SJHG Heartbeat

Heartbeat 152 **September 2011**

Optimal Use of HF Therapies Could Save Thousands of Lives

Physicians frequently '*play it safe*' with systolic heart failure (SHF) patients, and this strategy often means using less-effective treatment which results in increased mortality. This *Heartbeat* will explain how and why we can and should do better.

This month we have the pleasure of having a Guest Editor: Dr Gregg Fonarow.

A recent analysis of eligible SHF patients (left ventricular ejection fraction < 40%) concluded that they could benefit significantly if six therapies most advocated by the HF guidelines were all implemented.[1] It was estimated that these six could save almost 68,000 more lives than what is currently done.

The most pronounced survival gains from extending the treatments to all eligible patients "arose from those therapies where the treatment gaps and magnitude of benefits were largest," according to the authors, led by **Dr Gregg C Fonarow** (Ronald Reagan UCLA Medical Center, Los Angeles, CA). **"The greatest magnitude of benefit for potential lives saved would result from improved use of aldosterone-antagonist therapy."**

Five other HF treatments, in decreasing order of their potential for preventing deaths, if given to appropriate patients, were beta blockers, implantable cardioverter-defibrillators (ICDs), cardiac resynchronization therapy (CRT), hydralazine plus isosorbide dinitrate (ISDN), and ACE inhibitors or angiotensin receptor blockers (ARBs).

Each of these therapies has received the highest level recommendation (class I) in national HF guidelines, with proven benefits that outweigh the potential risks. And each should be given to eligible patients with HF, in the absence of contraindications.[2 3]

This analysis is based on a number of assumptions. For example, the effects of the treatments on mortality are based on randomized trials and the sum of the potential gains for each treatment individually. In a secondary analysis that assumed what may be a more realistic situation, in which treatment effects partially overlap in individual patients who receive more than one therapy, "each successive therapy resulted in 20% less benefit."

The purpose of these analyses was to quantify potential survival benefits that could result if guideline-recommended therapies were universally applied to all eligible patients and provide insight into the question of "whether we should invest in trying to implement existing therapies, to bridge these treatment gaps, or focus on experimental therapies."

Table 1 shows the potential benefits from each of these six therapies. I have highlighted aldosterone antagonists.

Table 1. Potential Survival Gains From Full Implementation of Evidence-Based, Guideline Recommended Heart Failure Therapies.

Recommended HF therapy	Eligible but untreated, % of current HF population*	Preventable deaths/year with optimal implementation (n)	Lives saved/yr, % of current HF population
ACE inhibitors or ARBs	20.4	6516	9.6
Beta blockers	14.4	12 922	19.0
Aldosterone antagonists	63.9	21 407	31.5
Hydralazine/ISDN	92.7	6655	9.8
CRT	61.2	8317	12.2
ICD	50.6	12 179	17.9

Why "play it safe"?

I want to address ***why*** doctors, at least in this specific instance, don't follow guidelines. The Hippocratic Oath we take at graduation says "do no harm". This is drummed into us in medical school, and the legal hammer is always over our heads—a possible lawsuit. It's no wonder why the "play it safe" philosophy predominates. A patient comes into the office and is feeling fine after discharge on a low dose beta blocker and ACE inhibitor along with furosemide. We can add an aldosterone antagonist and precipitate hyperkalemia. We can optimize doses of the ACE inhibitor and beta blocker (BB)—associated with more improved outcomes—and precipitate side effects.

Making appropriate adjustments and additions to a patient's medical regime takes further monitoring, work and time (with no extra pay) and is associated with increased risk **now**. The improved outcomes are out there *maybe*, *somewhere*, but no one is looking. Unfortunately, though, this leads to a strategy that is sub-optimal for patients.

The analysis makes a strong case for HF education and guidelines. But incentives will have to be realigned. Financial reward for better quality care and tort reform will both be necessary to *incentivize* compliance with guideline directed treatment. This is very difficult to implement without computerized patient records (CPR) and order entry to monitor compliance and deliver appropriate prompts.

In short, the under-use of some therapies like aldosterone antagonists (either eplerenone or spironolactone), considered the standard of care, might be driven in part by fear of adverse side effects.

Last November **the main results of the EMPHASIS-HF trial** (addressed in our **January 2011 Heartbeat**)[4] demonstrated that eplerenone was significantly better than placebo in reducing the risk for death and hospitalization in patients with SHF and mild symptoms. Now a new analysis of the trial, **presented by Bertram Pitt at the European Society of Cardiology meeting in Paris** last month, reinforces the earlier findings — and demonstrates an especially dramatic benefit in multiple high-risk subgroups.

Because EMPHASIS-HF was terminated early as a result of the obvious benefits, there was a possibility that the observed effect seen in the trial might have been exaggerated. In some countries, however, where eplerenone was not commercially available, the blinded study continued. Pitt therefore showed the results for the primary endpoint for an additional 10 months, in which no discernible attenuation of effect was observed:

- CV death or hospitalization for heart failure until March 2011:

21.1% for eplerenone versus 28.5% for placebo (HR 0.66, CI 0.57-0.77, p<0.0001)

Pitt also presented the results for high-risk subgroups, showing large reductions in the primary endpoint:

- Age 75 or older: 23.6% versus 32.7%, HR 0.66, CI 0.49-0.88, p=0.004
- Type 2 diabetes: 21.6% versus 35.3%, HR 0.54, CI 0.42-0.70, p<0.0001
- Renal impairment: 24.4% versus 34.5%, HR 0.62, CI 0.49-0.79, p<0.0001
- Systolic BP below median: 20.6% versus 29.4%, HR 0.63, CI 0.51-0.79, p<0.0001

Additionally, although potassium levels increased in patients on eplerenone in the high-risk subgroups, there were no significant increases in serious hyperkalemia or other related problems *recognizing that patients were closely monitored in this trial*.

The importance of adding aldosterone antagonist therapy is magnified by the fact that all of the outcome benefits are on top of the benefits from ACE inhibitor and BB therapy, which most were already receiving.

All patients with systolic dysfunction should be treated with an aldosterone antagonist, except for those with contraindications: GFR < 30mL/min and/or potassium levels above 5.5. *The benefits far outweigh the risk.* **The caveat here is that you must be willing to closely monitor potassium levels and renal function.** "While it is right to be concerned about the hyperkalemia, the tremendous outcome benefits completely justify the extra work required to use these drugs."

Back to our patient: The patient is at dry weight so we can delete the furosemide which has no long term benefits. Blood pressure, heart rate and renal function are all stable. This usually means we can double the beta blocker dose and add spironolactone. We prefer pushing the BB first because of larger benefits and because those benefits were superimposed on existing ACE-inhibitor therapy. Both adjustments should improve long term outcomes-especially the spironolactone. We usually check potassium levels and renal function in one week and again before we see them in one month assuming no new issues. At that time we would recheck an Echo and determine need for ICD and CRT.

Hopefully with performance improvement efforts and CPR we can abandon this "play it safe" strategy and do it better! Keep swinging!

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***Heartbeat* is a South Jersey Heart Group publication.**

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[1] Fonarow GC, et al. Potential impact of optimal implementation of evidence-based heart failure therapies on mortality. *Am Heart J* June 2011;161:1024-1030.

[2] Hunt SA, et al. ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult. *Circulation* 2005;112:e154-235.

[3] Hunt SA, et al. 2009 focused update incorporated into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults.

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[4] Maiese ML. Sparing a little could save a lot…Importance of aldosterone blockade. Heartbeat 146 January 2011. www.sjhg.org: Heartbeats