Heart Failure

Clinical Practice Guideline

This guideline is informational only. It is not intended or designed as a substitute for the reasonable exercise of independent clinical judgment by practitioners, considering each patient’s needs on an individual basis.

Guideline recommendations apply to populations of patients. Clinical judgment is necessary to design treatment plans for individual patients.

Approved by the National Guideline Directors
January 2010
# Table of Contents

**Introduction** ................................................................................................................................... 1

**Guideline Summary** .......................................................................................................................... 4

**Rationale Statements** .......................................................................................................................... 10

1. Sleep Apnea .......................................................................................................................... 10
2. Use of Statins in Heart Failure Patients without Documented Coronary Artery Disease ........ 12
3. Use of Thiazolidinediones (TZDs) ................................................................................................ 15
4. Use of Erythropoietin Analogs to Treat Anemia ................................................................. 17
5. Use of Diuretics ......................................................................................................................... 19

**Vasodilators in Left Ventricular Systolic Disorder (LVSD)** ......................................................... 21

6. Use of Renin-Angiotensin System Inhibitor/Blockers and/or Vasodilators ......................... 21
7. Target Dose of ACE Inhibitors .................................................................................................. 25
8. Appropriate Renal Function for Prescribing ACEIs ............................................................... 27
9. Combination Aspirin and ACEIs .............................................................................................. 28

**Beta-Blockers in LVSD** .................................................................................................................. 30

10. Use of Beta-Blockers in Addition to Standard Treatment ..................................................... 30
11. Which Beta-Blockers to Use ..................................................................................................... 32
12. Beta-Blockers with Concomitant Asthma or COPD .............................................................. 34
13. Aldosterone Antagonism ......................................................................................................... 36
14. Digoxin .................................................................................................................................... 38
15. Oral Anticoagulation - Warfarin ............................................................................................. 42
16. Calcium Channel Blockers ...................................................................................................... 45
17. Heart Failure with Preserved Ejection Fraction ..................................................................... 46

**Lifestyle Factors** .............................................................................................................................. 50

18. Sodium Restricted Diet ........................................................................................................... 50
19. Physical Activity ....................................................................................................................... 51
20. Pharmacological Management of LVSD Based on Patients’ Race/Ethnicity or Sex ............ 54
21. Target Blood Pressure ............................................................................................................. 57
22. Medications to Achieve Target Blood Pressure .................................................................... 58
23. Reassessment of Systolic Performance .................................................................................. 59
24. Omega-3 Supplementation ..................................................................................................... 59

**Appendix A: Criteria for Grading the Evidence** ........................................................................... 68
Appendix B: Supporting Documentation ................................................................. 70
  1. Sleep Apnea in Heart Failure Patients ................................................................. 70
     Problem Formulation ......................................................................................... 70
     Problem Formulation ......................................................................................... 70
     Search Strategy .................................................................................................. 71
     Evidence Tables ................................................................................................. 72
  2. Use of Statins in Heart Failure Patients without Documented Coronary Artery Disease ... 75
     Problem Formulation ......................................................................................... 75
     Search Strategy .................................................................................................. 75
     Evidence Tables ................................................................................................. 77
  3. Use of Thiazolidinediones (TZDs) ........................................................................ 79
     Problem Formulation ......................................................................................... 79
     Search Strategy .................................................................................................. 79
     Evidence Tables ................................................................................................. 80
  4. Use of Erythropoietin Analogs to Treat Anemia ...................................................... 83
     Problem Formulation ......................................................................................... 83
     Search Strategy .................................................................................................. 83
     Evidence Tables ................................................................................................. 84
  5. Use of Diuretics .................................................................................................... 87
     Problem Formulation ......................................................................................... 87
     Search Strategy .................................................................................................. 87
     Evidence Tables ................................................................................................. 89
  6. Use of Renin-Angiotensin System Inhibitor/Blockers and/or Vasodilators .............. 90
     Problem Formulation ......................................................................................... 90
     Search Strategy .................................................................................................. 91
  7. Target Dose of ACE Inhibitors .............................................................................. 95
     Problem Formulation ......................................................................................... 95
  8. Appropriate Renal Function for Prescribing ACEIs ............................................... 95
     Problem Formulation ......................................................................................... 95
  9. Combination Aspirin and ACEIs ............................................................................ 95
     Problem Formulation ......................................................................................... 95
     Evidence Tables ................................................................................................. 96

Vasodilators in Left Ventricular Systolic Disorder (LVSD) ............................................. 90
  6. Use of Renin-Angiotensin System Inhibitor/Blockers and/or Vasodilators .............. 90
     Problem Formulation ......................................................................................... 90
     Search Strategy .................................................................................................. 91
  7. Target Dose of ACE Inhibitors .............................................................................. 95
     Problem Formulation ......................................................................................... 95
  8. Appropriate Renal Function for Prescribing ACEIs ............................................... 95
     Problem Formulation ......................................................................................... 95
  9. Combination Aspirin and ACEIs ............................................................................ 95
     Problem Formulation ......................................................................................... 95
     Evidence Tables ................................................................................................. 96
Beta-Blockers in LVSD................................................................. 106
10. Use of Beta-Blockers in Addition to Standard Treatment ....................... 106
    Problem Formulation ....................................................................... 106

11. Which Beta-Blockers to Use............................................................... 106
    Problem Formulation ....................................................................... 106
    Search Strategy ............................................................................... 107

12. Beta-Blockers with Concomitant Asthma or COPD ................................ 108
    Problem Formulation ....................................................................... 108
    Evidence Tables ............................................................................. 109

13. Aldosterone Antagonism ..................................................................... 113
    Problem Formulation ....................................................................... 113
    Search Strategy ............................................................................... 113
    Evidence Tables ............................................................................. 115

14. Digoxin .............................................................................................. 117
    Problem Formulation ....................................................................... 117
    Search Strategy ............................................................................... 118

15. Oral Anticoagulation - Warfarin......................................................... 119
    Problem Formulation ....................................................................... 119
    Search Strategy ............................................................................... 120

16. Calcium Channel Blockers ................................................................. 122
    Problem Formulation ....................................................................... 122
    Search Strategy ............................................................................... 123

17. Heart Failure with Preserved Ejection Fraction.................................... 124
    Problem Formulation ....................................................................... 124
    Search Strategy ............................................................................... 125
    Evidence Tables ............................................................................. 126

Lifestyle Factors...................................................................................... 128
18. Sodium Restricted Diet ....................................................................... 128
    Problem Formulation ....................................................................... 128
    Search Strategy ............................................................................... 128

19. Physical Activity ................................................................................ 129
    Problem Formulation ....................................................................... 129
    Search Strategy ............................................................................... 129
    Evidence Tables ............................................................................. 131
20. Pharmacological Management of LVSD Based on Patients’ Race/Ethnicity or Sex ....... 136
   Problem Formulation ........................................................................................................ 136
   Search Strategy .............................................................................................................. 137
   Evidence Tables ............................................................................................................. 140

21. Target Blood Pressure ................................................................................................. 142
   Problem Formulation ...................................................................................................... 142
   Search Strategy ............................................................................................................... 142

22. Medications to Achieve Target Blood Pressure ......................................................... 143
   Problem Formulation ...................................................................................................... 143
   Search Strategy ............................................................................................................... 143

23. Reassessment of Systolic Performance ..................................................................... 144
   Problem Formulation ...................................................................................................... 144
   Search Strategy ............................................................................................................... 144

24. Omega-3 Supplementation ......................................................................................... 145
   Problem Formulation ...................................................................................................... 145
   Search Strategy ............................................................................................................... 145

References .......................................................................................................................... 146
Introduction

Kaiser Permanente’s National Guideline Program

The National Guideline Program (NGP) supports the development of a core set of explicit, scientifically-based clinical practice guidelines, practice resources, and evidence synopses to assist Kaiser Permanente (KP) physicians, administrators, and other health care professionals in determining the most effective medical practices.

This core set of evidence-based resources will:
- Create Programwide economies of scale,
- Support ongoing performance improvement activities,
- Consistently provide high quality resources for use in care delivery tools and systems, and
- Increase KP regions’ abilities to leverage clinical guidelines to improve clinical outcomes.

Clinical practice guidance, based on scientific evidence, is essential for providing high quality care and continuously improving on it. Such guidance needs to be integrated into the electronic medical record and other decision support tools to be accessible to clinicians at the point of care. In addition, engaging our members in collaborative, shared decision-making conversations regarding their personal preferences is an essential component of patient-centered quality care. Furthermore, cost-effectiveness of various evidence-based interventions and resource limitations are important considerations. This involves addressing health problems in ways that maximize the health of the population given the available resources.

Who are the National Guideline Directors’?

The National Guideline Directors (NGD) are a group of experts and advocates of evidence-based medicine who provide direction and oversight to the National Guideline Program (NGP). In this role, the NGD selects and approves topics for evidence-based knowledge products, owns Kaiser Permanente’s Common Methodology, and is responsible for quality assurance review. This group is composed of representatives from the Care Management Institute (CMI) and all eight regions.

What Is the Guideline Quality Committee?

The Guideline Quality (GQ) Committee is a subcommittee of the NGD consisting of a group of evidence experts from various KP regions and CMI who review and approve all the National Guidelines. This review ensures that the processes used to develop guideline content have adhered to KP evidence-based methods and that the labels applied to clinical recommendations therein are accurate (e.g., “evidence-based” or “consensus-based”).
How Are Guidelines Developed?

Guidelines are developed with the use of an “evidence-based methodology” and involve a systematic literature search, critical appraisal of the research design and statistical results of relevant studies, and grading of the sufficiency (quantity, quality, consistency, and relevancy) of the evidence for drawing conclusions. An evidence search includes literature published in peer-reviewed scientific journals, existing evidence-based guidelines, consensus-based statements from external professional societies and government health organizations, and clinical expert opinion of KP regional specialty groups. For additional information on evidence grading, see Appendix A.

To develop a or revise a guideline, CMI consultants work with a multidisciplinary Guideline Development Team (GDT). Each GDT consists of a core group of physicians, representing primary care and the specialties most affected by the guideline topic, and, as appropriate, other content experts from disciplines such as pharmacy, nursing, and health education. The members of a GDT are nominated by the respective National Guideline Directors to represent their regions. The GDT reviews the appraisal of the evidence and develops or revises clinical recommendations based on the current evidence. Each regional representative then presents the draft guideline recommendations to key experts and champions in their regions for critical review and support to improve the likelihood of implementation once the guideline is published.

How Often Are Guidelines Reviewed and Revised?

To keep current with changing medical practices, all guidelines are reviewed, and, if appropriate, revised at least every two years. To develop the Heart Failure Guideline, a multidisciplinary, interregional Guideline Development Team first met in November 2007 to define the scope of the guideline. The Project Management Team then performed systematic reviews of the medical literature on each of the clinical questions identified by the Guideline Development Team, assembled the evidence, and developed draft recommendations for review by the Guideline Development Team. All of the recommendations and supporting evidence were reviewed in depth by the Guideline Development Team in two conference calls in January and February, 2008. The National Guideline Directors’ Guideline Quality Committee reviewed and approved the guideline in May 2008.

A limited review was conducted in late 2009 resulting in a guideline with no changes to the recommendations published in January 2010. The format and organization of the guideline did undergo significant revision, however.

What Does It Mean for a Guideline to Be Evidence-Based?

Each clinical recommendation within a guideline is labeled as “evidence-based” or “consensus-based.” A recommendation is considered “evidence-based” if there has been a systematic review of the evidence, the evidence is sufficient, and the recommendation is consistent with the evidence. A recommendation can also be considered “evidence-based” if there is insufficient evidence but either no particular intervention is recommended or options are recommended without favoring one of the options over others. A recommendation is considered “consensus-based” if there has been a systematic review of the evidence, the evidence is insufficient to support an evidence-based recommendation, and the GDT decides to make a consensus recommendation.
What Does It Mean for a Guideline to Be Approved and National?

A recommendation that is consistent with the above policies is labeled as “National Guideline Directors Approved.” A recommendation that fails to satisfy those criteria is not approved and will be noted as such. A National Guideline Directors approved guideline for which at least 90% of the recommendations are approved by at least six of the eight KP regions is a "National Guideline." On the topics for which they exist, National Guidelines are the preferred evidence source for KP HealthConnect content.

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Acknowledgments
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Guideline Summary

This guideline is informational only. It is not intended or designed as a substitute for the reasonable exercise of independent clinical judgment by practitioners, considering each patient’s needs on an individual basis.

Guideline recommendations apply to populations of patients. Clinical judgment is necessary to design treatment plans for individual patients.

Note: In this guideline the term “heart failure” is used to refer to patients who have either heart failure with left ventricular systolic dysfunction (LVSD) or heart failure with preserved ejection fraction, unless otherwise distinguished.

Sleep Apnea

1A The GDT recommends against routine screening for sleep apnea in heart failure patients because of the lack of evidence that screening improves outcomes. Consensus-based

1B The GDT makes no recommendation for or against treating sleep apnea in heart failure patients to improve heart failure-related outcomes. Evidence-based: I*

Use of Statins in Heart Failure Patients without Documented Coronary Artery Disease

2 The GDT recommends that statins be used in the heart failure population just as they are in the general population according to the KP National Dyslipidemia Guidelines. Consensus-based

Use of Thiazolidinediones (TZDs)

3A The GDT recommends against the initiation of TZDs in heart failure patients unless there are no other alternatives for the treatment of diabetes. Consensus-based

3B The GDT recommends stopping TZDs in heart failure patients who suffer an exacerbation while on them. Consensus-based

3C The GDT makes no recommendations for or against discontinuing TZDs in heart failure patients who remain stable. Evidence-based: I

Use of Erythropoietin Analogs to Treat Anemia

4 The GDT makes no recommendation for or against the use of erythropoietin analogs to treat anemia in heart failure patients. Evidence-based: I

* Please note that only recommendations approved since the adoption in 2006 of evidence grading will use letters (A,B,C, etc.) to specify the grade of the evidence. Recommendations approved prior to 2006 will not include a letter grade following the statement “evidence-based.”
Use of Diuretics

5A Loop diuretics\(^*\) are recommended for the management of hypervolemia in heart failure. Use the minimal dosage needed to restore normal volume status. *Consensus-based*

5B Use combination loop\(^*\) and thiazide-type diuretics if the patient is unresponsive to loop diuretics alone. *Consensus-based*

Vasodilators in Left Ventricular Systolic Disorder (LVSD)

Use of Renin-Angiotensin System Inhibitor/Blockers and/or Vasodilators

6A It is strongly recommended that ACE inhibitors be given to patients with LVSD. *Evidence-based: A*

6B If the patient is intolerant to ACE inhibitors due to cough, allergy, or angioedema; angiotensin-receptor blockers\(^†\) are a recommended alternative. However, if ACEI-induced angioedema is severe, use caution when ARBs are used. *Evidence-based: B*

6C If both ACE inhibitors and ARBs\(^†\) are contraindicated, the combination of hydralazine and isosorbide dinitrate is recommended. *Evidence-based: B*

6D The routine addition of ARBs\(^†\) to ACE inhibitors is not recommended. If ARBs are added to ACE inhibitors it should be done for specific reasons, such as uncontrolled hypertension or insufficient vasodilation. This recommendation applies whether or not a patient is treated with beta-blockers. *Consensus-based*

Target Dose of ACE Inhibitors

7 It is recommended that the target dose of ACEIs be at least that used in major clinical trials in patients with LVSD.

- Lisinopril 20 mg daily
- Captopril 50 mg three times daily
- Enalapril 10 mg twice daily

*Consensus-based*

\(^*\) Furosemide, hydrochlorothiazide, and metolazone (Mykrox) are not FDA-approved for heart failure.

\(^†\) Valsartan is FDA-approved for heart failure; losartan and candesartan are not.
Appropriate Renal Function for Prescribing ACEIs

8A ACE inhibitors can be used for patients with serum creatinine levels up to 2.5 mg/dl or eGFR > 30 ml/min/1.73 m². *Consensus-based*

8B Use of ACE inhibitors in patients with serum creatinine levels higher than 2.5 mg/dl or eGFR < 30 ml/min/1.73 m² should be determined on a case-by-case basis. *Consensus-based*

Combination Aspirin and ACEIs

9 Aspirin (ASA) (81 mg) is recommended for patients taking ACE inhibitors for LVSD if they have concomitant cardiovascular disease (CVD). *Consensus-based*

Beta-Blockers in LVSD

Use of Beta-Blockers in Addition to Standard Treatment

10A Beta-blockers are strongly recommended for patients with LVSD NYHA class II-IV, or with asymptomatic LVSD (NYHA class I) and concomitant CAD. *Evidence-based: A*

10B Beta-blockers are recommended for patients with asymptomatic (NYHA class I) LVSD without concomitant CAD. *Consensus-based*

Which Beta-Blockers to Use

11A Carvedilol, metoprolol succinate or bisoprolol* are the recommended choices of beta-blockers for patients with LVSD. *Evidence-based: B*

11B Metoprolol tartrate* (short-acting formulation), titrated to maximum tolerated dosage, is an acceptable but less well-established alternative to carvedilol, metoprolol succinate or bisoprolol.* *Consensus-based*

Beta-Blockers with Concomitant Asthma or COPD

12A Cardioselective beta-blockers (metoprolol or bisoprolol*) are recommended for patients with LVSD and concomitant well-controlled asthma or COPD. Discuss the risks and benefits of treatment, and instruct the patient to report any increase in airway symptoms. *Evidence-based: B*

12B Carvedilol is an acceptable but less well-established option for patients with LVSD and well-controlled asthma or COPD. *Consensus-based*

* Not FDA-approved for heart failure.
Aldosterone Antagonism

13A In addition to standard treatment, spironolactone is recommended for patients with LVSD, EF < 35%, NYHA Class III or IV, and no contraindications. *Evidence-based: B*

13B Spironolactone is recommended for patients with LVEF < 40%, recent MI, either diabetes or signs of heart failure, and no contraindications. *Consensus-based*

13C It is an acceptable but less well-established option to use spironolactone in patients with EF < 40%, any symptom of heart failure, and no contraindications. *Consensus-based*

13D For most patients, a dose of spironolactone of 25 mg daily, or less is recommended. High doses may increase risk of serious hyperkalemia. *Evidence-based: B*

13E Eplerenone may be used as an alternative to spironolactone if gynecomastia is problematic. *Evidence-based: B*

Digoxin

14A Digoxin may be added to standard therapy of ACE inhibitors, diuretics, and beta-blockers for heart failure, to improve symptoms and reduce hospitalization. *Evidence-based: C*

14B Digoxin is not recommended for patients with few or no symptoms of heart failure who are in normal sinus rhythm, because it does not reduce mortality. *Evidence-based: D*

14C Because of possible toxicity, which may be more common in women, and for maximum benefit, use lower doses of digoxin, and consider maintaining serum digoxin levels to no more than 0.8 ng/ml. *Consensus-based*

Oral Anticoagulation - Warfarin

15A Warfarin is recommended for patients with LVSD and atrial fibrillation, unless contraindicated. *Evidence-based: B*

15B The routine use of warfarin for patients with LVSD in normal sinus rhythm has not been established. Its use should be based on a determination of the potential risks and benefits of treatment. *Consensus-based*

15C The use of warfarin is an option for LVSD patients in normal sinus rhythm, and with left ventricular thrombus on echocardiography or a history of thromboembolism. *Consensus-based*

Calcium Channel Blockers

16A Amlodipine* and felodipine* (second generation dihydropyridine calcium channel blockers) are options for the treatment of angina pectoris or hypertension in patients with LVSD. *Evidence-based: C*

16B The GDT recommends against the use of calcium channel blockers (CCBs) other than amlodipine* and felodipine* in patients with LVSD. *Evidence-based: D*

* Not FDA-approved for heart failure.
Heart Failure with Preserved Ejection Fraction

17 In patients with heart failure with preserved ejection fraction, treat the following concomitant conditions according to local and national guidelines: hypertension, rhythm abnormalities, ischemia, and edema. Consensus-based

Lifestyle Factors

Sodium Restricted Diet

18 Moderate sodium restriction, 2 to 2.4 grams (2,000 to 2,400 mg) per day, is recommended for patients with heart failure in order to assist in volume management, unless a low-sodium diet is contraindicated. It is recommended that clinicians reinforce and/or increase sodium restriction when fluid retention requires increasing doses of diuretics. Consensus-based

Physical Activity

19 Light to moderate aerobic activity and resistance training is recommended for patients with stable heart failure, unless contraindicated. Evidence-based: B

Pharmacological Management of LVSD Based on Patients’ Race/Ethnicity or Sex

20A For women* and nonwhite populations, management of ACE inhibitors, beta-blockers, and spironolactone should not be different from that in men and whites. Consensus-based

20B It is an option to add hydralazine and isosorbide dinitrate to standard heart failure therapy (including ACE inhibitors and beta-blockers) in blacks/African Americans and in patients who require additional vasodilation for uncontrolled hypertension or symptoms. Consensus-based

Target Blood Pressure

21 Target blood pressure for most patients is < 140/90mm Hg. Aim for a lower target blood pressure (< 130/80mm Hg) for patients with:

- Diabetes mellitus
- Renal disease
- Coronary artery disease

Consensus-based

* Please see the digoxin recommendation for the use of digoxin in women.
Medications to Achieve Target Blood Pressure

22A The following medications are recommended in patients with heart failure with preserved ejection fraction to control hypertension:
- Diuretics
- ACE inhibitors
- Angiotensin receptor blockers
- Beta-blockers
- Dihydropyridine calcium channel blockers

Consensus-based

22B The following medications are recommended in patients with systolic heart failure to control hypertension:
- Diuretics
- Beta-blockers
- ACE inhibitors or ARBs if intolerant of ACE inhibitors
- Hydralazine/isosorbide dinitrate
- Amlodipine or felodipine

Consensus-based

Reassessment of Systolic Performance

23A A follow-up measurement of LVEF is recommended after patients have received optimal medical therapy or revascularization if a change in cardiac function would impact candidacy for ICD therapy. Consensus-based

23B Repeat measurement of LVEF (after initial confirmation of LVSD) is an option in patients who have had a change in clinical status only if the results would affect therapy. Consensus-based

23C Repeat measurement of LVEF (after initial confirmation of LVSD) is not recommended in clinically stable patients when the results will not alter therapy. Consensus-based

Omega-3 Supplementation

24 Omega-3 supplementation (1g per day) is an option for heart failure patients with an ejection fraction less than 40% following consideration of benefits, risks and costs of the supplement to the patient.* Consensus-based

* Omega-3 supplementation should be not emphasized over drugs with a solid body of evidence demonstrating strong clinical benefit.
Rationale Statements

1. Sleep Apnea

1A The GDT recommends against routine screening for sleep apnea in heart failure patients because of the lack of evidence that screening improves outcomes. *Consensus-based*

1B The GDT makes no recommendation for or against treating sleep apnea in heart failure patients to improve heart failure-related outcomes. *Evidence-based: I*

*Rationale:*

Evidence Grade†
Evidence for Recommendation 1A, B: Insufficient

2009 Update
No new evidence was found, the recommendation remains unchanged.

Search Strategy
See Appendix B for more information.

2008 Guideline

Screening for Sleep Apnea
No relevant RCTs were identified that evaluated screening for sleep apnea in heart failure patients.

Treatment of Sleep Apnea
No relevant RCTs were identified that evaluated treating obstructive sleep apnea in heart failure patients. Two RCTs were identified that evaluated treating central sleep apnea with continuous positive airway pressure (CPAP) in heart failure patients. Central sleep apnea is more common in heart failure patients than in the general population.

The Canadian Continuous Positive Airway Pressure for Patients with Sleep Apnea and Heart Failure (CANPAP) trial tested the hypothesis that CPAP would improve the survival rate without heart transplantation of patients who have central sleep apnea and heart failure (Bradley et al., 2005). In this open-label, multicenter trial, 258 patients with heart failure and central sleep apnea (CSA) were randomly assigned to receive CPAP or no CPAP and were followed for a mean of two years. During follow-up, sleep studies were conducted and measurements of left ventricular ejection fraction (LVEF), exercise capacity, quality of life (QOL), and neurohormones were obtained.

* Please note that only recommendations approved since the adoption in 2006 of evidence grading will use letters (A,B,C, etc.) to specify the grade of the evidence. Recommendations approved prior to 2006 will not include a letter grade following the statement “evidence-based.”

† The criteria for grading the strength of the evidence as either “good,” “fair,” or “insufficient” adheres to the KP National Guideline Program’s “Policies and Procedures” documents entitled “Label and Language of Recommendations” and “KP System for Grading the Strength of a Body of Evidence,” which are located in Appendix A.
• After two years, the primary outcome of death or heart transplantation was similar in both groups (32 vs. 32 events, p = 0.54).

• The CPAP group showed significantly greater reductions in the frequency of episodes of apnea and hypopnea and in levels of norepinephrine (NE), as compared with the control group.

• The CPAP group showed significantly greater increases in mean nocturnal oxygen saturation, LVEF, and six-minute walking distance, as compared with the control group.

• No differences between the CPAP and control groups were found in the number of hospitalizations, QOL, or atrial natriuretic peptide levels.

Although CPAP attenuated central sleep apnea, improved nocturnal oxygenation, increased LVEF, lowered NE levels, and increased the distance walked in six minutes, it did not affect survival. The data did not support the use of CPAP to extend life in patients who have heart failure and sleep apnea.

A post hoc analysis of the CANPAP trial tested the hypothesis that suppression of CSA below a mean apnea-hypopnea index (AHI) of 15 would improve LVEF and heart transplant-free survival (Arzt et al., 2007). (2)

• CPAP patients were divided post hoc into those whose AHI was or was not reduced below 15, three months after the start of the study. Changes in LVEF and heart transplant-free survival in CPAP-CSA-suppressed (n = 57), and CPAP-CSA-unsuppressed (n = 43) patients were compared with those in the control group (n = 110).

• CPAP-CSA-suppressed subjects experienced a greater increase in LVEF (p = 0.001) at three months and significantly better transplant-free survival (hazard ratio (HR) = 0.371 [95% CI: 0.142 to 0.967], p = 0.043) than control subjects, whereas the CPAP-CSA-unsuppressed group did not (for LVEF p = 0.984, and for transplant-free survival, hazard ratio (HR) = 1.463 [95% CI: 0.751-2.85], p = 0.26).

The results suggested that in heart failure patients, CPAP might improve both LVEF and heart transplant-free survival if CSA is suppressed soon after its initiation.

A randomized trial among patients with congestive heart failure (CHF) with (n = 29) or without (n = 37) Cheyne-Stokes respiration and central sleep apnea (CSR-CSA) assessed the effect of CPAP on LVEF after three months, and the combined mortality–cardiac transplantation rate after the median 2.2-year follow-up period (Sin et al., 2000). (3)

• An intention-to-treat analysis in patients with CSR-CSA revealed a strong trend toward a lower mortality–cardiac transplantation event rate among those randomized to CPAP compared with the control group (33% event rate versus 56%, respectively).

• A treatment analysis revealed that patients who complied with CPAP therapy experienced a significant reduction in their mortality–cardiac transplantation rate compared with the control group (25% versus 56%, respectively).

• CPAP did not significantly reduce the mortality–cardiac transplantation rate in patients without CSR-CSA.
• CSR-CSA patients treated with CPAP experienced a significant increase in LVEF compared with control patients. In patients without CSR-CSA, neither the CPAP-treated nor the control group experienced any significant improvement in LVEF.

This trial showed improvement of cardiac function in CHF patients with CSR-CSA, but not in those without central sleep disorder. The results suggested that CPAP could reduce the combined mortality–cardiac transplantation rate in those CHF patients with CSR-CSA who comply with therapy.

**Conclusions**

**Treatment**

Treatment of central sleep apnea with CPAP in heart failure patients improved LVEF in all of the studies evaluated and survival rate without heart transplantation in some of the studies evaluated. In the largest trial (CANPAP), treatment with CPAP did not improve survival, QOL, or hospitalization rates. Because most of the studies were small, more evidence from large RCTs is needed before the GDT can make a recommendation for or against the treatment of central or obstructive sleep apnea to improve heart failure-related outcomes.

**Screening**

Given the lack of evidence regarding treatment and the lack of trials of screening for sleep apnea in heart failure patients, the GDT does not recommend routine screening for sleep apnea in heart failure patients at this time.

2. **Use of Statins in Heart Failure Patients without Documented Coronary Artery Disease**

2 The GDT recommends that statins be used in the heart failure population just as they are in the general population according to the KP National Dyslipidemia Guidelines.

**Consensus-based**

**Rationale:**

**Evidence Grade**

Evidence for Recommendation 2: Insufficient

**2009 Update**

No new evidence was found, the recommendation remains unchanged.

**Search Strategy**

See Appendix B for more information.

**2008 Guideline**

Heart failure patients without documented CAD are a large and not well-defined population. This population includes patients with ischemic, but not yet diagnosed, heart disease and those with heart disease of nonischemic origin. The indicated ischemic population lacks confirmation of the disease by appropriate tests (ECG, exercise tests, coronary angiography). Although these patients represent a large population in the daily clinical setting, they are not addressed as such in the literature. Trials address either ischemic patients with confirmed CAD or nonischemic patients with idiopathic or inflammatory dilated cardiomyopathy.
In the context of statin use, the distinction between ischemic and nonischemic etiology has relevant implications, since hypercholesterolemia, which is the first target of statin therapy, is a proven risk factor in ischemic heart disease, whereas its role in nonischemic heart disease is much less clear.

Short-term effects of statins on cardiac function symptoms were investigated in patients with idiopathic dilated cardiomyopathy, NYHA functional class II or III, and LVEF < 40% (Node, et al., 2003). All patients were on optimal, stable doses of beta-blockers for at least three months before randomization. The primary endpoints were changes in NYHA classification and LVEF. A secondary endpoint was change in brain natriuretic peptide (BNP).

- After 14 weeks, patients treated with simvastatin (5 to 10 mg/day) had a lower NYHA functional class than patients receiving placebo.
- Consistently with this finding, the LVEF improved in the simvastatin group but not in the placebo group.
- The plasma concentration of BNP was significantly lower in the simvastatin group than in the placebo group.
- Short-term statin therapy improved cardiac function, neurohormonal imbalance, and symptoms associated with idiopathic dilated cardiomyopathy.

An open-label, standard treatment-controlled, randomized study evaluated the safety, tolerability, and efficacy of statin therapy in patients with heart failure (NYHA class II or III) secondary to inflammatory dilated cardiomyopathy and moderately elevated low-density lipoprotein cholesterol levels (Wojnicz et al., 2006). For study participation, the clinical status of heart failure had to be unchanged for $\geq$ six months despite conventional heart failure therapy. Patients were randomized to receive atorvastatin (40 mg/day) or conventional treatment for heart failure (ACE inhibitor or ARB, beta-blocker, aldosterone blocker, and a diuretic). The primary combined efficacy endpoint was an increase of $> 5\%$ in the absolute LVEF and $\geq$ two selected criteria by echocardiography, and a decrease in NYHA functional class. Secondary efficacy endpoints included changes in LVEF, left ventricular dimensions, NYHA functional class, Minnesota Living with Heart Failure Questionnaire (MQL) score, and exercise tolerance.

- At six months, there was a significant improvement in the primary efficacy endpoint in the patients receiving atorvastatin in addition to standard therapy.
- Mean LVEF and NYHA functional class improved significantly in the atorvastatin group but remained unchanged in the control group.
- After six months, MQL scores and maximal exercise capacity were not significantly changed within or between treatment groups.
- The authors concluded that the addition of a moderate dose of atorvastatin to the conventional heart failure treatment was safe and well tolerated. It improved clinical outcomes in patients with inflammatory dilated cardiomyopathy with moderate hypercholesterolemia.
- One pilot study with a randomized, double-blind design followed the effect of atorvastatin (20 mg/day) in patients with nonischemic heart failure for 12 months (Sola, et al., 2006).
• Patients had a functional NYHA class II to IV and an LVEF ≤ 35% and were taking stable doses of heart failure medications (mainly ACE inhibitors or ARBs and beta-blockers) for three months before enrollment.

• The primary endpoint was change in LVEF. Secondary endpoints included changes in several markers of inflammation and/or oxidation.

• The LV systolic function improved significantly in the cohort of patients treated with atorvastatin, compared with a decline in systolic function in patients treated with placebo over the 12-month study period.

• There were reductions in both LV end-diastolic and end-systolic dimensions in the atorvastatin group compared with placebo.

• There was a reduction in serum levels of high sensitivity C-reactive protein in the atorvastatin group.

• The findings suggested that atorvastatin might retard the progression of adverse myocardial remodeling in patients with nonischemic heart failure.

• A small, multicenter, parallel-group, double-blind, placebo-controlled study assessed the effect of high-dose rosuvastatin (10 to 40 mg/day) in patients with LVEF < 40% and CHF of ischemic or nonischemic etiology (Krum, et al., 2007). Most patients had an idiopathic cardiomyopathy as etiology of heart failure, and most had symptoms in NYHA Class II. The patient population was actively treated with current standard of care for heart failure, i.e., ACE inhibitors or ARB and beta-blockers. The primary endpoint was change in LVEF, and secondary endpoints included change in echocardiographic parameters, neurohormonal and inflammatory markers, Packer composite score, death, and hospitalization for heart failure.

• High-dose rosuvastatin had no beneficial effect on LVEF, fractional shortening, LVEDD, or LVESD after six months.

• All other secondary endpoints were similar between the stain and placebo groups.

• The net effect of statins on left ventricular remodeling and clinical outcomes remained uncertain.

**Conclusion**

The studies reported here suggested a beneficial effect of statins on the specified outcomes in heart failure patients without known coronary artery disease, but the studies were very small and therefore not adequately powered to evaluate the effect of statins on clinical outcomes in this population. The evidence was insufficient to make a recommendation for or against the use of statins to treat nonischemic heart failure. The GDT recommends that statins be used to treat hyperlipidemia, as discussed in the KP National Dyslipidemia Guideline.
3. Use of Thiazolidinediones (TZDs)

3A The GDT recommends against the initiation of TZDs in heart failure patients unless there are no other alternatives for the treatment of diabetes. *Consensus-based*

3B The GDT recommends stopping TZDs in heart failure patients who suffer an exacerbation while on them. *Consensus-based*

3C The GDT makes no recommendations for or against discontinuing TZDs in heart failure patients who remain stable. *Evidence-based: I*

**Rationale:**

**Evidence Grade**

Evidence for Recommendation 3A, B, C: Insufficient

**2009 Update**

No new evidence was found, the recommendation remains unchanged.

**Search Strategy**

See Appendix B for more information.

**2008 Guideline**

The clinical use of thiazolidinediones (TZDs) for the treatment of hyperglycemia has been limited by the fact that they cause fluid retention, which may be a harbinger or sign of congestive heart failure (CHF). A relevant question in the context of heart failure patients is whether TZD-induced fluid retention can exacerbate symptoms or precipitate decompensation in patients with previously stable heart failure.

Most clinical trials and meta-analyses evaluating cardiovascular effects of TDZs have excluded patients with documented heart failure. Only two studies and one meta-analysis have included this patient population. In addition, the recommendations of the Joint American Heart Association and American Diabetes Association on TZD use in heart failure patients were summarized.

- A very small, randomized, double-blind, placebo-controlled study assessed acute cardiovascular effects of troglitazone in type 2 diabetic patients with heart failure (LVEF < 45%) (Ogino, et al., 2002). Blood pressure and echocardiographic findings were evaluated before and one, two, three, and four hours after a single dose of troglitazone (400 mg) or placebo was administered. The aim of the study was to evaluate the cardiovascular effects of troglitazone in patients with heart failure.
  - The left ventricular stroke volume, ejection fraction, and cardiothoracic ratio (E/A) increased in patients with CHF administered a single dose of troglitazone.
  - Plasma catecholamines decreased in troglitazone-treated patients.
  - Troglitazone had no effect on blood pressure or peripheral vascular resistance.
The results of this study suggested a positive inotropic effect of troglitazone. However, the study was too small to evaluate the various hemodynamic parameters, and the acute effects may not reflect longer-term troglitazone treatment effects.

- Dargie, et al. (2007) investigated the effects of rosiglitazone on LVEF in subjects with type 2 diabetes and pre-existing CHF. Patients were randomized to a 52-week treatment with rosiglitazone (4 to 8 mg/day) or placebo in addition to background antidiabetes therapy. Treatment was up-titrated to achieve target fasting plasma glucose < 126 mg/dl, and CHF medications were adjusted as appropriate.
  - The LVEF was similar in both groups at baseline and after 52 weeks of treatment.
  - Glycemic control (hemoglobin A1c) was better in the rosiglitazone group.
  - There were more adjudicated events of new or worsening edema and increased CHF medication in the rosiglitazone group.

After 52 weeks of treatment, rosiglitazone improved glycemic control but did not adversely affect LVEF in patients with type 2 diabetes and documented heart failure. In addition, more fluid-related events occurred with rosiglitazone.

- The effect of TZDs on CHF and cardiovascular death in patients with prediabetes and type 2 diabetes was evaluated in one meta-analysis of RCTs. Only randomized, double-blind, controlled trials of TZDs reporting risk estimates or frequency data for CHF and cardiovascular death were included for analysis. Seven trials were analyzed, including 20,191 patients. This population included patients with prediabetes, patients with type 2 diabetes without cardiovascular disease, patients with type 2 diabetes and established cardiovascular disease without CHF, and patients with type 2 diabetes with documented CHF (NYHA class I or II) and an ejection fraction of less than 40%.
  - The overall event rate for CHF was 2.3% in patients given TZDs and 1.4% in the control group. Patients given TZDs had an increased risk of CHF (RR = 1.72, 95% CI: 1.21 to 2.42, p = 0.002) compared with controls.
  - The overall event rate for cardiovascular death was 0.7% in both groups. The risk of cardiovascular death was not significantly increased with the use of TZDs as compared with controls (RR = 0.93, 95% CI: 0.67 to 1.29, p = 0.68).
  - Although the relative risk of CHF was similar across the trials, the absolute risk varied according to the severity of the glucometabolic state and the presence or absence and degree of cardiovascular disease at baseline.
  - Only one trial included patients with documented heart failure; the relative risk of CHF was 1.8 (95% CI: 0.55 to 6.02).
  - This meta-analysis showed that patients given TDZs had an increased risk for development of CHF across a wide background of cardiac risk.
Other Considerations
The American Heart Association and the American Diabetes Association published a consensus statement on the use of TZDs in patients with diabetes and symptomatic heart disease (Nesto, et al., 2003). In heart failure patients with NYHA class I or II, TZDs may be used cautiously, with initiation of treatment at the lower dosage of each drug (e.g., rosiglitazone 2 mg/day or pioglitazone 15 mg/day). Observation with gradual dose escalation is warranted to identify weight gain, edema, or an exacerbation of CHF. One should allow more time than usual to achieve a target HbA1c in these patients. In heart failure patients with symptoms and signs of NYHA class III or IV, TZDs should not be used at this time.

Conclusion
There is insufficient evidence to recommend TZD use in diabetic patients with documented heart failure, and there is limited evidence to suggest that TZDs may increase the development of heart failure. The GDT therefore recommends that TZD use be avoided in patients with heart failure who are not currently using them unless there are no alternative treatments possible and in heart failure patients whose symptoms worsen while on TZDs. The GDT makes no recommendations for or against discontinuing TZDs in stable heart failure patients who are currently on TZDs.

4. Use of Erythropoietin Analogs to Treat Anemia

The GDT makes no recommendation for or against the use of erythropoietin analogs to treat anemia in heart failure patients. Evidence-based: I

Rationale:

Evidence Grade
Evidence for Recommendation 4: Insufficient

2009 Update
No new evidence was found, the recommendation remains unchanged.

Search Strategy
See Appendix B for more information.

2008 Guideline

- Silverberg, et al. (12) conducted an RCT among 32 anemic patients with moderate to severe heart failure, randomized to receive subcutaneous EPO and intravenous iron or no anemia treatment. The effect of correcting anemia on cardiac and renal function and hospitalization was assessed. Congestive heart failure (CHF) treatment was maintained at the maximally tolerated levels, and the mean follow-up time was 8.2 months.
  - After EPO treatment, a significant difference between the two groups was observed in hemoglobin levels, ejection fraction, days in hospital, and intravenous furosemide.
  - The interaction between the study group and time trend was significant for all measurements (hemoglobin levels, NYHA class, ejection fraction, days in hospital, intravenous furosemide, and oral furosemide), which indicated that the change over time was significantly different in the two groups (i.e., deterioration in the control group and improvement in the treated group).
  - There were no deaths in the treatment group and four deaths in the control group.
The main finding was that correction of even mild anemia in patients with symptoms of moderate to severe CHF resulted in a significant improvement in cardiac function and NYHA functional class. The limitations of the study were its small sample size and the fact that it was not blinded.

A randomized, double-blind, placebo-controlled study (n = 38) of subcutaneous EPO and oral iron versus oral iron alone was conducted in patients with anemia and resistant advanced CHF. The study aimed to demonstrate effects of this anemia treatment on cardiac and renal functional parameters.

In the treatment group, significant improvements were seen after three months in hemoglobin levels, NYHA class, endurance time and walked distance on exercise testing, V.O₂, and anaerobic threshold.

There were significant decreases in plasma B-type natriuretic peptide (BNP) and serum creatinine levels and an increase in creatinine clearance after three months of EPO and oral iron treatment.

One year after the start of the study, hemoglobin was still higher in the treatment group than in the control group, and the rate of hospital admissions per patient over the year was significantly lower in the treatment group than in the control group.

One patient from the treatment and two patients from the control group died during the one-year follow-up period.

In anemic CHF patients, correction of anemia with EPO and oral iron led to improvement in clinical and laboratory signs of CHF, including NYHA class, measured exercise endurance, oxygen use during exercise, renal function, and plasma BNP levels, and the treatment reduced the need for hospitalization.

Subsequently, the investigators evaluated the effect of anemia correction with EPO and oral iron in patients with cardiorenal anemia syndrome. The main study outcomes were left ventricular (LV) systolic diameter and volume (LV systolic diameter and LVSV), LV diastolic diameter and volume (LVDD and LVDV), LV mass, LV ejection fraction (LVEF), pulmonary artery pressure (PAP), and BNP levels. The treatment and control groups consisted of 26 and 25 patients, respectively, and outcome measures were reported after four and 12 months of follow-up time. The initial four months of this RCT were double-blinded.

Over the 12-month period, hemoglobin increased significantly in the treatment group but not in the control group. Compared with the control group, the treatment group had lower LVDD, LV systolic diameter, LVDV, LVSV, LV mass, PAP, and BNP and higher LVEF.

Serum creatinine and creatinine clearance remained unchanged in both groups.

A total of five patients died: three in the control and two in the treatment group.

In anemic patients with CHF, correction of anemia with EPO and oral iron over one year led to an improvement in LV systolic function, LV remodeling, BNP levels, and PAP compared with a control group.
**Conclusion**
In anemic patients with resistant CHF, improvements in cardiac function, functional cardiac class, and hospitalization in small studies without adequate power suggested a beneficial effect of EPO treatment. Large RCTs will be needed to confirm these effects. The GDT therefore makes no recommendation for or against the use of erythropoietin analogs in patients with heart failure.

5. **Use of Diuretics**

5A Loop diuretics* are recommended for the management of hypervolemia in heart failure. Use the minimal dosage needed to restore normal volume status. *Consensus-based*

5B Use combination loop* and thiazide-type diuretics if the patient is unresponsive to loop diuretics alone. *Consensus-based*

**Rationale:**

**Evidence Grade**
Evidence for Recommendation 5A, B: Insufficient

**2009 Update**
No new evidence was found, the recommendation remains unchanged.

**Search Strategy**
See Appendix B for more information.

**2008 Guideline**
No new evidence was found, the recommendation remains unchanged.

**2006 Update**
No relevant RCTs or meta-analyses were identified in the peer-reviewed medical literature that addressed the use of diuretics for patients with heart failure.

**2004 Guideline**

**Management of Hypervolemia**
One meta-analysis (15) was found which summarized the evidence from RCTs for the use of diuretics, both loop and thiazide, in patients with heart failure.

- Eighteen RCTs conducted between 1966 and 1999 were included. The studies were designed as crossover or parallel trials. Some trials compared diuretic with placebo and other trials compared diuretic with active control, e.g., ACEI, digoxin or ibopamine.

- Three trials gave data on mortality (N = 221, 3/111 deaths in the diuretic group and 12/110 in the placebo group, OR = 0.25 (95% CI: 0.07 to 0.84). Four trials reported effects of diuretics on worsening heart failure, OR = 0.31 (95% CI: 0.15 to 0.62). The RALES trial of spironolactone, a potassium-sparing diuretic, was excluded from this meta-analysis because spironolactone was used as an aldosterone inhibitor in addition to other diuretics.

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* Furosemide, hydrochlorothiazide, and metolazone (Mykrox) are not FDA-approved for heart failure.
These results should be interpreted with caution, as the trials were small and inadequately powered to demonstrate clearly the effectiveness of the intervention on morbidity and mortality.

- Furosemide, the first loop diuretic, was reported in the literature in 1963 by Kleinfeld as a diuretic that “produced prompt diuretic response in patients with edema.” Three studies in the sixties compared furosemide with thiazide-type diuretics, Hutcheon, McFarland, and Verel.

  - Hutcheon compared the diuretic response in heart failure patients, 12 of whom were given polythiazide and 20 of whom were given furosemide. He found that the diuretic response to furosemide was significantly greater than to polythiazide.
  - McFarland studied 13 patients with heart failure who were generally refractory to other diuretics, including thiazides and mercurials. None of the patients failed to show a response to furosemide. In seven patients, the response was considered very effective when edema was reduced and symptoms of shortness of breath and nocturnal dyspnea disappeared.
  - Verel reported on a clinical crossover study in which furosemide was compared with hydrochlorothiazide in 14 patients with heart failure. Diets were controlled for sodium content. Furosemide was a more effective diuretic than hydrochlorothiazide, increasing urine-flow by a factor of 4.8 and sodium excretion by 4.6.

These studies evaluated the physiological changes of a loop diuretic compared with a thiazide-type diuretic. In all cases the loop diuretic was superior to the thiazide-type diuretic in volume reduction and symptom relief.

**Adding a Thiazide-Type Diuretic**

No studies were found which evaluated the effectiveness of adding a thiazide-type diuretic to a loop diuretic in patients unresponsive to loop diuretics alone.

- Six trials that compared the effectiveness of adding a thiazide-type diuretic to a loop diuretic were reviewed. Four trials were of patients with severe heart failure. The other two trials were in patients with renal insufficiency, included to address the question of the effectiveness of hydrochlorothiazide in combination with a loop diuretic in these patients.

- The primary outcome for the six trials was a change in diuresis and/or natriuresis. In all cases, the combination of a loop and a thiazide-type diuretic was superior to a loop diuretic alone in reducing edema in patients who were loop diuretic resistant. Hydrochlorothiazide was used in three of the six studies. The others trials tested bedrofluazide or metolazone.

**Conclusion**

Diuretics are needed for most patients to reduce hypervolemia and improve symptoms. Loop diuretics are more effective than thiazide-type diuretics. When patients are resistant to loop diuretics alone, combination loop and thiazide diuretics are effective for diuresis.
Vasodilators in Left Ventricular Systolic Disorder (LVSD)

6. **Use of Renin-Angiotensin System Inhibitor/Blockers and/or Vasodilators**

6A It is strongly recommended that ACE inhibitors be given to patients with LVSD. *Evidence-based: A*

6B If the patient is intolerant to ACE inhibitors due to cough, allergy, or angioedema; angiotensin-receptor blockers* are a recommended alternative. However, if ACEI-induced angioedema is severe, use caution when ARBs are used. *Evidence-based: B*

6C If both ACE inhibitors and ARBs† are contraindicated, the combination of hydralazine and isosorbide dinitrate is recommended. *Evidence-based: B*

6D The routine addition of ARBs† to ACE inhibitors is not recommended. If ARBs are added to ACE inhibitors it should be done for specific reasons, such as uncontrolled hypertension or insufficient vasodilation. This recommendation applies whether or not a patient is treated with beta-blockers. *Consensus-based*

Note: Evidence regarding the effectiveness of the combination of ACEIs and ARBs is conflicting, especially in patients taking beta-blockers. The GDT recommends against routinely prescribing ARBs for patients with LVSD who are taking an ACEI, regardless of beta-blocker status.

**Rationale:**

**Evidence Grade**
Evidence for Recommendation 6A, C: Good  
Evidence for Recommendation 6B: Fair  
Evidence for Recommendation 6D: Insufficient

**2009 Update**
No new evidence was found, the recommendation remains unchanged.

**Search Strategy**
See Appendix B for more information.

**2008 Guideline**
No new evidence was found, the recommendation remains unchanged.

**2006 Guideline**
New evidence was found that did not change the existing recommendation.

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* Valsartan is FDA-approved for heart failure; losartan and candesartan are not.
2004 Guideline

ACEI for LVSD

ACEI or ARBs

ACE inhibitors (ACEI) have been shown to be highly effective in reducing all-cause mortality, cardiovascular (CV) mortality, and combined endpoints of mortality and hospitalization. To date, studies that compared ACEIs with angiotensin-receptor blockers (ARBs) have failed to show that ARBs are superior or noninferior to ACEI. Thus, ACEIs should remain the first-line vasodilator for heart failure.

ACEIs vs. Placebo

No new evidence was found, the recommendation remains unchanged. Total mortality rates from two meta-analyses were:

0.77 (95% CI: 0.67 to 0.88) ARR = 6.1% NNT = 16 (Garg\(^\text{25}\))

0.80 (95% CI: 0.74 to 0.87) ARR = 3.8% NNT = 26 (Flather\(^\text{26}\))

(The Flather meta-analysis included the SOLVD trials and the post-MI and Heart Failure trials SAVE, AIRS, and TRACE.)

Conclusion

This evidence supports the use of ACE inhibitors as first-line treatment for left ventricular systolic dysfunction.

ACEIs vs. ARBs

New evidence was found that did not change the existing recommendation.

- The meta-analysis by Jong, et al., pooled data from RCTs of ARBs in patients with LVSD.\(^\text{27}\)
  Several of the trials included in the meta-analysis were reviewed separately. Pooling data from 17 trials showed that ARBs were not superior to ACEIs in improving survival. The OPTIMAAL\(^\text{28}\) and the CHARM\(^\text{29-33}\) studies were not included in Jong’s meta-analysis.
- The OPTIMAAL\(^\text{28}\) and the VALIANT trials included post-MI patients with heart failure.
- The OPTIMAAL\(^\text{28}\) study was a parallel group study that compared ARB (losartan) with ACEI (captopril) in 5,477 post-MI patients with LVSD. All-cause mortality, the primary endpoint, was not significantly different between losartan and captopril, RR = 1.13 (95% CI: 0.99 to 1.28). Reduction in cardiovascular deaths significantly favored captopril: losartan versus captopril RR = 1.17 (95% CI: 1.01 to 1.34).
- The VALIANT\(^\text{34}\) was a three-way comparison of valsartan, captopril, and valsartan plus captopril in 14,703 patients who were 0.5 to 10 days post-MI and had clinical or radiologic signs of heart failure. There were no significant differences in outcomes when valsartan was compared with captopril. In an a priori analysis, valsartan was not shown to be inferior to captopril.
**ARBs in ACEI-Intolerant Patients**

New evidence was found that did not change the existing recommendation.

- The CHARM\(^{(20)}\) RCTs compared the ARB candesartan with placebo in three distinct populations: patients taking ACEI and BB (CHARM-Added\(^{(35)}\)); patients who were ACEI-intolerant (CHARM-Alternative\(^{(31)}\)); and patients with preserved LV function (CHARM-Preserved\(^{(32)}\)). The CHARM-Added will be reviewed later in this rational and the CHARM-Preserved will be reviewed in the diastolic heart failure section.

- The CHARM-Alternative study\(^{(31)}\) compared candesartan with placebo in 2,028 patients with LVSD who were ACEI-intolerant. Results showed that candesartan significantly reduced cardiovascular death and hospitalization, [HR = 0.80 (95% CI: 0.66 to 0.96) for CV death] and [HR = 0.70 (95% CI: 0.60 to 0.81) for hospitalization].

- This evidence is supported by the subgroup analysis from the Val-HeFT,\(^{(36)}\) which found a significant reduction in combined endpoints when ARBs were compared with placebo in small group of patients who were ACEI-intolerant.

**ANGIOEDEMA**

Use of ARBs did not lead to angioedema in patients who had experienced angioedema when taking ACEIs.

- The CHARM-Alternative included 39 patients who had experienced ACEI-induced angioedema previous to the study. Angioedema occurred in three of these patients. Two of the three patients continued to take candesartan without reoccurrence. None of the cases of angioedema were life threatening. No case occurred in the placebo group.\(^{(31)}\)

- Gavras reported on a case series of ten patients who had ACEI-induced angioedema, and were subsequently treated with ARBs without any further episodes.\(^{(37)}\)

**Conclusion**

If a patient is ACEI-intolerant, or if ACEIs are contraindicated due to rash, angioedema, and/or cough, ARBs are recommended as an alternative medication.

**COMBINATION HYDRAZONE AND ISOSORBIDE DINITRATE**

No new evidence was found, the recommendation remains unchanged.

- V-HeFT-I,\(^{(38)}\) showed that combination hydralazine and isosorbide dinitrate was better than placebo in reducing mortality; RR = 0.34 (95% CI: 0.04 to 0.54).

- There have been no studies of combination hydralazine and isosorbide dinitrate in patients with LVSD who were ACEI- or ARB-intolerant, and no studies in patients with contraindications to ACEI or ARBs.

**Conclusion**

This recommendation is based both on the evidence that the combination of hydralazine and isosorbide dinitrate is better than no vasodilator therapy, and the consensus of the GDT.
**ADDITION OF ARBS TO ACEI, WITH AND WITHOUT Beta-BLOCKER USE**

New evidence was found that did not change the existing recommendation.

- The CHARM-Added trial of 2,548 patients compared the addition of candesartan or placebo to standard heart failure treatment of ACEI and beta-blockers. (Fifty-five percent of participants were on beta-blockers.) The overall hazard ratio for CV death or hospitalization for heart failure was 0.85 (95% CI: 0.75 to 0.96).

- Subgroup analysis comparing patients on and not on beta-blockers in the CHARM-Added trial showed that all-cause mortality and combined endpoints were as follows:

<table>
<thead>
<tr>
<th></th>
<th>All-cause Mortality</th>
<th>Combined Endpoints</th>
<th>n/N ARB vs. placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes BB</td>
<td>0.88 (0.72 to 1.08)</td>
<td>0.78 (0.65 to 0.93)</td>
<td>223/702 vs. 274/711</td>
</tr>
<tr>
<td>No BB</td>
<td>0.88 (0.73 to 1.07)</td>
<td>0.94 (0.79 to 1.12)</td>
<td>260/574 vs. 264/561</td>
</tr>
</tbody>
</table>

- The interaction of outcomes for patients on beta-blockers and those not on beta-blockers was not significant, \( p = 0.14 \). Thus, results were similar whether or not participants were taking beta-blockers.

- The RESOLVD study compared four study groups, listed below. There were no statistical differences in death rates among the groups, but there was a statistical difference for hospitalization (\( p = 0.04 \)).

<table>
<thead>
<tr>
<th>Treatment Group/(n)</th>
<th>Hospitalization rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARB or ACEI / (126)</td>
<td>6.8 %</td>
</tr>
<tr>
<td>ARB + ACEI / (86)</td>
<td>1.2 %</td>
</tr>
<tr>
<td>ARB + BB or ACEI + BB / (125)</td>
<td>8.0 %</td>
</tr>
<tr>
<td>ARB + ACEI + BB / (89)</td>
<td>12.6 %</td>
</tr>
</tbody>
</table>

- The VALIANT\(^{(34)}\) was a placebo controlled trial in 14,703 adults who had a recent MI (within 0.5 to 10 days) and clinical or radiological signs of heart failure (ejection fraction of \( \leq 35\% \)). There was no significant difference in total mortality when the following subgroups were compared:

  - Valsartan and captopril versus captopril with a beta-blocker (\( n = 6,882 \)), or without a beta-blocker (\( n = 2,910 \)), Hazard Ratio 0.94 (97.5% CI: 0.9 to 1.1); \( p \) value for between group comparison \( p = 0.31 \). Differences between the groups were not significant. Results were similar for combined endpoints.

- The Val-HeFT\(^{(36, 39)}\) raised concerns about the safety of adding an ARB to an ACEI when patients were taking beta-blockers. Subsequent trials have not confirmed that this combination is harmful.

  - The Val-HeFT randomized patients by baseline use of beta-blockers.
The analysis of this subgroup showed that patients taking ACEIs, ARBs and beta-blockers (n = 1,610) had a significant increase in all-cause mortality; RR = 1.44 (97.5% CI: 1.11 to 1.85) and a nonsignificant increase for combined endpoints, RR = 1.18 (97.5% CI: 0.97 to 1.45). The p value for subgroup interaction for mortality was p = 0.009 and for combined endpoints was 0.001.

The subgroup of 3,034 patients taking ACEI and ARB without a beta-blocker showed a risk reduction in the combined endpoint of 0.8 (97.5% CI: 0.7 to 0.95). The risk reduction for all-cause mortality in this group was not significantly different, 0.96 (97.5% CI: 0.83 to 1.12).

**Conclusion**

Evaluation of the patient subgroups taking combination ACEIs, ARBs, and beta-blockers showed either a nonsignificant difference in death rates (CHARM and VALIANT), a significant increase in death rate (Val-HeFT), or a significant increase in hospitalization rates (RESOLVD). The GDT has concluded that the evidence is conflicting and fails to clearly show the safety and effectiveness of triple drug therapy.

Evidence of effectiveness for ARBs added to ACEIs in patients who are not taking beta-blockers is also conflicting. There was a nonsignificant difference in mortality in the CHARM and VALIANT trials and a significant reduction in the Val-HeFT trial. The GDT concludes that there is insufficient evidence to recommend the routine use of the combination of ACEIs and ARBs for patients who are not taking beta-blockers.

### 7. Target Dose of ACE Inhibitors

It is recommended that the target dose of ACEIs be at least that used in major clinical trials in patients with LVSD.

- Lisinopril 20 mg daily
- Captopril 50 mg three times daily
- Enalapril 10 mg twice daily

*Consensus-based*

**Rationale:**

**Evidence Grade**

Evidence for Recommendation 7: Insufficient

**2009 Update**

No new evidence was found, the recommendation remains unchanged.

**Search Strategy**

See Appendix B for more information.

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* Combined endpoints were defined as cardiac arrest with resuscitation, hospitalization for heart failure, or administration of IV inotropes or IV vasodilators for four hours or more without hospitalization.
2008 Guideline
The doses listed in the recommendation were among those used in the major clinical trials of ACE inhibitors in patients with LVSD.

No new evidence was found, the recommendation remains unchanged.

2006 Guideline
No new evidence was found, the recommendation remains unchanged.

2004 Guideline
One RCT (n = 248) by Nanas(40) was found. It compared moderate-dose with high-dose enalapril in patients with LVSD.

♦ High-dose enalapril (target 60 mg daily; mean dose 42 ±19.3 mg) was compared with a standard dose (20 mg daily; mean dose 17.9 ±4.3 mg) for 12 months. There were no significant differences between medium-dose and high-dose groups for mortality; 18.03% versus 18.25%; HR = 0.998 (95% CI: 0.566 to 1.790).

These data suggest that increasing the dose of enalapril above that used in earlier RCTs did not provide additional benefits. Target doses in the CONSENSUS,(41) SOLVD(42) and V-HEFT(43) trials were 20 to 40 mg daily (mean dose 15 to 18.4 mg daily).*

Three RCTs studied the dose effect of ACEIs in patients with LVSD were found.

♦ The ATLAS trial(44) (n = 3,164) compared low-dose lisinopril (5 to 11 mg daily) with high-dose (32.5 to 35 mg daily). All-cause mortality was not significantly different between the groups, HR = 0.92 (95% CI: 0.82 to 1.03). However, a significant difference was observed in the combined endpoint of death or hospitalization; HR = 0.88 (95% CI: 0.82 to 0.96) when high-dose users were compared with lower-dose users.

♦ The NETWORK trial(45) (n = 1,532) compared three doses of enalapril: 5 mg, 10 mg, and 20 mg daily. The primary endpoint was the first occurrence of death, hospitalization for heart failure, or worsening heart failure. Results were not significantly different between the 20 mg and 5 mg doses; HR = 1.20 (95% CI: 0.86 to 1.68).

♦ The CHIPS(46) trial (n = 298) failed to enroll enough patients to obtain statistical significance for the primary endpoint of worsening heart failure. The trial compared medium-dose (100 mg daily) with low-dose (50 mg daily) captopril. The percent of patients who experienced worsening heart failure was 13.7% for low-dose compared with 22.4% for the higher dose, p = 0.088.

Conclusion
Because the evidence of effectiveness of high-dose ACEIs is contradictory, the GDT recommends that the target doses of ACEIs be at least those doses which have been used in major clinical trials. See Table 1.

* For simplicity, the doses are given as total daily doses, even though enalapril is given twice daily.
### Table 1: Medication Dosage Recommendations

<table>
<thead>
<tr>
<th>Medication*</th>
<th>Daily Target Dose</th>
<th>Mean Daily Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enalapril [CONSENSUS Trial(41)]</td>
<td>40 mg</td>
<td>36.8 mg</td>
</tr>
<tr>
<td>Enalapril [V-HeFT II(43)]</td>
<td>20 mg</td>
<td>15.0 mg</td>
</tr>
<tr>
<td>Enalapril [SOLVD(42)]</td>
<td>20 mg</td>
<td>11.2 mg</td>
</tr>
<tr>
<td>Captopril [SAVE(47)]</td>
<td>150 mg</td>
<td>NA</td>
</tr>
<tr>
<td>Ramipril [AIRE(48)]</td>
<td>10 mg</td>
<td>NA</td>
</tr>
<tr>
<td>Lisinopril [ATLAS high-dose(49)]</td>
<td>32.5 to 35 mg</td>
<td>33.2 mg</td>
</tr>
</tbody>
</table>

### 8. Appropriate Renal Function for Prescribing ACEIs

**8A** ACE inhibitors can be used for patients with serum creatinine levels up to 2.5 mg/dl or eGFR > 30 ml/min/1.73 m². **Consensus-based**

**8B** Use of ACE inhibitors in patients with serum creatinine levels higher than 2.5 mg/dl or eGFR < 30 ml/min/1.73 m² should be determined on a case-by-case basis. **Consensus-based**

**Rationale:**

**Evidence Grade**

Evidence for Recommendation 8A, B: Insufficient

**2009 Update**

No new evidence was found, the recommendation remains unchanged.

**Search Strategy**

See Appendix B for more information.

**2008 Guideline**

No new evidence was found, the recommendation remains unchanged. However, the GDT decided to add the corresponding eGFR measures of renal function.

**2006 Guideline**

No new evidence was found, the recommendation remains unchanged.

**2004 Guideline**

New evidence was found that did change the previous recommendation. The value of the serum creatinine level was changed from the previous guideline value of 3.0 mg/dl, to 2.5 mg/dl. This was done to be in alignment with the highest serum creatinine levels allowed in patients in the most important clinical trials.

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* Enalapril and ramipril are given twice daily, captopril three times daily, and lisinopril daily.
Most large RCTs specifically excluded patients with creatinine levels > 2.5 mg/dl. The CONSENSUS trial,\(^{(41)}\) which evaluated enalapril against placebo in NYHA class IV patients, allowed patients with creatinine levels as high as 3.6 mg/dl to participate. The average baseline creatinine in the CONSENSUS was 1.4 mg/dl compared with 1.2 mg/dl in the SOLVD trial. Generally, the trials comparing ACEIs with placebo in patients with LVSD reported an increase of serum creatinine from 10% to 15% from baseline.

Bakris, et al., performed a meta-analysis of RCTs that evaluated renal disease progression among patients with preexisting renal insufficiency.\(^{(50)}\) They found a “strong association between acute increases in serum creatinine of up to 30% that stabilize within the first two months of ACEI therapy and long-term preservation of renal functions. This relationship holds for persons with creatinine values of greater than 1.4 mg/dl.” The end result was a 55% to 75% reduction in the progression of renal disease compared with patients with normal renal function.

Weir, et al.,\(^{(51)}\) in his review of the safety of drugs that block the renin-angiotensin system in patients with diminished renal function, stated that: “one should expect an increase in serum creatinine level of up to 20%… This change should remain stable. If the serum creatinine continues to rise, it indicates that the patient has either diminished effective arterial blood volume or anatomic renal artery stenosis.”

**Conclusion**

The consensus of the GDT is that ACE inhibitors should be used for patients with creatinine levels up to 2.5 mg/dl. Use of ACE inhibitors in patients with higher creatinine levels should be determined on a case-by-case basis.

### 9. Combination Aspirin and ACEIs

Aspirin (ASA) (81 mg) is recommended for patients taking ACE inhibitors for LVSD if they have concomitant cardiovascular disease (CVD). **Consensus-based**

**Rationale:**

**Evidence Grade**

Evidence for Recommendation 9: Insufficient

**2009 Update**

No new evidence was found, the recommendation remains unchanged.

**Search Strategy**

See Appendix B for more information.

**2008 Guideline**

No new evidence was found, however, the recommendation was changed. The GDT decided to replace “low dose” with 81 mg to make the recommendation more specific and to be consistent with the KP National Coronary Artery Disease Treatment Guidelines.

**2006 Guideline**

No new evidence was found, the recommendation remains unchanged.
2004 Guideline
The KP National Coronary Artery Disease Secondary Prevention Guidelines document the benefits of aspirin in preventing recurrent cardiovascular events and reducing mortality in patients with coronary artery disease. Because this evidence is compelling, and there is a lack of good evidence to the contrary, the GDT recommends that patients with LVSD and concomitant CAD receive ASA in addition to ACEIs.

There were no RCTs found that compared morbidity and mortality in patients with LVSD who did not have concomitant CAD and were taking ACEI and aspirin versus those on ACEI alone.

Five studies addressing the co-administration of ACEI and ASA were found. Four of the studies were retrospective\(^{52-57}\) and one, the EPICAL study by Echemann,\(^{58}\) was a prospective, observational, community-based epidemiological study. The findings are briefly described below.

- The EPICAL\(^{58}\) trial (Echemann, et al.) followed 417 patients with LVSD, EF < 30%, 129 of whom were taking ASA. The authors do not state the numbers taking both ASA and ACEI but do state, without data, that they found no interaction with survival between ASA and ACEI.

- Krumholz, et al.,\(^{59}\) et al., evaluated mortality rates in 14,129 AMI patients with LVSD, 38% of whom received ASA and ACEI. They found an adjusted risk reduction of 0.81 (95% CI: 0.74 to 0.88) in patients receiving both ASA and ACEI compared with patients receiving either medication. This reduction was slightly lower than that seen in ASA-only or ACEI-only patients, but was not statistically significant.

- Guazzi, et al.,\(^{53}\) reported on a retrospective study evaluating the relationship between mortality and ASA dosage in patients with heart failure taking ACEI. Three hundred and forty-four patients taking ACEI were included in the evaluation, 31% of whom had experienced an MI. They were subdivided into three groups by the use of ASA (no ASA, low-dose \((\leq 160 \text{ mg/day})\), and high-dose \((\geq 325 \text{ mg/day})\). No difference in death rates was found when the no-ASA and low-dose groups were compared. However the mortality rate was significantly worse \((p = 0.009)\) when the high-dose ASA group was compared with the no-ASA and low-dose groups.

- Teo, et al.,\(^{54}\) extended the post hoc study of the SOLVD\(^{42}\) trial by including the SAVE, AIRE, TRACE, and HOPE trials. Data were combined from 22,060 individual patients and evaluated based on the baseline use or nonuse of ASA and ACEI, or control. The odds ratios for death were 0.74 (95% CI: 0.64 to 0.86) for the ACEI versus placebo groups that were not taking ASA, compared with 0.86 (95% CI: 0.77 to 0.97) for the ACEI versus placebo groups that were on ASA, \(p = 0.04\) for interaction of ASA. Similarly, composite endpoints for major vascular events comparing the no-ASA group with the ASA groups were 0.71 (95% CI: 0.62 to 0.81) and 0.80 (95% CI: 0.73 to 0.88) respectively, with \(p = 0.07\) for ASA interaction. However, baseline characteristics between the groups were strikingly different and covariant bias should be considered in interpreting these results.

- Aumegeat, et al.,\(^{55}\) performed a retrospective analysis on 755 patients with LVSD, 42% of whom were taking ASA. Using a Cox regression model, they did not find an interaction between ASA and ACEI.
Conclusion
The data on the interaction between ASA and ACEI are contradictory. Evidence derived from post hoc studies should be viewed with caution. Patients were not randomized to ASA and most information is from baseline data. For these reasons, the GDT recommends that ASA only be used where there is a clear indication, such as with concomitant cardiovascular disease.

Beta-Blockers in LVSD

10. Use of Beta-Blockers in Addition to Standard Treatment

10A Beta-blockers are strongly recommended for patients with LVSD NYHA class II-IV, or with asymptomatic LVSD (NYHA class I) and concomitant CAD. Evidence-based: A

10B Beta-blockers are recommended for patients with asymptomatic (NYHA class I) LVSD without concomitant CAD. Consensus-based

Rationale:

Evidence Grade
Evidence for Recommendation 10A: Good
Evidence for Recommendation 10B: Insufficient

2009 Update
No new evidence was found, the recommendation remains unchanged.

Search Strategy
See Appendix B for more information.

2008 Guideline
No new evidence was found, the recommendation remains unchanged.

2006 Guideline
New evidence was found that did not change the existing recommendation.

2004 Guideline

Beta-Blockers For LVSD NYHA Class II-IV, or With Asymptomatic LVSD & Concomitant CAD

One new meta-analysis was found that studied the relationship between the severity of disease and the benefits from beta-blockers. This study adds to the evidence basis but does not change the recommendations.

- Bouzamondo, et al.,(60) included 16 RCTs in which data on hospitalization and mortality were provided, and which had at least one death in each study arm. They reported that all-cause mortality was reduced by 22% (95% CI: 16 to 28) and hospitalization for worsening heart failure by 24% (95% CI: 20 to 29). Heterogeneity was significant (p = 0.035) for mortality rate but not for hospitalization (p = 0.13). When the data from the BEST(61) trial of bucindolol were excluded, heterogeneity for comparison of mortality rates was no longer significant.
• Brophy, et al., included 22 RCTs of beta-blockers compared with placebo in the meta-analysis.\(^{(62)}\) The odds ratio for mortality reduction was 0.65 (95% CI: 0.53 to 0.80) and the odds ratio for hospitalization 0.64 (95% CI: 0.53 to 0.79). Using Bayesian analysis, Brophy showed with 99% certainty that the addition of a beta-blocker to an ACE inhibitor could prevent at least two deaths in 100 patients in the first year.

• Both the BEST trial of bucindolol\(^{(61)}\) and the COPERNICUS trial of carvedilol\(^{(63)}\) in patients with NYHA class IV were published after this meta-analysis. Both of these studies were included in the Bouzamondo meta-analysis above.

Strong evidence from systematic reviews (meta-analyses) was found that adding a beta-blocker to ACE inhibitors significantly reduces morbidity and mortality in patients with LVSD and NYHA Class II-IV.\(^{(60, 62, 64-66)}\) The evidence to support the use of beta-blockers in patients with asymptomatic LVSD and concomitant CAD is based on the evidence of the effectiveness of beta-blockers in patients with CAD, and can be found in the KP National Coronary Artery Disease Guidelines.

No trials evaluating the use of beta-blockers in patients with LVSD without symptoms (NYHA Class I) were found.

**BETA-BLOCKERS FOR ASYMPTOMATIC LVSD WITHOUT CONCOMITANT CAD**

To date, studies have not included enough asymptomatic patients with LVSD to provide conclusive evidence of the benefits of beta-blockers in this group. However, their use may be supported by what is known about the pathophysiology of heart failure.

There are several explanations to explain the effectiveness of beta-blockers in heart failure. For example, the activation of the adrenergic nervous system during the development of heart failure contributes to increased expression of inflammatory cytokines (tumor necrosis factor and interleukin-1B)\(^{(67)}\) and both increased release and decreased uptake of norepinephrine, which has a deleterious effect on cardiac function.\(^{(68)}\) Beta-blockers appear to attenuate these effects.

Because of the potential of beta-blockers to slow the progression of heart failure, the GDT believes that asymptomatic patients will also benefit from the addition of beta-blockers to standard treatment for LVSD.

**Conclusion**

Beta-blockers have been shown to significantly reduce death in patients with symptomatic LVSD. The use of beta-blockers in patients with CAD is an established practice, a HEDIS measure, and is supported in the KP National CAD Guidelines. Based on this, the GDT strongly recommends the use of beta-blockers in patients with either symptomatic LVSD, or asymptomatic LVSD and concomitant CAD.

The use of beta-blockers in patients with asymptomatic LVSD but without CAD has not been specifically studied. However, because LVSD is a progressive disease and beta-blockers may slow the progress of the disease, the GDT recommends the use of beta-blockers in this population.
11. Which Beta-Blockers to Use

11A Carvedilol, metoprolol succinate or bisoprolol* are the recommended choices of beta-blockers for patients with LVSD. Evidence-based: B

11B Metoprolol tartrate* (short-acting formulation), titrated to maximum tolerated dosage, is an acceptable but less well-established alternative to carvedilol, metoprolol succinate or bisoprolol.* Consensus-based

Rationale:

Evidence Grade
Evidence for Recommendation 11A: Good
Evidence for Recommendation 11B: Insufficient

2009 Update
No new evidence was found, the recommendation remains unchanged.

Search Strategy
See Appendix B for more information.

2008 Guideline
No new evidence was found, the recommendation remains unchanged; however, to better reflect current pharmacy naming conventions, metoprolol CR/XL was changed to metoprolol succinate.

2006 Guideline
No new evidence was found, the recommendation remains unchanged.

2004 Guideline
New evidence was found that did change the previous recommendation.

Beta-Blockers for LVSD
One RCT was found that compared carvedilol with metoprolol tartrate (COMET(69)), and one new meta-analysis(60) was found. The results from the COMET trial changed the previous recommendation for the choice of beta-blockers for patients with LVSD.

Carvedilol, metoprolol CR/XL, and bisoprolol have been studied in large, placebo-controlled randomized trials(63, 70-73) These trials have shown significant reduction in all-cause mortality and hospitalization. RCTs with other beta-blockers have failed to show significant reduction in mortality.(61)

* Not FDA-approved for heart failure.
Bouzamondo’s meta-analysis pooled the data from RCTs of carvedilol, metoprolol (long- and short-acting), and bisoprolol. All three groups of beta-blockers significantly reduced death and hospitalization when compared with placebo. Below are the relative risk reductions:

<table>
<thead>
<tr>
<th></th>
<th>All-cause death</th>
<th>Hospitalization for heart failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carvedilol</td>
<td>0.37 (0.24 to 0.47)</td>
<td>0.29 (0.18 to 0.39)</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>0.31 (0.17 to 0.42)</td>
<td>0.28 (0.19 to 0.36)</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>0.29 (0.17 to 0.40)</td>
<td>0.32 (0.21 to 0.42)</td>
</tr>
</tbody>
</table>

**METOPROLOL TARTRATE**

- The COMET trial, a large multicenter RCT started in 1996, was published in July 2003. It is the first head-to-head comparison of any beta-blocker with a predetermined mortality outcome in patients with LVSD.
  - Compared with metoprolol tartrate (short-acting formulation), carvedilol reduced the risk of all-cause mortality by 17% (95% CI: 7 to 26%). The number needed to treat for 58 months to prevent one death was 18.
  - Patients in the COMET trial had a mean ejection fraction of 26%. The drug doses were carvedilol 25 mg twice daily (mean daily dose 41.8 mg) and metoprolol tartrate 50 mg twice daily (mean daily dose 85 mg). This has raised concerns that the beta-blockade from metoprolol was not comparable to the carvedilol dosage. Pharmacological studies of short-acting metoprolol and metoprolol CR/XL have shown that a dosage of 200 mg of the CR/XL formulation has a more pronounced beta-blockade effect than 150 mg of the short-acting formulation.

The results of the COMET trial suggest that metoprolol tartrate at a daily dose of 100 mg (mean 85 mg) is inferior to carvedilol at a dose of 50 mg daily (mean 41.8 mg). It is unknown if metoprolol CR/XL at 200 mg daily or metoprolol tartrate at an equivalent dose would also be inferior to carvedilol. Additional studies are needed to confirm if the differences shown in COMET were due to differences in medication rather than dosage.

Post hoc analysis of the MERIT-HF trial looked at outcomes at lower and higher doses of metoprolol CR/XL. However, the potential for bias in this study was very high and the results were deemed unreliable.

**Conclusion**

Based on these data, carvedilol, metoprolol CR/XL or bisoprolol are recommended as the beta-blockers of choice in patients with LVSD. However, due to the higher cost to patients of these beta-blockers compared with short-acting metoprolol, the GDT believes that 200 mg of short-acting metoprolol should be an option, based on shared decision-making with the patient.
12. **Beta-Blockers with Concomitant Asthma or COPD**

12A Cardioselective beta-blockers (metoprolol or bisoprolol*) are recommended for patients with LVSD and concomitant well-controlled asthma or COPD. Discuss the risks and benefits of treatment, and instruct the patient to report any increase in airway symptoms. *Evidence-based: B*

12B Carvedilol is an acceptable but less well-established option for patients with LVSD and well-controlled asthma or COPD. *Consensus-based*

**NOTE:** Mild to moderate asthma or COPD is not an absolute contraindication to the use of beta-blockers in patients with LVSD.

**Rationale:**

**Evidence Grade**
Evidence for Recommendation 12A: Good
Evidence for Recommendation 12B: Insufficient

**2009 Update**
No new evidence was found, the recommendation remains unchanged.

**Search Strategy**
See Appendix B for more information.

**2008 Guideline**
No new evidence was found, the recommendation remains basically unchanged. However, for Recommendation 12A, “mild to moderate” asthma was changed to “well-controlled” asthma to provide clarity and consistency with Recommendation 12B. This language is also consistent with the KP National Adult Asthma Guidelines.

**2006 Guideline**
No new evidence was found, the recommendation remains unchanged.

**2004 Guideline**
New evidence was found that did not change the existing recommendation. Salpeter’s systematic review, which was reviewed in the 2002 version of this guideline, was updated in 2002. The KP National Adult Asthma Guidelines also addresses this topic.

**Cardioselective Beta-Blockers for LVSD and Concomitant, Well-Controlled Asthma or COPD**

- Salpeter conducted two systematic reviews of placebo-controlled RCTs to evaluate the effect of cardioselective beta-blockers on FEV1, the incidence of symptoms, and use of inhaled short-acting beta-agonists in patients with reversible airway disease and COPD. *(76, 77)*
  - The meta-analysis of trials in patients with asthma showed that forced expiratory volume in 1 second (FEV1) was diminished with the administration of cardioselective beta-blockers in single dose trials, but not in the extended period studies: single dose: 7.98 L (95% CI: 6.19 to 9.77), \( p < 0.01 \); extended period -0.42 L (95% CI: -3.74 to 2.91), \( p = NS \).
However, there were no clinically significant adverse effects in the short-term RCTs and no change in symptoms. The response to beta-agonists compared with placebo for a single dose was +13.16% (95% CI: 10.76 to 15.56) \( p < 0.01 \) and for an extended period was 9.09% (95% CI: 3.07 to 15.11), \( p < 0.01 \).\(^{(78)}\)
- The meta-analysis for patients with COPD analyzed three subgroups:
- Group 1 - severe COPD (FEV\(_1\) < 50% [six trials]);
- Group 2 - COPD with a reversible component (FEV\(_1\) improvement of 15% after beta-agonists [seven trials]); and
- Group 3 - COPD with concomitant CVD, angina, ISH or HTN (eight trials).
Results in weighted mean difference (WMD) were:
- Group 1 - severe chronic airways obstruction
  - single dose -2.4% (95% CI: -8.67 to 3.87);
  - longer duration 2.2% (-8.62 to 2.41)
- Group 2 - COPD with reversible component
  - single dose -1.8% (95% CI: -7.01 to 3.41),
  - longer duration -1.26% (-5.78 to 3.25)
- Group 3 - COPD with CVD
  - single dose -1.8% (95% CI: -7.01 to 3.41)
  - longer duration -4.20% (95% CI: -9.32 to 0.92).
These results indicate that beta-blockers do not significantly affect FEV\(_1\) for patients with COPD. No increase in symptoms was noted for patients in these trials.\(^{(77)}\)

**CARVEDILOL FOR LVSD AND WELL-CONTROLLED ASTHMA OR COPD**
New evidence was found that did not change the existing recommendation. One prospective open-label cohort study was found that evaluated the effects of carvedilol, a noncardioselective beta-blocker, in patients with LVSD and concomitant asthma or COPD.
- Kotlyar, et al., \(^{(79)}\) studied 43 patients with COPD (n = 31) or asthma (n = 12) who began receiving carvedilol. They found that patients who did not have significantly reversible airflow limitations at baseline (as defined by > 15% reversibility) tolerated carvedilol well. Of the patients with asthma, 50% (six) were intolerant to carvedilol. Because of the small number of patients with asthma in this study, it is difficult to draw a definitive conclusion. However, truly hyper-responsive airway reactivity remains a contraindication to noncardioselective beta-blockers.

**Conclusion**
Because of the significant reduction in mortality from the use of beta-blockers in patients with LVSD, and the lack of evidence of clinically significant harm in patients with concomitant mild to moderate reversible airway disease or COPD, the GDT recommends the use of beta-blockers in this population.
13. **Aldosterone Antagonism**

13A In addition to standard treatment, spironolactone is recommended for patients with LVSD, EF < 35%, NYHA Class III or IV, and no contraindications. *Evidence-based: B*

13B Spironolactone is recommended for patients with LVEF < 40%, recent MI, either diabetes or signs of heart failure, and no contraindications. *Consensus-based*

13C It is an acceptable but less well-established option to use spironolactone in patients with EF < 40%, any symptom of heart failure, and no contraindications. *Consensus-based*

13D For most patients, a dose of spironolactone of 25 mg daily, or less is recommended. High doses may increase risk of serious hyperkalemia. *Evidence-based: B*

13E Eplerenone may be used as an alternative to spironolactone if gynecomastia is problematic. *Evidence-based: B*

**Rationale:**

**Evidence Grade**

Evidence for Recommendation 13A, D, E: Good

Evidence for Recommendation 13B, C: Insufficient

**2009 Update**

No new evidence was found, the recommendation remains unchanged.

**Search Strategy**

See Appendix B for more information.

**2008 Guideline**

No new evidence was found, the recommendation remains unchanged.

**2006 Guideline**

No new evidence was found, the recommendation remains unchanged.

**2004 Guideline**

**SPIRONOLACTONE FOR LVSD, EF < 35%, NYHA CLASS III OR IV, & NO CONTRAINDICATIONS**

- The RALES trial,\(^{(80)}\) a large multicenter RCT, compared the effects of spironolactone and placebo on mortality and hospitalization in patients with NYHA class III or IV LVSD. Spironolactone reduced all-cause mortality by 30%, RR = 0.70 (95% CI: 0.59 to 0.82) and hospitalization for cardiac causes by 30%, RR = 0.70 (95% CI: 0.60 to 0.82).

**SPIRONOLACTONE FOR LVSF < 40%, RECENT MI, DIABETES, OR SIGNS OF HEART FAILURE AND OPTIONAL SPIRONOLACTONE WITH EF < 40%, SYMPTOMS OF HEART FAILURE & NO CONTRAINDICATIONS**

New evidence was found that did not change the existing recommendation.

- One RCT, the EPHESUS trial, was found comparing eplerenone, a selective aldosterone blocker, with placebo in post-MI patients with an ≤ 40% and signs of heart failure or diabetes.\(^{(81)}\) All-cause mortality was reduced by 15%, RR = 0.85 (95% CI: 0.75 to 0.96) and CV death or hospitalization was reduced by 13%, RR = 0.87 (95% CI: 0.79 to 0.95).
The lower mortality benefit found in EPHESUS as compared with that in RALES, may be due to the higher ejection fraction (EF) (33% compared with 25% in RALES) in subjects, and the greater use of beta-blockers (75% compared with 11% in RALES).

There is no evidence showing a class effect between spironolactone and eplerenone. However, the GDT believes that the value of blocking aldosterone imparts additional survival benefits and recommends that the use of spironolactone, a generic drug covered by all drug coverage plans, be extended to the ‘less ill’ population as represented in the EPHESUS trial.

In addition to populations which have been studied in RCTs, the GDT believes there is potential benefit in using spironolactone in a wide range of patients, and thus suggests that it is optional to use or not use spironolactone in patients with EF ≤ 40%, any symptom of heart failure, and no contraindications.

**SPIRONOLACTONE ≤ 25 MG**

No new evidence was found, the recommendation remains unchanged.

- Risk of hyperkalemia with spironolactone: Reports subsequent to the publication of the RALES trial have found a much higher rate of hyperkalemia.
- Bozkurt, et al., in a retrospective cohort study of 104 patients with LVSD, reported that 12% of patients receiving spironolactone had serum potassium levels greater than 6 mEq/l.\(^{(82)}\)
- Other studies have suggested that the following situations may lead to serious hyperkalemia: renal insufficiency, diabetes, older age, risk of dehydration, and spironolactone dose greater than 25 mg.\(^{(83)}\)

**EPLERENONE**

The incidence of gynecomastia in patients taking eplerenone as compared with those taking spironolactone is much lower. In male patients with painful gynecomastia, eplerenone may be better tolerated.

### Comparison of Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>RALES (spironolactone)</th>
<th>EPHESUS (eplerenone)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Treatment</td>
<td>Placebo</td>
</tr>
<tr>
<td>Hyperkalemia*</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>Gynecomastia</td>
<td>10%</td>
<td>1%</td>
</tr>
</tbody>
</table>

* K > 6.0 mEq/l
Conclusion
The aldosterone antagonists spironolactone and eplerenone have been shown to effectively reduce mortality in patients with LVSD, though the RALES and EPHESUS trials evaluated different patient populations. There is no evidence that shows a class effect between spironolactone and eplerenone. However, the GDT believes that spironolactone will produce the same the beneficial outcomes seen in the EPHESUS trial with eplerenone, and thus recommends extending the consensus use of spironolactone to a broader population than that used in the RALES trial.

14. Digoxin
14A Digoxin may be added to standard therapy of ACE inhibitors, diuretics, and beta-blockers for heart failure, to improve symptoms and reduce hospitalization. Evidence-based: C

14B Digoxin is not recommended for patients with few or no symptoms of heart failure who are in normal sinus rhythm, because it does not reduce mortality. Evidence-based: D

14C Because of possible toxicity, which may be more common in women, and for maximum benefit, use lower doses of digoxin, and consider maintaining serum digoxin levels to no more than 0.8 ng/ml. Consensus-based

Rationale:

Evidence Grade
Evidence for Recommendation 14A: Fair (no trials of addition of digitalis to standard therapy)
Evidence for Recommendation 14B: Fair
Evidence for Recommendation 14C: Insufficient

2009 Update
No new evidence was found, the recommendation remains unchanged.

Search Strategy
See Appendix B for more information.

2008 Guideline
No new evidence was found, the recommendation remains unchanged.

2006 Guideline
No new evidence was found, the recommendation remains unchanged.

2004 Guideline
digoxin added to standard therapy
No new evidence was found, the recommendation remains unchanged.

- Clinical trials have shown that digitalis neither increases nor decreases mortality in patients with heart failure (both LVSD and diastolic heart failure). It does reduce the symptoms of heart failure and the need for hospitalization in patients with LVSD.

- One systematic review was found - Digitalis for Treatment of Congestive Heart Failure in Patients in Sinus Rhythm (Hood, 2001)(84) that evaluated digitalis versus placebo in 7,719 patients. A PubMed search from 11/29/2000 forward found two additional clinical trials that were excluded because their results did not include hospitalization or mortality data.
The meta-analysis concluded that digitalis has no effect on death rate \([\text{OR} = 0.98 (95\% \text{ CI: 0.89 to 1.09})]\).

- The results of this outcome are heavily weighted by the Digitalis Trial\(^{[85]}\) in which mortality was due to “worsening heart failure” or “other cardiac”, the latter possibly including arrhythmia. In the digitalis group there was a trend towards lower death rate due to worsening heart failure \((p = 0.06)\) and a significant increase in death from other cardiac causes \((p = 0.04)\). These opposite directional changes tend to counter-balance one another.

- Ten studies, excluding the Digitalis Trial, showed that digitalis significantly reduced hospitalization rates, \([\text{OR} =0.68 (95\% \text{ CI: 0.61 to 0.75})]\) and reduced clinical deterioration \([\text{OR} = 0.29 (95\% \text{ CI: 0.20 to 0.42})]\). The number needed to treat to prevent one hospitalization = 13 patients for 37 months. Quality of life was assessed in two trials, PROVED, 1993,\(^{[86]}\) and RADIANCE, 1993.\(^{[87]}\) The scores were significantly better for patients taking digitalis.

- NYHA class was assessed in seven studies. Results were significantly better with digitalis in three trials and not significant in the other four.

- There was no evidence that effects of digitalis differed by age, gender or duration of heart failure.

- There were no clinical trials found that evaluated the addition of digitalis to ACE inhibitors, diuretics, and beta-blocker therapy. In a meta-analysis of beta-blocker therapy, Brophy\(^{[62]}\) found 38 to 100\% of the patients in the clinical trials were on concomitant digitalis therapy.

**DIGOXIN NOT RECOMMENDED FOR FEW OR NO SIGNS OF HEART FAILURE OR NORMAL SINUS RHYTHM**

Analyses by Rathore, et al., of the Digitalis Investigation Group Trial (DIG) in 2002 to 2003, have shed more light on the role of digoxin as adjunctive therapy.

- In a DIG sub-group analysis, Rathore\(^{[88]}\) examined the relationship between serum digoxin concentration and outcomes in a post hoc analysis of 3782 male participants with \(\text{LVEF} \leq 45\%\).

  - They found that, compared with placebo, there was no difference in all-cause mortality in those with serum levels taken. However, results for numerous measures differed depending upon participants’ serum levels. On the whole, lower values resulted in increased effectiveness.

  - Participants with the lowest serum levels had an adjusted hazard ratio of 0.8 for all-cause mortality and of 0.66 for mortality due to worsening heart failure compared with placebo. For these measures, ratios for the middle range of serum levels and the highest group were not statistically different from those of patients on placebo.

  - Data for secondary outcomes are shown below.

  - There were insufficient data to evaluate women in these analyses. This was a post hoc study, and adjusted analyses took into account BMI and estimated glomerular filtration rate, important factors for digoxin absorption and excretion. However, there were many significant differences between the groups. The group with the highest serum digoxin concentration was also the oldest and had the most severe heart failure, which may have accounted for poorer digoxin clearance.
**Adjusted Outcomes & Hazard Ratios by Serum Digoxin Concentration Placebo = Referent**

<table>
<thead>
<tr>
<th>Adjusted Outcomes*</th>
<th>HR* (95% CI) by SDC 0.5 – 0.8 ng/ml</th>
<th>HR* (95% CI) by SDC 0.9 – 1.1 ng/ml</th>
<th>HR* (95% CI) by SDC 1.2 ng/ml or greater</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>0.80 (0.68 to 0.94)</td>
<td>0.89 (0.74 to 1.08)</td>
<td>1.16 (0.96 to 1.39)</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>0.86 (0.72 to 1.02)</td>
<td>0.93 (0.76 to 1.14)</td>
<td>1.21 (0.99 to 1.47)</td>
</tr>
<tr>
<td>mortality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Worsening heart</td>
<td>0.66 (0.49 to 0.89)</td>
<td>0.86 (0.63 to 1.17)</td>
<td>0.95 (0.69 to 1.31)</td>
</tr>
<tr>
<td>failure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause</td>
<td>0.83 (0.74 to 0.93)</td>
<td>1.02 (0.89 to 1.18)</td>
<td>0.90 (0.77 to 1.04)</td>
</tr>
<tr>
<td>hospitalization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospitalization</td>
<td>0.56 (0.46 to 0.67)</td>
<td>0.74 (0.60 to 0.92)</td>
<td>0.65 (0.52 to 0.82)</td>
</tr>
<tr>
<td>for worsening</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>heart failure</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Adjusted for age; race; body mass index; LVEF; NYHA class; cardiothoracic ratio; number of heart failure signs and symptoms; systolic blood pressure; heart rate; estimated glomerular filtration rate; duration of heart failure; primary cause of heart failure; history of MI, angina, diabetes, and hypertension; prior use of digoxin; and use of potassium-sparing diuretics, all other diuretics, ACE inhibitors, nitrates hydralazine, and other vasodilators.

In another post hoc analysis of the DIG trial, Rathore, et al.\(^{(89)}\) studied the impact of sex on primary and secondary outcomes in patients with heart failure, depressed LV systolic function and normal sinus rhythm. They looked at 764 women on placebo and 755 women on digoxin therapy.

- Women had significantly different characteristics than men at baseline. They were older, had a higher heart rate, systolic blood pressure and cardiothoracic ratio, and higher rates of being in NYHA functional class III or IV, having diabetes, hypertension, angina, and of previous digoxin use. They also had higher LVEFs, and lower rates of ischemia as their primary cause of heart failure, previous MI, presentation with rales, creatinine values, and initial dose of study medication.

- When women in the digoxin group were compared with women on placebo, the difference in the rate of death from any cause was not significant (digoxin = 33.1%; placebo = 28.9%; \( p = 0.078 \)). There was, however, a statistically significant difference in the interaction between sex and digoxin (absolute difference 5.8 (95% CI: 0.5 to 11.1); \( p = 0.034 \)).

- When multivariate analysis was used to correct for baseline differences, the sex/digoxin relationship was even more striking, as illustrated below for primary and secondary outcomes.
**Digoxin-Associated Risk of Death and Hospitalization in Women***
(adapted from Table 3\(^{(89)}\))

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Adjusted Hazard Ratio</th>
<th>95% CI</th>
<th>Adjusted p value – interaction between sex and digoxin(\dagger)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death from any cause</td>
<td>1.23</td>
<td>1.02 to 1.47</td>
<td>0.014</td>
</tr>
<tr>
<td>Death from CV causes</td>
<td>1.24</td>
<td>1.02 to 1.52</td>
<td>0.035</td>
</tr>
<tr>
<td>Death from worsening heart failure</td>
<td>1.17</td>
<td>0.87 to 1.04</td>
<td>0.026</td>
</tr>
<tr>
<td>Hospitalization for worsening heart failure</td>
<td>0.87</td>
<td>0.72 to 1.04</td>
<td>0.011</td>
</tr>
<tr>
<td>Death from worsening heart failure or hospitalization for worsening heart failure in ancillary trial</td>
<td>0.92</td>
<td>0.64 to 1.31</td>
<td>0.32</td>
</tr>
</tbody>
</table>

**Conclusion**

These findings are limited since they resulted from a post hoc analysis comparing groups with very different characteristics. The overall findings of the original DIG trial did not report significant differences between the sexes and it wasn’t designed to explore those differences.\(^{(90)}\) However, the GDT believes there may be reason for caution when prescribing digoxin for women.

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* Hazard ratios represent the risk of the outcome among patients randomly assigned to digoxin as compared with patients randomly assigned to placebo, and were obtained using Cox proportional-hazards model.

\(\dagger\) Values were adjusted for age; race; body-mass index; left ventricular ejection fraction; cardiothoracic rate; NYHA functional class; number of signs and symptoms of heart failure; serum creatinine level; systolic blood pressure; and presence or absence of diabetes, prior digoxin use, and concomitant use of diuretics, nitrates, and vasodilators. Comparison is with data for men (not shown).

\(\dagger\) P values are for the sex-and-digoxin-therapy interaction term entered in the Cox proportional-hazards model.
15. **Oral Anticoagulation - Warfarin**

15A Warfarin is recommended for patients with LVSD and atrial fibrillation, unless contraindicated. *Evidence-based: B*

15B The routine use of warfarin for patients with LVSD in normal sinus rhythm has not been established. Its use should be based on a determination of the potential risks and benefits of treatment. *Consensus-based*

15C The use of warfarin is an option for LVSD patients in normal sinus rhythm, and with left ventricular thrombus on echocardiography or a history of thromboembolism.  *Consensus-based*

**Rationale:**

**Evidence Grade**

Evidence for Recommendation 15A: Good  
Evidence for Recommendation 15B, C: Insufficient

2009 Update

No new evidence was found, the recommendation remains unchanged.

**Search Strategy**

See Appendix B for more information.

2008 Guideline

No new evidence was found, the recommendation remains unchanged.

2006 Guideline

No new evidence was found, the recommendation remains unchanged.

2004 Guideline

**WARFARIN FOR LVSD AND ATRIAL FIBRILLATION, UNLESS CONTRAINDICATED**

- The WASH (Warfarin Antiplatelet Study in Heart Failure)\(^{(91)}\) and the WATCH (Warfarin Antiplatelet Trial in Chronic Heart Failure)\(^{(92)}\) are ongoing RCTs that will provide evidence in the future for use of oral anticoagulants or antiplatelet agents in patients with heart failure and normal sinus rhythm.

- Patients with heart failure and atrial fibrillation are considered at high risk for thromboembolic events. There is good evidence that oral anticoagulants are effective in reducing morbidity and mortality in high risk patients. See the ACC/AHA/ECS/Guidelines for Management of Patients with Atrial Fibrillation.
Segal, et al\(^{(93)}\). evaluated the risk of stroke in patients with atrial fibrillation in a meta-analysis of randomized, controlled trials. The results showed antithrombotic agents are more effective at preventing stroke in patients with atrial fibrillation than placebo. Warfarin is more effective than placebo or aspirin.

| Results from Segal\(^{(93)}\) Meta-Analysis - OR (95\% CI) |
|---------------------------------|------|------|
|                                 | Strokes | Hemorrhage | Death |
| Warfarin vs. placebo            | 0.34 (0.25 to 0.46) | 2.35 (1.20 to 4.24) | 0.74 (0.53 to 1.04) |
| Aspirin vs. placebo             | 0.76 (0.44 to 1.33) | 0.81 (0.37 to 1.77) | 0.88 (0.66 to 1.19) |
| Warfarin vs. Aspirin            | 0.64 (0.43 to 0.96) | 1.60 (0.77 to 3.35) | 0.96 (0.58 to 1.58) |

No new evidence was found of harm or benefit from the long-term use of warfarin to prevent thromboembolic events in patients with LVSD and atrial fibrillation.

**Conclusion**

There is good evidence to support long-term use of anticoagulants for patients with LVSD and atrial fibrillation.

**Routine Use of Warfarin for LVSD in Normal Sinus Rhythm**

No new evidence was found, the recommendation remains unchanged.

Two systematic reviews of the use of oral anticoagulants in patients with LVSD and normal sinus rhythm were found - Sirajuddin\(^{(94)}\) and Lip.\(^{(95)}\)

- The Lip systematic review included three studies (published more than 50 years ago) that were not considered previously.
  - The inclusion criteria for the Lip systematic review were RCTs with and without placebo, lasting at least one month, in patients with heart failure. Eleven studies were reviewed. One pilot study (WASH), three observation studies, four large scale, nonrandomized, retrospective post hoc analyses, and three prospective studies performed over 50 years ago were included.
  - The three studies published in the 1950s were not identified by previous Evidence Searches. They were “small prospective studies of warfarin in heart failure with methods not considered reliable by modern standards.” “These earlier studies were performed in hospitalized patients with a high prevalence of rheumatic heart disease and atrial fibrillation.” Though Lip reports that oral anticoagulation was significantly effective in these studies, we believe the results are not reliable due to the inclusion of patients with other risk factors for thromboembolic events.
  - The results from the WASH pilot study showed that no significant difference in the composite endpoint of death/MI/stroke in patients treated with anticoagulants compared with no antithrombotic therapy (24\% versus 27\%).
The systematic review by Sirajuddin(94) added no new studies to the evidence evaluated by Lip’s systematic review.

**USE OF WARFARIN OPTIONAL FOR LVSD IN NORMAL SINUS RHYTHM & WITH LV THROMBUS OR A HISTORY OF THROMBOEMBOLISM**

No clinical trials were found that evaluated the use of anticoagulants vs. placebo to prevent thromboembolic events in patients with heart failure who did not have coexisting atrial fibrillation. Because of the potential for serious bleeding with warfarin therapy, the risks of anticoagulation should be carefully weighted against any potential benefit.

Baker, et al.,(96) performed an extensive literature search up until 1998 and found no clinical trials for the use of anticoagulants for patients with LVSD without atrial fibrillation. A search of MEDLINE; the Cochrane Database of Systematic Reviews; and bibliographies of recent review articles and guidelines, from September 1998 to June 2001, found no randomized, controlled trials on the topic.

The trials Baker found were mostly observational with one retrospective analysis of the V-HeFT I and II trials, which are discussed below. The author provided a narrative review of nine studies examining effectiveness and of five studies examining risk of major bleeding. Overall incidence of thromboembolism events was 1.9 per 100 patient years. Risk of major bleeding in patients on anticoagulants varied among trials from 4.4 per 100 patient years, to no difference from the controls.

Dunkman, et al.(97) analyzed the V-HeFT I and II trials and found no significant difference in thromboembolism events in patients on warfarin compared to those not on warfarin. However, patients on warfarin may have been at higher risk for thromboembolism events, for which he did not adjust.

No randomized, controlled trials were found that evaluated the effectiveness of warfarin in preventing thromboembolic events in patients with a left ventricular thrombus, though there were retrospective studies(47, 98-100) that showed that patients with a left ventricular thrombus and lower ejection fractions, ischemic cardiomyopathy, or of female gender were at increased risk of thromboembolism.

**Conclusion:**
The evidence is insufficient to support the use of anticoagulants in patients with LVSD without concomitant atrial fibrillation, with or without left ventricular thrombus. The GDT recommends that the use of anticoagulants in patients with LVSD in sinus rhythm with or without LV thrombus should be an option based on individual patient characteristics where the risks and benefits of treatment can be more accurately determined.
16. Calcium Channel Blockers

16A Amlodipine* and felodipine* (second generation dihydropyridine calcium channel blockers) are options for the treatment of angina pectoris or hypertension in patients with LVSD. **Evidence-based: C**

16B The GDT recommends against the use of calcium channel blockers (CCBs) other than amlodipine* and felodipine* in patients with LVSD. **Evidence-based: D**

**Evidence Grade**
Evidence for Recommendation 16A: Fair
Evidence for Recommendation 16B: Fair

**2009 Update**
No new evidence was found, the recommendation remains unchanged.

**Search Strategy**
See Appendix B for more information.

**2008 Guideline**
No new evidence was found, the recommendation remains unchanged.

**2006 Guideline**
No new evidence was found, the recommendation remains unchanged.

**2004 Guideline**
No new evidence was found, the recommendation remains unchanged.

- Clinical trials of amlodipine and felodipine (second generation dihydropyridine calcium channel blockers) have demonstrated that they are safe to use in patients with LVSD. Amlodipine and felodipine, when added to standard therapy of ACE inhibitors, diuretics and usually, digitalis, do not increase nor decrease survival.(101, 102) In the PRAISE trial, patients who received amlodipine were less likely to experience uncontrolled hypertension or angina.(103)

- Studies of other dihydropyridines, especially short-acting formulations such as nifedipine immediate release, have shown a trend towards harm. Non-dihydropyridines (diltiazem and verapamil) failed to show a mortality benefit, and in some cases, showed a trend towards harm, especially the short-acting formulations.(104)

**Conclusion**
Second generation dihydropyridine calcium channel blockers are safe to use in patients with LVSD. However, they should not be used for primary treatment.(105)

* Not FDA-approved for heart failure.
17. **Heart Failure with Preserved Ejection Fraction**

In patients with heart failure with preserved ejection fraction, treat the following concomitant conditions according to local and national guidelines: hypertension, rhythm abnormalities, ischemia, and edema. *Consensus-based*

**Rationale:**

**Evidence Grade**
Evidence for Recommendation 17A: Insufficient

**2009 Update**
No new evidence was found, the recommendation remains unchanged.

**Search Strategy**
See Appendix B for more information.

**2008 Guideline**
New evidence was found that did change the previous recommendation. Three RCTs were identified in the peer-reviewed medical literature published since the last update of these guidelines that addressed medication management for patients with heart failure with preserved ejection fraction.

- The objective of the ancillary Digitalis Investigation Group (DIG) trial was to assess the effect of digoxin, a Na⁺/K⁺ ATPase pump inhibitor, on the primary combined outcome of hospitalization for heart failure or death from heart failure in patients with preserved ejection fraction (LVEF ≥ 45%) and normal sinus rhythm at baseline (Ahmed, 2006). The ancillary DIG trial was conducted in parallel with the main DIG trial; a large, double-blind, randomized, multicenter, placebo-controlled trial.
  - During a mean follow-up of 37 months, 21% of the digoxin group and 24% of the placebo group experienced the primary combined outcome of hospitalization for heart failure or heart failure mortality (p = 0.136).
  - The rate of hospitalization for heart failure or death resulting from cardiovascular causes, the primary outcome of the CHARM-Preserved trial, was 29% in the digoxin group and 31% in the control group (p = 0.269).
  - The use of digoxin was associated with a trend toward a reduction in hospitalizations resulting from worsening heart failure (p = 0.094) and a trend toward an increase in hospitalizations for unstable angina (p = 0.061).
  - The study showed that digoxin had no effect on natural history endpoints, such as mortality and all-cause or cardiovascular hospitalization.
Two double-blind, randomized, multicenter, placebo-controlled trials assessed the effect of ACE inhibitors in heart failure patients with preserved ejection fraction: the Perindopril and Remodeling in Elderly with Acute Myocardial Infarction (PREAMI) trial and the Perindopril in Elderly People with Chronic Heart Failure (PEP-CHF) trial.

- The PREAMI trial compared the effect of perindopril versus placebo in patients 65 years or older who survived an acute myocardial infarction with preserved left ventricular function (LVEF ≥ 40%) and optimal apical 4- and 2-chamber views of the LV recorded for at least five complete cardiac cycles (Ferrari, 2006). The combined primary endpoint was death, hospitalization for heart failure, or left ventricular remodeling.

- The primary endpoint occurred in 35% of the perindopril group and 57% of the placebo group (p < 0.001). Remodeling occurred in 28% and 51% of the perindopril and placebo groups, respectively (p < 0.001). Treatment did not affect the rates of death, hospitalization for reinfarction or angina, or revascularization.

- The study showed that perindopril reduced left ventricular remodeling without affecting clinical outcome.

- The PEP-CHF trial compared perindopril with placebo in patients older than 70 years, treated with diuretics for a clinical diagnosis of chronic heart failure due to diastolic dysfunction (LVEF > 40%), who had had a cardiovascular hospitalization within the previous six months (Cleland, 2006). The primary endpoint was a composite of all-cause mortality and unplanned heart failure-related hospitalization.

- The trial did not achieve its primary endpoint because of low enrollment and event rates and a high rate of cessation of blinded therapy with the use of open-label ACE inhibitors. The statistical power of the trial was reduced to 35%.

- The primary endpoint occurred in 23.6% and 25.1% of the perindopril and placebo groups, respectively (p = 0.545), for the entire duration of follow-up.

- If confined to the first year of follow-up, the rates of the primary outcome and hospitalization for heart failure were reduced (p = 0.055 and p = 0.033, respectively).

- The risk of hospitalization for heart failure or cardiovascular death, the primary outcome of the CHARM-Preserved trial, was lower in the perindopril group (9.4%) than in the placebo group (14.8%) over one year (p = 0.018).

- The PEP-CHF trial did not show a statistically significant benefit of perindopril compared with placebo on long-term morbidity and mortality in patients with diastolic heart failure because of insufficient power of the trial.

**Conclusion:**
Digoxin is no longer recommended for treatment of patients with heart failure with preserved ejection fraction in normal sinus rhythm as a result of the ancillary DIG trial. The recommendation itself remains unchanged as “In patients with heart failure with preserved ejection fraction, treat the following concomitant conditions according to local and national guidelines: hypertension, rhythm abnormalities, ischemia, and edema.”
2006 Guideline
No new evidence was found, the recommendation remains unchanged.

2004 Guideline
New evidence was found that did not change the existing recommendation. One RCT for medication management of patients with diastolic heart failure was found: the CHARM-Preserved Trial.

- The CHARM-Preserved trial\(^{(32)}\) enrolled 3,029 patients with LVSD (EF > 40%). Of these, 1,514 patients were assigned to 32 mg candesartan daily and 1509 to placebo.
  - The primary endpoint was CV death or unplanned admission to hospital for management of worsening heart failure. The hazard ratio showed a nonsignificant difference between the treatment and placebo groups 0.89 (95% CI: 0.77 to 1.03), \(p = 0.118\).
  - The authors stated that "baseline characteristics associated with poorer prognosis were slightly more common in the candesartan group than in the placebo group." These were previous MI, stroke, current smoking, HTN, diabetes, cancer, and use of digitalis and diuretics.
  - Treatments associated with lower mortality were slightly less common in the candesartan group. These treatments were previous percutaneous coronary intervention, use of lipid-lowering drugs, ASA and spironolactone. The adjusted hazard ratio for primary endpoints was 0.86 (95% CI: 0.74 to 1.00), \(p = 0.051\).

The evidence previously reviewed identified five clinical studies. Four were small RCTs, and one was a cohort study; all included mortality data except the cohort study. The bulk of the data presented were for intermediate outcomes.

- Three of the four RCTs were placebo-controlled, double-blind, cross-over trials evaluating intermediate outcomes for verapamil, lisinopril, or losartan. The other was an unblinded, randomized trial of enalapril that also evaluated intermediate outcomes.\(^{(22, 109-112)}\)
- The cohort study (Philbin, 2000\(^{(113)}\)) showed that patients with ejection fractions greater than 50% did not realize mortality benefits from ACE inhibitors, although NYHA class improved by 0.3.
- None of these studies provided conclusive evidence of the effectiveness of medications in reducing the risk of mortality or morbidity in patients with diastolic heart failure.

Conclusion
Because of the lack of compelling evidence showing improved morbidity and mortality, treatment for diastolic heart failure is empirical and directed at the underlying etiology. The goal of medical management is to relieve symptoms and to treat concomitant conditions.
Suggested Management of Patients with Heart Failure with Preserved Ejection Fraction

Treatment for Fluid Retention:
Treat fluid retention with loop diuretics* (or thiazide diuretics if fluid retention is mild).

Blood Pressure Control:
Treat hypertension aggressively with diuretics, beta-blockers, or ACE inhibitors (goal: systolic blood pressure < 139, diastolic blood pressure < 89). Many consider beta-blockers and ACE inhibitors the first-line agents, with the choice between the two based on the need to lower the heart rate (see Heart Rate Control, below) and, as indicated, diuretics. ARBs and calcium channel blockers are considered second-line agents after ACEI and beta-blockers.

Heart Rate Control:
For patients with atrial fibrillation, restore and maintain normal sinus rhythm if possible. To lengthen diastolic filling time, control ventricular response rate with beta-blockers, digoxin, or calcium channel blockers (verapamil or diltiazem). For patients in sinus rhythm, slow sinus rate if possible to 55 to 75 bpm with beta-blockers.

Treat Ischemia:
Treat symptoms of ischemia with anti-anginal medications, e.g., beta-blockers, nitrates, or calcium channel blockers. Refer for invasive procedures as clinically indicated.

Patient Education:
Provide patient education. Patients with diastolic dysfunction will benefit from the same education provided for LVSD: low-sodium diet, daily weight monitoring, avoidance of excessive fluid intake, flexible diuretic doses based on weight changes, physical activity as tolerated, smoking cessation, and moderate consumption of alcohol.

* Not FDA-approved for heart failure.
Lifestyle Factors

18. Sodium Restricted Diet

18 Moderate sodium restriction, 2 to 2.4 grams (2,000 to 2,400 mg) per day, is recommended for patients with heart failure in order to assist in volume management, unless a low-sodium diet is contraindicated. It is recommended that clinicians reinforce and/or increase sodium restriction when fluid retention requires increasing doses of diuretics. Consensus-based

Rationale:

Evidence Grade
Evidence for Recommendation 18: Insufficient

2009 Update
No new evidence was found, the recommendation remains unchanged.

Search Strategy
See Appendix B for more information.

2008 Guideline
No new evidence was found, the recommendation remains unchanged.

2006 Guideline
No new evidence was found, the recommendation remains unchanged.

2004 Guideline
No new evidence was found, however, the GDT has revised the previous recommendation from “2 to 3 grams” to “2 to 2.4 grams” to be consistent with the JNC 7 publication on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.\(^{114}\)

- Dietary sodium restriction is recommended as a supplementary treatment for hypertension at a level of 2.4 grams/day, and since a large percentage of heart failure patients have high blood pressure, we have extended this recommendation to the heart failure population. Lower levels (2 grams/day) may be prescribed before trying increased doses of diuretics, or multiple diuretics.

- Although no large RCTs showing benefit with sodium restriction in patients with heart failure were found, sodium has been shown to aggravate fluid retention in physiological studies. Sodium restriction may also reduce the use of high-dose diuretics and their potential side effects. The rationale for restricting sodium in heart failure patients without a history of fluid retention, diuretics, or hypertension may not be as compelling.

- American College of Cardiology Guidelines (ACC)/American Heart Association Practice Guidelines (ACC/AHA)\(^{115}\) states that diuretics are generally combined with moderate sodium restriction (< 3 g daily). Most guidelines within Kaiser Permanente have included sodium restriction recommendations of < 2 to 3 g (2,000 to 3,000 mg) per day.

- Educating patients about reading food labels to determine sodium content may help them to maintain a low-sodium diet. The term “heart healthy” indicates low-fat, but not necessarily low-sodium.
19. Physical Activity

Light to moderate aerobic activity and resistance training is recommended for patients with stable heart failure, unless contraindicated. *Evidence-based: B*

**Rationale:**

**Evidence Grade**
Evidence for Recommendation 19: Good

**2009 Update**
No new evidence was found, the recommendation remains unchanged.

**Search Strategy**
See Appendix B for more information.

**2008 Guideline**
No new evidence was found, the recommendation remains unchanged.

**2006 Guideline**
New evidence was found that did not change the existing recommendation.
One RCT (Oka, 2000)\(^{(116)}\) was found that did not change the weight of the evidence.

**2004 Guideline**
New evidence was found that did not change the existing recommendation.

One meta-analysis, one large RCT, and one systematic review were found.
- The ExTraMATCH Collaborative\(^{(117)}\) conducted a prospective protocol meta-analysis of nine randomized, parallel group trials (including the McKelvie RCT discussed below) published since 1990, which met the criteria of: exercise training without other simultaneous intervention that could confound results, patients with stable heart failure (three months or more of stability), heart failure due to LVSD (LVEF ≤ 50%), exercise program length ≥ eight weeks, training involving at least both legs, and survival follow-up of at least three months.
- Results showed that physical activity in heart failure patients significantly reduces death from any cause, and the combined outcome of death or hospital admission for any reason.

<table>
<thead>
<tr>
<th>Effect of Training on Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Exercise Group, n (%)</strong></td>
</tr>
<tr>
<td>Death</td>
</tr>
<tr>
<td>Death or admission to hospital*</td>
</tr>
</tbody>
</table>

NNT = 17 to prevent one death in two years

* Assessed in eight of nine studies.
Effect of Training on Outcomes

- McKelvie, et al., conducted a randomized, controlled, single-blind study (EXERT) in 181 patients with NYHA Class I to III heart failure, of the effects of exercise training on functional capacity.\(^{118}\)
  - With 181 participants and one year of follow-up, it is the largest and longest such trial to date, with the most representative sample. Since it included both a hospital- and a home-based program, it is closer to a ‘real world’ situation than most previous trials.
  - Patients randomized to the exercise group took part in a supervised, hospital-based exercise program for three months. They were then given an exercise bicycle and free weights to use at home for an additional nine months.
  - Significant positive results were seen in:
    - Peak Oxygen Uptake (exercise test performance): Between baseline and three months, the exercise group improved 10%: p < 0.01. At three months, the exercise group had improved compared with the control group: p = 0.026. Between baseline and 12 months, exercise group improved 14%: p < 0.05.
    - Arm Curl (kg): Difference between groups at three months: exercise group improved by 0.7 over controls, p = 0.014.
    - Knee Extension (kg) Difference between groups at three months: exercise group improved by 2.12 over controls, p = 0.0001.
  - No significant differences were seen between the exercise and control groups for the following measures: peak oxygen uptake (at 12 months only – too few participants took test), six-minute walk test distance (three or 12 months, though both groups improved significantly at both intervals), submaximal heart rate (three or 12 months), arm curl (12 months only), knee extension (12 months only), ejection fraction, end-diastolic volume, and end-systolic volume (all three were only measured at three months), and QOL measures (three or 12 months).
  - No significant differences were seen between groups for total mortality, the composite of total mortality rate or hospitalization for heart failure, and the composite of total mortality rates or worsening heart failure. (The study was not sufficiently powered to draw conclusions about moderate numbers of events.)
  - Training did not result in a negative result in either ejection fraction or cardiac volumes.
  - This study showed some short-term improvements that were not able to be maintained in the unsupervised, home setting. The authors concluded that patients would need longer term, closely supervised activity programs in order to maintain motivation.
Lloyd-Williams, et al.,(119) published a systematic review that reviewed studies examining improvements in physical performance, quality of life, health care utilization, cost-effectiveness, and mortality. This was a survey of the literature, which did not produce combined, quantitative results. Thirty-one studies met the inclusion criteria. (The McKelvie RCT had not yet been published and was not included.)

- In most studies, exercise training was supervised and took place in the hospital. Most studies were very short-term and took place in selected subgroups. Forty-five percent (14/31) of studies lasted eight weeks or less. Sixty-five percent (20/31) had sample sizes of 25 or less; 26% (7/31) had sample sizes of 26 to 50; and 13% (4/31) had 51 to 150 participants.

- Eighty-seven percent of the 31 studies showed positive results in quality of life and physiological measures (e.g., peak VO2, peak O2 uptake, maximum heart rate, etc.).

- The authors concluded that limitations in the literature include: research is mostly lab-based and short-term, which does not consider adaptation of programs by patients in the community, studies are done in subgroups and don’t reflect the general population, studies are small-scale, and research does not focus on long-term outcomes. It is still unknown what should be the frequency, duration and intensity of activity for different groups. There are positive rates of completion and compliance, but these may be related to the short terms of the studies.

**Conclusion**

The new evidence has strengthened this recommendation significantly. Previously, there was only one RCT with 91 participants that reported on mortality outcomes. The ExTraMATCH meta-analysis, with 801 patients, provides us with definitive data on the advantages of physical activity in heart failure.
20. Pharmacological Management of LVSD Based on Patients’ Race/Ethnicity or Sex

20A For women* and nonwhite populations, management of ACE inhibitors, beta-blockers, and spironolactone should not be different from that in men and whites. *Consensus-based

20B It is an option to add hydralazine and isosorbide dinitrate to standard heart failure therapy (including ACE inhibitors and beta-blockers) in blacks/African Americans and in patients who require additional vasodilation for uncontrolled hypertension or symptoms. *Consensus-based

Rationale:

Evidence Grade
Evidence for Recommendation 20A, B: Insufficient

2009 Update
No new evidence was found, the recommendation remains unchanged.

Search Strategy
See Appendix B for more information.

2008 Guideline
New evidence was found that did not change the existing recommendation. One study was identified in the peer-reviewed medical literature that performed a post hoc analysis on subgroups in a large RCT among black/African American heart failure patients treated with a fixed-dose combination of isosorbide dinitrate and hydralazine.

- The African-American Heart Failure Trial (A-HeFT), a randomized, placebo-controlled, double-blind trial, demonstrated a reduction in mortality and improvement in a primary morbidity/mortality outcome in response to therapy with a fixed-dose combination of isosorbide dinitrate and hydralazine (FDC I/H) in black/African American patients with severe heart failure (n = 1050)(Taylor, 2004). (120)

- A post hoc analysis further defined the effect of FDC I/H across subgroups (Taylor, 2007). (121)
  - Treatment effects on mortality or first hospitalization for heart failure were consistent across subgroups. No significant interaction existed between gender and beneficial treatment effect in this black/African American population of heart failure patients: i.e., there were 100 events in women versus 166 events in men (p = 0.611).

Conclusion
The GDT has evaluated the new information and concluded that it does not require any changes in the existing recommendations for medical treatment of patients with heart failure based on race/ethnicity or sex.

* Please see the digoxin recommendation for the use of digoxin in women.
2006 Guideline
The recommendations were based on the African-American Heart Failure Trial (A-HeFT), a randomized, placebo-controlled, double-blind trial, which demonstrated a 40% reduction in mortality and a 40% improvement in a primary morbidity/mortality outcome in response to therapy with a fixed-dose combination of isosorbide dinitrate and hydralazine (FDC I/H) in black/African American patients with severe heart failure (n = 1050) (Taylor et al., 2004). (120)

2004 Guideline
New evidence was found that did not change the existing recommendation. The only studies found performed post hoc analyses on subgroups in large RCTs. These RCTs included comparisons of ACE inhibitors, combination hydralazine and isosorbide dinitrate, beta-blockers, and spironolactone to placebo. No compelling evidence was found to support treating heart failure differently on the basis of sex and/or race/ethnicity.

In 2003, a meta-analysis was performed on data from the 12 largest major clinical trials of LVSD (Shekelle, 2003 (122)), by race/ethnicity, sex, and diabetic status. Overall, reductions in all-cause mortality were found with beta-blockers in both men and women and with ACEIs in both blacks/African Americans and whites.

ACE INHIBITORS - SEX
• Data from six studies (n = 2,373 women; 10,213 men) were combined to examine heart failure mortality with use of ACE inhibitors. Findings are presented below (synopsis of Table 2 from Shekelle, et al.). Women showed less benefit than did men, but the relative risk ratio did not demonstrate a significant difference between the sexes. However, in the six studies in which hazard ratio data were presented, the difference between men and women was close to significant.

| Effect of ACE Inhibitors on Mortality From Heart Failure in Male & Female Patients |
|-------------------------------------|-------------------------------------|-------------------------------------|-------------------------------------|-------------------------------------|-------------------------------------|
| RR Male (95% CI) | RR Female (95% CI) | RRR (95% CI) | HR Male (95% CI) | HR Female (95% CI) | P value for HR |
| 0.82 (0.74 to 0.90) | 0.92 (0.81 to 1.04) | 1.15 (0.99 to 1.33) | 0.76 (0.66 to 0.87) | 0.84 (0.72 to 0.98) | 0.07 |

• Meta-analysis of studies with data for symptomatic versus asymptomatic LV dysfunction showed suggestive but nonsignificant differences between men and women in the mortality rate response to ACE inhibitors. The table below (Table 3 from Shekelle, et al.) shows that data. There was no benefit shown for asymptomatic women. Data for hazard ratios were not presented.
EFFECT OF ACE INHIBITORS ON MORTALITY FROM HEART FAILURE IN MALE & FEMALE PATIENTS REPORTED SEPARATELY FOR PREVENTION STUDIES AND TREATMENT STUDIES

<table>
<thead>
<tr>
<th>Analysis</th>
<th>RR Male (95% CI)</th>
<th>RR Female (95% CI)</th>
<th>RRR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment (symptomatic) studies</td>
<td>0.80 (0.68 to 0.93)</td>
<td>0.90 (0.78 to 1.05)</td>
<td>1.15 (0.88 to 1.51)</td>
</tr>
<tr>
<td>(n not shown)</td>
<td>(n = 1,079)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prevention (asymptomatic) studies</td>
<td>0.83 (0.71 to 0.96)</td>
<td>0.96 (0.75 to 1.22)</td>
<td>1.25 (0.94 to 1.65)</td>
</tr>
<tr>
<td>(n not shown)</td>
<td>(n = 1,294)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ACE INHIBITORS - RACE/ETHNICITY

- Trials for which subgroups were analyzed were typically multinational and multicentered. For this reason, we do not know the individual origins of persons/populations termed “black.” However, the term “black/African American” has been used throughout this document.

- Race/ethnicity data were only available for three of the 12 studies in the overall meta-analysis. (A number of studies were performed in countries without substantial black/African American populations.) Although the relative risk was found to be the same for whites as for blacks/African Americans, the large confidence intervals for blacks/African Americans may be due to the small number of black/African American participants available. Hazard ratios could not be presented due lack of applicable data.

EFFECT OF ACE INHIBITORS ON MORTALITY FROM HEART FAILURE IN BLACK/AFRICAN AMERICAN & WHITE PATIENTS

<table>
<thead>
<tr>
<th>RR White (95% CI)</th>
<th>RR Black (95% CI)</th>
<th>RRR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random effects pooled estimate</td>
<td>0.89 (0.82 to 0.97)</td>
<td>0.89 (0.74 to 1.06)</td>
</tr>
<tr>
<td>(n = 7,711)</td>
<td>(n = 800)</td>
<td></td>
</tr>
</tbody>
</table>

BETA-BLOCKERS – SEX

- Five studies of symptomatic heart failure were included in Shekelle, et al.

- No difference was seen in mortality rates of women versus men in response to beta-blocker use (carvedilol, metoprolol, and bucindolol). Data were analyzed with and without the BEST study, which used bucindolol, since it is thought to have a different mechanism than other beta-blockers. However, results were similar. Table 6 from Shekelle, et al. is shown below.

- Results for the hazard ratios were similar to those of the relative risks. Both women and men benefit from treatment with beta-blockers.

EFFECT OF BETA-BLOCKERS ON MORTALITY FROM HEART FAILURE IN MALE & FEMALE PATIENTS

<table>
<thead>
<tr>
<th>RR Male (95% CI)</th>
<th>RR Female (95% CI)</th>
<th>RRR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relative Risk Analysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Random effects pooled estimate</td>
<td>0.66 (0.59 to 0.75)</td>
<td>0.63 (0.44 to 0.91)</td>
</tr>
<tr>
<td>(n = 7,885)</td>
<td>(n = 2,134)</td>
<td></td>
</tr>
</tbody>
</table>
Beta-Blockers – Race/Ethnicity

Four studies contributed data for this analysis, and results were calculated with and without the BEST study (as above).

- The RR and HR results were similar. It appears that both black/African American and white heart failure patients have positive results from treatment with metoprolol, bisoprolol, or carvedilol; but that blacks/African Americans will not experience reduced mortality with bucindolol. Again, the lack of significance in the statistics for blacks/African Americans can likely be attributed to the small sample size. (Data are from Table 8 from Shekelle, et al.).

Effect of Beta-Blockers on Mortality from Heart Failure in Black/African American & White Patients

<table>
<thead>
<tr>
<th></th>
<th>RR White (95% CI)</th>
<th>RR Black (95% CI)</th>
<th>RRR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random effects pooled estimate (with BEST)</td>
<td>0.69 (0.55 to 0.85)</td>
<td>0.97 (0.68 to 1.37)</td>
<td>1.35 (1.07 to 1.71)</td>
</tr>
<tr>
<td>Random effects pooled estimate (without BEST)</td>
<td>0.63 (0.52 to 0.77)</td>
<td>0.67 (0.38 to 1.16)</td>
<td>1.17 (0.65 to 2.11)</td>
</tr>
</tbody>
</table>

This meta-analysis essentially confirms the conclusions of the GDT.

21. Target Blood Pressure

Target blood pressure for most patients is < 140/90 mm Hg. Aim for a lower target blood pressure (< 130/80 mm Hg) for patients with:
- Diabetes mellitus
- Renal disease
- Coronary artery disease

Consensus-based

Rationale:

Evidence Grade
Evidence for Recommendation 21: Insufficient

2009 Update
No new evidence was found, the recommendation remains unchanged.

Search Strategy
See Appendix B for more information.

2008 Guideline
No new evidence was found, the recommendation remains unchanged.

These recommendations are taken from the 2008 KP National Coronary Artery Disease Guidelines and the 2007 KP National Hypertension Guidelines.

2006 Guideline
No relevant RCTs or meta-analyses were identified in the peer-reviewed medical literature that addressed target blood pressure for patients with heart failure.
22. Medications to Achieve Target Blood Pressure

22A The following medications are recommended in patients with heart failure with preserved ejection fraction to control hypertension:

- Diuretics
- ACE inhibitors
- Angiotensin receptor blockers
- Beta-blockers
- Dihydropyridine calcium channel blockers

Consensus-based

22B The following medications are recommended in patients with systolic heart failure to control hypertension:

- Diuretics
- Beta-blockers
- ACE inhibitors or ARBs if intolerant of ACE inhibitors
- Hydralazine/isosorbide dinitrate
- Amlodipine or felodipine

Consensus-based

Rationale:

Evidence Grade
Evidence for Recommendation 22 A, B: Insufficient

2009 Update
No new evidence was found, the recommendation remains unchanged.

Search Strategy
See Appendix B for more information.

2008 Guideline
No new evidence was found. Given the lack of evidence on the relative efficacy of medications to control hypertension in heart failure patients, the GDT reached this consensus recommendation on the basis of their clinical experience, the KP National Hypertension Guidelines, and their understanding of underlying physiology and available treatments.

2006 Guideline
No relevant RCTs or meta-analyses were identified in the peer-reviewed medical literature that addressed medications to achieve target blood pressure for patients with heart failure.
23. **Reassessment of Systolic Performance**

23A A follow-up measurement of LVEF is recommended after patients have received optimal medical therapy or revascularization if a change in cardiac function would impact candidacy for ICD therapy. _Consensus-based_

23B Repeat measurement of LVEF (after initial confirmation of LVSD) is an option in patients who have had a change in clinical status only if the results would affect therapy. _Consensus-based_

23C Repeat measurement of LVEF (after initial confirmation of LVSD) is not recommended in clinically stable patients when the results will not alter therapy. _Consensus-based_

*Rationale:*

**Evidence Grade**
Evidence for Recommendation 23A, B, C: Insufficient

**2009 Update**
No new evidence was found, the recommendation remains unchanged.

**Search Strategy**
See Appendix B for more information.

**2008 Guideline**
No new evidence was found. Given the lack of evidence, the GDT reached these consensus recommendations on the basis of their clinical experience and understanding of underlying physiology and available treatments.

**2006 Guideline**
No relevant RCTs or meta-analyses were identified in the peer-reviewed medical literature that addressed the reassessment of systolic performance for patients with heart failure.

24. **Omega-3 Supplementation**

24 Omega-3 supplementation (1g per day) is an option for heart failure patients with an ejection fraction less than 40% following consideration of benefits, risks and costs of the supplement to the patient. * _Consensus-based_

*Rationale:*

**Evidence Grade**
Evidence for Recommendation 24: Insufficient

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* Omega-3 supplementation should be not emphasized over drugs with a solid body of evidence demonstrating strong clinical benefit.
2009 Guideline
There was a mid cycle update in early 2009 to incorporate this clinical question into this guideline.

Search Strategy
A comprehensive literature search of Cochrane, BMJ/Clinical Evidence, PubMed, and OVID databases was conducted to identify systematic reviews, meta-analyses, and randomized controlled trials (RCTs) on the use of omega-3 supplementation in patients with heart failure. One RCT was identified, the large-scale GISSI-HF trial, which assessed omega-3 supplementation in patients with heart failure of any cause (GISSI-HF Investigators 2008)\(^{(123)}\). GISSI-HF (2008) was the only trial included in this review as the other studies were found to be relevant to other patient populations (e.g., chronic kidney disease, coronary artery disease). See Appendix B for more information.

This is a consensus-based recommendation based on one large trial, GISSI-HF, which showed a marginal, but not statistically significant, clinical benefit of omega-3 supplementation.

Background - Cardiovascular Health and Omega-3 Studies
Previous studies have evaluated omega-3 supplementation in patients with coronary artery disease and myocardial infarction (MI). The GISSI-Prevenzione trial (1999) found lower mortality rates in patients who used omega-3 supplements after MI when compared with the control group (Gruppo Italiano et al., 1999)\(^{(124)}\). These results provided the first clinically controlled reporting of the potentially anti-arrhythmic properties of omega-3 supplementation. Results from a trial in patients with coronary artery disease have also suggested that omega-3 supplementation is associated with a 20% relative risk reduction of death in high-risk populations (Wang et al., 2006)\(^{(125)}\).

Overview of GISSI-HF Trial
The GISSI-HF study is the first large-scale, multi-center, randomized trial that was designed to assess the effects of omega-3 supplementation in patients with heart failure. This trial of 6,975 adults was undertaken in 326 cardiology and 31 internal medicine centers in Italy. Patients were eligible with heart failure of any cause that was classified according to the European Society of Cardiology (ESC) guidelines as New York Heart Association (NYHA) class II-IV, provided that they had their LVEF measured within 3 months before enrollment.

When LVEF was > 40%, the patient had to have been admitted at least once to the hospital for heart failure in the preceding year to meet the inclusion criteria. Patients were randomly assigned to receive either 1g of omega-3 daily \((n = 3,494)\) or placebo \((n = 3,481)\). Specifically, the treatment group received omega-3 as 850 to 882 mg eicosapentaenoic acid and docosahexaenoic acid (EPA/DHA) as ethyl esters. Patients without contraindications to statins were also randomly assigned to 10 mg p/day of oral rosuvastatin or corresponding placebo; these results appear in a separate publication (GISSI-HF Investigators 2008)\(^{(126)}\). All patients were followed up for a median of 3.9 years. Every study visit consisted of a cardiovascular examination, measurement of vital signs, 12-lead electro-cardiogram, a check of compliance, assessment of serious adverse events, and blood chemistry tests.
**Methodological Issues**

The hazard ratios for the co-primary outcomes were only statistically significant when adjusted for differences in select baseline characteristics of the two groups. The appropriateness of this adjustment was called into question in a letter to the editor published in the Lancet (Smith et al, 2009) \(^{(127)}\) and also by members of the GDT.

Therefore, further investigation of the GISSI-HF study rationale and design was conducted (Tavazzi et al, 2004). \(^{(128)}\) In addition, the appropriateness and validity of the adjustment for select baseline variables was examined in the context of a randomized controlled trial (Roberts et al, 1999) \(^{(129)}\), (Altman et al, 2001). \(^{(130)}\) In the design and rationale pre-study publication, the authors stated that they would consider performing an adjustment for baseline variables thought to be of prognostic significance. However, the specific prognostic variables were not specified at that time. In the study article itself, the authors stated that the prognostic factors could not be defined and they, therefore, chose to adjust only for those variables that were statistically unbalanced.

Whether such adjustment is appropriate remains a debatable issue. Some methodological literature indicates that the decision to adjust should not be based on finding statistically significant differences among the baseline characteristics, and the selection of the specific variables to adjust should not be determined by whether or not there are observed imbalances. In addition, any prognostic variables being considered for adjustment should be specified prior to the study. However, in discussions with other methodologists and researchers, it was felt that this type of adjustment can be reasonable and acceptable. \(^{(131, 132)}\)

Given that the appropriateness of the adjusted analysis remained an open issue, the GDT chose to take the most conservative position and determined that the unadjusted results would be used for the evaluation and assessment of the results.
Results
This study was designed with two co-primary endpoints: 1) time to death and 2) time to death or hospital admission for cardiovascular reasons (see Table 1 for specific causes of death for both groups). The authors established a 15% relative risk reduction in the mortality rate as their threshold for a clinically meaningful result. At nearly 4 years follow-up, 955 (27%) patients died from any cause in the treatment group and 1,014 (29%) in the placebo group [unadjusted HR 0.93 (95.5% CI: 0.852 - 1.021)], p = 0.124); see Kaplan-Meier survival curves in Figure 1. The other co-primary outcome (all-cause death or admission to a hospital for cardiovascular reasons) occurred in 1,981 (57%) patients in the treatment group and 2,053 (59%) in the placebo group [unadjusted HR 0.94 (99% CI: 0.869 - 1.022)], p = 0.059). Secondary health outcomes included cardiovascular mortality, cardiovascular mortality or admission for any reason, sudden cardiac death, admission for any reason, admission for cardiovascular reasons, and admission for heart failure, MI and stroke.

Table 1. Causes of Death

<table>
<thead>
<tr>
<th></th>
<th>n-3 PUFA (N = 3494)</th>
<th>Placebo (N = 3481)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total mortality</td>
<td>955 (27·3%)</td>
<td>1014 (29·1%)</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>20 (0·6%)</td>
<td>25 (0·7%)</td>
</tr>
<tr>
<td>Worsening heart failure</td>
<td>319 (9·1%)</td>
<td>332 (9·5%)</td>
</tr>
<tr>
<td>Presumed arrhythmic</td>
<td>274 (7·8%)</td>
<td>304 (8·7%)</td>
</tr>
<tr>
<td>Stroke</td>
<td>50 (1·4%)</td>
<td>44 (1·3%)</td>
</tr>
<tr>
<td>Other cardiovascular reasons</td>
<td>49 (1·4%)</td>
<td>60 (1·7%)</td>
</tr>
<tr>
<td>Neoplasia</td>
<td>107 (3·1%)</td>
<td>112 (3·2%)</td>
</tr>
<tr>
<td>Other non-cardiovascular reasons</td>
<td>97 (2·8%)</td>
<td>102 (2·9%)</td>
</tr>
<tr>
<td>Not known</td>
<td>39 (1·1%)</td>
<td>35 (1·0%)</td>
</tr>
</tbody>
</table>

Data are number (%). PUFA = polyunsaturated fatty acids.
Figure 1 – Kaplan-Meier Survival Curves: Co-Primary Endpoint (Probability of Death and Probability of All-Cause Death or Cardiovascular-Related Hospitalization)

PUFA=polyunsaturated fatty acids. *Estimates were calculated with a Cox proportional hazards model, with adjustment for admission to hospital for heart failure in the previous year, previous pacemaker, and aortic stenosis.
As previously noted, patients randomly assigned to omega-3 or placebo had also been randomly assigned to rosuvastatin or matching placebo. Following execution of a Cox proportional hazards model, the authors subsequently found no interaction between the effects of omega-3 supplements and rosuvastatin (interaction term p = 0.76 for all-cause death and p = 0.95 for all-cause death or cardiovascular-related hospitalization). This data confirms the authors’ hypothesis that the two interventions were independent.

With the exception of stroke, the HR for all other secondary outcomes favored the treatment group, although none of the results was statistically significant. Stroke occurred in more patients who received omega-3 supplementation; specifically, stroke was reported in 122 (3.5%) of treatment patients and in 103 (3.0%) in the placebo group (unadjusted p = 0.225). However, similar to the other outcomes, this increased incidence of stroke was not statistically significant. The rate of hemorrhagic events was similar in both groups.

Table 2 – Secondary Outcomes

<table>
<thead>
<tr>
<th></th>
<th>n-3 PUFA (N=3494)</th>
<th>Placebo (N=3481)</th>
<th>Adjusted HR (95% CI)*</th>
<th>p value</th>
<th>Unadjusted HR 95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients who died of a cardiovascular cause</td>
<td>712 (20.4%)</td>
<td>765 (22.0%)</td>
<td>0.90 (0.81-0.99)</td>
<td>0.045</td>
<td>0.92 (0.83-1.02)</td>
<td>0.121</td>
</tr>
<tr>
<td>Patients who had an SCD</td>
<td>307 (8.8%)</td>
<td>371 (10.2%)</td>
<td>0.93 (0.79-1.08)</td>
<td>0.333</td>
<td>0.96 (0.80-1.10)</td>
<td>0.413</td>
</tr>
<tr>
<td>Patients admitted</td>
<td>1986 (56.8%)</td>
<td>2208 (61.3%)</td>
<td>0.94 (0.88-1.00)</td>
<td>0.049</td>
<td>0.96 (0.90-1.02)</td>
<td>0.178</td>
</tr>
<tr>
<td>Patients admitted for heart failure</td>
<td>1635 (46.8%)</td>
<td>1867 (52.3%)</td>
<td>0.93 (0.87-0.99)</td>
<td>0.026</td>
<td>0.95 (0.89-1.02)</td>
<td>0.122</td>
</tr>
<tr>
<td>Patients admitted for heart failure and other reasons</td>
<td>2132 (61.3%)</td>
<td>2208 (63.1%)</td>
<td>0.94 (0.89-1.00)</td>
<td>0.043</td>
<td>0.96 (0.90-1.02)</td>
<td>0.159</td>
</tr>
<tr>
<td>Patients with stroke</td>
<td>107 (3.1%)</td>
<td>129 (3.7%)</td>
<td>0.82 (0.63-1.06)</td>
<td>0.121</td>
<td>0.82 (0.64-1.06)</td>
<td>0.135</td>
</tr>
<tr>
<td>Patients who died of a non-fatal MI</td>
<td>122 (3.5%)</td>
<td>103 (3.0%)</td>
<td>1.16 (0.89-1.51)</td>
<td>0.271</td>
<td>1.18 (0.91-1.53)</td>
<td>0.225</td>
</tr>
<tr>
<td>Ischaemic</td>
<td>97 (2.8%)</td>
<td>79 (2.3%)</td>
<td>1.23 (0.94-1.61)</td>
<td>0.145</td>
<td>1.23 (0.94-1.61)</td>
<td>0.145</td>
</tr>
<tr>
<td>Haemorrhagic</td>
<td>13 (0.4%)</td>
<td>10 (0.3%)</td>
<td>1.30 (0.83-2.04)</td>
<td>0.245</td>
<td>1.30 (0.83-2.04)</td>
<td>0.245</td>
</tr>
<tr>
<td>Not known</td>
<td>12 (0.3%)</td>
<td>14 (0.4%)</td>
<td>1.00 (0.61-1.67)</td>
<td>1.00</td>
<td>1.00 (0.61-1.67)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Data are number (%) unless otherwise stated. PUFA=polysaturated fatty acids. SCD=sudden cardiac death. MI=myocardial infarction. *95% CIwas calculated with a Cox proportional hazards model with adjustment for admission to hospital for heart failure, in the preceding year, previous pacemaker, and aortic stenosis.

Information on predefined subgroup analysis stratified by age, LVEF, ischemic and nonischemic causes, NYHA classification, diabetes, and cholesterol levels was also provided (see Table 3). With the exception of a nonsignificant trend towards a higher rate event in the subgroup with an EF > 40% treated with omega-3 compared to placebo, the authors again found a nonsignificant risk of all-cause death or admission to hospital for cardiovascular reasons from omega-3 supplementation for most of the predefined subgroups. A marginally significant benefit was found, however, for patients with LVEF ≤ 40, diabetes, and total cholesterol ≤ 4.87 mmol/L.
Table 3 – Predefined Subgroup Analysis

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>n-3 PUFA Events/patients (%)</th>
<th>Placebo Events/patients (%)</th>
<th>HR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt; 69 years (median)</td>
<td>856/1740 (49·2%)</td>
<td>906/1729 (52·4%)</td>
<td>0·92 (0·84–1·01)</td>
</tr>
<tr>
<td>Age ≥ 69 years (median)</td>
<td>1125/1754 (64·1%)</td>
<td>1147/1752 (65·5%)</td>
<td>0·96 (0·88–1·04)</td>
</tr>
<tr>
<td>LVEF ≤ 40%</td>
<td>1788/3161 (56·6%)</td>
<td>1871/3161 (59·2%)</td>
<td>0·94 (0·88–0·99)</td>
</tr>
<tr>
<td>LVEF &gt; 40%</td>
<td>193/333 (58·0%)</td>
<td>182/320 (56·9%)</td>
<td>1·02 (0·83–1·25)</td>
</tr>
<tr>
<td>Ischaemic cause</td>
<td>1079/1717 (62·8%)</td>
<td>1137/1750 (65·0%)</td>
<td>0·95 (0·87–1·03)</td>
</tr>
<tr>
<td>Non-ischaemic cause</td>
<td>902/1777 (50·8%)</td>
<td>916/1731 (52·9%)</td>
<td>0·94 (0·86–1·03)</td>
</tr>
<tr>
<td>NYHA II</td>
<td>1130/2226 (50·8%)</td>
<td>1170/2199 (53·2%)</td>
<td>0·93 (0·86–1·01)</td>
</tr>
<tr>
<td>NYHA III or IV</td>
<td>851/1268 (67·1%)</td>
<td>883/1282 (68·9%)</td>
<td>0·96 (0·87–1·05)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>623/992 (62·8%)</td>
<td>660/982 (67·2%)</td>
<td>0·89 (0·80–0·99)</td>
</tr>
<tr>
<td>No diabetes</td>
<td>1358/2502 (54·3%)</td>
<td>1393/2499 (55·7%)</td>
<td>0·96 (0·89–1·04)</td>
</tr>
<tr>
<td>Total cholesterol ≤ 4·87 mmol/L†</td>
<td>1033/1748 (59·1%)</td>
<td>1080/1719 (62·8%)</td>
<td>0·91 (0·84–0·99)</td>
</tr>
<tr>
<td>Total cholesterol &gt; 4·87 mmol/L†</td>
<td>929/1719 (54·0%)</td>
<td>957/1732 (55·3%)</td>
<td>0·96 (0·88–1·05)</td>
</tr>
</tbody>
</table>

We recorded no significant interactions for any subgroup analysis. PUFA=polyunsaturated fatty acids. NYHA=New York Heart Association. LVEF=left ventricular ejection fraction. * 95% CI was calculated with a Cox proportional hazards model. † Median value. Data for total cholesterol were available for 6918 patients (3467 n-3 PUFA, 3451 placebo).

The authors noted that neither blood pressure nor heart rate was significantly modified by the study treatment. Plasma concentrations of triglycerides decreased slightly from a median value of 1.42 mmol/L at baseline to 1.36 mmol/L after 1 year and 1.34 mmol/L after 3 years in omega-3 patients, but did not change in the placebo group. No differences were recorded in total, HDL or LDL cholesterol between patients in the omega-3 and placebo groups.

Permanent Discontinuation of Study Treatment

By the end of the study, 1,004 (29%) of patients in the treatment group and 1,029 (30%) in the placebo group were no longer taking the study drug (see Table 4). Reasons cited included adverse drug reactions (see below), patients’, practitioners’, or investigators’ decisions, and other (not specified).

The rate of patients who permanently discontinued taking the study drug due to adverse reactions were similar in both groups (102 [3%] vs. 104 [3%], p = 0.87); see Table 4). Adverse reactions included allergic reaction (not specified in the study), liver dysfunction, lipid abnormality, hepatocellular jaundice, subdural hematoma, muscle-related symptoms or serious adverse drug reaction (not specified in the study). In both groups, gastrointestinal disorders were the most frequent adverse reaction reported (96 [3%] omega-3 group vs. 92 [3%] placebo group).
Table 4 – Permanent Treatment Discontinuations

<table>
<thead>
<tr>
<th>Patients permanently discontinuing study treatment</th>
<th>n-3 PUFA (N=3494)</th>
<th>Placebo (N=3481)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADR</td>
<td>1004 (28.7%)</td>
<td>1029 (29.6%)</td>
<td>0.45</td>
</tr>
<tr>
<td>Patients’ decision</td>
<td>102</td>
<td>104</td>
<td></td>
</tr>
<tr>
<td>Practitioners’ decision</td>
<td>478</td>
<td>500</td>
<td></td>
</tr>
<tr>
<td>Investigators’ decision</td>
<td>33</td>
<td>41</td>
<td></td>
</tr>
<tr>
<td>Open label</td>
<td>266</td>
<td>257</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>11</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Patients permanently discontinuing study treatment due to ADR</td>
<td>102 (2.9%)</td>
<td>104 (3.0%)</td>
<td>0.87</td>
</tr>
<tr>
<td>Gastrointestinal disorder</td>
<td>96</td>
<td>92</td>
<td></td>
</tr>
<tr>
<td>Allergic reaction</td>
<td>3</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Liver dysfunction</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Lipid abnormality</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Hepatocellular jaundice</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Subdural haematoma</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Muscle-related symptoms</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Patients permanently discontinuing study treatment due to serious ADR</td>
<td>1 (&lt;0.1%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Subdural haematoma</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

PUFA=polyunsaturated fatty acids; ADR=adverse drug reaction.

**Conclusion:** In summary, the results for the unadjusted primary outcomes were not statistically significant. Had the adjusted results been used, the results would have been statistically significant. Since the appropriateness of the adjustment for select baseline variables remained unresolved, attention was directed to whether the results were clinically significant. The authors established a 15% relative risk reduction in the mortality rate as their threshold for a clinically meaningful result. The unadjusted lower end of the 95% confidence interval reached a HR of 0.85, indicating that a clinically significant effect could not be ruled out. At the same time, since the upper end of the CI extends below the threshold of meaningful clinical benefit, no definite conclusions can be drawn.

The increased incidence of stroke with omega-3 supplementation was not statistically significant for both the adjusted and unadjusted results. Looking at clinical significance, given the width of the confidence intervals that extend from a clinically meaningful reduction in stroke at one end to a clinically relevant increase in stroke risk at the other, no definite conclusions can be drawn about the potential benefit or harm of omega-3 supplementation on the risk of stroke.
For these reasons, this study provides inconclusive and, therefore, insufficient, evidence that omega-3 supplementation results in improved health outcomes for patients with heart failure with an ejection fraction less than 40%. Despite the lack of direct, statistically significant evidence, the GDT agreed to recommend the use of omega-3 supplements as an option for patients with heart failure with an ejection fraction less than 40%. The modest benefits identified in this trial warrant replication of the study.

**Omega-3 Dosing**

While studies using various dosages have demonstrated the effectiveness of omega-3 supplementation, there are no head-to-head trials comparing different formulations or doses of omega-3 supplementation in patients with heart failure. Despite the lack of direct evidence, the GDT felt it was clinically important to recommend a specific dose. Therefore, on a consensus basis, the GDT decided to recommend the dose shown to be minimally effective in the GISSI-HF trial (i.e., 1g of omega-3 supplement per day).

No recommendation was made for a specific formulation. The GDT determined that, based on the body of evidence for omega-3 supplements, the precise formulation does not appear to significantly impact its clinical effectiveness. In addition, there remains a lack of sufficient industry standardization for purity and composition of these supplements.
## Appendix A: Criteria for Grading the Evidence

### Label and Language of Recommendations

<table>
<thead>
<tr>
<th>RECOMMENDATION LABEL</th>
<th>RECOMMENDATION STATEMENT*</th>
<th>EVIDENCE BASE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence-Based, A</td>
<td>The GDT strongly recommends the intervention.</td>
<td>The intervention improves important health outcomes, based on good evidence, and the Guideline Development Team (GDT) concludes that benefits substantially outweigh harms and costs.</td>
</tr>
<tr>
<td>Evidence-Based, B</td>
<td>The GDT recommends the intervention.</td>
<td>The GDT concludes that the intervention improves important health outcomes, based on 1) good evidence that benefits outweigh harms and costs; or 2) fair evidence that benefits substantially outweigh harms and costs.</td>
</tr>
<tr>
<td>Evidence-Based, C</td>
<td>The GDT makes no recommendation for or against the intervention.†</td>
<td>Evidence is sufficient to determine the benefits, harms, and costs of an intervention, and there is at least fair evidence that the intervention improves important health outcomes. But the GDT concludes that the balance of the benefits, harms, and costs is too close to justify a general recommendation.</td>
</tr>
<tr>
<td>Evidence-Based, D</td>
<td>The GDT recommends against the intervention.</td>
<td>The GDT finds at least fair evidence that the intervention is ineffective, or that harms or costs outweigh benefits.</td>
</tr>
<tr>
<td>Evidence-Based, I</td>
<td>The GDT makes no recommendation for or against the intervention.†</td>
<td>The GDT concludes that evidence that the intervention is effective is lacking, of poor quality, or conflicting and the balance of benefits, harms, and costs cannot be determined.</td>
</tr>
</tbody>
</table>

### Consensus-Based Recommendations

<table>
<thead>
<tr>
<th>Consensus-Based</th>
<th>The GDT recommends the intervention.</th>
<th>The recommendation is based on the consensus of the GDT, typically in the setting of insufficient evidence.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consensus-Based</td>
<td>The GDT has determined that the intervention is an option.</td>
<td>The recommendation is based on the consensus of the GDT, typically in the setting of insufficient evidence.</td>
</tr>
<tr>
<td>Consensus-Based</td>
<td>The GDT recommends against the intervention.</td>
<td>The recommendation is based on the consensus of the GDT, typically in the setting of insufficient evidence.</td>
</tr>
</tbody>
</table>

Note that most consensus-based recommendations will have evidence grade "Insufficient." For the rare consensus-based recommendations which have "Good" or "Fair" evidence, the evidence must support a different recommendation, because if the evidence were good or fair, the recommendation would usually be evidence-based. In this kind of consensus-based recommendation the evidence label should point this out, e.g., "Good, supporting a different recommendation."

* All statements specify the population for which the recommendation is intended.
† At the discretion of the GDT, the recommendation may use the language, "option," but must list all the equivalent options.
<table>
<thead>
<tr>
<th>Level/Grade</th>
<th>Therapy/Prevention/Screening</th>
<th>Diagnosis</th>
<th>Prognosis/Etiology</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Grade GOOD</strong></td>
<td><strong>Type and number of studies</strong>&lt;br&gt;- At least one well-designed and conducted systematic review (SR)/meta-analysis (MA) (consider heterogeneity) of RCTs&lt;br&gt;- Two or more well-designed and conducted RCTs with narrow confidence intervals&lt;br&gt;- One well-designed and conducted multi-center RCT with narrow confidence intervals</td>
<td><strong>Type and number of studies</strong>&lt;br&gt;- At least one well-designed and conducted SRMA (consider heterogeneity) of cross-sectional studies using independent gold standard&lt;br&gt;- Two or more well-designed and conducted cross-sectional studies using an independent gold standard</td>
<td><strong>Type and number of studies</strong>&lt;br&gt;- At least one well-designed and conducted SRMA (consider heterogeneity) of prospective cohort studies&lt;br&gt;- Two or more well-designed and conducted prospective cohort studies</td>
</tr>
<tr>
<td></td>
<td><strong>Quality</strong>&lt;br&gt;- Low risk of bias&lt;br&gt;- Adequate sample size and power&lt;br&gt;- No major methodological concerns</td>
<td><strong>Quality</strong>&lt;br&gt;- Low risk of (verification) bias&lt;br&gt;- Independent gold standard&lt;br&gt;- No major methodological concerns</td>
<td><strong>Quality</strong>&lt;br&gt;- Low risk of bias&lt;br&gt;- Acceptable loss to follow-up (&lt; 20%)&lt;br&gt;- No major methodological concerns</td>
</tr>
<tr>
<td></td>
<td><strong>Consistency</strong>&lt;br&gt;- For SRMA, no major conflict in results (consider heterogeneity). If significant heterogeneity exists, drop to Poor&lt;br&gt;- For individual RCTs, no major conflict in results&lt;br&gt;- If major conflicts do exist, drop to &quot;Inadequate&quot;</td>
<td><strong>Consistency</strong>&lt;br&gt;- For SRMA, no major conflict in results (consider heterogeneity)&lt;br&gt;- For individual studies, consistent diagnostic accuracy</td>
<td><strong>Consistency</strong>&lt;br&gt;- For SRMA, no major conflict in results (consider heterogeneity)&lt;br&gt;- For individual studies, consistent diagnostic accuracy</td>
</tr>
<tr>
<td></td>
<td><strong>Relevance</strong>&lt;br&gt;- No compelling reason not to generalize published work to the target KP population</td>
<td><strong>Relevance</strong>&lt;br&gt;- No compelling reason not to generalize published work to the target KP population</td>
<td><strong>Relevance</strong>&lt;br&gt;- No compelling reason not to generalize published work to the target KP population</td>
</tr>
<tr>
<td><strong>Grade FAIR</strong></td>
<td><strong>Type and number of studies</strong>&lt;br&gt;- Single well-designed and conducted RCT with narrow confidence intervals&lt;br&gt;- Two or more RCTs of lower quality&lt;br&gt;- Well-designed and conducted SRMA of cohort studies (consider heterogeneity)</td>
<td><strong>Type and number of studies</strong>&lt;br&gt;- Single well-designed and conducted cross-sectional study&lt;br&gt;- Two or more cross-sectional studies of lower quality&lt;br&gt;- Well-designed and conducted SRMA of lower quality studies</td>
<td><strong>Type and number of studies</strong>&lt;br&gt;- Single well-designed and conducted prospective cohort study&lt;br&gt;- Two or more prospective cohort studies of lower quality&lt;br&gt;- Well-designed and conducted SRMA (consider heterogeneity) of either retrospective cohort studies, case control or untreated control arms in RCTs</td>
</tr>
<tr>
<td></td>
<td><strong>Quality</strong>&lt;br&gt;- Minor methodological concerns</td>
<td><strong>Quality</strong>&lt;br&gt;- Minor methodological concerns&lt;br&gt;- Independent gold standard</td>
<td><strong>Quality</strong>&lt;br&gt;- Minor methodological concerns&lt;br&gt;- Independent gold standard</td>
</tr>
<tr>
<td></td>
<td><strong>Consistency</strong>&lt;br&gt;- For SRMA, no major conflict in results (consider heterogeneity)&lt;br&gt;- For individual studies, no major conflict in results&lt;br&gt;- If major conflicts do exist, drop to &quot;Inadequate&quot;</td>
<td><strong>Consistency</strong>&lt;br&gt;- For SRMA, no major conflict in results (consider heterogeneity)&lt;br&gt;- For individual studies, no major conflict in results</td>
<td><strong>Consistency</strong>&lt;br&gt;- For SRMA, no major conflict in results (consider heterogeneity)&lt;br&gt;- For individual studies, no major conflict in results</td>
</tr>
<tr>
<td></td>
<td><strong>Relevance</strong>&lt;br&gt;- No compelling reason not to generalize published work to the target KP population</td>
<td><strong>Relevance</strong>&lt;br&gt;- No compelling reason not to generalize published work to the target KP population</td>
<td><strong>Relevance</strong>&lt;br&gt;- No compelling reason not to generalize published work to the target KP population</td>
</tr>
<tr>
<td><strong>Grade INSUFFICIENT</strong></td>
<td><strong>Type and number of studies</strong>&lt;br&gt;- Single RCT of lower quality or insufficient size&lt;br&gt;- Cohort study</td>
<td><strong>Type and number of studies</strong>&lt;br&gt;- Single cross-sectional study of lower quality&lt;br&gt;- Case-control study</td>
<td><strong>Type and number of studies</strong>&lt;br&gt;- Single prospective cohort study of lower quality&lt;br&gt;- Retrospective cohort study&lt;br&gt;- Untreated control arm of RCT&lt;br&gt;- Case series</td>
</tr>
<tr>
<td></td>
<td><strong>Quality</strong>&lt;br&gt;- Major methodological concerns (i.e., lack of concealed allocation, inadequate blinding, no ITT analysis)</td>
<td><strong>Quality</strong>&lt;br&gt;- Major methodological concerns (non-consecutive, poor or non-independent gold standard)</td>
<td><strong>Quality</strong>&lt;br&gt;- Major design or methodological concerns (sampling bias, high dropout, non-blinded outcome assessment, lack of adjustment for confounders)</td>
</tr>
<tr>
<td></td>
<td><strong>Consistency</strong>&lt;br&gt;- Studies that are well-designed and conducted (Good or Fair) but with major conflict in results&lt;br&gt;- SRMA with major conflict in results (consider heterogeneity)</td>
<td><strong>Consistency</strong>&lt;br&gt;- Studies that are well-designed and conducted (Good or Fair) but with major conflict in results</td>
<td><strong>Consistency</strong>&lt;br&gt;- Studies that are well-designed and conducted (Good or Fair) but with major conflict in results</td>
</tr>
<tr>
<td></td>
<td><strong>Relevance</strong>&lt;br&gt;- Compelling reasons why the results do not apply to the target KP population</td>
<td><strong>Relevance</strong>&lt;br&gt;- Compelling reasons why the results do not apply to the target KP population</td>
<td><strong>Relevance</strong>&lt;br&gt;- Compelling reasons why the results do not apply to the target KP population</td>
</tr>
</tbody>
</table>

*Evidence is graded with respect to the degree it supports the specific clinical recommendation. For example, there may be good evidence that Drug A and Drug B are effective for Condition X, but no evidence that Drug A is more effective than Drug B. If the recommendation is to use either Drug A or Drug B, the evidence is good. If the recommendation is to use Drug A in preference to Drug B, the evidence is insufficient.*
Appendix B: Supporting Documentation

1. Sleep Apnea in Heart Failure* Patients

Screening for Sleep Apnea in Heart Failure Patients

Problem Formulation

<table>
<thead>
<tr>
<th>Clinical Question:</th>
<th>Does screening for sleep apnea in heart failure patients improve outcomes?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population:</td>
<td>Adults with heart failure</td>
</tr>
<tr>
<td>Health Intervention:</td>
<td>Screening for sleep apnea</td>
</tr>
<tr>
<td>Most Important Health Outcomes Associated with the Intervention:</td>
<td>♦ Mortality due to cardiac causes ♦ All-cause mortality ♦ Hospitalization ♦ NYHA Class or equivalent</td>
</tr>
</tbody>
</table>

Treating Sleep Apnea in Heart Failure Patients

Problem Formulation

<table>
<thead>
<tr>
<th>Clinical Question:</th>
<th>Does treating sleep apnea in heart failure patients improve outcomes?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population:</td>
<td>Adults with heart failure and sleep apnea</td>
</tr>
<tr>
<td>Health Intervention:</td>
<td>Continuous positive airway pressure (CPAP)</td>
</tr>
<tr>
<td>Most Important Health Outcomes Associated with the Intervention:</td>
<td>♦ Mortality due to cardiac causes ♦ All-cause mortality ♦ Hospitalization ♦ NYHA Class or equivalent</td>
</tr>
</tbody>
</table>

* In this guideline, the term “heart failure” is used to refer to patients who have either heart failure with left ventricular systolic dysfunction (LVSD) or heart failure with preserved ejection fraction, unless otherwise distinguished.
## Search Strategy

<table>
<thead>
<tr>
<th>Database:</th>
<th>Search Terms:</th>
<th>Article Type and Other Limits:</th>
<th>Search Date</th>
<th>No. Included / Total Retrieved†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cochrane Systemic Reviews</td>
<td>“heart failure” AND “sleep apnea”</td>
<td>Clinical Trials</td>
<td>1966 – Nov 2007</td>
<td>0/0</td>
</tr>
<tr>
<td>Cochrane Systemic Reviews</td>
<td>“heart failure” AND “Cheyne Stokes Respiration”</td>
<td>Clinical Trials</td>
<td>1966 – Nov 2007</td>
<td>0/0</td>
</tr>
<tr>
<td>PubMed</td>
<td>(sleep apnoea[Text Word] OR (&quot;sleep apnea syndromes&quot;[TIAB] NOT Medline[SB]) OR &quot;sleep apnea syndromes&quot;[MeSH Terms] OR sleep apnea[Text Word]) AND ((&quot;heart&quot;[MeSH Terms] OR heart[Text Word]) AND failure[All Fields])</td>
<td>Human, English, All Adult: 19+ years, RCTs, meta-analysis, only items with abstracts</td>
<td>1966 – Nov 2007</td>
<td>3†/29</td>
</tr>
<tr>
<td>PubMed</td>
<td>Cheyne[All Fields] AND Stokes[All Fields]</td>
<td>Human, English, All Adult: 19+ years, RCTs, meta-analysis, only items with abstracts</td>
<td>1966 – Nov 2007</td>
<td>3†/17</td>
</tr>
<tr>
<td>PubMed</td>
<td>&quot;Mass Screening&quot;[Mesh] AND &quot;Sleep Apnea Syndromes&quot;[Mesh] AND (&quot;heart&quot;[MeSH Terms] OR heart[Text Word]) AND failure[All Fields])</td>
<td>Human, English, All Adult: 19+ years, RCTs, meta-analysis, only items with abstracts</td>
<td>1966 – May 6, 2008</td>
<td>0/1</td>
</tr>
</tbody>
</table>

* Note: “No. Included” refers to studies that are relevant to the problem formulation and, therefore, are included in this analysis of the evidence. “Total Retrieved” refers to the number of studies retrieved in the search, regardless of relevance. Because individual studies can be captured in multiple databases, they may be counted more than once in the number included.

† The same publications.
## Evidence Tables

**RCTs of Treatment of Sleep Apnea in Patients with Heart Failure**

### Table 1.1: Bradley (2005) CANPAP trial

<table>
<thead>
<tr>
<th>N</th>
<th>Sample Ages (Mean ± SD yr)</th>
<th>Male (%)</th>
<th>Sleep Time (min)</th>
<th>AHI (Mean ± SD no./hr)</th>
<th>Ejection Fraction (Mean ± SD %)</th>
<th>NYHA Class (%)</th>
<th>Follo w-Up Time (Mean n)</th>
<th>Change in AHI</th>
<th>Change in NE</th>
<th>Change in Nocturnal O₂ Saturation</th>
<th>Change in LVEF</th>
<th>Change in 6-min Walking Distance</th>
<th>Study Qualit y† Biase s*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Control:</strong> 130</td>
<td>63.5 ± 9.8</td>
<td>95</td>
<td>304 ± 84</td>
<td>40 ± 17</td>
<td>24.2 ± 7.6</td>
<td>66</td>
<td>34</td>
<td>2 years</td>
<td>32</td>
<td>0.54</td>
<td>–2 ± 18</td>
<td>&lt;0.001</td>
<td>–1.03 ± 1.84</td>
</tr>
<tr>
<td><strong>CPAP:</strong> 128</td>
<td>63.2 ± 9.1</td>
<td>98</td>
<td>308 ± 82</td>
<td>40 ± 15</td>
<td>24.8 ± 7.9</td>
<td>67</td>
<td>33</td>
<td>2 years</td>
<td>32</td>
<td>0.54</td>
<td>–21 ± 16</td>
<td>0.02</td>
<td>0.02 ± 0.99</td>
</tr>
</tbody>
</table>

AHI = apnea-hypopnea index  
CI = confidence interval  
CPAP = continuous positive airways pressure  
CSA = Cheyne-Stokes respiration  
CSR = central sleep apnea  
LVEF = left ventricular ejection fraction  
NE = norepinephrine  
NR = not reported  
NS = not significant  
NYHA = New York Heart Association  
RR = relative risk reduction  
† Study quality measured by Jadad Scoring System (1 to 5 = low to high)  
*Biases: N: none; 1: sample attrition >15%; 2: sample selection bias; 3: detection bias (e.g., measurement error, ITT analysis, power); 4: study procedure biases (e.g., blinding, randomization); 5: incomplete data presentation
Table 1.2: Arzt (2007)

<table>
<thead>
<tr>
<th>N</th>
<th>Sample Ages (Mean ± SD yr)</th>
<th>% Male</th>
<th>NYHA (%)</th>
<th>LVEF (Mean ± SD %)</th>
<th>Total Sleep Time (Mean ± SD min)</th>
<th>AHI (Mean ± SD no./hr)</th>
<th>Central Apnea/ Hypopnea (Mean ± SD %)</th>
<th>Mean SaO2 (Mean ± SD %)</th>
<th>Primary Outcome (after 2 years)</th>
<th>LVEF (% Change after 3 mo)</th>
<th>Study Quality †</th>
<th>Biases*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control: 110</td>
<td>63.6 ± 10</td>
<td>95</td>
<td>II</td>
<td>24.2 ± 7.5</td>
<td>308 ± 88</td>
<td>38 ± 16</td>
<td>93.0 ± 3.2</td>
<td>23</td>
<td>0.016</td>
<td>0.4 (-0.6-1.5)</td>
<td>3</td>
<td>4, 5</td>
</tr>
<tr>
<td>CPAP-CSA- suppressed: 57</td>
<td>60.3 ± 9.1</td>
<td>100</td>
<td>III</td>
<td>25.6 ± 8.1</td>
<td>320 ± 77</td>
<td>34 ± 13</td>
<td>93.4 ± 3.6</td>
<td>5</td>
<td>3.6 (2.1-5.1)</td>
<td>3.6 (2.1-5.1)</td>
<td>3</td>
<td>4, 5</td>
</tr>
<tr>
<td>CPAP-CSA- unsuppressed: 43</td>
<td>65.2 ± 9.2a</td>
<td>93</td>
<td>IV</td>
<td>23.7 ± 7.2</td>
<td>315 ± 72</td>
<td>47 ± 14b</td>
<td>93.2 ± 3.5</td>
<td>30</td>
<td>0.3 (-1.0-1.6)</td>
<td>0.3 (-1.0-1.6)</td>
<td>3</td>
<td>4, 5</td>
</tr>
</tbody>
</table>

Post hoc analysis of CANPAP trial

a p ≤ 0.05 compared with CPAP-CSA-suppressed group
b p ≤ 0.05 compared with control and CPAP-CSA-suppressed group
c p ≤ 0.05 compared with baseline and the CPAP-CSA-suppressed and -unsuppressed groups

AHI = apnea-hypopnea index
CI = confidence interval
CPAP = continuous positive airways pressure
CSA = Cheyne-Stokes respiration
CSR = central sleep apnea
LVEF = left ventricular ejection fraction
NE = norepinephrine
NR = not reported
NS = not significant
NYHA = New York Heart Association
RR = relative risk reduction
† Study quality measured by Jadad Scoring System (1 to 5 = low to high)
*Biases: N: none; 1: sample attrition >15%; 2: sample selection bias; 3: detection bias (e.g., measurement error, ITT analysis, power); 4: study procedure biases (e.g., blinding, randomization); 5: incomplete data presentation
### Table 1.3: Sin (2000)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Follow-up Time (Mean yr)</th>
<th>Control CPAP</th>
<th>Baseline LVEF (Mean ± SD %)</th>
<th>Change in LVEF at 3 mo (p Value)</th>
<th>Death and Cardiac Transplantation (Event Rate, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>N</td>
<td>Sample Ages (Mean ± SD)</td>
<td>% Male</td>
<td>NYHA (≥III, %)</td>
</tr>
<tr>
<td>CSR-CSA</td>
<td>No CSR-CSA</td>
<td>CSR-CSA</td>
<td>No CSR-CSA</td>
<td>CSR-CSA</td>
<td>CSR-CSA</td>
</tr>
<tr>
<td>No</td>
<td>CSR-CSA</td>
<td>No CSR-CSA</td>
<td>Total</td>
<td>% Male</td>
<td>NYHA (≥III, %)</td>
</tr>
<tr>
<td>19.8 ± 9.0</td>
<td>23.6 ± 7.9</td>
<td>NS</td>
<td>NS</td>
<td>NS (0.71)</td>
<td>56</td>
</tr>
<tr>
<td>20.6 ± 11.3</td>
<td>22.8 ± 10.2</td>
<td>NS</td>
<td>NS</td>
<td>NS (0.12)</td>
<td>33</td>
</tr>
</tbody>
</table>

AHI = apnea-hypopnea index
CI = confidence interval
CPAP = continuous positive airways pressure
CSA = Cheyne-Stokes respiration
CSR = central sleep apnea
LVEF = left ventricular ejection fraction
NE = norepinephrine
NR = not reported
NS = not significant
NYHA = New York Heart Association
RR = relative risk reduction
† Study quality measured by Jadad Scoring System (1 to 5 = low to high)
*Biases: N: none; 1: sample attrition >15%; 2: sample selection bias; 3: detection bias (e.g., measurement error, ITT analysis, power); 4: study procedure biases (e.g., blinding, randomization); 5: incomplete data presentation
2. **Use of Statins in Heart Failure Patients without Documented Coronary Artery Disease**

**Problem Formulation**

<table>
<thead>
<tr>
<th>Clinical Question:</th>
<th>Should statins be given to heart failure patients without documented coronary artery disease (CAD)?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population:</td>
<td>Adults with heart failure without documented CAD</td>
</tr>
<tr>
<td>Health Intervention:</td>
<td>Usual care plus statin therapy</td>
</tr>
<tr>
<td>Comparison:</td>
<td>Usual care</td>
</tr>
<tr>
<td>Most Important Health Outcomes</td>
<td>♦ Mortality due to cardiac causes ♦ All-cause mortality ♦ Hospitalization ♦ NYHA Class or equivalent ♦ Cardiac events</td>
</tr>
</tbody>
</table>

**Search Strategy**

<table>
<thead>
<tr>
<th>Database:</th>
<th>Search Terms:</th>
<th>Article Type and Other Limits:</th>
<th>Search Date</th>
<th>No. Included / Total Retrieved</th>
</tr>
</thead>
<tbody>
<tr>
<td>PubMed</td>
<td>(&quot;hydroxymethylglutaryl-coa reductase inhibitors&quot;[TIAB] NOT Medline[SB]) OR &quot;hydroxymethylglutaryl-coa reductase inhibitors&quot;[MeSH Terms] OR &quot;hydroxymethylglutaryl-coa reductase inhibitors&quot;[Pharmacological Action] OR statins[Text Word]) AND (&quot;heart&quot;[MeSH Terms] OR heart[Text Word]) AND failure[All Fields])</td>
<td>Human; English; All Adult: 19+ years; RCTs, meta-analysis; only items with abstracts; including &gt;50 pts</td>
<td>1966 - 11/07</td>
<td>3/47</td>
</tr>
<tr>
<td>Database</td>
<td>Search Terms:</td>
<td>Article Type and Other Limits:</td>
<td>Search Date</td>
<td>No. Included / Total Retrieved</td>
</tr>
<tr>
<td>----------</td>
<td>--------------</td>
<td>-------------------------------</td>
<td>-------------</td>
<td>-----------------------------</td>
</tr>
<tr>
<td>PubMed</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

("hydroxymethylglutaryl-coa reductase inhibitors"[TIAB] NOT Medline[SB]) OR "hydroxymethylglutaryl-coa reductase inhibitors"[MeSH Terms] OR "hydroxymethylglutaryl-coa reductase inhibitors"[Pharmacological Action] OR statins[Text Word]) AND (nonischemic[All Fields] AND ("heart"[MeSH Terms] OR heart[Text Word]) AND failure[All Fields])) | Human; English; All Adult: 19+ years; RCTs, meta-analysis; only items with abstracts; including >50 pts | 1966 - 11/07 | 3/8 |
| PubMed   | 

("hydroxymethylglutaryl-coa reductase inhibitors"[TIAB] NOT Medline[SB]) OR "hydroxymethylglutaryl-coa reductase inhibitors"[MeSH Terms] OR "hydroxymethylglutaryl-coa reductase inhibitors"[Pharmacological Action] OR statins[Text Word]) AND (nonischemic[All Fields] AND ("heart"[MeSH Terms] OR heart[Text Word]) AND failure[All Fields])) | Human; English; All Adult: 19+ years; RCTs, meta-analysis; only items with abstracts; including >50 pts | 1966 - 11/07 | 2/8 |
| PubMed   | 

("hydroxymethylglutaryl-coa reductase inhibitors"[TIAB] NOT Medline[SB]) OR "hydroxymethylglutaryl-coa reductase inhibitors"[MeSH Terms] OR "hydroxymethylglutaryl-coa reductase inhibitors"[Pharmacological Action] OR statins[Text Word]) AND ("cardiomyopathy, dilated"[MeSH Terms] OR dilated cardiomyopathy[Text Word]) | Human; English; All Adult: 19+ years; RCTs, meta-analysis; only items with abstracts; including >50 pts | 1966 - 11/07 | 3/8 |
## Evidence Tables

### Randomized Trials of Statin Treatment of Heart Failure Patients without Documented CAD

#### Table 2.1: Node (2003) RCT

<table>
<thead>
<tr>
<th>N</th>
<th>Sample Ages (Mean ± SD yr)</th>
<th>% Female</th>
<th>Follow-up Time</th>
<th>NYHA (Mean ± SD)</th>
<th>LVEF (Mean ± SD)</th>
<th>Study Quality†</th>
<th>Biases*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simvastatin: 24</td>
<td>55 ± 3</td>
<td>35</td>
<td>14 weeks</td>
<td>2.39 ± 0.07</td>
<td>2.36 ± 0.07</td>
<td>4</td>
<td>3, 4</td>
</tr>
<tr>
<td>Placebo: 27</td>
<td>53 ± 4</td>
<td>28</td>
<td></td>
<td>2.04 ± 0.06</td>
<td>2.32 ± 0.05</td>
<td>0.01</td>
<td></td>
</tr>
</tbody>
</table>

**Comment:** Small study with short follow-up

#### Table 2.2: Wojnicz (2006) RCT

<table>
<thead>
<tr>
<th>N</th>
<th>Sample Ages (Mean ± SD yr)</th>
<th>% Female</th>
<th>Follow-up Time</th>
<th>NYHA Class II/III (n)</th>
<th>% LVEF</th>
<th>Primary Endpoint† (%)</th>
<th>p</th>
<th>Study Quality†</th>
<th>Biases*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin: 36</td>
<td>37 ± 11</td>
<td>22.2</td>
<td>6 months</td>
<td>26/10</td>
<td>27 ± 7</td>
<td>58.8</td>
<td>0.004</td>
<td>2</td>
<td>2, 3, 4</td>
</tr>
<tr>
<td>Ctrl: 38</td>
<td>39 ± 1.0</td>
<td>15.8</td>
<td></td>
<td>27/11</td>
<td>29 ± 7</td>
<td>24.3</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Comment:** Open-label, standard treatment-controlled, small study

†Increase of >5% in the absolute LVEF determined by radionuclide ventriculography and ≥2 selected criteria by echocardiography and a decrease in NYHA functional class

---

FU = follow-up
LVEF = left ventricular ejection fraction
LVEDD = left ventricular end-diastolic diameter
LVESD = left ventricular end-systolic diameter
NS = not significant
NYHA = New York Heart Association
RCT = randomized, controlled trial

†Study quality measured by Jadad Scoring System. (1 to 5 = low to high)
*Biases: N: none; 1: sample attrition >15%; 2: sample selection bias; 3: detection bias (e.g., measurement error, ITT analysis, power); 4: study procedure biases (e.g., blinding, randomization)
### Table 2.3: Sola (2005) RCT

<table>
<thead>
<tr>
<th>N</th>
<th>Sample Ages (Mean ± SD yr)</th>
<th>% Female</th>
<th>Ejection Fraction (Mean ± SD %)</th>
<th>NYHA class (%)</th>
<th>Follow-up Time</th>
<th>Primary Endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>LVEF</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>LVEDD</td>
<td>LVEDS</td>
<td>Study Quality†</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Biases*</td>
</tr>
<tr>
<td>Atorvastatin: 54</td>
<td>53.3 ± 6.2 54.1 ± 6.9</td>
<td>36 38</td>
<td>33 ± 5 33 ± 4 30 26</td>
<td>II I V</td>
<td>12 months</td>
<td>33 ± 5 33 ± 5</td>
</tr>
<tr>
<td>Placebo: 54</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Comment: Pilot study

### Table 2.4: Krum (2007) RCT

<table>
<thead>
<tr>
<th>N</th>
<th>Sample Ages (Mean ± SD yr)</th>
<th>Follow-up Time</th>
<th>% Female</th>
<th>Etiology (%)</th>
<th>NYHA Class II / III (%)</th>
<th>% LVEF (Mean ± SD)</th>
<th>% Δ LVEF (mean ± SD)</th>
<th>p</th>
<th>Study Quality†</th>
<th>Biases*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosuvastatin: 40</td>
<td>64 ±11.9 59.4 ±14.9</td>
<td>6 months</td>
<td>20 20</td>
<td>88.5 73.4</td>
<td>88/13 89/11</td>
<td>29.3 ±9.1 28.9 ±10.0</td>
<td>3.2 ±3.8 5.3 ±1.5</td>
<td>0.276</td>
<td>4 3</td>
<td></td>
</tr>
<tr>
<td>Placebo: 45</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Comment: Small study

FU = follow-up  
LVEF = left ventricular ejection fraction  
LVEDD = left ventricular end-diastolic diameter  
LVESD = left ventricular end-systolic diameter  
NS = not significant  
NYHA = New York Heart Association  
RCT = randomized, controlled trial

†Study quality measured by Jadad Scoring System. (1 to 5 = low to high)  
*Biases: N: none; 1: sample attrition >15%; 2: sample selection bias; 3: detection bias (e.g., measurement error, ITT analysis, power); 4: study procedure biases (e.g., blinding, randomization)
3. Use of Thiazolidinediones (TZDs)

Problem Formulation

<table>
<thead>
<tr>
<th>Clinical Question:</th>
<th>Should TZDs (thiazolidinediones) be avoided in heart failure patients who have diabetes?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population:</td>
<td>Adults with heart failure and diabetes</td>
</tr>
<tr>
<td>Health Intervention:</td>
<td>Initiating or stopping thiazolidinediones in patients with heart failure and diabetes who are already receiving standard treatment for heart failure and diabetes</td>
</tr>
<tr>
<td>Most Important Health Outcomes:</td>
<td>Mortality due to cardiac causes</td>
</tr>
<tr>
<td></td>
<td>All-cause mortality</td>
</tr>
</tbody>
</table>

Search Strategy

<table>
<thead>
<tr>
<th>Database:</th>
<th>Search Terms:</th>
<th>Article Type and Other Limits:</th>
<th>Search Date:</th>
<th>No. Included / Total Retrieved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cochrane Systemic Reviews</td>
<td>“heart failure” AND “glitazones”</td>
<td>Clinical Trials</td>
<td>1966-11/07</td>
<td>0/0</td>
</tr>
<tr>
<td>Cochrane Systemic Reviews</td>
<td>“heart failure” AND “thiazolidinediones”</td>
<td>Clinical Trials</td>
<td>1966-11/07</td>
<td>2*/5</td>
</tr>
<tr>
<td>PubMed</td>
<td>(“heart”[MeSH Terms] OR heart[Text Word]) AND failure[All Fields]) AND (“thiazolidinediones”[TIAB] NOT Medline[SB]) OR &quot;thiazolidinediones”[MeSH Terms] OR glitazones[Text Word])</td>
<td>Human, English, All Adult: 19+ years, RCTs, meta-analysis, only items with abstracts</td>
<td>1966-11/07</td>
<td>3*/14</td>
</tr>
</tbody>
</table>

In addition, the databases of the American Heart Association and American Diabetes Association were searched to identify relevant publications or statements that were missed by the search strategy.

* Studies overlap.
### Evidence Tables

**Trials of Treatment of Heart Failure Patients with Glitazones**

**Table 3.1: Dargie (2007)**

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Sample Ages (Mean ± SD yr)</th>
<th>% Female</th>
<th>Follow-up Time (Mean)</th>
<th>NYHA Class (%)</th>
<th>Worsening CHF</th>
<th>New or Worsening Edema</th>
<th>Increase in CHF Medication</th>
<th>All-Cause Mortality or Worsening CHF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosiglitazone: 108</td>
<td>15.7</td>
<td>64.3 ± 8.8</td>
<td>20.9</td>
<td>52 wk</td>
<td>35.2 43.6</td>
<td>64.8 56.4</td>
<td>4.5 3.5</td>
<td>25.5 8.8</td>
<td>0.005 0.037 10.6 7.5 1.283 1.283 0.513 – 3.209 0.59</td>
</tr>
<tr>
<td>Placebo: 110</td>
<td></td>
<td>63.9 ± 8.6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Mean ± SD)</td>
<td></td>
<td></td>
<td>(Mean ± SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Mean ± SD)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study Quality† Biases*</th>
<th>Baseline</th>
<th>Wk 52</th>
<th>AMD</th>
<th>95% CI</th>
<th>p</th>
<th>Baseline</th>
<th>Week 52</th>
<th>Adjusted Mean Difference</th>
<th>95% CI</th>
<th>p</th>
<th>Study Quality† Biases*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>7.8 ± 1.3</td>
<td>7.3 ± 1.2</td>
<td>0.65</td>
<td>-0.94 – -0.37</td>
<td>&lt;0.0001</td>
<td>34.1 ± 7.4</td>
<td>36.3 ± 7.5</td>
<td>1.42</td>
<td>-0.21 – 3.04</td>
<td>0.09</td>
<td>4</td>
</tr>
</tbody>
</table>
**Table 3.2: Ogino (2002)**

<table>
<thead>
<tr>
<th>N</th>
<th>Sample Ages (Mean ± SD yr)</th>
<th>Female</th>
<th>NYHA Class (%)</th>
<th>Follow-up Time (Mean)</th>
<th>Placebo</th>
<th>Troglitazone</th>
<th>Placebo</th>
<th>Troglitazone</th>
<th>Placebo</th>
<th>Troglitazone</th>
<th>Study Quality†</th>
<th>Biases*</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>51.6 ± 4.7</td>
<td>1</td>
<td>6, 1</td>
<td>1, 2, 3, and 4 hours</td>
<td>NR</td>
<td>37.1 ± 1.9</td>
<td>NR</td>
<td>62.6 ± 6.3</td>
<td>62.9 ± 6.9</td>
<td>69.5 ± 6.0a</td>
<td>2</td>
<td>3.4</td>
</tr>
</tbody>
</table>

Comment: Very small study assessing only acute effects

<table>
<thead>
<tr>
<th>E/A Ratio</th>
<th>Plasma Catecholamines: Epinephrine/Norepinephrine (pg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>Troglitazone</td>
</tr>
<tr>
<td>Baseline</td>
<td>2 hr</td>
</tr>
<tr>
<td>NR</td>
<td>0.96 ± 0.08</td>
</tr>
<tr>
<td>0.99 ± 0.09</td>
<td>1.12 ± 0.11a</td>
</tr>
</tbody>
</table>
### Table 3.3: Meta-Analyses

<table>
<thead>
<tr>
<th>Name/Study</th>
<th>Study Population</th>
<th>Results</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lago (2007)</td>
<td>Randomized, double-blind, controlled trials of TZDs (rosiglitazone or pioglitazone)</td>
<td>Primary endpoints</td>
<td>In 20,191 patients with prediabetes or type 2 diabetes in seven randomized trials, the risk of CHF was higher in patients given TZDs than in controls. The risk of cardiovascular death was the same in both groups.</td>
</tr>
<tr>
<td># studies found: 661 # studies included: 7</td>
<td>4 trials: rosiglitazone vs placebo 1 trial: rosiglitazone vs metformin and sulfonylurea 1 trial: rosiglitazone vs glimepiride 1 trial: pioglitazone vs glibenclamide</td>
<td>CHF: 2.3% in treatment group and 1.4% in control group (RR 1.72, 95% CI: 1.21–2.42, p=0.002)</td>
<td>Biases:</td>
</tr>
<tr>
<td>Databases: Embase, Medline, Database of Abstracts of Reviews of Effects (DARE), Cochrane Library</td>
<td>Pooled results of each of the trials showed that an increased risk of CHF was associated with both rosiglitazone and pioglitazone</td>
<td>Cardiovascular death: 0.7% in both treatment and control groups (RR 0.93, 95% CI: 0.67–1.29, p=0.68)</td>
<td>Definitions of heart failure differed between included trials</td>
</tr>
<tr>
<td>Time frame: January 1998 – March 2007</td>
<td>Sequential exclusion of each trial from the analysis did not affect the overall relative risks.</td>
<td>Insufficient follow-up durations</td>
<td></td>
</tr>
<tr>
<td>DerSimonian and Laird random-effect models were used to obtain pooled relative risks (risk ratios, RR) and associated 95% CIs for outcomes with an intention-to-treat approach as a measure of association. Natural log transformations were done on RR calculations. A fixed-effects model was used for all analyses. Where heterogeneity was suggested, random-effects model was applied and indicated.</td>
<td>Results showed no heterogeneity of effects across studies (I²=22.8%, p=0.26), which indicated a class effect for TZDs.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

For use within Kaiser Permanente only. 01/10
4. Use of Erythropoietin Analogs to Treat Anemia

Problem Formulation

<table>
<thead>
<tr>
<th>Clinical Question:</th>
<th>Should erythropoietin analogs be used to treat anemia in heart failure patients?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population:</td>
<td>Adults with heart failure and anemia</td>
</tr>
<tr>
<td>Health Intervention:</td>
<td>Erythropoietin analogs added to standard treatment</td>
</tr>
</tbody>
</table>
| Most Important Health Outcomes: | Mortality due to cardiac causes  
|                      | All-cause mortality  
|                      | Hospitalization  
|                      | NYHA Class or equivalent |

Search Strategy

<table>
<thead>
<tr>
<th>Database:</th>
<th>Search Terms:</th>
<th>Article Type and Other Limits:</th>
<th>Search Date</th>
<th>No. Included / Total Retrieved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cochrane Systemic Reviews</td>
<td>“Anemia” and “EPO” and “heart failure”</td>
<td>Clinical Trials</td>
<td>1966-11/07</td>
<td>0/0</td>
</tr>
<tr>
<td>PubMed</td>
<td>(EPO[All Fields] AND (&quot;heart&quot;[MeSH Terms] OR heart[Text Word]) AND failure[All Fields]))</td>
<td>Human, English, All Adult: 19+ years, Clinical Trials, RCTs, meta-analysis, only items with abstracts</td>
<td>1966-11/07</td>
<td>3/16*</td>
</tr>
</tbody>
</table>

* Two new studies.
**RCTs on EPO Treatment of Anemia in Patients with Heart Failure**

### Table 4.1: Silverberg (2001)

<table>
<thead>
<tr>
<th>N</th>
<th>Sample Ages (Mean ± SD yr)</th>
<th>Male</th>
<th>Follow-up Time (Mean ± SD)</th>
<th>Hb (Mean ± SD g%)</th>
<th>NYHA class (Mean ± SD)</th>
<th>Hospital Days (Mean ± SD)</th>
<th>Ejection Fraction (Mean ± SD)</th>
<th>IV Furosemide (Mean ± SD mg/wk)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control: 16</td>
<td>72.2 ± 9.9</td>
<td>75.3 ± 14.6</td>
<td>12/16 11/16</td>
<td>8.2 ± 2.6 mo</td>
<td>10.9 ± 0.8</td>
<td>10.3 ± 1.2</td>
<td>10.8 ± 0.8</td>
<td>12.9 ± 11a</td>
</tr>
<tr>
<td>EPO &amp; Fe: 16</td>
<td>75.3 ± 14.6</td>
<td>12/16 11/16</td>
<td>8.2 ± 2.6 mo</td>
<td>10.9 ± 0.8</td>
<td>10.3 ± 1.2</td>
<td>10.8 ± 0.8</td>
<td>12.9 ± 11a</td>
<td>3.5 ± 0.7</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
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<td></td>
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<td></td>
</tr>
</tbody>
</table>

*p< 0.05 for interaction time x group, measured by analysis of variance with repeated measures over time, comparing the control versus treatment groups

*p< 0.05 compared with baseline

<table>
<thead>
<tr>
<th>Oral Furosemide (Mean ± SD mg/day)</th>
<th>Study Quality</th>
<th>Biases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before</td>
<td>After</td>
<td>2</td>
</tr>
<tr>
<td>136.2 ± 86.1</td>
<td>175.0 ± 113.0</td>
<td>4</td>
</tr>
<tr>
<td>132.2 ± 38.9</td>
<td>64.4 ± 39.1</td>
<td></td>
</tr>
</tbody>
</table>

EPO & Fe = erythropoietin and iron

Hb = hemoglobin

LVDD = left ventricular diastolic diameter

LVEF = left ventricular ejection fraction

LV systolic diameter = left ventricular systolic diameter

NYHA = New York Heart Association

V. O$2$ = peak oxygen consumption

† Study quality measured by Jadad Scoring System. (1 to 5 = low to high)

*Biases: N: none; 1: sample attrition >15%; 2: sample selection bias; 3: detection bias (e.g., measurement error, ITT analysis, power); 4: study procedure biases (e.g., blinding, randomization); 5: incomplete data presentation
### Table 4.2: Palazzuoli (2006)

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Sample Ages (Mean ± SD yr)</th>
<th>Male/Female Ratio</th>
<th>Follow-up Time (Mean ± SD)</th>
<th>LVEF (Mean ± SD %)</th>
<th>NYHA Class (Mean ± SD)</th>
<th>Hb (Mean ± SD g/dl)</th>
<th>Distance Walked (Mean ± SD m)</th>
<th>V.O₂ (Mean ± SD ml/kg per minute)</th>
<th>Study Quality†</th>
<th>Biases*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control: 20 EPO &amp; Fe: 18</td>
<td>75 ± 6</td>
<td>10/8</td>
<td>3.5 ± 0.8 mo</td>
<td>28 ± 6</td>
<td>3.4 ± 0.6</td>
<td>3.6 ± 0.4</td>
<td>10.6 ± 0.7</td>
<td>285 ± 68</td>
<td>12.5 ± 3.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EPO &amp; Fe = erythropoietin and iron</td>
<td></td>
<td></td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>Hb = hemoglobin</td>
<td></td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>LVDD = left ventricular diastolic diameter</td>
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<tr>
<td>LVEF = left ventricular ejection fraction</td>
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<tr>
<td>LV systolic diameter = left ventricular systolic diameter</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>NYHA = New York Heart Association</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>V. O₂ = peak oxygen consumption</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study quality measured by Jadad Scoring System. (1 to 5 = low to high)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biases: N: none; 1: sample attrition &gt;15%; 2: sample selection bias; 3: detection bias (e.g., measurement error, ITT analysis, power); 4: study procedure biases (e.g., blinding, randomization); 5: incomplete data presentation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* p< 0.05 (intergroup and intragroup)
### Table 4.3: Palazzuoli (2007)

<table>
<thead>
<tr>
<th>N</th>
<th>Sample Ages (Mean ± SD yr)</th>
<th>Male/Female Ratio</th>
<th>Follow-up Time (Mean ± SD)</th>
<th>NYHA Class (Mean ± SD)</th>
<th>Hb (Mean ± SD g/dl)</th>
<th>Creatinine (Mean ± SD mg/dl)</th>
<th>LVEF (Mean ± SD %)</th>
<th>LVDD (Mean ± SD mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Baseline</td>
<td>12 mo</td>
<td>Baseline</td>
<td>12 mo</td>
<td>Baseline</td>
</tr>
<tr>
<td>Control: 25</td>
<td>72 ± 6</td>
<td>16/9</td>
<td>4 and 12 mo</td>
<td>3.4 ± 0.4</td>
<td>3.5 ± 0.5</td>
<td>10.6 ± 0.7</td>
<td>10.5 ± 0.6</td>
<td>2.4 ± 0.6</td>
</tr>
<tr>
<td>EPO &amp; Fe: 26</td>
<td>74 ± 6</td>
<td>15/11</td>
<td></td>
<td>3.3 ± 0.6</td>
<td>2.7 ± 0.5</td>
<td>10.4 ± 0.6</td>
<td>12.4 ± 0.8</td>
<td>2.5 ± 3</td>
</tr>
</tbody>
</table>

*a p<0.05 compared with baseline
b p<0.05 intergroup comparison

<table>
<thead>
<tr>
<th>LV Systolic Diameter (Mean ± SD mm)</th>
<th>Study Quality</th>
<th>Biases*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline 50.7 ± 4.9 49.5 ± 4.8</td>
<td>5</td>
<td>3,4</td>
</tr>
<tr>
<td>12 mo 51.6 ± 5.1 46 ± 4.7</td>
<td>5</td>
<td>3,4</td>
</tr>
</tbody>
</table>

EPO & Fe = erythropoietin and iron
Hb = hemoglobin
LVDD = left ventricular diastolic diameter
LVEF = left ventricular ejection fraction
LV systolic diameter = left ventricular systolic diameter
NYHA = New York Heart Association
V. O = peak oxygen consumption
† Study quality measured by Jadad Scoring System. (1 to 5 = low to high)
*Biases: N: none; 1: sample attrition >15%; 2: sample selection bias; 3: detection bias (e.g., measurement error, ITT analysis, power); 4: study procedure biases (e.g., blinding, randomization); 5: incomplete data presentation
5. Use of Diuretics

Problem Formulation

| Clinical Question: | • Should diuretics be used to manage hypervolemia in patients with systolic and/or diastolic heart failure?  
• In patients who are not responding to appropriate dosage of a loop diuretic alone, should a thiazide diuretic be added? |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Population:</td>
<td>Adults with heart failure, either systolic and/or diastolic, with signs and symptoms of volume overload.</td>
</tr>
</tbody>
</table>
| Health Intervention: | • Diuretics, loop or thiazide  
• Combination loop and thiazide diuretic |
| Most Important Health Outcomes: | • Mortality due to cardiac causes  
• All-cause mortality  
• Hospitalization |

Search Strategy

Only RCTs or meta-analyses were included that included outcomes for hospitalization and or death in patients with LVSD.

<table>
<thead>
<tr>
<th>Database:</th>
<th>Search Terms:</th>
<th>Article Type and Other Limits:</th>
<th>Search Date</th>
<th>No. Included / Total Retrieved</th>
</tr>
</thead>
</table>
| PubMed         | "Heart Failure, Congestive"[MeSH] AND "Diuretics"[MeSH]                                                                  | Clinical Trials  
|                |                                                                                                                       | Meta-analysis  
English, Human | 09/2005 - 11/27/2007 | 0/0              |
<p>| Cochrane       | Heart Failure                                                                                                           | Systematic reviews | 10/03               | 0/13            |
| Cochrane       | Heart Failure, Congestive                                                                                               | Systematic reviews | 3/01                | 0/3              |
| Clinical Evidence | Heart Failure, diuretic therapy                                                                                        | Systematic reviews and RCTs | 10/03               | 0/0              |</p>
<table>
<thead>
<tr>
<th>Database:</th>
<th>Search Terms:</th>
<th>Article Type and Other Limits:</th>
<th>Search Date</th>
<th>No. Included / Total Retrieved</th>
</tr>
</thead>
<tbody>
<tr>
<td>PubMed</td>
<td>&quot;Heart Failure, Congestive&quot;[MESH] AND metolazone/therapeutic use[MESH]</td>
<td>Clinical Trials English, Human, All Adult: 19+ years</td>
<td>03/01</td>
<td>0/33</td>
</tr>
<tr>
<td>PubMed</td>
<td>&quot;Heart Failure, Congestive/ drug therapy&quot;[MESH] AND metolazone/therapeutic use[MESH]</td>
<td>English, Human, All Adult: 19+ years</td>
<td>03/01</td>
<td>0/12</td>
</tr>
</tbody>
</table>

Note: The literature search for the 2006 update was conducted by Clin-eGuide and is documented in the 2006 Heart Failure Guideline.
**Evidence Tables**

**Table 5.1: Meta-Analysis of RCT Comparing Diuretic with Placebo or Active Control**

<table>
<thead>
<tr>
<th>Meta-Analysis</th>
<th>Studies Selected</th>
<th>Studies Included</th>
<th>Results OR (95% CI)</th>
<th>Comments / Heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Faris R, et al.</td>
<td>Databases searched: Medline, Embase, 1996 to 1999</td>
<td>18 trials with 928 patients were included. 8 trials were placebo controlled. Mortality data was available in 3 placebo controlled trials.</td>
<td>Mortality: 3 trials N = 221 Diuretics 3/111 (2.7%) vs. placebo 12/110 (10.9%) 0.25 (0.07 to 0.84) Effect of diuretic withdrawal on worsening heart failure: 4 trials diuretic vs. placebo 0.31 (0.15 to 0.62) Effect of diuretic vs. active control on worsening heart failure: 4 trials 0.34 (0.10 to 1.21) active control compared loop diuretic with ACEI, or Ibopamine Effect of diuretic on exercise capacity: 6 trials 0.37 (0.10 to 0.64) Active control included ACEI, digoxin or Ibopamine</td>
<td>Fixed effects model used to analyze data. RALES trial data excluded because most patients were on another diuretic, and spironolactone was not considered a typical diuretic. All trials were small and inadequately powered to demonstrate clearly the effectiveness of the intervention on morbidity and mortality. There was great variability in the type of intervention, clinical characteristics of patients and assessment of severity, etiology of heart failure, study durations, concomitant medications, outcome measure and drop-out rates. There is also heterogeneity in the action of the diuretics, loop and thiazide, and the dosage.</td>
</tr>
</tbody>
</table>

### Vasodilators in Left Ventricular Systolic Disorder (LVSD)

#### 6. Use of Renin-Angiotensin System Inhibitor/Blockers and/or Vasodilators

**Problem Formulation**

| Clinical Questions: | • Which renin-angiotensin system inhibitor/blocker and/or vasodilators are recommended for patients with LVSD?  
• Can ARBs be used in place of ACE inhibitors in patients who have ACE inhibitor-induced angioedema, rash, or cough?  
• What is the alternative medication if ACE inhibitors or ARBs are contraindicated?  
• Should ARBs be given to patients already taking an ACE inhibitor and a beta-blocker?  

| Populations: | • Adults with LVSD who do not have contraindications to ACE inhibitors, ARBs, or combination hydralazine and isosorbide dinitrate  
• Adults with LVSD who are ACEI-intolerant  
• Adults with LVSD in whom ACEI and ARBs are contraindicated  

| Health Intervention: | • ACE inhibitors  
• Angiotensin II receptor blockers  
• Combination ACE inhibitors and ARBs  

| Most Important Health Outcomes: | • All-cause mortality  
• Mortality due to cardiac causes  
• Hospitalization |
Search Strategy

Studies selected for review were RCTs or meta-analyses of RCTs that evaluated the effectiveness of vasodilator medication versus placebo or previously accepted medication. When there was no evidence from RCTs, the GDT considered data from other clinical trials, such as observational studies and retrospective post hoc analysis of RCTs to inform consensus recommendations. Study endpoints were at least one of the following:

- All-cause death rate
- Death due to cardiac causes
- Hospitalization rate

<table>
<thead>
<tr>
<th>Database:</th>
<th>Search Terms:</th>
<th>Article Type and Other Limits:</th>
<th>Search Date</th>
<th>No. Included / Total Retrieved</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Meta-analysis; English, Human</td>
<td>09/2005 - 12/15/07</td>
<td>0/5</td>
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<tr>
<td></td>
<td></td>
<td>RCT, English, Human</td>
<td>09/2005 - 12/16/07</td>
<td>0/99</td>
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<td></td>
<td>RCT, English, Human</td>
<td>09/2005 - 12/16/07</td>
<td>0/3</td>
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<tr>
<td>PubMed</td>
<td>&quot;Heart Failure, Congestive&quot;[MeSH] AND &quot;Creatinine&quot;[MeSH] AND &quot;Angiotensin-Converting Enzyme Inhibitors/adverse effects&quot;[MeSH]</td>
<td>English; Human</td>
<td>09/2005 - 12/16/07</td>
<td>0/1</td>
</tr>
<tr>
<td>Database:</td>
<td>Search Terms:</td>
<td>Article Type and Other Limits:</td>
<td>Search Date</td>
<td>No. Included / Total Retrieved</td>
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<td>--------------------------------------------------------</td>
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<td>-------------------------------</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Clinical Trial, English, Human</td>
<td>09/2005 - 12/16/07</td>
<td>0/270</td>
</tr>
<tr>
<td>Cochrane</td>
<td>heart failure</td>
<td>Systematic reviews</td>
<td>11/01/2000 - 10/01/03</td>
<td>0/35</td>
</tr>
<tr>
<td>Weekly Scanning of journal TOCs</td>
<td>No terms</td>
<td>Articles of interest</td>
<td>On-going</td>
<td>1/1</td>
</tr>
<tr>
<td>PubMed</td>
<td>&quot;heart failure, congestive&quot;[MESH] AND &quot;Angiotensin-Converting Enzyme Inhibitors&quot;[MESH]</td>
<td>RCT, English, Human</td>
<td>11/01/2000 - 10/01/03</td>
<td>0/69</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Meta-analysis; English, Human</td>
<td>11/01/2000 - 10/01/03</td>
<td>0/6</td>
</tr>
<tr>
<td>Database</td>
<td>Search Terms</td>
<td>Article Type and Other Limits</td>
<td>Search Date</td>
<td>No. Included / Total Retrieved</td>
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<tr>
<td>Database:</td>
<td>Search Terms:</td>
<td>Article Type and Other Limits:</td>
<td>Search Date</td>
<td>No. Included / Total Retrieved</td>
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<td>----------</td>
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<td>-----------------------------</td>
</tr>
<tr>
<td>PubMed</td>
<td>&quot;heart failure, congestive&quot;[MeSH Terms] AND &quot;aspirin&quot;[MeSH Terms] OR aspirin[Text Word]</td>
<td>English; Human</td>
<td>11/01/2000 - 10/01/03</td>
<td>0/12</td>
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<tr>
<td>PubMed</td>
<td>&quot;heart failure, congestive&quot;[MeSH Terms] OR aspirin[Text Word]</td>
<td>Meta-analysis, English, Human</td>
<td>11/01/2000 - 10/01/03</td>
<td>1/1</td>
</tr>
<tr>
<td>PubMed</td>
<td>&quot;Angioneurotic Edema&quot;[MeSH] AND &quot;Angiotensin-Converting Enzyme Inhibitors&quot;[MeSH]</td>
<td>Clinical Trial, English, Human</td>
<td>11/01/2000 - 10/01/03</td>
<td>0/19</td>
</tr>
</tbody>
</table>

Note: The literature search for the 2006 update was conducted by Clin-eguide and is documented in the 2006 Heart Failure Guideline.
7. Target Dose of ACE Inhibitors

**Problem Formulation**

<table>
<thead>
<tr>
<th><strong>Clinical Question:</strong></th>
<th>What is the target dose of ACE inhibitors?</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Population:</strong></td>
<td>Adults with LVSD who do not have contraindications to ACE inhibitors</td>
</tr>
<tr>
<td><strong>Health Intervention:</strong></td>
<td>Low-dose ACEI</td>
</tr>
</tbody>
</table>
| **Most Important Health Outcomes:** | ♦ Mortality due to cardiac causes  
♦ All-cause mortality  
♦ Hospitalization |

8. Appropriate Renal Function for Prescribing ACEIs

**Problem Formulation**

<table>
<thead>
<tr>
<th><strong>Clinical Question:</strong></th>
<th>At what level of renal function should clinicians stop prescribing ACE inhibitors to patients with LVSD?</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Population:</strong></td>
<td>Adults with LVSD who have an elevated serum creatinine level</td>
</tr>
<tr>
<td><strong>Health Intervention:</strong></td>
<td>ACE inhibitors</td>
</tr>
</tbody>
</table>
| **Most Important Health Outcomes:** | ♦ Mortality due to cardiac causes  
♦ All-cause mortality  
♦ Hospitalization |

9. Combination Aspirin and ACEIs

**Problem Formulation**

<table>
<thead>
<tr>
<th><strong>Clinical Question:</strong></th>
<th>Can aspirin be given concurrently to patients with LVSD who are taking ACE inhibitors?</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Population:</strong></td>
<td>Adults with LVSD and concomitant cardiovascular disease (CVD) who are being treated with ACE inhibitors</td>
</tr>
<tr>
<td><strong>Health Intervention:</strong></td>
<td>ACEI plus aspirin</td>
</tr>
</tbody>
</table>
| **Most Important Health Outcomes:** | ♦ Mortality due to cardiac causes  
♦ All-cause mortality  
♦ Hospitalization |
### Table 9.1: Overview of Studies of ACEI, ARBs and Comparisons of ACEI vs. ARBs

<table>
<thead>
<tr>
<th>Study</th>
<th>ACEI vs. Placebo</th>
<th>ARB vs. Placebo</th>
<th>ARB vs. ACEI</th>
<th>Treatment Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Garge, ACEI meta-analysis</td>
<td>0.77 (0.67 to 0.88)</td>
<td>---</td>
<td>---</td>
<td>ACEI vs. placebo</td>
</tr>
<tr>
<td>Flather, ACEI meta-analysis</td>
<td>0.80 (0.74 to 0.87)</td>
<td>---</td>
<td>---</td>
<td>ACEI vs. placebo</td>
</tr>
<tr>
<td>ELITE II</td>
<td>---</td>
<td>---</td>
<td>1.13 (0.95 to 1.35)</td>
<td>ARB vs. ACEI</td>
</tr>
<tr>
<td>Val-HeFT subgroup death</td>
<td>---</td>
<td>0.58 (0.33 to 1.03)</td>
<td>1.02 (0.88 to 1.18)</td>
<td>ARB vs. placebo + std treatment</td>
</tr>
<tr>
<td>CHARM-Alternative</td>
<td>---</td>
<td>0.80 (0.66 to 0.96)</td>
<td>---</td>
<td>ACEI vs. placebo</td>
</tr>
<tr>
<td>Combined</td>
<td></td>
<td>0.87 (0.77 to 0.97)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OPTIMAAL (heart failure + post-MI)</td>
<td></td>
<td>1.13 (0.99 to 1.28)</td>
<td></td>
<td>ARB vs. ACEI</td>
</tr>
<tr>
<td>VALIANT (heart failure + post-MI)</td>
<td></td>
<td>1.00 (0.90 to 1.11)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jong, ARB meta-analysis</td>
<td>---</td>
<td>0.68 (0.92 to 1.29)</td>
<td>1.09 (0.92 to 1.29)</td>
<td>ARB vs. placebo</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>ARB + ACEI vs. ACEI</th>
<th>ARB + ACEI + BB</th>
<th>ARB + ACEI – BB</th>
<th>Treatment Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Val-HeFT death</td>
<td>---</td>
<td>1.44 (1.11 to 1.85)</td>
<td>0.96 (0.82 to 1.12)</td>
<td>ARB vs. placebo + std treatment</td>
</tr>
<tr>
<td>Combined</td>
<td>---</td>
<td>1.18 (0.97 to 1.45)</td>
<td>0.80 (0.70 to 0.95)</td>
<td></td>
</tr>
<tr>
<td>CHARM-Add death</td>
<td>0.85 (0.71 to 0.97)</td>
<td>0.78 (0.65 to 0.93)</td>
<td>0.94 (0.79 to 1.12)</td>
<td>ACEI + ARB</td>
</tr>
<tr>
<td></td>
<td>0.89 (0.77 to 1.02)</td>
<td>0.88 (0.72 to 1.08)</td>
<td>0.88 (0.73 to 1.07)</td>
<td></td>
</tr>
<tr>
<td>VALIANT (heart failure + post-MI)</td>
<td>0.98 (0.89 to 1.09)</td>
<td>1.05 (0.90 to 1.20)</td>
<td>0.94 (0.80 to 1.10)</td>
<td>ARB + ACEI + ACEI</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ACEI</td>
</tr>
<tr>
<td>Jong, meta-analysis</td>
<td>1.04 (0.91 to 1.20)</td>
<td>---</td>
<td>---</td>
<td></td>
</tr>
</tbody>
</table>
### Table 9.2: Meta-Analyses of RCTs of ARBs in LVSD

<table>
<thead>
<tr>
<th>Study</th>
<th>Studies</th>
<th>Odds Ratio (95% CI)</th>
<th>Comments</th>
</tr>
</thead>
</table>
| Jong P. et. al.                 | Search dates 1996 to May 2001; Studies were included if: NYHA classes II – IV; comparison ARBs with placebo or ACEI; RCTs, lasting at least 4 weeks that reported death or hospitalization; 17 studies included, 26 excluded; CHARM, OPITMAAL and VALIANT not completed at the time of the meta-analysis | All-cause Mortality: Random Effects | ARBs vs. control (active or placebo)                         0.96 (0.75 to 1.23)  
|                                 |                                                                         | heterogeneity p = 0.10                                                                 | 883/7,060 791/5,409                                                                 |
|                                 |                                                                         | Fixed Effects                                                                   | ARB vs. placebo                          0.68 (0.38 to 1.22)  
|                                 |                                                                         | heterogeneity p = 0.18                                                                | 32/1628 18/631                                                                 |
|                                 |                                                                         | ARB vs. ACEI 1.09 (0.92 to 1.29)  
|                                 |                                                                         | heterogeneity p = 0.14                                                                | 326/2,518 288/2,164                                                                 |
|                                 |                                                                         | ARB+ACEI vs. ACEI 1.04 (0.91 to 1.20)  
|                                 |                                                                         | heterogeneity p = 0.32                                                                | 526/2,989 489/2,723                                                                 |
|                                 |                                                                         | Hospitalization Random Effects                                                                               | ARBs vs. controls (active or placebo)                         0.86 (0.69 to 1.06)  
|                                 |                                                                         | heterogeneity p = 0.11                                                                | 727/5,336 788/4,695                                                                 |
|                                 |                                                                         | Fixed Effects                                                                   | ARB vs. placebo (1 trial only)                          0.67 (0.29 to 1.51)  
|                                 |                                                                         | heterogeneity p = 1.0  
|                                 |                                                                         | 15/179 11/91                                                                        | 11/91                                                                                   |
|                                 |                                                                         | ARB vs. ACEI 0.95 (0.80 to 1.13)  
|                                 |                                                                         | heterogeneity p = 0.12                                                                | 333/2,257 321/2,053                                                                 |
|                                 |                                                                         | ARB+ACEI vs. ACEI 0.74 (0.64 to 0.86)  
|                                 |                                                                         | heterogeneity p = 0.19                                                                | 379/2,900 463/2,660                                                                 |
|                                 |                                                                         | Substitution of a fixed effects model for a random effects did not change the interpretation of treatment effect on all-cause mortality but did result in statistically significant benefit of reduced hospitalization. |                                                                                         |
Table 9.3: Lee (2004)

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Indication</th>
<th>Subject Characteristics</th>
<th>Age of Subjects</th>
<th>Study Design</th>
<th>Clin-eguide Evidence Grade</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lee VC, Rhew DC, Dylan M, et al. Meta-analysis: angiotensin-receptor blockers in chronic heart failure and high-risk acute myocardial infarction. Annals of Internal Medicine 2004;141(9):693-704</td>
<td>Heart failure</td>
<td>NYHA class II-IV; ejection fraction: 0.30 - 0.45.</td>
<td>Mean, 54 – 73 years</td>
<td>Meta-analysis</td>
<td>A1</td>
<td>Candesartan; losartan; valsartan</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Duration</th>
<th>No. of Subjects</th>
<th>Study controls</th>
<th>Outcome</th>
<th>Study Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 weeks – 2.7 years</td>
<td>24 trials including 38,080 patients</td>
<td>Placebo</td>
<td>All-cause mortality Heart failure Hospitalizations</td>
<td>1) ARBs reduced all-cause mortality (odds ratio [OR], 0.83 [95% CI: 0.69 to 1.00]) and hospitalization for heart failure (OR, 0.64 [95% CI: 0.53 to 0.78]) as compared with placebo; 2) for ARBs vs ACE inhibitors, all-cause mortality (OR, 1.06 [95% CI, 0.90 to 1.26]) and hospitalization for heart failure (OR, 0.95 [95% CI: 0.80 to 1.13]) did not differ; 3) for combinations of ARBs plus ACE inhibitors vs ACE inhibitors alone, all-cause mortality was not reduced (OR, 0.97 [95% CI: 0.87 to 1.08]), but hospitalizations for heart failure were reduced (OR, 0.77 [95% CI: 0.69 to 0.87])</td>
</tr>
</tbody>
</table>
### Table 9.4: RCTs - ARBs (candesartan) and ACEI: The CHARM trials

<table>
<thead>
<tr>
<th>CHARM TRIALS</th>
<th>Trial Design</th>
<th>Study Populations</th>
<th>Results Hazard Ratio (95% CI)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pfeffer MA, et al.</td>
<td>Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-Overall programme</td>
<td>The CHARM trials were designed as randomized, double-blinded, controlled trials to compare candesartan with placebo in three distinct populations: in place of ACEI in ACEI-intolerant patients added to ACEI in heart failure with LVEF &gt; 40% Mean follow-up 37.7 months 0.1% lost to follow-up Intention to treat analysis</td>
<td>All-cause mortality for 3 trials 0.91 (0.83 to 1.00)  $p = 0.055$ 886/3,803 945/3,796 Adjusted 0.90 (0.82 to 0.99)  $p = 0.032$ CV deaths for the 3 trials Unadjusted 0.88 (0.79 to 0.97) Adjusted 0.87 (0.78 to 0.96) Test for heterogeneity across trials: $p = 0.37$ and $p = 0.43$</td>
<td>Changes in creatinine levels:  - At 6 weeks, 0.09 mg/dl in candesartan and 0.01 in the placebo group  - Creatinine doubled in 6% of candesartan patients and 4% of placebo patients. Reduction in all-cause death was primarily due to a 12% reduction in CV deaths. The annual death rate in the placebo group with reduced LVEF was 9% compared with 4% for patients with EF &gt; 40%.</td>
</tr>
<tr>
<td>Overall 7,599 patients 3,803 to 32 mg candesartan 3,796 to placebo</td>
<td>Patients 18 years and older with symptomatic heart failure and NYHA class II to IV Eligible patients were enrolled in one of three trials Exclusions: creatinine ≥ 3 mg/dl K+ ≥ 5.5 mmol/L, renal artery stenosis, symptomatic hypotension, use of ARB in last 2 weeks. Discontinuation rate for all trials was 23% for candesartan and 19% for placebo, $p = 0.0001$</td>
<td>CV deaths for the 3 trials</td>
<td></td>
<td></td>
</tr>
<tr>
<td>37.7 months</td>
<td>Unadjusted 0.88 (0.79 to 0.97)</td>
<td></td>
<td></td>
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<tr>
<td>Mean follow-up 37.7 months</td>
<td>Adjusted 0.87 (0.78 to 0.96)</td>
<td></td>
<td></td>
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<tr>
<td>0.1% lost to follow-up</td>
<td>Test for heterogeneity across trials: $p = 0.37$ and $p = 0.43$</td>
<td></td>
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<tr>
<td>Intention to treat analysis</td>
<td>Patients with EF &lt; 40% - All-cause mortality 0.88 (0.79 to 0.98) - CV Death 0.84 (0.79 to 0.95)</td>
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<tr>
<td>Granger CB et al.</td>
<td>Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial.</td>
<td>Patients with LVSD who were ACEI intolerant Reason for ACEI intolerance: - cough 72% - hypotension 13% - renal dysfunction 11% - angioedema 4% - other 10% Mean follow-up 33.7 month The trial was not designed to detect all-cause mortality.</td>
<td>CV death or hospitalization for heart failure (primary endpoint) Unadjusted 0.77 (0.67 to 0.89) 334/1,013 406/1,015 Adjusted 0.70 (0.60 to 0.81) CV death Unadjusted 0.85 (0.71 to 1.02) Adjusted 0.80 (0.66 to 0.97) Total Mis 75/1,013 48/1,015 1.52 (1.06 to 2.18) $p = 0.025$ favors placebo All-cause mortality Unadjusted 0.87 (0.74 to 1.03) 265/1,013 296/1,015 Adjusted 0.83 (0.70 to 0.99)</td>
<td>One patient had to stop candesartan due to angioedema. That patient had a previous history of ACEI-induced angioedema. (2.6%) Two other patients with ACEI-induced angioedema had a reoccurrence and continued on candesartan. No patients in the control group had angioedema. Creatinine increase: 31 of 134 patients who discontinued ACEI due to increased creatinine, discontinued candesartan. 12 of 100 patients in the control group discontinued due to creatinine elevation.</td>
</tr>
<tr>
<td>N = 2,028 n = 1,013 candesartan n = 1,015 placebo</td>
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<tr>
<td>At first visit 65% taking BB. 30% of candesartan and 29% of placebo patients discontinued medication permanently. By study end, 24% of the candesartan and 22% placebo group who survived had discontinued medications.</td>
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</tr>
<tr>
<td>CHARM TRIALS</td>
<td>Trial Design</td>
<td>Study Populations</td>
<td>Results Hazard Ratio (95% CI)</td>
<td>Comments</td>
</tr>
<tr>
<td>--------------</td>
<td>--------------</td>
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<td>-----------------------------</td>
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</tr>
<tr>
<td>McMurray JJ, et al.</td>
<td>Patients with EF ≤ 40% taking ACEI randomized to the addition of candesartan or placebo Mean follow-up - 41 months</td>
<td>N = 2,548 n = 1,276 candesartan n = 1,272 placebo Baseline medications: 55% BB 17% spironolactone At study end, 66% taking BBs Discontinuation rates: 24% candesartan 18% placebo</td>
<td>CV death or hospitalization for heart failure (primary endpoint) Unadjusted 0.85 (0.75 to 0.96) 483/1,276 538/1,272 Adjusted 0.85 (0.75 to 0.96) CV death Unadjusted 0.84 (0.72 to 0.98) 302/1,276 347/1,272 Adjusted 0.83 (0.71 to 0.97) All-cause mortality Unadjusted 0.89 (0.77 to 1.02) 377/1,276 412/1,272 All-cause mortality in subgroups taking &amp; not taking BB Yes BB 0.88 (0.72 to 1.08) 175/702 196/711 No BB 0.88 (0.73 to 1.07) 202/574 217/561 Combined endpoints in subgroups taking &amp; not taking BB p = 0.14 for interaction Yes BB 0.78 (0.65 to 0.93) 223/702 274/711 No BB 0.94 (0.79 to 1.12) 260/574 264/561</td>
<td>The authors state the differences between the Val-HeFT and their study with respect to BB+ACEI+ARB is that the Val-HeFT was under-powered 35% vs. 55% on BB or that the type or dosage of ARB could have accounted for the difference. The authors of the Val-HeFT do not give the end of study use of BB. Notably, the interaction in the Val-HeFT between ACEI+ARB vs. ACEI+ARB+BB in combined endpoint was significant where as in the CHARM it was not significant.</td>
</tr>
</tbody>
</table>
### Table 9.5: Comparison of ARB or ACEI, ARB + ACEI and BB or placebo: RESOLVD trial

<table>
<thead>
<tr>
<th>RESOLVD</th>
<th>Trial Design</th>
<th>Study Populations</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>McKelvie RS, et al. Comparative impact of enalapril, candesartan or metoprolol alone or in combination on ventricular remodelling in patients with congestive heart failure. Eur Heart J. 2003 Oct;24(19):1727-34</td>
<td>Patients with EF &lt; 0.40 and 6-min walk distance &lt; 500 m who were on ARBs, ACEIs, or ARB + ACEI were randomized to also receive BB or placebo. RESOLVD follow-up = 43 weeks, final 24 weeks included BB or placebo.</td>
<td>426 of 768 patients receiving ARB, ACEI or ARB+ACEI were randomized to BB or placebo</td>
<td>Hospitalization rate</td>
<td>none</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ARB alone or ACEI alone = 126</td>
<td>ARB or ACEI 6.8%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ARB + ACEI = 86</td>
<td>ARB + ACEI 1.2%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ARB + BB or ACEI + BB = 125</td>
<td>ARB + BB or ACEI + BB 8.0%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ARB + ACEI + BB = 89</td>
<td>ARB + ACEI + BB 12.6%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Daily dose</td>
<td>ARB = candesartan 8 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ACEI = enalapril 20 mg</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>BB = metoprolol CR 200 mg</td>
<td></td>
</tr>
</tbody>
</table>
Table 9.6: Majani (2005)

<table>
<thead>
<tr>
<th>Author</th>
<th>Study Name</th>
<th>Indication</th>
<th>Subject Characteristics</th>
<th>Age of Subjects</th>
<th>Study Design</th>
<th>Clin-eguide Evidence Grade</th>
<th>Treatment (Name, Dose, Route, Frequency)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Majani G, Giardini A, Opasich C, et al. Effect of valsartan on quality of life when added to usual therapy for heart failure: results from the Valsartan Heart Failure Trial. Journal of Cardiac Failure 2005;11(4):253-9</td>
<td>Val-HeFT</td>
<td>Heart failure</td>
<td>Patients had heart failure of NYHA class I-IV with etiologies that included coronary disorders (n = 1678), idiopathic cardiomyopathy (n = 951), hypertension (n = 203) and others (n = 176). The mean duration of disease was 51 months.</td>
<td>Mean, 63 years</td>
<td>RCT</td>
<td>A1</td>
<td>Valsartan, 80 – 320 mg/day, PO, bid</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Duration</th>
<th>No. of Subjects</th>
<th>Study Control</th>
<th>Outcome</th>
<th>Study Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 38 mo (mean, 23 mo)</td>
<td>3010</td>
<td>Placebo</td>
<td>Minnesota Heart Failure Symptom Questionnaire Quality of life</td>
<td>Valsartan was associated with significantly lesser increases in Minnesota Heart Failure Symptom Questionnaire scores compared with placebo in patients with congestive heart failure. Increases in the overall score and scores for the emotional and physical domains were 0.4, 0, and 0.2, respectively, for valsartan and 2.4, 0.4, and 1.2, respectively, for placebo (p &lt; 0.01, p &lt; 0.05, and p = 0.01 between treatments, respectively)</td>
</tr>
</tbody>
</table>
### Table 9.7: Val-HEFT: Valsartan Added to Standard Treatment for LVSD

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Design</th>
<th>Population</th>
<th>Study Size &amp; Treatment Groups</th>
<th>Outcomes / Results (97.5% CI: )</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohn JN, et al.</td>
<td>RCT Multinational Multicenter Placebo-controlled Two treatment arms, standard therapy plus valsartan compared with standard therapy alone. Patients were randomized based on use or nonuse of beta-blockers</td>
<td>N = 5,010</td>
<td>Valsartan: 2,511 Control: 2,499 Final dose - valsartan 160 mg bid</td>
<td>RR (97.5% CI: )</td>
<td>RR (97.5% CI: )</td>
</tr>
</tbody>
</table>

#### Inclusion Criteria
- Age > 18 years
- EF < 40%
- Dilated left ventricle
- NYHA class II – IV
- Clinically stable

#### Exclusion Criteria:
- Valve disease
- Recent MI or CVA
- Creatinine > 2.5 mg/dl

#### Average age: 62
- Baseline medication:
  - 85% diuretic
  - 67% digoxin
  - 35% Beta-blocker
  - 93% ACEI in adequate dose

#### Study population:
- 62% class II
- 36% class III
- 2% class IV
- 7 patients lost to follow-up

#### 9.9% of valsartan patients and 7.2% of placebo patients withdrew due to adverse drug reactions.

#### Primary endpoints:
- All-cause mortality: 1.02 (0.88 to 1.18) p = 0.80
- Combined endpoints*: 0.87 (0.77 to 0.97) p = 0.009

#### Benefits appeared very early in treatment
- Reduction in hospitalization rate
- RRR 27% (13.9% vs. 18.5% in placebo) p = 0.00001

#### Subgroup analysis:
- All-causes mortality subgroup interaction p = 0.009 n
- ACEI+ ARB +BB 1.44 (1.10 to 1.85) 1,610
- ACEI+ ARB 0.97 (0.82 to 1.13) 3,034
- ARB 0.58 (0.33 to 1.03) 226
- ARB+BB 0.8 (0.37 to 1.78) 140

#### Combined endpoints subgroup interaction p = 0.001
- ACEI+ ARB +BB 1.18 (0.97 to 1.45) 1,610
- ACEI+ ARB 0.83 (0.69 to 0.95) 3,034
- ARB 0.56 (0.37 to 0.89) 226
- ARB+BB 0.58 (0.29 to 1.13) 140

#### Study sponsored by Novartis Pharma AG
- Data collection and analysis performed by Novartis
- Authors' Conclusions: Valsartan has neutral effect on mortality but significantly reduced combined endpoint of mortality and morbidity.

The data raise the possibility that the combination of ACEI and beta-blocker and valsartan may exert an unfavorable effect.
### Table 9.8: RCT post-MI with LVSD Comparison for Losartan vs. Captopril: OPTIMAAL

<table>
<thead>
<tr>
<th>Study, Total n</th>
<th>Treatment Groups Size &amp; Drug</th>
<th>Study Population</th>
<th>Results Relative Risk of losartan compared with captopril (95% CI)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dickstein K, Kjekshus J and the OPTIMAAL Steering Committee, for the OPTIMAAL Study Group. Effects of losartan and captopril on mortality and morbidity in high risk patients after acute myocardial infarction: the OPTIMAAL randomized trial. Lancet 2002;360:752-60. N = 5477</td>
<td>Losartan-treated group n = 2,744 Captopril-treated group n = 2,733 Follow up: 2.7 year Initial N: 5,477 Final N: 4,394</td>
<td>Inclusion criteria: Acute MI defined as: a history of typical chest pain for &gt; 20 minutes, ST elevation on electrocardiograph or, an increase in cardiac markers above the decision level AND Signs or symptoms of heart failure during the acute phase or a new Q-wave anterior infarction or reinfarction. Exclusion criteria: Hypotension, current receipt of an ACE inhibitor or ARB, unstable angina, stenotic valvular heart disease, dysrhythmia, planned coronary revascularization</td>
<td>Primary outcome All-cause mortality 499/2,744 vs 447/2,733 Sudden cardiac death Resuscitated cardiac arrest 1.19 (0.99 to 1.43) MI (fatal/nonfatal) 1.03 (0.89 to 1.18) CV Death 1.17 (1.01 to 1.34) All-cause hospitalization 1.03 (0.97 to 1.10)</td>
<td>Conclusions: There was a nonsignificant difference in total mortality and a significant difference in CV mortality in favor of captopril, suggesting that ACE inhibitors should remain the first choice treatment in patients after complicated AMI. Losartan was better tolerated and associated with fewer discontinuations. Limitations: There was no placebo group in this trial. Although the role of losartan in patients intolerant of ACE inhibition is not clearly defined, because Losartan was better tolerated and associated with significantly fewer discontinuations than captopril in these study subjects, the study investigators conclude that it can be considered in patients intolerant of ACE inhibition.</td>
</tr>
</tbody>
</table>
### Table 9.9: RCT - Addition of Valsartan to Standard Treatment for Heart Failure: VALIANT

<table>
<thead>
<tr>
<th>Study, Total n</th>
<th>Treatment Groups Size &amp; Drug</th>
<th>Study Population</th>
<th>Results</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pfeffer MA, McMurray JJ, Velazquez EJ, et al. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. N Engl J Med 2003;349:1893-906. N = 14,703</td>
<td>Valsartan Group (n = 4,909) Valsartan + beta-blocker (n = 3,468) Not on BB (n=1441) Captopril Group (n = 4,909) Captopril + beta-blocker (n = 3,443) Not on BB (n=1,466) Valsartan + Captopril Group (n = 4,885) Valsartan + Captopril + beta-blocker (n = 3,439) Not on BB (n = 1,446)</td>
<td>Patients 18 years and older with recent acute myocardial infarction (in the last 0.5 – 10 days) which was complicated by clinical or radiologic signs of heart failure, signs of LVSD (EF ≤ 0.35), or both. Systolic BP had to be &gt; 100 mm Hg and serum creatinine (&lt; 2.5 mg/dl). Exclusion criteria included ACEI-intolerance or contraindication to an ACEI or ARB.</td>
<td>Total Mortality: No significant difference in the following groups: Those on beta-blockers vs. those who were not - Valsartan vs. captopril; p = 0.98 Valsartan + captopril vs. captopril alone; p = 0.31 (HR = 0.94) (97.5% CI: 0.9 to 1.1)</td>
<td>none</td>
</tr>
</tbody>
</table>

### Table 9.10: RCT - Standard Dose vs. High-Dose Enalapril in LVSD

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment Groups Size &amp; Drug</th>
<th>Study Population</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nanas, JN. Outcome of patients with congestive heart failure treated with standard versus High-doses of enalapril: a multicenter study. High Enalapril Dose Study Group. J Am Coll Cardiol 2000; 36:2090-5. Follow up: treatment period was 12 months</td>
<td>248 patients with ejection fraction of ≤ 35% randomized to receive a maximal tolerated dose of Enalapril in two treatment groups. Rx1 (n = 122) Enalapril up to 20 mg/day Rx2 (n = 126) Enalapril up to 60 mg/day Large Enalapril trials – For CONSENSUS, SOLVD (treatment), SOLVD (prevention) and V-HEFT II the final mean dose was 15 to 18.4 mg/day The intended dose was 40 mg/day for CONSENSUS and 20 mg/day for the other trials. Small-scale studies have shown large doses of ACE inhibitors produce greater hemodynamic and clinical improvement compared with customary doses.</td>
<td>N = 248 mean LVEF 20% age 56.3 ± 12 years NYHA Class 42% class II 44% class III 11% class IV The trial was prospective and randomized. Treatment and functional status evaluation were open-label, evaluation of LV function was blinded. Analysis was by intention-to-treat. The trial had 80% power to detect a between-group difference of 13%. Concomitant medications: digoxin 93% diuretic 100% No significant differences in characteristics between the two groups of patients at enrollment.</td>
<td>Primary endpoint: all-cause mortality No significant differences found in survival, clinical and hemodynamic variables between patients receiving standard and those receiving high-doses of enalapril. After 12 months follow-up: Rx1: 22 or 18% of patients died Rx2: 23 or 18% of patients died HR 0.998 (95% CI: 0.556 to 1.790) Rx1 Mean dose achieved 17.9 ± 4.3 mg/day Rx2 Mean dose achieved 42 ± 19.3 mg/day</td>
</tr>
</tbody>
</table>
Beta-Blockers in LVSD

10. Use of Beta-Blockers in Addition to Standard Treatment

Problem Formulation

<table>
<thead>
<tr>
<th>Clinical Question:</th>
<th>Should beta-blockers be used, in addition to standard treatment, for patients with LVSD?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population:</td>
<td>Adults with LVSD on standard therapy for heart failure and without contraindications to beta-blockers</td>
</tr>
<tr>
<td>Health Problem:</td>
<td>Heart failure due to left ventricular systolic dysfunction (LVSD)</td>
</tr>
</tbody>
</table>
| Most Important Health Outcomes: | • Mortality due to cardiac causes  
• All-cause mortality  
• Hospitalization |

11. Which Beta-Blockers to Use

Problem Formulation

<table>
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<tr>
<th>Clinical Question:</th>
<th>Which beta-blockers are most effective?</th>
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</thead>
<tbody>
<tr>
<td>Population:</td>
<td>Adults with LVSD on standard therapy for heart failure and without contraindications to beta-blockers</td>
</tr>
<tr>
<td>Health Problem:</td>
<td>Heart failure due to left ventricular systolic dysfunction (LVSD)</td>
</tr>
</tbody>
</table>
| Most Important Health Outcomes: | • Mortality due to cardiac causes  
• All-cause mortality  
• Hospitalization |
# Search Strategy

Only RCTs or meta-analyses were included that included outcomes for hospitalization and/or death in patients with LVSD.

<table>
<thead>
<tr>
<th>Database</th>
<th>Search Terms</th>
<th>Article Type and Other Limits</th>
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<th>No. Included / Total Retrieved</th>
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<td></td>
<td></td>
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<td>09/2005 - 12/02/07</td>
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<tr>
<td>PubMed</td>
<td>For use of BBs with concomitant asthma or COPD: Search &quot;Heart Failure, Congestive&quot;[MeSH] AND (&quot;Pulmonary Disease, Chronic Obstructive&quot; [MeSH] OR Asthma) AND &quot;Adrenergic beta-Antagonists&quot;[MeSH]</td>
<td>English</td>
<td>09/2005 - 12/02/07</td>
<td>0/29</td>
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<tr>
<td>Cochrane</td>
<td>Heart Failure</td>
<td>Systematic reviews</td>
<td>6/3/03</td>
<td>0/13</td>
</tr>
<tr>
<td>Clinical Evidence</td>
<td>Heart Failure</td>
<td>Systematic reviews and RCTs</td>
<td>5/30/03</td>
<td>0/6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RCT, English, Human</td>
<td>11/01/2000 - 7/29/03</td>
<td>4/92</td>
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<tr>
<td>PubMed</td>
<td>For use of BBs with concomitant asthma or COPD: Search &quot;Heart Failure, Congestive&quot;[MeSH] AND (&quot;Pulmonary Disease, Chronic Obstructive&quot; [MeSH] OR Asthma) AND &quot;Adrenergic beta-Antagonists&quot;[MeSH]</td>
<td>English</td>
<td>1/01/1966 - 8/06/03</td>
<td>1/19</td>
</tr>
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**Note:** The literature search for the 2006 update was conducted by Clin-eguide and is documented in the 2006 Heart Failure Guideline.
12. Beta-Blockers with Concomitant Asthma or COPD

**Problem Formulation**

<table>
<thead>
<tr>
<th>Clinical Question:</th>
<th>Can beta-blockers be safely used for patients with LVSD and concomitant asthma or COPD?</th>
</tr>
</thead>
</table>
| **Population:**   | • Adults with LVSD and asthma, or COPD with a reversible component  
                   | • Adults with LVSD and COPD without a reversible component |
| **Health Intervention:** | Beta-blockers added to standard treatment for LVSD |
| **Most Important Health Outcomes:** | • Mortality due to cardiac causes  
                                          | • All-cause mortality  
                                          | • Hospitalization |
Evidence Tables

RCTs of the Use of Beta-Blockers in LVSD

*Table 12.1: Bergstrom (2004)*

<table>
<thead>
<tr>
<th>Author</th>
<th>Study Name</th>
<th>Indication</th>
<th>Subject Characteristics</th>
<th>Age of Subjects</th>
<th>Study Design</th>
<th>Clin-eguide Evidence Grade</th>
<th>Treatment (Name, Dose, Route, Frequency)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bergstrom A, Andersson B, Edner M, et al. Effect of carvedilol on diastolic function in patients with diastolic heart failure and preserved systolic function. Results of the Swedish Doppler-echocardiographic study (SWEDIC). European Journal of Heart Failure 2004;6(4):453-61</td>
<td>SWEDIC</td>
<td>Heart failure</td>
<td>Patients had a wall motion index of 45% and abnormal diastolic function as evidenced by at least one of the following criteria: an E:A ratio lower than the age-related reference value (n = 81); an isovolumic relaxation time longer than the age-related reference value (14); a normal E:A ratio in combination with either a pulmonary vein systolic/diastolic velocity less than the age-related reference value (1), or a pulmonary vein atrial reversal duration greater than mitral atrial duration.</td>
<td>48 – 84 years (mean, 66 years)</td>
<td>RCT</td>
<td>B2</td>
<td>Carvedilol ≤ 100 mg/day PO bid</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Duration</th>
<th>No. of Subjects</th>
<th>Study Control</th>
<th>Outcomes</th>
<th>Study Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 months</td>
<td>113</td>
<td>Placebo</td>
<td>Deceleration time of early diastolic filling Heart failure event rate Heart rate Left atrial dimension Left ventricular end diastolic dimension Left ventricular end systolic dimension NYHA class</td>
<td>Carvedilol and placebo had similar overall effects on echocardiographic evidence of diastolic dysfunction in patients with heart failure characterized by left ventricular diastolic dysfunction and preserved systolic function. However, carvedilol significantly increased the E:A ratio compared with placebo (p &lt; 0.05)</td>
</tr>
</tbody>
</table>
### Table 12.2: Summary Table of RCTs for Beta-Blockers in LVSD

(All trials are randomized, blinded, and used intention-to-treat analysis. All except COMET, which is head-to-head, are placebo controlled.)

<table>
<thead>
<tr>
<th>Study, Sample Size &amp; Duration</th>
<th>Drug</th>
<th>Duration</th>
<th>Mean Age</th>
<th>Mean EF</th>
<th>% Class II</th>
<th>% Class III</th>
<th>% Class IV</th>
<th>Target Daily Dose % at Target</th>
<th>Mean Dose</th>
<th>All-cause Mortality Results (95% CI)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIBIS I(71) N = 641 T = 320, C = 321</td>
<td>Bisoprolol</td>
<td>22.8</td>
<td>60</td>
<td>25%</td>
<td>0</td>
<td>95</td>
<td>5</td>
<td>5 mg 59%</td>
<td>3.8 mg</td>
<td>RR 0.79 (0.57 to 1.01) RRR 0.21</td>
<td>Study underpowered to detect reduction in mortality.</td>
</tr>
<tr>
<td>CIBIS II(72) N = 2,647 T = 1,327, C = 1,320</td>
<td>Bisoprolol</td>
<td>15.6</td>
<td>61</td>
<td>28%</td>
<td>0</td>
<td>83</td>
<td>17</td>
<td>10 mg 57%</td>
<td>15% 7.5 mg 18% 5 mg</td>
<td>RR 0.68 (0.60 to 0.83) RRR 0.32 NNT 18</td>
<td></td>
</tr>
<tr>
<td>US Carvedilol(73) N = 2,289 T = 696, C = 398</td>
<td>Carvedilol</td>
<td>58</td>
<td>58</td>
<td>23%</td>
<td>53</td>
<td>44</td>
<td>3</td>
<td>50 mg 80%</td>
<td>45 mg</td>
<td>RRR 0.65 (0.39 to 0.80) RRR 0.27 (0.30 to 0.45) hospitalization</td>
<td></td>
</tr>
<tr>
<td>COPERNICUS(133) N = 2,289 T = 1,156, C = 1,133</td>
<td>Carvedilol</td>
<td>10.4</td>
<td>63</td>
<td>20%</td>
<td>0</td>
<td>?</td>
<td>Most</td>
<td>50 mg 78%</td>
<td>37 mg</td>
<td>RRR 0.35 (0.19 to 0.48) RRR 0.24 (0.13 to 0.33) death or hospitalization</td>
<td></td>
</tr>
<tr>
<td>RESOLVD(134) N = 426 T = 214, C = 212</td>
<td>Metoprolol CR/XL</td>
<td>6</td>
<td>61</td>
<td>29%</td>
<td>69%</td>
<td>23%</td>
<td>&lt; 1%</td>
<td>200 mg 81%</td>
<td>156 mg</td>
<td>RR 0.47 (0.20 to 1.05) RRR 0.53 RR 2.97 (1.09 to 7.96) Hospitalization for heart failure</td>
<td></td>
</tr>
<tr>
<td>MDC (135, 136) Metoprolol tartrate immediate release</td>
<td>12</td>
<td>47</td>
<td>22%</td>
<td>47%</td>
<td>47%</td>
<td>4%</td>
<td>100 to 150</td>
<td>108 mg</td>
<td>OR 1.07 (0.61 to 1.88)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MERIT-HF(137, 138) N = 3,991 T = 1,990, C = 2,001</td>
<td>Metoprolol CR/XL</td>
<td>12</td>
<td>64</td>
<td>28%</td>
<td>41%</td>
<td>55%</td>
<td>4%</td>
<td>200 mg 64%</td>
<td>159 mg</td>
<td>RR 0.66 (0.55 to 0.81) RRR 0.34 NNT 28 RR 0.87 p = 0.004 hospitalization</td>
<td></td>
</tr>
<tr>
<td>COMET (69) N = 3029 C = 1,511, M = 1,518</td>
<td>Carvedilol vs. metoprolol tartrate immediate release</td>
<td>58</td>
<td>62</td>
<td>26%</td>
<td>48%</td>
<td>48%</td>
<td>4%</td>
<td>Metoprolol 100 mg 87% Carvedilol 50 mg 75%</td>
<td>M = 85 mg C = 41.8 mg</td>
<td>RR 0.83 (0.74 to 0.93) RRR 0.17 NNT 18 RR 0.93 (0.86 to 1.10) all-cause hospitalization or death</td>
<td></td>
</tr>
</tbody>
</table>
### Table 12.3: Meta-Analyses of RCTs of Beta-Blockers in LVSD

<table>
<thead>
<tr>
<th>Study</th>
<th>Studies</th>
<th>Results</th>
<th>Comments/ Heterogeneity</th>
</tr>
</thead>
</table>
| Bouzamondo(60)         | Study inclusion criteria: Randomized and controlled trial of oral beta-blockers  
Data on hospitalization and mortality  
At least one death in each study arm  
16 trials included (no. reviewed not stated)  
Last search date not stated, newest citation 2002 | Relative Risk Reduction (95% CI)  
Mortality: 0.22 (0.16, 0.28)  
NNT = 22  
Hospitalization for worsening heart failure: 0.24 (0.20, 0.29)  
Heterogeneity p = 0.035  
Selective (metoprolol & bisoprolol): 0.30 (0.21, 0.38)  
Nonselective (carvedilol): 0.37 (0.24, 0.47)  
Heterogeneity p = 0.13 | Heterogeneity:  
When results from the BEST trial (bucindolol) were excluded, the heterogeneity for mortality was not significant between the trials.  
There was no heterogeneity in the comparison among the subgroups. |
| Brophy meta-analysis(62) | Study inclusion criteria: Randomized and controlled trial of beta-blockers vs. placebo  
Data on mortality  
105 reviewed, 22 included  
Last search date 2000 | Odds Ratio (95% CI)  
Mortality, all-causes: 0.65 (0.53, 0.80)  
Selective BBs: 0.67 (0.57, 0.79)  
Nonselective BBs: 0.52 (0.28, 0.89)  
Hospitalization, all-causes: 0.64 (0.53, 0.79) | NYHA class IV < 5%  
Analysis was by Bayesian hierarchical model.  
Though discussion about heterogeneity was included, no value for $\sigma^2$ was given.  
The BEST study was not included in these results. |
### Table 12.4: Salpeter Beta-Blockers and Airway Disease: Systematic Reviews

<table>
<thead>
<tr>
<th>Study, Total n</th>
<th>Treatment Groups Size and Drug Study Population</th>
<th>Results (95% CI)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salpeter, et al 2002(78) (meta-analysis) Cardioselective beta-blockers for reversible airway disease. Cochrane Database Syst Rev. 2002; (1): CD002992.</td>
<td>Patients with asthma ≥ 15% increase in FEV₁ after beta-agonist Single dose interventions: placebo, single dose for an extended period of intravenous or oral cardioselective beta-blockers, beta-agonist (intravenous or inhaled) given after placebo, beta-agonist (intravenous or inhaled) given after single dose of intravenous or oral cardioselective beta-blockers</td>
<td>FEV₁ % Reduction (time after dose not specified) mean % (95% CI) Single Dose: 7.98(6.19 to 9.77), p &lt; 0.01 Extended period: -0.42 (-3.74 to 2.91), p = ns</td>
<td>Significant percent reduction of FEV₁ found for single dose treatment, no significant reduction found in the longer duration treatment Statistically significant response to beta-agonist in both single and extended doses Increase in response to beta-agonist</td>
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<tr>
<td></td>
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<td>Percent Increase in Beta-Agonist Response, mean % (95% CI) Single Dose: 13.16% (10.76 to 15.56) p &lt; 0.01 Extended period: 9.09% (3.07 to 15.11), p &lt; 0.01</td>
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<tr>
<td>Salpeter, 2001(77) Cardioselective beta-blockers for chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2002; (2): CD003566.</td>
<td>Patients with COPD (FEV₁&lt;80% of normal predicted value) Selection Criteria RCTs, single or double blinded, single dose or longer durations effect of cardioselective beta-blockers on FEV₁ Three subgroups analyzed: Severe COPD FEV₁ &lt;50% (6 trials) COPD with a reversible component FEV₁ improvement of 15% after beta-agonists (7 trials) COPD with concomitant CVD, angina, ISH or HTN (8 trials) Heterogeneity: variation between trials was not significant: Single-dose trials was p=0.62 Longer duration studies was p= 0.4 Symptoms p = 1</td>
<td>Results in weighted mean difference (WMD) Severe Chronic airways obstruction Single Dose* -2.4% (-8.67 to 3.87) Longer duration* 2.2% (-8.62 to 2.41) COPD with reversible component Single Dose* -1.8% (-7.01 to 3.41) Longer duration* 1.26% (5.78 too 3.25) COPD with CVD Single Dose* -1.8% (-7.01 to 3.41) Longer duration* 4.20% (9.32 too 0.92) No increase in symptoms was seen in any of the studies.</td>
<td>These trials were all small so the possibility of a type 2 error cannot be ignored (showing no difference when there was one.) The results indicate that the use of cardioselective beta-blockers is safe in patients who have COPD, with or without a reversible component, and in a subgroup of patients with concomitant angina, ISH or HTN.</td>
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13. Aldosterone Antagonism

Problem Formulation

<table>
<thead>
<tr>
<th>Clinical Question:</th>
<th>Should medications that antagonize aldosterone be used for patients with LVSD who are on standard treatment for heart failure?</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>If so, what is the appropriate dosage and monitoring of therapy?</td>
</tr>
<tr>
<td>Population:</td>
<td>Adults with LVSD who do not have contraindications to spironolactone or eplerenone.</td>
</tr>
<tr>
<td>Health Intervention:</td>
<td>Addition of spironolactone to standard treatment for LVSD</td>
</tr>
<tr>
<td></td>
<td>Addition of eplerenone to standard treatment for LVSD</td>
</tr>
<tr>
<td>Most Important Health Outcomes:</td>
<td>Mortality due to cardiac causes</td>
</tr>
<tr>
<td></td>
<td>All-cause mortality</td>
</tr>
<tr>
<td></td>
<td>Hospitalization</td>
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</tbody>
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Search Strategy

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<td>Heart Failure</td>
<td>Systematic reviews and RCTs</td>
<td>11/11/03</td>
<td>0/35</td>
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</table>

Note: The literature search for the 2006 update was conducted by Clin-eguide and is documented in the 2006 Heart Failure Guideline.

* Same RCT identified by both search criteria.
† Same RCT identified by both search criteria.
# Evidence Tables

## Table 13.1: RCT Eplerenone vs. Placebo EPHESUS Trial

<table>
<thead>
<tr>
<th>Study &amp; design</th>
<th>Study Populations</th>
<th>Intervention &amp; Compliance</th>
<th>Results RR (95% CI) eplerenone vs. placebo</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pitt B et. al.</td>
<td>N = 6,632 treatment = 3,319 placebo = 3,313 No baseline difference between groups 90% of patients in the study had signs of heart failure</td>
<td>Eplerenone initial 25 mg/day titrated to 50 mg daily Concomitant therapy: ACEI 87% BBs 75% ASA 88% Diuretic 60%</td>
<td>All deaths 0.85 (0.75, 0.96) 14.4% vs. 16.7% ARR 2.3%, NNT 43</td>
<td>The magnitude of the death rate in the placebo group was lower and the aldosterone blockade was smaller than in the RALES trial of spironolactone. The authors attribute that to the greater use of beta-blockers and the higher EF. Mean EF was 33% compared with 25% for the RALES study.</td>
</tr>
<tr>
<td></td>
<td>Multicenter multinational, blinded allocation by center, placebo controlled RCT Intention to treat analysis Mean follow-up 16 months Powered to detect difference in mortality</td>
<td>Mean follow-up 16 months Mean EF 33%</td>
<td>Death form CV causes or hospitalization 0.87 (0.79, 0.95) 26.7% vs. 30.0% ARR 3.4% NNT 30</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Adverse events: Hyperkalemia (K&gt;6.0) 5.5% treatment Gynecomastia 0.5% treatment</td>
<td>3.9% placebo 0.6% placebo</td>
<td></td>
</tr>
</tbody>
</table>


*Intention to treat analysis Mean follow-up 16 months Powered to detect difference in mortality*
### Table 13.2: RALES: Spironolactone

<table>
<thead>
<tr>
<th>Study &amp; Design</th>
<th>Population Size &amp; Treatment Groups</th>
<th>Interventions &amp; Compliance</th>
<th>Results RR (CI: 95%) spironolactone vs. placebo</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pitt B, et al</td>
<td>Inclusion criteria: NYHA class IV in previous 6 months, current class III or IV EF =&lt;35% Exclusion criteria: potassium-sparing diuretics creat &gt;2.5mg/dl K+ &gt;5.0mmol/L N = 1663 N = 822 treatment N = 841 placebo No significant baseline difference between groups</td>
<td>Initial dose 25 mg could be adjusted to 50 mg Mean dosage spironolactone 26 mg/day Median follow-up 24mo Discontinuations: 200 placebo, 214 spironolactone Discontinued for heart transplant (11 placebo, 8 spironolactone) Concomitant Medicaions: 11% Beta-blocker 95% ACE I 100% Loop Diuretic 74% Digitalis 37% Aspirin</td>
<td>Trial ended early due to significant survival benefit of spironolactone <strong>Primary endpoint: all-cause mortality:</strong> RR 0.70 (0.59-0.82) p&lt;0.001 ARR 11% NNT 9 <strong>Secondary endpoints</strong> Death from cardiac causes: RR 0.64 (0.51-0.80) p&lt;0.001, ARR 10% Hospitalization: RR 0.70 (0.59-0.82) p&lt;0.001 Mean EF 25%</td>
<td>Adverse events: Discontinuation due to adverse events 8% treatment 5% placebo Gynecomastia 10% treatment group 1% placebo Hyperkalemia 2% treatment group 1% placebo</td>
</tr>
</tbody>
</table>
## 14. Digoxin

### Problem Formulation

<table>
<thead>
<tr>
<th>Clinical Question:</th>
<th>What is the effectiveness of digoxin in patients with systolic and/or diastolic heart failure and in normal sinus rhythm?</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Population:</strong></td>
<td>Adults with heart failure due to left ventricular systolic dysfunction or heart failure from diastolic dysfunction, who are receiving standard therapy of a vasodilator, a beta-blocker, and a diuretic and have normal sinus rhythm</td>
</tr>
<tr>
<td><strong>Health Intervention:</strong></td>
<td>Digoxin added to vasodilator, beta-blocker and diuretic therapy</td>
</tr>
</tbody>
</table>
| **Most Important Health Outcomes:** | ♦ Mortality due to cardiac causes  
♦ All-cause mortality  
♦ Hospitalization due to worsening heart failure |
**Search Strategy**

Studies selected for review were RCTs or meta-analyses of RCTs that evaluated the effectiveness of digoxin medication versus placebo. Study endpoint was at least one of the following:

- All-cause death rate
- Death due to cardiac causes
- Hospitalization rate due to worsening heart failure

<table>
<thead>
<tr>
<th>Database:</th>
<th>Search Terms:</th>
<th>Article Type and Other Limits:</th>
<th>Search Date</th>
<th>No. Included / Total Retrieved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cochrane</td>
<td>Digoxin</td>
<td>Systematic reviews</td>
<td>09/03</td>
<td>0/10</td>
</tr>
<tr>
<td>Cochrane</td>
<td>Digoxin</td>
<td>Systematic reviews</td>
<td>04/2001</td>
<td>1/10</td>
</tr>
<tr>
<td>PubMed</td>
<td>&quot;heart failure, congestive&quot;[MeSH Terms] AND &quot;digoxin&quot;[MeSH Terms]</td>
<td>Clinical trial, English, Human</td>
<td>11/01 - 09/03</td>
<td>0/17</td>
</tr>
<tr>
<td>PubMed</td>
<td>“cardiac glycosides/therapeutic use”[MESH] AND &quot;heart failure, congestive&quot;[MeSH Terms]</td>
<td>Clinical trial, English, Human</td>
<td>11/01 - 09/03</td>
<td>0/19</td>
</tr>
<tr>
<td>PubMed</td>
<td>&quot;cardiac glycosides/therapeutic use&quot;[MESH] AND &quot;heart failure, congestive&quot;[MeSH Terms]</td>
<td>Clinical trial, English, Human, Adult</td>
<td>04/2001</td>
<td>0/109</td>
</tr>
</tbody>
</table>
## 15. Oral Anticoagulation - Warfarin

### Problem Formulation

| Clinical Question: | Should warfarin be used in patients with LVSD and atrial fibrillation?  
|                   | Should warfarin be used in patients in normal sinus rhythm with LVSD, with or without a LV thrombus? |
| Population:       | Adults with LVSD and atrial fibrillation  
|                   | Adults with LVSD in normal sinus rhythm with or without a left ventricular thrombus. |
| Health Intervention: | Warfarin added to standard treatment for LVSD |
| Most Important Health Outcomes: | Mortality due to cardiac causes  
|                           | All-cause mortality  
|                           | Hospitalization  
|                           | Thromboembolic events |
## Search Strategy

Studies selected for review were RCTs or meta-analyses of RCTs that evaluated the effectiveness of digoxin medication versus placebo. Study endpoint was at least one of the following:
- All-cause death rate
- Death due to cardiac causes
- Hospitalization rate due to worsening heart failure
- Thromboembolic events

<table>
<thead>
<tr>
<th>Database:</th>
<th>Search Terms:</th>
<th>Article Type and Other Limits:</th>
<th>Search Date</th>
<th>No. Included / Total Retrieved</th>
</tr>
</thead>
<tbody>
<tr>
<td>PubMed (Heart Failure)</td>
<td>&quot;heart failure, congestive&quot; [MeSH Terms] AND &quot;warfarin&quot;[MeSH Terms]</td>
<td>Human, English</td>
<td>09/01/05 - 01/01/08</td>
<td>0/9</td>
</tr>
<tr>
<td>PubMed (atrial fibrillation)</td>
<td>&quot;Atrial Flutter&quot;[MeSH] OR &quot;Atrial Fibrillation&quot; [MeSH] AND &quot;drug therapy&quot;[Subheading] AND &quot;Anticoagulants&quot; [MeSH]</td>
<td>Human, English Meta-analysis</td>
<td>09/01/05 - 01/01/08</td>
<td>0/1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Human, English Meta-analysis</td>
<td>09/01/05 - 01/01/08</td>
<td>0/16</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Human, English Randomized, Controlled trial</td>
<td>09/01/05 - 01/01/08</td>
<td>0/16</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Human, English Clinical trials</td>
<td>09/01/05 - 01/01/08</td>
<td>0/28</td>
</tr>
<tr>
<td>Cochrane</td>
<td>Heart Failure and warfarin or anticoagulants</td>
<td>Systematic reviews</td>
<td>12/15/03</td>
<td>0/22</td>
</tr>
<tr>
<td>Cochrane</td>
<td>Heart Failure and warfarin or anticoagulants</td>
<td>Systematic reviews</td>
<td>June 2001</td>
<td>1/47</td>
</tr>
<tr>
<td>Clinical Evidence</td>
<td>Heart Failure</td>
<td>none</td>
<td>12/15/03</td>
<td>0/1</td>
</tr>
<tr>
<td>PubMed</td>
<td>(&quot;heart failure, congestive&quot; OR &quot;heart failure, congestive/drug therapy&quot;) AND (anticoagulants/tu OR anticoagulants)</td>
<td>English, Human Clinical Trial</td>
<td>June 2001</td>
<td>0/23</td>
</tr>
<tr>
<td></td>
<td></td>
<td>English, Human Meta-analysis</td>
<td>June 2001</td>
<td>1/1</td>
</tr>
<tr>
<td>Database: (atrial fibrillation)</td>
<td>Search Terms:</td>
<td>Article Type and Other Limits:</td>
<td>Search Date / Total Retrieved</td>
<td></td>
</tr>
<tr>
<td>-------------------------------</td>
<td>---------------</td>
<td>---------------------------------</td>
<td>------------------------------</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Human, English RCT 6/01/00 - 12/31/03</td>
<td>0/15</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Human, English Clinical trials 6/01/00 - 12/31/03</td>
<td>0/23</td>
<td></td>
</tr>
<tr>
<td>American College of Cardiology</td>
<td>Guidelines for atrial fibrillation</td>
<td>None 2001 - 2003</td>
<td>0/0</td>
<td></td>
</tr>
</tbody>
</table>

**Note:** The literature search for the 2006 update was conducted by Clin-eguide and is documented in the 2006 Heart Failure Guideline.
16. **Calcium Channel Blockers**

**Problem Formulation**

<table>
<thead>
<tr>
<th>Clinical Question</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>- Are dihydropyridine calcium channel blockers recommended for patients with LVSD?</td>
<td></td>
</tr>
<tr>
<td>- If so, which medications can be used?</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Population</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults with LVSD who are on standard therapy of vasodilators, beta-blockers and diuretics and still have hypertension or symptoms of angina pectoris</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Health Intervention</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>- Amlodipine or felodipine added to vasodilators, beta-blockers, and diuretics</td>
<td></td>
</tr>
<tr>
<td>- Calcium channel blockers other than amlodipine or felodipine added to vasodilators, beta-blockers, and diuretics</td>
<td></td>
</tr>
<tr>
<td>- No calcium channel blocker added to vasodilators, beta-blockers, and diuretics</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Most Important Health Outcomes</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>- Mortality due to cardiac causes</td>
<td></td>
</tr>
<tr>
<td>- All-cause mortality</td>
<td></td>
</tr>
<tr>
<td>- Hospitalization</td>
<td></td>
</tr>
<tr>
<td>- Other outcomes reported from trials or meta-analyses where mortality was an endpoint</td>
<td></td>
</tr>
</tbody>
</table>
## Search Strategy

<table>
<thead>
<tr>
<th>Database</th>
<th>Search Terms</th>
<th>Article Type and Other Limits</th>
<th>Search Date</th>
<th>No. Included / Total Retrieved</th>
</tr>
</thead>
<tbody>
<tr>
<td>PubMed</td>
<td>&quot;Calcium Channel Blockers&quot;[MESH] OR &quot;Calcium Channel Blockers&quot;[text word] AND &quot;heart failure, congestive&quot;[MESH] OR &quot;heart failure&quot;[text word]</td>
<td>Meta-analysis, All ages, English, Human</td>
<td>09/01/05 - 01/03/08</td>
<td>0/83</td>
</tr>
<tr>
<td>PubMed</td>
<td>&quot;Calcium Channel Blockers&quot;[MESH] OR &quot;Calcium Channel Blockers&quot;[text word] AND &quot;heart failure, congestive&quot;[MESH] OR &quot;heart failure&quot;[text word]</td>
<td>Randomized, controlled trials, all ages, human, English</td>
<td>09/01/05 - 01/03/08</td>
<td>0/543</td>
</tr>
<tr>
<td>Cochrane</td>
<td>Heart failure</td>
<td>Systematic reviews</td>
<td>09/2003</td>
<td>0/64</td>
</tr>
<tr>
<td>Cochrane</td>
<td>Heart failure</td>
<td>Systematic reviews</td>
<td>3/2001</td>
<td>0/23</td>
</tr>
</tbody>
</table>

**Note:** The literature search for the 2006 update was conducted by Clin-eguide and is documented in the 2006 Heart Failure Guideline.
# 17. Heart Failure with Preserved Ejection Fraction

## Problem Formulation

<table>
<thead>
<tr>
<th>Clinical Question:</th>
<th>What is the appropriate medication management for patients with heart failure with preserved ejection fraction?</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Population:</strong></td>
<td>Adults with signs and symptoms of heart failure but with preserved ejection fraction.</td>
</tr>
<tr>
<td></td>
<td>The ACC defines heart failure with preserved ejection fraction as having symptoms and signs of heart failure with normal LVEF and no valvular abnormalities on echocardiography. Every effort should be made to exclude other possible explanations or disorders that may present in a similar manner.</td>
</tr>
<tr>
<td><strong>Health Intervention:</strong></td>
<td>Any pharmacological treatment to improve outcomes in patients with heart failure with preserved ejection fraction</td>
</tr>
</tbody>
</table>
| **Most Important Health Outcomes:** | ♦ Mortality due to cardiac causes  
♦ All-cause mortality  
♦ Hospitalization |
## Search Strategy

<table>
<thead>
<tr>
<th>Database</th>
<th>Search Terms:</th>
<th>Article Type and Other Limits:</th>
<th>Search Date</th>
<th>No. Included / Total Retrieved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cochrane Heart Group</td>
<td></td>
<td>Systematic reviews</td>
<td>12/2003</td>
<td>0/71</td>
</tr>
<tr>
<td>Clinical Evidence</td>
<td>Heart failure</td>
<td>None</td>
<td>12/2003</td>
<td>0/0</td>
</tr>
<tr>
<td>Weekly scanning of journal TOCs</td>
<td></td>
<td>Meta-analysis, RCTs or Clinical Trials</td>
<td>On-going</td>
<td>1†/1</td>
</tr>
<tr>
<td>PubMed</td>
<td>&quot;heart failure, congestive&quot;[MeSH Terms] AND &quot;diastolic dysfunction&quot;[All Fields])</td>
<td>All Adult: 19+ years, Human, English</td>
<td>08/2001</td>
<td>1/51</td>
</tr>
</tbody>
</table>

*Note: The literature search for the 2006 update was conducted by Clin-eguide and is documented in the 2006 Heart Failure Guideline.*

* Ferrari et al. (2006) was found in both PubMed searches.

† The same RCT was identified in both searches.
### Table 17.1: CHARM-Preserved Trial

<table>
<thead>
<tr>
<th>CHARM-Preserved Trial</th>
<th>Trial Design</th>
<th>Study Populations</th>
<th>Results Hazard Ratio (95% CI) candesartan vs. placebo</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yusuf S, et al.</td>
<td>The CHARM-Preserved trial was a randomized, double-blinded, controlled trial to compare candesartan with matching placebo. Target dose - 32 mg daily Physicians were free to prescribe all other heart failure medications except an ARB Mean follow-up - 36.6 months 3 patients lost to follow-up (2 in candesartan and 1 in placebo group) Intention-to-treat analysis Committee adjudicating results was blinded to CHARM program and treatment assignment</td>
<td>Overall 3,029 patients were randomized: 1,514 to 32 mg candesartan; 1,509 to placebo. Inclusion criteria were: age 18 years or older NYHA class II or higher LVEF &gt;40% Baseline differences: previous MI, stroke, current smoking, HTN, diabetes, cancer, and use of digitalis and diuretics were slightly more common in the candesartan group. Previous PCI: use of lipid-lowering drugs, ASA and spironolactone were less common in the candesartan group. Discontinuation rate for all trials was 23% for candesartan and 19% for placebo, ( p = 0.0001 )</td>
<td>Primary outcome: 0.89 (0.77 to 1.03) ( p = 0.118 ) Relative risk reduction 11% Covariate Adjusted 0.86 (0.74 to 1.00) ( p = 0.051 ) CV death 0.99 (0.80 to 1.22) Non-CV death 1.10 (0.79 to 1.52) <strong>Hospitalization for worsening heart failure</strong> 230/1,514 (15%) vs. 279/1,509 (18%) ( p = 0.017 ) <strong>Medication discontinuation at study end</strong> 270 (18%) vs. 204 (14%) ( p = 0.001 )</td>
<td>The authors stated that there were baseline differences but do not state whether they were significant or not. The annual death rate in the placebo group with reduced LVEF was 9% compared with 4% for patients with EF &gt; 40%.</td>
</tr>
</tbody>
</table>

**Primary outcome** was CV death or unplanned admission to hospital for management of worsening heart failure.

**Secondary outcomes** were: CV death, hospitalization for heart failure, or nonfatal MI; CV death, hospitalization for heart failure, nonfatal MI, nonfatal stroke, or coronary revascularization; death (any cause) or hospitalization for heart failure; and development of new diabetes.
### Table 17.2: RCTs of Treatment of Patients with Heart Failure with Preserved Ejection Fraction

<table>
<thead>
<tr>
<th>Name</th>
<th>N</th>
<th>Sample Ages (Mean ± SD yr)</th>
<th>% Female</th>
<th>Ejection Fraction (Mean ± SD, %)</th>
<th>NYHA Class (%)</th>
<th>Follow-up Time (Mean)</th>
<th>Primary Endpoint: Heart Failure Hospitalization or Death (%)</th>
<th>HR</th>
<th>95% CI</th>
<th>p</th>
<th>Study Quality †</th>
<th>Biases*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ahmed (2006); Ancillary DIG trial</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digoxin 492</td>
<td>Placebo 496</td>
<td>66.7 ± 10.7</td>
<td>66.9 ± 9.9</td>
<td>42.1 40.3</td>
<td>62.4 ± 21.3</td>
<td>61.1 ± 19.8</td>
<td>19.1 20.6</td>
<td>59.3 56.9</td>
<td>20.7 21.0</td>
<td>0.8 1.6</td>
<td>37 mo</td>
<td>21</td>
</tr>
<tr>
<td><strong>Ferrari, (2006); PREAMI trial</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perindopril 631</td>
<td>Placebo 621</td>
<td>72 ± 6</td>
<td>73 ± 5</td>
<td>35 35</td>
<td>59</td>
<td>59</td>
<td>77 81</td>
<td>22 18</td>
<td>1</td>
<td>1</td>
<td>12 mo</td>
<td>35</td>
</tr>
<tr>
<td><strong>Cleland, (2006); PEP-CHF trial</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perindopril 424</td>
<td>Placebo 426</td>
<td>75 (72-79)</td>
<td>75 (72-79)</td>
<td>54 57</td>
<td>65 (56-66)</td>
<td>64 (56-66)</td>
<td>77 74</td>
<td>23 26</td>
<td>2.1 years</td>
<td>23.6</td>
<td>25.1</td>
<td>0.92</td>
</tr>
</tbody>
</table>

CI: = confidence interval  
HR = hazard ratio  
NYHA = New York Heart Association  
RR = risk reduction  
†Study quality measured by Jadad Scoring System (1 to 5 = low to high).  
*Biases: N: none; 1: sample attrition >15%; 2: sample selection bias; 3: detection bias (e.g., measurement error, ITT analysis, power); 4: study procedure biases (e.g., blinding, randomization)
Lifestyle Factors

18. Sodium Restricted Diet

Problem Formulation

<table>
<thead>
<tr>
<th>Clinical Question</th>
<th>Should patients with heart failure (systolic and/or diastolic heart failure) restrict sodium intake?</th>
<th>If so, what is the appropriate daily consumption of sodium?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>Adults with heart failure, for whom a decrease in sodium intake is not contraindicated.</td>
<td>Adults with heart failure, for whom fluid retention requires increased diuretic intervention and a decrease in sodium intake is not contraindicated</td>
</tr>
</tbody>
</table>

Health Intervention | Sodium restricted diet |

Most Important Health Outcomes | Mortality due to cardiac causes | Hospitalization | All-cause mortality | Symptoms of heart failure |

Search Strategy

<table>
<thead>
<tr>
<th>Database:</th>
<th>Search Terms:</th>
<th>Article Type and Other Limits:</th>
<th>Search Date</th>
<th>No. Included / Total Retrieved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cochrane</td>
<td>Heart Failure, Congestive</td>
<td>Systematic Reviews</td>
<td>11/2003</td>
<td>0/66</td>
</tr>
<tr>
<td>Cochrane</td>
<td>Heart Failure, Congestive</td>
<td>Systematic Reviews</td>
<td>3/2001</td>
<td>0/44</td>
</tr>
</tbody>
</table>

Note: The literature search for the 2006 update was conducted by Clin-eguide and is documented in the 2006 Heart Failure Guideline.
19. Physical Activity

Problem Formulation

| Clinical Question: | • Should patients with systolic and/or diastolic heart failure be advised to exercise?  
• If so, how much and what type of exercise is appropriate for someone with systolic and/or diastolic heart failure? |
| Population: | Adults with heart failure and no contraindications to light to moderate physical activity |
| Health Intervention: | Light to moderate physical activity |
| Most Important Health Outcomes: | • Mortality due to cardiac causes  
• All-cause mortality  
• Hospitalization  
• Symptoms of heart failure  
• Quality of life |

Search Strategy

Studies selected for review were clinical trials where study endpoint was at least one of the following:
• All-cause death rate
• Death due to cardiac causes
• Hospitalization rate
• Quality of life scores
• Symptom scores

<table>
<thead>
<tr>
<th>Database:</th>
<th>Search Terms:</th>
<th>Article Type and Other Limits:</th>
<th>Search Date</th>
<th>No. Included / Total Retrieved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cochrane</td>
<td>Congestive heart failure</td>
<td>Systematic reviews</td>
<td>12/03</td>
<td>0/66</td>
</tr>
<tr>
<td>Cochrane</td>
<td>Congestive heart failure</td>
<td>Systematic reviews</td>
<td>3/2001</td>
<td>0/44</td>
</tr>
<tr>
<td>Database</td>
<td>Search Terms</td>
<td>Article Type and Other Limits</td>
<td>Search Date</td>
<td>No. Included / Total Retrieved</td>
</tr>
<tr>
<td>----------</td>
<td>--------------</td>
<td>-------------------------------</td>
<td>-------------</td>
<td>------------------------------</td>
</tr>
<tr>
<td>PubMed</td>
<td>(((&quot;heart failure, congestive/rehabilitation&quot;[MeSH] AND (&quot;heart failure congestive/mortality&quot; [MeSH]) AND Clinical Trial[ptyp]) AND English[Lang]) AND &quot;adult&quot;[MeSH Terms]) AND &quot;human&quot;[MeSH Terms])</td>
<td>Adults 19+ years, English, Human</td>
<td>6/29/01</td>
<td>1/48</td>
</tr>
</tbody>
</table>

* The Piepoli meta-analysis\(^{(117)}\) (Jan. 16, 2004) was found by searching heart.org.
### Evidence Tables

**Table 19.1: Meta-Analysis of Studies on Physical Activity in Heart Failure**

<table>
<thead>
<tr>
<th>Meta-Analysis</th>
<th>Studies Selected</th>
<th>Studies Included</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
</table>
| ExTraMATCH Collaborative, exercise training meta-analysis of trials in patients with chronic heart failure (ExTraMATCH). BMJ 2004;328:189-295, Prospective protocol used | Criteria:  
Randomized parallel group controlled trials  
Exercise training w/o other simultaneous intervention that could confound results  
Patients with stable heart failure (3 months or more of stability)  
Heart failure due to LVSD (LVEF ≤ 50%)  
Exercise program ≥8 weeks  
Training involves at least both legs  
Survival f/u of ≥3 months  
101 potential reports identified representing 41 potential datasets | Nine datasets met eligibility criteria  
Eight were European, one from U.S.  
All used intention-to-treat-analysis | Number of patients ranged from 27 – 181  
Duration of training ranged from 8 weeks in small trial to ≥ one year in largest 5 studies  
Mean follow up from 159 – 2284 days.  
No apparent publication bias was found.  
N = 801 patients. Exercise group = 395; Control group = 406 | Limits:  
Unable to use data from one study ( n=25) for secondary outcome.  
Since these trials must be open, it is possible that medications were administered differently to different groups. However, investigators reported no differences.  
No report on heterogeneity. |
|                                                                              | Exercise Group, n (%)  
Death  88/395 (22)  
Death or admission to hosp* 127/354 (36) | Control Group, n (%)  
P  
105/406 (26)  
173/367 (47) | p  
0.015  
0.018 |  
*assessed in 8 of 9 studies  
NNT – 17 to prevent 1 death in 2 years |
**Table 19.2: Systematic Review of Studies on Physical Activity in Heart Failure**

<table>
<thead>
<tr>
<th>Systematic Review</th>
<th>Studies Selected</th>
<th>Studies Included</th>
<th>Results</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lloyd-Williams, F et al. Exercise training and heart failure: a systematic review of current evidence. Br J General Practice 2002 52:47-55.</td>
<td>Databases searched: Medline, Science Citation Index, Social Sciences Citation Index, DIDS, Bandolier, Cochrane Database of Systematic Review, NHS National Research Register and Current Research in Britain. Reviewed papers published between 1966 and December 2000 (included latest key journal editions not yet in databases). Search terms: exercise training, physical training, aerobic, anaerobic, heart failure, left ventricular failure, and cardiac failure. Reference lists of included articles were also searched. Outcomes of excluded studies: the effects of drugs upon the physical performance of patients with heart failure and the biomedical changes in patients with heart failure as a result of exercise. Included: English language papers, randomized controlled trials or clinical trials. Outcomes: Effects of physical training in terms of physical performance, QOL, or cost effectiveness or health care utilization.</td>
<td>31 studies met the SR criteria 14 were prospective RCTs, 8 were randomized crossover trials, 2 were non-RCTs, and 7 were pre-test/post-test studies.</td>
<td>General Description</td>
<td>Limits English only studies Authors and experts were not consulted.</td>
</tr>
</tbody>
</table>

In most studies, exercise training was supervised and took place in the hospital. 45% (14/31) of studies lasted 8 weeks or less. Of RCTs, only 43% (6/14) described randomization method, and those which did were often vague. 74% (23/31) described inclusion criteria (and, in some, exclusion criteria). However, just 42% (13/31) described the recruitment procedure adopted. These tended to be convenience sample or volunteers. 26% of studies excluded patients with diabetes; 52% excluded those with COPD. 65% (20/31) had sample sizes of 25 or less; 26% (7/31) had sample sizes of 26 to 50; and 13% (4/31) had 51 to 150 participants.

**Patient Age**
Mean age was below 65 yrs in 74% of the studies, although heart failure is much more common in an older group of patients. One studies had a mean age of 70 yrs, and one of 81 yrs.

**Patient Compliance and Completion**
Completion rates were not reported for 5 studies. Completion rates for exercise training in 15 studies were between 90 – 100%, and were between 50 – 89% for 11 studies. Compliance rates were not reported for 15 and were >80% for 12 studies. 4 studies reported rates between 50 – 80%.

**Nature and Intensity of Exercise**
11 studies used a cycle ergometer; 14 used a combination program (cycle and/or walking, jogging, swimming, circuit training). 5 studies did muscle training (knee extensor or leg); 2 used a walking program. No studies assessed patient acceptance and ability to adopt program on a long-term basis. 8 studies had a home-based component and 7 provided them with a cycle ergometer and/or treadmill for home use. One study specified an individualized walking program for 1 yr. No study with a home component reported on the pros and cons of this approach when compared with the hospital-based approach.

**Outcomes**
Of the many physiological outcomes reported, the most common with positive results were oxygen uptake (23/31), resting heart rate (15/31), maximal heart rate (11/31), sub-maximal heart rate (9/31), SBP (8/31), and ventilation (8/31). 52% assessed QOL (16/31), and of these, 69% (11/16) reported positive results. 4 studies looked at the relationship between QOL results and physiological measures. Varied approaches and instruments were used to measure QOL. Utilization and mortality were addressed in 1 study. (See Belardinelli study in 2002 Heart Failure Guidelines.)
### Table 19.3: RCTs - Physical Activity

<table>
<thead>
<tr>
<th>Author</th>
<th>Indication</th>
<th>Subject Characteristics</th>
<th>Age of Subjects</th>
<th>Study Design</th>
<th>Clin-eguide Evidence Grade</th>
<th>Treatment</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Duration</th>
<th>No. of Subjects</th>
<th>Study controls</th>
<th>Outcome</th>
<th>Study Endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 months</td>
<td>24</td>
<td>Usual care</td>
<td>Self-efficacy expectations scale scores for walking, stair climbing, lifting, and general activities</td>
<td>Only individuals randomized to the exercise group reported a significant improvement in self-efficacy for walking (p =0.04). No differences were found in perceived self-efficacy for lifting (p =0.49), climbing (p =0.25), or general activities (p =0.13) in either group after 3 months of participation in the exercise program</td>
</tr>
</tbody>
</table>
### Table 19.4

<table>
<thead>
<tr>
<th>Study, Total n</th>
<th>Treatment Groups Size &amp; Intervention</th>
<th>Study Population</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>McKelvie RS et al. Effects of exercise training in patients with heart failure: The Exercise Rehabilitation Trial (EXERT) Am Heart J 2002;144:23-30. N = 181 Randomized, controlled, single-blind (blinded endpoint evaluation; stratification by center) Two Canadian centers</td>
<td>Exercise Group – beginning n = 90 n at three months = 80 final n = 64 Three months' supervised training in aerobics to a heart rate of 60-70% of measured maximum heart rate response (cycle, treadmill and ergometry) for 30min/ session. Two sessions per week at study center and one/week at home (walking only). Resistance training: Arm curl, knee extension and leg press performed individually w/ each limb. Increasing intensity of 40-60% of 1 rep max. Ten reps for arm and 15 for leg – 3 sets exercise/ session For months 3-12 pts given exercise bicycle and free weights and instructed to continue training at home 3x/ week. Control Group – beginning n = 91 three months’ n = 83 final n = 75 Control patients given no formal exercise guidelines. Told to continue with usual level of activity. Baseline and 3- and 12-months testing for both groups. All patients were reviewed monthly.</td>
<td>Inclusion: Patients with stable heart failure on ACEI, diuretics, and digoxin as necessary at baseline. LVEF&lt;40%, NYHA class I to III, 6-minute walk test distance &lt;500 meters. Exclusion: Inability to attend regular exercise training sessions, testing limited by angina or leg claudication, abnormal BP response during exercise, cerebrovascular or musculoskeletal disease preventing testing or training, respiratory limitation, poorly controlled cardiac arrhythmia, any noncardiac condition affecting regular exercise training or decreasing survival.</td>
<td>Peak Oxygen Uptake (exercise test performance – L/min) Between baseline and 3 months, exercise group improved significantly: p &lt; 0.01 At 3 months, the exercise group improved compared with the control group: p = 0.026 Between baseline and 12 months, exercise group improved significantly: p &lt; 0.05 At 12 months, the exercise group improved compared with the control group: p = NS Note: there was no significant difference between groups at baseline. Six-Minute Walk Test Distance (meters) Between baseline and 3 months, exercise group increased walk distance: 22± 5, p &lt;0.01 Between baseline and 3 months, control group increased walk distance: 20± 9, p &lt;0.01 At 12 months, exercise group increased walk distance: 17± 8, p &lt;0.05 Between baseline and 12 months, control group increased walk distance: 20± 9, p &lt;0.05 There were no significant differences found between groups at 3 months (p = 0.36) or 12 months (p = 0.81) Note: there was no significant difference between groups at baseline. See table below for additional outcomes.</td>
<td></td>
</tr>
</tbody>
</table>
Table 19.5: Baseline and changes in oxygen uptake, muscle strength, cardiac function, and quality of life at three months and 12 months*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Baseline</th>
<th>Change at 3 months</th>
<th>Change at 12 months</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Exercise</td>
<td>Control</td>
<td>Exercise</td>
</tr>
<tr>
<td>Submax HR (beats/min) ± SEM</td>
<td>102 ± 2</td>
<td>103 ± 2</td>
<td>-2 ± 2 (n = 77)</td>
<td>-6 ± 2</td>
</tr>
<tr>
<td></td>
<td>(n = 91)</td>
<td>(n = 90)</td>
<td>(n = 77)</td>
<td>(n = 77)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-6 ± 2 (n = 77)</td>
<td>-4 ± 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(n = 65)</td>
<td>(n = 65)</td>
</tr>
<tr>
<td>Arm curl (kg) ± SEM</td>
<td>8.1 ± 0.4</td>
<td>8.8 ± 0.4</td>
<td>0.50 ± 0.16 (n = 80)</td>
<td>1.20 ± 0.23 (n = 76)</td>
</tr>
<tr>
<td></td>
<td>(n = 80)</td>
<td>(n = 80)</td>
<td>(n = 76)</td>
<td>(n = 76)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.07 ± 0.31 (n = 71)</td>
<td>0.61 ± 0.33 (n = 60)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(n = 71)</td>
<td>(n = 71)</td>
</tr>
<tr>
<td>Knee extension (kg) ± SEM</td>
<td>16.6 ± 0.8</td>
<td>17.1 ± 0.8</td>
<td>0.67 ± 0.29 (n = 78)</td>
<td>2.79 ± 0.44 (n = 75)</td>
</tr>
<tr>
<td></td>
<td>(n = 78)</td>
<td>(n = 78)</td>
<td>(n = 75)</td>
<td>(n = 75)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.47 ± 0.54 (n = 69)</td>
<td>1.10 ± 0.61 (n = 59)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(n = 69)</td>
<td>(n = 69)</td>
</tr>
<tr>
<td>Leg press (kg) ± SEM</td>
<td>64.0 ± 1.8</td>
<td>66.8 ± 2.1</td>
<td>1.07 ± 0.65 (n = 79)</td>
<td>2.48 ± 0.79 (n = 76)</td>
</tr>
<tr>
<td></td>
<td>(n = 79)</td>
<td>(n = 79)</td>
<td>(n = 76)</td>
<td>(n = 76)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.60 ± 1.12 (n = 60)</td>
<td>1.57 ± 1.14 (n = 60)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(n = 60)</td>
<td>(n = 60)</td>
</tr>
<tr>
<td>Ejection fraction ± SEM</td>
<td>27.7 ± 0.9</td>
<td>28.2 ± 0.8</td>
<td>1.6 ± 0.7 (n = 81)</td>
<td>0.2 ± 0.7 (n = 80)</td>
</tr>
<tr>
<td></td>
<td>(n = 81)</td>
<td>(n = 80)</td>
<td>(n = 80)</td>
<td>(n = 80)</td>
</tr>
<tr>
<td>EDV (ml) ± SEM</td>
<td>412 ± 23</td>
<td>425 ± 26</td>
<td>5 ± 14 (n = 80)</td>
<td>27 ± 23 (n = 80)</td>
</tr>
<tr>
<td>ESV (ml) ± SEM</td>
<td>313 ± 20</td>
<td>321 ± 20</td>
<td>-10 ± 14 (n = 80)</td>
<td>11 ± 23 (n = 80)</td>
</tr>
<tr>
<td>MLHF ± SEM</td>
<td>28.6 ± 2.1</td>
<td>32.5 ± 2.5</td>
<td>-1.2 ± 1.5 (n = 73)</td>
<td>-3.9 ± 1.9 (n = 70)</td>
</tr>
<tr>
<td></td>
<td>(n = 73)</td>
<td>(n = 70)</td>
<td>(n = 70)</td>
<td>(n = 70)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-3.3 ± 1.7 (n = 67)</td>
<td>-3.4 ± 2.4 (n = 57)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(n = 67)</td>
<td>(n = 57)</td>
</tr>
</tbody>
</table>

P value is comparison of exercise versus control. EDV, end-diastolic volume; ESV, end-systolic volume; MLHF, Minnesota Living with Heart Failure questionnaire score

* Table II from article,(118)
## 20. Pharmacological Management of LVSD Based on Patients’ Race/Ethnicity or Sex

### Problem Formulation

| Clinical Question: | ✷ Should medication management of patients with heart failure be different based on the patient’s race/ethnicity or sex?  
|                    | ✷ Should hydralazine and ISDN be added to ACE inhibitors and/or beta-blockers to treat black/African American patients with heart failure? |
| Population:        | ✷ Females with LVSD  
|                    | ✷ Nonwhite patients with LVSD |
| Health Intervention: | Use of ACE inhibitors, beta-blockers, digoxin, spironolactone, and combination hydralazine and isosorbide dinitrate in males and in whites |
| Most Important Health Outcomes: | ✷ Mortality due to cardiac causes  
|                               | ✷ All-cause mortality  
|                               | ✷ Hospitalization |
### Search Strategy

<p>| Database: Cochrane Systemic Reviews | Search Terms: “gender” and “heart failure” | Article Type and Other Limits: Clinical Trials | Search Date: 2006 - 12/2007 | No. Included / Total Retrieved: 0/0 |
| Database: Cochrane Systemic Reviews | Search Terms: “race” and “ethnicity” and “heart failure” | Article Type and Other Limits: Clinical Trials | Search Date: 2006 - 12/2007 | No. Included / Total Retrieved: 0/0 |
| Database: PubMed | Search Terms: &quot;continental population groups&quot;[MeSH Terms] OR Race[Text Word] AND ((&quot;heart&quot;[MeSH Terms] OR heart[Text Word]) AND failure[All Fields]) | Article Type and Other Limits: Human, English, All Adult: 19+ years, Clinical Trials, RCTs, meta-analysis, only items with abstracts | Search Date: 02/2006 - 12/2007 | No. Included / Total Retrieved: 1/27 |
| Database: PubMed | Search Terms: &quot;sex&quot;[MeSH Terms] OR sex[Text Word] AND ((&quot;heart&quot;[MeSH Terms] OR heart[Text Word]) AND failure[All Fields]) | Article Type and Other Limits: Human, English, All Adult: 19+ years, Clinical Trials, RCTs, meta-analysis, only items with abstracts | Search Date: 02/2006 - 12/2007 | No. Included / Total Retrieved: 2/65 |</p>
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<tr>
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<th>Search Terms:</th>
<th>Article Type and Other Limits:</th>
<th>Search Date</th>
<th>No. Included / Total Retrieved</th>
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<tbody>
<tr>
<td>PubMed</td>
<td>(&quot;adrenergic beta-antagonists&quot;[TIAB] NOT Medline[SB]) OR &quot;adrenergic beta-antagonists&quot;[MeSH Terms] OR &quot;adrenergic beta-antagonists&quot;[Pharmacological Action] OR Beta-blockers[Text Word]) AND (&quot;continental population groups&quot;[MeSH Terms] OR Race[Text Word]) AND (&quot;heart&quot;[MeSH Terms] OR heart[Text Word]) AND failure[All Fields])</td>
<td>Human, English, All Adult: 19+ years, Clinical Trials, RCTs, meta-analysis, only items with abstracts</td>
<td>02/2006 - 12/2007</td>
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<td>------------</td>
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<td>--------------------------------</td>
<td>-------------</td>
<td>------------------------------</td>
</tr>
<tr>
<td>Cochrane</td>
<td>Heart Failure</td>
<td>Systematic reviews</td>
<td>9/2003</td>
<td>0/120</td>
</tr>
<tr>
<td></td>
<td>Heart Failure, Congestive</td>
<td>Systematic reviews</td>
<td>3/2001</td>
<td>0/35</td>
</tr>
<tr>
<td>PubMed</td>
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<td>Clinical Trials</td>
<td>11/00 - 10/03</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>Meta-analyses</td>
<td>11/00 - 10/03</td>
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<tr>
<td></td>
<td>(((“Heart Failure, Congestive”[MESH] OR “Heart Failure, Congestive/drug therapy”[MESH]) AND “Negroid Race”[MESH])</td>
<td>Meta-analyses</td>
<td>8/01</td>
<td>3/73</td>
</tr>
<tr>
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<td>(((“Heart Failure, Congestive”[MESH] OR “Heart Failure, Congestive/drug therapy”[MESH]) AND “Australoid Race”[MESH] OR “Caucasoid Race”[MESH] OR “Mongoloid Race”[MESH])</td>
<td>Clinical Trials</td>
<td>11/00 - 10/03</td>
<td>0/237</td>
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<td></td>
<td>Meta-analyses</td>
<td>11/00 - 10/03</td>
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<td>Meta-analyses</td>
<td>8/01</td>
<td>0/0</td>
</tr>
<tr>
<td>PubMed</td>
<td>(((“Heart Failure, Congestive”[MESH] OR &quot;heart failure”[text word]) AND &quot;Sex Characteristics” [MESH]) OR (((&quot;sex factors”[MESH])</td>
<td>Clinical Trials</td>
<td>11/00 - 10/03</td>
<td>0/1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Meta-analyses</td>
<td>11/00 - 10/03</td>
<td>0/0</td>
</tr>
<tr>
<td></td>
<td>(((“Heart Failure, Congestive”[MESH] OR &quot;heart failure”[text word]) AND &quot;Sex Characteristics” [MESH]) OR (((&quot;sex factors”[MESH])</td>
<td>English, Human</td>
<td>8/01</td>
<td>0/35</td>
</tr>
</tbody>
</table>

**Note:** The literature search for the 2006 update was conducted by Clin-eguide and is documented in the 2006 Heart Failure Guideline.

* Article found was the Agency for Healthcare Research and Quality Evidence Report/Technology Assessment, Number 82, Pharmacologic Management of Heart Failure and Left Ventricular Systolic Dysfunction: Effect in Female, Black and Diabetic Patients, and Cost-Effectiveness, Summary, which was the basis of the meta-analysis described in the rationale statement and the evidence table.
### Evidence Tables

#### Table 20.1: Post Hoc Subgroup Analysis of the African-American Heart Failure Trial

<table>
<thead>
<tr>
<th>Name</th>
<th>N</th>
<th>All-Cause Mortality or First Hospitalization (Events)</th>
<th>p</th>
<th>Follow-up Time (Mean)</th>
<th>Study Quality†</th>
<th>Biases*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taylor (2007)</td>
<td>Female: 420, Male: 630</td>
<td>100, 166</td>
<td>0.611</td>
<td>18 mo</td>
<td>5</td>
<td>5</td>
</tr>
</tbody>
</table>

†Study quality measured by Jadad Scoring System.

*Biases: N: none; 1: sample attrition >15%; 2: sample selection bias; 3: detection bias (e.g., measurement error, ITT analysis, power); 4: study procedure biases (e.g., blinding, randomization); 5: incomplete data presentation

#### Table 20.2: Hydralazine & Isosorbide Dinitrate for LVSD: African-American Heart Failure (A-HeFT) Trial

<table>
<thead>
<tr>
<th>Authors</th>
<th>Study Name</th>
<th>Indication</th>
<th>Subject Characteristics</th>
<th>Age of Subjects</th>
<th>Study Design</th>
<th>Clin-eguide Evidence Grade</th>
<th>Treatment (Name, Dose, Route, Frequency)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taylor AL, Ziesche S, Yancy C, et al, African-American Heart Failure Trial Investigators</td>
<td>A-HeFT</td>
<td>Congestive heart failure, heart failure</td>
<td>Patients had New York Heart Association class III or IV heart failure with a duration of ≥3 mo and a left ventricular &lt;35% OR (ejection fraction &lt;45% with end-diastolic diameter 2.9 cm/m² or &gt;6.9 cm on echocardiography). Patients were receiving stable therapy for heart failure and their body weight had varied by &lt;2.5% in the 2 weeks preceding randomization.</td>
<td>≥18 years</td>
<td>Multicenter (161 centers), randomized, double-blind</td>
<td>A1</td>
<td>Hydralazine/isosorbide-dinitrate 112.5/60 then 225/120 mg/day, PO, tid</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Duration</th>
<th>No. of Subjects</th>
<th>Study Controls</th>
<th>Outcomes</th>
<th>Study Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 18 mo (mean, 10 mo)</td>
<td>1050</td>
<td>Placebo comparison</td>
<td>Death rate, Diastolic blood pressure, Heart failure event rate, Heart rate, Hospitalization, Minnesota Heart Failure Symptom questionnaire, Systolic blood pressure, Treatment failure rate</td>
<td>Hydralazine/isosorbide dinitrate significantly decreased all-cause mortality, hospitalization for heart failure, and Minnesota Heart Failure Symptom Questionnaire scores compared with placebo in Black patients with heart failure (p &lt; 0.05, p = 0.001, and p &lt; 0.05, respectively)</td>
</tr>
</tbody>
</table>
Table 20.3: Meta-Analysis – Efficacy of ACEI and Beta-Blockers in LVSD by Race and Sex

<table>
<thead>
<tr>
<th>Study</th>
<th>Studies</th>
<th>Results (95% CI) - Effects on Mortality</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shekelle PG, et al.</td>
<td>Efficacy of angiotensin-converting enzyme inhibitors and beta-blockers in the management of left ventricular systolic dysfunction according to race, sex, and diabetic status. A meta-analysis of major clinical trials. J Am Coll Cardiol 2003;41(9):1529-38</td>
<td>Initial study criteria: Randomized and controlled trial of ACE inhibitors and/or beta-blockers. At least 12 weeks follow-up. Mortality outcomes. 39 reports of ACE inhibitors and 35 of beta-blockers were identified.</td>
<td></td>
</tr>
<tr>
<td>N = varies by analysis</td>
<td>Source of Data: PD = published data IPD = individual patient data</td>
<td>Final studies included = 12</td>
<td></td>
</tr>
</tbody>
</table>

ACE Inhibitor Trial Name: | Drug | Source of Data: |
--- | --- | --- |
AIRE | Ramipril | PD |
CONSENSUS | Enalapril | IPD |
SAVE | Trandolapril | PD |
SMILE | Zofenopril | PD |
SOLVD-Prev'n | Enalapril | IPD |
SOLVD-Tx | Enalapril | IPD |
TRACE | Trandolapril | IPD |

Beta-Blocker Trial Name: | Drug | Source of Data: |
--- | --- | --- |
BEST | Bucindolol | PD |
CIBIS-II | Bisoprolol | PD |
COPERNICUS | Carvedilol | IPD |
MERIT-HF | Metoprolol | IPD |
US Carvedilol Study | Carvedilol | PD |

ACE Inhibitors:
- Sex – Random effects pooled estimates (6 studies – n=2,373 women, 10,213 men)
  - RR Males: 0.82 (0.74 – 0.90)
  - RR Females: 0.92 (0.81 – 1.04)
  - Relative Risk Reduction: 1.15 (0.99 – 1.33)
  - HR Males: 0.76 (0.66 – 0.87)
  - HR Females: 0.84 (0.72 – 0.98)
- P value for HR: 0.0
- Sex – Effects reported separately for prevention (asymptomatic: n=1,724 women, n for men not given) and treatment studies (symptomatic: n=1,079 women, n for men not given) – 6 studies
- Treatment Studies
  - RR Males: 0.83 (0.71 – 0.96)
  - RR Females: 0.96 (0.75 – 1.22)
  - Relative Risk Reduction: 1.25 (0.94 – 1.65)

Beta-blockers:
- Note: data were analyzed with and without the BEST study [bucindolol] and results were similar.
- Sex – Random effects pooled estimates (5 studies – n=2,134 women, 7,885 men)
  - RR Males: 0.66(0.59 – 0.75)
  - RR Females: 0.63 (0.44 – 0.91)
  - Relative Risk Reduction: 0.99 (0.70 – 1.41)
- Black and White Race
  - Random effects pooled estimates with BEST (4 studies: n=5,824 whites, 1,172 blacks)
  - RR Whites: 0.69 (0.55 – 0.85)
  - RR Blacks: 0.97 (0.68 – 1.37)
  - Relative Risk Reduction: 1.35 (1.07 – 1.71)
  - Random effects pooled estimates without BEST (3 studies: n=5,824 whites, 545 blacks)
  - RR Whites: 0.63 (0.52 – 0.77)
  - RR Blacks: 0.67 (0.38 – 1.16)
  - Relative Risk Reduction: 1.17 (0.65 – 2.11)

Heterogeneity: The authors mention that there were substantial differences between studies but no statistics measuring heterogeneity were given.
21. Target Blood Pressure

Problem Formulation

<table>
<thead>
<tr>
<th>Clinical Question</th>
<th>What is the appropriate target blood pressure in heart failure patients?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>Adults with heart failure with elevated blood pressure</td>
</tr>
<tr>
<td>Health Intervention</td>
<td>Target blood pressure goal of &lt; 130/80 mm Hg</td>
</tr>
</tbody>
</table>
| Most Important Health Outcomes | • Mortality due to cardiac causes  
|                               | • All-cause mortality                                                 |
|                               | • Hospitalization                                                     |

Search Strategy

<table>
<thead>
<tr>
<th>Database:</th>
<th>Search Terms:</th>
<th>Article Type and Other Limits:</th>
<th>Search Date</th>
<th>No. Included / Total Retrieved</th>
</tr>
</thead>
</table>

Note: The original literature search was conducted by Clin-eguide and is documented in the 2006 Heart Failure Guideline.
22. Medications to Achieve Target Blood Pressure

Problem Formulation

<table>
<thead>
<tr>
<th>Clinical Question</th>
<th>What medications should be used to achieve the appropriate target blood pressure in heart failure?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>Adults with heart failure without documented CAD</td>
</tr>
<tr>
<td>Health Intervention</td>
<td>Medications to control hypertension to desired levels</td>
</tr>
</tbody>
</table>
| Most Important Health Outcomes | * Mortality due to cardiac causes  
* All-cause mortality  
* Hospitalization |

Search Strategy

<table>
<thead>
<tr>
<th>Database</th>
<th>Search Terms</th>
<th>Article Type and Other Limits</th>
<th>Search Date</th>
<th>No. Included / Total Retrieved</th>
</tr>
</thead>
</table>

Note: The original literature search was conducted by Clin-eguide and is documented in the 2006 Heart Failure Guideline.
23. Reassessment of Systolic Performance

Problem Formulation

<table>
<thead>
<tr>
<th>Clinical Question</th>
<th>How often should reassessment of systolic performance take place?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>Adults with heart failure without documented CAD</td>
</tr>
<tr>
<td>Health Intervention</td>
<td>Reassessment of systolic performance</td>
</tr>
</tbody>
</table>

**Most Important Health Outcomes**
- Mortality due to cardiac causes
- All-cause mortality
- Hospitalization
- NYHA Class or equivalent

Search Strategy

<table>
<thead>
<tr>
<th>Database:</th>
<th>Search Terms:</th>
<th>Article Type and Other Limits:</th>
<th>Search Date</th>
<th>No. Included / Total Retrieved</th>
</tr>
</thead>
</table>

Note: The original literature search was conducted by Clin-eGuide and is documented in the 2006 Heart Failure Guideline.
# 24. Omega-3 Supplementation

## Problem Formulation

<table>
<thead>
<tr>
<th>Clinical Question</th>
<th>Should patients with heart failure be treated with omega-3 fatty acid* supplements to improve heart failure-related outcomes?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>Adults with heart failure on standard therapy with vasodilators, BBs, and diuretics</td>
</tr>
<tr>
<td>Health Intervention</td>
<td>Omega-3 fatty acid supplements</td>
</tr>
</tbody>
</table>
| Side Effects      | • GI disturbances  
|                   | • Stroke (ischemic and hemorrhagic)  
|                   | • Bleeding                                                                                                         |
| Most Important Health Outcomes | • Mortality due to cardiac causes  
|                   | • All-cause mortality  
|                   | • Hospitalization                                                                                                    |

## Search Strategy

<table>
<thead>
<tr>
<th>Database: Cochrane Systematic Reviews</th>
<th>Search Terms: “heart failure” AND “omega-3”</th>
<th>Article Type and Other Limits: Clinical trials</th>
<th>Search Date: 1966 – Feb 2009</th>
<th>No. Included / Total Retrieved: 0/3</th>
</tr>
</thead>
<tbody>
<tr>
<td>PubMed</td>
<td>“heart failure” AND “omega-3” OR &quot;omega-3 fatty acid desaturase&quot; [Substance Name] OR &quot;omega-(3-azidophenoxy) undecanoic acid&quot; [Substance Name] OR &quot;Fatty Acids, Omega-3&quot;[MeSH Major Topic] OR &quot;fish oils [Mesh] OR eicosapentanoic acid [Substance Name] OR docosahexaenoic acids [Mesh]”</td>
<td>RCTs, meta-analyses, systematic reviews</td>
<td>1966 – Feb 2009</td>
<td>1/6</td>
</tr>
<tr>
<td>OVID</td>
<td>“heart failure” AND “omega-3” OR &quot;omega-3 fatty acid desaturase&quot; [Substance Name] OR &quot;omega-(3-azidophenoxy) undecanoic acid&quot; [Substance Name] OR &quot;Fatty Acids, Omega-3&quot;[MeSH Major Topic] OR &quot;fish oils [Mesh] OR eicosapentanoic acid [Substance Name] OR docosahexaenoic acids [Mesh]”</td>
<td>RCTs, meta-analyses, systematic reviews</td>
<td>1966 – Feb 2009</td>
<td>0/5</td>
</tr>
</tbody>
</table>

* Omega-3 fatty acids are also known as n-3 polyunsaturated fatty acids (PUFA).
References


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(70) Rationale, design, and organization of the Metoprolol CR/XL Randomized Intervention Trial in Heart Failure (MERIT-HF). The International Steering Committee. Am J Cardiol 1997; 80(9B):54J-58J. PM:9375952


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