Patient-Oriented, Translational Research: Research Article

American Journal of Nephrology

Am J Nephrol 2019;50:333–344
DOI: 10.1159/000503713

Received: September 10, 2019
Accepted: September 25, 2019
Published online: October 25, 2019

Design and Baseline Characteristics of the Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease Trial

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Keywords
Kidney · Mineralocorticoid · Diabetes · Aldosterone · Outcomes · Clinical

Abstract

Background: Among diabetics, those with kidney disease have exceptionally high rates of cardiovascular (CV) morbidity and mortality, and progression of their underlying disease. Finerenone is a novel, non-steroidal, selective mineralocorticoid-receptor antagonist which has shown to reduce albuminuria in type 2 diabetes (T2D) patients with chronic kidney disease (CKD), while revealing only a low risk of hyperkalemia. However, the effect of finerenone on renal and CV outcomes has not been investigated in long-term trials yet. ***Methods:*** The Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease (FIDELIO-DKD) trial aims to assess the efficacy and safety of finerenone compared to placebo at reducing clinically important renal and CV outcomes in T2D patients with CKD. FIDELIO-DKD is a randomized, double-blind, placebo-controlled, parallel-group, event-driven trial running in 47 countries with an expected duration of approximately 5.5 years. FIDELIO-DKD randomized 5,734 patients with an estimated glomerular filtration rate (eGFR) ≥25–<75 mL/min/1.73 m^2 and albuminuria (urinary albumin-to-creatinine ratio ≥30–≤5,000 mg/g). The study has at least 90% power to detect a 20% reduction in the risk of primary outcome (overall two-sided significance level $\alpha = 0.05$), the composite of time to first occurrence of kidney failure, a sustained decrease of eGFR ≥40% from baseline over at least 4 weeks, or renal death. ***Conclusion:*** FIDELIO-DKD will determine whether an

FIDELIO-DKD Phase 3 investigators and site list are included in the online supplementary files

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optimally treated cohort of T2D patients with CKD at high risk of renal and CV events will experience cardiorenal benefits with the addition of finerenone to their treatment regimen.

Background

Worldwide, over 2.5 million people receive renal replacement therapy, and this number is projected to grow and be more than double in 2030 [1]. Type 2 diabetes (T2D) is the most common cause of end-stage renal disease (ESRD) in the Western world, except for Taiwan, which has a higher prevalence of ESRD than the US [2]. Moreover, this trend in ESRD is rapidly increasing in Asia and Latin America [1].

The current pharmacological strategy to reduce the rate of progression of kidney disease is the optimization of blood pressure control, lipid levels, and glycemic control, and has been in place since the 1990s [3]. Following the advent of the angiotensin-receptor blocker (ARB) trials almost 20 years ago [4, 5], the sodium-glucose cotransporter-2 (SGLT2) inhibitor canagliflozin added to a renin – angiotensin system (RAS) blocker recently demonstrated a 34% relative risk reduction of the renal-specific composite endpoint of ESRD, a doubling of creatinine level, or death from renal causes [6]. For many years, T2D patients who have chronic kidney disease (CKD) and albuminuria >300 mg/day have had guideline directives to use angiotensin-converting enzyme inhibitors (ACEIs) or ARBs [7, 8]. From mid-June 2019 onwards, SGLT2 inhibitors have been recommended in addition for patients with T2D with albuminuria >300 mg/g if their estimated glomerular filtration rate (eGFR) is >30 mL/min/1.73 m^2, to reduce cardiovascular (CV) events, with increasing evidence that they may also slow kidney disease progression [9].

While optimizing therapy with RAS blockers and SGLT2 inhibitors has markedly slowed CKD progression, it has not stopped it fully [6, 10]. Despite the use of ACEIs, ARBs, and the concomitant use of SGLT2 inhibitors, the rate of ESRD remains unacceptably high, with more than twice the normal decline in kidney function [6]. Mineralocorticoid receptor antagonists (MRAs) such as spironolactone demonstrate renoprotective effects in preclinical studies [11, 12] and are known to reduce albuminuria and blood pressure in patients with kidney disease, well-documented surrogates of CKD progression in men [13–15]. Thus, antagonism of mineralocorticoid receptor (MR) might be effective in slowing CKD progression in T2D [16–19].

Finerenone is a novel, non-steroidal, selective MRA that has much greater MR selectivity than spironolactone and better MR affinity than eplerenone in vitro [20]. Furthermore, unlike spironolactone and eplerenone, which reach higher concentrations in renal tissue in comparison to cardiac tissue [21], finerenone is distributed relatively equally between the heart and the kidney, at least in rodents [22]. Lastly, its non-steroidal structure allows it to bind to the MR with high affinity and to inhibit recruitment of transcriptional co-activators involved in the expression of hypertrophic and pro-fibrotic genes more effectively than steroidal MRAs [23, 24]. This unique binding mode and lack of other hormonal stimulation compared to spironolactone mitigates against untoward effects like gynecomastia [25, 26].

In a trial involving T2D patients with a clinical diagnosis of CKD (Mineralocorticoid-Receptor Antagonist Tolerability Study-Diabetic Nephropathy), finerenone compared to placebo showed only small mean changes in serum potassium and a low incidence of hyperkalemia leading to a low number of discontinuations with no evidence of a dose – response relationship. Furthermore, finerenone compared to placebo demonstrated a statistically significant reduction in urinary albumin-to-creatinine ratio (UACR) at doses starting from 7.5 mg on top of standard of care (including an ACEI or ARB) after 90 days of treatment [27].

These findings provided the rationale for initiating a large-scale Phase III program with finerenone investigating renal and CV outcomes in T2D patients with all stages of CKD in 2 large-scale outcome trials. In this study, we describe the design of the Finerenone in reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease trial (FIDELIO-DKD; ClinicalTrials.gov identifier: NCT02540993) and present the baseline characteristics of enrolled patients.

Patients and Methods

General Description

FIDELIO-DKD is an international, multicenter, randomized, double-blind, placebo-controlled, parallel-group, event-driven study, formally designed to assess whether finerenone reduces cardiorenal morbidity and mortality in T2D patients with CKD when used in addition to standard of care.

Study Population

The inclusion and exclusion criteria are summarized in Table 1. Patients included in the trial are aged ≥18 years with T2D and a clinical diagnosis of CKD, pre-treated with ACEIs or ARBs for at least 4 weeks before the run-in visit, and had serum potassium ≤4.8 mEq/L at both the run-in and screening visits. Patients had to

Table 1. Inclusion and exclusion criteria

Inclusion criteria	Written informed consent signed before any study-specific procedure
	Men or women aged 18 years and older
	Women of child-bearing potential with a negative pregnancy test and agreeing to use adequate contraception
	Patients with T2D mellitus as defined by the American Diabetes Association
	Patients with a clinical diagnosis of CKD based on either of the following criteria at the run-in and screening visits: –Persistent high albuminuria defined as UACR ≥30 mg/g (≥3.4 mg/mmol) but <300 mg/g (<33.9 mg/mmol) and eGFR ≥25 but <60 mL/min/1.73 m^2 (CKD-EPI) and presence of diabetic retinopathy in the medical history or –Persistent very high albuminuria defined as UACR ≥300 mg/g (≥33.9 mg/mmol) and eGFR ≥25 but <75 mL/min/1.73 m^2 (CKD-EPI)
	Prior treatment with ACEIs and ARBs
	Serum potassium ≤4.8 mmol/L at both the run-in and screening visits
Exclusion criteria	
Medical and surgical history	Known significant non-diabetic renal disease, including clinically relevant renal artery stenosis
	UACR >5,000 mg/g (>565 mg/mmol) at the run-in or screening visit
	Glycosylated hemoglobin >12% (>108 mmol/mol) at the run-in or screening visit
	Uncontrolled arterial hypertension with mean sitting SBP ≥170 mm Hg or mean sitting DBP ≥110 mm Hg at the run-in visit or mean sitting SBP ≥160 mm Hg or mean sitting DBP ≥100 mm Hg at the screening visit
	SBP <90 mm Hg at the run-in or screening visit
	Patients with a clinical diagnosis of chronic heart failure with reduced ejection fraction and persistent symptoms (New York Heart Association class II–IV) at the run–in visit
	Stroke, transient ischemic cerebral attack, acute coronary syndrome, or hospitalization for worsening heart failure, in the 30 days before the screening visit
	Dialysis for acute renal failure in the 12 weeks before the run-in visit
	Renal allograft in place or a scheduled kidney transplant in the 12 months after the run-in visit
	Known hypersensitivity to the study treatment (active substance or excipients)
	Addison's disease
	Hepatic insufficiency classified as Child-Pugh C
Medication and drug use	Concomitant therapy with eplerenone, spironolactone, any renin inhibitor, or potassium-sparing diuretic which cannot be discontinued at least 4 weeks before the screening visit
	Concomitant therapy with both ACEIs and ARBs which cannot be discontinued for the purpose of the studies
	Concomitant therapy with potent cytochrome P450 isoenzyme 3A4 inhibitors or inducers (to be stopped at least 7 days before randomization)
Other	Any other condition or therapy which would make the patient unsuitable for the studies and would not allow participation for the full planned study period (e.g., active malignancy or other condition limiting life expectancy to <12 months)
	Pregnant or breast-feeding or intention to become pregnant during the studies
	Previous assignment to treatment during the studies
	Previous (within 30 days before randomization) or concomitant participation in another clinical study (i.e., Phase I–III clinical studies) with investigational medicinal product, except for participation in the run-in and screening periods of Studies 17,530 and 16,244
	Close affiliation with the investigational site: for example, a close relative of the investigator or dependent person (e.g., employee or student of the investigational site)

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; DKD, diabetic kidney disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure; UACR, urine albumin-to-creatinine ratio; T2D, type 2 diabetes.

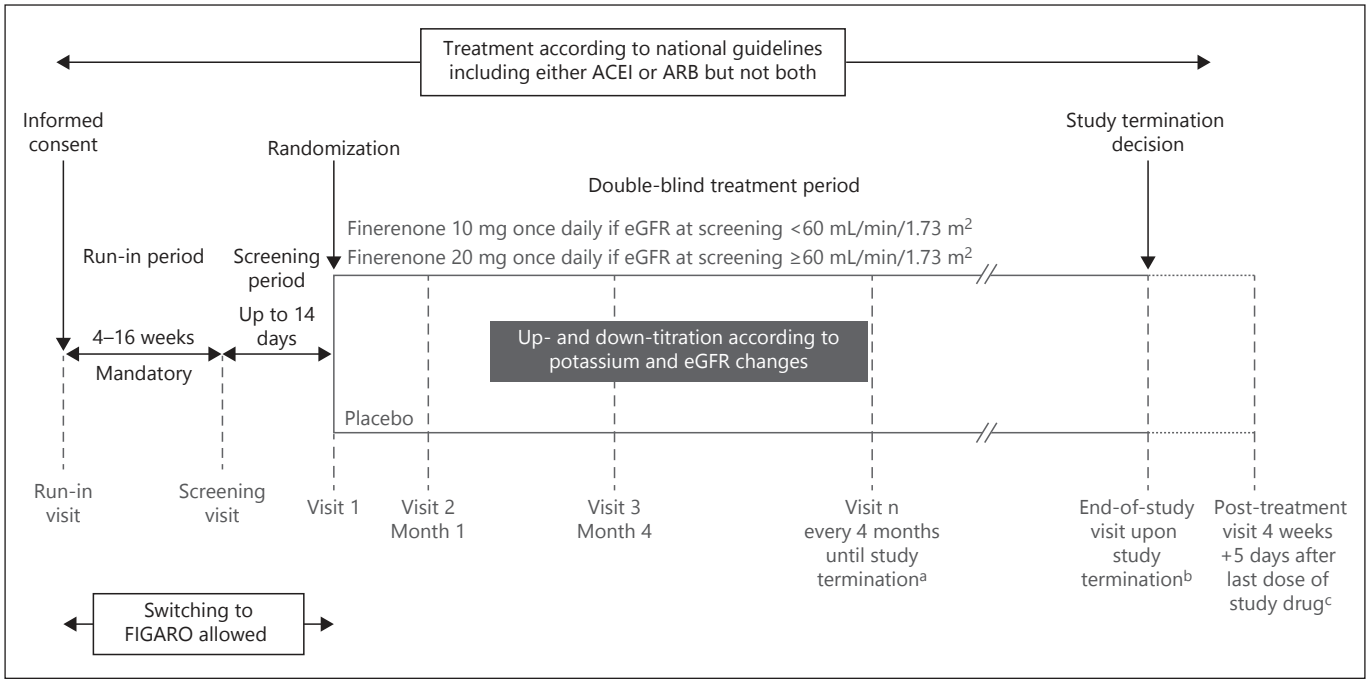

Fig. 1. Study design of FIDELIO-DKD. [a] Scheduled visits will continue even if the study drug treatment is discontinued; [b] End-of-study visit will take place only after the sponsor has officially terminated the study; [c] For all patients who have received the study drug. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; eGFR, estimated glomerular filtration rate; FIGARO, Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease.

have persistent high albuminuria (defined as UACR ≥30 but <300 mg/g), eGFR ≥25 but <60 mL/min/1.73 m^2, and presence of diabetic retinopathy in the medical history, or persistent very high albuminuria (defined as UACR ≥300 mg/g) and eGFR ≥25 but <75 mL/min/1.73 m^2.

Two recruitment caps were pre-specified and closed per region. The first cap limited the randomization of patients with high albuminuria and diabetic retinopathy in the medical history to approximately 10% of all patients randomized. The second cap limited the randomization of patients with very high albuminuria and eGFR 60–75 mL/min/1.73 m^2 to 10% of all patients randomized with very high albuminuria at screening.

Study Design

The study design of FIDELIO-DKD is illustrated in Figure 1. After signing the informed consent, a run-in visit was performed. If the patient met all inclusion criteria and none of the exclusion criteria, a mandatory run-in period that could last between a minimum of 4 and a maximum of 16 weeks started. At the end of the run-in period, a screening visit to confirm the patient's eligibility again took place, with subsequent randomization within 2 weeks.

To account for the high variability of UACR and eGFR, patients were permitted to switch either after the run-in or screening visit between FIDELIO-DKD and the second study of the program, Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease (FIGARO-DKD; ClinicalTrials.gov identifier: NCT02545049), before being randomized. As CKD in T2D is a disease continuum and variations in eGFR and UACR within the boundaries of this disease continuum do not affect the clinical risk, the switching of patients before randomization was deemed justified and necessary to reduce the burden on candidate study participants (run-in and screening assessments were not repeated after switching). A switchover from either trial was permitted only once.

Due to the anticipated recruitment period of >2 years and the progressive nature of the underlying disease, re-screening was permitted once. Conditions for re-screening were amended in 2017 to shorten the re-screening period from 6 to 3 months and to allow re-screening even if the reason for the initial screen failure was an elevated blood potassium value (serum potassium >4.8 mEq/L).

Eligible patients were randomized 1:1 via an interactive telephone/web-based system to receive once-daily treatment with either finerenone or placebo. Treatment assignment was determined by computer-generated random sequence with stratification by region (North America, Latin America, Europe, Asia, Other), eGFR category at screening (25–<45, 45–<60, and ≥60 mL/min/1.73 m^2), and category of albuminuria at screening (high or very high).

The starting dose of study drug was selected based on eGFR measured at the screening visit: patients started on finerenone 10 mg/day or matching placebo if their eGFR was 25–<60 mL/min/1.73 m^2; if their eGFR was ≥60 mL/min/1.73 m^2, the starting dose was 20 mg/day. Up-titration of study drug to 20 mg/day is permitted at any time after Visit 2 (Month 1), down-titration to 10 mg/day at any time after start of treatment. Patients are instructed to take the study drug tablet orally, once daily at approximately the same time every day.

Central laboratory values, including serum potassium and serum creatinine, were obtained at all study visits and used for con-

firmation of patients' eligibility, safety monitoring, renal endpoint reporting, and end-of-study statistical analysis. From Visit 1 onwards, blood potassium and serum creatinine are measured at all on-treatment visits at a local laboratory. The investigators are instructed to use these local values for dose titrations and safety monitoring. Patients' safety is monitored with physical examinations (including measurements of weight and vital signs) and 12-lead electrocardiograms at regular intervals throughout the study. Patients are assessed for adverse events and study endpoints at each visit and are requested to complete health-related quality-of-life questionnaires (EQ-5D-5L and Kidney Disease Quality of Life) at baseline and yearly thereafter.

The study protocol was approved by International Review Boards, independent Ethics Committees, and competent authorities according to national and international regulations. FIDELIO-DKD is conducted in accordance with the ICH Harmonised Tripartite Guideline for Good Clinical Practice. All study participants provided written informed consent before entering the study.

Objectives and Endpoints

The primary endpoint of FIDELIO-DKD is a composite of time to first occurrence of kidney failure, a sustained decrease of eGFR ≥40% from baseline over at least 4 weeks, or renal death. The component kidney failure is defined as either the occurrence of ESRD or eGFR <15 mL/min/1.73 m^2, confirmed by a second measurement at the earliest 4 weeks after the initial measurement. ESRD is defined as the initiation of chronic dialysis (hemo- or peritoneal dialysis) for at least 90 days or renal transplantation. The eGFR threshold of 15 mL/min/1.73 m^2 is consistent with the definition of kidney failure from Kidney Disease: Improving Global Outcomes [28] and was chosen to include an objective component to the endpoint because the decision to initiate dialysis therapy or kidney transplantation may be affected by factors other than eGFR.

The main pre-specified secondary endpoint is a composite of time to first occurrence of CV mortality and morbidity, as measured by the composite endpoint of time to first occurrence of CV death, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for heart failure.

Other secondary endpoints include time to all-cause mortality, time to all-cause hospitalization, change in UACR from baseline to 4 months, and a composite endpoint of time to first occurrence of kidney failure or sustained decrease in eGFR ≥57% from baseline over at least 4 weeks or renal death.

Statistical Considerations

Statistical Analyses

The primary efficacy endpoint for the statistical analysis is the time to first occurrence of the composite of onset of (i) kidney failure, (ii) a sustained decrease of eGFR ≥40% from baseline over at least 4 weeks, or (iii) renal death. Events included in the primary analysis will be counted from the day of randomization onwards until the planned end-of-study visit following the study sponsor's decision to terminate the study. Patients without a primary efficacy endpoint event will be censored at the date of their last contact with complete information on all components of the primary composite endpoint (up to and including the end-of-study visit). In case a non-renal death occurs within 5 months from the last visit (4 monthly visits plus maximum allowed time window of 30 days) and a subsequent clinic visit had been planned, the non-renal death date will be used as the censoring date.

To test for superiority of finerenone over placebo in prolonging the time to the first primary efficacy endpoint event, the null hypothesis of equal hazards in the 2 treatment groups will be evaluated via a log-rank test, stratified by the stratification factors region, eGFR category at screening, and category of albuminuria at screening. The treatment effect will be expressed as a hazard ratio with a corresponding confidence interval from a stratified Cox regression model. The statistical analyses will follow the intention-to-treat principle and will be based primarily on the full analysis set, consisting of all randomized patients considered valid for analysis. An analysis on the per protocol set, excluding patients with relevant deviations from the protocol, will be conducted as a sensitivity analysis in which only events occurring within 30 days after permanent treatment discontinuation will be considered.

To control the multiplicity arising from multiple tests, a weighted Bonferroni-Holm procedure will be used for the primary renal efficacy endpoint and the key secondary CV endpoint, followed by a hierarchical testing procedure of further secondary efficacy endpoints (as in the order given above). The weights assigned to the primary efficacy endpoint and the key secondary endpoint are given as 2/3 and 1/3, resulting in a minimal local two-sided alpha level of 3.3333 and 1.6667%, respectively, which will be increased to 5% for one test if the null hypothesis for the other test can be rejected. The full alpha level of 5% will be passed along hierarchically to the further secondary endpoints in a serial gatekeeping approach, that is, if and only if both the primary endpoint and the key secondary endpoint show significance. Within the hierarchy of the secondary endpoints, the full alpha is forwarded to the next null hypothesis as long as the previous null hypothesis is rejected, otherwise confirmatory testing stops at this point. As described under *Powering and Sample Size*, the actual significance levels used during the final analysis will be slightly adjusted based on the formal interim analysis. The testing strategy is further illustrated in Figure 2. To declare the study successful, it will be considered sufficient to reject the null hypothesis related to the primary renal endpoint or key secondary CV endpoint.

Powering and Sample Size

As an event-driven study, FIDELIO-DKD has a power of 90% to detect a 20% relative risk reduction of finerenone versus placebo in the primary efficacy endpoint (equaling a hazard ratio of 0.8) based on a total of 1,068 patients with primary renal events and applying the log-rank test at a two-sided significance alpha level of 3.3333%. Further assumptions at the planning stage included an annual placebo event rate of 12% (assumed to be unaffected by treatment discontinuations), a common annual lost-to-follow-up rate of 0.7% in both treatment groups, an annual finerenone discontinuation rate of 5%, and a total treatment duration between 44 and 48 months, consisting of a recruitment period of 33 and 41 months with an equal recruitment pattern during the accrual period and a maximum treatment period of the last recruited patient of 11 and 7 months, respectively. Taking the ramp-up time during recruitment into consideration, this leads to an estimated required number of approximately 4,800 patients to be randomized. Assuming a screening failure rate of 50%, 9,600 patients need to be screened. To account for the lower-than-assumed event rates for the primary endpoint as observed during the conduct of the trial, the originally planned number of randomized patients was increased by approximately 1,000 patients.

One formal interim analysis is planned to be conducted when approximately 712 primary efficacy endpoint events (i.e., 2/3 of the

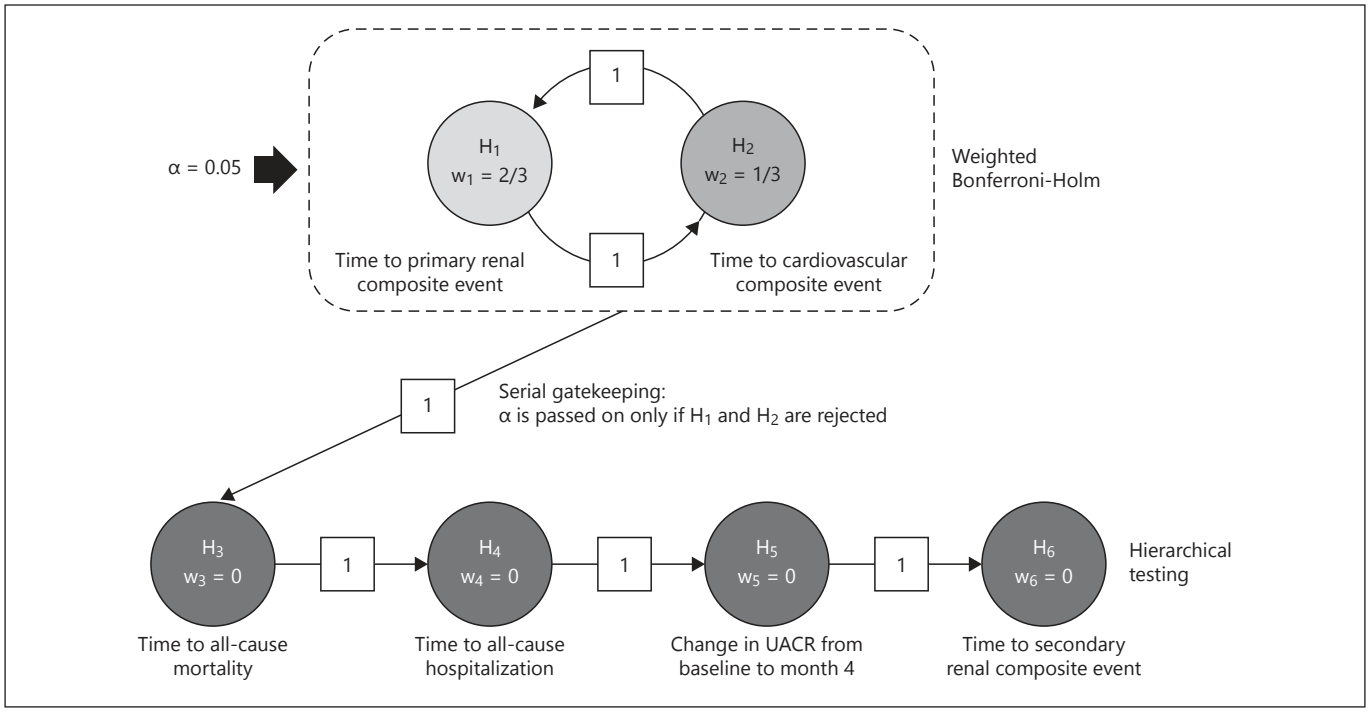

Fig. 2. Statistical testing strategy of primary and secondary efficacy endpoints for FIDELIO-DKD. UACR, urinary albumin-to-creatinine ratio.

finally intended number) have been observed. To guide the decision regarding early stopping of the study for success at the interim analysis, the Haybittle-Peto rule will be used, requiring a two-sided *p* value below 0.00270 for both the null hypotheses corresponding to the primary renal efficacy endpoint and the key secondary CV endpoint to be rejected and leading to a minimal alpha adjustment for the respective tests at the final analysis stage. Additionally, for lack of efficacy, a non-binding futility approach will be used to allow stopping the study at the interim analysis stage if the conditional power of rejecting the null hypothesis related to the primary endpoint at the final stage given the interim data falls to an unacceptably low level of 10% or less.

Additional Statistical Considerations

For analysis, Austria, Belgium, Denmark, Finland, France, Germany, Ireland, Italy, Netherlands, Norway, Portugal, Spain, Sweden, Switzerland, and the United Kingdom are considered in Western Europe; Bulgaria, Czech Republic, Greece, Hungary, Lithuania, Poland, Romania, Russia, Slovakia, Turkey, and Ukraine in Eastern Europe.

Results

Recruitment of patients for FIDELIO-DKD began in September 2015 and was completed in June 2018. A total of 13,911 individuals, including 604 patients who were re-screened, were enrolled at 1,062 sites in 47 countries, resulting in 5,734 randomized patients. During the run-in or screening phase but before randomization, 1,374 patients switched over from FIGARO-DKD. The rate of screening failure in all patients enrolled was 58.8 and 14.9% in patients who switched. Sixty patients in FIDELIO-DKD were excluded from the full analysis set due to substantial Good Clinical Practice violations, resulting in 5,674 patients (99.0%) in whom the primary analysis will be performed.

More than 40% of the patients were recruited in Europe, with a similar number in Western and Eastern Europe, 16.6% in North America, 10.5% in Latin America, 27.8% in Asia, and 3.5% in Australia, New Zealand, and South Africa (region "Other").

The overall trial population is predominately male (70.2%) and white (65.9%), with a mean age of 65.6 years and a mean duration of diabetes of 16.6 years. At baseline, mean glycosylated hemoglobin was 7.7%, mean eGFR 44.3 mL/min/1.73 m^2, mean serum potassium 4.4 mEq/L, and median UACR 851 mg/g. Most patients (88.4%) had eGFR <60 mL/min/1.73 m^2 and 54.9% eGFR <45 mL/min/1.73 m^2; the majority of patients (87.4%) had very high albuminuria at baseline.

At baseline, 3,727 patients (65.7%) were taking ARBs and 1,942 (34.2%) ACEIs, as requested by the protocol, and almost all patients (97.4%) were on glucose-lowering

Table 2. Baseline characteristics

	Total (n = 5,674)
Age, years, mean (SD)	65.6 (9.1)
Gender, male, *n* (%)	3,984 (70.2)
Race, *n* (%)	
White	3,738 (65.9)
Asian	1,434 (25.3)
Black/African American	267 (4.7)
Other[a]	216 (3.8)
Region, *n* (%)	
Europe	2,358 (41.6)
Western Europe	1,251 (22.0)
Eastern Europe	1,107 (19.5)
North America	944 (16.6)
Latin America	593 (10.5)
Asia Pacific	1,579 (27.8)
Other	200 (3.5)
BMI, kg/m^2, mean (SD)	31.1 (6.0)
Duration of diabetes, years, mean (SD)	16.6 (8.8)
Systolic blood pressure, mm Hg, mean (SD)	138 (14)
Diastolic blood pressure, mm Hg, mean (SD)	76 (10)
Heart rate, beats/min, mean (SD)	72 (11)
eGFR (CKD-EPI), mL/min/1.73 m^2, mean (SD)	44.3 (12.6)
eGFR (CKD-EPI), mL/min/1.73 m^2, *n* (%)	
≥60	656 (11.6)
45 to <60	1,900 (33.5)
25 to <45	2,981 (52.5)
<25	135 (2.4)
Median UACR, mg/g (25th–75th percentile)	851 (446–1,634)
UACR category, mg/g, *n* (%)	
<30	25 (0.4)
30 to <300	685 (12.1)
≥300	4,960 (87.4)
Serum potassium, mEq/L, mean (SD)	4.4 (0.5)
HbA1c, %, mean (SD)	7.7 (1.3)
ACEIs, *n* (%)	1,942 (34.2)
ARBs, *n* (%)	3,727 (65.7)
Beta-blockers, *n* (%)	2,963 (52.2)
Diuretics, *n* (%)	3,210 (56.6)
Loop diuretics	1,618 (28.5)
Thiazide diuretics	1,356 (23.9)
Calcium antagonists, *n* (%)	3,585 (63.2)
Statins, *n* (%)	4,213 (74.3)
Platelet aggregation inhibitors, *n* (%)	3,222 (56.8)
Glucose-lowering therapies, *n* (%)	5,526 (97.4)
Insulin	3,636 (64.1)
Metformin	2,486 (43.8)
Acarbose	323 (5.7)
Sulfonylurea	1,329 (23.4)
DPP-4 inhibitors	1,521 (26.8)
GLP-1 agonists	395 (7.0)
SGLT2 inhibitors	258 (4.5)
Arterial hypertension, *n* (%)	5,501 (97.0)
Diabetic retinopathy, *n* (%)	2,657 (46.8)
Diabetic neuropathy, *n* (%)	1,448 (25.5)
Lipid metabolism disorders, *n* (%)	2,546 (44.9)
History of CV disease, *n* (%)	2,602 (45.9)
Coronary artery disease	1,693 (29.8)
Peripheral arterial disease	920 (16.2)
Myocardial infarction	765 (13.5)
Ischemic stroke	685 (12.1)
Carotid endarterectomy	71 (1.3)
Heart failure, *n* (%)	423 (7.5)

[a] American Indian/Alaska Native, Native Hawaiian/other Pacific Islander or multiple entries.

BMI, body mass index; eGFR, estimated glomerular filtration rate; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; UACR, urine albumin-to-creatinine ratio; HbA1c, hemoglobin A1c; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide 1; SGLT2, sodium-glucose cotransporter-2; CV, cardiovascular.

medication. Approximately 2/3 (64.1%) were using insulin, while metformin was the most frequently used glucose-lowering oral drug at baseline. Glucagon-like peptide 1 agonists were used by 7.0% of patients, while 4.5% were using SGLT2 inhibitors.

At baseline, nearly all patients (97.0%) had arterial hypertension as concomitant disease, and 46.8% had diabetic retinopathy. Less than half (45.9%) had CV disease (CVD) in the medical history: 29.8% had coronary artery disease, 13.5% myocardial infarction, 12.1% ischemic stroke, 16.2% peripheral artery disease, and 1.3% had a carotid endarterectomy. Only 7.5% of all patients suffered from heart failure at baseline, which is related to the protocol-requested exclusion of all patients with heart failure with reduced ejection fraction with New York Heart Association class II–IV at run-in and screening. Further information about the baseline characteristics can be found in Table 2 and in online supplementary Table S1 (see www.karger.com/doi/10.1159/000503713).

Discussion

Treatment of CKD in general has evolved over the last few decades, resulting in a slowing of progression of kidney disease from 10 to 12 mL/min/year to approximately 2 mL/min/year in patients with an eGFR <60 mL/min/1.73 m^2, normal decline being around 0.7–0.9 mL/min/year

[10]. Newer treatments to help glycemic control have also translated into further slowing of CKD progression (eGFR decline of 1.85 mL/min/year) as well as further reduction of CV events in T2D patients [6, 29]. However, despite this promising progress T2D patients with CKD still exhibit residual cardiorenal morbidity and mortality.

Since 2001, numerous trials assessing various agents with a variety of mechanisms have failed to slow CKD progression over RAS blockers. Attempts were made to reduce the high CV and renal risk in patients already taking RAS inhibitor monotherapy by adding a second RAS blocker: in the Veterans Affairs Nephropathy in Diabetes trial, an ACEI in combination with an ARB [30], and in the Aliskiren Trial in T2D using Cardiorenal Endpoints, the combination of an ARB with the renin inhibitor aliskiren were investigated [31]. Dual RAS blockade increased the frequency of serious adverse events such as acute kidney injury, hyperkalemia, or stroke, and therefore cannot be recommended in T2D patients with CKD.

More recently, the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation study investigating canagliflozin in patients with T2D and CKD with very high albuminuria found a 30% risk reduction for progression to ESRD, doubling of serum creatinine, or CV or renal death over placebo in patients already receiving RAS blockers [6]. In a meta-analysis by Zelniker et al. [32], the effect of SGLT2 inhibitors on major adverse CV events (i.e., myocardial infarction, stroke, or CV death) and renal outcomes was analyzed. SGLT2 inhibitors reduced major adverse CV events by 11%, with benefit seen only in patients with atherosclerotic CVD (14% risk reduction) and not in those without. SGLT2 inhibitors reduced the risk of CV death or hospitalization for heart failure by 23%, with a similar benefit in patients with and without atherosclerotic CVD and with and without a history of heart failure. The magnitude of benefit of SGLT2 inhibitors varied with baseline renal function and showed a lesser reduction in progression of renal disease in patients with more severe kidney disease at baseline.

The use of SGLT2 inhibitors was very low in general when FIDELIO-DKD started recruitment in September 2015. Despite not restricting the use of SGLT2 inhibitors in enrolled patients, it was even lower in the targeted study population, since the initiation of treatment with SGLT2 inhibitors in patients with eGFR <60 mL/min/1.73 m^2 was prohibited, and it was recommended to stop treatment with SGLT2 inhibitors in patients with eGFR persistently <45 mL/min/1.73 m^2. At baseline, 4.5% of all randomized patients were treated with SGLT2 inhibitors. During the trial, the use of SGLT2 increased slightly but is still low (<10% of patients). Most likely the data collected will not be sufficient for a meaningful subgroup analysis. However, in previous trials treatment with an MRA has never been investigated on top of a RAS blocker in this group of non-heart failure patients and hence the results of FIDELIO-DKD will be able to generate hypotheses for further investigations.

Inflammation and fibrosis mediated by MR overactivation are also observed in the kidney [33]. The resulting glomerular podocyte injury and mesangial cell proliferation may manifest as glomerular injury, renal vasoconstriction, and albuminuria. Targeting MR overactivation with MRAs, based on the studies conducted so far, showed a sustained reduction in albuminuria of ≥30%, a biomarker that has now been validated as surrogate for slowing CKD progression [13, 34, 35]. It is therefore reasonable to assume that MR blockade, if safe, may offer additional benefit when added to monotherapy with a RAS blocker by attenuating aldosterone breakthrough, and through inhibition of deleterious effects of aldosterone, such as renal inflammation and fibrosis.

The currently available steroidal MRAs, spironolactone and eplerenone, have been investigated in clinical studies that varied between 4 and 52 weeks in duration and assessed the effects on albuminuria in different CKD populations. However, to date, all studies are plagued with hyperkalemia as a major complication of this class. In a recent meta-analysis, Yang et al. [36] concluded that treatment with spironolactone in patients with moderate to severe (stage 3–4) CKD was associated with a lower risk of ESRD (relative risk 34%) but was complicated by a higher risk of hyperkalemia-associated hospitalization (3 times greater risk). They concluded that the renoprotective benefit of spironolactone may be offset by the hyperkalemia risk. In another clinical study of heart failure patients, Trevisan et al. [37] concluded that in an unselected cohort of new users of MRAs, hyperkalemia was very common and frequently followed by therapy interruption, especially among participants with CKD. As a result, the median time on MRA treatment during the initial 12 months of treatment was 179 days (130–346 days), with 24% of remaining patients on therapy after 12 months. Participants with CKD were at highest risk of hyperkalemia and discontinuation. In an investigation analyzing electronic medical records of a diverse US population, Collins et al. [38] found that serum potassium elevation even above 5 mEq/L was associated with an increase in CV risk. Hyperkalemia requiring dose reduction or even discontinuation of a RAS inhibitor may also have

a negative impact on the prognosis in T2D patients with CKD or heart failure [38].

Hyperkalemia is a disabler of renal function-preserving medications. In a post hoc analysis from the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan study, Miao et al. [39] demonstrated that patients who achieved mean serum potassium ≥5 mEq/L during follow-up had a 43% higher risk of the composite endpoint of doubling of serum creatinine or ESRD after controlling for potential confounders. They concluded that treatment with losartan is associated with a high risk of elevated serum potassium levels in patients with diabetes mellitus and nephropathy. These elevated serum potassium levels are in turn associated with an increased risk of renal progression and offset the renoprotective effects of losartan. Given that the major risk factors for hyperkalemia are eGFR <45 mL/min/1.73 m^2 or serum potassium >4.5 mEq/L on diuretics [40], it is clear that those with CKD in T2D patients will be at highest risk, so we restricted recruitment to patients with potassium levels up to 4.8 mEq/L.

Finerenone is a novel, non-steroidal, selective MRA that is associated with lower rates of hyperkalemia compared to steroidal MRAs [41]. In the Mineralocorticoid-Receptor Antagonist Tolerability Study-Diabetic Nephropathy Study, finerenone induced a dose-dependent reduction of UACR, with the largest placebo-corrected reduction (–38%) in the group being treated with 20 mg once daily. Finerenone dosages over 90 days of treatment resulted in small declines in eGFR (~2–4 mL/min/1.73 m^2) and blood pressure (3–5 mm Hg) as well as small changes in serum potassium (+0.2 mEq/L) [27].

FIDELIO-DKD is the largest renal study recruited to specifically investigate the progression of kidney disease in T2D patients with CKD. While the primary focus is on renal outcomes, potential benefits on CV events will be assessed as well. Unlike previous outcome trials where the levels of albuminuria and kidney function were advanced into stages 3 and 4, FIDELIO-DKD has also included a cohort of patients with lower levels of albuminuria (high albuminuria defined as UACR ≥30 but <300 mg/g) and stage 2 CKD (eGFR 60–75 mL/min/1.73 m^2). FIDELIO-DKD is part of a larger Phase III program that consists of 2 large-scale, event-driven outcome trials, FIDELIO-DKD and FIGARO-DKD, an event-driven trial investigating the cardiorenal effects of finerenone in T2D patients with less advanced kidney disease. Complemented by the results of FIGARO-DKD where even T2D patients with stage 2 CKD with high and very high albuminuria and stage 1 CKD patients with very high albuminuria are included, the program will allow evaluation of the effects of finerenone in the broadest spectrum of CKD patients with T2D ever investigated. Finerenone was developed neither as an antihypertensive agent nor as a glucose-lowering drug being repurposed for a population with kidney impairment. Instead, it was designed to alleviate disease burden in patients with cardiorenal diseases, especially in T2D patients.

The results of FIDELIO-DKD will determine whether an optimally treated cohort of T2D patients with CKD at high risk of progression of their renal disease and CV events will experience cardiorenal benefits with the addition of finerenone to their treatment regimen. Results are expected in 2020.

Acknowledgements

The authors express their sincere appreciation to all involved colleagues in the study centers for their participation in this trial. The authors would like to acknowledge all the patients who are participating in this trial. The authors thank the study coordinators Stefania Collamati (Bayer SpA, Milan, Italy), Michelle King, Laurence West, Angela May (all Bayer PLC, Reading, UK), Anna Lindroth (Bayer AB, Solna, Sweden), Cecilia Fedorov (PRA Health Sciences, Bayer Inc., Mississauga, Canada), Lydia Christopher (SLS Services, Bayer PLC, Reading, UK), GoUne You (Bayer Korea Ltd., Seoul, South Korea), Dirk Alta (Bayer B.V., Mijdrecht, The Netherlands), data managers Jeannette Gerstner, Jacobus Buytendach (Bayer AG, Berlin, Germany), and Martin Gregory (PRA Health Sciences, Bayer AG, Berlin, Germany), and Statistical Analysts Cosima Klein, Aziz Tuemer and Dominik Habel (all Bayer AG, Berlin, Germany). Special thanks to Meike Brinker (Bayer AG, Wuppertal, Germany) for her continuous support of the program in different important roles and to UI Yen Morgenthaler (Bayer AG, Berlin, Germany) for her continuous Medical Writing support.

Statement of Ethics

The study protocol was approved by International Review Boards, independent Ethics Committees, and competent authorities according to national and international regulations. FIDELIO-DKD is conducted in accordance with the ICH Harmonised Tripartite Guideline for Good Clinical Practice. All participants provided written, informed consent before entering the study.

Disclosure Statement

G.L.B. reports research funding, paid to the University of Chicago Medicine, from Bayer, Janssen, and Vascular Dynamics; he acted as a consultant for Merck, Vascular Dynamics, Relypsa, Boehringer Ingelheim, Sanofi, Pfizer, Novo Nordisk, Ionis, and AstraZeneca; is an editor of American Journal of Nephrology, Nephrology, and Hypertension, and section editor of UpToDate; and is an associate editor of Diabetes Care and Hypertension Research.

R.A. is a member of data safety monitoring committees for AstraZeneca and Ironwood Pharmaceuticals; a member of steering committees of randomized trials for Akebia, Bayer, Janssen, GlaxoSmithKline, Relypsa, and Sanofi and Genzyme US Companies; a member of adjudication committees for Bayer, Boehringer Ingelheim, and Janssen; and a member of a scientific advisory board or a consultant for Bird Rock Bio, Celgene, Daiichi Sankyo, Inc., Eli Lilly, Relypsa, Reata, Takeda Pharmaceuticals, USA, and ZS Pharma; he has served as associate editor of the American Journal of Nephrology and Nephrology Dialysis and Transplantation and has been an author for UpToDate; and he has received research grants from the U.S. Veterans Administration and the National Institutes of Health. S.D.A. has received research support from Abbott Vascular and Vifor International, and personal fees from Boehringer Ingelheim, Bayer, AstraZeneca, Novartis, Vifor International, Impulse Dynamics, Respicardia, and St. Jude Medical. B.P. reports consultant fees for Bayer, AstraZeneca, Sanofi, scPharmaceuticals, SQ Innovation, G3 Pharmaceuticals, Sarfez, Vifor, Cereno, Ardelyx, KBP Biosciences and Windtree Pharmaceuticals; he has stock options for KBP Biosciences, SQ Innovation, Sarfez, scPharmaceuticals, Cereno and G3 Pharmaceuticals, and Relypsa; he also holds a patent for site-specific delivery of eplerenone to the myocardium (US patent #9931412). L.M.R. has served as advisor/speaker for AstraZeneca, Bayer, Daiichi Sankyo, Medtronic, Novartis, and Recordati. C.N., P.K., and P.S. are full-time employees of Bayer AG, Division Pharmaceuticals, Germany. A.C.F. is a full-time employee of Bayer S.A., Brazil. G.F. reported that he is a committee member of trials and registries sponsored by Bayer, Novartis, Servier, Vifor, Medtronic, and Boehringer Ingelheim.

Funding Sources

FIDELIO-DKD is a research study conducted and funded by Bayer AG.

Author Contributions

The sponsor designed the study in conjunction with the Executive Committee (EC). G.L.B. wrote the first draft of the paper, had full access to the study design information, and had final responsibility for the decision to submit for publication. All authors provided input for the preparation of subsequent drafts and approved the final version for submission. Technical editorial assistance was provided by Lynda Chang, PhD, of McCann Health, and was funded by Bayer AG. All authors reviewed and approved the manuscript.

Appendix

Program Management and Committees

FIDELIO-DKD is a research study conducted and funded by Bayer AG. The study protocol was written by the sponsor in close collaboration with the members of the EC.

The EC supervised the conduct of the program, supported the protocol development, and provided ongoing scientific guidance. The members of the EC are G.L.B., G.F., B.P., and L.M.R., as well as R.A. (Chairman of the Renal Clinical Event Committee) and S.D.A. (Chairman of the Cardiovascular Clinical Event Committee). A steering committee including the EC members, worldwide country lead investigators, and additional content experts is responsible for scientific guidance and local implementation of the protocols. The authors are responsible for drafting and editing this design and baseline paper and its content.

Data Monitoring Committee

Periodic assessments of safety and efficacy are performed in FIDELIO-DKD by an independent Data Monitoring Committee, which also oversees the safety and efficacy in FIGARO-DKD. One interim analysis for overwhelming efficacy in terms of reducing the primary renal efficacy endpoint as well as the main secondary CV endpoint was pre-specified to occur after accrual of 67% of the planned primary renal efficacy endpoints. Members of the independent Data Monitoring Committee are Murray Epstein (Chair), Aldo P. Maggioni (Chair), Glenn M. Chertow, Gerald DiBona, Jean Rouleau, Jose Lopez-Sendon, and Tim Friede (Statistician).

Central Clinical Event Committee

All potential outcome events are independently reviewed and adjudicated by a Clinical Event Committee, which consists of 3 sub-committees (cardiac, renal, and neuro). All potential outcome events are randomly distributed to 2 members of the appropriate sub-committee. If there is disagreement between the 2 initial reviewers, the event will be distributed to a third reviewer. If the third reviewer does not agree with either of the first 2 reviewers, the event will be reviewed at a panel meeting to reach a decision.

Members of the Renal Clinical Event Committee are R.A. (Chair), Pantelis Sarafidis, Alan Jardine, Phyllis August, Sankar Navaneethan, and Titte Srinivas; members of the Cardiac Clinical Event Committee are S.D.A. (Chair), Andrew Coats, Piotr Ponikowski, John Teerlink, Barry Greenberg, James Januzzi, Stephan von Haehling, and Wolfram Doehner; members of the Neuro Clinical Event Committee are Wolfram Doehner (Chair), Turgut Tatlisumak, Lauren Phillips, Carlos Kase, and Hans Diener.

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