

Adverse Drug Events and Associated Factors in Heart Failure Therapy Among the Very Elderly



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ABSTRACT

Introduction

Heart failure (HF) is common in older adults and standard therapy involves the use of multiple medications. We assessed the nature, frequency, and factors associated with adverse drug events (ADEs) associated with standard HF therapy among older adults greater than 75 years of age. The efficacy and predictors of ADEs were assessed in this patient population, as well.

Methods

Systematic review using standardized databases including MEDLINE, Ageline, and CINAHL from January 1st 1988 to January 1st, 2010 and references from published literature. Randomized trials and studies with observational, cohort, and cross-sectional design were included. Two investigators independently selected the studies and extracted the data ($\kappa = 0.86$).

Results

Twenty-five studies were identified. ADEs were reported in 13/23 (57%) studies. Syncope, bradycardia, and hypotension as a result of beta blockers occurred in greater frequency compared to younger populations. Spironolactone therapy resulted in increased rates of hyperkalemia, acute renal failure, and medication discontinuation. Factors associated with ADEs included advanced age, poor left ventricular function, and increasing New York Heart Association Class. Efficacy of beta blockers and ACE inhibitors appears to extend to the elderly population, but the magnitude of effect size is unclear. Very few studies reported associations between ADE and patients' comorbidities (4/13 studies, 31%) or functional status (3/13 studies, 23%).

Conclusion

ADEs in CHF therapy among the very elderly occurred at a greater frequency, but were generally poorly characterized

in the literature despite a relatively common occurrence. Further studies are warranted.

Keywords: congestive heart failure, heart failure, adverse drug events, medication side effects, elderly, frailty, medical comorbidities

INTRODUCTION

Heart Failure (HF) is an extremely common condition in the elderly. In fact, the median age of onset for HF is 75, with half of the patients with the condition being over 80.^(1,2,3) Many medical therapies have been shown to reduce the morbidity and mortality associated with systolic HF; however, the average age of study participants has not been representative of the majority of the patients with the condition.^(4,5,6) Much of the evidence used to justify the benefit of therapies has been extrapolated to the elderly population in whom cardiovascular physiology is altered, pharmacokinetics and dynamics are different, and drug interactions and susceptibility to side effects are increased.^(7,8,9)

It was our hypothesis that elderly patients would experience adverse drug events (ADEs) at a higher rate than conventional trials have reported, and that concepts such as frailty and medical comorbidities have not been extensively evaluated to see if there are predictors of ADEs. A secondary hypothesis was that there would be a small amount of high-quality data to support the current heart failure treatment paradigm in people over the age of 75.

The purpose of this study was to quantify the degree of ADEs in the elderly population related to their HF therapy, understand their nature and, if it differs from the younger populations studies, establish whether the therapies are efficacious, and determine whether there are predictors of adverse ADEs related to the elderly population.

METHODS

A systematic review was performed using standardized databases including MEDLINE, AgeLine, CINAHL, and the Cochrane

Reviews, from January, 1988, to January 1st, 2010. References from the published literature were also included. Keywords included: congestive heart failure, heart failure, adverse drug events, medication side effects, polypharmacy, elderly, frailty, and medical comorbidities. Meta-analyses, randomized controlled trials (RCTs), observational studies, and reviews were included. Only studies involving patients with a median or mean age of 75 years, or with a treatment arm that involved patients with a median or mean age of 75 years, were included. Medications reviewed included angiotensin-converting enzyme inhibitors, beta blockers, spironolactone, and digoxin.

Two reviewers (VC and MB) independently examined each study based on the prespecified inclusion criteria. Where there was disagreement, a third reviewer (RS) was included, and consensus was reached as to whether the article would be included or not. Data was independently extracted and examined by VC and RS targeting prespecified variables: medications used, adverse events measured, point prevalence of those events, hospitalizations, mortality, symptom control, comorbidities measures, functionality, and frailty. Variables of interest measured that were not prespecified were tolerability, undertreatment, or special study populations such as diabetics or patients with atrial fibrillation. A standardized data extraction form in Microsoft Excel format was used. A post-hoc analysis of study quality was performed on trials, as well as observational data. Studies were only included if they had Jadad scores of 2 for RCTs or Newcastle-Ottawa Quality Assessment scores of 6 or greater.^(10,11)

Side effect rates from the observational data were pooled for comparison when possible and compared to rates noted in the randomized control trials. Data heterogeneity was controlled for using Cochran's Q statistic. The Cochran's Q statistic was not intended to be the statistical test of choice; however, given the large number of observational and cohort studies, it was felt to be the most appropriate, despite the inherent biases and lack of power to attain firm conclusions.

RESULTS

Our initial literature search yielded a total of 213 studies. After we reviewed the titles and abstract, a total of 25 papers met inclusion criteria and were selected for final analysis. (Figure 1) The kappa statistic was 0.86 for inter-rater reliability. More than half of the studies (13) represented heart failure patients with systolic dysfunction. While diastolic dysfunction is very prominent in the elderly, there were only two studies that investigated this population specifically. There were six papers that included patients with both systolic and diastolic dysfunction. The studies are summarized in Table 1.

Adverse Drug Events

Beta Blockers

A total of seven studies evaluated beta blocker use for heart failure in the elderly. ADE rates from the observational

studies^(12,13,14,15,16,17) were pooled and compared to randomized control trial data from the SENIORS⁽¹⁸⁾ and COPERNICUS⁽¹⁹⁾ trials. The SENIORS trial is a randomized control trial using nebivolol in the elderly population, with a mean age of 79. The COPERNICUS trial explicitly stated adverse event rates related to carvedilol in patients with a mean age of 63. It was used as a benchmark for the incidence of medication side effects in randomized control trials in the nonelderly population.

There were discrepancies in the incidence of adverse events between the elderly and nonelderly groups treated with beta blockers. Four percent (48/1101) of the review study cohort experienced bradycardia, as did 11% of the patients in the SENIORS trial.⁽¹⁸⁾ In comparison, only 2% (22/1156) of the younger patients in the COPERNICUS trial did.⁽¹⁹⁾ The incidence of hypotension was 13% (106/829) in the review cohort, 8% (82/1067) in SENIORS, and only 2% (22/1156) in COPERNICUS. There were similar rates of syncope with 17% (29/176) in the review cohort and 16% (166/1067) in SENIORS, while again a large discrepancy with only 2% (19/1156) of patients experiencing these symptoms in COPERNICUS. (Table 2)

Many other adverse events were reported in a non-uniform manner and could, therefore, not be compared. These included: bronchospasm, shortness of breath, arrhythmias, worsening functional status, and gastrointestinal complaints.

The most common beta blockers studied in descending order were carvedilol, bisoprolol, and nebivolol. A mean follow-up period of 14.93 months was observed. Pooled tolerability in all seven studies was 65.57% (1811/2762). The tolerability of carvedilol in the COPERNICUS trial was 70%.⁽¹⁹⁾ The mean tolerated dose for carvedilol was 31.73 mg daily. The mean dose for bisoprolol was 7.6 mg daily, and the mean tolerated dose for nebivolol was 7.7 mg daily.

ACE Inhibitors

Three studies reported ADEs in relation to ACE inhibitor use.^(20,21,22) The first was a randomized, double-blind trial evaluating the use of quinapril in 36 diastolic heart failure patients. The other two studies looked at initiating chronic therapy, but specifically did not look at how those medications administered chronically resulted in adverse events, which was the focus of our study. The point prevalence of adverse events in the 36 patients treated with quinapril in the first study did not lend themselves to any comparisons due to the small numbers. No valuable comparisons came out of evaluating the ACE inhibitor studies.

Spironolactone

Three studies evaluated the use of spironolactone.^(23,24,25) Dinsdale *et al.*⁽²³⁾ looked at the use of spironolactone in a retrospective case series of 64 patients hospitalized with heart failure at their institution, with a mean age of 85. Spironolactone was prescribed in conjunction with an ACE

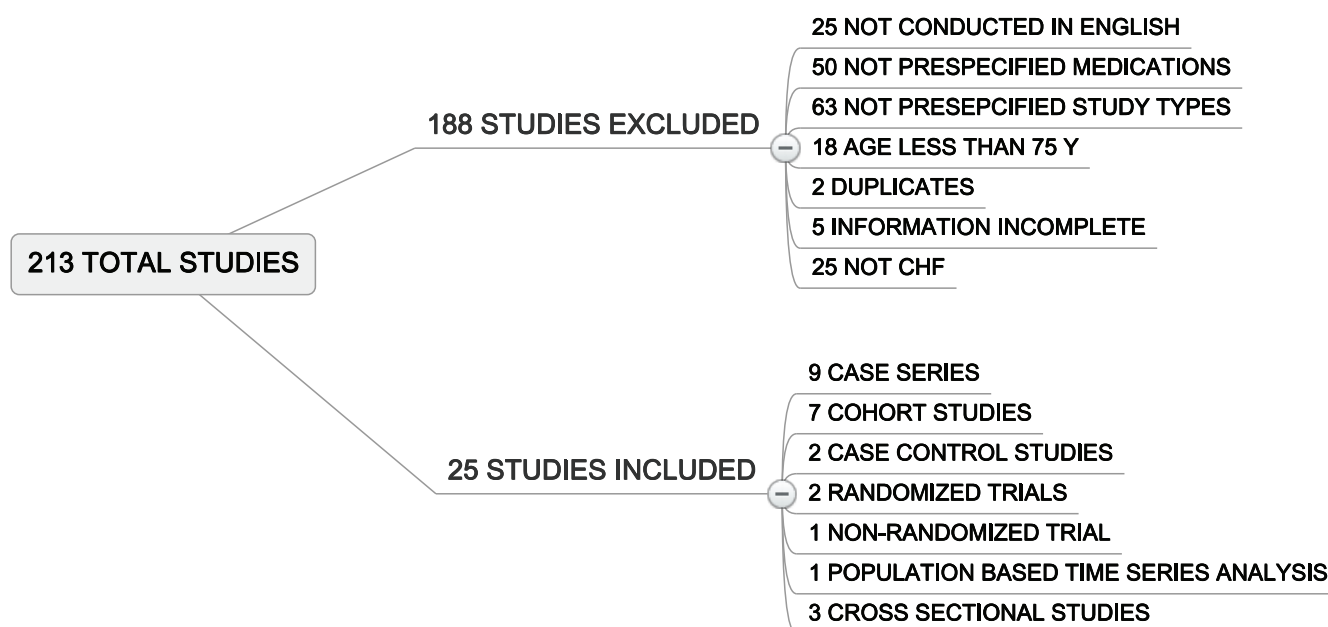


FIGURE 1. Reasons for exclusion

inhibitor. The rate of adverse drug events in this cohort was compared to the RALES study participants. The definition of an adverse drug event was uniform across both studies.

The rate of severe hyperkalemia in the Dinsdale study was between 11% for severe (> 6.0 mmol/L), and 36% for hyperkalemia in general (> 5.5 mmol). The rate of serious hyperkalemia in the RALES trial was only 2%. Forty-three percent of patients in the Dinsdale study had to discontinue spironolactone because of acute renal failure, hyperkalemia, or postural hypotension. Only 8% of patients in the RALES trial discontinued the medication.^(23,6) (Table 3).

In a population-based time series analysis, Juurlink *et al.*⁽²⁴⁾ evaluated the rates of hyperkalemia-associated hospitalizations and death after the online publication of the RALES trial in 1999. They showed that as prescriptions increased from 34/1000 to 149/1000, hyperkalemia-related hospitalizations increased from 2.2/1000 to 11/1000, and hyperkalemia-associated deaths increased from 0.3/1000 to 2/1000. The mean age of patients in this cohort was 78.5 years of age. The goal of this study was to elaborate on the differences between patients treated in randomized control trials with frequent follow-up and strict inclusion criteria, as compared to “real-life” patients, some of whom do not fit the specifications for receiving the medication. It is notable that patients experiencing the majority of the side effects are above 75 years of age.

Butler *et al.*⁽²⁵⁾ looked at the addition of spironolactone to 18 systolic heart failure patients with a mean age of 80 years of age. Nine patients had a baseline serum creatinine above 150 mmol/L, and nine patients had a serum creatinine below 150 with a mean of 89.6. The addition of spironolactone resulted in hyperkalemia in six patients, or 66% of patients with baseline serum creatinines above 150, and only

one patient with a normal serum creatinine. All potassium levels returned to normal when the dose of spironolactone was decreased to 12.5 mg daily from 25. No other serious side effects were found that required discontinuation of the medication.

Digoxin

Three studies looked at ADEs in relation to digoxin use. Carosella *et al.*⁽²⁶⁾ looked at over 20,000 patients hospitalized for HF in Italy between 1988 and 1993. They found that although the mean prescribed dose of digoxin was lower in the elderly, age was an independent risk factor of ADEs. Other predictors of ADRs were daily dosage of digoxin > 0.25 mg, serum creatinine > 120 micrograms/L, the number of drugs taken prior to admission, administration of amiodarone, propafenone, quinidine, or verapamil.

Misiaszek *et al.*⁽²⁷⁾ looked specifically at the elderly in long-term care facilities and found that 33% of patients with HF were being prescribed digoxin. Most of these patients had atrial fibrillation. The authors found that 26% of these patients were at risk for adverse events because their serum concentrations were greater than 1.5, or because they were being prescribed medications that increased their risk of ADEs.

Comorbidities and Functional Status as a Predictor of ADEs

Out of 24 studies, 16 measured medical comorbidities in some manner. Nine studies used a validated index, and six used a nonsystematic approach. The most commonly used validated models were the Charlson and Elixhauser comorbidities

TABLE 1.
Summary of CHF studies by standard medical therapy

Study	Study Design	Study Population	Medication	Outcome	Tolerability	Efficacy	Adverse Drug Events	Comments
Beta Blockers								
Baxter <i>et al.</i> (2002)	Observational Study Mean follow-up of 13 weeks	N=51 Mean age 78 years Systolic dysfunction	Bisoprolol Mean dose 7.6 mg/day	Tolerability	69% (35/51) patients	N/A	Symptomatic hypotension, hypotension, fatigue, GI disturbance, worsening CHF, bronchospasms, rash, insomnia	Improved GHQ and HAD scores No differences in Guyatt CHF, CMSS, 6-minute walk test
Sin <i>et al.</i> (2002)	Population-based Cohort Study Median follow-up 21 months	N=11,942 Mean age 79 years, Charlson score >2 Systolic dysfunction	Beta blockers Metoprolol	Morbidity Mortality	N/A	Reductions in all cause mortality (HR=0.72), mortality due to heart failure (HR=0.65), hospitalizations for heart failure (HR=0.82)	N/A	
Witham <i>et al.</i> (2004)	Retrospective Study Heart failure clinic	N=226 Mean age 73.3 years Systolic dysfunction	Beta blockers Carvedilol > Bisoprolol > Atenolol > Metoprolol, Sotalol	Tolerability	69.7% Age >75 80% Age <75	N/A	Breathlessness, fatigue, bradycardia, light headedness, dizziness, hypotension	Predictors of tolerability included NYHA status and LV function via univariate analysis
Lawless <i>et al.</i> (2005)	Observational study No follow-up	N=360 Mean age 75.5 vs. 52.7 years Systolic dysfunction	Carvedilol	Tolerability	84.7% Age >70 79.9% Age <70	N/A	Dyspnea and weakness (age >70), hypotension, bradycardia, heart block, worsening heart failure, syncope, dizziness, gastrointestinal symptoms	
Cioffi <i>et al.</i> (2005)	Observational Study Italian heart failure units 1-year follow-up	N=240 Mean age 76.6 years Systolic dysfunction Chronic atrial fibrillation	Carvedilol	Tolerability	87.9% (29/33) Stable sinus rhythm 93.1% (95/102) Chronic atrial fibrillation	N/A	Worsening heart failure, bradycardia, bronchospasms, ventricular arrhythmias	

TABLE 1.
Summary of CHF studies by standard medical therapy (Continued)

Study	Study Design	Study Population	Medication	Outcome	Tolerability	Efficacy	Adverse Drug Events	Comments
Flather <i>et al.</i> (2005) SENIORS Study	Randomized Controlled Trial	N=2128	Nebivolol	Composite all cause mortality and cardiovascular hospital admission	N/A	31.1% (332/1067) vs. 35.3% (375/1061)	Bradycardia, decreased angina and unstable angina	Benefits appears after 6 months of treatment
	Mean follow-up of 21 months	Mean Age 76 years Systolic and Diastolic Dysfunction	Mean dose 7.7 mg/daily			All cause Mortality and cardiovascular hospital admission; HR 0.86; 95 CI 0.74-0.99		
Krum <i>et al.</i> (2006) COLA II	Observational Study	N=1030	Carvedilol	Tolerability	80% Overall, with age 70-75 years 84.3%, 76- 80 years 76.8%, >80 years 76.8%	Improvements in NYHA class, LVEF	Worsening heart failure, symptomatic hypotension, bradycardia, amiodarone use	Subgroup analysis according to age
	6-month follow-up	Systolic dysfunction	Mean dose 31.2 mg/day, although varied with age, with progressive diminution in dose with advancing age		Significant diminution of tolerability with advanced age and NYHA class (62.7% NYHA IV)			Predictors of tolerability included advanced age, low diastolic BP, LVEF, obstructive airways, diabetes
Sindaco <i>et al.</i> (2007)	Observational Study	N=252	Carvedilol	Safety Tolerability, Efficacy in diabetics and non diabetics	93.7% Diabetic	Improvements in NYHA Class, MR severity LVEF (more in non-diabetics)	Bradycardia, acute bronchospasm, worsening functional status (nondiabetics)	No metabolic difference in FBS, HbA1C, Creatinine
	Specialized heart failure clinics	Mean age 76.5 years	Mean dose 23.5 mg/day		92.2%			
	1-year follow-up	Systolic dysfunction			Nondiabetic	No differences in incidence of hospitalizations or mortality		
ACE Inhibitors								
Schwartz <i>et al.</i> (1991)	Observational Study	N=20	Enalapril 20 mg/Day	Safety Creatinine	16/20 No effect on kidney function	N/A	N/A	N/A
	Hospitalization	Mean age 76 years Severe CHF	Furosemide maintenance		4/20 had rapid renal dysfunction			

TABLE 1.
Summary of CHF studies by standard medical therapy (Continued)

Study	Study Design	Study Population	Medication	Outcome	Tolerability	Efficacy	Adverse Drug Events	Comments
Mets <i>et al.</i> (1992)	Observational Study 3-hour follow-up	N=97 Mean age 83.7 years Unknown dysfunction	Captopril 6.25 mg	Hypotensive effect of first dose 6.25 mg Captopril	54% had a SBP fall of at least 15% BP fall generally fell within 60 mins Greatest BP drop took place within 150 mins	N/A	Transient agitation and dizziness	
Haffner <i>et al.</i> (1995)	Double-blind parallel group comparison, multicentre 3- and 6-month follow-up	N=80 Captopril mean age 77 years Enalapril mean age 75 years Unknown dysfunction	Captopril 12.5 mg BID Enalapril 2.5 mg BID	Hemodynamics: BP, HR Renal Function: GFR	No differences on GFR, although more patients given Captopril had improvement in GFR at 3 and 6 months	N/A	Enalapril: symptomatic hypotension, gastrointestinal symptoms Captopril	
Gambassi <i>et al.</i> (2000)	Retrospective Study SAGE database 1-year follow-up	N=19,492 Mean age ACEI 83.9 years Mean age Digoxin 85.4 years	ACEI vs. Digoxin	1-year mortality, morbidity and physical function	N/A	Overall mortality rate ACEI was more than 10% less than Digoxin users Trend towards reduced hospitalizations Rate of functional decline was 2.5%-30% reduced among ACEI users (RR0.74; 95% CI 0.69-0.80)	Used 5-item 6-level activities of daily living (ADL) Scale	

TABLE 1.
Summary of CHF studies by standard medical therapy (Continued)

Study	Study Design	Study Population	Medication	Outcome	Tolerability	Efficacy	Adverse Drug Events	Comments
Ahmed <i>et al.</i> (2003)	Retrospective Study Medicare beneficiaries	N=1090 Mean age 79 years Unknown Dysfunction	ACEI	Association of LVEF evaluation and ACEI with 3-year survival	N/A	Both left ventricular function evaluation (HR 0.83; 95% CI 0.71-0.98) and ACE inhibitor use (HR 0.77; 95% CI 0.66-0.91) were associated with a lower 3-year mortality rate	N/A	
Zi <i>et al.</i> (2003)	Double-blind randomized study, single center 6-month follow-up	N=74 Mean age 78 years Diastolic Dysfunction	Quinapril	Functional status	Significant mean 6-minute walk distance increased in Quinapril group, but not significant between groups	N/A	Worsening heart failure, chest infection, hypotension, cough, dizziness, tiredness, rehospitalization, cough	
Ahmed <i>et al.</i> (2005)	Case Control Study 11 Alabama hospitals 4-year follow-up	N=295 Mean age 78.5 years Systolic dysfunction	ACEI	4-year survival using propensity score methods	N/A	Significant 2-fold increase in the risk of 4-year mortality (HR 2.33) if not on ACEI	N/A	
Trewet <i>et al.</i> (2007)	Retrospective Cohort Study Kansas Medicaid beneficiaries	N=470 Mean age 81	ACEI	All Cause Hospitalization	N/A	Non significant 23% higher risk of 4-year mortality if on ACEI	N/A	Hospitalizations were not decreased by ACEI use

TABLE 1.
Summary of CHF studies by standard medical therapy (Continued)

Study	Study Design	Study Population	Medication	Outcome	Tolerability	Efficacy	Adverse Drug Events	Comments
Spironolactone								
Butler <i>et al.</i> (2002)	Observational Study 28-day follow-up	N=18 Mean age 80.6 years Unknown dysfunction	Spironolactone 25 mg/day	Hyperkalemia (K>5 mmol/l)	6/9 RI vs. 1/9 no RI developed hyperkalemia	N/A	Compared between those with renal impairment (RI) Cr >150 mmol/l vs. no RI	
Juurink <i>et al.</i> (2004)	Population-based, Time Series Study Health care databases	N=12,422 Mean age 78.6 years Unknown dysfunction	Spironolactone 25 mg/day	Hyperkalemia requiring hospitalization	2.4 → 11 per 1000 rate of hospitalization for hyperkalemia 0.3 → 2.0 per 1000 mortality from hyperkalemia	N/A		
Dinsdale <i>et al.</i> (2005)	Retrospective Study	N=66 Mean age 85 years Systolic and Diastolic Dysfunction	Spironolactone 25 mg/day	Hyperkalemia >6 mmol/l Renal Failure >354 mmol/l	30/64 Hyperkalemia 11% Renal Failure	N/A	Hypotension/postural hypotension	Predictors of adverse drug events included intercurrent illness
Furosemide								
Van Kraaig <i>et al.</i> (1999)	Prospective Observational	N=20 Mean Age 75 Diastolic Heart Failure	Withdrawal of Furosemide	Post Prandial Hypotension, Stroke Volume	11/20 Patients safely discontinued Furosemide Decreased in postprandial SBP by 14 mmHg	N/A	Orthostatic postprandial hypotension	

TABLE 1.
Summary of CHF studies by standard medical therapy (Continued)

Study	Study Design	Study Population	Medication	Outcome	Tolerability	Efficacy	Adverse Drug Events	Comments
Digoxin								
Carosella <i>et al.</i> (1996) GIFA	Observational Study, multicenter 3 annual surveys Hospitalized	N=20,047 Mean age 75 years Unknown dysfunction	Digoxin Mean dose 0.17 mg/day	Adverse Drug Reactions	2.1% of patients experienced ADRs to Digoxin 4 events mild ADRs 24 events severe ADRs	N/A	Cardiac arrhythmias more common than gastrointestinal symptoms	Predictors of ADR include advance age (>80 years), dose >0.25 mg, Cr > 120 mmol/l, >6 drugs taken prior to admission, other medications (Amiodarone, Propafenone, Quinidine, Verapamil)
Misiaszek <i>et al.</i> (2005)	Cross-sectional	Long-term Care Mean age 85	Digoxin	Prevalence of Digoxin Use Risk For Adverse Events	1/3 of LTC Residents with HF were on Digoxin 26% of those people were at increased risk of toxicity	N/A	Not measured	
Combination of Medications								
Heckman <i>et al.</i> (2004)	Cross-sectional	N=1223	ACE Inhibitors	Prevalence of HF Medications used to treat HF	HF prevalence was 20% ACEI were prescribed in 55% of residents	N/A	N/A	N/A
Jensen <i>et al.</i> (2008)	Cohort Specialized HF Clinics	N=150	Beta Blockers, ACE Inhibitors, and Spironolactone	Adverse Event Predictors, Target Doses, Appropriate Prescription	Beta Blockers prescribed in 25% of residents N/A	N/A	N/A	Age, COPD, Renal Dysfunction, Diabetes, and Pulse Pressure had Negative prognosis

TABLE 2.

Adverse drug events compared between observational, RCT data in those over 75 and RCT data in patients less than 75 years of age

Side Effect	Pooled Observational Data (Mean age >75)	Seniors Trial (Mean age 79)	Copernicus Trial (Mean Age 63)
Bradycardia	4% (48/1101)	11% (118/1067)	1.5% (17/1156)
Hypotension	13% (106/829)	8% (82/1067)	1.9% (22/1156)
Worsening HF	5% (44/912)	24% (256/1067)	Not Reported
Weakness/Fatigue	19% (51/222)	7% (72/1067)	Not Reported
Syncope	17% (29/171)	16% (166/1067)	1.6% (19/1156)

TABLE 3.

Adverse drug events related to spironolactone therapy

Side Effect	Dinsdale et al. N = 64	Butler et al. N = 18	RALES N = 1663
Hyperkalemia >5.5 mmol/L	36%	33%	2%
Acute Kidney Injury	37.5%	0	Not Reported
Discontinuation	34%	0	8%

measures. Despite the fact that the authors seemed very cognizant of the fact that medical comorbidities might impact health outcomes, only three studies attempted to correlate comorbidities with impact.

Krum *et al.*⁽¹³⁾ published a prospective observational study on the tolerability of carvedilol in a cohort of 1030 elderly patients with systolic heart failure. Key measures that may predict tolerability were measured at baseline, and the ability to remain on 6.25 mg twice daily at six months were measured. Factors associated with decreased medication tolerance were: advanced age, obstructive airways disease, advanced NYHA class, and hospitalization in the previous six months. Factors that increased tolerability were higher ejection fractions, increased systolic and diastolic blood pressures, and the presence of diabetes. With all things considered, the beta blocker was tolerated in 80% of patients overall in patients that were greater than 75 years of age.

A study by Witham *et al.*⁽¹⁷⁾ compared the tolerability of carvedilol in 110 patients with a mean age of 80 years to 116 patients with a mean age of 65 years of age. This study did agree with higher NYHA class and lower LV function as predictors of failing a trial of beta blocker therapy. The data of this study did conflict with the previous study in that age, and a diagnosis of obstructive airways disease did not predict treatment failure.

This study was specifically looking at the tolerability of beta blocker therapy in the elderly, and found no difference in tolerability between the patients less than 75 when compared to patients greater than 75 years of age. It used the Charlson Comorbidity Index, and found that the older patients did have a higher rate of symptomatic heart failure, musculoskeletal complaints, hypertension, and stroke. Despite these comorbidities being present, none of these predicted beta blocker failure from side effects, except for those already mentioned.

In the retrospective study performed by Dinsdale *et al.*,⁽²³⁾ medical comorbidities were not measured in a validated scale, but the authors did attempt to see whether comorbidities were predictors of adverse events, specifically hyperkalemia and acute renal failure. No significant relationship was found between age, baseline creatinine, ACE inhibitor dose, NYHA class, diabetes, intensity of monitoring, or number of medications, and the aforementioned adverse events. Predictors of ADEs are summarized in Table 4.

Functional status was measured in three trials.^(22,28,29) The impact of functional status on adverse drug events and overall tolerability was not measured.

Efficacy

Beta Blockers

The SENIORS trial was a prospective, randomized control trial to evaluate the use of nebivolol in elderly patients with systolic HF. One thousand and sixty-seven (1067) patients were randomized to receive 10 mg daily of nebivolol, and 1061 to placebo, and were followed for 21 months. The mean age of the study participants was 76, with 37% being female. The mean ejection fraction was 36%, with 35% of participants having an ejection fraction of less than 35%. The primary combined outcome of hospitalization or mortality occurred in 31.1% of patients treated with nebivolol and 35.3% in the placebo group, with a hazard ratio of 0.86 (0.74–0.99). Mortality occurred in 15.8% on nebivolol and 18.1% in the placebo group, with a nonsignificant hazard ratio of 0.88 (0.71–1.08; $p = 0.21$).⁽¹⁸⁾

The hazard ratio for mortality when specified by age group revealed a statistically significant reduction of 0.79 (0.63–0.98) in patients less than 75.2 years of age, and a nonsignificant hazard ratio of 0.92 (0.75–1.12) for those aged greater than 75.2 years of age.⁽¹⁸⁾ Nebivolol appears to have a significant impact on mortality and hospitalizations in the elderly, but its benefits appear to be disproportionately greater in younger patients.

TABLE 4.
Predictors of adverse events/tolerability

<i>Study</i>	<i>Krum et al. 2006 Carvedilol</i>	<i>Dinsdale et al. 2005 Spironolactone</i>	<i>Witham et al. 2005 Beta Blockers</i>	<i>Carosella et al. 1996 Digoxin</i>
PREDICTOR				
Older Age	Increased ADE	No Effect	No Effect	Increased ADE
Advanced NYHA	Increased ADE	No Effect	Increased ADE	Not Studied
Increased LVEF	Decreased ADE	No Effect	Decreased ADE	Not Studied
Increased DBP	Decreased ADE	Not Studied	Not Studied	Not Studied
Increased SBP	Decreased ADE	Not Studied	Not Studied	Not Studied
Presence of COPD	Increased ADE	Not Studied	No Effect	Not Studied
Intercurrent Illness	Not Studied	Increased ADE	Not studied	Not Studied
Higher Diuretic Dose	Not Studied	Not Studied	No Effect	Not Studied
Multiple Medications	Not Studied	No Effect	Not Studied	Increased ADE
Digoxin Dose Greater than 0.25 mg	Not Studied	Not Studied	Not Studied	Increased ADE
Creatinine > 120 mmol/L	Not Studied	Not Studied	Not Studied	Increased ADE

Sin and McAlister⁽⁵⁾ evaluated in retrospective fashion a cohort of 1162 patients treated with beta blockers for heart failure. An evaluation of ACE inhibitor therapy was performed as a secondary analysis. After controlling for age, sex, Charlson score, hypertension, and ischemic heart disease, beta blocker therapy was associated with a hazard ratio of 0.72 (0.65–0.80) for all cause mortality, and 0.82 (0.74–0.92) for heart failure hospitalizations. The effect was dose-related. Those receiving higher doses of beta blockade had statistically significant lower rates of all cause mortality and heart failure hospitalizations than those who received lower doses.

The benefits were extended to those with chronic obstructive pulmonary disease, diabetes, systolic blood pressures less than 100, and bradycardia at baseline. Of note, 22% of the population sampled had a Charlson Comorbidity Index of at least 2. The systolic function of these patients was not stated. The most commonly used beta blockers were metoprolol, sotalol (which was excluded from the analysis), and atenolol.

Ace Inhibitors

In the study published by Sin and McAlister,⁽⁵⁾ analysis of patients taking ACE inhibitors was also undertaken. Four thousand nine hundred and eight patients (4908) were prescribed ACE inhibitors during specified study period. The overall reduction in all cause mortality was 0.59 (0.55–0.62). The reduction in heart failure-related hospitalizations was 0.93 (0.87–1.00). A dose-dependent effect was also present with a hazard ratio of 0.67 (0.61–0.72) for those taking lower doses of ACE inhibitors, and 0.55 for those taking higher doses.⁽⁷⁾

Ahmed *et al.*⁽³⁰⁾ published a propensity analysis of 295 patients with systolic heart failure and a mean age of 78.5 years. The authors evaluated patients discharged from hospital with an indication for ACE inhibitors. Patients prescribed ACE inhibitors were compared to patients that had an indication to be on an ACE inhibitor and were not prescribed one. Adherence to an ACE inhibitor regimen was specifically documented by following prescriptions. Patients that should have been on an ACE inhibitor that were not prescribed one

had a mortality hazard ratio of 1.47 (1.03–2.08). The mean survival rate of those not prescribed ACE inhibitors was 22%, with a mean survival time of 627 days. The survival rate of those prescribed ACE inhibitors was 33%, with a mean survival time of 829 days.⁽³⁰⁾

In a previous study published by Ahmed *et al.*,⁽³¹⁾ 1090 patients with a mean age of 79.1, ACE inhibitor use and evaluation of LV ejection fraction were both associated with decreased mortality in a three-year follow-up period post-hospitalization for heart failure. ACE inhibitors conferred a hazard ratio of 0.76 (0.71–0.96). In this study, the relative proportions of patients with systolic and diastolic heart failure were not reported. Sixty-one percent of patients had died after the three-year follow-up period.

Luthi *et al.*⁽³²⁾ performed a retrospective cohort evaluation of 621 patients with a mean age of 77.4 years. All of these patients had systolic heart failure. Patients were assessed on whether or not they had received ACE inhibitor therapy post-hospitalization for heart failure. Compared to those who had received an ACE inhibitor, those who did not receive an ACE inhibitor had a hazard ratio of 1.63 for mortality. Even patients who were receiving lower-than-recommended doses of ACE inhibitors had a nonsignificant hazard ratio of 1.3 (0.86–1.97).

Gambassi *et al.*⁽²⁹⁾ performed a retrospective cohort study. They compared the effect of digoxin therapy versus ACE inhibitor therapy. A mortality benefit was noted; however, the interpretation of this trial was difficult because ACE inhibitor and digoxin therapy are not considered equivalent therapy in the general HF population. Elderly patients did have a mortality benefit if they took ACE inhibitors as opposed to Digoxin.

CONCLUSION

In retrospect, there is a relative paucity of high quality studies to guide heart failure therapy in the elderly. The conclusions drawn from this study must be taken with caution because of the reliance on data from smaller observational studies and many retrospective studies. Perhaps the most important conclusion is that there is more work that needs to be done to characterize ADEs in the elderly, understand the magnitude of the effect size of these medications on morbidity and mortality, and understand whether the potential side effects outweigh the benefits in a quality-adjusted life years analysis.

Despite the limitations, the data in this review seems to suggest that there is an increased adverse drug event rate in relation to beta blocker and spironolactone therapy. The increased adverse drug event rate was noted in observational studies, population-based studies, and randomized control trials. In the case of beta blockers, specifically increased amounts of bradycardia, hypotension, and syncope were noted.^(12,13,14,15,16,17,18)

Studies on spironolactone revealed increased rates of hyperkalemia, acute renal failure, and medication discontinuation, although study populations were small.^(23,24,25)

Given the mere suggestion that the older persons with heart failure experience adverse events to a greater degree, we feel that further characterization in prospective studies is warranted.

It is possible that the less rigorous follow-up that patients receive outside of randomized controlled trials could contribute to the increased rates of ADEs. It remains unclear, however, how age and frailty could be independent predictors. The increased events rates in both the RCT and observational data when compared to younger patients do beg that question.

With regards to efficacy, it appears that the benefits of beta blockers and ACE inhibitors extend to the very elderly heart failure population. This trend was noted in both large-scale retrospective analyses, as well as a prospective blinded randomized control trial in the case of beta blockers.^(5,18,19) The effect appears to apply to both hospitalizations and mortality; however, the magnitude of the effect size was not equal across all studies.

In the SENIORS trial, the magnitude of the effect size was smaller than it was in the younger patient populations, and statistical significance was not gained when measuring mortality as an endpoint. It is possible that the class effect shared between metoprolol, carvedilol, and bisoprolol for systolic heart failure does not translate directly to the use of nebivolol. Another possibility, which the study seemed to suggest, is that the population greater than 75 did not benefit as much from the intervention and skewed the results in a negative fashion. The patients under 75 did benefit in a similar magnitude to other heart failure studies with similar relative risk reductions.⁽¹⁸⁾

Despite the fact that the elderly do have multiple medical comorbidities and that they were measured in many studies, there are no clear predictors of adverse events based on a validated prediction model. For beta blockers, advanced NYHA class and decreased left ventricular ejection fraction predicted poor tolerability in two studies. Possible predictors include advanced age, obstructive airways disease, and baseline blood pressure, although the data were conflicting. Further evaluation is necessary. Functional status was measured but not utilized in predicting outcomes with any HF therapy.^(13,17,23)

Additional information that would be valuable in this patient population is the measurement of quality-adjusted life years. Patients may survive longer and avoid hospitalization, but if the side effects that they experience severely diminish the quality of the life that they experience, perhaps the therapy is not as valuable in this patient population as it clearly is in patients with a mean age of approximately 65.

In the study by Sin and McCalister,⁽⁵⁾ the mortality benefits were seen despite controlling for adverse events such as bradycardia. Despite that fact, perhaps living longer while experiencing significant side effects or functional impairment imposed by these medications is not what these patients desire.

There were several limitations in our study. The first is the strong dependence upon observational data due to paucity of data from randomized studies. In spite of this, the

observational studies, specifically related to the efficacy of beta blocker and ACE inhibitor therapies, were very large and of higher quality.^(5,18) Perhaps this allows for stronger external validity for the conclusions made with regard to these topics. We did attempt to control for heterogeneity where possible, but even this methodology has its limitations in terms of minimizing bias.

The spironolactone studies were small in number, and utilized smaller populations. Also, we attempted to extrapolate answers from studies that the original design of the study was not constructed to answer. Specifically, the focus of the Juurlink study was not to relate increased rates of adverse events to age, but to the application of RCT data to “real-life” circumstances. However, the fact that the findings of increased ADEs in an older population did parallel the findings of the observational data strengthens the overall conclusions made.^(23,24,25)

The second limitation is the nonuniform group of patients involved. ACE inhibitor, beta blocker therapy, spironolactone, and digoxin are indicated for the reduction of morbidity and mortality for systolic heart failure only. Some of the observational studies utilized did not distinguish between the two.

Patients with diastolic heart failure are sometimes mistakenly treated with systolic HF medications. Diastolic HF is extremely common in the elderly. We felt that it was important to include the diastolic heart failure patients in order to detect if there were significant number of diastolic heart failure patients that were being inappropriately treated and being exposed to side effects without any hope of benefiting from the medications. We did not find this explicitly in this study. However, including these patients increased the heterogeneity of our study. Where possible, the distinction between the two has been made in the manuscript.

Our study points to the need for randomized control trials for systolic heart failure in the elderly, specifically with the medications that are already known to be efficacious in younger populations. The adverse event rates need to be measured in a comprehensive manner. The standardized measurement of medical comorbidities, functional status, and quality of life are essential. Finally, the above information should be analyzed to see whether or not prediction rules exist for adverse events and tolerability.

CONFLICT OF INTEREST DISCLOSURES

The authors declare that no conflicts of interest exist.

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