

Pharmacotherapy for Heart Failure in Patients with Renal Insufficiency

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Clinical trials have demonstrated that angiotensin-converting enzyme (ACE) inhibitors, β -blockers, and spironolactone improve survival in patients with heart failure. Because patients with heart failure and renal insufficiency have been underrepresented in these trials, little evidence is available to guide clinicians in the optimal management of patients with both conditions. Approximately one third to one half of patients with heart failure have renal insufficiency (estimated glomerular filtration rate [GFR] <60 mL/min per 1.73 m²), and renal insufficiency is among the strongest predictors of mortality in patients with heart failure. Evidence supports the use of ACE inhibitors to improve survival in patients with moderate renal insufficiency (GFR, 30 to 60 mL/min per 1.73 m²), but there is little evidence with which to weigh the risks and

benefits in patients with more advanced renal dysfunction. β -Blockers improve survival in patients with heart failure, and their beneficial effect is unlikely to differ according to renal function. Spironolactone improves outcomes in patients with advanced heart failure, but renal insufficiency appears to increase risk for hyperkalemia and limits the use of the drug in patients with severe renal insufficiency. Future clinical trials in heart failure should include a representative number of patients with renal insufficiency to improve the evidence base and outcomes in this vulnerable population.

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The survival of patients with heart failure can increase with the use of angiotensin-converting enzyme (ACE) inhibitors, angiotensin-receptor blockers (ARBs), β -blockers, and spironolactone. All major guidelines on heart failure recommend ACE inhibitors and β -blockers as standard therapy for patients with heart failure and left ventricular dysfunction (1, 2). Unfortunately, participants in the clinical trials were not representative of all patients with heart failure; on average they were younger, were more likely to be white and male, exclusively had left ventricular systolic dysfunction, and had fewer comorbid conditions than typical patients with heart failure (3). Another important group, patients with moderate and severe renal insufficiency, has also been relatively underrepresented or excluded from clinical trials. Thus, evidence has been inadequate to guide the management of patients with heart failure and renal insufficiency.

Renal insufficiency is relevant to the treatment of heart failure, in part because of its prevalence and its association with mortality. In the Studies of Left Ventricular Dysfunction (SOLVD) Treatment trial, one third of outpatients with moderate heart failure had an estimated glomerular filtration rate (GFR) less than 60 mL/min per 1.73 m² (4), and half of the participants in the Second Prospective Randomized study of Ibopamine on Mortality and Efficacy (PRIME-II), a clinical trial of patients with severe heart failure, had this degree of renal dysfunction (5). Renal insufficiency was associated with a twofold greater adjusted risk for death compared with normal renal function in the PRIME-II trial and was associated with a 40% increased risk in the SOLVD trials (4, 5).

Renal function is also important for the management of heart failure because several important medications, including ACE inhibitors, ARBs, spironolactone, and digoxin, may be associated with an increased risk for adverse effects in patients with renal insufficiency. Current

heart failure guidelines give few recommendations for managing heart failure complicated by renal dysfunction other than citing the serum creatinine levels used as exclusion criteria in the clinical trials (1–3). In this paper, I offer evidence-based insights into the balance between benefit and harm when treating heart failure in the presence of renal insufficiency and suggest directions for future research.

CLASSIFICATION OF RENAL FUNCTION

An initial challenge for determining the effect of renal insufficiency on heart failure therapy is the inconsistent definitions of renal insufficiency. Measuring GFR is expensive, time-consuming, and cumbersome and requires a radiolabeled isotope. Serum creatinine levels have been commonly used in research studies and clinical practice; however, they are insensitive markers for renal insufficiency, and they have a nonlinear association with GFR that varies by age, sex, race, and lean body mass. Rather than rely on the serum creatinine levels, clinicians should estimate renal function by using either the Cockcroft–Gault equation $[(140 - \text{age}) \times \text{body weight (kg)} \times 0.85 \text{ if female}] / [72 \times \text{serum creatinine level (mg/dL)}]$ or the Modification of Diet in Renal Disease formula (6, 7). A panel convened by the National Kidney Foundation defined moderate renal insufficiency as a GFR of 30 to 60 mL/min per 1.73 m², severe renal insufficiency as a GFR of 15 to 30 mL/min per 1.73 m², and kidney failure as a GFR less than 15 mL/min per 1.73 m² (8). I use these definitions through the remainder of this paper.

ACE INHIBITORS

Efficacy in Patients with Heart Failure and Renal Insufficiency

Angiotensin-converting enzyme inhibitors are the cornerstone of heart failure therapy and improve survival for

Table 1. Selected Placebo-Controlled Trials in Patients with Heart Failure: Renal Function of Participants and Medication Efficacy*

Drug	Study (Reference)	Renal Function Exclusion Criteria: Creatinine Level, $\mu\text{mol/L}$ (mg/dL)	Mean Creatinine Level, $\mu\text{mol/L}$ (mg/dL)	Relative Risk (95% CI)		Renal Insufficiency Subgroup Analysis?
				All-Cause Mortality	Heart Failure Hospitalizations	
ACE inhibitors						
Enalapril	CONSENSUS (11)	>300 (3.4)	124 (1.4)†	0.73	NA	Yes
Enalapril	SOLVD Prevention (9)	>175 (2.0)	106 (1.2)	0.92 (0.79–1.08)	0.80 (0.70–0.91)‡	No
Enalapril	SOLVD Treatment (10)	>175 (2.0)	106 (1.2)	0.84 (0.74–0.95)	0.74 (0.66–0.72)‡	No
Captopril	SAVE (13)	>221 (2.5)	117 (1.3)	0.81 (0.68–0.97)	0.78 (0.63–0.96)	No
Trandolapril	TRACE (14)	>200 (2.3)	NA	0.78 (0.67–0.91)	0.71 (0.56–0.89)	No
Ramipril	AIRE (15)	NA	NA	0.73 (0.60–0.89)	NA	No
Angiotensin-receptor blocker						
Valsartan	Val-HeFT (16)	NA	NA	1.02 (0.88–1.18)	0.87 (0.77–0.97)	No
β-Blocker						
Metoprolol	MERIT-HF (17)	NA	NA	0.66 (0.53–0.81)	0.65	No
Bisoprolol	CIBIS-II (18)	>300 (3.4)	NA	0.66 (0.54–0.81)	0.80 (0.71–0.91)§	No
Carvedilol	Australia/New Zealand Heart Failure Research Collaborative Group (19)	>250 (2.8)	NA	0.76 (0.42–1.36)	0.68 (0.40–1.17)	No
Carvedilol	U.S. Carvedilol Study Group (20)	Clinically important renal disease	NA	0.35 (0.20–0.61)	0.73 (0.55–0.97)	No
Carvedilol	COPERNICUS (21)	>250 (2.8)	133 (1.5)†	0.65 (0.52–0.81)	0.76 (0.67–0.87)‡	No
Spironolactone	RALES (22)	>221 (2.5)	106 (1.2)†	0.70 (0.60–0.82)	0.70 (0.59–0.82)§	Yes
Hydralazine–Nitrates	V-HeFT (23)	NA	NA	0.66 (0.46–0.96)	NA	No
Digoxin	DIG (24)	>265 (3.0)	110 (1.3)	0.99 (0.91–1.07)	0.72 (0.66–0.79)	No

* ACE = angiotensin-converting enzyme; AIRE = Acute Infarction Ramipril Efficacy; CIBIS-II = Cardiac Insufficiency Bisoprolol Study II; CONSENSUS = Cooperative North Scandinavian Enalapril Survival Study; COPERNICUS = Carvedilol Prospective Randomized Cumulative Survival; DIG = Digitalis Investigation Group; MERIT-HF = Metoprolol CR/XL Randomized Intervention Trial in congestive Heart Failure; NA = not available; RALES = Randomized Aldactone Evaluation Study; SAVE = Survival and Ventricular Enlargement Trial; SOLVD = Studies of Left Ventricular Dysfunction; TRACE = Trandolapril Cardiac Evaluation; Val-HeFT = Valsartan in Chronic Heart Failure; V-HeFT = Vasodilator-Heart Failure Trial.

† Median level is shown in table.

‡ Includes death and hospitalization.

§ All-cause hospitalization.

|| Cardiovascular hospitalization.

patients with heart failure and left ventricular dysfunction. Studies have shown the efficacy of ACE inhibitors in all symptomatic classes of patients with systolic heart failure (9–12). The effect of ACE inhibitors in patients with heart failure and renal insufficiency—as defined by GFR in this paper—is not easy to determine, however, because 1) exclusions in the clinical trials were based on serum creatinine levels rather than estimated GFR, 2) only a small proportion of patients included in these trials had creatinine levels greater than 175 $\mu\text{mol/L}$ (2.0 mg/dL), and 3) most studies did not report subgroup analyses based on renal function.

The Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS), a trial of patients with severe heart failure, included the highest proportion of patients with renal insufficiency among the ACE inhibitor trials (Table 1). The stated enrollment criteria for CONSENSUS excluded patients with a serum creatinine level greater than 300 $\mu\text{mol/L}$ (3.4 mg/dL); however, only 26 of 253 participants had a serum creatinine level greater than 175 $\mu\text{mol/L}$ (2.0 mg/dL) and none had a serum creatinine level greater than 250 $\mu\text{mol/L}$ (2.8 mg/dL) (25). The median serum creatinine level was 123 $\mu\text{mol/L}$ (1.4 mg/dL), and the mean estimated GFR was 45 mL/min per 1.73 m², indicating moderate renal insufficiency on average. Partic-

ipants assigned to the enalapril group of the study had 31% lower mortality at 1 year, and those with baseline serum creatinine levels greater than and less than the median had similar survival benefit (26, 27).

CONSENSUS offers good evidence for the efficacy of ACE inhibitors in patients with heart failure and moderate renal insufficiency. However, the study did not include many patients with severe renal insufficiency (estimated GFR ≤ 30 mL/min per 1.73 m²), so the tradeoff between efficacy and safety of ACE inhibitors in these patients remains unknown. Careful use of ACE inhibitors should be attempted in patients with severe renal insufficiency because of the potential to improve survival, but many patients will not tolerate these agents because of hyperkalemia and worsened renal function. In patients with moderate or severe renal insufficiency, therapy with low doses of ACE inhibitors should be initiated (for example, 2.5 to 5.0 mg of lisinopril) and the dose should be increased gradually with careful monitoring of renal function and serum electrolytes (13–15).

Safety in Patients with Heart Failure and Renal Insufficiency

The most common rationale for not using ACE inhibitors in patients with heart failure is the fear of complica-

tions attributable to worsened renal function (28–30). In CONSENSUS, 35% of patients assigned to enalapril had increases in serum creatinine level of 30% or greater at the first follow-up visit; in all but a few patients, the creatinine level returned to normal by the follow-up measure even without a reduction in the ACE inhibitor dose (11, 25). Among patients whose creatinine levels increased more than 30%, the mean initial increase was 49% but the subsequent creatinine level was only 9% greater than baseline. Most important, the survival benefit from ACE inhibition appeared similar among patients with and without substantial elevations (>30%) in serum creatinine level (25, 31) (Table 1).

In the combined SOLVD trials, whose patients had less severe heart failure than those in CONSENSUS, the incidence of worsened renal function (increase in serum creatinine level $\geq 44 \mu\text{mol/L}$ [0.5 mg/dL] from baseline) was 16% in patients assigned to enalapril compared with 12% in patients assigned to placebo (9, 10, 32). The Assessment of Lisinopril and Survival (ATLAS) trial compared low and high doses of lisinopril on clinical outcomes

for patients with moderate to severe heart failure (29, 33). Although discontinuation rates were greater among patients in the high-dose group with baseline creatinine levels of 133 to 221 $\mu\text{mol/L}$ (1.5 to 2.5 mg/dL), ACE inhibitors were generally well tolerated by patients with renal insufficiency (34–36) (Table 2).

These studies should allay fears that ACE inhibitors are likely to cause irreversible harm to patients with heart failure and moderate renal insufficiency. In one third of patients with the most severe heart failure, creatinine levels increase substantially (>30%) independent of baseline renal function; however, only a small fraction of patients require discontinuation of therapy, and creatinine levels return to baseline in most patients even without dose adjustment (25). Measures to reduce the incidence of renal complications include initiating ACE inhibitor therapy when patients are volume replete, using low doses, and avoiding nonsteroidal anti-inflammatory drugs (NSAIDs) (30, 37–39). Severely increased creatinine levels that do not return to normal during follow-up could suggest renovascular disease, particularly in elderly patients (40).

Table 2. Incidence of Worsened Renal Function with Use of Angiotensin-Converting Enzyme Inhibitors and Angiotensin-Receptor Blockers in Patients with Heart Failure*

Study (Reference)	Drug	Patients	New York Heart Association Class	Definition of Worsened Renal Function	Time to Follow-up	Incidence of Worsened Renal Function	Discontinuation Rate for Worsened Renal Function
		<i>n</i>				%	
Packer et al. (34)	Captopril or enalapril	104	IV	Increase in BUN >7.14 $\mu\text{mol/L}$ (20 mg/dL) or increase in serum creatinine level, 35 $\mu\text{mol/L}$ (0.4 mg/dL)	1–3 mo	33	11.5
Gottlieb et al. (35)	Quinapril, 10 mg	20	III, IV	Any decrease in GFR	7 wk	25	0
CONSENSUS (11)	Enalapril, 40 mg	127	IV	Increase in serum creatinine level, 30%	6 mo	35	4.7
	Placebo	126				18	3.2
SOLVD (Treatment and Prevention Trials) (9, 10)	Enalapril	3379	I, II, III	Increase in creatinine level, 44 $\mu\text{mol/L}$ (0.5 mg/dL)	2.6 y	16	NA
	Placebo	3379				12	
TRACE (14)	Trandolapril, 4 mg	876	Any	Renal dysfunction	2–4 y	14	3
	Placebo	873				11	1
AIRE (15)	Ramipril, 10 mg	1004	I, II, III	NA	15 mo	NA	1.5
	Placebo	982				NA	1.2
ATLAS (29)	Creatinine level <133 $\mu\text{mol/L}$ (1.5 mg/dL)	Lisinopril 35 mg (1.5 mg/dL)	II, III, IV	Renal dysfunction/hyperkalemia†	54 mo	5.4	0.8
						5 mg	4.1
	Creatinine level $\geq 133 \mu\text{mol/L}$ (1.5 mg/dL)	Lisinopril 35 mg (1.5 mg/dL)				15.6	6.0
						5 mg	15.6
ELITE (36)	Captopril, 150 mg	370	II, III	Increase in creatinine level, 27 $\mu\text{mol/L}$ (0.3 mg/dL)	48 wk	10.5	0.8
	Losartan, 50 mg	352				10.5	1.4
Val-HeFT (16)	Valsartan, 160 mg	2511	II–IV	Renal impairment	23 mo	NA	1.1
	Placebo	2499				NA	0.2

* AIRE = Acute Infarction Ramipril Efficacy; ATLAS = Assessment of Treatment with Lisinopril and Survival; BUN = blood urea nitrogen; CONSENSUS = Cooperative North Scandinavian Enalapril Survival Study; ELITE = Evaluation of Losartan in the Elderly; GFR = glomerular filtration rate; NA = not available; SOLVD = Studies of Left Ventricular Dysfunction; TRACE = Trandolapril Cardiac Evaluation; Val-HeFT = Valsartan in Chronic Heart Failure.

† Renal dysfunction defined as kidney function abnormality, kidney failure, uremia, increased creatinine level, increased nonprotein nitrogen level.

Use of NSAIDs and Aspirin with ACE Inhibitors

Nonsteroidal anti-inflammatory drugs are associated with worsened outcomes in patients with heart failure (41) because they oppose the beneficial effects of ACE inhibitors by inhibiting the local production of prostacyclin (42). Patients with decreased renal perfusion due to hypovolemia or renal insufficiency are at particularly increased risk for adverse effects from combined use of ACE inhibitors and NSAIDs (43). Because of their mechanism of action, the new cyclooxygenase-2-selective NSAIDs, celecoxib and rofecoxib, are probably as risky in patients with heart failure as other NSAIDs and should also be avoided; however, no study has compared them with traditional NSAIDs in patients with heart failure.

Aspirin use may also antagonize prostacyclin production in patients with heart failure who are taking ACE inhibitors and may antagonize the beneficial effect of these drugs (44). Although several observational studies found a negative interaction between aspirin and ACE inhibitors in patients with heart failure (45–47), a meta-analysis of four large, placebo-controlled trials found a survival benefit from ACE inhibition even among patients with heart failure who were receiving aspirin (48). Patients with ischemic heart failure who cannot tolerate both aspirin and an ACE inhibitor because of renal dysfunction pose a challenging dilemma. If reducing the aspirin dose to 81 mg does not improve ACE inhibitor tolerance, then I recommend substituting aspirin for an alternative antiplatelet agent, such as clopidogrel; however, no clinical studies have evaluated this scenario.

ARBs

The ARBs have been compared with ACE inhibitors for their effect on survival and renal complications in heart failure. Although the Evaluation of Losartan in the Elderly (ELITE) trial found a mortality benefit in favor of losartan compared with captopril, the larger ELITE-2 trial did not confirm this finding; rather, it found no difference (36, 49). The incidence of worsened renal function (increase in creatinine level, 27 $\mu\text{mol/L}$ [0.3 mg/dL]) also did not differ (10.5%) in the two groups (36). Because the mean serum creatinine level ($\pm\text{SD}$) was $106 \pm 35 \mu\text{mol/L}$ ($1.2 \pm 0.4 \text{ mg/dL}$) in ELITE, most participants probably did not have renal insufficiency.

The Valsartan in Chronic Heart Failure Trial (Val-HeFT) compared the ARB valsartan with placebo in 5010 patients with heart failure, most of whom were receiving ACE inhibitors (16). Mortality did not differ between groups, but valsartan reduced the risk for hospitalization. In addition, valsartan reduced mortality among the 366 patients who were not taking ACE inhibitors (50). In summary, ARBs appear to improve survival in patients who cannot tolerate ACE inhibitors because of cough. Unfortunately, patients who experience hyperkalemia or wors-

ened renal function while taking ACE inhibitors are likely to have the same complications with an ARB (51).

β -BLOCKERS

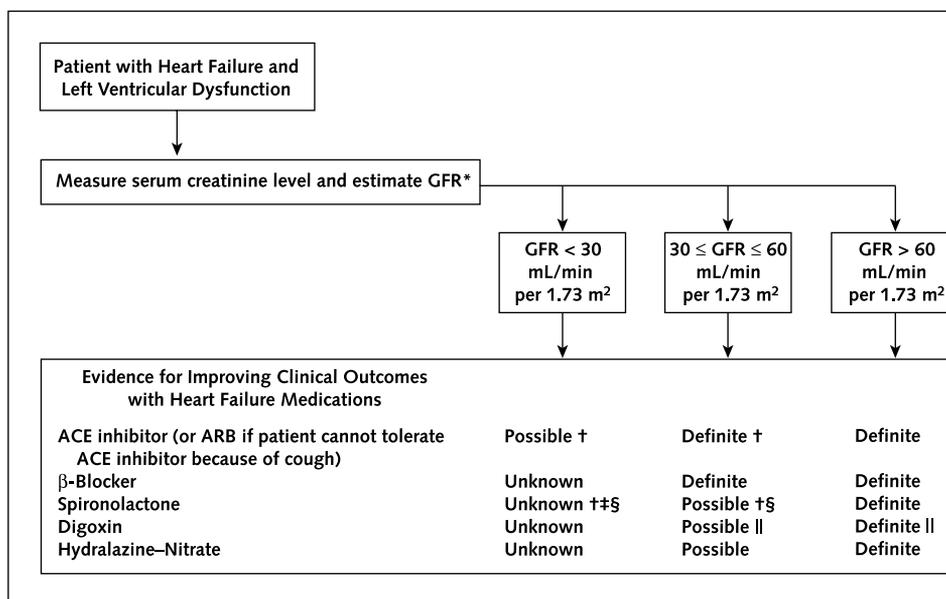
Clinical trials using bisoprolol, carvedilol, and metoprolol have found that β -blockers reduce mortality by 35% in patients with heart failure and left ventricular dysfunction (52). One trial did not mention renal function as an exclusion criterion (17), three trials excluded patients with creatinine levels greater than 250 to 300 $\mu\text{mol/L}$ (2.8 to 3.4 mg/dL) (18, 19, 21), and one trial excluded patients with “clinically important renal disease” (20). None of the large clinical trials of β -blockers in heart failure has reported any subgroup analyses based on renal function. One observational study that evaluated the association of β -blockers with survival after myocardial infarction in patients with left ventricular dysfunction found a similar survival benefit among patients with serum creatinine levels greater than or less than 175 $\mu\text{mol/L}$ (2.0 mg/dL) (53).

In contrast to ACE inhibitors, there is less physiologic rationale for a clinical effect of β -blockers to differ in patients with heart failure who have and do not have renal insufficiency. Few adverse renal events were reported in the large, placebo-controlled clinical trials (18, 19, 21). Cardiac output and renal blood flow may initially decrease after initiation of β -blocker therapy, leading to hypotension and worsened renal function. Over time, however, ejection fraction increases with use of β -blockers and renal blood flow may even improve over baseline (54, 55). In all patients with heart failure, adverse events from β -blockers can be limited by initiating therapy at the lowest possible dose and by increasing the dose gradually every 2 weeks. Despite the absence of evidence on the use of β -blockers in patients with heart failure and renal insufficiency, I believe they should be used in persons with or without renal dysfunction. Because metoprolol and carvedilol are predominantly cleared by the liver, these agents may be safer in patients with renal insufficiency than nadolol and atenolol, which are at least partially cleared by the kidney (56). Subgroup analyses from the β -blocker clinical trials should be conducted to confirm the beneficial effect of these drugs on clinical outcomes and to determine their safety in patients with heart failure and renal insufficiency.

SPIRONOLACTONE

In the Randomized Aldactone Evaluation Study (RALES), spironolactone reduced mortality by 30% in patients with severe heart failure (22). The RALES investigators excluded patients with a serum creatinine level of 221 $\mu\text{mol/L}$ (2.5 mg/dL) or greater; the median creatinine level was 106 $\mu\text{mol/L}$ (1.2 mg/dL). A significant treatment benefit was observed in patients with creatinine levels greater than and less than the median. Only 2% of patients assigned to spironolactone in RALES experienced serious hyperkalemia (potassium level $\geq 6.0 \text{ mmol/L}$), and the study

Figure. Treatment algorithm for patients with systolic heart failure, based on renal function.



Renal function should be categorized by estimated glomerular filtration rate (*GFR*), which can be calculated from the serum creatinine level. Evidence supporting a beneficial effect on clinical outcomes from each medication within subgroups of renal function is evaluated as definite, possible, or unknown by the author. These definitions are based on the range of renal function represented within the clinical trials and the reporting of results specific to patients with renal insufficiency. ACE = angiotensin-converting enzyme; ARB = angiotensin-receptor blocker. *Using Cockcroft–Gault equation (6) or Modification of Diet in Renal Disease formula (7). †Careful monitoring of renal function and electrolytes. ‡Possibly harmful because of hyperkalemia risk. §Consider withholding therapy during states of volume depletion because of hyperkalemia risk. ||Shown to help reduce hospitalization but not mortality.

did not report an association of renal function with hyperkalemia. Patients in RALES, however, were treated with an average furosemide dose of 80 mg, which may have limited hyperkalemia. The proportions of patients in RALES with an estimated *GFR* less than 30 mL/min per 1.73 m² and 30 to 60 mL/min per 1.73 m² have not been published.

Subsequent case series have noted increased incidence of serious hyperkalemia since dissemination of the RALES findings. One hospital-based study noted 19 patients with serious hyperkalemia (potassium level ≥ 6.0 mmol/L) after treatment with spironolactone; 15 of these patients had serum creatinine levels greater than 175 $\mu\text{mol/L}$ (2.0 mg/dL) at admission (57). Schepkens and colleagues (58) reported an analysis of 25 cases of severe hyperkalemia (mean potassium level, 7.7 mmol/L) that occurred during combined therapy with an ACE inhibitor and spironolactone; the average baseline creatinine level in these patients was 168 $\mu\text{mol/L}$ (1.9 mg/dL). Obialo and colleagues (59) described 18 cases of hyperkalemia in elderly patients with heart failure receiving spironolactone who had renal insufficiency (estimated *GFR* < 60 mL/min per 1.73 m²) but normal creatinine levels. A unifying theme across these and other case series (60, 61) is that most hyperkalemia cases during spironolactone therapy occur in patients with heart failure and renal insufficiency. However, the incidence of hyperkalemia in such patients cannot be determined from case series. I suggest avoiding spironolactone in patients with heart failure whose *GFR* is less than 30 mL/min per

1.73 m² but using it cautiously in patients with a *GFR* of 30 to 60 mL/min per 1.73 m² at a dosage no higher than 25 mg/d. Spirolactone should be withheld in patients with heart failure and renal insufficiency who have intercurrent illnesses (such as diarrhea) because dehydration appears to predispose toward hyperkalemia.

HYDRALAZINE–NITRATE

The Vasodilator-Heart Failure Trial (V-HeFT) demonstrated that the hydralazine–nitrate combination conferred a survival advantage compared with placebo or prazosin (23). The baseline renal function of the participants and the effect of baseline renal function on the study outcomes have not been presented. The second V-HeFT demonstrated that enalapril improved survival compared with the hydralazine–nitrate combination (62). Because hydralazine–nitrate requires frequent dosing, this treatment regimen is most useful in patients with heart failure who cannot tolerate an ACE inhibitor or ARB.

DIGOXIN

Digitalis is the oldest therapy for heart failure, and digoxin remains one of the most commonly prescribed drugs to treat heart failure (63). Because the clearance of digoxin varies linearly with *GFR*, renal function may affect the safety of digoxin (64–67). The Digitalis Investigation Group (DIG) evaluated the efficacy of digoxin in a double-

blind, placebo-controlled trial (24). An exclusion criterion in DIG was a serum creatinine level greater than 265 $\mu\text{mol/L}$ (3.0 mg/dL), but the median creatinine levels were 115 $\mu\text{mol/L}$ (1.3 mg/dL) in men and 97 $\mu\text{mol/L}$ (1.1 mg/dL) in women. Overall, digoxin did not affect survival but led to a 28% reduction in heart failure hospitalizations (68). In addition, a recent subgroup analysis found digoxin to be harmful in women in the DIG trial (69). No studies have evaluated whether the effect of digoxin on clinical outcomes differs by renal function. To be used safely in patients with heart failure and renal insufficiency, digoxin therapy should be initiated without a loading dose and maintained at a low dose (0.125 mg), perhaps on alternating days (64).

DIRECTIONS FOR FUTURE RESEARCH

Many questions on the care of patients with heart failure and renal insufficiency remain unanswered. Some of these important questions can be addressed by using the existing data collected in clinical trials, such as the distribution of renal function in each study and the safety and efficacy of the intervention in patients with renal insufficiency. The investigators of these trials should reexamine these data and publish the findings relevant to patients with heart failure and renal insufficiency. In addition, future research trials in heart failure should include more patients with renal insufficiency. Interventions could include medications whose efficacy remains unproven in severe renal insufficiency, such as ACE inhibitors and spironolactone, or new drugs. Studies are also needed to better define renal function in patients with heart failure. Current prediction equations should be evaluated against the gold standard of GFR measurement in patients with heart failure, and a GFR prediction equation specific to heart failure may be necessary.

SUMMARY

At least one third of patients with heart failure have renal insufficiency, which is associated with substantially increased mortality. Although clinical trials have shown that several medications improve survival and reduce hospitalizations in patients with heart failure, most included few patients with moderate and severe renal insufficiency. Rather than rely on serum creatinine levels, clinicians should estimate GFR to categorize renal function. The available data indicate that ACE inhibitors offer a survival advantage in patients with heart failure and mild and moderate renal insufficiency; their use in patients with severe renal insufficiency requires caution because of the potential risk for adverse events (Figure). The effect of β -blockers on improved heart failure survival is less likely to differ by renal function, but the β -blocker trials have not addressed the subgroup with moderate and severe renal insufficiency. The risk for hyperkalemia with spironolactone appears to be increased in renal insufficiency, and the safety of this

drug has not been evaluated in patients with severe renal insufficiency. The safety of digoxin in patients with severe renal insufficiency is also unknown. Future studies of current and future medications in patients with renal insufficiency are needed to improve the evidence base for treatment in this vulnerable population.

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