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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

Table 1 Definition, Prevalence, and Distribution of CKD/GFR and Albuminuria in HFREF and HFPEF

Stages of CKD		Prevalence			Levels of Kidney Dysfunction	Distribution		
Stage	Description	General Population	HFREF*	HFPEF	GFR (ml/min/1.73 m^2)	General Population	HFREF	HFPEF
1	Kidney damage with normal or ↑ GFR	3.3	2.8	NA	≥90	64.3	8.2	8.2
2	Kidney damage with mild ↓ GFR	3.0	10.6	NA	60–89	31.2	37.2	34.9
3	Moderate ↓ GFR	4.3	45.5	46.1	30–59	4.3	45.5	46.1
4	Severe ↓ GFR	0.2	7.8	8.1	15–29	0.2	7.8	8.1
5	Kidney failure	0.2	1.3	2.7	<15 (or dialysis)	0.2	1.3	2.7
Albuminuria					UACR (mg/g creatinine)			
Normo-albuminuria					M <17/F <25†	88.3	66.2	60.2
Micro-albuminuria					M 17–250/F 25–355†	10.6	25.4	28.5
Macro-albuminuria					M >250/F >355†	1.1	8.4	11.3

Values are percentages, unless otherwise indicated. *Prevalences of stages 1 and 2 of chronic kidney disease (CKD) in heart failure with reduced ejection fraction (HFREF) from Masson et al. (14) (the GISSI-HF trial) (see the Online Appendix for a list of all trial acronyms). Distribution of albuminuria from combined numbers from the CHARM and GISSI-HF trials (13,14). Distribution of estimated glomerular filtration rate (GFR) in HFREF and heart failure with preserved ejection fraction (HFPEF) from McAlister et al. (6) and represent data on the basis of GFR. †Male (M) <2.5, 2.5–25 and > 25 mg/mmol, female (F) <3.5, 3.5–25 and >25 mg/mmol. creatinine, respectively. Adapted from Kidney Disease Outcomes Quality Initiative classification.

NA = not available; UACR = urinary albumin to creatinine ratio.

stage 4 to 5 CKD, but there are no conclusive data. Care should be taken to monitor renal function and electrolytes in these patients to achieve optimal benefit-risk ratio.

Angiotensin II Receptor Blockers

Stage 3 CKD. In the recent HEAAL (Heart failure Endpoint evaluation of Angiotensin II Antagonist Losartan) study, where high (150 mg daily) versus lower (50 mg daily) doses of losartan were evaluated, eGFR dichotomized at 75 ml/min/1.73 m^2 did not modify the beneficial effects of higher-dose losartan (22). In the CHARM-alternative trial with candesartan (target dose 32 mg daily, achieved 23 mg daily), there was no significant interaction between baseline eGFR and the effect of candesartan treatment, suggesting that the benefit

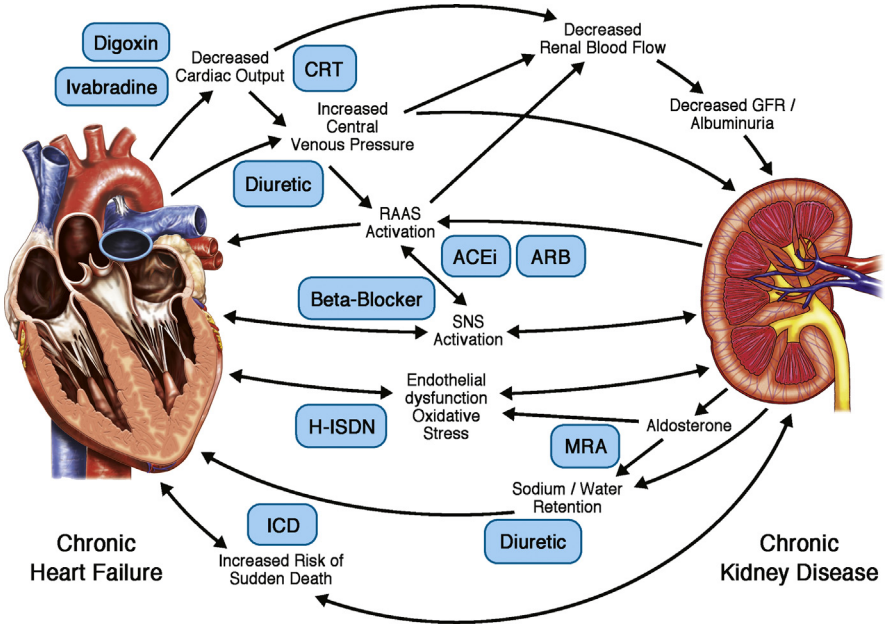

Figure 1 Pathophysiologic Pathways of the Interaction Between Heart Failure and Renal Dysfunction and the Effect of Evidence-Based Treatment

ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; CRT = cardiac resynchronization therapy; GFR = glomerular filtration rate; H-ISDN = hydralazine and isosorbide-dinitrate; ICD = implantable cardioverter-defibrillator; MRA = mineralocorticoid receptor antagonist; RAAS = renin angiotensin aldosterone system; SNS = sympathetic nervous system.

Table 2 Characteristics of ACEi Studies

Study*	n	Design	Primary Outcome	LVEF	NYHA	Renal Function Exclusion; Creatinine, mg/dl (μmol/l)	Baseline Renal Function (sCr)	CKD	Concomitant Therapy				Renal Subgroup Analysis	Relative Risk (Primary Outcome Study) (95% CI)
									ACEi/ARB	BBL	MRA	Digoxin		
CONSENSUS	253	Enalapril vs. Placebo	ACM	NA	100% IV	>3.4 (300)	1.4 mg/dl	NA	50	3	42	93	Yes	HR: 0.73 (long-term HR: 0.70 (0.54–0.89)
SOLVD Treatment	2,569	Enalapril vs. Placebo	ACM	25	30% III	>2.0 (175)	1.2 mg/dl	36	50	8	9†	67	Yes	ACM: HR: 0.84 (0.74–0.95) CKD: HR: 0.88 (0.73–1.06) HF hosp CKD: HR: 0.59 (0.48–0.73) No significant interaction between CKD and treatment
SOLVD Prevention	4,228	Enalapril vs. Placebo	ACM	28	67% I	>2.0 (175)	1.2 mg/dl	21	50	24	4†	12	No	HR: 0.92 (0.79–1.08)
SAVE	2,231	Captopril vs. Placebo	ACM	31	60% Killip I	>2.5 (221)	1.3 mg/dl	33	50	35	NA	26	Yes	HR: 0.81 (0.68–0.97) CKD: HR: 0.72 (0.55–0.94)
AIRE	2,006	Ramipril vs. Placebo	ACM	NA	NA	NA	NA	NA	50	22	NA	12	No	HR: 0.73 (0.60–0.89)
TRACE	1,749	Trandolapril vs. Placebo	ACM	NA	59% Killip ≥II	>2.3 (200)	NA	40‡	50	16	NA	28	No	HR: 0.78 (0.67–0.91)
NETWORK	1,532	Enalapril 2.5 vs. 5.0 vs. 10 mg b.i.d.	ACM, HF hosp or WHF	NA	64% II	>2.3 (200)	NA	NA	100	11	NA	24	No	HR: 1.20 (0.86–1.68) for 2.5 vs. 10 mg b.i.d.
ATLAS	3,164	High- vs. low-dose Lisinopril	ACM	23	77% III	>2.5 (221)	1.3 mg/dl	NA	100	11	NA	67	Yes	HR: 0.92 (0.82–1.03) sCr >1.5 mg/dl: HR: 1.02 (0.86–1.21) No significant interaction between sCr and high- vs. low-dose

Values are percentages, unless otherwise indicated. Studies that included >250 patients and small but important studies are presented. *Please see the Online Appendix for a list of all trial acronyms. †In the SOLVD studies, type of potassium sparing diuretics were not recorded. This figure represents all types, which is thought to predominantly include spironolactone. ‡Figure from screened TRACE population (77).

ACEi = angiotensin-converting enzyme inhibitor; ACM = all-cause mortality; AP = angina pectoris; ARB = angiotensin II receptor blocker; b.i.d. = ; BBL = beta blocker; CI = confidence interval; CKD = chronic kidney disease; HF = heart failure; hosp = hospital stay; HR = hazard ratio; LVEF = left ventricular ejection fraction; MI = myocardial infarction; MRA = mineralocorticoid receptor antagonist; NA = not available; NYHA = New York Heart Association functional class; OR = odds ratio; sCr = serum creatinine; WHF = worsening heart failure.

Table 3 Pharmacological Treatments Indicated in Patients With HF and Stage 3–5 CKD

Practical Considerations	Stage 3 CKD (eGFR 30–59 ml/min/1.73 m^2) Evidence*	Ref. #	Stage 4–5 CKD (eGFR <30 ml/min/1.73 m^2) Evidence*	Ref. #
ACEi				
An ACEi is recommended in all patients with EF ≤40% and stage 3 CKD and might be considered in stage 4–5 CKD with careful monitoring of renal function and electrolytes.	Strong	(18–21)	Weak	(18,21)
BBL				
A BBL is recommended in all patients with EF ≤40% and stage 3 CKD and should be considered in stage 4–5 CKD.	Strong	(34–37)	Moderate	(34–36,38)
MRA				
An MRA is recommended in all patients with EF ≤35%, persisting symptoms despite ACEi and BBL therapy, and stage 3 CKD. In stage 4–5 CKD, MRA should not be given.	Strong	(7,31,33)	Absent	—
ARB				
An ARB is recommended in patients with EF ≤40% and intolerance to ACEi or having symptoms despite ACEi and BBL and intolerant of a MRA and stage 3 CKD. Add-on ARB might be considered in stage 4–5 CKD with careful monitoring of renal function and electrolytes.	Moderate	(27,78)	Weak	(30)
Digoxin				
Might be considered in patients with sinus rhythm, EF ≤35%, who do not tolerate BBL, or on top of BBL, ACEi, and/or ARB/MRA and stage 3–5 CKD with careful monitoring of electrolytes and digoxin levels (stage 4–5 CKD).	Weak	(40)	Weak	(40)
Ivabradine				
Should be considered in patients in sinus rhythm with an EF ≤35%, a heart rate ≥70 beats/min, and persisting symptoms despite treatment with BBL (or intolerance), ACEi and an MRA (or ARB), and stage 3 CKD.	Moderate	(41,42)	Absent	—
H-ISDN				
Might be considered as an alternative to an ACEi or ARB, if neither is tolerated, on top of BBL and MRA, in patients with an EF ≤45%, and dilated LV (or EF ≤35%) and stage 3 CKD.	Weak	(43,44)	Absent	—
Diuretics				
Diuretics should be considered in any patient with signs and symptoms of congestion and volume overload and stage 3–5 CKD with careful monitoring of renal function and electrolytes.	Absent	—	Absent	—
ICD				
Secondary prevention An ICD is indicated in a patient with a history of ventricular arrhythmia and hemodynamic instability or survivors of cardiac arrest, and stage 3 CKD, and might be considered in stage 4–5 CKD.	Strong	(53,55,56)	Absent	—
Primary prevention An ICD is indicated in ischemic and nonischemic etiology of patients with EF ≤35%, symptomatic HF, and stage 3 CKD, and might be considered in stage 4–5 CKD.	Strong	(49,52)	Weak	(57)
CRT				
CRT is indicated in symptomatic patients (NYHA II–IV), on optimal medical therapy, in SR, with QRS duration >120 ms, LBBB QRS morphology and EF ≤35% (or QRS >130 ms and EF ≤30%) and stage 3 CKD, and might be considered in stage 4–5 CKD.	Strong	(58,59,79,80)	Absent	—
CRT should be considered in symptomatic patients (NYHA II–IV), on optimal medical therapy, in SR, with QRS duration >150 ms, irrespective of QRS morphology and EF ≤35% and stage 3 CKD, and might be considered in stage 4–5 CKD.	Moderate	(59,80)	Absent	—

*Evidence on the basis of number and type of trials and outcomes.

CRT = cardiac resynchronization therapy; EF = ejection fraction; eGFR = estimated glomerular filtration rate; H-ISDN = hydralazin and isosorbide-dinitrate; ICD = implantable cardioverter-defibrillator; LBBB = left bundle branch block; LV = left ventricle; MRA = mineralocorticoid receptor antagonist; Ref = references; SR = sinus rhythm; other abbreviations as in Table 2.

observed with angiotensin II receptor blocker (ARB) treatment in this population was similar across CKD subgroups (unpublished data). Studies on ARB versus ACEi therapy in patients with HF or LV dysfunction after MI have not reported renal subgroup analyses (23–26).

Stage 4 and 5 CKD. There are no data available on ARBs as single renin angiotensin aldosterone system (RAAS)-blockade in stage 4 and 5 CKD.

There is limited evidence for the use of single ARB therapy in patients with stage 3 CKD, whereas there is an absence of data on the effect of ARB in severe renal dysfunction.

Dual RAAS Blockade: Add-On ARB Therapy

Stage 3 CKD. In Val-HeFT (Valsartan Heart Failure Trial), valsartan (target dose 160 mg b.i.d., achieved dose 254 mg daily) reduced the composite mortality-morbidity endpoint but not the co-primary all-cause mortality endpoint. This benefit of treatment was consistent when baseline eGFR was dichotomized at 60 ml/min/1.73 m^2 (Table 4) (27). Similarly, in the CHARM-Added trial, the beneficial effect of candesartan on the primary composite outcome of CV death or HF hospital stay was evident in patients with both preserved and reduced kidney function as determined by sCr </≥2.0 mg/dl (28). There was no

Table 4 Characteristics of ARB Studies

Study*	n	Design	Primary Outcome	LVEF	NYHA	Renal Function Exclusion; Creatinine, mg/dl (μmol/l)	Baseline Renal Function (eGFR or sCr)	CKD	Concomitant Therapy				Renal Subgroup Analysis	Relative Risk (Primary Outcome Study) (95% CI)
									ACEi/ARB	BBL	MRA	Digoxin		
Val-HeFT	5,010	Valsartan vs. Placebo	ACM	27	36% III	>2.5 (221)	58 ml/min/1.73 m^2	58	93	35	NA	67	Yes	HR: 1.02 (0.88–1.18)† CKD: HR: 1.01 (0.85–1.20)†
CHARM-Added	2,548	Candesartan vs. Placebo	CV mortality or HF hosp	28	73% III	>3.0 (265)	NA	33†	100	55	17	58	Yes	HR: 0.85 (0.75–0.96) No significant interaction between creatinine and treatment‡
CHARM-Alternative	2,028	Candesartan vs. Placebo	CV mortality or HF hosp	30	49% III	>3.0 (265)	NA	43†	50	55	24	45	Yes	HR: 0.77 (0.67–0.89) No significant interaction between creatinine and treatment‡
HEAAL	3,846	High- vs. Low-dose Losartan	ACM or HF hosp	33	30% III	>2.5 (221)	1.10 mg/dl	NA	100	72	38	42	Yes	HR: 0.90 (0.82–0.99) CKD: HR: 0.98 (0.85–1.13) No significant interaction between CKD and treatment effect
ACEi vs. ARBs														
ELITE	722	Captopril vs. Losartan	WRF	31	65% II	>2.5 (221)	1.20 mg/dl	NA	100	59	NA	57	Yes	RR for WRF 2% (−51%–+36%) ACM: RR 0.46 (0.05–0.69) for losartan
ELITE II	3,152	Captopril vs. Losartan	ACM	31	52% II	>2.5 (221)	NA	NA	100	22	22	50	No	HR: 1.13 (0.95–1.35)
OPTIMAAL	5,477	Captopril vs. Losartan	ACM	NA	32% I	NA	1.13 mg/dl	NA	100	79	NA	11	NO	HR: 1.13 (0.99–1.28)
VALIANT	14,703	Valsartan vs. Valsartan + Captopril vs. Captopril	ACM	35	48% II	>2.5 (221)	1.1 mg/dl	NA	39	70	9	NA	Yes	Valsartan: HR 0.98 (0.87–1.09) Valsartan+Captopril HR: 1.00 (0.89–1.11) No interaction between creatinine and treatment effect

Values are percentages, unless otherwise indicated. Studies that included >250 patients and small but important studies are presented. *Please see the Online Appendix for a list of the trial acronyms. †In the Val-HeFT study, time to first morbid event was significantly reduced in overall population: HR: 0.87 (95% CI: 0.77–0.97), including patients with CKD: HR: 0.86 (95% CI: 0.74–0.99). ‡On the basis of entire CHARM cohort (28).

CV = cardiovascular; other abbreviations as in Tables 2 and 3.

significant interaction between baseline eGFR and this beneficial effect of candesartan (unpublished data). In contrast, in patients post-MI or at high CV risk, addition of an ARB to an ACEi does not improve outcome and might cause deterioration of renal function (29).

Stage 4 and 5 CKD. One study in hemodialysis patients with HF assessed the effect of addition of an ARB to standard therapy (100% ACEi, 60% beta-blocker, 50% digoxin) on outcome (30). In that small trial (332 patients), telmisartan (target dose 80 mg daily, achieved dose 75 mg daily) significantly improved the primary endpoint of all-cause mortality as well as the secondary endpoints of HF hospital stay or CV mortality.

Add-on ARB therapy should be considered in patients with chronic HF who do not tolerate an MRA, even if they have stage 3 CKD. Data in stage 4 to 5 CKD are limited to 1 study in hemodialysis patients but, in that study, did demonstrate benefit. Care should be taken to monitor renal function and electrolytes in a similar fashion as ACEi therapy.

Mineralocorticoid Receptor Antagonists

Stage 3 CKD. In RALES (Randomized Aldactone Evaluation Study) (target dose 50 mg daily, achieved 26 mg daily), a total of 48% of patients had eGFR <60 ml/min/1.73 m^2 (Table 5) (31). In an interaction analysis, spironolactone improved outcome irrespective of renal function (32). The EPHESUS (Eplerenone Post-Acute Hospitalization and Survival Study in Heart Failure) trial enrolled patients with a reduced ejection fraction and evidence of HF (or diabetes mellitus) after recent MI (33). There was an interaction between baseline sCr and the effect of treatment on all-cause mortality, whereby eplerenone was not associated with improved outcome in patients with sCr above 1.10 mg/dl. However, there was no such interaction for the co-primary endpoint of CV death or hospital stay. The most convincing and latest evidence comes from the recent EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure) trial, where 33% of patients had eGFR <60 ml/min/1.73 m^2 (7). The effect of eplerenone (target dose 50 mg daily, achieved 39 mg daily) on the primary composite endpoint of HF hospital stay or CV death was consistent in patients dichotomized at an eGFR <60 ml/min/1.73 m^2.

Stage 4 and 5 CKD. There are no data available on MRA therapy in patients with HF and stage 4 and 5 CKD, and eplerenone is contraindicated in patients with stage 4 and 5 CKD.

There is convincing evidence for a significant treatment benefit with the use of MRA in the setting of HF with moderate renal dysfunction (stage 3 CKD), but no data are available in stage 4 and 5 CKD.

Beta-Blockers

Stage 3 CKD. Despite the absence of robust evidence that beta-blockers worsen renal function, trials in HF have

Table 5 Characteristics of MRA Studies

Study*	n	Design	Primary Outcome	LVEF	NYHA	Renal Function Exclusion; Creatinine, mg/dl (μmol/l)	Baseline Renal Function (eGFR or sCr)	Concomitant Therapy					Renal Subgroup Analysis	Relative Risk (Primary Outcome Study) (95% CI)
								CKD	ACEi/ARB	BBL	MRA	Digoxin		
RALES	1,663	Spironolactone vs. Placebo	ACM	25	69% III	>2.5 (221)	1.2 mg/dl	48	94	10	50	73	Yes	HR: 0.70 (0.60–0.82) CKD: HR: 0.68 (0.56–0.84) No significant interaction between CKD and treatment
EPHESUS	6,632	Eplerenone vs. Placebo	ACM	33	NA	>2.5 (221)	79 ml/min/1.73 m^2	33	86	75	50	NA	Yes	HR: 0.85 (0.75–0.96) sCr >1.1 mg/dl upper CI crosses 1, p for interaction = 0.03
EMPHASIS	2,737	Eplerenone vs. Placebo	CV mortality or HF hosp	26	100% II	eGFR <30 ml/min/1.73 m^2	71 ml/min/1.73 m^2	33	93	87	50	27	Yes	HR: 0.66 (0.56–0.78) No significant interaction between CKD and treatment

Values are percentages, unless otherwise indicated. Studies that included >250 patients and small but important studies are presented. *Please see the Online Appendix for a list of the trial acronyms.
Abbreviations as in Tables 2, 3, and 4.

excluded patients with severe kidney dysfunction, possibly because of concerns about reduced renal excretion of certain drugs (Table 6). In the MERIT-HF (Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure) study, the beneficial effect of metoprolol (target dose 200 mg daily, achieved 159 mg daily) on clinical outcome was consistent across the eGFR categories examined (eGFR <45, 45 to 60, and >60 ml/min/1.73 m^2) (34). Significant interactions were found between metoprolol therapy and baseline eGFR: the effect of metoprolol was more pronounced in patients with eGFR <45 ml/min/1.73 m^2. The CIBIS-II (Cardiac Insufficiency Bisoprolol Study II) trial showed that the beneficial effect of bisoprolol (target dose 10 mg daily, achieved 8.6 mg daily) was present across all categories of eGFR. Numerically, all-cause mortality did not improve in patients with eGFR <60 ml/min/1.73 m^2, but there was no significant treatment interaction (35). In the SENIORS (Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with Heart Failure) trial the effect of nebivolol (target dose 10 mg daily, achieved dose 7.7 mg daily) in patients with reduced eGFR was not different from the effect in patients with eGFR above 60 ml/min/1.73 m^2 (36). Finally, a meta-analysis of the effect of carvedilol in the COPERNICUS (Carvedilol Prospective Randomized Cumulative Survival) and CAPRICORN (Carvedilol Post Infarct Survival Control in LV Dysfunction) trials showed that this beta-blocker significantly improved outcome in patients with eGFR between 45 and 60 ml/min/1.73 m^2. There was no interaction between the effect of carvedilol treatment and eGFR categories (<45 vs. 45 to 60 ml/min/1.73 m^2) (37).

Stage 4 and 5 CKD. Data from both the MERIT-HF and CIBIS-II trials suggest that beta-blockers are clearly effective in patients with eGFR <45 ml/min/1.73 m^2 (34,35). Especially in the MERIT-HF study, the metoprolol/placebo hazard ratio was 0.41 (95% confidence interval: 0.25 to 0.68) in the 493 patients with eGFR <45 ml/min/1.73 m^2 (12% of the whole study population). This subgroup had a mean eGFR of 36.6 ± 6.8 ml/min/1.73 m^2, which included patients with eGFR <30 ml/min/1.73 m^2. In the SENIORS study, only 3.1% of patients had stage 4 CKD, but no subgroup analysis has been performed on these patients. As described earlier, in a meta-analysis of the CAPRICORN and COPERNICUS studies, there was no significant interaction between baseline eGFR and the effect of carvedilol, suggesting that carvedilol might improve outcome irrespective of renal function (37). However, only 8% of all patients in these studies had stage 4 CKD. In 1 small trial in hemodialysis patients with HF, carvedilol significantly improved the secondary combined endpoint of all-cause mortality and CV death (38).

Large subgroup analyses from landmark trials have shown clear mortality and morbidity benefit for beta-blocker therapy in the general HF population with stage 3 CKD, and it seems likely that beta-blockers improve outcome in HF patients with severe renal dysfunction (stage 4 and 5 CKD).

Digoxin

Stage 3 CKD. Only 1 landmark placebo-controlled randomized trial, the DIG (Digitalis Investigation Group) study, examined the effects of adding digoxin (target dose individually determined, median achieved dose 0.25 mg daily, with 1% taking 0.5 mg daily) to treatment with a diuretic and ACEi in patients with HFREF (Table 7) (39). Shlipak et al. (40) examined whether baseline renal function modified the effect of digoxin and showed that the effect of this treatment was consistent across 3 eGFR categories studied (i.e., <30, 30 to 60, and >60 ml/min/1.73 m^2).

Stage 4 and 5 CKD. There was no interaction between baseline renal function and the effect of digoxin in 218 patients with stage 4 CKD in the DIG study. Moreover, in another analysis of the DIG study, digoxin reduced mortality in 289 patients with sCr >2.0 mg/dl, with a significant interaction between the effect of digoxin and baseline sCr, with a stronger effect of digoxin in patients with higher baseline sCr (40). Given the renal excretion of digoxin and the risk of digoxin intoxication especially in renal insufficiency, careful monitoring or renal function and especially potassium, in addition to digoxin concentration monitoring, is indicated with the use of digoxin. This is supported by findings in the DIG study, where patients with eGFR <30 ml/min/1.73 m^2 were treated with the lowest doses of digoxin but still had the highest serum digoxin levels.

Digoxin might be considered in patients with stage 3 to 5 CKD, with careful monitoring of digoxin concentrations and electrolytes.

Ivabradine

The effect of ivabradine on mortality and morbidity in patients with LV systolic dysfunction was studied in 2 studies (SHIFT [Systolic Heart failure treatment with the IF inhibitor ivabradine Trial] and BEAUTIFUL [Morbidity-mortality Evaluation of the If inhibitor ivabradine in patients with coronary disease and left-ventricular dysfunction] trials), but a renal subgroup analysis has not been published in either (Table 7) (41,42). Considering the pharmacological effect of ivabradine, it is unlikely to cause deterioration in renal function, and because renal clearance accounts for 20% of ivabradine clearance, there is no need for dose adjustment in patients with renal impairment, although there are no data in patients with creatinine clearance <15 ml/min.

Hydralazine and Isosorbide-Dinitrate

No renal subgroup analyses are available from the V-HeFT (Vasodilator Heart Failure Trial) studies (43,44). A-HeFT (African-American Heart Failure Trial), in African-American HF patients, did not show significant interaction between a history of "renal insufficiency" and the effect of hydralazine and isosorbide-dinitrate (H-ISDN) therapy

Table 6 Characteristics of BBL Studies

Study*	n	Design	Primary Outcome	LVEF	NYHA	Renal Function Exclusion; Creatinine, mg/dl (μmol/l)	Baseline Renal Function (eGFR or sCr)	CKD	Concomitant Therapy				Renal Subgroup Analysis	Relative Risk (Primary Outcome Study) (95% CI)
									ACEi/ARB	BBL	MRA	Digoxin		
MDC	383	Metoprolol vs. Placebo	ACM	22	49% III	NA	1.14 mg/dl	NA	80	50	NA	79	No	HR: 0.68 (0.38–1.06)
CIBIS	641	Bisoprolol vs. Placebo	ACM	25	95% III	>3.4 (300)	NA	NA	90	50	NA	56	No	HR: 0.80 (0.56–1.15)
US-Carvedilol	1,094	Carvedilol vs. Placebo	ACM	22	44% III	Clinically important renal disease	NA	NA	95	64	NA	91	No	HR: 0.35 (0.20–0.61)
MERIT-HF	3,991	Metoprolol vs. Placebo	ACM	28	56% III	NA	67 ml/min/1.73 m^2	37	95	50	NA	63	Yes	HR: 0.66 (0.53–0.81) GFR <45: HR: 0.41 (0.25–0.68) GFR 45–60: HR: 0.68 (0.45–1.02) p value for interaction = 0.095
CIBIS-II	2,647	Bisoprolol vs. Placebo	ACM	28	83% III	>3.4 (300)	65 ml/min/1.73 m^2	43	96	50	10	52	Yes	HR: 0.66 (0.54–0.81) GFR <45: HR: 0.71 (0.48–1.05) GFR 45–60: HR 0.69 (0.46–1.04) No significant interaction between GFR and treatment
COPERNICUS	2,289	Carvedilol vs. Placebo	ACM	20	100% III/IV	>2.8 (247.5)	1.53 mg/dl	61†	97	50	20	66	Yes	HR: 0.65 (0.52–0.81) CKD: HR: 0.76 (0.63–0.93)† No significant interaction between GFR and treatment
CAPRICORN	1,959	Carvedilol vs. Placebo	ACM	33	NA	Renal impairment	NA	61†	98	50	NA	NA	Yes	HR: 0.77 (0.60–0.98)§ CKD: HR: 0.76 (0.63–0.93)‡ No significant interaction between GFR and treatment
BEST	2,708	Bucindolol vs. Placebo	ACM	23	92% III	>3.0 (265)	NA	NA	91‖	50	4	92	No	HR: 0.90 (0.78–1.02)
COMET	3,029	Metoprolol vs. Carvedilol	ACM	26	49% II	NA	NA	NA	92	100	11	60	No	HR: 0.83 (0.74–0.93)
SENIORS	2,128	Nebivolol vs. Placebo	ACM or CV hosp	36	39% III	Significant renal dysfunction	65 ml/min/1.73 m^2	42	82‖	50	28	39	Yes	HR: 0.86 (0.74–0.99)¶ GFR <55: HR: 0.81 (0.64–1.03)¶
ACEi vs. BBL therapy														
CIBIS-III	1,010	Bisoprolol vs. enalapril, either first	ACM or ACH	29	49% II	>2.5 (220)	1.13 mg/dl	NA	100	100	13	NA	UYes	HR: 0.94 (0.77–1.16) No significant interaction between GFR and treatment

Values are percentages, unless otherwise indicated. Studies that included >250 patients and small but important studies are presented. *Please see the Online Appendix for a list of the trial acronyms. †CKD rate in combined CAPRICORN and COPERNICUS population. ‡From cumulative HR from meta-analysis of COPERNICUS and CAPRICORN studies. §ACM data. Primary endpoint of the CAPRICORN study was time to ACM or cardiovascular hospital stay: HR: 0.92 (95% CI: 0.80–1.07). ‖ACEi only, because ACEi and ARB were not reported as combined treatment. ¶ACM data, overall: HR: 0.88 (95% CI: 0.71–1.08); CKD, HR: 0.76 (95% CI: 0.56–1.03).

ACH = all-cause hospital stays; other abbreviations as in Tables 2, 3, and 4.

(target dose 225 mg hydralazine/120 ISDN, achieved dose in 68%) (44).

Diuretics

Diuretics are indicated in patients with symptoms and/or signs of congestion (1,2). Current guidelines advocate using the minimum dose necessary to achieve "dry weight" and to reduce the dose, if possible, so as to prevent dehydration and deterioration in renal function. Paradoxically, it has recently been recognized that diuretics might improve renal function if there is renal venous congestion, emphasizing that diuretic needs might change according to the clinical status of patients and that dose should be fine-tuned on an individual basis (45). No specific data are available that show improvement in outcome in patients with HF and renal impairment, and only 1 small meta-analysis showed a possible prognostic benefit of loop diuretics in the general HF population. There is also a call for a shift toward novel loop diuretics such as torsemide, because small randomized trials might suggest improvement in clinical outcome, but to date the pooling of studies does not suggest improved outcome in the entire HF population (46–48). Therefore, start and titration of diuretic therapy is dependent on individual patient characteristics, including vital signs, symptoms, and signs of congestion and baseline renal function.

Implantable-Cardioverter Defibrillator Therapy

Approximately 8 trials examined the role of implantable-cardioverter defibrillator (ICD) therapy for primary (49–52) and secondary (53–56) prevention of fatal ventricular arrhythmia in ischemic and nonischemic populations (Table 8). Although renal dysfunction was not an exclusion criterion in these trials, baseline renal function was reported only in the MADIT (Multicenter Automatic Defibrillator Implantation Trial), MADIT II (Multicenter Automatic Defibrillator Implantation Trial II), and SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial) (Table 8) (49,50,52). Only 1 subgroup analysis has been published looking at patients with stage 3 CKD. This subgroup analysis from the MADIT II study showed beneficial effects of ICD therapy in all patients, including those with eGFR between 35 and 60 ml/min/1.73 m^2, without evidence of significant interaction between ICD therapy and renal function (57). Numerically, the beneficial effect of ICD therapy was not observed in 80 patients with eGFR <35 ml/min/1.73 m^2. However, the interaction between baseline eGFR and the effect of ICD therapy was not statistically different, suggesting that the overall effect of the study also applied to this specific patient cohort (57).

Patients with stage 3 to 5 CKD were not excluded from ICD trials, and the treatment effect seems independent of renal function. Therefore these patients should be considered for ICD therapy.

Cardiac Resynchronization Therapy

Stage 3 CKD. The landmark CARE-HF (Cardiac Resynchronization Heart Failure) trial provides the best data on the effects of cardiac resynchronization therapy (CRT) in patients with stage 3 CKD (Table 9) (58). Overall, CRT led to a 37% relative risk reduction in all-cause mortality in the CARE-HF trial. There was no interaction between baseline GFR and the effect of treatment (i.e., CRT led to a relative risk reduction in mortality of 33% in patients with CKD). In patients with milder symptoms and stage 3 CKD in the MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization) trial, the benefit of CRT-D, compared with an ICD, was similar to that in the entire population, with no interaction between renal function and effect of treatment (59,60). In the RAFT (Resynchronization Defibrillation for Ambulatory Heart Failure Trial), CRT improved outcome in patients with and without CKD, without a significant interaction between baseline renal function and the effect of treatment (61). Importantly, almost 50% of patients had eGFR <60 ml/min/1.73 m^2 in the RAFT and MADIT-CRT studies, suggesting that the overall findings are generalizable. From a pathophysiological perspective, CRT improves cardiac output and thereby probably improves renal perfusion and function (62). This was confirmed in a systematic review of CRT in CKD, where CRT not only improved eGFR but also clinical outcome (63).

Stage 4 and 5 CKD. Although patients with a sCr >3.0 mg/dl were excluded from the MADIT-CRT and MIRACLE (Multicenter InSync Randomized Clinical Evaluation) trials, a large proportion had CKD, defined as an eGFR <60 ml/min/1.73 m^2 (as did many in the CARE-HF (Cardiac Resynchronization Heart Failure) and RAFT studies), meaning that some patients with stage 4 and 5 CKD were included in these trials (59,64). However, the effect of therapy in these patients has not been reported (58,59,61,64).

There is convincing evidence for the use of CRT therapy in patients with mild to severe HF and stage 3 CKD, whereas there are no specific data on the effect of CRT in stage 4 to 5 CKD.

Absolute and Relative Risk Reduction in Patients With Stage 3 to 5 CKD

Because patients with stage 3 to 5 CKD have much higher rates of death and hospital stay than patients with little or no renal dysfunction, the absolute risk reduction with the treatments discussed earlier is potentially much greater in the former patients. For instance, in the MERIT-HF study, the absolute risk reductions with metoprolol in patients with an eGFR >60, 45 to 60, and <45 ml/min/1.73 m^2 for all-cause mortality were 2.5%, 3.95%, and 12.6%, respectively. This resulted in a number needed to treat for 18 months of 40, 26, and 8 to prevent 1 death for each eGFR category.

Table 7 Characteristics of Studies of Other Pharmacological Therapies

Study*	n	Design	Primary Outcome	LVEF	NYHA	Renal Function Exclusion; Creatinine, mg/dl (μmol/l)	Baseline Renal Function (eGFR)	CKD	Concomitant Therapy				Renal Subgroup Analysis	Relative Risk (Primary Outcome Study) (95% CI)
									ACEi/ARB	BBL	MRA	Digoxin		
Digoxin														
DIG	6,800	Digoxin vs. Placebo	ACM	28	31% III	>3.0 (265)	NA	46	94	NA	NA	50	Yes	HR: 0.99 (0.91–1.07)† GFR <30: HR: 0.93 (0.65–1.35)† GFR 30–60: HR: 0.95 (0.85–1.07)† No significant interaction between GFR and treatment
Ivabradine														
BEAUTIFUL	10,917	Ivabradine vs. Placebo	CV mortality or HF/MI hosp	32	61% II	Severe renal disease	NA	NA	90	87	27	NA	No	HR: 1.00 (0.91–1.10)
SHIFT	6,558	Ivabradine vs. Placebo	CV mortality or HF hosp	29	50% II	Severe renal disease	75 ml/min/1.73 m^2	NA	78‡	90	60	22	No	HR: 0.82 (0.75–0.90)
H-ISDN														
V-HeFT I	642	H-ISDN vs. Prazosin vs. Placebo	ACM	30	NA	Severe intrinsic renal disease	NA	NA	NA	NA	NA	100	No	H-ISDN: HR: 0.78 (0.58–1.04) Prazosin: HR: 1.11 (0.85–1.46) (both vs. placebo)
V-HeFT II	804	H-ISDN vs. Enalapril	ACM	29	50% II	Severe intrinsic renal disease	NA	NA	50	NA	NA	100	No	HR: 1.23 (0.97–1.55)
A-HEFT	1,050	H-ISDN vs. Placebo	ACM or HF hosp and QoL	24	96% III	Severe renal disease	NA	17	70†	74	39	60	Yes	ACM: HR: 0.57 (0.37–0.89) No significant interaction between CKD and treatment

Values are percentages, unless otherwise indicated. Studies that included >250 patients and small but important studies are presented. *Please see the Online Appendix for a list of trial acronyms. †The overall effect of digoxin on the combined endpoint of heart failure hospital stays and mortality was: HR: 0.75 (95% CI: 0.69–0.82), in GFR <30: HR: 0.77 (95% CI: 0.55–1.08), and in GFR 30–60 HR: 0.84 (95% CI: 0.76–0.93). ‡ACEi only, because ACEi and ARB were not reported as combined treatment.

MI = myocardial infarction; QoL = quality of life; other abbreviations as in Tables 2, 3, and 4.

Table 8 Characteristics of ICD Studies

Study*	n	Design	Primary Outcome	LVEF	NYHA	Renal Function Exclusion; Creatinine, mg/dl (μmol/l)	Baseline Renal Function†	CKD	Concomitant Therapy				Renal Subgroup Analysis	Relative Risk (Primary Outcome Study) (95% CI)
									ACEi/ARB	BBL	MRA	Digoxin		
MADIT	196	ICD vs. CMT	ACM	26	61% II/III	NA	20% BUN >25 mg/dl	NA	57	21	NA	48	No	HR: 0.46 (0.26–0.82)
AVID	1,013	ICD vs. CMT	ACM	32	9% III	NA	8%‡	NA	69	29	NA	43	No	HR: 0.62, p < 0.02
CASH	288	ICD vs. BBL vs. Amio	ACM	46	73% II/III	NA	NA	NA	41	33	NA	21	No	HR: 0.77, 1-sided p = 0.08
CIDS	659	ICD vs. Amio	ACM	34	11% III/IV	NA	NA	NA	NA	27	NA	26	No	RRR: 19.7% (−7.7% to 40.0%) p = 0.14
CAT	104	ICD vs. CMT	ACM	24	35% III	NA	NA	NA	96	4	NA	81	No	OR: 0.82 (0.59–1.12)§
MADIT II	1,232	ICD vs. CMT	ACM	23	25% III	End-stage renal disease	69 ml/min/1.73 m^2	38	69	70	NA	57	Yes	HR: 0.69 (0.51–0.93) GFR 35–60: HR: 0.74 (0.48–1.15) GFR <35: HR: 1.09 (0.49–2.43) No significant interaction between GFR and treatment
DEFINITE	458	ICD vs. CMT	ACM	21	21% III	NA	NA	NA	86	85	NA	42	No	HR: 0.65 (0.40–1.06)
SCD-HeFT	2,521	ICD vs. CMT vs. Amio	ACM	25	30% III	NA	1.12 (0.9–1.3) mg/dl	NA	85	69	NA	70	No	Amio vs. CMT HR: 1.06 (0.86–1.30) ICD vs. CMT HR: 0.77 (0.62–0.96)

Values are percentages, unless otherwise indicated. Studies that included >250 patients and small but important studies are presented. *Please see the Online Appendix for a list of the trial acronyms. †sCr (mg/dl [μmol/l]), eGFR (ml/min/1.73 m^2), or percentage CKD. ‡Renal disease in the AVID study was defined as glomerulonephritis, acute tubular necrosis, renal insufficiency, chronic renal infections, or chronic renal failure. The eGFR was not available. §From Youn et al. (81).

Amio = amiodarone; BUN = blood urea nitrogen; CMT = conventional medical therapy; LVESV = left ventricular end systolic volume; 6MWT = 6-min walk test; OMT = optimal medical therapy; OR = odds ratio; RRR = relative risk reduction; RV = right ventricular; other abbreviations as in Tables 2, 3, 4, and 7.

Table 9 Characteristics of Studies on CRT

Study*	n	Design	Primary Outcome	LVEF	NYHA	Renal Function Exclusion; Creatinine, mg/dl (μmol/l)	Baseline Renal Function†	CKD	Concomitant Therapy				Renal Subgroup Analysis	Relative Risk (Primary Outcome Study) (95% CI)
									ACEi/ARB	BBL	MRA	Digoxin		
MUSTIC-SR	67	Cross over CRT on/off	6MWT	23	100% III	NA	NA	NA	96	28	22	48	No	399 vs. 326 m $p < 0.001$
MUSTIC-AF	43	Cross over CRT on/off	6MWT	26	95% III	NA	NA	NA	100	23	16	58	No	341 vs. 359 m $p > 0.05$
MIRACLE	453	ICD+CRT (on) vs. ICD+CRT (off)	NYHA, 6MWT, QoL	22	90% III	>3.0 (265)	NA	38	92	59	NA	78	Yes	Δ QoL −18.0 vs. −9.0, $p = 0.001$ CRT effective in all GFR categories
CONTAK-CD	490	ICD+CRT (on) vs. ICD+CRT (off)	Composite endpoint	21	68% III/IV	NA	NA	NA	88	47	NA	69	No	RRR 15% $p = 0.35$
MIRACLE-ICD	369	ICD+CRT (on) vs. ICD+CRT (off)	NYHA, 6MWT, QoL	24	89% III	>3.0 (265)	NA	NA	91	60	NA	NA	No	Δ QoL −17.5 vs. −11.0 $p = 0.02$
COMPANION	1,520	ICD (on) +CRT vs. ICD (off) +CRT vs. OMT	ACM or ACH	21	85% III	NA	23% renal dysfunction	NA	90	68	54	NA	No	CRT vs. OMT: HR: 0.81 (0.69–0.96) ICD vs. CRT: HR: 0.80 (0.68–0.95)
CARE-HF	813	CRT vs. CMT	ACM	25	6% IV	NA	60 (46–73)	50	95	72	56	43	Yes	HR: 0.63 (0.51–0.77) CKD HR: 0.67 (0.50–0.89) No significant interaction between CKD and treatment
REVERSE	610	CRT (on) vs. CRT (off)	HF clinical change	26	82% II	>3.0 (265)	86 ± 33	29	96	95	NA	NA	Yes	21% vs. 16% worsened No interaction between CKD and treatment effect
MADIT-CRT	1,820	CRT+ICD vs. ICD	ACM or HF events	24	85% II	>3.0 (265) BUN >70 mg/dl	1.2 ± 0.4 24% BUN >26 mg/dl	NA	77‡	93	32	25	Yes	HR: 0.66 (0.52–0.84) CKD: HR: 0.67 (0.50–0.89) No significant interaction between CKD and treatment
RAFT	1,798	CRT+ICD vs. ICD	ACM or HF hosp	23	20% III	None	60 ± 20	50	97	90	42	34	YES	HR: 0.75 (0.64–0.87) No significant interaction between CKD and treatment

Values are percentages, unless otherwise indicated. Studies that included >250 patients and small but important studies are presented. *Please see the Online Appendix for a list of the trial acronyms. †sCr (mg/dl [μmol/l]), eGFR (ml/min/1.73 m^2), or percentage CKD. ‡ACEi only; ARB use was 20%.

Abbreviations as in Tables 2, 3, 4, 7, and 8.

Table 10 Incidence of WRF and Hyperkalemia in HF Trials

Study*	n	Treatment	Definition WRF	Incidence WRF	Discontinuation for WRF	Incidence Hyperkalemia	Discontinuation for Hyperkalemia
ACEi							
CONSENSUS	127	Enalapril	>30% increase in sCr	35	5	7	NA
	126	Placebo		18	3	4	
SOLVD Treatment	1,285	Enalapril	Increase in sCr above	10.7	NA	6.4	NA
	1,284	Placebo	2 mg/dl	7.7	NA	2.5	
SOLVD Prevention	2,111	Enalapril	NA	NA	NA	1.1	NA
	2,117	Placebo				0.4	
SAVE	1,115	Captopril	>0.3 mg/dl increase	6.4	NA	NA	NA
	1,116	Placebo	in sCr	5.7			
TRACE	876	Trandolapril	'Renal dysfunction'	13.7	2	4.9	NA
	873	Placebo		10.8	1	2.6	
NETWORK	506	Enalapril 2.5 mg	Increase in sCr above	3.0	NA	1.6	NA
	510	Enalapril 5.0 mg	2.3 mg/dl	5.3		2.2	
	516	Enalapril 10 mg		5.8		3.3	
AIRE	1,004	Ramipril	NA	1.5	NA	NA	NA
	982	Placebo		1.2			
ATLAS	1,596	Lisinopril low	NA	7	0.4	4	0.1
	1,568	Lisinopril high		10	0.3	6	0.4
BBL							
US-Carvedilol	696	Carvedilol	NA	7	0.3	NA	NA
	398	Placebo		5	0.3		
SENIORS	1,060	Nebivolol	'Renal failure'	10.1	0.1	NA	NA
	1,052	Placebo		7.4	0.1		
MRA							
RALES	822	Spironolactone	>30% decrease in eGFR	17	9.3	2	NA
	841	Placebo	during titration	7	8.3	1	
EPHESUS	3,319	Eplerenone	>20% decrease in eGFR	16.9	NA	5.5	NA
	3,313	Placebo	in 1 month	14.7		3.9	
EMPHASIS	1,360	Eplerenone	'Renal failure'	1.9	0.3	8.0	1.1
	1,369	Placebo		2.3	0.4	3.7	0.9
ARBs							
SPICE	179	Candesartan	'Renal Insufficiency'	NA	3.9	2.2	NA
	91	Placebo			3.3	2.2	
Val-HeFT	2,511	Valsartan	'Renal impairment'	NA	1.1	NA	NA
	2,499	Placebo			0.2		
CHARM-Added	1,276	Candesartan	Doubling of sCr	7	8†	3	3.4
	1,272	Placebo		6	4†	1	0.7
CHARM-Alternative	1,013	Candesartan	Doubling of sCr	5.5	6.1†	3	1.9
	1,015	Placebo		1.6	2.7†	1.3	0.3
CHARM-Preserved	1,514	Candesartan	Doubling of sCr	6	4.8†	2	1.5
	1,509	Placebo		3	2.4†	1	0.6
HEAAL	1,921	Losartan low	'Renal impairment'	17	1.9	7	0.2
	1,913	Losartan High		24	3	10	0.5
ARBs vs. ACEi							
ELITE	722	Captopril	Persisting >0.3 mg/dl	10.5	0.8	23‡	1.6
		Losartan	increase in sCr	10.5	1.4	19‡	0.9
OPTIMAAL	2,733	Captopril	NA	NA	<0.5	NA	<0.5
	2,744	Losartan			<0.5		<0.5
VALIANT	4,909	Captopril	'Renal dysfunction'	3.0§	0.8	0.9§	0.1
	4,909	Valsartan		4.9§	1.1	1.3§	0.1
	4,885	Captopril + Valsartan		4.8§	1.3	1.2‡	0.2
Other							
A-HEFT	517	H-ISDN	'Acute kidney failure'	1.5	0.4	2.9	NA
	527	Placebo		2.8	0.2	1.9	

Values are percentages, unless otherwise indicated. Only studies with published data are shown. *Please see the Online Appendix for a list of trial acronyms. †Increase in sCr. ‡Persisting increase >0.5 mg/dl from baseline. §Requiring dose reduction, but not discontinuation.

Abbreviations as in Tables 2, 3, 4, 7, and 8.

Finally, in a subgroup analysis of the RALES trial, the absolute risk reduction with spironolactone in patients with an eGFR 30 to 60 ml/min/1.73 m^2 was 10.3% compared with 6.4% in those with an eGFR of ≥60 ml/min/1.73 m^2 (number needed to treat 10 vs. 16 for 3 years to prevent 1 death) (32).

Safety of Evidence-Based Therapies in HF Patients With Renal Dysfunction

RAAS-inhibitors: worsening renal function. Physicians are often concerned that initiation of an ACEi, ARB, or MRA will lead to deterioration in renal function, and indeed an increase in sCr often occurs, although it is usually small (32,65–68). This concern might be amplified by the perception that worsening renal function (WRF) is associated with increased mortality in patients with HF, although this is not entirely correct, as explained in the following (69).

During initiation of an ACEi or ARB, between 10% and 35% of patients experience some increase in sCr (Table 10). In the CONSENSUS trial, the incidence of a substantial increase in sCr (30% to 100%) was 24%, whereas 11% even had more than doubling of sCr (70). Early WRF occurred in as much as 10% of patients in the SOLVD studies (66). In the CHARM program, the incidence of doubling of sCr was higher in the candesartan (5.5% to 7%) than in the placebo groups (1.6% to 6%) (71,72). In head-to-head comparisons, the risk of WRF is similar with ARBs as with ACEi, and the frequency of WRF is higher on higher-dosage regimens of ARB or ACEi (19,24,26,73). The effect of MRAs on change in eGFR in clinical trials showed similarities with that observed in trials with ACEi and ARBs. After an initial fall in eGFR, the gradual decline in renal function over time with an MRA runs parallel to that in the placebo group (67). In clinical trials at least, the incidence of clinically important renal dysfunction seems to have been similar in the placebo and MRA group (e.g., approximately 2% in the EMPHASIS-HF trial) (7).

Recently, it has become clear that deterioration in renal function induced by inhibition of the RAAS does not have the same adverse prognostic implications as other types of WRF in HF. For example, WRF after initiation of enalapril in the SOLVD trial did not confer increased risk of death, compared with an increase in creatinine in the placebo group (66). Even in the CONSENSUS trial, where most patients experienced an increase in creatinine with enalapril, ACE inhibition led to a striking improvement in survival (68). Similarly, in the RALES trial, spironolactone caused more WRF than placebo, but WRF was not associated with worse outcome in the spironolactone group, in contrast to WRF occurring in the placebo group (32).

Clearly, however, an extreme deterioration in renal function is not acceptable and is dangerous. However, the exact degree of WRF that should mandate dose-reduction or discontinuation of RAAS blockade is uncertain. From the large clinical trials, a decrease in eGFR of even 20% to 30% with ACEi, ARB, or MRA therapy with these treatments does not seem to attenuate the reduction in CV event rates. Therefore it seems that, although WRF (in these magnitudes) is unwanted, it should not be a reason to withhold or discontinue therapy. The latest guidelines suggest that an increase in creatinine of up to 50% above baseline or to an absolute 266 μmol/l (3 mg/dl)/eGFR <25 ml/min/1.73 m^2, whichever is the smaller, is acceptable (1,2). If sCr increases with a RAAS blocker, nephrotoxic drugs should be stopped if possible and/or the dose of the diuretic reduced. If these interventions are not relevant, not possible, or have no effect and renal function deteriorates to the extent described in the preceding text, the dose of the RAAS-inhibitor should be halved and sCr checked within 2 weeks. If the sCr increases by >100% or to >310 μmol/l (3.5 mg/dl)/eGFR <20 ml/min/1.73 m^2, RAAS blockade should be stopped.

Other therapies. Beta-blockers have little if any effect on renal function in patients with HF. An analysis from the SOLVD trial indicated that beta-blocker treatment at baseline was associated with a reduced risk of deterioration in renal function during follow-up, although this was an observational analysis, and patients had not been randomized to a beta-blocker or placebo (74). As discussed earlier, diuretics can cause hypotension, dehydration, and renal dysfunction (75). Therefore, diuretic dose should be altered on the basis of individual symptoms, signs, and electrolytes, including renal function. Other therapies, including ivabradine, digoxin, and H-ISDN, are not known to cause renal dysfunction.

RAAS-Inhibitors: Hyperkalemia

Patients with CKD are at increased risk for the development of hyperkalemia, and this risk is further increased by the introduction of RAAS inhibitors. Table 10 reviews the incidence of hyperkalemia in different clinical trials. Hyperkalemia is most frequently observed with the initiation of MRA therapy, but 6.4% of patients in the SOLVD Treatment trial were reported to have developed hyperkalemia with enalapril therapy. In the large MRA studies, the incidence of hyperkalemia ranged from 2% to 11.8%, depending on the definition (7,31,33). Importantly, no deaths attributable to hyperkalemia were reported in any of the MRA studies. Hyperkalemia occurred mostly in patients with low baseline eGFR, in those with WRF during therapy, and most importantly in those receiving spironolactone or eplerenone in the RALES and EMPHASIS-HF trials, respectively (32,76). A stringent monitoring of potassium levels in patients started on an MRA regimen seems warranted. For instance, in the EMPHASIS-HF trial, eplerenone was started only if the serum potassium level was no more than 5.0 mmol/l. Thereafter, the dose of eplerenone was decreased if the serum potassium level was 5.5 to 5.9 mmol/l during follow-up and withheld if the serum potassium rose above 6.0 mmol/l. Reassessment of potassium was done 72 h after dose reduction, and patients were re-challenged with eplerenone, only if potassium levels were below 5.0 mmol/l. This regimen was found to be highly effective, because the incidence of hyperkalemia leading to study drug withdrawal was not different from placebo (7). The new American College of Cardiology Foundation/American Heart Association guidelines support these recommendations (2). These findings highlight the importance of both hyperkalemia and rigorous

Table 11 Pharmacokinetic Properties and Advised Dose Adjustment in Patients With Reduced eGFR

Drug Class	Elimination	Dose Adjustments
ACEi		
Captopril	Predominantly renal $T_{1/2}$ 2 h	eGFR >40: no adjustment eGFR 20–40: one-half dosage eGFR 10–20: one-fourth dosage Dialysis: one-eighth dosage
Enalapril	100% renal $T_{1/2}$ 11 h	eGFR 30–80: no adjustment eGFR 10–30: one-half dosage Dialysis: only dose on dialysis days
Lisinopril	Predominantly renal $T_{1/2}$ 13 h	eGFR 30–80: no adjustment eGFR 10–30: one-half dosage Dialysis: only dose on dialysis days
Ramipril	Predominantly renal $T_{1/2}$ 13–17 h	eGFR 30–60: no adjustment eGFR 10–30: one-half dosage Dialysis: only dose on dialysis days
Trandolapril	33% renal 67% fecal $T_{1/2}$ 47–98 h	eGFR 10–70: no adjustment eGFR <10: maximum dose 2 mg daily
ARBs		
Candesartan	33% renal 67% fecal (bile) $T_{1/2}$ 9 h	Starting dose 4 mg
Valsartan	13% renal 83% fecal $T_{1/2}$ 6 h	eGFR >10: no adjustment no experience in eGFR <10 or dialysis
Losartan	35% renal 58% fecal (bile) $T_{1/2}$ 2 h	No adjustment
MRA		
Eplerenone	67% renal 32% fecal $T_{1/2}$ 3–5 h	eGFR >60: no adjustment eGFR 30–60: dose every other day eGFR <30: contraindicated
Spironolactone	Predominantly renal Also fecal $T_{1/2}$ 1.5 h	Contraindicated in 'severe renal failure'
BBL		
Bisoprolol	95% renal (50% inactive metabolite) $T_{1/2}$ 10–12 h	No information of pharmacokinetics in patients with reduced renal function
Carvedilol	Metabolization in liver Elimination fecal $T_{1/2}$ 6 h	No adjustment if systolic blood pressure is above 100 mm Hg
Metoprolol (CR/XL)	Metabolization in liver 100% renal of inactive metabolites $T_{1/2}$ 3.5–9 h (XL/CR)	Lower dosages in patients with reduced GFR. No formal advice
Nebivolol	38% renal 48% fecal $T_{1/2}$ 10–50 h	Mild-moderate eGFR: no adjustment Reduced eGFR: start at one-half dosage

Continued on the next page

monitoring, especially during up-titration and in patients with impaired renal function.

Renal Excretion of Pharmacological Therapies

Finally, the dose of several evidence-based treatments should be adjusted according to GFR, because their clearance from the circulation depends on renal function (Table 11). The dose of ACEi should be halved in patients in stage 4 and 5 CKD or given every other day in patients on dialysis. The same advice applies to MRAs, although eplerenone is not indicated in patients with eGFR <30 ml/min/1.73 m^2. Although most beta-blockers are cleared from the circulation to some extent by the kidneys, dose reduction is only required in patients with a severely reduced eGFR to achieve similar heart rate reductions compared with patients with normal renal function.

Conclusions: Recommendations for Clinical Practice

In general, the recommendations for medical therapy in HF patients with concomitant renal dysfunction are not qualitatively different from those in patients with preserved

Table 11 Continued

Drug Class	Elimination	Dose Adjustments
Other		
Digoxin	Predominantly renal $T_{1/2}$ 30–40 h	Loading and maintenance dose reduced on the basis of baseline eGFR
Hydralazine	100% metabolization	Prolong dose interval in severe renal impairment
ISDN	100% metabolization	Reduce dosages in severe renal impairment
Ivabradine	20% renal $T_{1/2}$ 11 h	No adjustment
Loop diuretics		
Furosemide	Predominantly renal $T_{1/2}$ 0.5–1 h	Unknown/dependent of urine output Consider higher dosages to achieve similar decongestion
Bumetanide	Metabolization in liver (50%) 50% renal $T_{1/2}$ 1 h	Unknown/dependent of urine output Consider higher dosages to achieve similar decongestion
Torsemide	Metabolization in liver (80%) 20% renal $T_{1/2}$ 3.5 h	Unknown/dependent of urine output Consider higher dosages to achieve similar decongestion

$T_{1/2}$ = half-life; other abbreviations as in Tables 2, 3, 4, 7, and 8.

renal function (Fig. 2) (1,2). Although there is less robust evidence of benefit in HF patients with a reduced GFR, subgroup analyses of the trials testing the major classes of drugs (ACEi, beta-blockers, MRAs, and ARBs) and devices (ICD/CRT) suggest that the relative risk reductions are similar (and absolute risk reductions greater), although these therapies might cause unwanted effects. Especially in patients with stage 4 and 5 CKD, care should be taken to assess whether possible beneficial effects might outweigh the potential risks associated with the initiation of this therapy. In all patients, frequent assessment of renal function and electrolytes (potassium) is essential to guide dose adjustment and (dis)continuation of therapy. Treatment discontinuation might be temporary and should follow the algorithms successfully implemented in clinical trials (e.g., the CHARM/EMPHASIS-HF trials), and this close monitoring is often best facilitated within disease management programs. Importantly, attempts should be made to reinstate the evidence-based therapy, once either renal function has improved or stabilized. For any HF patient with renal dysfunction (i.e., a patient with a greatly increased risk of death or HF hospital stay in the immediate future), the focus should be not only on survival but also on quality of life and time spent out of hospital. Considering that most evidence-based therapies are even more effective in reducing hospital stay than they are at decreasing mortality, each should at least be considered in patients with stage 3 to 5 CKD but their use must also be individualized.

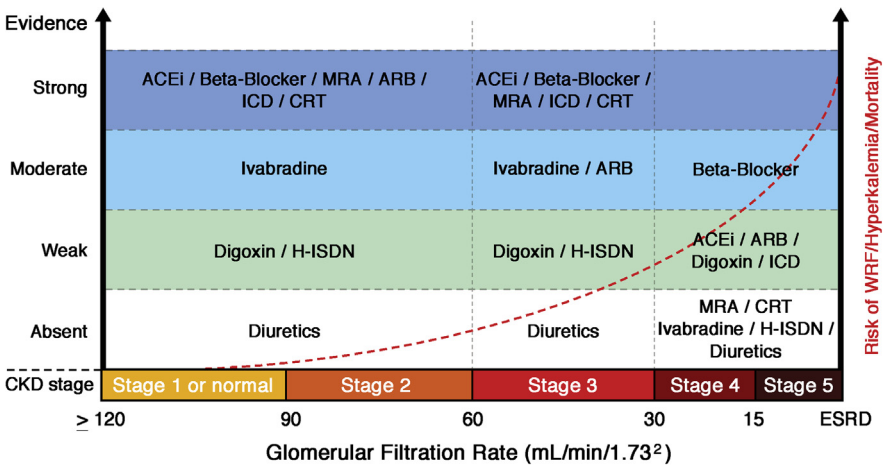

Figure 2 Strength of Evidence of Improvement in Clinical Outcome for Each Treatment Group According to CKD Stages

Strength of evidence according to American Heart Association/European Society of Cardiology heart failure guidelines for stage 1 and 2 CKD and according to Table 3 for stage 3 to 5 CKD. **Right y-axis and line** show hypothetical exponential increase in risk of worsening renal function (WRF)/hyperkalemia and mortality associated with more severe renal dysfunction. Other abbreviations as in Figure 1.

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Key Words: evidence-based treatment ■ heart failure ■ pharmacological treatment ■ renal insufficiency.

APPENDIX

For a complete list of trial acronyms, please see the online version of this article.