SJHG Heartbeat

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News You Can Use…In the Office Tomorrow

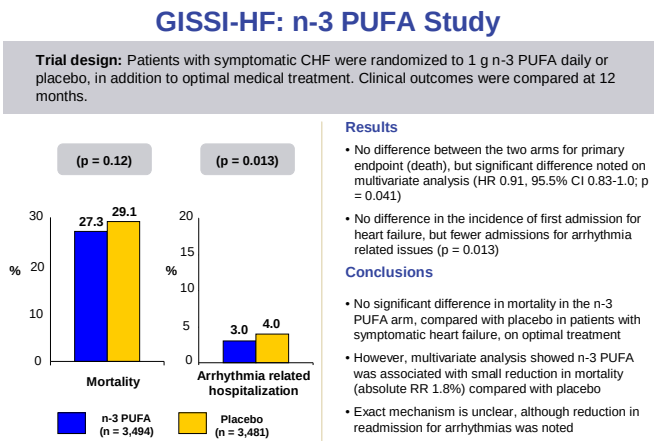
This *Heartbeat* will review some recent studies that should affect your office practice tomorrow.

- Add omega-3 polyunsaturated fatty acids to your treatment of heart failure patients.
- Discontinue atenolol usage and /or delete from patients taking it. Beta blockers **NOT** for HBP.
- Only use ARBs for secondary CV risk reduction if ACE-inhibitors aren't tolerated. They're not as good.

Nothing Fishy about It: Heart failure patients benefit from omega-3 fatty acids — but not from rosuvastatin

Mortality from heart failure (HF) remains unacceptably high. Results from primary prevention and secondary prevention trials have shown benefit for statins and omega-3 (n-3) polyunsaturated fatty acids (PUFAs) in coronary artery disease patients (CAD), thus precipitating study of their potential benefit in HF.

No prior large scale n-3 PUFA trials have been conducted in patients with HF. In the first, the GISSI-HF investigators randomized 6975 patients in class II–IV chronic HF to 1 g daily of n-3 PUFAs (850–882 mg eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA] as ethyl esters in the ratio of 1:1·2) or matching placebo, in addition to their other medications.[1] Median follow-up was 3.9 years. Death from any cause was reduced from 29% with placebo to 27% (9% relative risk reduction [RR]) in those treated with n-3 PUFAs. The co-primary outcome of death or admission to hospital for a cardiovascular (CV) event was also reduced (8% relative RR) Absolute RR was 1.8% and 2.3% respectively corresponding to 56 patients needing to be treated to avoid one death, or 44 to avoid one event in approximately 4 years. Although the improvements in clinical outcomes were modest, they were additive to those of other therapies that are standard of care in HF.



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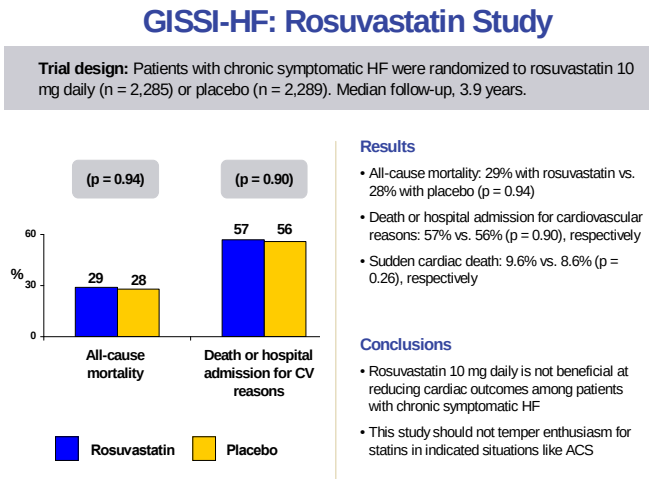
The first large-scale randomized trial with a clinical outcome for statin use in patients with symptomatic HF was reported last year. CORONA (Controlled Rosuvastatin Multinational Trial in Heart Failure) randomized 5011 patients with a history of ischemia to receive rosuvastatin 10 mg daily or placebo.[2] All patients were in New York Heart Association (NYHA) class II–IV, with a left-ventricular ejection fraction no higher than 40%, or 35% for those in NYHA class II. Over a median follow-up of 33 months, there were no significant

differences in the composite primary endpoint of all-cause mortality, CV mortality, or non-fatal CAD events. There were statistically significant, but modest, reductions in the number of admissions to a hospital for CV events, and, in a post-hoc analysis, in non-fatal ischemic events.

By contrast with the findings in the CORONA trial, the secondary outcomes of hospital admission for any cause, CV cause, or HF cause were not favorably affected in the GISSI-HF trial report of statin therapy in patients with chronic HF.[3] There were also no significant differences in myocardial infarction, stroke, or sudden cardiac death, with statin added to standard background therapy for HF, during a median follow-up of 4574 patients in NYHA class II–IV for 3·9 years. They were enrolled, irrespective of the cause of HF or left-ventricular ejection fraction, and randomized to rosuvastatin 10 mg or placebo. There were no discernible improvements in clinical outcomes in any clinically relevant subgroup. Together, these two well-conducted clinical trials establish that, although statin therapy lowers concentrations of LDL cholesterol, is well tolerated, and seems reasonably safe, it does not produce meaningful improvements in survival in patients with chronic HF.



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Conclusions: The benefits of n-3 PUFAs are small in absolute terms but incremental to those of current HF therapies. PUFAs are safe, well tolerated and inexpensive. The equivalent study dosage would be **3 1gm OTC fish oil capsules** (1 capsule of over-the-counter (OTC) fish oil is equivalent to 300 mg of EPA and DHA), or one 1gm of Lavaza.[4] *Omega-3 PUFAs are now indicated across the cardiac spectrum—for primary and secondary CAD and HF risk reduction.*

Results from these two trials reinforce the idea that findings in populations without HF may or may not extrapolate to patients with HF. For n-3 fatty acid supplementation, benefits observed in other populations apply to patients with HF. For statins, the benefits don't seem to. Every effort should be made to apply those therapies which are evidenced-based to all eligible patients with heart failure (Table 1).

Table 1. Proven Effective Treatments for HF

Therapy	Relative-risk reduction in all-cause mortality
Angiotensin-converting-enzyme inhibitors or angiotensin-receptor antagonists	17–25%
β blockers	34–35%
Aldosterone antagonists *	15–30%
Hydralazine-isosorbide dinitrate *	43%
Implantable cardiac defibrillator *	23%
Cardiac resynchronization therapy *	36%
n-3 polyunsaturated fatty acid supplementation **	9%

* For patients with specific indications

** First new life-prolonging therapy for HF in 7 years

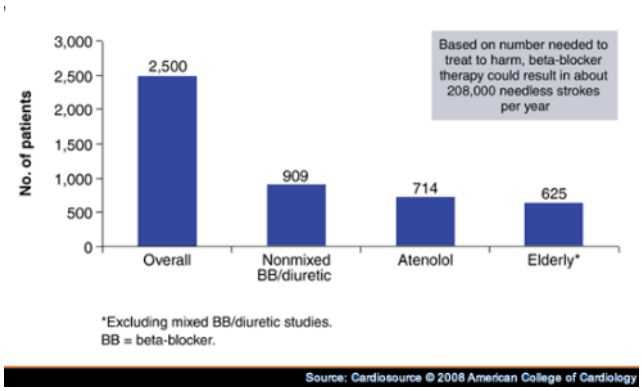
Beta-Blockers Bradycardia Harmful in Hypertension…or is It just Atenolol?

In the last few years, questions have been raised about the use of beta-blockers as first-line therapy for high blood pressure (HBP). One large meta-analysis from 1998 demonstrated that although BP was lowered with beta-blockers, these drugs were ineffective in preventing CAD,

CV, and all-cause mortality.[5] Numerous large studies and meta-analyses have suggested that patients with uncomplicated HBP may be at greater risk of stroke with no benefit for the endpoints of all-cause mortality and CV morbidity and mortality.[6]

This recent analysis includes a look at the risk/benefit ratio. Compared with other antihypertensive agents, the number needed to harm (NNH) for beta-blockers are 2,500 patients, (i.e., treatment of 2,500 patients with beta-blockers for 1 year results in one excess stroke). However, the NNH drops precipitously based on variables such as the beta-blocker studied and the age of the patient population.

Number of Patients Needed to Treat with Beta-Blockers to Cause One Excess Stroke.



Given that 52 million patients have HBP, beta-blocker therapy could potentially result in about 208,000 needless strokes per year compared with other antihypertensive agents. As always, the NNH should be weighed against the potential benefits. However, the study's authors note because no study to date has shown the beneficial effects of beta-blockers for all-cause mortality, CV morbidity, and CV mortality when used as monotherapy for HBP, "their use for this indication clearly violates the principle of *primum non nocere*."

The article also reviews a variety of other problems associated with beta-blocker therapy including suboptimal BP-lowering efficacy of beta-blockers compared with other antihypertensive agents, frequent intolerance and poor compliance rate, and association with small but systematic weight gain (as much as 1.2 kg).

Additional evidence to discard beta-blockers for primary hypertension is provided by a new systemic review showing that slowing heart rate (HR) with beta blockers in patients with primary hypertension is associated with an increased risk of CV events and death associated with the slower HR they induce.[7] This systematic review of 9 randomized controlled trials that reported HR, investigated the role of HR on the risk of CV events in patients with HBP treated with a beta-blocker. In contrast to patients with MI, HF and known CAD (where slower HR and decreased sympathetic activity are good), a slower HR with a beta-blocker was associated with increased risk of CV events and death among hypertensive patients: the slower the HR, the greater the risk.

These findings could be explained by an increase in central aortic pressure and/or pulse pressure (PP) with pharmacological HR lowering. The central aortic pressure depends on wave reflection from the periphery. In patients with slower HR, the reflected wave reaches the next wave in systole (instead of diastole), and hence may increase central aortic pressure. Thus, pharmacologically induced bradycardia leads to dyssynchrony or uncoupling between outgoing and reflected wave, thereby elevating central aortic pressure. In fact, in the CAFE (Conduit Artery Functional End Point) study), for the same peripheral blood pressure, 4.3 mm Hg higher central aortic systolic blood pressure and 3.0 mm Hg higher central aortic pulse pressure were noted with atenolol-based treatment compared with the amlodipine-based treatment, resulting in a 14% higher risk of coronary events and 23% increase in stroke rate.[8] A second possible explanation could be related to an increase in PP. As mean arterial pressure is a product of cardiac output (heart rate x stroke volume) and peripheral vascular resistance, a decrease in HR with a beta-blocker should result in higher stroke volume, serving to maintain cardiac output. A higher stroke volume, in turn,

results in increased systolic pressure and decreased diastolic pressure, thus elevating PP. Pulse pressure has been identified as an independent predictor of CV events among patients with hypertension.

Messerli and his colleagues do state, "Further studies are needed to establish causation. It should also be noted that the beta blocker used in the studies was mainly atenolol (78%), and hence, any meaningful extrapolation of these results to other beta blockers, including the newer vasodilating beta blockers, should be done with caution." We need more study to determine *whether it's atenolol that's bad or whether it's reduction of heart rate that's bad.*

The newer vasodilating beta blockers (carvedilol which is now generic or nebivolol [Bystolic—Forest/Mylan] may well not have any of these detrimental effects because they are vasodilatory which could offset the slowing of HR by decreasing wave reflection from the periphery.

Conclusions: With these additions to the evidence, beta-blockers will remain as indicated for HF, for after MI, and for tachyarrhythmias, but no longer for primary HBP in the absence of these compelling indications.

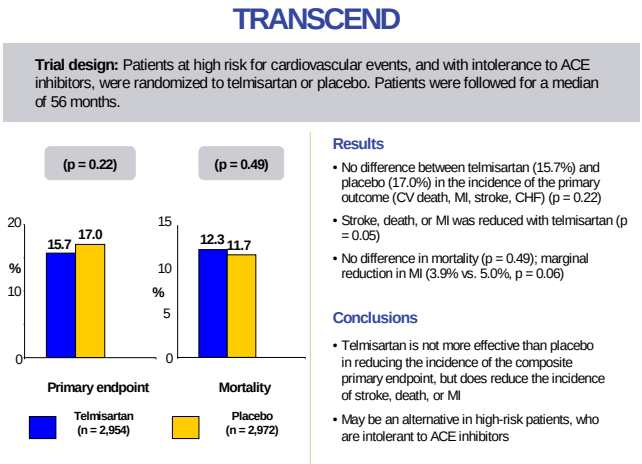
It is time to remove atenolol from our list of beta-blockers and substitute safer alternatives (no benefit when compared to placebo and increased CV risk and stroke compared to other anti-hypertensive medications).[9]

If you think a patient needs a beta-blocker for primary hypertension, carvedilol should be the beta-blocker of choice—because of its vasodilatory effects. In the presence of HF or even LV dysfunction post-MI, carvedilol is associated with the best outcome data and it doesn't adversely affect insulin resistance. Nebivolol is a cardio-selective beta blocker (safer in patients with reactive airways disease) but not available as a generic and is more costly.

ARBs did not TRANSCEND—Telmisartan Not Better Than Placebo in ACE-Inhibitor-Intolerant Patients

Angiotensin-converting enzyme (ACE) inhibitors are known to reduce major CV events but aren't tolerated in 10-20% of patients. Angiotensin-receptor blockers (ARBs) are thought to be equivalent because of similar pharmacology, and some speculate about their superior benefits as well as tolerability.

In the TRANSCEND trial, investigators assessed the effectiveness of an ARB in patients who were intolerant to ACE inhibitors.[10] After a 3-week run-in period, 5926 patients who had CVD or diabetes with end-organ damage, many of whom were concomitantly taking other proven therapies for their conditions, were randomized to receive telmisartan (80 mg/day) or placebo over a median follow-up of 56 months. Telmisartan (Micardis) was well tolerated by patients who were intolerant to ACE inhibitors, but it had no significant effect on the primary study outcome — a composite of CV death, MI, stroke, or hospitalization for HF. It modestly reduced the risk of the composite outcome of (hospitalizations for) CV death, MI or stroke.



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Conclusion: Considering that telmisartan was recently shown to be noninferior to ramipril in the ONTARGET trial,[11] this 8% relative-risk reduction was surprisingly small, perhaps because this study population received more lipid-lowering therapy, beta-blockers, and antiplatelet drugs than did the subjects in previous clinical trials. These findings suggest that the clinical effects of ARBs are less robust than those of ACE inhibitors and ARBs should be only used to prevent CV events in patients who cannot tolerate ACE inhibitors. This information added to cost savings makes the choice of ACE-inhibitors first an easy decision.

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[1] GISSI-HF Investigators, Effect of n-3 polyunsaturated fatty acids in patients with chronic heart failure (the GISSI-HF trial): a randomized, double-blind, placebo-controlled trial. *Lancet* October 4 2008; 372: 1223-1230.

[2] J Kjekshus, E Apetrei and V Barrios *et al.*, CORONA Group. Rosuvastatin in older patients with systolic heart failure. *N Engl J Med* 2007; 357: 2248–2261.

[3] GISSI-HF Investigators. Effect of rosuvastatin in patients with chronic heart failure (the GISSI-HF trial) a randomized double-blind, placebo-controlled trial. *Lancet* October 4 2008; 372: 1231-39.

[4] Maiese ML. Update on omega-3 fatty acids and CV protection. *Heartbeat* June 2008; 126: 1-3. (www.sjhg.org *Heartbeat*).

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[5] Messerli FH, Grossman E, Goldbourt U. Are beta-blockers efficacious as first-line therapy for hypertension in the elderly? A systematic review. *JAMA* 1998; 279: 1903-07.

[6] Bangalore S, Messerli FH, Kostis JB, Pepine CJ. Cardiovascular protection using beta-blockers: A critical review of the evidence. *J Am Coll Cardiol* 2007; 50: 563-72.

[7] Bangalore S, Sawhney S, Messerli FH. Relation of beta-blocker–induced heart rate lowering and cardio protection in hypertension *J Am Coll Cardiol* October 28 2008; 52: 1482-89.

[8] Williams B, Lacy PS, Thom SM, et al. Differential impact of blood pressure-lowering drugs on central aortic pressure and clinical outcomes: principal results of the Conduit Artery Function Evaluation (CAFE) study *Circulation* 2006; 113: 1213-25.

[9] Carlberg B, Samuelsson O, Linchome LH. Atenolol in hypertension: is it wise? *Lancet* November 6 2004; 364: 1684-89.

[10] The TRANSCEND Investigators. Effects of the angiotensin-receptor blocker telmisartan on cardiovascular events in high-risk patients intolerant to angiotensin-converting enzyme inhibitors: a randomized controlled trial. *Lancet* September 27 2008; 372: 1174-83.

[11] The ONTARGET Investigators. Renal outcomes with telmisartan, ramipril, or both, in people at high vascular risk (the ONTARGET study): a multicentre, randomized, double-blind, controlled trial. *Lancet* August 16 2008; 372: 547-53.