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Comparative Effectiveness Research in Heart Failure Therapies Women, Elderly Patients, and Patients with Kidney Disease

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No two patients have an identical form of the disease and it was desired to eliminate as many of the obvious variations as possible. This planning is a fundamental feature of the successful trial. To start out upon a trial with all and sundry included, and with the hope that the results can be sorted out statistically in the end is to court disaster.

—Sir A.B. Hill, 1951¹

INTRODUCTION

The incidence and prevalence of heart failure (HF) has increased during recent decades as a result of an aging population and improvements in treatment and survival of cardiovascular disease. Morbidity and mortality for HF are substantial, with more than 1.1 million hospital discharges in 2006 and almost 3.5 million outpatient visits in 2007. Estimated direct and indirect costs in 2010 amount to almost \$40 billion.²

Randomized controlled trials (RCTs) have identified effective HF treatments, but the patients included in these trials often represent a select subgroup of all patients with HF. RCT participants are often male, young, and with fewer and less severe comorbid conditions. Conversely, HF patients in daily practice are often old, female, and with extensive comorbid conditions.^{3,4} Thus, one is left with the dilemma described in the quote above: How can one determine effective treatments for HF populations that are underrepresented in RCTs?

The recently coined term “comparative effectiveness research” (CER) describes a field that aims to fill in the gaps in the evidence base. CER is defined, in part, as research that provides “direct comparison of effective interventions and their study in patients who are typical of day-to-day clinical care.”⁵ This article discusses methodological considerations in CER followed by a review of existing CER for pharmacologic management in HF, focusing on 3 special patient populations with HF: women, older patients, and patients with kidney disease.

METHODOLOGICAL CONSIDERATIONS FOR CER

Conventional RCTs commonly enroll the minimum number of patients required to establish efficacy and are generally not well powered to evaluate efficacy in clinically relevant subgroups. This methodology poses a significant challenge when providing treatment recommendations or formulating guidelines that can be generalized to under-represented patient populations.

RCT design could include certain methodological approaches to minimize bias among subgroups and allow for CER. One option is to recruit a large sample of patients using minimally restrictive inclusion and exclusion criteria—the “large sample trial.” In this way, the population enrolled more closely resembles the target population with the disease.

Analyses of trial data can assess treatment effect similarities across patient subgroups, with the groups of interest specified a priori. The first step is to examine outcomes in each subgroup, typically displayed in a forest diagram; the next is to test for subgroup by treatment interaction in a regression model. If a significant interaction emerges, then stratified subgroup analysis is justified. Investigators and readers should be cautious about multiplicity in subgroup analysis: the more the number of hypotheses that are tested, the more likely that the results are significant due to of chance alone. For example, at a significance of $\alpha = 0.05$, 10 subgroup comparisons yield a 40% probability that one of the conclusions is due to chance alone; 5 subgroup comparisons yield a 23% probability that one of the conclusions is due to chance alone.^{1,6}

With the preponderance of evidence to support certain HF therapies, additional RCTs to address special populations are unlikely. CER with observational, nonrandomized data may be useful in examining outcomes in subgroups that are underrepresented in RCTs. However, the treatment groups may not be comparable because the choice to treat is often related to patient characteristics, which are also related to the outcome. Several quasiexperimental study designs can address this limitation, and interested readers are referred to the references for more information about these advanced methods.^{7–9}

WOMEN

Women represent almost 60% of incident HF cases and HF hospitalizations but only 20%–30% of clinical trial participants.³ Disease characteristics differ between the sexes: antecedent hypertension and preserved ejection fraction are more prevalent among women, whereas antecedent coronary artery disease is less prevalent among women compared with men with HF.^{10,11} Because there is biological potential for women to respond differently to

various HF therapies compared with men, establishing efficacy and effectiveness of each specific HF therapy in women is important.

Beta-Blockers

Beta-blockers have the most evidence supporting their use in women with HF and reduced left ventricular ejection fraction (LVEF) (Table 1). Three major beta-blocker RCTs included subgroup or post hoc analysis to examine sex-specific treatment effect. A post hoc analysis of the Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF) showed a nonsignificant sex by treatment interaction ($P = .14$).^{12,13} In the stratified analysis, metoprolol treatment yielded a 21% decrease in the combined end point of hospitalizations and death in women ($P = .044$), compared with an 18% decrease in men ($P = .001$). Stratified analyses from 2 carvedilol RCTs, as well as the results of pooled trials and meta-analysis of beta-blocker trials, also support the benefits of beta-blocker use in women with HF and reduced LVEF.^{14–16}

Observational studies also suggest that beta-blockers are clinically effective in both women and men with HF. One such study used a large, Canadian discharge database and examined outcomes after HF hospitalization according to beta-blocker prescription. In the sex-stratified analysis, beta-blockers conferred similar survival benefits in men and women; no sex by treatment interaction was found.¹⁷ Another study of patients with HF discharged with beta-blocker therapy showed that patients with reduced LVEF had a significantly lower risk-adjusted mortality. In contrast, both men and women with preserved LVEF derived no benefit from beta-blocker therapy.¹⁸

Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers

Several RCTs have demonstrated that angiotensin-converting enzyme (ACE) inhibitor treatment in patients with HF and reduced LVEF reduces mortality (Table 2), and a meta-analysis demonstrated similar treatment effects in both men and women. The meta-analysis included 7 trials and 2898 women; the investigators found a relative risk (RR) of 0.92 (95% confidence interval [CI], 0.81–1.04) for mortality in treated women, compared with 0.82 (95% CI, 0.74–0.90) in men. Although the confidence interval for the treatment effect in women crosses 1, the sex-specific estimates were statistically similar.¹⁶ Observational studies also support the use of ACE inhibitors in women with HF and reduced LVEF.¹⁹

The Candesartan in Heart failure Assessment of Reduction in Mortality (CHARM-Overall) trial included 2400 women and provided a sex by treatment interaction analysis. The primary outcome, time to cardiovascular death or HF admission, was reduced by 18% in the treatment arm, with an insignificant sex by treatment interaction term ($P = .87$).²⁰

Aldosterone Receptor Antagonists

Aldosterone receptor antagonists were tested in 3 large RCTs in patients with reduced LVEF (Table 3). The Randomized Aldactone Evaluation Study (RALES) showed a significant reduction in mortality in the treatment arm, with similar effects in men and women.²¹ Results from the Eplerenone Post-Acute Myocardial Infarction Efficacy and Survival Study (EPHESUS) showed a 15% reduction in all-cause mortality; in the sex-stratified analysis,

the mortality reduction was significant for women but not for men. However, the sex by treatment interaction term was insignificant ($P = .44$), suggesting similar effects in men and women.²²

More recently, the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF) study provided further support for aldosterone receptor antagonists in women. In this RCT in mild HF with reduced LVEF, eplerenone significantly reduced all-cause mortality by 24% (adjusted hazard ratio [HR], 0.76; 95% CI, 0.62–0.93) and the primary end point of death from cardiovascular cause or HF hospitalization by 27% (adjusted HR, 0.63; 95% CI, 0.54–0.74). The sex by treatment interaction term was nonsignificant, and the sex-stratified analysis revealed significant reduction in the primary end point for both men and women treated with eplerenone.²³

Digoxin

Among the HF therapies, the Digoxin Investigators Group (DIG) trial results received much publicity for sex-specific treatment effects. The original investigation found that digoxin had a significant effect on HF hospitalization but did not alter mortality.²⁴ A subsequent post hoc analysis revealed more deaths among women in the treatment arm, 33.1% versus 28.9%, and a significant sex by treatment interaction term ($P = .014$),²⁵ suggesting that there may be increased drug toxicity in women. Further investigations of the DIG trial showed that sex-specific treatment effects disappeared at lower serum digoxin levels.²⁶ The findings of the DIG trial have not been confirmed in other studies.

Summary

Evaluation from RCTs and CER thus far suggests that most HF therapies have similar treatment effects in men and women, with the possible exception of digoxin. However, the studies described earlier have limitations. None were designed to specifically test sex by treatment interactions. Furthermore, HF with preserved LVEF is more common among women, but almost all RCTs include only patients with reduced LVEF and there are few observational studies of treatment in patients with preserved LVEF. As a result, there is no reliable evidence on which to base treatment of many women with HF seen in daily clinical practice. Several RCTs are underway to test various therapies in patients with HF and preserved LVEF and should shed light on treatment of women.^{27–29}

ELDERLY PATIENTS

The prevalence of HF increases from 2% to 3% at age 65 years to more than 80% in persons older than 80 years. HF is also the most common reason for hospitalization in elderly patients. The average age of HF onset is more than 75 years; this figure approaches 80 years in the Medicare population.^{30,31} Yet, the mean age of RCT participants is 61 years and many older patients with HF do not meet enrollment criteria.^{3,4} Comorbid conditions account for many of the RCT exclusions, although some trials exclude patients based on age alone. Older patients may metabolize medications differently compared with younger patients and may experience higher risk of adverse effects attributable to treatment. Thus,

establishing effectiveness and safety of each specific HF therapy in the older patient population with HF is important.

Beta-Blockers

Stratified analyses of beta-blocker RCTs by age are limited because of small sample sizes, particularly for the oldest patients (see Table 1). In the US Carvedilol Heart Failure Study, the investigators divided the cohort into older and younger than 59 years old and found mortality benefit in both age groups.¹⁴ In the second carvedilol RCT, COPENICUS, the investigators stratified at age 65 years and found similar treatment effects in older and younger groups.¹⁵ A post hoc analysis of MERIT-HF studied trial participants aged 65 years and older and found a 37% reduction in all-cause mortality (RR, 0.63; 95% CI, 0.48–0.83) among patients treated with metoprolol succinate, with a trend toward benefit in patients aged 75 years and older (RR, 0.71; 95% CI, 0.42–1.19). Older patients treated with metoprolol did not have an increased rate of adverse events (such as bronchospasm, depression, and dizziness) that resulted in therapy discontinuation.³²

Two investigations have focused exclusively on older patients with HF, including the Carvedilol Open Assessment II (COLA II) study and the Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors with Heart Failure (SENIORS). In the COLA II study, more than 1000 patients with HF aged 70 years and older were followed up after administering carvedilol; more than 80% of the recipients continued the medication for 3 or more months, suggesting that side-effect concerns should not limit beta-blocker prescription to elderly patients with HF.³³ SENIORS was an RCT of nebivolol, including patients with HF aged 70 years and older with reduced LVEF. The investigators found a significant reduction in the combined outcome of all-cause mortality and cardiovascular hospitalization in the nebivolol arm (HR, 0.86; 95% CI, 0.74–0.99) but no significant effect on all-cause mortality (HR, 0.88; 95% CI, 0.71–1.08).³⁴

The Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF) study provides important observational data in support of beta-blocker treatment in the elderly. This registry included patients with a median age of approximately 80 years, with one-fourth of patients older than 85 years; more than half the patients had preserved LVEF. Among patients with reduced LVEF, beta-blocker therapy yielded a 23% mortality reduction and the age by treatment interaction term was nonsignificant ($P = .87$). Beta-blocker therapy did not improve outcomes in patients with preserved LVEF.¹⁸

ACE Inhibitors and Angiotensin II Receptor Blockers

Flather and colleagues³⁵ performed a meta-analysis of 5 ACE inhibitor trials (see Table 2) and included a subgroup analysis by age. They found a significant 20% reduction in all-cause mortality among those treated with ACE inhibitors and a nonsignificant age by treatment interaction term ($P = .47$). In the subgroup analysis, mortality was significantly reduced among patients aged 65 to 75 years. For patients older than 75 years, mortality was reduced by 5%, although the confidence interval crossed 1, probably because of the small

sample size.³⁵ Although the age by treatment interaction term was nonsignificant, a firm conclusion cannot be drawn about patients older than 75 years.

Observational studies also support the use of ACE inhibitors in older patients with reduced LVEF. A publication from the National Heart Care Project, a Center for Medicare and Medicaid Services initiative, reported that ACE inhibitor use among Medicare beneficiaries resulted in a 14% relative reduction in 1-year mortality risk (RR, 0.86; 95% CI, 0.82–0.90). Furthermore, this study stratified the cohort according to age and found that the oldest old (age 85 years and older) had an apparent mortality benefit with ACE inhibitors or angiotensin II receptor blockers (ARBs).³⁶

The CHARM-Overall trial, which found a mortality benefit for patients with HF treated with candesartan, also performed a subgroup analysis according to age. The study reported a significant mortality benefit for patients aged 65 to 75 years and older than 75 years; the age by treatment interaction term was nonsignificant ($P = .26$).²⁰

Aldosterone Receptor Antagonists

Both RALES and EPHESUS examined outcomes by age (see Table 3). RALES found a significant mortality reduction for patients aged 67 years and older treated with spironolactone.²¹ EPHESUS reported a nonsignificant age by treatment interaction ($P = .23$) for patients treated with eplerenone.²² EMPAHSIS-HF also reported an age-stratified analysis, which showed no evidence of treatment heterogeneity between younger and older participants.²³

Digoxin

The original DIG trial publication did not report age-stratified results, so one must rely on post hoc analysis to infer treatment effects in elderly patients with HF. Ahmed and colleagues²⁶ examined outcomes according to serum digoxin levels and found that patients with levels 0.5 to 0.9 ng/dL experienced a 23% reduction in all-cause mortality. In the age-stratified analysis, the treatment effect was similar in patients aged 70 years and older. In addition, age was a significant predictor of higher drug levels, suggesting that with careful dosing and close monitoring, older patients may benefit from digoxin.

Summary

Evidence regarding the effectiveness and safety of HF treatment among older patients is limited, mainly because of patient exclusions from RCTs. Although age-stratified analyses suggest that HF therapies are effective for older patients, the very old (ie, age 80 years and older) are rarely included in RCTs. In addition, comorbid conditions are the norm among older patients seen in daily practice, a feature that is not represented in RCT participants.³⁷ Thus, it is difficult to draw firm conclusions from RCTs about how to treat older patients with HF. Observational data can provide some insight, but accounting for confounders in a nonrandomized design is difficult.

CER for older patients with HF should focus on safety, in addition to mortality and morbidity outcomes, because older patients are more prone to adverse events and side

effects.^{38,39} The importance of safety outcomes was highlighted in an investigation following the publication of RALES, which illustrated increased hyperkalemia and hyperkalemia-associated deaths among an HF cohort aged 65 years and older.⁴⁰ Although it is difficult to address safety outcomes because of the low occurrence of adverse events, these investigations are particularly important in CER pertaining to older patients, who are more likely to have HF with preserved LVEF. Identifying therapies that are safe and effective in patients with preserved LVEF will be particularly applicable to the cohort of older patients with HF.

KIDNEY DISEASE

More than two-thirds of patients with HF also have kidney disease.^{41–43} Kidney disease severity has been shown to predict mortality in patients with HF and has consistently been shown to be an independent risk factor for adverse cardiovascular events and mortality in broader populations.^{43–46} Medications such as renin-angiotension-aldosterone system (RAAS) inhibitors and beta-blockers reduce HF mortality and morbidity in the general population with HF, but little is known about their treatment effectiveness and safety in patients with HF and kidney disease. Most HF RCTs have excluded patients with elevated serum creatinine concentrations and/or reduced estimated glomerular filtration rates (eGFR).

Beta-Blockers

Post hoc analyses of beta-blocker RCTs provide evidence to support the use of beta-blockers in patients with HF and mild to moderate kidney disease (see Table 1). MERIT-HF reported a 19% (95% CI, 10%–27%) lower risk in the primary end point of all-cause mortality or first hospitalization.⁴⁷ A subsequent secondary analysis of MERIT-HF data showed similar benefit in all-cause mortality across categories of eGFR (P for interaction = .095).⁴⁸ However, very few patients had an eGFR of less than 45 mL/min/1.73 m², given the exclusion criteria of the original trial.

The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II) reported a 34% (95% CI, 19%–56%) lower risk of all-cause mortality in the beta-blocker group.⁴⁹ A subsequent secondary analysis showed that approximately one-third of patients in the bisoprolol and placebo groups had an estimated creatinine clearance of less than 30 mL/min and found similar reductions in all-cause mortality after stratifying by creatinine clearance.⁵⁰ The SENIORS trial found similar benefits of nebivolol, but included only patients with mildly reduced kidney function.^{34,51}

To date, there has been only 1 RCT of beta-blockers in patients with end-stage renal disease (ESRD) on hemodialysis with HF.⁵² In that study, all patients had an LVEF of less than 35% and symptomatic HF. At 2 years, the group receiving carvedilol demonstrated a 49% (95% CI, 18%–68%) lower risk of all-cause mortality compared with patients receiving placebo and also experienced fewer HF hospitalizations than the placebo group.

Because of the consistent benefit seen across categories of kidney function in several trials, as well as the support from large-scale observational studies,^{18,42} beta-blockers seem to be effective in patients with HF with various degrees of kidney disease.

ACE Inhibitors

Two major RCTs showing benefit of ACE inhibitors in reducing mortality in symptomatic patients with HF, the Studies of Left Ventricular Dysfunction (SOLVD)⁵³ and Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS)⁵⁴ trials, included significant proportions of patients with kidney disease (see Table 2). Patients in the SOLVD-Treatment trial randomized to receive enalapril had a 16% (95% CI, 5%–26%) lower risk of all-cause mortality compared with patients randomized to placebo. Although the SOLVD-Treatment trial excluded patients with serum creatinine concentrations greater than 2.5 mg/dL, approximately 36% of patients had an eGFR less than 60 mL/min.⁴⁴ Similarly, CONSENSUS showed reduced 6-month mortality rates in patients with severe HF treated with enalapril and had a liberal creatinine cutoff, allowing serum creatinine concentrations up to 3.4 mg/dL. Although neither trial formally assessed kidney disease in subgroup analyses, these data, along with results from observational studies,⁴² provide support for the use of ACE inhibitors in patients with mild kidney disease and HF.

Angiotensin Receptor Blockers

ARBs are recommended for the treatment of HF among patients who cannot tolerate ACE inhibitors. Although some ARB RCTs included subgroup analyses for patients with kidney disease, most of these trials excluded patients with more advanced kidney disease. For example, a post hoc analysis of CHARM-Overall showed that candesartan was equally effective in the reduction in the primary end point in patients with a serum creatinine concentration of 2.0 mg/dL or greater versus less than 2.0 mg/dL (P for interaction = .63).²⁰ However, CHARM-Overall excluded patients with serum creatinine concentrations of 3.0 mg/dL or more.

The Heart failure Endpoint evaluation of Angiotensin II Antagonist Losartan (HEAAL) study is one of the few clinical trials that examined kidney disease as a prespecified subgroup.⁵⁵ In this trial comparing losartan 150 mg daily with losartan 50 mg daily, the higher dose of losartan was associated with a 10% (95% CI, 1%–18%) lower risk of death or HF hospitalization. These results did not differ by category of eGFR (P = .11 for interaction). However, as with CHARM, HEAAL excluded patients with a serum creatinine concentration greater than 2.5 mg/dL. Therefore, although ARBs seem to be effective for the treatment of patients with HF and mild kidney disease, there are no data regarding patients with HF and more severe kidney disease.

Aldosterone Antagonists

Aldosterone antagonists reduce mortality in the general population with HF and may be equally effective in patients with mild kidney disease (see Table 3). RALES demonstrated a 30% lower mortality rate in patients with severe HF randomized to receive spironolactone or placebo.²¹ Kidney disease was a prespecified subgroup, and a similar benefit of spironolactone was seen in patients with a baseline serum creatinine concentration more than and less than 1.2 mg/dL. Improved mortality and morbidity in patients with HF and kidney disease has also been seen with eplerenone. Both EPHEsus and EMPHASIS-HF examined kidney disease as a pre-specified subgroup and demonstrated similar benefits of eplerenone in patients with reduced kidney function as with higher kidney function.^{22,23}

However, as with RALES, EPHESUS excluded patients with serum creatinine concentrations greater than 2.5 mg/dL and EMPHASIS-HF excluded patients with eGFR less than 30 mL/ min/1.73 m², so the effect of eplerenone among patients with more severe kidney disease is unknown.

RAAS Inhibitors in Patients with ESRD on Dialysis

There have been no RCTs to date of ACE inhibitors in patients with ESRD on dialysis and HF, and patients on dialysis have been excluded from RCTs of ACE inhibitors in the general population with HF. However, a study examined the addition of the ARB telmisartan to ACE inhibitors in patients on hemodialysis with symptomatic left HF.⁵² In this 3-year study, patients receiving telmisartan experienced a 49% (95% CI, 39%–62%) lower risk of all-cause mortality, as well as lower risks of cardiovascular mortality and HF hospitalization. The remarkably large risk reduction is consistent with 2 previous studies of ARB monotherapy in patients on hemodialysis (but without HF),^{56,57} but the possibility of false-positive results remains, because of the small sample sizes and the lack of significant benefit of ARBs added to ACE inhibitors on all-cause mortality seen in 2 large RCTs in the general population with HF.^{58,59}

Safety of RAAS Inhibitors in Kidney Disease

ACE inhibitors decrease glomerular filtration pressure by dilating the efferent arteriolar in the glomerulus, which would be expected to increase serum creatinine concentration, particularly in patients with underlying kidney disease. A recent consensus statement from the National Kidney Foundation states that an increase in serum creatinine concentration is not of concern unless it exceeds 30% to 50% or does not stabilize by about 4 weeks after the initiation of the ACE inhibitor.⁶⁰ In SOLVD, a significantly larger proportion of patients treated with enalapril had an increase in serum creatinine levels to greater than 2.0 mg/dL compared with placebo (10.7% vs 7.7%, $P<.01$).⁵³ Similarly, in CONSENSUS, patients treated with enalapril had an increase in serum creatinine levels by 10% to 15% in the first 2 to 3 weeks of treatment, with a mean increase in serum creatinine levels of 14% at 24 weeks; no significant increase in the mean serum creatinine level was seen in the placebo group.⁵⁴ However, the rates of medication discontinuation due to increased serum creatinine levels were similar between the 2 groups.^{53,54,61} Thirteen patients in CONSENSUS experienced a doubling of serum creatinine levels, most often associated with hypotension or intercurrent illnesses, which reversed on withdrawal of the ACE inhibitor, diuretic, or both.⁶²

Hyperkalemia may also result after ACE inhibitor initiation in patients with HF and kidney disease. In SOLVD-Treatment, 6.4% of patients in the enalapril group had an increase in the serum potassium concentration to greater than 5.5 mmol/L, compared with 2.2% in the placebo group ($P<.01$). However, the clinical significance of the hyperkalemia in SOLVD-Treatment is unclear, as the number of patients who had to discontinue the ACE inhibitor as a result of hyperkalemia was not reported. A review of 6 clinical trials of ACE inhibitors in patients with moderate to advanced kidney disease, but without HF, found that only 2.0% of patients developed increases in serum potassium concentrations greater than 5.6 mmol/L and only 0.8% required termination of the ACE inhibitor as a result of hyperkalemia.¹⁶ Because

none of the trials included patients with systolic HF, the safety of ACE inhibitors in patients with concomitant kidney disease and HF cannot be assessed.

ARBs may also increase serum creatinine and potassium concentrations, as seen in CHARM-Alternative⁶³ and the Effect of Losartan in the Elderly (ELITE) trials. In the ELITE trial, which randomized patients to receive losartan or captopril, 10.5% of patients in both groups reached the primary end point of renal dysfunction, defined as an increase in the serum creatinine level by 0.3 mg/dL or more.⁶⁴ In patients with ESRD on dialysis, treatment with ARBs did not result in a greater incidence of hyperkalemia compared with placebo.^{52,56,57}

Hyperkalemia is also a major concern when treating patients with HF and kidney disease with aldosterone antagonists. The incidence of serious hyperkalemia was remarkably low in RALES (2%),²¹ whereas in EPHESUS, the rate of serious hyperkalemia was 10.1% in patients with a baseline creatinine clearance of less than 50 mL/min.²² Moreover, aldosterone antagonists in a real-world setting may have higher adverse event rates. For example, a study conducted in Canada found a nearly threefold increase in hyperkalemia-associated hospitalizations and hyperkalemia-associated deaths after the publication of RALES.⁴⁰ Conversely, a study conducted in Scotland did not find an increase in hyperkalemia-associated adverse events.⁶⁵ In EPHESUS, the rate of serious hyperkalemia was 10.1% higher in patients with a baseline creatinine clearance of less than 50 mL/min.²² Current guidelines provide recommendations for minimizing the risk of hyperkalemia in patients treated with aldosterone antagonists, including avoidance of concomitant use of nonsteroidal antiinflammatory drugs, discontinuation of potassium supplementation, smaller initial doses of aldosterone antagonists, and close monitoring of serum potassium and creatinine concentrations, especially in patients taking higher doses of ACE inhibitors. Aldosterone antagonists are not recommended in patients with creatinine clearances less than 30 mL/min or baseline serum potassium concentration greater than 5 meq/L.⁶⁶

In summary, adverse effects such as increases in serum creatinine levels and hyperkalemia were uncommon and often reversible in the setting of a carefully monitored RCT but may be more common in the real-world clinical practice. Serum creatinine and potassium concentrations must be closely monitored when using RAAS inhibitors, especially in patients with more advanced kidney disease who are not yet on dialysis.

Digoxin

The original DIG trial excluded patients with a serum creatinine concentration greater than 3.0 mg/dL, and few patients had advanced kidney disease: 54% of the cohort had an eGFR greater than 60 mL/min/1.73 m², 43% had an eGFR of 30 to 60 mL/min/1.73 m², and only 3% had an eGFR less than 30 mL/min/1.73 m².²⁴ In a post hoc analysis, no benefit (and no increased risk) of digoxin on all-cause mortality or on the combined end point of death or HF hospitalization was seen across levels of kidney function (*P* for interaction = .19 and .54, respectively).⁴⁶

Summary

At present, there is limited CER regarding the appropriate treatment of HF patients with concomitant kidney disease, making it difficult to draw conclusions regarding the effectiveness of HF medications in this population. The available evidence from RCTs provides support for the use of ACE inhibitors, ARBs, and beta-blockers in patients with mild to moderate kidney disease. Treatment with aldosterone antagonists may also be beneficial. In all cases, the serum creatinine and potassium concentrations must be carefully monitored to prevent adverse effects, as the safety of these medications in patients with moderate to severe kidney disease remains largely untested. Data for patients with HF and ESRD on dialysis are even sparser, although treatment with beta-blockers and perhaps an ACE-I or ARB is warranted. The relative paucity of data underscores the need for future RCTs of HF to include patients across all levels of kidney disease, because this special population, at high risk for poor clinical outcomes and adverse medication side effects, may also have the most to gain from effective treatment strategies.

CONCLUDING REMARKS

CER is a key component to improving HF management. Many patients in clinical practice are dissimilar to the patients in RCTs, so alternative sources of information must guide treatment. There is reasonable evidence to support the use of most HF therapeutics in women but less evidence to support use in elderly patients and patients with kidney disease. Safety issues are of particular concern in these special populations.

The American Recovery and Reinvestment Act of 2009 marked a milestone in clinical research by allocating \$1.1 billion for CER.⁵ The expansion of electronic medical records and statistical methods, in conjunction with this new source of funding, will create opportunities to study HF outcomes in special populations and provide more evidence to improve management strategies in these vulnerable patients with HF.

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KEY POINTS

- Comparative effectiveness research is a key component in improving heart failure (HF) management.
- Many of the patients in clinical practice are dissimilar to the patients in randomized controlled trials, so alternative sources of information must guide treatment.
- There is reasonable evidence to support the use of most HF therapeutics in women but less evidence to support use in older patients and patients with kidney disease.

Table 1

Characteristics of selected beta-blocker trials with mortality benefit

Study	Inclusion Criteria	Intervention	Mean Age (Years)	Percentage of Women (n/Total)	CKD Exclusion	Subgroup Analysis
US Carvedilol Heart Failure Study ¹⁴	Symptomatic HF and EF 35%	Carvedilol vs placebo	58.0	23 (256/1094)	Clinically important renal disease	Yes
Carevedilol Prospective Randomized Cumulative Survival Study ¹⁵	NYHA class IV HF and EF 25%	Carvedilol vs placebo	63.3	21 (470/2289)	Creatinine 2.8 mg/dL	Yes
Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure ^{12,67}	NYHA class II–IV HF and EF 40%	Metoprolol succinate vs placebo	63.8	23 (898/3991)	None	Yes
Cardiac Insufficiency Bisoprolol Study II ⁴⁹	NYHA class III–IV HF and EF 35%	Bisoprolol vs placebo	61.0	19 (515/2647)	Creatinine 3.4 mg/dL	No ^a
Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors with Heart Failure ^{34,68}	Age 70 y and EF 35% or HF hospitalization within the previous 12 mo	Nebivolol vs placebo	76.1	37 (785/2128)	Creatinine 2.8 mg/dL	Yes
Carvedilol or Metoprolol European Trial ^{169,70}		Carvedilol vs metoprolol tartrate	62.0	20 (612/3029)	Serious systemic disease with reduced life expectancy	Yes

Abbreviations: EF, ejection fraction; NYHA, New York Heart Association.

^aIncluded subgroup analysis, but not related to age, sex, or kidney function.

Table 2
Characteristics of selected angiotensin-converting enzyme inhibitor trials with mortality benefit

Study	Inclusion Criteria	Intervention	Mean Age (Years)	Percentage of Women (n/Total)	CKD Exclusion	Subgroup Analysis
Cooperative North Scandinavian Enalapril Survival Study ⁵⁴	NYHA Class IV HF and clinical signs/ symptoms of HF	Enalapril vs placebo	70.5	23 (59/253)	Creatinine 3.4 mg/dL	No
Studies of Left Ventricular Dysfunction—Treatment ⁵³	HF and EF 35%	Enalapril vs placebo	60.8	20 (505/2569)	Creatinine 2.0 mg/dL	No ^a
Studies of Left Ventricular Dysfunction—Prevention ⁶¹	EF 35% and no treatment of HF (diuretics, digoxin, vasodilators)	Enalapril vs placebo	59.1	7 (294/4228)	Creatinine 2.0 mg/dL or dialysis	No ^a
Acute Infarction Ramipril Efficacy Study ^{71,72}	AMI and signs/symptoms of HF	Ramipril vs placebo	65.0	26 (525/1986)	Recognized contraindications to ACE-I therapy	Yes
Survival of Myocardial Infarction Long-Term Evaluation Study ⁷³	Anterior wall myocardial infarction	Zofenopril vs placebo	64.1	27 (428/1556)	Creatinine 2.5 mg/dL	Yes
Trandolapril Cardiac Evaluation Study ⁷⁴	Acute myocardial infarction and EF 35%	Trandolapril vs placebo	67.5	28 (498/1749)	Creatinine 2.3 mg/dL	Yes
Survival and Ventricular Enlargement Trial ⁷⁵	AMI and EF 40%	Captopril vs placebo	59.4	18 (390/2231)	Creatinine 2.5 mg/dL	No

Abbreviations: EF, ejection fraction; NYHA, New York Heart Association.

^a Included subgroup analysis, but not related to age, sex, or kidney function.

Table 3

Characteristics of selected aldosterone antagonist trials with mortality benefit

Study	Inclusion Criteria	Intervention	Mean Age (Years)	Percentage of Women (n/Total)	CKD Exclusion	Subgroup Analysis
The Randomized Aldactone Evaluation Study ²¹	NYHA Class II or IV HF and EF 35%	Spironolactone vs placebo	65.0	27 (446/1663)	Creatinine 2.5 mg/dL	Yes
Eplerenone Post-Acute Myocardial Infarction Efficacy and Survival Study ²²	Acute myocardial infarction and EF 40%	Eplerenone vs placebo	64.0	29 (1918/6632)	Creatinine 2.5 mg/dL	Yes
Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure ²³	NYHA Class II HF, age 55 y, EF 35%	Eplerenone vs placebo	68.6	22 (610/2737)	eGFR 30 mL/min/1.73 m ²	Yes

Abbreviations: EF, ejection fraction; NYHA, New York Heart Association.