The investigators also examined trends across the 35-year follow-up intervals. The prevalence of preserved systolic function heart failure grew from 38% to 54%, which was attributed to increased admission rates. The number of patients admitted with reduced systolic function heart failure disease was consistent. Controlling for age had little effect on apparent growth. The number of heart failure cases grew significantly during the 15-year period in both cohorts by hospital type.

In this cohort of hospitalized heart failure patients, those with preserved ejection fraction had slightly better survival. After controlling for demographics and year of admission, patients' adjusted 5-year mortality hazard ratio was 0.96 (95% CI, 0.92-1.00). The advantage appeared to be driven by patients younger than 65 years (mortality hazard ratio, 0.87; $P = .003$), compared with those older than 65 years (mortality hazard ratio, 0.97; $P = .06$). Preserved-LVEF patients showed stable death rates, whereas mortality decreased modestly over time for reduced-LVEF heart failure patients ($P = .005$).

Study Limitations

There are a number of limitations to this study that must be noted. Left ventricular function measurements were missing in more than one quarter of the patient population, and it is impossible to know the true prevalence of preserved versus reduced systolic function or temporal trends in this cohort with that many data missing. This study included both community patients and those from other parts of the country who were referred to the Mayo Clinic. Thus, it is not a true community cohort study. The demographics in Olmsted County are not nationally representative, so the study observations may or may not apply to the more racially, ethnically, and socioeconomically diverse population of the entire United States. The use of the LVEF cutpoint of 50% is arbitrary, and there is not general acceptance as to whether systolic heart failure should be defined as LVEF greater than 40 or greater than 50.

Summary

Despite these limitations, this report does extend the findings of other studies in showing that the prevalence of heart failure with preserved ejection fraction increased over a 15-year period. This study also showed that the mortality rates for these patients are high and have remained unchanged during this time. Heart failure with preserved ejection has thus become the most common form of heart failure among hospitalized patients.[4] There continues to be no evidence-based therapies that benefit these patients. As such, there have been no improvements in survival over the past decades. These disturbing findings should prompt further studies to better define the pathophysiology of heart failure with preserved systolic function and to develop effective treatments. ■

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References

1. Hunt SA, Abraham WT, Chin MH, et al. ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure). American College of Cardiology Web site. Available at: http://circ.ahajournals.org/cgi/content/full/112/12/e154. Accessed November 15, 2006.
2. Yancy CW, Lopatin M, Stevenson LW, et al. Clinical presentation, management, and in-hospital outcomes of patients admitted with acute decompensated heart failure with preserved systolic function: a report from the Acute Decompensated Heart Failure National Registry (ADHERE) Database. *J Am Coll Cardiol*. 2006;47:76-84.
3. Lenzen MJ, Scholte op Reimer WJ, Boersma E, et al. Differences between patients with a preserved and a depressed left ventricular function: a report from the EuroHeart Failure Survey. *Eur Heart J*. 2004;25:1214-1220.
4. Owan TE, Hodge DO, Herges RM, et al. Trends in prevalence and outcome of heart failure with preserved ejection fraction. *N Engl J Med*. 2006;355:251-259.

Risk Reduction

Lowering Levels of Lipids and Homocysteine

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New data address whether reducing levels of lipids and homocysteine decreases cardiovascular risk. It is now recognized that lipid-lowering therapy with statins is beneficial in a wide variety of patient populations,[1] but a new study considers whether the benefits of statin therapy are related to the intensity of cholesterol lowering. In addition, 2 new trials examine the use of the B vitamins folic acid and vitamin B_{12} to lower homocysteine levels.

Meta-Analysis of Cardiovascular Outcome Trials Comparing Intensive Versus Moderate Statin Therapy

Cannon CP, Steinberg BA, Murphy SA, et al.

J Am Coll Cardiol. 2006;48(3):438-445

Inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase (statins) currently are the single most powerful class of lipid-lowering drugs available, and their efficacy in reducing coronary morbidity and mortality has been established by several large secondary and primary intervention trials.[2] During the past several years, numerous additional effects of statins on vascular cells have been identified that could modulate atherogenesis, plaque rupture, or thrombosis. Some of these effects appear to be independent of cholesterol lowering. Therefore, it had not been entirely clear whether the important factor was just to get patients on some dose of some statin, irrespective of cholesterol lowering, or whether the benefits of statin therapy were related to the intensity of cholesterol lowering. To address this question, Cannon and colleagues[3] conducted a meta-analysis comparing the reduction of cardiovascular outcomes with high-dose statin therapy versus standard-dose statin therapy. The investigators searched PubMed and article references for randomized controlled trials of intensive versus standard statin therapy that enrolled more than 1000 patients with either stable coronary heart disease or acute coronary syndromes. Four trials were identified: Treating to New Targets (TNT), Incremental Decrease in End Points Through Aggressive Lipid-Lowering (IDEAL), Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction (PROVE IT-TIMI)-22, and Aggrastat to Zocor (A to Z). The authors performed a meta-analysis of the relative odds of the major outcomes of death and cardiovascular events in patients treated with high-dose statin therapy versus standard statin therapy.

Findings

A total of 27,548 patients were enrolled in the 4 trials investigated. The combined analysis yielded a 16% odds reduction in coronary death or myocardial infarction ($P < .00001$), as well as a 16% odds reduction of coronary death or any cardiovascular event ($P < .00001$) in patients treated with high-dose versus standard-dose statin therapy. No difference was observed in total or non-cardiovascular mortality, but a trend toward decreased cardiovascular mortality (odds reduction, 12%; $P = .054$) was observed. From this outcome, the authors concluded that intensive lipid lowering with high-dose statin therapy provides a significant benefit over standard-dose therapy for preventing predominantly nonfatal cardiovascular events.

Limitations

One limitation to this study is that it combined trials comparing different medications and different doses together into one meta-analysis. It is not possible to determine the differences based on study drug or dosing schedule from these data. A second limitation, as the authors correctly note, is that the duration of treatment and follow-up differed among the trials. In addition, the study does not directly address the question of whether it is the nonlipid effects of high-dose statin therapy or the lower lipid levels that affected the outcomes.

Homocysteine Lowering and Cardiovascular Events After Acute Myocardial Infarction

Bonaa KH, Njolstad I, Ueland PM, et al.

N Engl J Med. 2006;354(15):1578-1588

Overwhelming evidence has shown that, in a wide spectrum of patients, statin therapy is beneficial in reducing cardiovascular events, and, in some patients, cardiovascular mortality.[4] Statin therapy reduces cardiovascular risk by about 25% to 40%, which leaves many patients still at risk despite statin therapy.[5] A strategy that could possibly produce additional cardiovascular risk reduction is lowering serum homocysteine levels. Epidemiological studies of serum homocysteine levels have shown evidence of a positive association between the homocysteine level and the risk of occlusive vascular disease,[3] but until recently there had been very little randomized controlled clinical trial data demonstrating that lowering homocysteine levels reduces cardiovascular risk. Plasma total homocysteine can be lowered with the B vitamins folic acid and B_{12}. The Norwegian Vitamin trial and the Heart Outcomes Prevention Evaluation (HOPE)-2 trials were undertaken to test whether use of folic acid and vitamin B_{12} to lower homocysteine levels would reduce cardiovascular risk.

Bonaa and colleagues[6] randomized 3749 men and women who had had an acute myocardial infarction within the previous 7 days. Participants were randomly assigned, in a 2-by-2 factorial design, to receive 1 of the following 4 treatments:

- 0.8 mg of folic acid, 0.4 mg of vitamin B_{12}, and 40 mg of vitamin B_6
- 0.8 mg of folic acid and 0.4 mg of vitamin B_{12}
- 40 mg of vitamin B_6
- Placebo

Study medication was given in a single capsule, taken once per day. For the first 2 weeks after enrollment, the combination-therapy groups received a loading dose of 5 mg of folic acid per day, whereas the other 2 groups received placebo. The primary endpoint was a composite of new nonfatal and fatal myocardial infarction, nonfatal and fatal stroke, and sudden death attributed to CHD.

Findings

The mean total homocysteine level was lowered by 27% among patients randomized to receive folic acid plus vitamin B_{12}. Despite this effective reduction in homocysteine levels, such treatment had no significant effect on the primary endpoint (relative risk [RR], 1.08; 95% confidence interval [CI], 0.93-1.25; $P = .31$). Also, treatment with vitamin B_6 alone did not show significant benefit with regard to the primary endpoint (RR of the primary endpoint, 1.14; 95% CI, 0.98-1.32; $P = .09$). Of concern in the group randomized to receive combined therapy with folic acid, vitamin B_{12}, and vitamin B_6 was a trend toward an increased risk of the primary endpoint that was nearly statistically significant (RR, 1.22; 95% CI, 1.00-1.50; $P = .05$). From these results, the authors determined that treatment with B vitamins did not lower the risk of recurrent cardiovascular disease after acute myocardial infarction, and, in fact, they noted a harmful effect from combined B vitamin treatment in these postmyocardial infarction patients. They concluded that such treatment should not be recommended.

Homocysteine Lowering with Folic Acid and B Vitamins in Vascular Disease

Lonn E, Yusuf S, Arnold MJ, et al., for the Heart Outcomes Prevention Evaluation (HOPE) 2 Investigators

N Engl J Med. 2006;354(15):1567-1577

In a trial by the Heart Outcomes Prevention Evaluation (HOPE) 2 Investigators,[7] 5522 patients ages 55 years or older who had vascular disease or diabetes were randomized to receive daily treatment with either the combination of 2.5 mg of folic acid, 50 mg of vitamin B_6, and 1 mg of vitamin B_{12} or with placebo for an average of 5 years. The primary outcome was a composite of death from cardiovascular causes, myocardial infarction, and stroke.

Findings

Mean plasma homocysteine levels decreased by 0.3 mg/L in the active-treatment group and *increased* by 0.1 mg/L in the placebo group. As compared with placebo, active treatment did not significantly decrease the risk of death from cardiovascular causes (RR, 0.96; 95% CI, 0.81-1.13), myocardial infarction (RR, 0.98; 95% CI, 0.85-1.14), or any of the secondary outcomes. Fewer patients assigned to active treatment than to placebo had a stroke (RR, 0.75; 95% CI, 0.59-0.97); however, more patients in the active-treatment group were hospitalized for unstable angina (RR, 1.24; 95% CI, 1.04-1.49). From these results, the authors concluded that supplements combining folic acid and vitamins B_6 and B_{12} did not reduce the risk of major cardiovascular events in patients with vascular disease.

Conclusion

The data suggest that there is no clinical benefit to the use of folic acid and vitamin B_{12} (with or without the addition of vitamin B_6) in patients with established vascular disease. It is not clear why the hypothesis failed, given the strength of the epidemiologic evidence associating elevated serum homocysteine levels with adverse cardiovascular outcomes. Possibilities include the higher-risk nature of these patients, who already have vascular disease; the possibility that combination therapy with B vitamins is not the optimal way to reduce homocysteine; or perhaps that other complicated metabolic consequences of lowering homocysteine levels in this way ensued. For the time being, however, data do not support the use of combination B vitamin therapy to lower cardiovascular risk. ■

References

1. Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet*. 2005;366:1267-1278.
2. Gotto AM Jr. Statin therapy: where are we? Where do we go next? *Am J Cardiol*. 2001;87:13B-18B.
3. Cannon CP, Steinberg BA, Murphy SA, et al. Meta-analysis of cardiovascular outcome trials comparing intensive versus moderate statin therapy. *J Am Coll Cardiol*. 2006;48:438-445.
4. Wilt TJ, Bloomfield HE, MacDonald R, et al. Effectiveness of statin therapy in adults with coronary heart disease. *Arch Intern Med*. 2004;164:1427-1436.
5. Davidson MH. Reducing residual risk for patients on statin therapy: the potential role of combination therapy. *Am J Cardiol*. 2005;96:3K-13K.
6. Bonaa KH, Njolstad I, Ueland PM, et al. Homocysteine lowering and cardiovascular events after acute myocardial infarction. *N Engl J Med*. 2006;354:1578-1588.
7. Lonn E, Yusuf S, Arnold MJ, et al., for the Heart Outcomes Prevention Evaluation (HOPE) 2 Investigators. Homocysteine lowering with folic acid and B vitamins in vascular disease. *N Engl J Med*. 2006;354:1567-1577.