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ORIGINAL ARTICLE

Impedance-based remote monitoring in patients with heart failure and concomitant chronic kidney disease

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Abstract

Aims Remote monitoring (RM) of thoracic impedance represents an early marker of pulmonary congestion in heart failure (HF). Chronic kidney disease (CKD) may promote fluid overload in HF patients. We investigated whether concomitant CKD affected the efficacy of impedance-based RM in the OptiLink HF trial.

Methods and results Among HF patients included in the OptiLink HF trial, time to the first cardiovascular hospitalization and all-cause death according to the presence of concomitant CKD was analysed. CKD was defined as GFR $<$ 60 mL/min/1.73 m^2 at enrolment. Of the 1002 patients included in OptiLink HF, 326 patients (33%) had HF with concomitant CKD. The presence of CKD increased transmission of telemedical alerts (median of 2 (1-5) vs. 1 (0–3); P = 0.012). Appropriate contacting after alert transmission was equally low in patients with and without CKD (57% vs. 59%, P = 0.593). The risk of the primary endpoint was higher in patients with CKD compared with patients without CKD (hazard ratio (HR), 1.62 [95% confidence interval (CI), 1.16–2.28]; P = 0.005). Impedance-based RM independently reduced primary events in HF patients with preserved renal function, but not in those with CKD (HR 0.68 [95% CI, 0.52–0.89]; P = 0.006).

Conclusions The presence of CKD in HF patients led to a higher number of telemedical alert transmissions and increased the risk of the primary endpoint. Inappropriate handling of alert transmission was commonly observed in patients with chronic HF and CKD. Guidance of HF management by impedance-based RM significantly decreased primary event rates in patients without CKD, but not in patients with CKD.

Keywords Remote monitoring; Implantable cardioverter-defibrillator; Heart failure; Telemedicine; Chronic kidney disease

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Introduction

Despite remarkable improvements in pharmacotherapy, chronic heart failure (HF) is still associated with significantly increased morbidity and mortality rates.[1] Chronic kidney disease (CKD) represents a common and prognostically unfavourable comorbidity in patients with chronic HF that can promote cardiac decompensation.[2] The timely detection of fluid overload in HF patients can help to reduce signs and symptoms of congestion, and eventually prevent HF hospitalization.[3] Current generations of implanted cardioverter-defibrillators (ICD) and cardiac resynchronization devices (CRT-D, cardiac resynchronization therapy - defibrillator) enable remote monitoring (RM) of intrathoracic impedance, which closely correlates with the pulmonary fluid status, thus serving as an early indicator of preceding cardiac decompensation.[4–6] The randomized, OptiLink HF trial[7] studied the effects of ICD-/CRT-D-based RM of intrathoracic impedance in 1002 patients with chronic HF. RM failed to reduce the risk of the composite endpoint of all-cause death or first cardiovascular (CV) hospitalization, which has been attributed to insufficient handling of fluid alerts.[8] However, patients with concomitant CKD are exposed to a higher risk of fluid overload compared with patients with preserved renal function.[9] Thus, we investigated whether con-

comitant CKD affected the efficacy of impedance-based RM in patients with HF with reduced ejection fraction included in the OptiLink HF study.

Methods

The design and results of OptiLink HF trial have been published previously.[7,10] Enrolled patients had chronic HF symptoms (NYHA functional class II or III), exhibited a reduced left ventricular ejection fraction of ≤35%, and had to receive a guideline-recommended ICD/CRT-D device 3–21 days prior to study inclusion. Furthermore, the implanted devices had to be equipped with OptiVol™ (Medtronic Inc, Minneapolis, MN, USA) fluid status monitoring and telemedicine functionality. The OptiLink HF trial was approved by the ethical committees of all participating centres and was registered to ClinicalTrials.gov (NCT00769457). All patients gave written consent before enrolment into the trial. The authors had direct access to the primary data collected in the trial.

Study procedures

A total of 1002 patients were enrolled in the OptiLink HF trial and randomly assigned 1:1 to either the intervention arm or the usual care (UC). Within the intervention arm, the telemedicine function of the implanted ICD/CRT-D devices was turned on, notifying treating physicians about FTC (fluid threshold crossing) events via text messages, which were inaudible to patients. These FTC events occurred, when the Optivol™ fluid index level, which was based on the intrathoracic impedance, exceeded the programmed FTC alert threshold. After FTC transmission, a protocol-specified intervention algorithm had to be followed by the treating physicians.[10] In brief, physicians were obliged to contact the patients by phone within two working days after alert transmission, to assess any HF symptoms and the overall condition. Based on symptoms and signs suggestive of fluid overload, for example, significant weight gain, the physicians were instructed to take therapeutic measures. These included non-medical interventions such as fluid intake restrictions, and medical interventions, particularly increasing diuretics dosages. Moreover, physicians were able to take no actions at all and to reprogram the FTC alert threshold, for instance, if they identified specific reasons for the transmitted alert other than fluid overload such as pneumonia. The decision about the necessary therapeutic intervention was left at the physicians' discretion. If the Optivol™ fluid level persisted above the programmed FTC alert threshold, the patients had to be contacted up to three additional times in the following 2 weeks. Within this time, the intrathoracic impedance was supposed to decrease below the FTC alert threshold. In case the intrathoracic impedance remained above the programmed FTC alert threshold, the physicians were instructed to ask the patients for an in-office or in-hospital visit for further diagnostics. In the UC arm, the telemedicine function was turned off. All patients were followed for a minimum of 18 months. The primary endpoint of the OptiLink HF trial was the composite of all-cause death or first CV hospitalization.

Comparison between patients with and without chronic kidney disease

Among HF patients included in the OptiLink HF trial, we compared the frequency of telemedical alert transmissions, frequency of appropriate contacts after alert transmission, and the time to the primary endpoint of the OptiLink HF trial according to the presence of concomitant CKD. CKD at baseline was defined as GFR < 60 mL/min/1.73 m^2. The definition of appropriate contacts was in compliance with recent analysis[9] and had to meet all of the following criteria: (i) initial telephone contact within two working days after FTC transmission, (ii) follow-up contacts according to study protocol, and (iii) medical intervention initiated after FTC due to cardiac decompensation.

Statistical analysis

Continuous variables were tested for normal distribution by visual inspection of quantile plots. Normally distributed values are reported as mean ± standard deviation (SD), while non-normally distributed values are reported as median and first to third interquartile range (Q1–Q3). Continuous variables between two groups were compared with the Wilcoxon rank-sum test, while the Kruskal–Wallis test was used for comparing continuous variables between more than two groups. Comparisons for categorical variables were performed with the Pearson chi-square test. The survival curves of the patients were calculated by the Kaplan–Meier method and compared with the log-rank test. Stratified Cox proportional hazards regression models were used to calculate hazards ratios (HRs) and associated 95% confidence interval (CI). Stratifying values comprised baseline characteristics, such as left ventricular ejection fraction, history of atrial fibrillation, age, gender, and type of implanted device (ICD vs. CRT-D). All analyses were performed with SPSS statistical software (version 26.0, IBM Inc., Chicago, IL, USA). All authors had full access to the data and take full responsibility for their integrity.

Results

Patient characteristics

Out of the 1002 patients enrolled in the OptiLink HF trial, 326 patients had HFrEF and concomitant CKD. Patients with CKD

were older (71 ± 8 vs. 64 ± 11 years; $P < 0.001$) and had higher NYHA functional class (88% vs. 78% in NYHA III; $P < 0.001$) than patients without CKD (*Table* 1). Moreover, hypertension (79% vs. 68%; $P < 0.001$) and diabetes (43% vs. 31%; $P < 0.001$) were more common in patients with CKD than in those without CKD. On the contrary, no significant differences existed between patients with and without CKD regarding gender (83% vs. 78% male; $P = 0.129$), left ventricular ejection fraction (26.1 ± 6.1% vs. 26.9 ± 6.1%; $P = 0.07$), and left ventricular end-diastolic diameter (64.2 ± 8.2 vs. 65.1 ± 8.5 mm; $P = 0.23$). The percentage of ESC guideline-recommended HF pharmacotherapy was equally high in patients with and without CKD (*Table 1*).

Alert transmissions in patients with and without chronic kidney disease

The presence of CKD was associated with more frequent transmissions of FTC alerts. In patients with HF and concomitant CKD, a median number of 2 (1–5) FTC alert transmissions occurred during follow-up as compared with a median of 1 (0–3) FTC in patients without CKD ($P = 0.012$) (*Table 2*). In both patient groups with and without CKD, FTC crossings were mainly caused by cardiac decompensation (59% in CKD vs. 59% without CKD; $P = 0.794$). Furthermore, there was an equally high percentage of FTC alerts for unclear reasons: 32% in CKD vs. 33% without CKD ($P = 0.862$). Of note, the initiation of any medical intervention (pharmacologic or non-pharmacologic) after FTC alert transmission was low in patients with and without concomitant CKD (35% in CKD vs. 34% without CKD; $P = 0.539$). Accordingly, FTC alert transmissions in patients with CKD were handled appropriately in only 57%, which was similar to 59% in patients with preserved renal function ($P = 0.593$) (*Table 2*).

Cardiovascular events in patients with and without chronic kidney disease

The primary endpoint occurred in 163 (50%) patients with HF and CKD as opposed to 245 patients (36.2%) with HF and preserved renal function (*Table 3*). In a multivariate Cox regression analysis, which comprised age, hypertension, diabetes, functional class, cardiac resynchronization therapy, atrial fibrillation, and cardiomyopathy aetiology, concomitant CKD was independently associated with a significantly higher risk of the primary endpoint (HR, 1.62 [95% CI, 1.16–2.28]; $P = 0.005$) (*Figures 1* and *2*). In addition, CV hospitalizations and hospitalizations for HF were more likely in patients with CKD than in patients without (*Table 3*). Interestingly, within 30 days after FTC alert transmissions, patients with CKD were at a higher risk of both CV and HF hospitalizations compared with patients without CKD (*Table 3*). Moreover, compared with UC, impedance-based RM independently reduced the primary event rate in HF patients with preserved renal function (HR 0.68 [95% CI, 0.52–0.89]; $P = 0.006$), while this was not observed for HF patients with CKD (HR 0.71 [95% CI, 0.94–1.3]; $P = 0.705$) (*Figures 1* and *2*). Of note, these effects were already evident after 60 days and mainly driven by a significant risk reduction regarding the time to the first CV hospitalization (Supporting Information, *Figure S1*). On the other hand, impedance-based RM significantly decreased risk of the secondary endpoint of all-cause death in patients with CKD but had no effect on all-cause mortality in patients without CKD (Supporting Information, *Figure S2*).

Table 1 Patient characteristics at the time of randomization (baseline) in relation to the presence of concomitant chronic kidney disease.

Characteristics	Patients with CKD ($n = 326$)	Patients without CKD ($n = 676$)	P
Age (years)	70.5 ± 8.4	64.2 ± 10.7	<0.001
Male sex	269 (83%)	530 (78%)	0.129
Hypertension	258 (79%)	460 (68%)	<0.001
Diabetes	140 (43%)	209 (31%)	<0.001
Hyperlipoproteinaemia	169 (52%)	319 (47%)	0.168
Active smoking	33 (10%)	103 (15%)	0.027
NYHA class at randomization			<0.001
II	39 (12%)	152 (22%)	
III	287 (88%)	524 (78%)	
LVEF at admission (%)	26.1 ± 6.1	26.9 ± 6.1	0.07
LVEDD at admission (mm)	64.2 ± 8.2	65.1 ± 8.5	0.23
CRT-D device (%)	235 (72%)	392 (58%)	<0.001
Atrial fibrillation	117 (36%)	161 (24%)	<0.001
Ischaemic cardiomyopathy	201 (62%)	344 (51%)	0.001
ACEi/ARB during FU	297 (91%)	618 (91%)	0.868
Beta blocker during FU	326 (100%)	676 (100%)	0.538
MRA during FU	182 (56%)	413 (61%)	0.112

Normally distributed values are reported as mean ± standard deviation (SD); non-normally distributed values are reported as median and Q1–Q3. Categorical values are reported as *n* (%).
ACEI, angiotensin-converting-enzyme inhibitors; ARB, angiotensin II receptor blocker; CKD, chronic kidney disease; CRT-D, cardiac resynchronization therapy - defibrillator; FU, follow-up; LVEF, left-ventricular ejection fraction; LVEDD, left-ventricular end-diastolic diameter; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association.

Table 2 Frequency and handling of telemedical alerts in relation to the presence of chronic kidney disease at baseline

	Patients with CKD (n = 171)	Patients without CKD (n = 334)	P
Total no. of FTC alert transmissions	568	797	
FTC alert transmissions (median) per patient	2 (1–5)	1 (0–3)	0.012
FTC caused by cardiac decompensation (%)	59	59	0.794
FTC not caused by cardiac decompensation (%)	9	8	0.511
FTC due to unclear reason (%)	32	33	0.862
Appropriate handling after FTC alert transmission (%)	57	59	0.593
Initiation of any medical intervention after FTC alert transmission (%)	35	34	0.539
Initiation of pharmacological intervention after FTC alert transmission (%)	28	27	0.466
Initiation of non-pharmacological intervention only after FTC alert transmission (%)	7	7	0.256
Immediate admission to hospital/clinic after FTC alert transmission (%)	3	5	0.085

Normally distributed values are reported as mean ± SD; non-normally distributed values are reported as median and Q1–Q3. Categorical values are reported as n (%).
CKD, chronic kidney disease; FTC, fluid threshold crossing.

Table 3 Clinical events in relation to the presence of chronic kidney disease at baseline

	Patients with CKD (n = 326)	Patients without CKD (n = 676)	P
Occurrence of the primary endpoint (CV hospitalization and all-cause death)	163 (50%)	245 (36%)	<0.001
Total no. of CV hospitalizations	296 (91%)	467 (69%)	<0.001
Total no. of HF hospitalizations	188 (58%)	262 (39%)	<0.001
All-cause death	56 (17%)	66 (10%)	<0.001
Total no. of CV hospitalizations within 30 days after FTC alert transmission	38 (12%)	36 (5%)	0.008
Total no. of HF hospitalizations within 30 days after FTC alert transmission	26 (8%)	26 (4%)	0.028

Normally distributed values are reported as mean ± SD; non-normally distributed values are reported as median and Q1–Q3. Categorical values are reported as n (%).
CKD, chronic kidney disease; CV, cardiovascular; FTC, fluid threshold crossing; HF, heart failure.

Discussion

The present analysis of the OptiLink HF trial underlines the prognostic impact of concomitant CKD in HF patients, which independently increased the risk for the composite endpoint of all-cause death or CV hospitalization. Moreover, it points out the importance towards appropriate handling of telemedical alerts indicating fluid overload in HF patients with CKD, as their risk of CV and HF hospitalizations within 30 days after alert transmission was particularly high. In addition, RM was associated with a reduced risk of the composite endpoint in patients with preserved renal function, while these effects were diminished in patients with CKD. On the contrary, guidance of HF management by impedance-based RM led to a significantly decreased all-cause mortality in the high-risk population of HF patients with concomitant CKD, while this did not account for patients without CKD.

RM of ICD-/CRT-D devices effectively contributes to the reduction of system-related complications.[11] For example, RM allows the early detection of T wave oversensing or lead fracture, therefore preventing the delivery of inappropriate shocks.[12] In addition, telemedical device interrogation helps to save important resources in the health care system and represents a particular relevant tool during pandemics to decrease the risk of potential infections for both patients and healthcare workers alike.[13] Besides its system-related advantages, RM of parameters such as heart rate, heart rhythm, and activity index is an essential benefit to guide the management of HF patients.[14] Moreover, ICD-/CRT-devices are capable of monitoring intrathoracic impedance, a non-invasive parameter, which is inversely associated with pulmonary fluid level.[15–17] However, impedance-based RM failed to decrease the risk of the composite of all-cause death and CV hospitalization in the prospective, randomized OptiLink HF trial.[7]

In contrast to the non-haemodynamic parameter intrathoracic impedance, direct haemodynamic measurements are able to detect worsening HF at an even earlier stage. For instance, the CardioMEMS™ device allows the RM of the pulmonary artery pressure as an indicator of fluid status, which has resulted in a significant reduction in HF hospitalizations in the CHAMPION trial.[18] However, important differences between the therapy algorithms in the OptiLink HF and CHAMPION trial have to be acknowledged. While diuretic therapy in the CHAMPION trial[18] had to follow specific guidelines, physicians in OptiLink HF[7] were able to decide about the necessary therapeutic measures by themselves. This might have resulted in a remarkably low rate of appropriately handled telemedical alerts in the intervention group of the OptiLink

Figure 1 Time from randomization to all-cause death or first cardiovascular hospitalization in relation to randomization and the presence of chronic kidney disease at baseline. CKD, chronic kidney disease; CV, cardiovascular; UC, usual care.

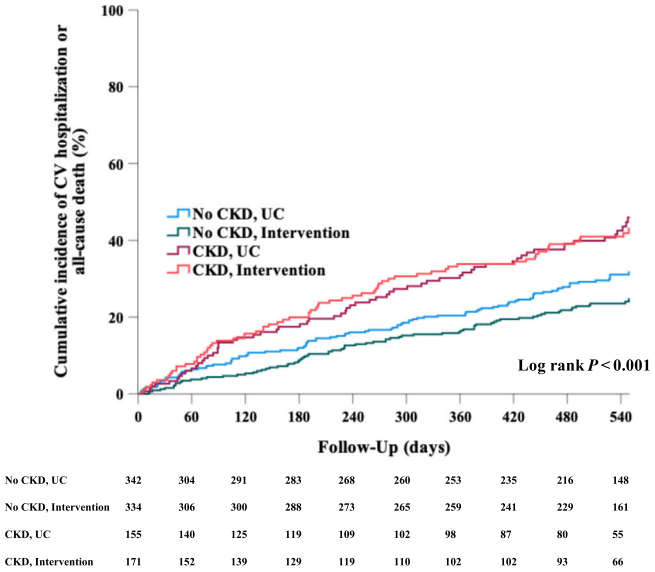
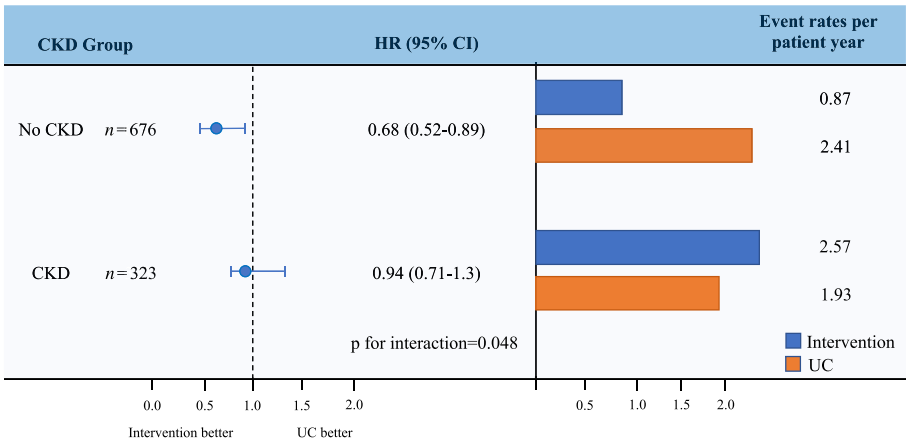


Figure 2 Primary event rates in relation to randomization and the presence of chronic kidney disease at baseline. CI, confidence interval; CKD, chronic kidney disease; HR, hazard ratio; UC, usual care.



HF trial.[8] As also shown herein, the probability of appropriate contacting after FTC alert transmission was independent of the presence of concomitant CKD. Accordingly, FTC alert transmissions in patients with CKD and preserved renal function were handled appropriately in less than 60%. Interestingly, in a post hoc analysis of the CHAMPION trial, RM with CardioMEMS™ only reduced HF hospitalization rates when treating physicians adjusted diuretic therapy according to elevated pulmonary artery pressures.[19] Moreover, the GUIDE-HF trial[20] studied the efficacy of CardioMEMS™-based RM in a large cohort of HF patients. Compared with usual care, RM with CardioMEMS™ failed to significantly decrease the risk of the combined endpoint of all-cause mortality and HF events,[20] although these findings may have been influenced by the COVID-19 pandemic.[21] As a result, it is important to study potential pit-falls and sub-group interactions in RM and to identify patient cohorts that may require a more rigorous RM.

CKD is a common risk factor in HF patients. Moderate to severe CKD can be found in approximately half of all HF patients, and independently increases morbidity and mortality.[22] Furthermore, impaired kidney function may limit the utilization of guideline-recommended drug therapy, shown to improve survival of HF patients.[23] As a result of de-

creased diuresis, CKD may lead to accumulation of body fluid, which can facilitate cardiac decompensation, and eventually cause HF hospitalization.[2] Analogously, in our post hoc analysis of the OptiLink HF trial, the presence of concomitant CKD was an independent predictor of the composite endpoint of all-cause death or first CV hospitalization. Additionally, within 30 days after transmission of FTC alerts, patients with CKD were at a significant higher risk of both CV and HF hospitalizations compared with patients with preserved renal function.

Remarkably, impedance-based RM had no effect on the occurrence of the primary endpoint in patients with CKD but resulted in a significant decrease in primary event rates in patients without CKD. These effects were already detectable after 60 days and mainly driven by a significant risk reduction of the secondary endpoint, that is, time to the first CV hospitalization. As a result, one could speculate that patients with CKD require a more extensive decongestive therapy compared with patients without CKD. This hypothesis is supported by a previous study, which evaluated the maximum diuresis and body weight loss following tolvaptan administration in 153 acutely decompensated HF patients.[24] It was shown that the diuretic response gradually decreased with advancing CKD stage. Moreover, our findings underline the potential beneficial effects using impedance-based RM in the management of HF patients without CKD.

Furthermore, guidance of HF management by impedance-based RM resulted in a significantly decreased risk of all-cause death in patients with concomitant CKD, but not in patients with preserved renal function. Thus, it could be concluded that the early detection of pulmonary congestion by impedance-based RM in patients with CKD may not have been able to prevent symptomatic cardiac decompensation with subsequent CV hospitalization but helped to initiate a more extensive decongestive therapy early enough to reduce all-cause mortality in this high-risk patient population.

Limitations

As this analysis of the OptiLink HF trials was conducted post hoc, it should be regarded as hypothesis-generating. Moreover, the kidney function was only evaluated at study enrolment and not during the trial to assess potential interactions between disease progression and efficacy of impedance-based RM in CKD patients. In addition, patients with a creatinine of $>$2.5 mg/dL were excluded from the OptiLink HF trial. Furthermore, there was no information about the exact dose of diuretics to investigate whether patients with CKD require higher doses after FTC alert transmissions than patients with preserved renal function to prevent subsequent hospitalizations. Another potential confounder is the rather high number of unclear FTC alerts. However, as discussed before,[8] this may represent the challenges of impedance-based RM in the routine clinical practice. The low intervention rates might be the result of a lacking confidence in abnormal intrathoracic impedance being an indicator of preceding cardiac decompensation, particularly in asymptomatic patients. Thus, it might be of importance to empower physicians in adjusting diuretic therapy according to intrathoracic impedance. Additionally, the OptiLink HF trial was not powered to reliably assess potential differences between the intervention and control arm regarding the secondary endpoint of all-cause death. Therefore, we did not perform a multiplicity adjustment. At last, during the OptiLink HF trial, the HF treatment did not include sodium-glucose cotransporter-2 inhibitors.

Conclusions

In the OptiLink HF trial, the presence of concomitant CKD in HF patients independently increased the risk regarding the primary endpoint of all-cause death or CV hospitalization. Appropriate handling of telemedical alerts was equally low in patients with and without CKD. Within 30 days after telemedical alert transmission, HF patients with CKD were at a higher risk of CV and HF hospitalizations compared with patients with preserved renal function. Compared with UC, patients without CKD profited significantly from impedance-based RM to reduce risk of all-cause death or CV hospitalization. In the high-risk population of HF patients with CKD, the positive effects of impedance-RM regarding the primary endpoint diminished. Therefore, patients with CKD might require a more extensive decongestive therapy after telemedical alert transmission compared with patients without CKD to prevent symptomatic cardiac decompensation and subsequent CV hospitalization.

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Conflict of interest

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Time from randomization to first cardiovascular hospitalization in relation to randomization and the presence of chronic kidney disease at baseline. Abbreviations: CI = confidence interval; CKD = chronic kidney disease; CV = cardiovascular, HR = hazard ratio, pt. = patients, UC = usual care.

Figure S2. Time from randomization to all-cause death in relation to randomization and the presence of chronic kidney disease at baseline. Abbreviations: CI = confidence interval; CKD = chronic kidney disease; CV = cardiovascular, HR = hazard ratio, pt. = patients, UC = usual care.

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