD), or death from renal or CV causes. A renal-specific composite outcome included a 40% decrease in eGFR to <60 mL/min/1.73 m^2, ESRD, or death from renal cause.

Safety end points were assessed in all patients who received at least one dose of study drug (the safety population). For amputations, fractures, and malignancies, events ocurring from first dose until the end of trial were included in the analyses. The remaining safety outcomes were assessed on treatment, which included all events that occurred after the first dose of the study drug to the earlier of 30 (for serious adverse events [SAEs]) or 7 (for nonserious AEs) days after the last dose of the study drug or the closing visit. Major hypoglycemia was defined as symptomatic events requiring external assistance due to the severe impairment of consciousness with prompt recovery after glucose or glucagon administration. The urinary tract and genital infections collected were only those that were either serious or led to the discontinuation of the study drug.

Statistical Analysis

Prespecified age-groups were <65, ≥65 and <75, and ≥75 years. The data presented in the main article are for three age-groups (<65, ≥65 to <75, and ≥75 years) to enable the description of data from all age subgroups, including 65 to <75 years, which comprised 39.7% of the study population. Efficacy and safety data limited to the prespecified age-groups are included in the Supplementary Material.

Baseline characteristics are reported as frequencies and percentages for categorical variables and as median and interquartile range (IQR) for continuous variables. Incidence rates and log-rank test for trend *P* values in efficacy and safety end points are reported for the three age-groups.

Analyses were performed on an intention-to-treat basis. Hazard ratios (HRs) and 95% CIs were determined from Cox regression models with stratification factor (atherosclerotic cardiovascular disease or multiple CV risk factors and hematuria status) as strata in models comparing treatment in age-groups.

Mixed models for repeated measures in HbA_{1c}, weight, systolic blood pressure, and diastolic blood pressure were analyzed to produce least squares mean estimates and 95% CIs in each treatment and age-group. Attainment of glycemic and weight targets was compared between groups using logistic regression models. *P* values for the covariate of interest were adjusted for baseline HbA_{1c} or weight accordingly.

There was no statistical adjustment for multiple comparisons. All analyses were performed using SAS software, version 9.4 (SAS Institute Inc., Cary, NC) and Stata version 14.2 (College Station, TX).

RESULTS

Baseline Characteristics

The study included 9,253 patients age <65 years, 6,811 patients age ≥65 to <75

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years, and 1,096 patients age ≥75 years. Their baseline characteristics are shown in Supplementary Table 1. Chronic kidney disease and history of heart failure were more prevalent with increasing age as was use of ACE inhibitors or angiotensin receptor blockers (ARBs), diuretics, loop diuretics, and antiplatelet therapy.

Efficacy

Overall incidence rates of the dual primary composite efficacy end points and of their individual components were higher with increasing age. Incidence rates of CVD/HHF were 10.9, 14.8, and 26.7 ($P < 0.0001$) and those of MACE were 20.9, 24.7, and 37.4 cases per 1,000 person-years in age-groups <65, ≥65 to <75, and ≥75 years, respectively ($P < 0.0001$).

Dapagliflozin reduced the composite CVD/HHF consistently, with HR 0.88 (95% CI 0.72, 1.07), 0.77 (0.63, 0.94), and 0.94 (0.65, 1.36) in age-groups <65, ≥65 to <75, and ≥75 years, respectively (interaction *P* value 0.5277). The HR for dapagliflozin for MACE was 0.93 (95% CI 0.81, 1.08), 0.97 (0.83, 1.13), and 0.84 (0.61, 1.15) in age-groups <65, ≥65 to <75, and ≥75 years, respectively (interaction *P* value 0.7352). Rates of HHF were reduced with dapagliflozin, with HR 0.88 (95% CI 0.68, 1.15), 0.60 (0.46, 0.79), and 0.81 (0.50, 1.30), respectively, in age-groups <65, ≥65 to <75, and ≥75 years (interaction *P* value 0.1402). The other components of the primary end points as well as all-cause mortality were unchanged, with effects consistent across all age-groups (Fig. 1).

The cardiorenal secondary composite outcome (sustained decrease of 40% or more in eGFR to <60 mL/min/1.73 m^2, new ESRD, or death from renal or CV causes) was reduced with dapagliflozin versus placebo, with HR 0.72 (95% CI 0.59, 0.88), 0.80 (0.65, 0.98), and 0.82 (0.52, 1.29) in age-groups <65, ≥65 to <75, and ≥75 years, respectively (interaction *P* value 0.7299). Similar results were observed for the renal-specific composite outcome (Fig. 1). Efficacy end points by dichotomous age-groups showed similar results with no age-based treatment interactions (Supplementary Fig. 1).

Metabolic Outcomes

Changes in HbA_{1c}, weight, and blood pressure by age subgroups and treatment allocation are shown in Fig. 2. Baseline HbA_{1c} in the elderly and very elderly was lower compared with the younger population (median levels 8.2 [IQR 7.5, 9.3], 7.9 [7.3, 8.7], and 7.8 [7.2, 8.5] in age-groups <65, ≥65 to <75, and ≥75 years, respectively; *P*-trend <0.0001). Nevertheless, significant and similar declines in HbA_{1c} with dapagliflozin versus placebo were observed for all age-groups (Fig. 2). At 1 year, least squares mean difference between the treatment groups was −0.58 (95% CI −0.63, −0.53), −0.46 (−0.51, −0.41), and −0.51 (−0.63, −0.40) in age-groups <65, ≥65 to <75, and ≥75 years, respectively (all $P < 0.0001$). At 1, 2, and 3 years, patients allocated to dapagliflozin versus placebo, at all age subgroups, were statistically

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	Dapagliflozin		Placebo				
	n/N (%)	Rates per 1000 person- years	n/N (%)	Rates per 1000 person- years	Hazard ratio (95% CI)	p value	p interaction
CVD / HHF							
< 65 years	189/4631 (4.1%)	10.2	211/4622 (4.6%)	11.6	0.88 (0.72, 1.07)	0.1902	0.5277
65-< 75 years	176/3413 (5.2%)	12.8	225/3398 (6.6%)	16.7	0.77 (0.63, 0.94)	0.0099	
≥ 75 years	52/538 (9.7%)	25.2	60/558 (10.8%)	28.2	0.94 (0.65, 1.36)	0.7330	
MACE							
< 65 years	366/4631 (7.9%)	20.3	385/4622 (8.3%)	21.5	0.93 (0.81, 1.08)	0.3478	0.7352
65-< 75 years	323/3413 (9.5%)	24.2	332/3398 (9.8%)	25.2	0.97 (0.83, 1.13)	0.6509	
≥ 75 years	67/538 (12.5%)	33.2	86/558 (15.4%)	41.4	0.84 (0.61, 1.15)	0.2722	
CVD							
< 65 years	102/4631 (2.2%)	5.4	109/4622 (2.4%)	5.8	0.92 (0.70, 1.21)	0.5460	0.7953
65-< 75 years	115/3413 (3.4%)	8.2	111/3398 (3.3%)	8.0	1.03 (0.79, 1.34)	0.8238	
≥ 75 years	28/538 (5.2%)	13.1	29/558 (5.2%)	12.9	1.06 (0.63, 1.78)	0.8315	
HHF							
< 65 years	102/4631 (2.2%)	5.5	113/4622 (2.4%)	6.2	0.88 (0.68, 1.15)	0.3624	0.1402
65-< 75 years	81/3413 (2.4%)	5.9	133/3398 (3.9%)	9.9	0.60 (0.46, 0.79)	0.0003	
≥ 75 years	29/538 (5.4%)	14.1	40/558 (7.2%)	18.8	0.81 (0.50, 1.30)	0.3768	
Myocardial infarction							
< 65 years	199/4631 (4.3%)	11.0	227/4622 (4.9%)	12.6	0.86 (0.71, 1.04)	0.1205	0.8621
65-< 75 years	162/3413 (4.7%)	12.0	173/3398 (5.1%)	13.0	0.93 (0.75, 1.15)	0.5139	
≥ 75 years	32/538 (5.9%)	15.7	41/558 (7.3%)	19.3	0.85 (0.54, 1.36)	0.5020	
Any stroke							
< 65 years	126/4631 (2.7%)	6.9	119/4622 (2.6%)	6.5	1.04 (0.81, 1.34)	0.7483	0.6388
65-< 75 years	106/3413 (3.1%)	7.8	113/3398 (3.3%)	8.4	0.94 (0.72, 1.22)	0.6223	
≥ 75 years	23/538 (4.3%)	11.2	31/558 (5.6%)	14.6	0.81 (0.47, 1.39)	0.4475	
Death from any cause							
< 65 years	212/4631 (4.6%)	11.3	248/4622 (5.4%)	13.2	0.84 (0.70, 1.01)	0.0706	0.3537
65-< 75 years	246/3413 (7.2%)	17.6	248/3398 (7.3%)	17.9	0.99 (0.83, 1.18)	0.8692	
≥ 75 years	71/538 (13.2%)	33.3	74/558 (13.3%)	33.0	1.05 (0.76, 1.46)	0.7483	
Cardiorenal composite outcome							
< 65 years	167/4631 (3.6%)	9.0	226/4622 (4.9%)	12.3	0.72 (0.59, 0.88)	0.0015	0.7299
65-< 75 years	169/3413 (5%)	12.3	210/3398 (6.2%)	15.5	0.80 (0.65, 0.98)	0.0289	
≥ 75 years	34/538 (6.3%)	16.2	44/558 (7.9%)	20.3	0.82 (0.52, 1.29)	0.3928	
Renal-specific composite outcome							
< 65 years	65/4631 (1.4%)	3.5	121/4622 (2.6%)	6.6	0.53 (0.39, 0.71)	<.0001	0.8293
65-< 75 years	56/3413 (1.6%)	4.1	101/3398 (3%)	7.5	0.55 (0.40, 0.76)	0.0003	
≥ 75 years	6/538 (1.1%)	2.9	16/558 (2.9%)	7.4	0.38 (0.15, 0.98)	0.0452	

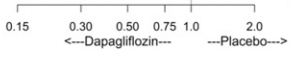

Figure 1—Efficacy outcomes by age-groups. CVD, cardiovascular death.

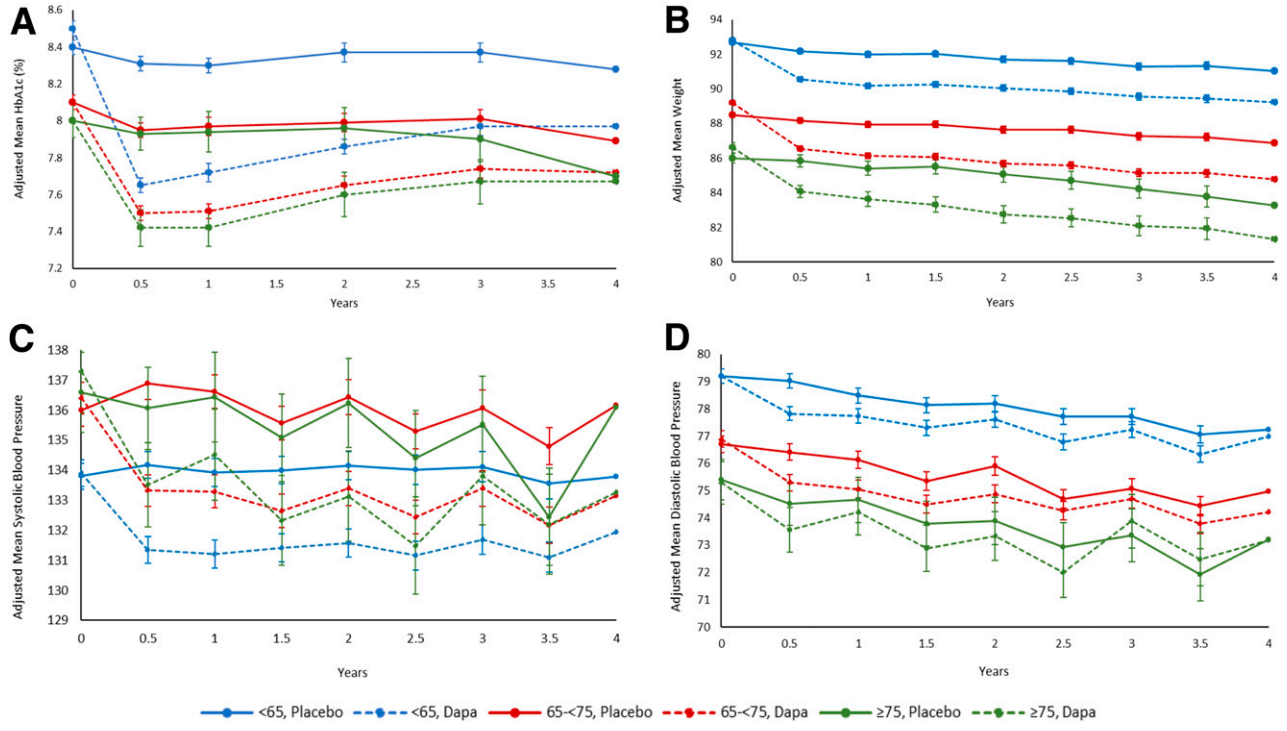

Figure 2—Changes in metabolic parameters over time. Change in HbA_{1c} (*A*), weight (*B*), systolic blood pressure (*C*), and diastolic blood pressure (*D*) with dapagliflozin vs. placebo according to age-group. Dapa, dapagliflozin.

more likely to attain an HbA_{1c} of <7.0% (excluding age ≥75 years at year 3) or <8.0% or to reduce their HbA_{1c} by ≥0.5% (Fig. 3). The effect was somewhat attenuated at year 4, particularly in the very elderly.

Dapagliflozin yielded a greater reduction in weight versus placebo, and this was maintained in all age-groups during the entire study period (all $P < 0.0001$) (Fig. 2). Patients allocated to dapagliflozin versus placebo were more likely to attain a 5% weight loss at all age-groups, which was sustained throughout the study (Fig. 3). In the 4th year, a 5% weight reduction was observed in 37.0% vs. 23.2%, 40.5% vs. 24.6%, and 52.9% vs. 31.2% with dapagliflozin versus placebo in age-groups <65, ≥65 to <75, and ≥75 years, respectively (all $P < 0.0001$).

Safety

SAEs in the overall safety population were more common in the elderly and very elderly compared with the younger patients, with incidence rates of 107.3, 131.2, and 191.1 cases per 1,000 person-years in age-groups <65, ≥65 to <75, and ≥75 years, respectively ($P < 0.0001$). The incidence of SAEs was lower with dapagliflozin versus placebo overall in the trial, and this pattern was consistent regardless of age, with HR 0.93 (95% CI 0.86, 1.00), 0.88 (0.81, 0.95), and 1.02 (0.85, 1.21) in age-groups <65, ≥65 to <75, and ≥75 years, respectively, with no age-based treatment interaction (interaction *P* value 0.2667) (Fig. 4). Moreover, no heterogeneity across age-groups was observed for any of the outcomes assessed, although the number of events in the very elderly was often quite small, yielding wide CIs in this age category.

Major hypoglycemia events increased with increasing age in the overall safety population, with incidence rates of 1.7, 2.6, and 6.5 cases per 1,000 person-years in age-groups <65, ≥65 to <75, and ≥75 years, respectively ($P < 0.0001$). Major hypoglycemia was less frequent with dapagliflozin versus placebo, with the effect more predominantly observed in the age-group ≥65 vs. <65 years (HR 0.53 [95% CI 0.34, 0.83] vs. 0.97 [0.58, 1.64], respectively; interaction *P* value 0.0896) (Supplementary Fig. 2). Overall fractures were more common in the elderly and very elderly, with incidence rates of 11.2, 15.8, and 17.4 cases per 1,000 person-years in age-groups <65, ≥65 to <75, and ≥75 years, respectively ($P < 0.0001$), yet events were balanced between the dapagliflozin and placebo groups at all age subgroups studied, with no heterogeneity. Events of volume depletion in the overall safety study population increased with increasing age, with incidence rates of 5.6, 7.8, and 14.9 cases per 1,000 person-years in age-groups <65, ≥65 to <75, and ≥75 years, respectively ($P < 0.0001$). Similarly, AKI was reported overall at higher rates with increasing age, with incidence rates of 4.2, 5.4, and 9.3 cases per 1,000 person-years in age-groups <65, ≥65 to <75, and ≥75 years, respectively ($P = 0.0001$). Volume depletion events were balanced between the dapagliflozin and placebo groups, and AKI events were overall fewer with dapagliflozin versus placebo, with no age-based treatment interaction. The amputation rate did not differ by age ($P = 0.3201$) and was balanced between dapagliflozin and placebo, with no age-based treatment interaction. Diabetic ketoacidosis was rare, but more events were observed with dapagliflozin versus placebo, consistently across age-groups. Genital infections that led to the discontinuation of the study drug were more common with dapagliflozin versus placebo, and there were two SAE genital infections in each treatment arm, with no heterogeneity. There was no statistically significant increase in urinary tract infections (serious

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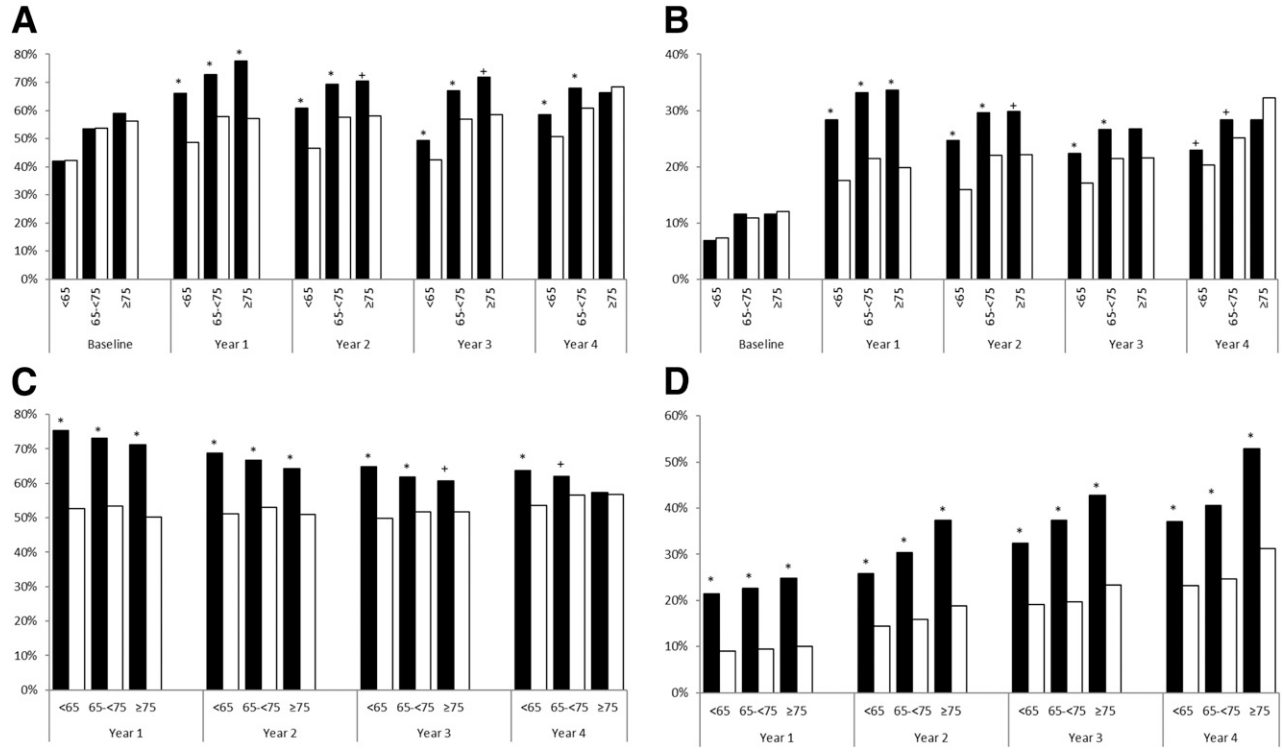

Figure 3—Attainment of HbA_{1c} and weight targets. Percentage of patients attaining HbA_{1c} <8 (*A*), HbA_{1c} <7 (*B*), reducing HbA_{1c} by >0.5% (*C*), or reducing weight by >5% (*D*) with dapagliflozin vs. placebo by age-group. Black bars, dapagliflozin; white bars, placebo. *$P < 0.0001$; +$P < 0.05$.

or leading to drug discontinuation) with dapagliflozin versus placebo in the overall population or in any of the age-groups. Overall malignancies were balanced between treatment arms across all age-groups (Fig. 4).

Safety end points by dichotomous age-groups revealed consistent results with no age-based treatment interaction for any of the outcomes (Supplementary Fig. 2).

CONCLUSIONS

In this manuscript, we present analyses of data from the DECLARE–TIMI 58 study that establish the beneficial CV and renal effects of dapagliflozin in a robust number of elderly and very elderly participants. The overall pattern of efficacy and safety of dapagliflozin was consistent regardless of age.

Care of older patients with diabetes represents an ongoing challenge. Rates of HHF, CV disease, and MI are increased in those age ≥65 years and are markedly increased in patients with age ≥75 years. The robust reduction in HHF observed with dapagliflozin is thus of great clinical significance, particularly when viewed in light of the fact that many of these patients were already treated with standard of care, including ACE inhibitors, ARBs, β-blockers, and diuretics. Although fewer events of MACE were observed in patients treated with dapagliflozin, it did not result in a significant reduction in the incidence of MACE. The study met its primary safety noninferiority end point for MACE across all studied age-groups.

SAEs, though generally more frequent in older versus younger individuals, were not increased in the elderly or the very elderly with dapagliflozin versus placebo, and there was no age-based treatment interaction for any of the safety outcomes assessed. Several adverse outcomes are of particular concern in older patients with diabetes. Events of volume depletion increase with increasing age, and there is greater concern related to possible adverse consequences of volume depletion in older patients, including falls and kidney injury. In that respect, the observed reduction in HHF and renal benefit with dapagliflozin with no excess risk of volume depletion and fewer events of AKI is reassuring. Older adults are at higher risk of hypoglycemia from both insulin and sulfonylurea treatment as a result of insulin deficiency, progressive renal insufficiency, and higher rates of cognitive deficits, which may cause difficulty in disease management, i.e., glucose monitoring and adjustment of insulin dosing (1). Hypoglycemia should be particularly avoided in older patients due to their greater risk of other major adverse outcomes secondary to hypoglycemia, such as falls or fractures (1). Patients randomized to dapagliflozin versus placebo in addition to standard of care attained superior glycemic control with lower rates of hypoglycemia, irrespective of age, highlighting the benefit of the drug.

The greater morbidity of the elderly and very elderly population in our study, as reflected by higher rates of baseline HF and chronic kidney disease, strengthens the clinical impact of our results, which demonstrate consistent efficacy and safety of dapagliflozin extending across all age-groups.

The paradigm of diabetes treatment has shifted from a glucose-focused approach to the pursuit of a therapeutic regimen that will yield a reduction in morbidity and mortality. This is particularly true in the elderly, whose life expectancy is shorter and for whom event rates are higher (13). Treatment goals for T2DM in the elderly should be individualized; thus, in healthy patients with good functional status, few comorbidities, and intact cognitive function, goals

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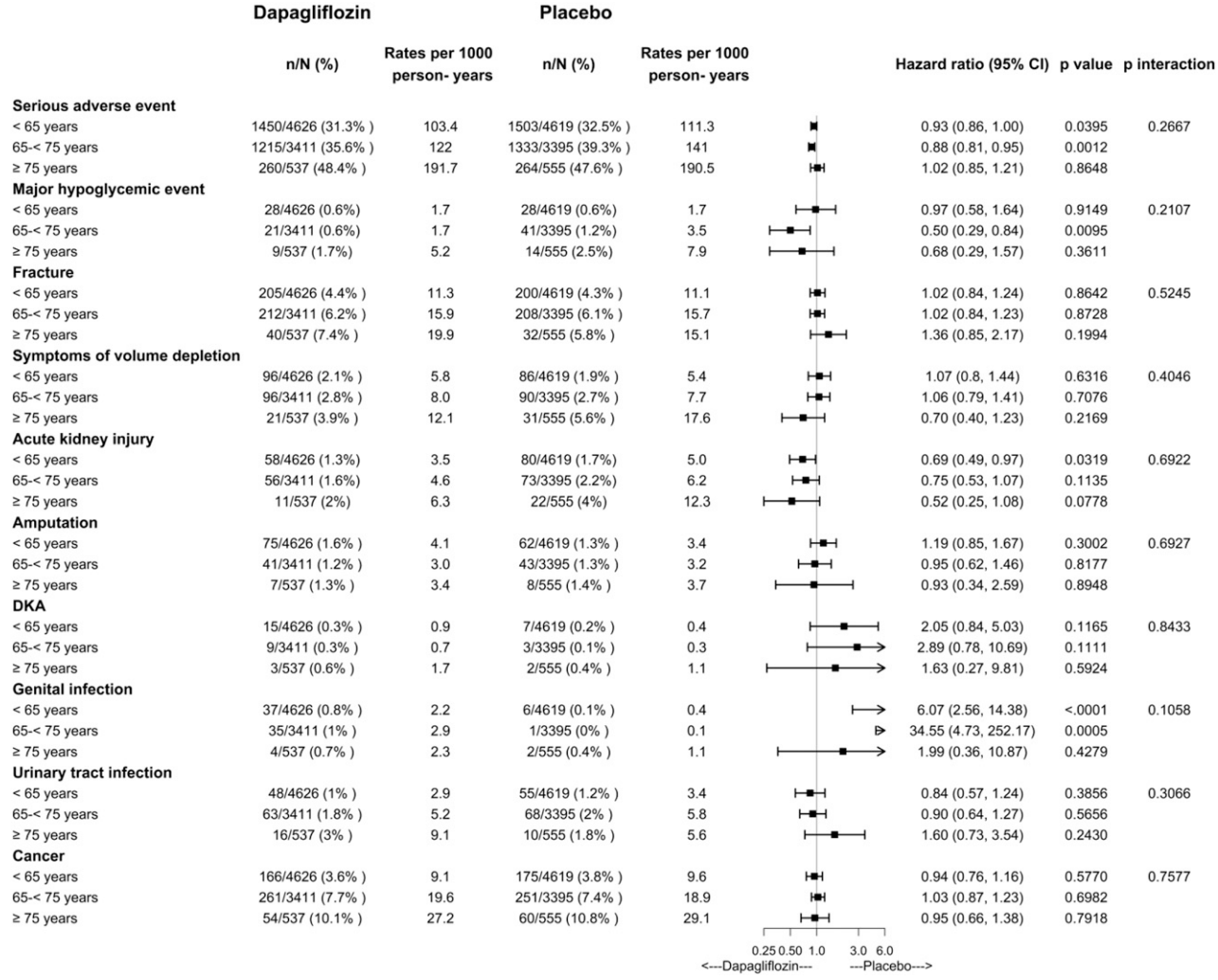

Figure 4—Safety outcomes by age-groups. DKA, diabetic ketoacidosis.

may be similar to those of younger adults. However, in patients with an intermediate remaining life expectancy, targets should be less stringent as part of individualized care and a target HbA_{1c} <8.0% may be acceptable (13). Dapagliflozin enabled more patients to attain a clinically significant HbA_{1c} reduction, whether striving for the standard or less stringent target.

Weight loss is generally not a treatment goal in the very elderly population; nevertheless, in our analysis, we observed sustained weight loss across all age-groups. This did not appear to lead to any untoward effects in the elderly during the time frame of the study, although notably, median BMI was 31.1 and 30.2 kg/m^2 at baseline in the elderly and very elderly patients in the study, respectively. SGLT2 inhibitors have been shown to reduce adipose tissue mass while maintaining lean body mass (14), changes which are probably beneficial at all ages.

Few studies have been published to date on the use of SGLT2 inhibitors in the elderly. A randomized, double-blind, age-stratified trial of dapagliflozin versus placebo demonstrated a beneficial effect of dapagliflozin on glucose, weight, and blood pressure across all age-groups studied, with no outstanding safety issues in the elderly or very elderly, although not many very elderly patients were included (15). Postmarketing reports from Japan reported no age-related safety issues with tofogliflozin, ipragliflozin, and canagliflozin, yet these studies are limited by the lack of comparator and dependence upon physician reporting of AEs (16–18).

The efficacy and safety of other glucose-lowering agents in the elderly have been studied. Dipeptidyl peptidase 4 (DPP-4) inhibitors showed no CV benefit in any age-group studied, and safety outcomes of DPP-4 inhibitors were shown to be similar in older versus younger patients (19,20). GLP-1 receptor agonists have also shown efficacy and safety in the elderly that are comparable to that of younger patients, and post hoc analysis of the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial proposed greater benefit in the elderly (21). Our study is the first to substantiate the efficacy and safety of an SGLT2 inhibitor in the elderly and very elderly and may pave the way for relaxing the warning placed on this drug in the geriatric population, although individualization of therapy is pivotal, particularly in this vulnerable population.

Some limitations of our study should be noted. Creatinine clearance <60 mL/min was an exclusion criterion in the

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study, and this may have led to exclusion of the frailer elderly patients, which are more prone to volume depletion, AKI, fractures, and other adverse outcomes. Moreover, there were no assessments of cognitive function, functional capacity, or frailty at baseline or at any time during the study; however, as a randomized trial, one would expect that these unmeasured features would be balanced between groups. Additionally, the very elderly subgroup consisted of a small subset (6.4%) of the total population of 17,160, and the number of events was small, yet it still accounted for 1,096 participants. Finally, the analyses of metabolic outcomes were post hoc and should be considered exploratory.

In conclusion, our study establishes the CV and renal benefits of dapagliflozin in the elderly and very elderly. The overall efficacy and safety of dapagliflozin were consistent regardless of age; thus, this drug may be considered a valuable glucose-lowering agent regardless of age.

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AstraZeneca was involved in the study design, data collection, data analysis, interpretation, and writing of the manuscript.

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