Efficacy of finerenone in primary cardiovascular prevention: A mechanistic analysis using the AHA PREVENT™ risk score

Ashish Verma,[1] Rajiv Agarwal,[2] Stefan D. Anker,[3] Sophie E. Claudel,[1] Bertram Pitt,[4] Peter Rossing,[5,6] Luis M. Ruilope,[7,8] Anand Vaidya,[9] Sushrut S. Waikar,[1] Insa M. Schmidt,[1,10] Sonia Gomez,[11] Margarida Seco,[12] Zihe Zheng,[13] Gerasimos Filippatos,[14] for the FIDELIO-DKD and FIGARO-DKD Investigators

[1]Department of Medicine, Section of Nephrology, Boston Medical Center, and Boston University Chobanian & Avedisian School of Medicine, Boston, MA, USA; [2]Indiana University School of Medicine, and Richard L. Roudebush VA Medical Center, Indianapolis, IN, USA; [3]Department of Cardiology (CVK) of German Heart Center Charité, German Centre for Cardiovascular Research (DZHK) partner site Berlin, Charité Universitätsmedizin, Berlin, Germany; [4]Department of Medicine, University of Michigan School of Medicine, Ann Arbor, MI, USA; [5]Steno Diabetes Center Copenhagen, Copenhagen, Denmark; [6]Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark; [7]Cardiorenal Translational Laboratory and Hypertension Unit, Institute of Research imas12, Madrid, Spain; [8]CIBER-CV, Hospital Universitario 12 de Octubre, Madrid, Spain; [9]Division of Endocrinology, Diabetes, and Metabolism, Mass General Brigham, and Harvard Medical School, Boston, MA, USA; [10]Hamburg Center for Kidney Health (HCKH), III. Department of Medicine, University Medical Center Hamburg-Eppendorf, Hamburg, Germany; [11]Syneos Health LLC (providing service to Bayer), Morrisville, NC, USA; [12]Global Medical Affairs Cardiorenal, Bayer Portugal SA, Lisbon, Portugal; [13]Medical Affairs Cardio-Renal Division, Bayer U.S. LLC, Whippany, NJ, USA; [14]National and Kapodistrian University of Athens, School of Medicine, Department of Cardiology, Attikon University Hospital, Athens, Greece

Corresponding author:
Dr Ashish Verma
Boston Medical Center, Boston, MA 02118, USA
Ashish.Verma@bmc.org

FIDELITY
FInerenone in chronic kiDney diseasE and type 2 diabetes: Combined FIDELIO-DKD and FIGARO-DKD Trial programme analYsis

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- **IMS** and **SG** have nothing to declare.
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Background

Individuals with **T2D** and **CKD** are at a **heightened CV risk** before even experiencing a first CV event. **HF** is a leading **initial manifestation** of this risk[1,2]

Finerenone, a non-steroidal MRA, is recommended for patients with **T2D and CKD** to **reduce CV events** and **CKD progression**[1,3–5]

In the prespecified **FIDELITY** analysis, which pooled data from the phase III FIDELIO-DKD*[,6] and FIGARO-DKD#[,7] trials, **finerenone reduced the risk of CV events in patients with T2D and CKD versus placebo**, even in patients without a history of CVD, and the benefit of finerenone was **primarily attributed to a reduction in HHF**[7]

However, trial results provide an average relative effect. **The extent to which absolute benefit can be predicted from an individual's baseline risk and whether finerenone alters that risk over time remains uncertain**

The **AHA PREVENT™ equations** estimate the **10-year risk of total CVD, ASCVD, and HF in adults without a history of CVD**. These equations are the first to incorporate eGFR, with optional inclusion of UACR and HbA1c, making them well-suited for individuals with T2D and CKD[7,8]

*NCT02540993);#NCT02545049

AHA, American Heart Association; ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate (eGFR); HbA1c, glycated hemoglobin; HF, heart failure; HHF, hospitalization for heart failure; MRA, mineralocorticoid receptor antagonist; PREVENT, Predicting Risk of EVENTs; T2D, type 2 diabetes; UACR, urinary albumin-to-creatinine ratio

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Aims and methods

In this *post hoc* analysis of the FIDELITY pooled dataset,[1] we aimed to determine whether:

1. The relative and absolute effect of finerenone varied based on baseline PREVENT™ total CVD, ASCVD, and HF risk
2. The observed event rates aligned with PREVENT™-predicted rates
3. Finerenone reduced the progression of predicted risk over a 48-month period

Study design and participants

FIDELITY
N=12,990

R 1:1
- Finerenone 10 or 20 mg once daily
- Placebo

Key eligibility criteria

✓
- Adults with CKD and T2D
- Maximum tolerated doses of ACEi/ARB for ≥4 weeks
- Serum [K^+] ≤4.8 mmol/L*

✗
- HFrEF and NYHA Class II–IV
- Uncontrolled arterial hypertension
- HbA1c >12%

For this analysis, only the subset of **patients without a history of CVD** at baseline were included (**n=7050**)

Stratification by PREVENT™ risk scores

Risk scores for CVD (PREVENT-CVD) were calculated at baseline, months 4, 12, 24, 36 and 48, and were calculated separately using both the base models and full models:

- **Base model:** Included age, SBP, total and HDL cholesterol, BMI, diabetes status, tobacco use, the use of lipid-lowering and antihypertensive drugs, and eGFR, with separate algorithms by sex
- **Full model:** Same characteristics as base model with the addition of UACR and HbA1c

Patients were **stratified into tertiles of baseline PREVENT™ risk score** (lower, middle, and upper tertiles) for the base and full models

Outcomes

- **PREVENT-CVD**: time to first occurrence of a non-fatal CV event[#]
- **PREVENT-HF**: time to first HHF event
- **PREVENT-ASCVD**: time to first non-fatal MI or non-fatal stroke

All statistical analyses were exploratory[‡]

*At screening and during run-in; [#]HHF, non-fatal myocardial infarction, or non-fatal stroke; [‡]statistical analyses were exploratory, and no adjustments were made for multiple comparisons. A two-sided p-value <0.05 was considered to indicate statistical significance

ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blocker; ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; CKD, chronic kidney disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; [K^+], potassium concentration; NYHA, New York Heart Association; R, randomization; SBP, systolic blood pressure; T2D, type 2 diabetes; UACR, urinary albumin-to-creatinine ratio

1. Agarwal R, *et al. Eur Heart J* 2022;43:474–484

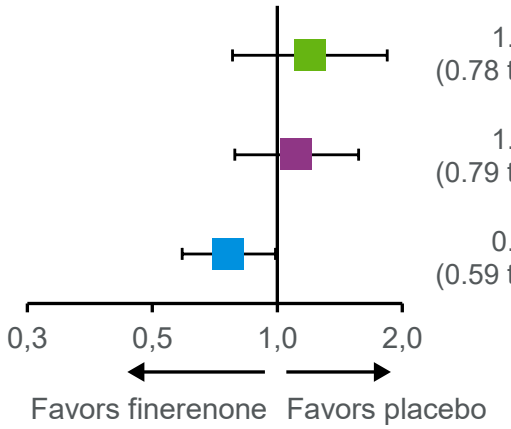
Baseline characteristics by PREVENT-CVD risk score tertile (base model)

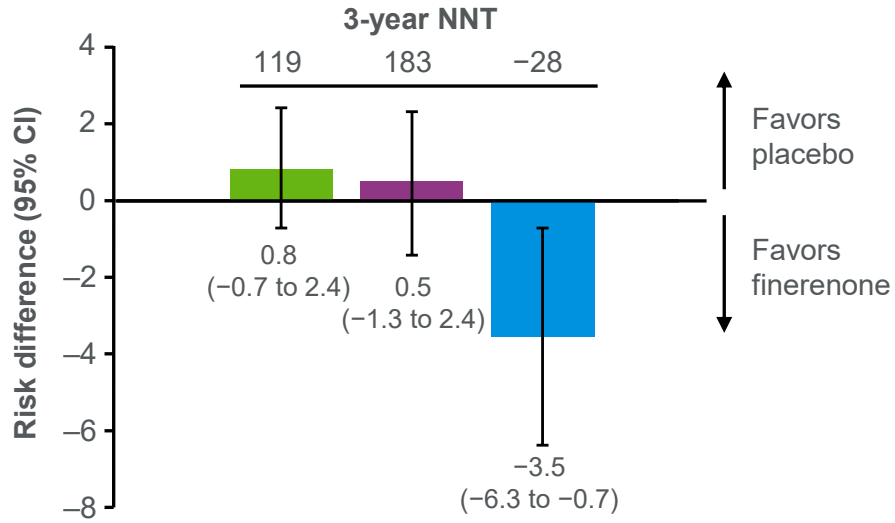
Characteristic	Lower tertile (<14.7%)		Middle tertile (≥14.7%–<23.2%)		Upper tertile(≥23.2%)	
	Finerenone (n=1142)	Placebo (n=1207)	Finerenone (n=1218)	Placebo (n=1133)	Finerenone (n=1159)	Placebo (n=1191)
Age, years, mean (SD)	55.3 (8.1)	55.0 (8.5)	64.4 (7.3)	64.6 (7.3)	69.7 (8.2)	69.6 (8.5)
Female, n (%)	456 (39.9)	453 (37.5)	368 (30.2)	342 (30.2)	382 (33.0)	366 (30.7)
Race, n (%)						
White	655 (57.4)	693 (57.4)	807 (66.3)	731 (64.5)	785 (67.7)	783 (65.7)
Asian	354 (31.0)	361 (29.9)	298 (24.5)	317 (28.0)	245 (21.1)	287 (24.1)
Black or African American	57 (5.0)	65 (5.4)	34 (2.8)	36 (3.2)	47 (4.1)	48 (4.0)
Other*	76 (6.7)	88 (7.3)	79 (6.5)	49 (4.3)	82 (7.1)	73 (6.1)
BMI, kg/m^2, mean (SD)[#]	31.8 (6.6)	31.9 (6.7)	31.5 (6.5)	31.0 (6.1)	31.0 (5.6)	30.9 (5.9)
T2D duration, years, mean (SD)[#]	12.4 (7.4)	12.6 (7.5)	14.7 (8.1)	14.8 (8.4)	16.4 (8.9)	16.3 (9.0)
eGFR, mL/min/1.73 m^2, mean (SD)	76.9 (19.9)	77.5 (19.9)	62.1 (19.0)	61.7 (18.8)	42.9 (14.6)	43.2 (14.9)
UACR, mg/g, median (Q1–Q3)[#]	582 (311–1188)	550 (306–1113)	547 (226–1098)	534 (216–1119)	597 (203–1302)	601 (214–1368)
SBP, mmHg, mean (SD)	131.6 (12.5)	131.4 (12.9)	137.1 (13.2)	137.4 (13.6)	142.2 (14.1)	141.3 (14.0)
Serum potassium, mmol/L, mean (SD)	4.3 (0.4)	4.3 (0.4)	4.3 (0.4)	4.3 (0.4)	4.4 (0.4)	4.4 (0.5)
HbA1c, mean (SD)[#]	7.8 (1.4)	7.8 (1.5)	7.6 (1.4)	7.7 (1.3)	7.7 (1.3)	7.5 (1.3)
HDL ≥40/50 mg/dL for men/women, n (%)	693 (60.7)	762 (63.1)	683 (56.1)	655 (57.8)	527 (45.5)	584 (49.0)
Smoking, n (%)						
Never	666 (58.3)	688 (57.0)	597 (49.0)	521 (46.0)	581 (50.1)	577 (48.4)
Former	325 (28.5)	360 (29.8)	390 (32.0)	398 (35.1)	357 (30.8)	381 (32.0)
Current	151 (13.2)	159 (13.2)	231 (19.0)	214 (18.9)	221 (19.1)	233 (19.6)
Baseline medications, n (%)						
RASi	1140 (99.8)	1207 (100)	1216 (99.8)	1133 (100)	1157 (99.8)	1186 (99.6)
Statins	747 (65.4)	816 (67.6)	789 (64.8)	771 (68.0)	720 (62.1)	730 (61.3)
Diuretics	426 (37.3)	474 (39.3)	578 (47.5)	540 (47.7)	682 (58.8)	699 (58.7)
SGLT-2i	136 (11.9)	127 (10.5)	76 (6.2)	61 (5.4)	31 (2.7)	37 (3.1)
GLP-1 agonists	101 (8.8)	114 (9.4)	107 (8.8)	73 (6.4)	78 (6.7)	65 (5.5)

Baseline characteristics are shown for the base model. In the full PREVENT-CVD model, tertile thresholds were <22.6%,≥22.6%–<33.4%, and ≥33.4% for the lower, middle and upper tertiles, respectively.
In the*Inclusive of American Indian or Alaska Native, Hawaiian or other Pacific Islander, or not reported/multiple; #Measurements missing from ≤12 participants
BMI, body mass index; eGFR, estimated glomerular filtration rate; GLP-1, glucagon-like peptide-1; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; IQR, interquartile range; RASi, renin–angiotensin system inhibitor; SBP, systolic blood pressure; SD, standard deviation; SGLT-2i, sodium-glucose co-transporter-2 inhibitor; T2D, type 2 diabetes; UACR, urinary albumin-to-creatinine ratio

Non-fatal cardiovascular events* by PREVENT-CVD risk score (full model analysis)

Finerenone		Placebo		Hazard ratio (95% CI)	*p*-interaction
Events n/N (%)	IR n/1000 PY	Events n/N (%)	IR n/1000 PY		
45/1152 (3.9)	11.8	39/1197 (3.3)	9.8	1.20 (0.78 to 1.84)	
71/1193 (6.0)	18.7	60/1158 (5.2)	16.4	1.11 (0.79 to 1.57)	0.414
101/1174 (8.6)	31.7	133/1176 (11.3)	42.0	0.76 (0.59 to 0.99)	



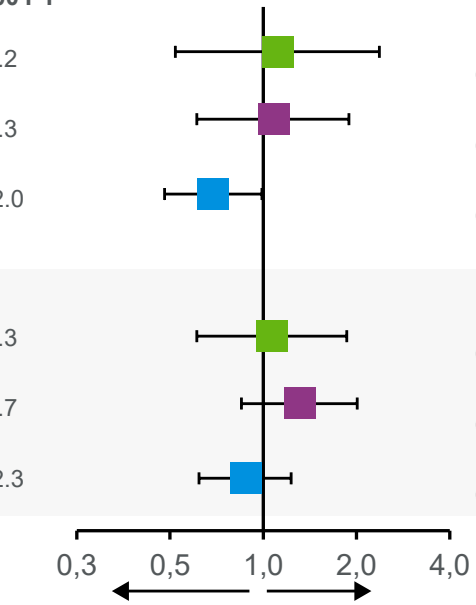


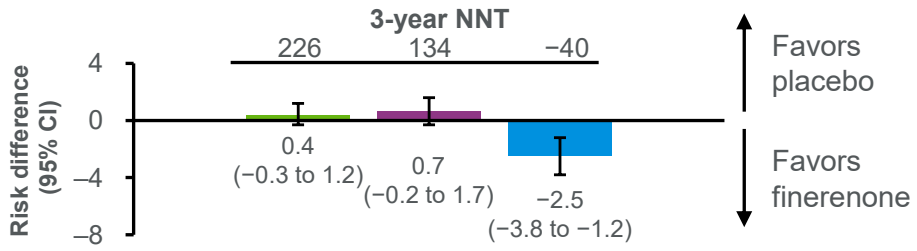
Lower tertile Middle tertile Upper tertile

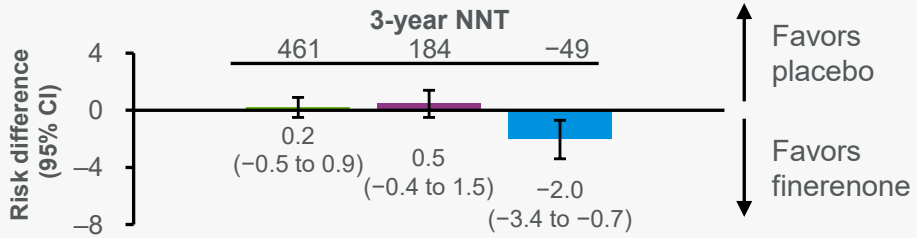
*Outcomes include HHF, non-fatal MI or non-fatal stroke.
HRs and CIs were calculated using a Cox proportional hazards models. Stratification factors included region, and eGFR and albuminuria levels at screening. Covariates included treatment, baseline PREVENT™ tertile, and treatment × PREVENT™ interaction. Treatment effect heterogeneity between tertiles was assessed via the interaction *p*-value calculated using the Wald test which investigates the null hypothesis that the regression coefficient is equal to zero. Risk differences and NNTs were calculated using the estimated 3-year cumulative incidence of events based on Aalen–Johansen estimates, using all-cause death as a competing risk.
CI, confidence interval; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HF, heart failure; HHF, hospitalization for HF; HR, hazard ratio; IR, incidence rate; MI, myocardial infarction; NNT, number needed to treat; PY, patient-years.

Non-fatal cardiovascular events* by PREVENT-HF and PREVENT-ASCVD risk category (full model analysis)

	Finerenone		Placebo		Hazard ratio (95% CI)	*p*-interaction
	Events n/N (%)	IR n/1000 PY	Events n/N (%)	IR n/1000 PY		
PREVENT-HF	14/1150 (1.2)	3.6	13/1198 (1.1)	3.2	1.12 (0.52 to 2.37)	
	26/1209 (2.2)	6.7	23/1141 (2.0)	6.3	1.08 (0.61 to 1.89)	0.778
	51/1156 (4.4)	15.7	73/1193 (6.1)	22.0	0.69 (0.48 to 0.99)	
PREVENT-ASCVD	25/1136 (2.2)	6.6	25/1213 (2.1)	6.3	1.07 (0.61 to 1.86)	
	51/1200 (4.3)	13.4	36/1151 (3.1)	9.7	1.31 (0.85 to 2.01)	0.823
	64/1183 (5.4)	19.3	72/1167 (6.2)	22.3	0.88 (0.62 to 1.23)	



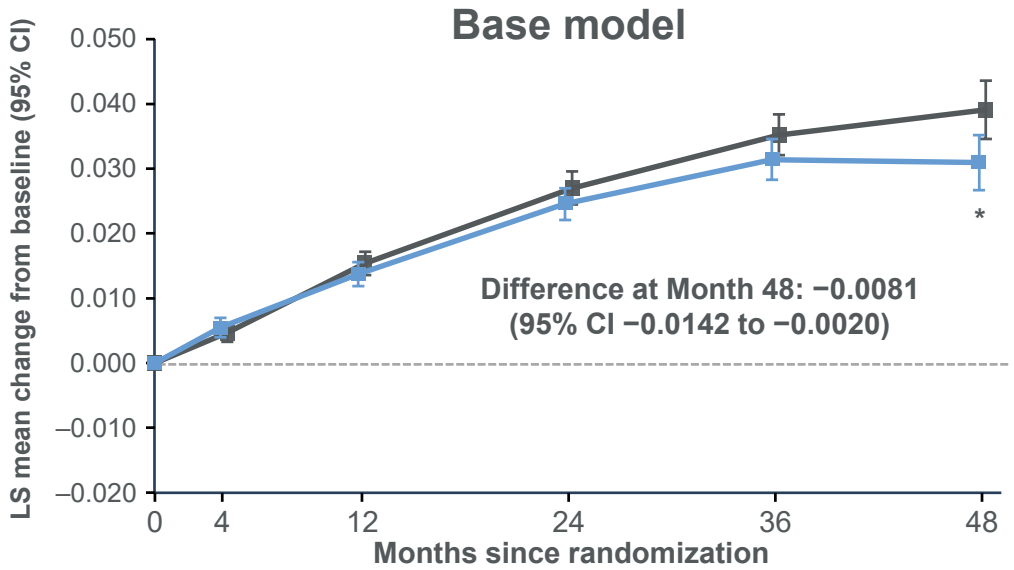




Lower tertile Middle tertile Upper tertile

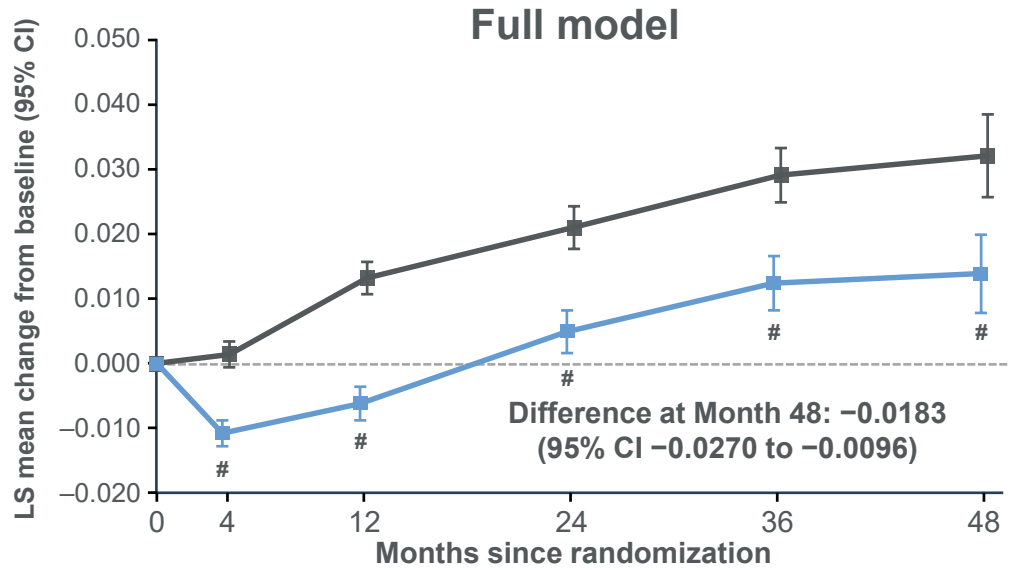
*Outcomes were HHF for the PREVENT-HF model and non-fatal MI or non-fatal stroke events for the PREVENT-ASCVD model.
HRs and CIs were calculated using a Cox proportional hazards models. Stratification factors included region, and eGFR and albuminuria levels at screening. Covariates included treatment, baseline PREVENT™ tertile, and treatment × PREVENT™ interaction. Treatment effect heterogeneity between tertiles was assessed via the interaction *p*-value calculated using the Wald test which investigates the null hypothesis that the regression coefficient is equal to zero. Risk differences and NNTs were calculated using the estimated 3-year cumulative incidence of events based on Aalen–Johansen estimates, using all-cause death as a competing risk.
ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HF, heart failure; HHF, hospitalization for HF; HR, hazard ratio; IR, incidence rate; MI, myocardial infarction; NNT, number needed to treat; PY, patient-years.

Change from baseline in PREVENT-CVD risk score (base and full model analysis)



Number at risk

Finerenone	3519	3373	3260	2750	1682	583
Placebo	3531	3375	3266	2735	1664	578



Number at risk

Finerenone	3519	3373	3260	2750	1682	583
Placebo	3531	3375	3266	2735	1664	578

Finerenone Placebo

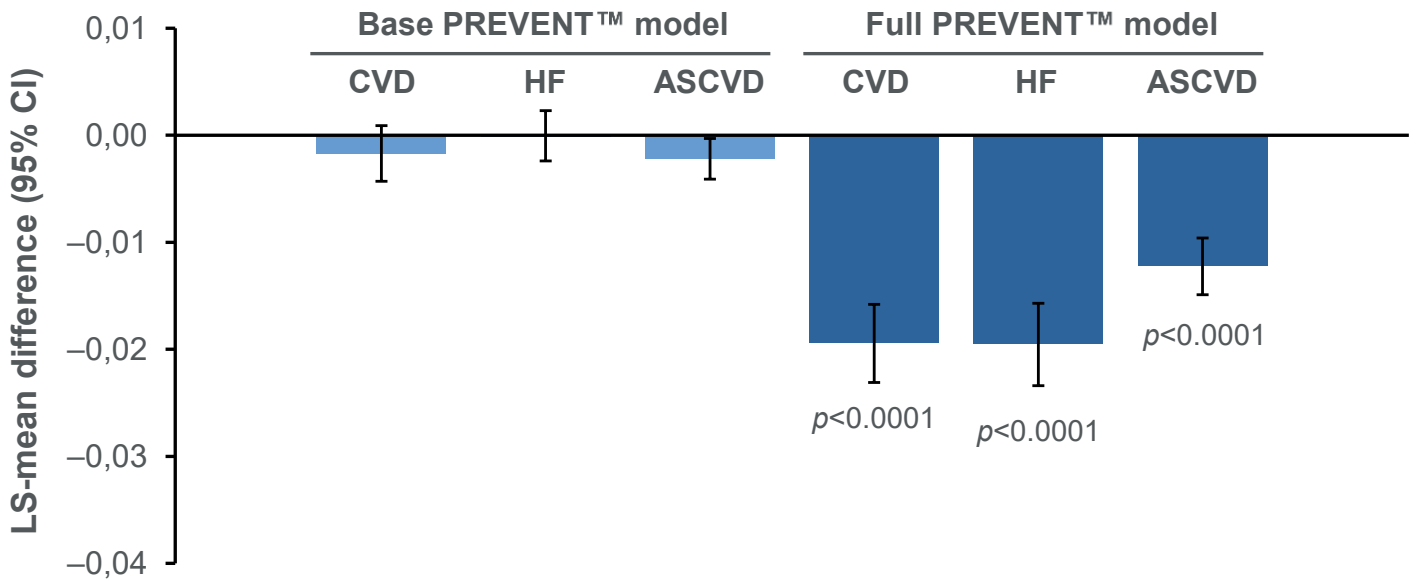
Linear mixed-effects model with factors treatment group, region, eGFR category at screening, type of albuminuria at screening, time, treatment × time, study, study × treatment, baseline value nested within type of albuminuria at screening and baseline value × time as covariates

*$p<0.01$; #$p\leq0.0001$.

CI, confidence interval; LS, least squares.

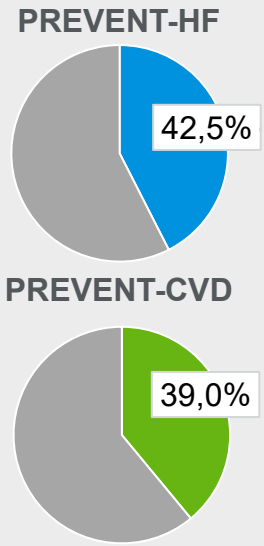
Landmark analysis at month 12 to assess the clinical benefit of finerenone (base and full model analysis for all outcomes*)

Difference in PREVENT™ score for finerenone versus placebo at month 12



	Base PREVENT™ model			Full PREVENT™ model		
	CVD	HF	ASCVD	CVD	HF	ASCVD
Translation factor	0.942	0.927	0.925	0.962	0.948	0.950
Predicted HR	**~0.99**	**~1.00**	**~0.98**	**~0.93**	**~0.90**	**~0.94**

Proportion of the treatment effect mediated by PREVENT™ score change (full model)



*Outcomes were HHF for the PREVENT-HF model, non-fatal MI or non-fatal stroke events for the PREVENT-ASCVD model, and HHF, non-fatal MI or non-fatal stroke for the PREVENT-CVD model.
Landmark analysis tested whether the on-treatment reduction in PREVENT-CVD, PREVENT-HF, and PREVENT-ASCVD score observed with finerenone versus placebo translates into a reduction in clinical CV events. The landmark was set at month 12 (primary) with month 4 as a sensitivity landmark
ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; CVD, cardiovascular disease; HF, heart failure; HHF, hospitalization for HF; HR, hazard ratio; LS, least squares; MI, myocardial infarction.

Conclusions

When total CVD risk was assessed using the full model PREVENT™ equation, the absolute benefit of finerenone was nominally significant in patients with the highest risk score at baseline (upper tertile)

- The benefit of finerenone appears to be driven by a reduction in HHF rather than a reduction in atherosclerotic events
- Albuminuria also appears to be a partial mediator of the effect of finerenone

Finerenone slowed the increase in predicted CVD risk, which was significantly different from placebo after 4 months of treatment when UACR and HbA1c were included as measures of risk (full model)

In people with CKD and T2D without established CVD, finerenone improves CV risk, mainly by preventing HF and partly through lowering albuminuria. The full PREVENT™ equation may help to identify patients who are likely to experience the greatest absolute benefit

CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; HbA1c, glycated hemoglobin; HF, heart failure; HHF, hospitalization for heart failure; T2D, type 2 diabetes; UACR, urinary albumin-to-creatinine ratio