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Effects of Dapagliflozin in Patients with Membranous Nephropathy

Glenn M. Chertow[a] Hiddo Lambers Heerspink[b, c] Patrick B. Mark[d, e] Jamie P. Dwyer[f] Michal Nowicki[g] David C. Wheeler[h] Ricardo Correa-Rotter[i] Peter Rossing[j, k] Robert D. Toto[l] Anna Maria Langkilde[m] Niels Jongs[b]

[a]Departments of Medicine, Epidemiology and Population Health, and Health Policy, Stanford University School of Medicine, Stanford, CA, USA; [b]Department of Clinical Pharmacy and Pharmacology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands; [c]The George Institute for Global Health, UNSW Sydney, Sydney, NSW, Australia; [d]School of Cardiovascular and Metabolic Health, University of Glasgow, Glasgow, UK; [e]Renal and Transplant Unit, Queen Elizabeth University Hospital, Glasgow, UK; [f]Division of Nephrology and Hypertension, University of Utah, Salt Lake City, UT, USA; [g]Department of Nephrology, Hypertension and Kidney Transplantation, Central University Hospital, Medical University of Lodz, Lodz, Poland; [h]Department of Renal Medicine, University College London, London, UK; [i]The National Medical Science and Nutrition Institute Salvador Zubiran, Mexico City, Mexico; [j]Steno Diabetes Center Copenhagen, Herlev, Denmark; [k]Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark; [l]Department of Internal Medicine, UT Southwestern Medical Center, Dallas, TX, USA; [m]BioPharmaceuticals R&D, AstraZeneca, Gothenburg, Sweden

Keywords

Chronic kidney disease · Dapagliflozin · Estimated glomerular filtration rate · Membranous nephropathy · Sodium-glucose cotransporter 2 inhibitor

Abstract

Introduction: Despite the provision of renin-angiotensin-aldosterone-system inhibitors and immunosuppressive therapies, membranous nephropathy often progresses to end-stage kidney disease (ESKD). The objective of this pre-specified analysis was to assess the safety and efficacy of dapagliflozin in patients with membranous nephropathy enrolled in the DAPA-CKD trial. ***Methods:*** Patients with an estimated glomerular filtration rate (eGFR) of 25–75 mL/min/1.73 m^2 and urinary albumin-to-creatinine ratio (UACR) 200–5,000 mg/g were randomized to dapagliflozin 10 mg once daily or placebo, along with standard-of-care and followed for median 2.4 years. The primary endpoint was a composite of ≥50% sustained decline in eGFR, ESKD, or kidney or cardiovascular death. Exploratory efficacy endpoints included eGFR slope and UACR. ***Results:*** Among DAPA-CKD participants with membranous nephropathy, 19 were randomized to dapagliflozin and 24 to placebo. The mean (SD) age was 59.9 ± 12.1 years, the mean eGFR was 45.7 ± 12.1 mL/min/1.73 m^2, and the median UACR was 1,694.5 (25%, 75% range 891–2,582.5) mg/g. Two of 19 (11%) patients randomized to dapagliflozin and five of 24 (21%) randomized to placebo experienced the primary composite endpoint. Total and chronic mean eGFR slopes for dapagliflozin and placebo were −3.87 and −4.29 and −2.66 and −4.22 mL/min/1.73 m^2/year, respectively; corresponding between-group mean differences were 0.42 and 1.57 mL/min/1.73 m^2/year. Dapagliflozin reduced geometric mean (SEM) UACR relative

karger@karger.com
www.karger.com/gdz

Correspondence to:
Glenn M. Chertow, gchertow@stanford.edu

to placebo (−29.3% ± 1.2% vs. −3.6% ± 1.1%; between-group mean difference [95% CI] −26.7 [−50.4, 8.3]). Four (21%) patients randomized to dapagliflozin and seven (29%) randomized to placebo experienced a serious adverse event. ***Conclusion:*** In membranous nephropathy, the effects of dapagliflozin on kidney disease progression and albuminuria were generally favorable; there was insufficient power to justify formal inference testing.

Introduction

Membranous nephropathy is among the most severe forms of glomerular disease and the most common form of nephrotic syndrome in adults worldwide. Despite the provision of renin-angiotensin-aldosterone-system (RAAS) inhibitors and a variety of immunosuppressive therapies, membranous nephropathy often progresses to end-stage kidney disease (ESKD). Classic teaching suggests that up to one-third of patients experience spontaneous remission, approximately one-third progress to ESKD, and the remaining roughly one-third of patients variably experience complications of nephrotic syndrome and/or impaired kidney function [1]. Most studies of membranous nephropathy have focused on the safety and efficacy of a variety of immunosuppressive regimens aimed at inducing remission of nephrotic syndrome. Initial studies suggested that high-dose glucocorticoids might be effective [2]; however, subsequent studies definitively refuted that contention. Ponticelli et al. [3–5] developed a cyclic regimen alternating monthly infusions of the alkylating agent chlorambucil and high-dose glucocorticoids and demonstrated a marked improvement in remission rates relative to glucocorticoids alone. Alternative approaches using cyclophosphamide rather than chlorambucil, calcineurin inhibitors, or rituximab, with or without glucocorticoids, have also been tested in trials of induction therapy of modest sample size [6–12].

Relatively few trials of non-immunosuppressive therapies aiming to slow the progression of membranous nephropathy have been conducted; those that have been completed and whose results have been published were small in number and short in duration. Nevertheless, angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) have been considered standard-of-care and incorporated into published clinical practice guidelines [13].

The Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) trial showed that in patients with chronic kidney disease (CKD), with and without type 2 diabetes, the sodium-glucose cotransporter 2 (SGLT2) inhibitor dapagliflozin reduced risks of CKD progression, hospitalized heart failure or cardiovascular death, and all-cause mortality [14]. In the current report, we evaluate the effects of dapagliflozin on the decline in kidney function and degree of albuminuria in patients with membranous nephropathy.

Methods

DAPA-CKD was a randomized, double-blind, placebo-controlled, multicentre clinical trial; manuscripts describing the trial design [15], baseline characteristics [16], primary results [14], and results stratified by diabetes status [17], history of cardiovascular disease [18], and several other baseline clinical characteristics have been previously published [19–24]. The trial was conducted at 386 sites in 21 countries from February 2017 to June 2020 and registered at clinicaltrials.gov (NCT03036150). All participants provided written informed consent before any study-specific procedure commenced. The safety of participants in the trial was overseen by an independent Data Monitoring Committee. The trial was conducted according to the principles of the Declaration of Helsinki. Ethics committees at all participating centers approved the protocol.

Participants

Adults with CKD, with or without type 2 diabetes, and with an estimated glomerular filtration rate (eGFR) of 25–75 mL/min/1.73 m^2 and urinary albumin-to-creatinine ratio (UACR) 200–5,000 mg/g were eligible for participation. We required participants to be treated with a stable maximally tolerated dose of a RAAS inhibitor (ACE inhibitor or ARB) for ≥4 weeks unless medically contraindicated. Key exclusion criteria included documented diagnosis of type 1 diabetes, polycystic kidney disease, lupus nephritis, or anti-neutrophil cytoplasmic antibody-associated vasculitis. Noteworthy for the current analysis was a specific exclusion of patients receiving cytotoxic therapy, immunosuppressive therapy, or other immunotherapy for primary or secondary kidney disease – including membranous nephropathy – within 6 months of enrollment. Any more remote history of immunosuppressive therapy was unknown. A complete list of inclusion and exclusion criteria and the trial protocol have been previously published [14, 15].

Procedures

Participants were randomly assigned to dapagliflozin 10 mg daily or matching placebo, in accordance with the sequestered, fixed-randomization schedule, with the use of balanced blocks to ensure an approximate 1:1 ratio of the two regimens. Randomization was stratified by diabetes status and UACR (≤ or >1,000 mg/g). We calculated eGFR using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) [25] equation and incorporated results from the equation as originally defined, including a term for self-reported race (black vs. non-black). Recruitment of patients with eGFR 60–75 mL/min/1.73 m^2 was limited to no more than 10% of trial participants. Participants and all study personnel (except the Independent Data Monitoring Committee) were

masked to treatment allocation. After randomization, in-person study visits were performed at 2 weeks; at 2, 4, and 8 months; and at 4-month intervals thereafter. At each follow-up visit, study personnel recorded vital signs, obtained blood and urine samples, and recorded information on potential study endpoints, adverse events, concomitant therapies, and study drug adherence.

Endpoints

The primary composite endpoint was time to ≥50% sustained decline in eGFR (confirmed by a second serum creatinine measurement after at least 28 days), onset of ESKD (defined as maintenance dialysis for at least 28 days, kidney transplantation, or eGFR <15 mL/min/1.73 m^2, confirmed by a second measurement after at least 28 days), or death from a kidney or cardiovascular cause. Secondary endpoints were time to a: (1) composite kidney endpoint of ≥50% sustained decline in eGFR, ESKD or death from kidney disease; (2) composite cardiovascular endpoint defined as hospitalization for heart failure or cardiovascular death; and (3) death from any cause. We also prespecified change in eGFR slope and UACR as exploratory efficacy endpoints. All events were adjudicated by a masked, independent Clinical Events Adjudication Committee; quantitative assessments of eGFR were obtained from our central laboratory.

Statistical Analysis

The overall analytic approach, power calculation, and prespecified statistical analysis plan have been previously published [14, 15]. All analyses presented here followed the intention-to-treat principle. We did not expect to have sufficient power to identify any treatment-related change in the proportion of, or time to, the primary composite or secondary endpoints. Thus, we considered changes in eGFR slope and albuminuria as primary efficacy outcomes of interest. We analyzed the effects of dapagliflozin on the mean on-treatment eGFR slope by fitting a two-slope mixed effects linear spline model (with a knot at week 2) with a random intercept and random slopes for treatment. The model included fixed effects for treatment, baseline eGFR, stratification factors (diabetes status and UACR) and a continuous, fixed covariate for time to visit, assuming an unstructured variance-covariance matrix. We computed the mean total slope as a weighted combination of the acute and chronic slopes to reflect the mean rate of eGFR change until the last on-treatment visit. We also presented the pattern of change in mean eGFR using a restricted maximum likelihood repeated measures approach. This analysis included the fixed, categorical effects of treatment, visit and treatment-by-visit interaction as well as the continuous, fixed covariates of baseline eGFR and baseline eGFR-by-visit interaction. The same repeated measures approach was used to fit the change in UACR over time. Owing to the small sample size, we present results for descriptive purposes without inference testing. We performed all analyses with R version 4.0.2 (R Foundation).

Results

Baseline Characteristics

The current analysis included 43 patients with membranous nephropathy reported as the cause of kidney disease by the investigator, of whom 10 had concomitant type 2 diabetes; in 38 (88.4%), the diagnosis of membranous nephropathy was confirmed by kidney biopsy. Of the 43 patients with membranous nephropathy, 19 were randomized to dapagliflozin and 24 to placebo. Patients assigned to dapagliflozin or placebo had similar baseline characteristics (Table 1). Overall, mean age was 59.9 ± 12.1 years; 11 (26%) were women and 10 (47%) were non-white. Mean eGFR was 45.7 ± 12.1 mL/min/1.73 m^2 and median UACR 1,694.5 (25%, 75% range 891–2,582.5) mg/g. Relative to the trial population, the mean eGFR was slightly higher and the median UACR was substantially higher [14].

Effects of Dapagliflozin on the Primary Composite and Secondary Endpoints

The median follow-up for the assessed population was 26.5 months. Two of 19 (11%) patients randomized to dapagliflozin (one with ≥50% eGFR decline and one who required maintenance dialysis) and five of 24 (21%) patients randomized to placebo (four with ≥50% eGFR decline and one with eGFR <15 mL/min/1.73 m^2) experienced the primary composite endpoint (shown in Fig. 1a); the same number of participants experienced the secondary composite kidney endpoint. One patient in each group experienced the secondary composite cardiovascular endpoint; 1 patient randomized to dapagliflozin and 2 patients randomized to placebo died during follow-up.

Effects of Dapagliflozin on eGFR Slope

Between baseline and week 2, patients with membranous nephropathy randomized to dapagliflozin experienced a larger mean acute reduction in eGFR compared to those randomized to placebo (−3.15 ± 1.46 vs. −0.33 ± 1.29 mL/min/1.73 m^2). Thereafter, mean annual rates of eGFR decline with dapagliflozin and placebo were −2.66 ± 1.36 and −4.22 ± 1.21 mL/min/1.73 m^2 per year, respectively. The total slope, which combines the acute slope and chronic slope, was −3.87 ± 1.38 and −4.29 ± 1.23 mL/min/1.73 m^2 per year in the dapagliflozin and placebo groups, respectively (shown in Fig. 1b).

Effects of Dapagliflozin on UACR

At baseline, median UACR (25%, 75% range) in the dapagliflozin and placebo groups was 1,609 (844.2–2,283.5) and 1,730 (1,049.6–2,681.1) mg/g, respectively. Over the course of the trial, the mean (SEM) change from baseline was −29.3% ± 1.2% in the dapagliflozin group and −3.6% ± 1.1% in the placebo group. Figure 1c shows UACR levels in the current population throughout the trial.

Table 1. Baseline characteristics of patients with membranous nephropathy (n = 43)

Characteristic	Dapagliflozin (n = 19)	Placebo (n = 24)	Total (n = 43)
Age, years, mean (SD)	61.5 (10.8)	58.5 (13.0)	59.9 (12.1)
Sex (female), n (%)	6 (31.6)	5 (20.8)	11 (25.6)
Race and ethnicity, n (%)			
White	9 (47.4)	14 (58.3)	23 (53.5)
Asian	8 (42.1)	8 (33.3)	16 (37.2)
Others	2 (10.5)	2 (8.3)	4 (9.3)
Weight, kg, mean (SD)	75 (18.0)	84 (18.0)	80 (18.3)
BMI, kg/m^2, mean (SD)	26.2 (4.9)	30.6 (6.6)	28.7 (6.2)
Current smoker, n (%)	4 (21.1)	6 (25.0)	10 (23.3)
Systolic blood pressure, mm Hg, mean (SD)	137.3 (17.3)	128.7 (14.5)	132.5 (16.2)
Diastolic blood pressure, mm Hg, mean (SD)	81.9 (10.6)	73.5 (9.7)	77.2 (10.9)
HbA1c, %, mean (SD)	5.8 (0.7)	6.2 (1.1)	6.0 (1.0)
eGFR, mL/min/1.73 m^2, mean (SD)	46.9 (11.4)	44.8 (12.8)	45.7 (12.1)
Hemoglobin, g/L, mean (SD)	127.1 (17.1)[a]	133.2 (11.9)	130.6 (14.5)[b]
Potassium, mmol/L, mean (SD)	4.6 (0.6)	4.6 (0.5)	4.6 (0.5)
UACR, mg/g, median (25%, 75% range)	1,609.0 (844.2, 2,283.5)	1,730.0 (1,049.6, 2,681.1)	1,694.5 (891.0, 2,582.5)
Type 2 diabetes (yes), n (%)	3 (15.8)	7 (29.2)	10 (23.3)
Heart failure (yes), n (%)	0 (0)	1 (4.2)	1 (2.3)
ACE inhibitor (yes), n (%)	6 (31.6)	5 (20.8)	11 (25.6)
ARB (yes), n (%)	14 (73.7)	19 (79.2)	33 (76.7)
Diuretics (yes), n (%)	7 (36.8)	13 (54.2)	20 (46.5)
Statins (yes), n (%)	14 (73.7)	15 (62.5)	29 (67.4)

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; UACR, urinary albumin-to-creatinine ratio. [a]n = 18. [b]n = 42.

Safety of Dapagliflozin in Patients with Membranous Nephropathy

Four (21%) patients randomized to dapagliflozin and seven (29%) randomized to placebo experienced a serious adverse event. Reasons for SAE in patients randomized to dapagliflozin included: worsening glomerulonephritis (n = 1); pyelonephritis (n = 1); sepsis, lactic acidosis, and ESKD (n = 1); and benign intraductal papillary neoplasm (n = 1). Reasons for SAE in patients randomized to placebo included: chest pain (n = 1); skin neoplasm (not specified as benign or malignant) (n = 1); worsening nephrotic syndrome and gangrene (n = 1); ESKD (n = 1); stroke and seizure (n = 1); stroke and death (n = 1); and lung cancer with fever and neutropenia (n = 1).

Discussion

The DAPA-CKD study assessed the effect of dapagliflozin in patients with CKD due to several underlying aetiologies, all of whom exhibited at least a modest degree of albuminuria; 97% of participants were treated with RAAS inhibitors at baseline. Investigator-reported causes of CKD were collected at the time of participant enrollment. After patients with IgA nephropathy (n = 270) and focal segmental glomerulosclerosis (n = 115), those with membranous nephropathy comprised the third largest group with a diagnosed glomerular disease other than diabetic nephropathy [16]. In this prespecified analysis, we demonstrate that among participants with membranous nephropathy, dapagliflozin appeared to attenuate the eGFR slope and reduce proteinuria.

Dozens of clinical trials conducted over the past half-century have compared alternative therapies aiming to induce remission of nephrotic syndrome and, ultimately, to preserve kidney function and prevent ESKD in patients with membranous nephropathy. Commonly employed regimens have included high-dose glucocorticoids, alternating monthly doses of alkylating agents (chlorambucil or cyclophosphamide) and high-dose glucocorticoids, calcineurin inhibitors with or without glucocorticoids, and more recently, rituximab with or without other agents [13]. The Kidney Disease Improving Global Outcomes (KDIGO) 2021 Clinical Practice Guideline for Glomerular Diseases considered cyclophosphamide + glucocorticoids as optimal therapy for

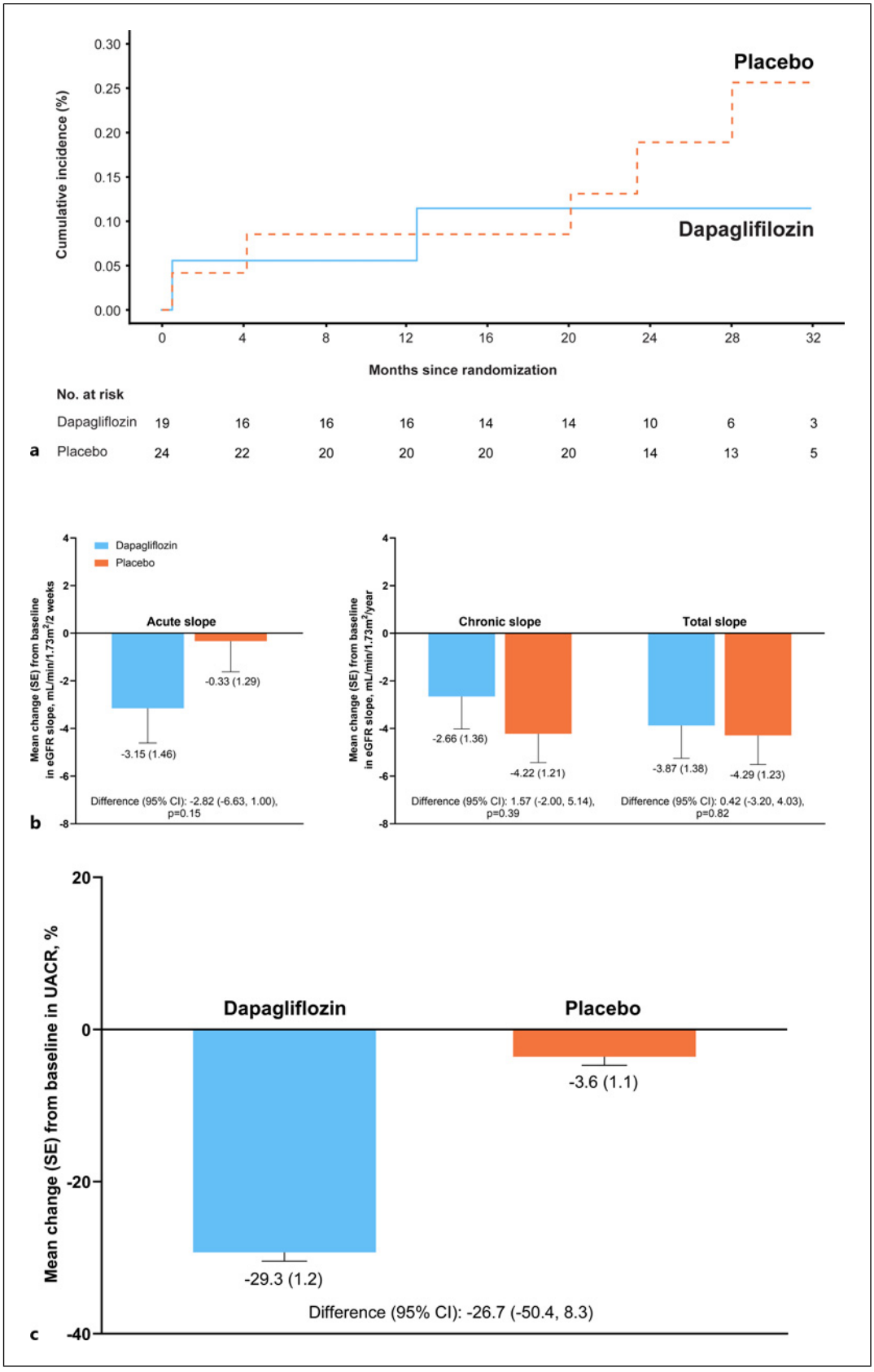

Fig. 1. a Cumulative incidence of the primary composite endpoint. **b** Mean ± SE for acute change in eGFR (baseline to 2 weeks), and total and chronic eGFR slopes (integrated over the study period) in patients with membranous nephropathy. **c** Mean ± SE for UACR (integrated over the study period) in patients with membranous nephropathy.

patients at very high risk of kidney disease progression, and the same regimen or rituximab ± calcineurin inhibitors for patients at high risk of kidney disease [26]. Complete or partial remission of nephrotic syndrome has generally been the principal goal of induction therapy with immunosuppressive agents.

Fewer studies have examined the role of maintenance therapies for membranous nephropathy. ACE inhibitors or ARBs are considered standard-of-care [27], despite limited evidence and an attenuated response relative to the proteinuria-reducing effects of these agents in diabetic kidney disease and other glomerular diseases. Gansevoort et al. [28] studied the proteinuria-reducing effects of non-steroidal anti-inflammatory drugs (n = 28) and ACE inhibitors (n = 14) relative to controls (n = 14). Over 18 months of follow-up, ACE inhibitors (relative to control antihypertensive agents) yielded larger absolute and relative reductions in 24-h protein excretion (9.8 ± 1.4 g to 3.9 ± 0.7 g vs. 6.9 ± 0.8 g to 5.5 ± 0.8 g). Ruggenenti et al. [29] treated 14 patients with persistent high-grade proteinuria (24-h protein excretion ≥3 g for at least 6 months) with enalapril 2.5–20 mg daily for 2 months and showed a modest reduction in 24-h protein excretion (7.1 ± 4.9 g to 5.0 ± 2.9 g). In the Ramipril Efficacy in Nephropathy trial [30], 352 patients with non-diabetic CKD and baseline 24-h protein excretion ≥1 g at baseline were randomized to ramipril 10 mg daily or placebo. Overall, 166 patients (78 randomized to ramipril and 88 randomized to placebo) had baseline protein excretion of ≥3 g per day. Randomization was unblinded at the time of the second interim analysis owing to significantly lower rates of decline in kidney function (measured by plasma clearance of iohexol) in patients with high-grade proteinuria randomized to ramipril compared with placebo (0.53 vs. 0.88 mL/min per month, corresponding to 6.4 vs. 10.6 mL/min/year, p = 0.03). Lower rates of kidney function decline were observed in patients with the most pronounced early reductions in proteinuria. Data for patients with membranous nephropathy were not reported separately. It is noteworthy that in a contemporary time-matched cohort of patients from Kaiser Permanente Northern California with primary nephrotic syndrome, diagnosed with either minimal change disease, focal segmental glomerulosclerosis or membranous nephropathy, fewer than one-third of patients were treated with ACE inhibitors (25.2%) or ARB (7.4%), despite a high proportion of patients with hypertension at baseline (40.6%) and high rates of progression to ESKD [31]. A similarly low proportion of patients (29%) with membranous nephropathy enrolled in the Cure Glomerulopathy (CureGN) cohort were receiving ACE inhibitors or ARBs at the time of cohort entry [32].

Our findings have clinical implications for the management of patients with membranous nephropathy who share clinical characteristics of DAPA-CKD trial participants and who are already on RAAS inhibitors. Although the number of patients was insufficient to demonstrate a significant reduction in the primary composite or secondary kidney composite endpoints or to definitively show attenuation of eGFR slope or reduction in albuminuria, all results numerically favored patients randomized to dapagliflozin. Additional "real world" data or pooled data from other randomized trials of SGLT2 inhibitors in non-diabetic kidney disease will be necessary to complement the data available here.

Dapagliflozin was well tolerated in patients with membranous nephropathy, confirming its established safety profile in diabetic kidney disease and other types of non-diabetic glomerular disease, including IgA nephropathy and focal segmental glomerulosclerosis. Clinicians should be reassured by the fact that there were no cases of diabetic ketoacidosis or hypoglycemia in participants with membranous nephropathy receiving dapagliflozin and that there was no increase in the occurrence of other serious adverse events relative to placebo.

There are several limitations to these analyses. The DAPA-CKD study was not specifically designed to test any hypotheses in patients with membranous nephropathy or other less common kidney diseases, and the modest sample size limited the precision of estimates of treatment effects on study endpoints. However, the analyses presented herein were planned for in the original study design, without knowing a priori how many participants with membranous nephropathy or other specific glomerular diseases would ultimately be enrolled. We lacked data on serum anti-antiphospholipase A2 antibody titers, which may be used by clinicians to guide diagnostic and therapeutic strategies in membranous nephropathy [26]. Finally, and perhaps most importantly, we restricted the eGFR (25–75 mL/min/1.73 m^2) and UACR (200–5,000 mg/g) ranges at study screening; thus, we were unable to assess the effect of dapagliflozin in: (1) patients with membranous nephropathy and higher-grade proteinuria (UACR >5,000 mg/g); (2) patients with UACR 200–5,000 mg/g with normal or near normal kidney function, a sizeable fraction of whom experience progression to ESKD; or (3) patients with more advanced CKD (eGFR <25 mL/min/1.73 m^2).

In summary, among patients with membranous nephropathy without overt nephrotic syndrome or

requiring high-potency immunosuppression, the effects of dapagliflozin on kidney disease progression and albuminuria were generally favorable; there was insufficient power to justify formal inference testing. While dapagliflozin appeared safe, owing to the small sample size and wide confidence limits, efficacy results should be considered hypothesis-generating.

Acknowledgments

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Statement of Ethics

All participants provided written informed consent before any study-specific procedure commenced. The safety of participants in the trial was overseen by an independent Data Monitoring Committee. The trial was conducted according to the principles of the Declaration of Helsinki. Ethics committees at all participating centers approved the protocol. The trial protocol was approved by a central or local ethics committee at each trial site. Full details and the associated protocol were published with the primary manuscript [14].

Conflict of Interest Statement

G.M.C. served on the Executive Committee of the DAPA-CKD trial. He has served on the Board of Directors of Satellite Healthcare, a non-profit dialysis provider. He has served as Chair or Co-Chair of Trial Steering Committees with Akebia, CSL Behring, Sanifit, and Vertex. He has served as an Advisor to Applaud, Ardelyx, Calico, CloudCath, Durect, Eliaz Therapeutics, Miromatrix, Outset, Renibus, and Unicycive. He has served on Data Safety Monitoring Boards with Bayer, Mineralys, and ReCor. H.J.L.H. reported receiving research support from and serving as a consultant for AstraZeneca during the conduct of the study; serving as a consultant for Bayer, Chinook Tx, CSL Behring, Dimerix, Eli Lilly, Fresenius, Gilead, Novartis, and Travere Therapeutics outside the submitted work; receiving grants and research support from Boehringer Ingelheim and Janssen outside the submitted work; and receiving grants and clinical trial study medication from, and serving as a consultant for Novo Nordisk outside the submitted work. P.B.M. reported receiving lecture fees and travel to meetings support from Vifor, AstraZeneca, Pharmacosmos, Napp, Astellas, lecture fees from Novartis, Astellas, GSK and grants from Boehringer Ingelheim outside the submitted work. J.P.D. reported receiving fees from AstraZeneca for the conduct of this study; fees from Sanofi-Aventis and CSL Behring as part of a steering committee; fees from Novo Nordisk for outcome adjudication for a trial; fees from Goldfinch Bio, Birdrock Bio, and Boehringer Ingelheim for study design; personal fees from Bayer. M.N. reported receiving honoraria from Boehringer Ingelheim, Swixx Biopharma, Roche, Sanofi Genzyme and Omeros. D.C.W. reported receiving personal fees from AstraZeneca during the conduct of the study; personal fees from Astellas, Boehringer Ingelheim, Bayer, GlaxoSmithKline, Janssen, Gilead, Merck Sharp and Dohme, George Clinical, Intas, ProKidney, Tricida, Vifor, and Zydus outside the submitted work; and performing guideline development for KDIGO. R.C.-R. reported receiving personal fees from AstraZeneca, during the conduct of the study; personal fees from Boehringer Ingelheim, personal fees from Amgen, personal fees from Janssen, grants from GlaxoSmithKline, grants and personal fees from Novo Nordisk, personal fees from Medtronic, outside the submitted work. P.R. reported receiving grants and other from AstraZeneca, during the conduct of the study; from Novo Nordisk, Gilead, Bayer, Sanofi-Aventis, and Eli Lilly, outside the submitted work. R.D.T.'s contribution to this manuscript was supported in part by endowments from the Mary M. Conroy Professorship in Kidney Diseases and the Houston J and Florence A Dosswell Center for Development of New Approaches for the Treatment of Hypertension. He also reported receiving personal fees from AstraZeneca, during the conduct of the study; personal fees from AstraZeneca, Bayer Pharma, Calliditas, Boehringer Ingelheim, Relypsa, Amgen, and Novartis, outside the submitted work. A.M.L. reported being a full-time employee and shareholder of AstraZeneca during the conduct of the study. N.J. reports travel grants from AstraZeneca.

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Author Contributions

G.M.C., H.J.L.H., D.C.W., P.R., and A.M.L. contributed to the concept and design of the study. G.M.C., H.J.L.H., D.C.W., R.C.R., P.R., and R.D.T. contributed to data acquisition. G.M.C., H.J.L.H., P.B.M., J.P.D., M.N., D.C.W., R.C.R., P.R., R.D.T., A.M.L., and N.J. contributed with analysis and or interpretation of data. N.-J. performed the statistical analysis. G.M.C., H.J.L.H., and N.-J. wrote the first draft of the manuscript. All authors approved the final, submitted version.

Data Availability Statement

Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data sharing policy described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure. Data for studies directly listed on Vivli can be requested through Vivli at www.vivli.org. Data for studies not listed on Vivli could be requested through Vivli at https://vivli.org/members/enquiries-about-studies-not-listed-on-the-vivli-platform/. AstraZeneca Vivli member page is also available outlining further details: https://vivli.org/ourmember/astrazeneca/.

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