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STATE-OF-THE-ART PAPER

Current Evidence on Treatment of Patients With Chronic Systolic Heart Failure and Renal Insufficiency

Practical Considerations From Published Data

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Chronic kidney disease (CKD) is increasingly prevalent in patients with chronic systolic heart failure. Therefore, evidence-based therapies are more and more being used in patients with some degree of renal dysfunction. However, most pivotal randomized clinical trials specifically excluded patients with (severe) renal dysfunction. The benefit of these evidence-based therapies in this high-risk patient group is largely unknown. This paper reviews data from randomized clinical trials in systolic heart failure and the interactions between baseline renal dysfunction and the effect of randomized treatment. It highlights that most evidence-based therapies show consistent outcome benefit in patients with moderate renal insufficiency (stage 3 CKD), whereas there are very scarce data on patients with severe (stage 4 to 5 CKD) renal insufficiency. If any, the outcome benefit might be even greater in stage 3 CKD compared with those with relatively preserved renal function. However, prescription of therapies should be individualized with consideration of possible harm and benefit, especially in those with stage 4 to 5 CKD where limited data are available. (J Am Coll Cardiol 2014;63:853–71) © 2014 by the American College of Cardiology Foundation

Most randomized controlled trials in chronic heart failure (HF) systematically excluded patients with severe renal dysfunction, often because of concern that the investigational treatment might cause further deterioration in kidney function. Yet these patients are at particularly high risk of adverse cardiovascular (CV) outcomes and might have much to gain from evidence-based therapies, if tolerated. International guidelines also express caution about the use of angiotensin-converting enzyme inhibitors (ACEi) and mineralocorticoid receptor antagonists (MRA) in patients with renal impairment, advising restriction of the use of ACEi and MRAs to those with estimated glomerular filtration rate (eGFR) >30 ml/min/1.73 m^2 (1,2). Heart failure patients with renal dysfunction are undertreated with respect to disease-modifying therapies, probably as a result of their exclusion from trials and the caution expressed in guidelines (3). There have been a few small clinical trials in patients with end-stage renal disease with and without HF, but most did not investigate major fatal or nonfatal clinical events (4). In this review, we analyze whether there is evidence (or not) that the key disease-modifying therapies used in HF are of benefit in patients with renal dysfunction.

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Classification of Chronic Kidney Disease and Prevalence of Renal Dysfunction and Albuminuria in HF

The distribution of eGFR and prevalence of the different stages of chronic kidney disease (CKD) in the general population and in patients with heart failure with reduced (HFREF) and preserved ejection fraction (HFPEF) is presented in Table 1 (5,6). In both HFREF and HFPEF, renal dysfunction determined by reduced GFR is more prevalent compared with the general population. Patients

Abbreviations and Acronyms

ACEi = angiotensin-converting enzyme inhibitor
ARB = angiotensin II receptor blocker
CKD = chronic kidney disease
CRT = cardiac resynchronization therapy
CV = cardiovascular
eGFR = estimated glomerular filtration rate
ICD = implantable cardioverter defibrillator
HF = heart failure
H-ISDN = hydralazine and isosorbide-dinitrate
HFPEF = heart failure with preserved ejection fraction
HFREF = heart failure with reduced ejection fraction
KDOQI = Kidney Disease Outcomes Quality Initiative
LV = left ventricular
MRA = mineralocorticoid receptor antagonist
MI = myocardial infarction
sCr = serum creatinine
WRF = worsening renal function

with mild CKD (Kidney Disease Outcomes Quality Initiative [KDOQI] stage 1 and 2) have, generally, not been excluded from clinical trials and represent approximately one-third of patients included in randomized controlled trials. Similarly, approximately 30% to 35% of patients enrolled in recent clinical trials in HF had moderately severe (stage 3) CKD, although patients with severe renal dysfunction (stage 4 CKD) were usually excluded, except in studies in truly elderly patients where a greater proportion of patients (40% to 57%) had stage 3 to 4 CKD, in keeping with cohort studies and registries (7–12). Importantly, the KDOQI stages are not only dependent on eGFR but also require evidence of kidney damage (proteinuria or albuminuria) in stages 1 and 2 where eGFR is relatively preserved. Although just over 10% of the general population have albuminuria, approximately one-third of patients with both HFREF and HFPEF have increased urinary albumin excretion (Table 1), and this has been linked to adverse clinical outcome. These data come from CHARM (Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity) and GISSI-HF (Gruppo Italiano per lo Studio della Sopravvivenza dell'Insufficienza cardiac Heart Failure) trials (see the Online Appendix for a list of all trial acronyms), where none of the randomized treatments (candesartan, rosuvastatin or n-3 polyunsaturated fatty acids) showed a reduction in the level of urinary albumin excretion (13,14). On the basis of KDOQI recommendations, classification of CKD should take into account both eGFR and extent of albuminuria. The pathophysiology of concomitant cardiorenal failure has been reviewed extensively (15). Figure 1 gives a simplified overview of possible cardiorenal interactions and where each of the therapies that will be discussed could influence these associations.

Single Renin Angiotensin Aldosterone System Blockade: ACE Inhibitors

Moderate renal dysfunction—stage 3 CKD: eGFR 30 to 59 ml/min/1.73 m^2. In the first major ACEi trial in patients with severe HF, the CONSENSUS (Cooperative North Scandinavian Enalapril Survival Study) trial (enalapril; target dose 20 mg b.i.d., achieved 18.4 mg daily), most patients probably had a reduced GFR, because the mean serum creatinine (sCr) was 1.45 ± 0.05 mg/dl (128 ± 4 μmol/l), corresponding to an eGFR of approximately 47 ml/min/1.73 m^2 (on the basis of mean characteristics) (Table 2). In a subgroup analysis with patients stratified above and below the median sCr value 1.39 mg/dl (123 μmol/l, eGFR 49 ml/min/1.73 m^2), enalapril significantly improved outcome in patients with worse renal function but not in those with better renal function, although no formal interaction analysis was performed (16). By contrast, another substudy showed that although there was a significant relative risk reduction of 45% in patients with sCr ≤140 μmol/l (1.58 mg/dl) ($p = 0.01$), this effect was smaller (39%) and not significant in patients with sCr >140 μmol/l, although again no interaction analysis was performed (17).

In the SOLVD Treatment (Studies of Left Ventricular Dysfunction Treatment) trial, enalapril (target dose 10 mg b.i.d., achieved 16.6 mg daily) significantly reduced the occurrence of CV death and HF hospital stays in the subgroup of patients with eGFR <60 ml/min/1.73 m^2. There was no interaction between the beneficial effect of enalapril on mortality and morbidity and baseline eGFR (dichotomized at 60 ml/min/1.73 m^2) (18). In the ATLAS (Assessment of Treatment with Lisinopril and Survival) trial, which showed better outcomes with high- compared with low-dose lisinopril, there was no significant interaction between baseline sCr stratified at 1.5 mg/dl and the effect of treatment (19). In the SAVE (Survival and Ventricular Enlargement) study, which included patients with left ventricular (LV) dysfunction after myocardial infarction (MI), baseline eGFR dichotomized at 60 ml/min/1.73 m^2 did not modify the beneficial effect of captopril on mortality and CV mortality/morbidity (20).

Severe renal dysfunction—stage 4 and 5 CKD: eGFR <30 ml/min/1.73 m^2. In the CONSENSUS trial, few patients (estimated 12%) with severe renal dysfunction (i.e., creatinine clearance <30 ml/min) were included (16,21). As mentioned in the preceding text, the subgroups of patients with sCr >140 μmol/l (eGFR <43 ml/min/1.73 m^2) did show a reduction in events, but this was not statistically significant, which was probably due to the low number ($n = 76$) of patients. In the absence of an interaction analysis, it is likely that the overall effect of enalapril in the CONSENSUS trial also applied to this patient group (16,17). In the SOLVD Treatment study, the beneficial effect of enalapril was not affected by adjusting for baseline eGFR (18). In patients with an eGFR <45 ml/min/1.73 m^2 (11% of patients), enalapril reduced both the risk of CV and HF hospital stays to the same extent as in other patients. However, an analysis of the effect of treatment in patients with an eGFR <30 ml/min/1.73 m^2 was not reported.

There is reasonable and consistent evidence of improvement in outcome with ACEi in patients with HF (or LV systolic dysfunction after MI) and stage 3 CKD (Table 3). It is possible that ACEi are also of benefit in patients with