Clinical Outcomes by Albuminuria Status with Dulaglutide versus Insulin Glargine in Participants with Diabetes and CKD: AWARD-7 Exploratory Analysis

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Abstract

Background In the AWARD-7 trial of participants with type 2 diabetes (T2DM) and moderate-to-severe CKD, dulaglutide (DU) treatment slowed decline in eGFR compared with insulin glargine (IG). Treatment with doses of either DU or IG resulted in similar levels of glycemic control and BP. The aim of this analysis was to determine the risk of clinical event outcomes between treatment groups.

Methods Participants with T2DM and CKD categories 3–4 were randomized (1:1:1) to 0.75 or 1.5 mg DU weekly or IG daily as basal therapy, with titrated insulin lispro, for 1 year. The time to occurrence of the composite outcome of ≥40% eGFR decline, ESKD, or death due to kidney disease was compared using a Cox proportional-hazards model.

Results Patients treated with 1.5 mg DU weekly versus IG daily for 1 year had a lower risk of ≥40% eGFR decline or ESKD events in the overall study population (5% versus 11%; hazard ratio, 0.45; 95% CI, 0.20 to 0.97; \( P = 0.04 \)). Most events occurred in the subset of patients with macroalbuminuria, where risk of the composite outcome was substantially lower for 1.5 mg DU versus IG (7% versus 22%; hazard ratio, 0.25; 95% CI, 0.10 to 0.68; \( P = 0.006 \)). No deaths due to kidney disease occurred.

Conclusions Treatment with 1.5 mg DU weekly was associated with a clinically relevant risk reduction of ≥40% eGFR decline or ESKD compared with IG daily, particularly in the macroalbuminuria subgroup of participants with T2DM and moderate-to-severe CKD.


Introduction

The growing prevalence of diabetes mellitus is one of the main drivers of the CKD epidemic (1). CKD occurring in a person with diabetes is generally characterized by high levels of albuminuria, low GFR, or both. Over time, progressive GFR decline leads to kidney failure or death (2,3). Albuminuria is a major risk factor for CKD progression, particularly in those with macroalbuminuria (4).

Recent evidence from clinical trials suggests that treatment of type 2 diabetes mellitus (T2DM) with glucagon-like peptide-1 receptor agonists (GLP-1 RAs) confers kidney-protective effects (5,6). Studies designed to assess cardiovascular safety of GLP-1 RAs in T2DM have shown a reduced risk of both macroalbuminuria onset and decline in eGFR, largely driven by reduction in macroalbuminuria events (6–9). Furthermore, slower decline in eGFR was suggested by a post hoc analysis of participants with eGFR <60 ml/min per 1.73 m² in one of these studies (9). A secondary outcome of the study of dulaglutide versus insulin glargine in participants with T2DM and moderate-to-severe CKD (AWARD-7) showed that treatment with dulaglutide, a GLP-1 RA, was associated with slowed eGFR decline and reduced urinary albumin-creatinine ratio (UACR) compared with insulin glargine (10). Recent meta-analyses show that early change in albuminuria and GFR slope may be used as surrogate end points in clinical trials for CKD progression under certain conditions (11). In the active-comparator study (AWARD-7), the observed benefit on eGFR occurred with comparable control of hyperglycemia and BP, and similar use of renin-angiotensin system inhibitors, in the dulaglutide-treated and insulin glargine–treated groups (10). Notably, rates of hypoglycemia were about 50% less in the dulaglutide treatment groups. Treatment with dulaglutide also resulted in weight loss, whereas insulin-glargine treatment produced weight gain (12). However, weight changes were not linked to changes in eGFR (12).

In contemporary clinical trials, CKD outcomes are often defined as an eGFR decline of ≥40%, ESKD, or
death due to kidney disease (13). The objective of this exploratory analysis was to determine the risk of these clinical outcomes between dulaglutide and insulin-glargine groups in the overall study population and in subgroups determined on the basis of albuminuria status.

Materials and Methods

Study Design and Participants

This was an exploratory analysis of the AWARD-7 study, a 1-year, randomized, multicenter, open-label (blinded to dulaglutide dose), clinical trial that compared the effect of dulaglutide (plus premeal insulin lispro) versus insulin glargine (plus premeal insulin lispro) as basal glucose-lowering therapy. Participants with T2DM and categories 3–4 CKD were randomized (1:1:1) to 0.75 or 1.5 mg dulaglutide weekly or insulin glargine, all of which were given in combination with premeal insulin lispro. Details of the AWARD-7 study (NCT01621178, registered June 8, 2012) were previously published (10).

Adults aged ≥18 years with T2DM and moderate-to-severe CKD (eGFR ≥15 and <60 ml/min per 1.73 m²) were eligible for inclusion in the study. At screening, participants had a hemoglobin A1c of ≥7.5% (≥58.5 mmol/mol) and ≤10.5% (≤91.3 mmol/mol). They were required to receive an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker at the maximal tolerated dose for at least 1 month before screening. However, if these medications were not tolerated or were contraindicated, participants were still allowed to enroll. Key exclusion criteria included type 1 diabetes mellitus, stage 5 CKD or expectation of kidney replacement therapy (dialysis or kidney transplantation) in the next 6 months, history of solid organ transplant, and systolic BP ≥150 mm Hg or diastolic BP ≥90 mm Hg. The full list of eligibility criteria was provided in the primary paper (10).

AWARD-7 was performed in accordance with the Declaration of Helsinki, the International Ethical Guidelines of the Conference for International Organizations of Medical Sciences, and the Good Clinical Practice guidelines of the International Conference on Harmonization. Local institutional review boards approved the protocol for each site. All participants provided written informed consent.

Study Outcomes

The overall main outcome was time to event for the composite end point of persistent eGFR decline ≥40% from baseline at two or more consecutive visits, ESKD, or death due to kidney disease. ESKD was defined on the basis of investigator-reported events that included chronic dialysis, kidney transplant, or adverse events reported as ESKD. Chronic dialysis was defined as reported by investigators or as an adverse event with the Medical Dictionary for Regulatory Activities (MedDRA; version 19.1)–preferred term of “dialysis, dialysis device insertion, hemodialysis, hemofiltration, peritoneal dialysis, continuous hemodiafiltration, or artificial kidney device user.” Kidney transplant was defined as reported by investigators or with an adverse event with the MedDRA–preferred term of “kidney and liver transplant, kidney and pancreas transplant, kidney replacement therapy, or kidney transplant.” Additional ESKD events were identified using the MedDRA–preferred term of “diabetic ESKD, renal failure, ESKD.” These outcomes were also evaluated in subgroups by baseline albuminuria status as follows: normoalbuminuria, UACR of <30 mg/g; microalbuminuria, UACR of 30–300 mg/g; and macroalbuminuria, UACR of >300 mg/g.

Statistical Analyses

Baseline demographic data were summarized using means and SDs for continuous variables and percentages for categorical variables. The eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) Creatinine (main analysis) and CKD-EPI Cystatin C Equations (hereafter, eGFR-creatinine and eGFR-cystatin C, respectively). Treatment-group comparisons were assessed for the time to the occurrence of the composite end point of ≥40% eGFR decline or ESKD using a Cox proportional-hazards model, displayed with Kaplan-Meier curves. Because no kidney disease-related deaths occurred during the study, this component could not be analyzed. Least-squares means (LSMs) and SEMs for eGFR were based on a mixed-effects model for repeated measures with a log transformation. Tests of treatment effects were performed at a two-sided α level of 0.05, and two-sided 95% CIs are reported (10).

Results

Demographics and Baseline Clinical Characteristics

Of 576 participants in AWARD-7, 192 received 1.5 mg dulaglutide once weekly, 190 received 0.75 mg dulaglutide once weekly, and 194 received insulin glargine once daily as basal therapy. Baseline characteristics were balanced between these treatment groups (Table 1). At baseline, participants with microalbuminuria or macroalbuminuria had progressively lower mean eGFRs than those with normoalbuminuria (Table 1).

eGFR over Time

eGFR calculated with serum cystatin C did not change significantly over 1 year in the dulaglutide treatment groups (LSM, −0.7 ml/min per 1.73 m² for both dose groups), but declined significantly from baseline in the insulin-glargine group (LSM, −3.3 ml/min per 1.73 m²) in the main analysis of the overall study population, as previously reported (Supplemental Table 1) (10). In participants with baseline macroalbuminuria, eGFR-creatinine was significantly higher in the 1.5 mg dulaglutide group than in the insulin-glargine group (26 weeks LSM±SEM, 31.4±0.9 versus 27.5±0.7 ml/min per 1.73 m², P=0.001; 52 weeks, 29.1±1.2 versus 25.2±1.0 ml/min per 1.73 m², P=0.01) (Figure 1A), whereas no significant difference was observed between the 0.75 ml/min gluaglutide group and the insulin-glargine group. These data are consistent with eGFR-cystatin C, for which the eGFR was significantly higher in both dulaglutide groups than in the insulin-glargine group (Supplemental Table 1): 1.5 mg dulaglutide versus insulin glargine (26 weeks, 31.8±0.9 versus 27.2±0.7 ml/min per 1.73 m², P<0.001; 52 weeks, 29.6±1.1 versus 25.4±0.9 ml/min per 1.73 m², P=0.003); 0.75 mg dulaglutide versus insulin glargine (26 weeks, 31.1±0.9 versus 27.2±0.7 ml/min per 1.73 m², P<0.001; 52 weeks, 28.5±1.1 versus 25.4±0.9 ml/min per 1.73 m², P=0.02). In participants without baseline
### Table 1. Demographics and baseline clinical characteristics by albuminuria status

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>1.5 mg Dulaglutide (N=192)</th>
<th>0.75 mg Dulaglutide (N=190)</th>
<th>Insulin Glargine (N=194)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Normoalbuminuria, n</strong></td>
<td>34</td>
<td>44</td>
<td>48</td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>18 (53)</td>
<td>23 (52)</td>
<td>29 (60)</td>
</tr>
<tr>
<td>Age (yr), mean (SD)</td>
<td>68.6 (7.9)</td>
<td>69.5 (7.0)</td>
<td>67.8 (7.7)</td>
</tr>
<tr>
<td>Duration of diabetes (yr), mean (SD)</td>
<td>16.0 (8.6)</td>
<td>15.9 (8.0)</td>
<td>18.8 (11.4)</td>
</tr>
<tr>
<td>HbA1c (%), mean (SD)</td>
<td>8.7 (1.0)</td>
<td>8.3 (1.0)</td>
<td>8.5 (1.0)</td>
</tr>
<tr>
<td>eGFR-creatinine (ml/min per 1.73 m²), mean (SD)</td>
<td>43.8 (13.0)</td>
<td>44.2 (9.0)</td>
<td>42.9 (12.5)</td>
</tr>
<tr>
<td>eGFR-cystatin C (ml/min per 1.73 m²), mean (SD)</td>
<td>46.2 (17.3)</td>
<td>46.2 (15.8)</td>
<td>44.1 (14.2)</td>
</tr>
<tr>
<td>UACR (mg/g), median (min, max)</td>
<td>9 (1, 30)</td>
<td>13 (2, 30)</td>
<td>10 (1, 29)</td>
</tr>
<tr>
<td><strong>Microalbuminuria, n</strong></td>
<td>74</td>
<td>61</td>
<td>56</td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>31 (42)</td>
<td>25 (41)</td>
<td>27 (48)</td>
</tr>
<tr>
<td>Age (yr), mean (SD)</td>
<td>65.9 (8.3)</td>
<td>67.6 (7.2)</td>
<td>66.3 (7.2)</td>
</tr>
<tr>
<td>Duration of diabetes (yr), mean (SD), yr</td>
<td>18.0 (8.6)</td>
<td>19.5 (9.8)</td>
<td>18.8 (8.5)</td>
</tr>
<tr>
<td>HbA1c (%), mean (SD)</td>
<td>8.5 (0.7)</td>
<td>8.6 (1.1)</td>
<td>8.6 (0.9)</td>
</tr>
<tr>
<td>eGFR-creatinine (ml/min per 1.73 m²), mean (SD)</td>
<td>40.2 (12.6)</td>
<td>38.9 (12.5)</td>
<td>42.0 (11.8)</td>
</tr>
<tr>
<td>eGFR-Cystatin C (ml/min per 1.73 m²), mean (SD)</td>
<td>38.3 (12.5)</td>
<td>37.6 (12.8)</td>
<td>40.6 (12.9)</td>
</tr>
<tr>
<td>UACR (mg/g), median (min, max)</td>
<td>102 (32, 298)</td>
<td>108 (31, 299)</td>
<td>107 (30, 289)</td>
</tr>
<tr>
<td><strong>Macroalbuminuria, n</strong></td>
<td>84</td>
<td>84</td>
<td>90</td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>39 (46)</td>
<td>38 (45)</td>
<td>45 (50)</td>
</tr>
<tr>
<td>Age (yr), mean (SD)</td>
<td>62 (8.9)</td>
<td>60.1 (8.2)</td>
<td>61.3 (8.5)</td>
</tr>
<tr>
<td>Duration of diabetes (yr), mean (SD)</td>
<td>17.8 (8.9)</td>
<td>17.9 (8.3)</td>
<td>18.6 (7.2)</td>
</tr>
<tr>
<td>HbA1c (%), mean (SD)</td>
<td>8.6 (0.9)</td>
<td>8.7 (1.2)</td>
<td>8.6 (1.0)</td>
</tr>
<tr>
<td>eGFR-creatinine (ml/min per 1.73 m²), mean (SD)</td>
<td>34.0 (12.8)</td>
<td>35.0 (12.6)</td>
<td>33.9 (12.6)</td>
</tr>
<tr>
<td>eGFR-Cystatin C (ml/min per 1.73 m²), mean (SD)</td>
<td>32.7 (12.3)</td>
<td>33.6 (11.0)</td>
<td>33.7 (15.0)</td>
</tr>
<tr>
<td>UACR (mg/g), median (min, max)</td>
<td>1043 (310, 8708)</td>
<td>1184 (304, 7678)</td>
<td>1372 (301, 7644)</td>
</tr>
</tbody>
</table>

n, number of participants within subgroups; N, total number of participants; HbA1c, glycated hemoglobin; eGFR-creatinine; eGFR determined using the Chronic Kidney Disease Epidemiology Collaboration Creatinine Equation; eGFR-cystatin C, eGFR determined using the Chronic Kidney Disease Epidemiology Collaboration Cystatin C Equation; UACR, urinary albumin-creatinine ratio; min, minimum; max, maximum.

*Normoalbuminuria: UACR, <30 mg/g.

*Microalbuminuria: UACR, 30–300 mg/g.

*Macroalbuminuria: UACR, >300 mg/g.
macroalbuminuria, no significant eGFR differences were observed between treatment groups (Figure 1B).

**Clinical Outcomes in the Overall Study Population**

In the main analysis for time to event, the hazard ratio (HR) for the composite end point of ≥40% eGFR-creatinine decline or ESKD events was significantly lower for the 1.5 mg dulaglutide group compared with the insulin-glargine group (HR, 0.45; 95% CI, 0.20 to 0.97; \( P=0.042 \); Figure 2, Table 2). Proportionally fewer participants experienced a ≥40% eGFR decline or an ESKD event in the 1.5 mg dulaglutide group (10/192; 5%) compared with the 0.75 mg dulaglutide group (16/190; 8%) and the insulin-glargine group (16/194; 8%).

**Figure 1.** Changes in eGFR by albuminuria status. eGFR (calculated by Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] Creatinine Equation) presented as geometric least-squares mean (LSM, SEM) from log-transformed analysis by macroalbuminuria status at baseline: (A) macroalbuminuria; (B) no macroalbuminuria. †P values are reported for statistical significance at the 26- and 52-week prespecified analysis points versus insulin glargine.

**Figure 2.** Time to first event for the composite outcome of ≥40% eGFR decline or ESKD in all participants. HR, hazard ratio.
glargine group (21/194; 11%) (Figure 3A, Table 2). The 1.5 mg dulaglutide group had the lowest proportion of participants with the outcome of ≥40% eGFR decline alone (2/192; 1%) versus 0.75 mg dulaglutide (7/192; 4%) and insulin glargine (6/194; 3%) (Figure 3B). Although fewer participants experienced the composite outcome of ≥40% eGFR decline or ESKD in the 0.75 mg dulaglutide group (16/190; 8%) compared with the insulin-glargine group (21/194; 11%), the comparison was not statistically significant (HR, 0.79; 95% CI, 0.41 to 1.51; Table 2). The 1.5 mg dulaglutide group had the lowest proportion of participants with the outcome of ESKD events (8/192; 4%) versus 0.75 mg dulaglutide (14/190; 7%) and insulin glargine (16/194; 8%) (Figure 3C).

In general, comparable results were observed for ≥40% eGFR-cystatin C decline (Table 2). However, the comparison to the insulin-glargine group missed statistical significance due to one more event in the 1.5 mg dulaglutide group according to the eGFR-cystatin C (11/192; 6%; HR, 0.49; 95% CI, 0.23 to 1.04; P=0.08; Table 2).

Clinical Outcomes by Albuminuria Status

The majority of events occurred in participants with macroalbuminuria at baseline, whereas few events occurred in participants with baseline microalbuminuria or normalalbuminuria (Table 2). In participants with macroalbuminuria, the HR for the composite end point of ≥40% eGFR-creatinine decline or ESKD events was markedly lower for the 1.5 mg dulaglutide group compared with the insulin-glargine group (HR, 0.25; 95% CI, 0.10 to 0.68; P=0.006; Figure 4, Table 2). The proportion of participants with the composite outcome of ≥40% eGFR decline or ESKD was significantly lower in the 1.5 mg dulaglutide group (6/84; 7%) versus the insulin-glargine group (20/90; 22%); 0.75 mg dulaglutide (14/84; 17%) was not significantly different from insulin glargine (Figure 5A, Table 2).

In participants with baseline microalbuminuria, very few events occurred over 1 year. As such, no detectable differences were observed between treatment groups (Figure 5B). In those with normal levels of albuminuria at baseline, no events occurred in the insulin-glargine or the 0.75 mg dulaglutide groups, whereas two events occurred in the 1.5 mg dulaglutide group (Figure 5C). Comparable results were observed for the albuminuria subgroups with eGFR-cystatin C (Table 2).

Discussion

In this exploratory analysis of AWARD-7, patients receiving glucose-lowering therapy with 1.5 mg dulaglutide weekly, compared with insulin-glargine treatment, had reduced risk of ≥40% eGFR decline or ESKD over 1 year. These data suggest the prior observations of slowing eGFR decline in the group treated with 1.5 mg dulaglutide may extend to reducing the risk for clinical event outcomes in participants with T2DM and moderate-to-severe CKD (10). This finding predominated in those with macroalbuminuria, the group that measurably lost eGFR over the 1-year time frame of the study. The potential effect of dulaglutide to reduce the risk of ≥40% eGFR decline or ESKD is particularly noteworthy because the study participants had advanced CKD, a group for whom interventions to prevent progression are lacking.

In participants with T2DM and normal kidney function, previous analyses showed that treatment with dulaglutide was associated with decreased onset of albuminuria (14). These findings are consistent with early GLP-1 RA studies (15–17), and results from subsequent studies of GLP-1 RAs in the cardiovascular outcomes trials, which also had a preponderance of participants with normal kidney function or primarily early stage CKD (6–9,18,19). These cardiovascular outcomes trials showed that treatment of participants with T2DM at high cardiovascular risk was associated with decreased risk for CKD outcomes, primarily driven by reduced onset of macroalbuminuria. However, in these studies, only about 20% of participants had an eGFR of <60 ml/min per 1.73 m², and glycemic control was better in the GLP-1 RA intervention group (7,8,18). Better glycemic control could have contributed to the observed albuminuria findings, and the small proportion of participants with CKD is a major limitation for evaluation of eGFR decline. In the Researching Cardiovascular Events with a Weekly Incretin in Diabetes (REWIND) trial, treatment with dulaglutide was associated with a reduced risk for ≥40% eGFR decline of about a third (19). In a secondary analysis from the Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results (LEADER) trial, treatment with liraglutide was also associated with slowing eGFR decline in a subgroup of participants with an eGFR of between 30 and 59 ml/min per 1.73 m² (9). However, in the AWARD-7 study conducted in participants with T2DM and moderate-to-severe CKD, once-weekly treatment with dulaglutide was associated with significantly slower decline in eGFR, compared with treatment with insulin glargine, at similar levels of glycemic control and BP (10). The FLOW study (NCT03819153) in participants with T2DM and moderate-to-severe CKD is now prospectively testing the effect of semaglutide on clinical event outcomes for CKD in a phase-3 clinical trial.

AWARD-7 had a unique design because of the active comparator arm (insulin glargine), and because of the attainment of similar glycemic control in participants with T2DM and moderate-to-severe CKD in all treatment groups, thus eliminating a potential contribution of differences in glycemic control to effects on kidney function. Notably, nearly half of the participants had macroalbuminuria and almost a third had an eGFR of <30 ml/min per 1.73 m² (10). This analysis showed that 1-year treatment with 1.5 mg dulaglutide weekly was associated with a significant reduction of the risk for ≥40% eGFR decline or ESKD, compared with insulin glargine overall. However, most events occurred in the subgroup with macroalbuminuria. A high event rate was expected because these participants started with a lower baseline eGFR, and macroalbuminuria forecasts more rapid eGFR decline. As such, prevention of ≥40% eGFR decline and ESKD events was most evident among participants with macroalbuminuria, who had a 75% risk reduction, suggesting a potentially pronounced effect of dulaglutide to delay progression in participants with advanced CKD. Many outcome events were ESKD, which was not unexpected due to the number of participants with a baseline eGFR of <30 ml/min per 1.73 m². Event rates for ≥40% eGFR decline were also reduced in the group.
Table 2. Risk for development of composite of ≥40% eGFR decline or ESKD events by baseline albuminuria status

<table>
<thead>
<tr>
<th></th>
<th>≥40% eGFR Decline by eGFR-Creatinine, eGFR-Cystatin C, or ESKD Events</th>
<th>1.5 mg Dulaglutide (N=192)</th>
<th>0.75 mg Dulaglutide (N=190)</th>
<th>Insulin Glargine (N=194)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N (%) HR (95% CI)</td>
<td>n/N (%) HR (95% CI)</td>
<td>n/N (%) HR (95% CI)</td>
<td>n/N (%) HR (95% CI)</td>
</tr>
<tr>
<td><strong>Overall population</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>eGFR-creatinine</td>
<td>10/192 (5) 0.45 (0.20 to 0.97)*</td>
<td>16/190 (8) 0.79 (0.41 to 1.51)</td>
<td>21/194 (11)</td>
<td></td>
</tr>
<tr>
<td>eGFR-cystatin C</td>
<td>11/192 (6) 0.49 (0.23 to 1.04)</td>
<td>15/190 (8) 0.73 (0.38 to 1.42)</td>
<td>21/194 (11)</td>
<td></td>
</tr>
<tr>
<td><strong>Normoalbuminuria (UACR, &lt;30 mg/g)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>eGFR-creatinine</td>
<td>2/34 (6) NA</td>
<td>0/44 NA</td>
<td>0/48 NA</td>
<td></td>
</tr>
<tr>
<td>eGFR-cystatin C</td>
<td>3/34 (9) NA</td>
<td>0/44 NA</td>
<td>1/48 (2)</td>
<td></td>
</tr>
<tr>
<td><strong>Microalbuminuria (UACR, 30–300 mg/g)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>eGFR-creatinine</td>
<td>2/74 (3) 1.59 (0.14 to 17.48)</td>
<td>2/61 (3) 1.96 (0.18 to 21.66)</td>
<td>1/56 (2)</td>
<td></td>
</tr>
<tr>
<td>eGFR-cystatin C</td>
<td>2/74 (3) 1.59 (0.14 to 17.48)</td>
<td>2/61 (3) 1.96 (0.18 to 21.66)</td>
<td>1/56 (2)</td>
<td></td>
</tr>
<tr>
<td><strong>Macroalbuminuria (UACR, &gt;300 mg/g)</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>eGFR-creatinine</td>
<td>6/84 (7) 0.25 (0.10 to 0.68)*</td>
<td>14/84 (17) 0.72 (0.36 to 1.43)</td>
<td>20/90 (22)</td>
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<tr>
<td>eGFR-cystatin C</td>
<td>6/84 (7) 0.26 (0.10 to 0.71)*</td>
<td>13/84 (16) 0.70 (0.34 to 1.41)</td>
<td>19/90 (21)</td>
<td></td>
</tr>
</tbody>
</table>

eGFR-creatinine, eGFR determined using the Chronic Kidney Disease Epidemiology Collaboration Creatinine Equation; eGFR-cystatin C, eGFR determined using the Chronic Kidney Disease Epidemiology Collaboration Cystatin C Equation; n, number of participants with events; N, total number of participants; HR, hazard ratio relative to insulin glargine; UACR, urinary albumin-creatinine ratio; NA, not applicable.

*Statistically significant versus insulin glargine (P<0.05).
treated with 1.5 mg dulaglutide weekly compared with the insulin-glargine group. As such, these observations on clinical event outcomes align with the previous findings of slower eGFR decline in participants with macroalbuminuria treated with dulaglutide. The strengths of this exploratory analysis include the evaluation of ≥40% eGFR decline and ESKD event outcomes in an understudied population with T2DM and moderate-to-severe CKD, and the general consistency between the eGFR-creatinine and eGFR–cystatin C results by central laboratory measurements, which support that these results are not affected by body weight loss (12). It is relevant that the reduction in ≥40% eGFR–cystatin C decline events narrowly missed statistical significance due to one more event in the 1.5 mg dulaglutide group compared with eGFR-creatinine. Notably, the results in the macroalbuminuria subgroup were consistent for ≥40% eGFR decline events using both creatinine (HR, 0.25; 95% CI, 0.10 to 0.68) and cystatin C (HR, 0.26; 95% CI, 0.10 to 0.71). Also, the AWARD-7 study was limited to a 1-year treatment duration and was not powered to evaluate clinical event outcomes.

Therefore, the study did not have adequate opportunity to fully assess treatment effects, such as those that may occur in participants without macroalbuminuria. Although the ESKD events were not adjudicated and were based on investigator-reported events, adjudication would not likely change the results, as investigators typically report these events accurately (20).

In conclusion, this exploratory analysis from AWARD-7 found potentially meaningful benefits of 1.5 mg dulaglutide weekly compared with insulin glargine daily on clinical event outcomes for participants with T2DM and moderate-to-severe CKD. The reduced risk of ≥40% eGFR decline or ESKD was observed primarily in participants with macroalbuminuria, suggesting a possible beneficial effect of dulaglutide among patients with advanced CKD.

Disclosures
B. Rayner received honoraria from AstraZeneca, Boehringer Ingelheim, Merck, Novartis, Sanofi, and Servier, and served on advisory boards for AstraZeneca and Servier. F.T. Botros, M. Konig, A.Y.M. Kwan, M.C. Lakshmanan, and L. Shurzinske are employees of AstraZeneca and Boehringer Ingelheim.

Figure 3. | Proportion of all study participants with composite outcome of (A) ≥40% eGFR decline or ESKD and (B and C, respectively) the individual components at 52 weeks. Data are presented as percentage of participants with eGFR decline ≥40% from baseline at 52 weeks, or participants reaching ESKD at 52 weeks. ESKD events were determined on the basis of investigator report. n, number of participants in the specified treatment arm reaching the measured outcome; N, total number of participants in the specified treatment arm.

![Figure 3](image)

Figure 4. | Time to first event for the composite outcome of ≥40% eGFR decline or ESKD in participants with baseline macroalbuminuria.

![Figure 4](image)
Figure 5. | Proportion of participants with composite outcome of ≥40% eGFR decline or ESKD by albuminuria status. (A) Proportion of participants with the composite kidney outcome in participants with baseline normoalbuminuria. Composite outcome included proportion of participants experiencing ≥40% eGFR decline or ESKD. ESKD events were determined on the basis of investigator report. Data are presented as percentage of participants experiencing composite outcome through 52 weeks. n, number of participants in the specified treatment arm reaching the measured outcome; N, total number of participants in the specified treatment arm.

and shareholders of Eli Lilly and Company. K.R. Tuttle is a consultant for AstraZeneca, Boehringer Ingelheim, Eli Lilly and Company, Gilead, and Goldfinch Bio.

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Author Contributions
F.T. Botros was responsible for project administration, is the guarantor of this work and, as such, takes responsibility for the integrity of the data and the accuracy of the data analysis; F.T. Botros, M. Konig, M.C. Lakshmanan, and K.R. Tuttle conceptualized the study; F.T. Botros, L. Shurzinske, and K.R. Tuttle were responsible for resources; and all authors contributed to the analysis and interpretation of data, wrote the original draft, and reviewed and edited the manuscript.

Supplemental Material
This article contains the following supplemental material online at http://kidney360.asnjournals.org/lookup/suppl/doi:10.34067/KID.K3602020000585/DCSupplemental.

Supplemental Table 1. Untransformed change from baseline in eGFR (CKD-EPI creatinine equation and cystatin C equation) by macroalbuminuria status at baseline (ml/min per 1.73 m²).

References


Received: September 29, 2020 Accepted: December 7, 2020
Table S1. Untransformed change from baseline in eGFR (CKD-EPI creatinine equation and cystatin C equation) by macroalbuminuria status at baseline (mL/min/1.73m²)

<table>
<thead>
<tr>
<th></th>
<th>Overall Study Population</th>
<th>Macroalbuminuria</th>
<th>No Macroalbuminuria</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>DU 1.5 mg (N=192)</td>
<td>DU 0.75 mg (N=190)</td>
<td>Insulin Glargine (N=194)</td>
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<td>eGFR (CKD-EPI Creatinine), mL/min/1.73m²</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Baseline</td>
<td>38.1±13.2</td>
<td>38.3±12.3</td>
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<tr>
<td>Change from baseline</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Week 26</td>
<td>-0.1 (-1.2, 1.0)&quot;</td>
<td>-0.4 (-1.4, 0.7)&quot;</td>
<td>-1.9 (-3.0, -0.9)**</td>
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<tr>
<td>Week 52</td>
<td>-1.1 (-2.4, 0.2)&quot;</td>
<td>-1.5 (-2.8, -0.2)*</td>
<td>-2.9 (-4.2, -1.6)**</td>
</tr>
<tr>
<td>eGFR (CKD-EPI Cystatin C), mL/min/1.73m²</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>37.3 ± 14.2</td>
<td>37.7 ± 13.7</td>
<td>38.3 ± 14.8</td>
</tr>
</tbody>
</table>
Some of these data have been published previously.10

Data presented as least-squares mean (95% CI) for change from baseline at Week 26 and 52; safety population, MMRM analysis of untransformed data. *Baseline values presented as mean ± SD. †P<0.05 change from baseline; ‡P<0.01 change from baseline; §P<0.05 for comparison with insulin glargine; ¶P<0.01 for comparison with insulin glargine.

Abbreviations: CKD EPI = Chronic Kidney Disease-Epidemiology; DU = dulaglutide; eGFR = estimated glomerular filtration rate; N = total number of participants; SD = standard deviation.
Table S1. Untransformed change from baseline in eGFR (CKD-EPI creatinine equation and cystatin C equation) by macroalbuminuria status at baseline (mL/min/1.73m²)

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<td></td>
</tr>
<tr>
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<td>-0.4 (-1.4, 0.7)**</td>
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</tr>
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<td>Week 52</td>
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<td>-1.5 (-2.8, -0.2)**</td>
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<td>eGFR (CKD-EPI Cystatin C), mL/min/1.73m²</td>
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<td>38.3 ± 14.8</td>
</tr>
</tbody>
</table>
### Change from baseline

<table>
<thead>
<tr>
<th>Week 26</th>
<th>0.8 (-0.7, 2.3)</th>
<th>1.1 (-0.4, 2.5)</th>
<th>-3.0 (-4.4, -1.5)</th>
<th>0.1 (-2.2, 2.3)</th>
<th>0.9 (-1.3, 3.1)</th>
<th>-4.0 (-6.1, -1.8)</th>
<th>0.6 (-1.3, 2.6)</th>
<th>0.6 (-1.4, 2.5)</th>
<th>-2.6 (-4.5, -0.6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 52</td>
<td>-0.7 (-2.5, 1.0)</td>
<td>-0.7 (-2.4, 1.1)</td>
<td>-3.3 (-5.1, -1.6)</td>
<td>-0.5 (-3.6, 2.7)</td>
<td>-0.7 (-3.8, 2.4)</td>
<td>-5.5 (-8.5, -2.5)</td>
<td>-1.6 (-3.7, -0.5)</td>
<td>-1.4 (-3.5, 0.7)</td>
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Some of these data have been published previously.\(^{10}\)

Data presented as least-squares mean (95% CI) for change from baseline at Week 26 and 52; safety population, MMRM analysis of untransformed data. *Baseline values presented as mean ± SD. *\(^P<0.05\) change from baseline; **\(^P<0.01\) change from baseline; #\(^P<0.05\) for comparison with insulin glargine; ##\(^P<0.01\) for comparison with insulin glargine.

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