

Bibliography

Note: The following bibliography is adapted from the National Heart Care Annotated Clinical Bibliography (last updated October 31, 2003). The entire bibliography may be found at http://www.medqic.org/cms-service/stream/asset/AnnBibUpdate10_03final.pdf?asset_id=1293123.

1. SOLVD Investigators.

Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure.

N Engl J Med 1991;325:293–302.

- ♥ The best evidence in the literature that ACE-I reduces mortality. Randomized 2,569 patients with CHF and LVEF less than 35 percent to either enalapril (target dose 10 mg bid, actual mean daily dose 16.6 mg/day) or placebo. Over 48 months of follow-up, the risk of mortality was 16 percent lower, and the rate of hospitalization was 26 percent lower in those treated with enalapril. During the enrollment period (4/86–3/89), 28 percent of patients were excluded because they were already being treated with an ACE-I.

2. SOLVD Investigators.

Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions.

N Engl J Med 1992;327:685–91.

- ♥ A second arm of the SOLVD study in which 4,228 patients without symptomatic CHF but with left ventricular dysfunction were randomized to enalapril or placebo. The reduction in mortality with ACE-I was not statistically significant, but fewer treated patients developed heart failure or were hospitalized for heart failure.

3. Garg R, Yusuf S.

Overview of randomized trials of angiotensin-converting enzyme inhibitors on mortality and morbidity in patients with heart failure.

JAMA 1995;273:1450–56.

- ♥ A meta-analysis of studies of ACE-I in heart failure, including unpublished data. Provides the best estimate of mortality reduction with ACE-I (23 percent), and best evidence that mortality reduction is a classwide effect for ACE-I (not confined to enalapril).

Bibliography

4. Pitt B, Segal R, Martinez FA, Meurers G, Cowley AJ, Thomas I, Deedwania PC, Ney DE, Snively DB, Chang PI.
Randomized trial of losartan versus captopril in patients over 65 with heart failure (Evaluation of losartan in the elderly study, ELITE).
Lancet 1997;349:747–52.
 - ♥ Randomized 722 patients over the age of 65 who had not been treated with an ACE-I to either losartan or captopril. The primary endpoint of the study was the change in creatinine, but a 46 percent reduction in mortality occurred for the losartan group. To date, it is the only evidence that ARBs may have an effect on mortality. It is not considered to have demonstrated the efficacy of ARBs because it was not designed to test a mortality hypothesis. The small sample size makes it relatively likely that the results are due to chance. Nevertheless, these results have motivated several studies that are designed to assess the mortality effects of ARBs alone or in combination with ACE-I. The results of this study were superseded by the results of the ELITE II trial described below.

5. Pitt B, Poole-Wilson PA, Segal R, Martinez FA, Dickstein K, Camm AJ, Konstam MA, Riegger G, Klingler GH, Neaton J, Sharma D, and Thiyagarajan B for the ELITE II Investigators.
Effect of losartan compared with captopril on mortality in patients with symptomatic heart failure: randomized trial—the Losartan Heart Failure Survival Study ELITE II.
Lancet 2000;355:1582–87.
 - ♥ The ELITE II study compared the ACE inhibitor captopril with the angiotensin receptor blocker (ARB) losartan in patients over the age of 60 with heart failure and an ejection fraction less than 40 percent. The study was designed to assess whether mortality was lower for patients treated with one drug compared with the other. 3,152 patients were treated for an average of 1.5 years. Mortality was 17.7 percent in the losartan group and 15.9 percent in the captopril group—a difference that was not statistically significant. Based on the statistical design of the study, it is not possible to say the two drugs have an equivalent effect on mortality. This study is the first of three major clinical trials comparing ACE inhibitors and ARBs. There is consensus that the results of this study should not change current practice—ARBs remain a second line treatment for heart failure behind ACE inhibitors.

6. Cohn JN, Johnson G, Ziesche S, Cobb F, Francis G, Tristani F, Smith R, Dunkman B, Loeb H, Wong M, Bhat G, Goldman S, Fletcher RD, Doherty J, Hughes CV, Carson P, Cintron G, Shabetai R, Haakenson C.
A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure.
N Engl J Med 1991;325:303–10.
 - ♥ This study, known as VHeFT-II, demonstrated that the ACE-I was more effective than the combination of hydralazine and nitrates in reducing mortality. In the previous VHeFT study (*N Engl J Med* 1986;314:1547–52) the hydralazine/nitrate

combination had been shown to reduce mortality significantly.

7. Ligtenberg G, Blankestijn PJ, Oey L, Klein IHH, Dijkhorst-Oei LT, Boomsma F, Wieneke GH, Van Hueffelen AC, Koomans HA.
Reduction of sympathetic hyperactivity by enalapril in patients with chronic renal failure.
N Engl J Med 1999;340:1321–8.
 - ♥ There has been skepticism about the value of ACE-I in patients with renal failure. In this study, sympathetic nervous system activity (higher levels of which are associated with higher mortality in heart failure) were measured in 14 patients in response to either enalapril or the calcium channel blocker amlodipine. Enalapril treatment lowered sympathetic nerve activity, while amlodipine increased it.
8. Krumholz HM, Wang Y, Parent EM, Mockalis J, Petrillo M, Radford MJ.
Quality of care for elderly patients hospitalized with heart failure.
Arch Intern Med 1997;157:2242–47.
 - ♥ An analysis of 1,535 charts of Medicare patients with principal diagnosis of heart failure in 1994. 75 percent of eligible patients had LVEF measured, and 86 percent of eligible patients received an ACE inhibitor at discharge.
9. Krumholz HM, Parent EM, Tu N, Vaccarino V, Wang Y, Radford MJ, Hennen J.
Readmission after hospitalization for congestive heart failure among Medicare beneficiaries.
Arch Intern Med 1997;157:99–104
 - ♥ Analyzed administrative data from 17,448 Connecticut hospital Medicare discharges with a principal diagnosis of heart failure over a four-year period from 1990–1994. The six-month readmission rate was 44 percent, and heart failure was the reason for 18 percent of readmissions. Male gender, increasing comorbidity, and prior admission within six months were independent predictors of readmission.
10. Havranek EP, Abrams F, Stevens E, Parker K.
Determinants of mortality in elderly patients with heart failure: The role of angiotensin-converting enzyme inhibitors.
Arch Intern Med 1998;158:2024–2028.
 - ♥ Analyzed abstracted data from 1,016 Medicare discharges in Colorado during 1994. 54 percent of patients with systolic dysfunction identified during the hospitalization were discharged on ACE inhibitors. Mortality at one year was 24 percent in those treated with ACE inhibitors and 36 percent in those not treated. Increasing comorbidity, ACE inhibitor prescription, hospital, and absence of cardiology consultation were independent predictors of mortality.
11. Philbin EF, Andreou C, Rocco TA, Lynch LJ, Baker SL.
Patterns of angiotensin-converting enzyme inhibitor use in congestive heart failure in two community hospitals.
Am J Cardiol 1996;77:832–38.

Bibliography

- ♥ Chart review of 424 patients admitted to two New York hospitals with CHF DRG during 1992. Using a broader age range than in the Medicare-based studies, the authors found younger age and better renal function predicted ACE inhibitor prescription. Six-month mortality was reported as 9 percent in those treated with ACE inhibitors and 19 percent in those not so treated, with mortality rates determined by chart review only.
12. Large State Peer Review Organization Consortium.
Heart failure treatment with angiotensin-converting enzyme inhibitors in hospitalized Medicare patients in 10 large states.
Arch Intern Med 1997;157:1103–08.
- ♥ 55 percent of 6,794 Medicare patients with heart failure in 1993 and 1994, and 73 percent of patients judged to be ideal candidates, were discharged on ACE inhibitors. Higher rates of ACE inhibitor prescription were associated with younger age, lower ejection fraction, shorter length of stay, and creatinine less than 3.0 mg/dl.
13. Smith NL, Psaty BM, Pitt B, Garg R, Gottdiener JS, Heckbert SR.
Temporal patterns in the medical treatment of congestive heart failure with angiotensin-converting enzyme inhibitors in older adults 1989 through 1995.
Arch Intern Med 1998;158:1074–80.
- ♥ Analyzed data from the Cardiovascular Health Study, an epidemiologic survey of 5,201 men and women over the age of 65. All participants underwent echocardiography and were assessed for a diagnosis of CHF. Among those with CHF and low LVEF, the percentage of patients treated with ACE inhibitors did not change during the period 1989–1994, remaining at approximately 50 percent.
14. Packer M, Poole-Wilson P, Armstrong PW, Cleland JGF, Horowitz JD, Massie BM, Ryden L, Thygesen K, Uretsky BF, the ATLAS Study Group.
Comparative effects of low and high doses of the angiotensin-converting enzyme inhibitor, lisinopril, on morbidity and mortality in chronic heart failure.
Circulation 1999;100:2312–8.
- ♥ This study addressed the issue of whether or not the high doses of ACE inhibitors used in clinical trials are superior to the low doses commonly used in clinical practice. Patients with heart failure and ejection fraction less than 30 percent were randomized to receive either lisinopril 2.5–5.0 mg/day or 32.5–35 mg/day. Patients were excluded from the study if they could not tolerate lisinopril 15 mg/day. Approximately 20 percent of patients were discontinued from study drug and treated with open label ACE inhibitor. There was no difference in mortality between the two treatment arms. A secondary endpoint defined after the study began, the combination of mortality and all-cause hospitalizations, was reached 12 percent less often in patients treated with the high dose over approximately four years of follow-up.
 - ♥ There are serious flaws in the design and execution of this study, making it difficult to

base policy recommendations on the results. It is probably best interpreted as showing small benefits with use of higher ACE inhibitor doses without significant increases in serious adverse effects.

15. Akosah KO, Schaper A, Briggs K, Sundaram R, Devine S.

ACE-I therapy in CHF patients too ill to qualify for evidence based clinical trials.

Chest 2000;118:133S.

- ♥ Taken together, these two studies demonstrate that low blood pressure should be a rare reason for not treating a patient with heart failure with an ACE inhibitor. In the first paper, data from the SOLVD trial were analyzed retrospectively. Patients treated with enalapril were no more likely to be withdrawn because of adverse events than were patients treated with placebo. Hypotension was reported in only 2.0 percent of patients, and was the reason for discontinuation in only 0.5 percent. In the second study, reported in an abstract, 18 percent of patients referred to a specialized heart failure clinic presented with a systolic blood pressure of < 100 mmHg; 17/18 could be successfully treated with an ACE inhibitor.

16. Exner DV, Dries DD, Domanski MJ, Cohn JN.

Lesser response to angiotensin-converting enzyme inhibitor therapy in black as compared to white patients with left ventricular dysfunction.

New Engl J Med 2001;344:1351–7.

- ♥ This article is of great potential interest to the quality improvement community because some have used it as a basis for suggesting that African American race should be an exclusion from quality indicators assessing ACE inhibitor use in heart failure patients. We believe it wrong to interpret the results of the article in this manner.
- ♥ The article is a retrospective analysis of studies known as SOLVD (annotated bibliography articles 1 and 2 above). The authors assessed outcome by self-reported race, and adjusted for severity of illness by matching black and non-black patients by ejection fraction, therapy, gender, and age. They also adjusted for NYHA class and history of hypertension or diabetes. They adjusted for socioeconomic factors with educational level achieved and presence or absence of perceived financial distress.
- ♥ There were no differences between black and white patients with respect to mortality. Black patients on enalapril were as likely as black patients on placebo to require hospitalization for heart failure; non-black patients on enalapril were significantly less likely to require hospitalization for heart failure compared with non-black patients on placebo.
- ♥ Although the study raises interesting questions it cannot be considered definitive. The major problems with the study include:
 - o The study is retrospective and involves a relatively small number of patients.
 - o The endpoint for which a difference was seen, that of hospitalization for heart failure, is a poor indicator of worsening heart failure and would never be considered an

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- o adequate endpoint in a clinical trial.
 - o The variables used to adjust for differences in baseline disease severity and socioeconomic status are approximate at best.
 - o It appears the doses used to treat the black patients were inadequate, as assessed by blood pressure changes and by projection of data in the hypertension literature.
 - ♥ More importantly, using skin color and facial features as markers for genetic differences in pharmacology is a concept without validity. This point is made more fully in an editorial by one of the editors of the journal (Scwartz RS. Racial profiling in medical research. *N Engl J Med* 2001;344:1392–3.)
17. Cohn JN and Tognoni G for the Valsartan Heart Failure Trial Investigators.
A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. *N Engl J Med* 2001;345:1667–75.
- ♥ This trial randomized 5,010 patients with NYHA class II-IV heart failure, ejection fraction less than 40 percent, and a dilated left ventricle to receive either valsartan (an ARB—angiotensin-receptor blocker) or placebo in addition to their usual heart failure therapy. This background therapy included an ACE inhibitor in about 93 percent, diuretics in about 86 percent, digoxin in about 67 percent, and a beta blocker in about 34 percent of patients.
 - ♥ The primary endpoints for the study were mortality and mortality plus morbidity. Neither valsartan nor placebo was superior to the other with respect to mortality. With respect to morbidity plus mortality, patients in the valsartan group were significantly about 13 percent less likely to die, be hospitalized for heart failure, require inotropic drugs to treat heart failure as an outpatient, or be resuscitated from a cardiac arrest. This finding was probably the result of a 27 percent reduction in risk of hospitalization for patients receiving valsartan.
 - ♥ These results have not translated into widespread advocacy of adding an ARB to the regimens of patients receiving ACE inhibitors, because of the results of a subgroup analysis that was not prespecified (and is therefore statistically less reliable). In this analysis, among the 1,610 patients receiving the combination of a beta blocker and an ACE inhibitor at baseline, addition of the ARB was associated with an increase in mortality. Because beta blockers and ACE inhibitors are now considered standard therapies (see references 1 and 2 above), the safety of addition of an ARB is in doubt.
18. Jong P, Demers C, McKelvie RS, Liu PP.
Angiotensin-receptor blockers in heart failure: meta-analysis of randomized controlled trials. *J Am Coll Cardiol* 2002;39:463–70.
- ♥ Integrating angiotensin receptor blockers (ARBs) into guideline-based treatment of heart failure has been a challenge. These agents were accepted into clinical practice based on their pharmacology before the emergence of clinical data. This situation has

made the design and acceptance of quality indicators considerably more difficult. Several recent trials of ARBs have helped clarify these issues. This quantitative data synthesis by Jong and colleagues suggests ARBs are probably equally effective as ACE inhibitors in reducing mortality and hospitalization rates for patients with systolic dysfunction. There is no benefit to adding ARBs to ACE inhibitors with respect to mortality. The possibility remains that the combination may reduce morbidity compared to either drug alone. There is also remaining concern that the combination of ARB plus ACE inhibitor plus beta blocker may have deleterious effects, and thus combination ARB/ACE-I therapy cannot yet be considered rational.

19. Greenberg BH.

Angiotensin-receptor blockers in heart failure: A work in progress.

J Am Coll Cardiol 2002;40:1422–4.

- ♥ The issue of ACE inhibitors versus angiotensin receptor blockers (ARBs) for systolic heart failure remains somewhat contentious for those presenting heart failure indicators to clinicians. This editorial by a leader in the field nicely summarizes the current state of knowledge and the justification for continuing to consider ACE inhibitors the first-line therapy for systolic heart failure.

20. Jong P, Yusuf S, Rousseau MF, Ahn SA, Bangdiwala SI.

Effect of enalapril on 12-year survival and life expectancy in patients with left ventricular systolic dysfunction: A follow-up study.

Lancet 2003;361:1843–8.

- ♥ The SOLVD trial demonstrated conclusively that the ACE inhibitor enalapril decreased mortality in patients with heart failure and reduced ejection fraction, and decreased hospitalization rates but not mortality in patients with asymptomatic reduction in ejection fraction. This study is a 12-year follow-up of patients treated in both the treatment and the prevention arms of the SOLVD trial.
- ♥ At 12-year follow-up, there was a statistically significant reduction in mortality for the asymptomatic patients treated with enalapril (50.9 percent) compared with those treated with placebo (56.4 percent).
- ♥ This study is important because it lends further weight to recommendations to treat all patient with low (less than 40 percent) ejection fraction.

21. Shekelle PG, Rich MW, Morton SC, Atkinson SW, Tu W, et al.

Efficacy of ACE inhibitors and beta-blockers in the management of left ventricular systolic dysfunction according to race, gender, and diabetic status: A meta-analysis of major clinical trials.

J Am Coll Cardiol 2003;41:1529–38.

- ♥ Despite the strong evidence base for treatment of heart failure patients with ACE inhibitors and betablockers, some investigators and some clinicians have expressed doubt about the efficacy of these agents in some subgroups of patients, in particular African Americans and the elderly. Because women have been generally under-

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represented in heart failure trials, concern about efficacy by gender has also been questioned.

- ♥ This meta-analysis is particularly useful in that it contradicts retrospective subgroup analysis of some clinical trials, and supports the efficacy of both ACE inhibitors and beta-blockers in African Americans.
- ♥ Interestingly, the study was unable to demonstrate efficacy of ACE inhibitors in asymptomatic women, although the Jong study summarized above should allay those concerns.

22. Shlipak MG

Pharmacotherapy for heart failure patients with renal insufficiency.

Ann Int Med 2003;138:917–24.

- ♥ Physician concern about potential adverse consequences of ACE inhibitors in patients with renal insufficiency has been demonstrated to contribute to under-prescription of ACE inhibitors for heart failure. This review article documents a low incidence of adverse effects in this setting, and should be useful to allay concerns about ACE inhibitor treatment in this setting. It also gives data on which to weigh risks and benefits for treatment with other heart failure agents in this setting.

The **CHARM** studies. This interlocked set of studies addresses several issues regarding the treatment of heart failure with angiotensin-receptor blockers (ARBs). At the time of publication of this bibliography, there is controversy over whether or not the results of these studies should change guideline recommendations for the treatment of heart failure with ACE inhibitors and/or ARBs, and thus heart failure quality indicators.

23. McMurray JJV, Ostergren J, Swedberg K, Granger CB, Held P, et al.

Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting enzyme inhibitors: The CHARM-Added trial. *Lancet* 2003;362:767–71.

- ♥ 2,548 patients with heart failure and an ejection fraction less than 40 percent who were already receiving an ACE inhibitor were randomized to get either no added treatment or added treatment with the ARB candesartan. The study was not designed with sufficient power to detect differences in all-cause mortality, and there were none after 41 months of follow-up. The patients treated with candesartan in addition to an ACE inhibitor had significantly lower cardiovascular mortality and were significantly less likely to be hospitalized for heart failure. Controversy has resulted from at least two sources.
- ♥ First, other agents for treatment of heart failure have been held to a standard of demonstrating reduction in all-cause mortality; CHARM-Added did not meet this standard. Second, it is now known that beta blockers reduce mortality in heart failure due to systolic dysfunction, but nearly half of the patients in CHARM-Added were not receiving these agents at baseline (beta blockers were not standard

- treatment when CHARM-Added was designed). Many argue that CHARM-Added has therefore not addressed the relevant clinical question of whether an ARB added to standard therapy (ACE inhibitor, beta blocker, and, in some patients, spironolactone) reduces mortality.
- ♥ Retrospective analysis of a prior study known as Val-HeFT (previously described in this annotated bibliography) suggested that the combination of an ACE inhibitor, an ARB, and a beta blocker might actually increase mortality. Results of the larger CHARM-Added study suggest the combination at least is safe.
24. Yusuf S, Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJV, et al. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM Preserved Trial. *Lancet* 2003;362:777–81.
- ♥ This is one of the first large-scale randomized trials to investigate treatment of patients with heart failure with preserved left ventricular systolic function (PLVSF). Patients with an ejection fraction greater than 40 percent and heart failure were randomized to candesartan or placebo. The primary outcome of the study (cardiovascular death plus hospitalization for heart failure) did not reach statistical significance. Fewer patients treated with candesartan were hospitalized for heart failure. Controversy over the application of the results of CHARM-Preserved center around the fact that the overall results of the study were negative but the results of one of the secondary analyses (hospitalization for heart failure) was positive. Some argue that this is sufficient grounds to treat all patients with heart failure with PLVSF with an ARB; others argue this endpoint is subject to bias and of limited value and should not direct therapy.
25. Pfeffer MA, McMurray JJV, Velasquez EJ, Rouleau JL, Kober L, et al. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. *N Engl J Med* 2004;349:1893–1906.
- ♥ This study, known by the acronym **VALIANT**, adds significantly to our understanding of the proper roles of ARBs relative to ACE inhibitors for treatment of left ventricular systolic function, particularly after MI but also in the setting of heart failure. 14,703 patients who had had an AMI within the previous 10 days and had evidence of heart failure or reduced ejection fraction were randomized to receive the ARB valsartan, the ACE inhibitor captopril, or a combination of both drugs. Mortality over 24 months of follow-up among the three groups was 19.9 percent, 19.5 percent, and 19.3 percent for the three groups, respectively, allowing the investigators to conclude that valsartan was statistically not inferior to captopril. Although this is not statistically the same as being able to conclude that the effects of the drugs are equivalent, it is the first large clinical trial that can be cited as supporting use of ARBs as first-line therapy on equal footing with ACE inhibitors. Response

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to these data from expert consensus groups thus far has been mixed and continues to evolve. The impact of the VALIANT trial on performance measures depends on the result of that evolution.