EDITORIAL COMMENT

Delivering the Cumulative Benefits of Triple Therapy to Improve Outcomes in Heart Failure

Too Many Cooks Will Spoil the Broth*

John G. F. Cleland, MD, FACC, Andrew L. Clark, MD
Kingston-Upon-Hull, United Kingdom

One of the great scourges of the Victorian era was tuberculosis. A huge research effort led to dramatic advances in a broad range of medical sciences, from epidemiology to thoracic surgery. Even before treatment was very effective, sanitoria were established near most large communities, staffed by doctors, nurses, therapists, and surgeons capable of delivering a wide range of therapy. Initially, nonpharmacological and pharmacological treatments, including digitalis (1), were ineffective. The first breakthrough in the 1940s, streptomycin, led to optimism, but hopes were dashed as the disease evolved and became resistant to therapy. Subsequently, the development of dual and then triple therapy overcame the problem of resistance, allowing the disease to be contained, although not eliminated.

See page 1226

The analogy between tuberculosis and heart failure (HF) in Western society is striking, but our response to these epidemics are disparate. Heart failure, just like tuberculosis, progressed and evolved despite the introduction of single therapies. Triple-therapy for HF secondary to left ventricular systolic dysfunction has arrived (2), as has the need for careful monitoring to avoid toxic side effects and for patients to adhere to relatively complex treatment regimens. A well-proven series of interventions, each with a relatively modest benefit (Fig. 1), may reduce two-year mortality cumulatively by 50% to 60% (Fig. 2) (2). However, heart failure appears a more complex and recalcitrant condition than tuberculosis. Most patients with HF require chronic diuretic therapy and some would consider routine use of antithrombotic agents, statins, and digoxin, although evidence of a worthwhile benefit for any of these for most patients is lacking (3–6). There is evidence that implantable defibrillators, cardiac resynchronization devices, and possibly left ventricular assist systems have an important role for the management of a substantial minority of patients (2,7,8). Unfortunately, although a lot of money is spent treating patients with HF in a haphazard fashion, little effort has been spent, so far, on organizing infrastructure for their care.

A city with a population of one million should provide services to manage at least 10,000 patients with HF, provide about 140 hospital beds for its management, and expect about 2,000 to 3,000 new cases each year and about 5,000 admissions (9,10). How then should care for patients with HF be organized? Disseminating information to all physicians and expecting them all to implement guidelines for the management of HF is not effective (11–13) because of the relative complexity of diagnosis and management and because there are many competing guidelines for other cardiological and noncardiological conditions. Most hospital-based physicians have already become specialists in some disease area and most will feel it inappropriate that they should take the lead in organizing services for patients with HF (12,13). Primary care physicians could provide the common investigations required and manage triple therapy, but by seeking out a large enough number of patients to acquire the necessary skills and experience, they would inevitably become specialists. Subspecialization means that many cardiologists do not have the skills, experience, or inclination to organize and implement a high standard of care for patients with HF (14).

Braunstein et al. (15), in this issue of the Journal, examined the Medicare records of over 100,000 patients aged 65 years with HF and examined the effect of noncardiac comorbidities on outcome over one year. Fifty percent of patients were age >80 years, 60% were women, only 51% were reported to have coronary disease, and only 10% were primarily looked after by a cardiologist, consistent with previously known data (16–18). It is likely that most patients had preserved left ventricular systolic function (18). Sixty-five percent of the patients had one or more hospitalizations during one-year follow-up, a remarkable statistic in itself and higher than epidemiological studies (10,17) or clinical trials have suggested, perhaps reflecting the age of the patients (10). Forty percent of patients had >5 noncardiac comorbidities, and these patients accounted for >80% of admissions. The most common comorbidities were hypertension (55%), diabetes mellitus (31%), chronic lung disease (26%), ocular disease (24%), and hypercholesterolemia (21%). Only 50% of admissions were thought to be preventable, of which slightly more than half were for HF. Many comorbidities were associated with a modest increase in the risk of preventable admissions and mortality but, intriguingly, some were associated with a substantially lower risk, most notably hypercholesterolemia and hypertension.

Excessive attention to comorbidity may impair the treatment of HF (16,19). Braunstein et al. (15) suggest that too much focus on the management of HF may lead to neglect of comorbid conditions and that this could be detrimental to patient care. However, it is far from clear that advice

*Editorials published in the Journal of the American College of Cardiology reflect the views of the authors and do not necessarily represent the views of JACC or the American College of Cardiology.

From the University of Hull, Kingston-Upon-Hull, United Kingdom.
proffered by those who are not HF specialists is safe or effective for patients with HF. There is no specific role for renal physicians in the management of patients with HF until dialysis is required. There is no evidence that better control of glycemia improves the outcome of diabetic patients with HF. There is no evidence of improved outcome with specialist care for most patients with chronic lung disease; only now is the safety and efficacy of steroids and bronchodilator therapy being tested (20). Likewise, there is no evidence that mood disorders in patients with HF respond to conventional therapy, that pharmacological treatment for depression is safe, or that specialist advice is more effective than a sympathetic “ear” from a nurse or doctor (21,22). What is important is to ensure that the above comorbidities are not used as false excuses for withholding effective triple therapy given in adequate doses.

Cardiologists also fail to practice evidence-based medicine, are often to blame for unnecessary investigation and unwarranted polytherapy (23), and have generally failed to recognize that the relationships between traditional risk markers for cardiovascular disease, such as hypertension, hypercholesterolemia, obesity, and cardiovascular morbidity

![Figure 1](image1.png)

**Figure 1.** Effects of therapy on two-year mortality in landmark trials of heart failure of varying symptomatic severity. βB = beta-blocker; AA = aldosterone antagonist; ACEi = angiotensin-converting enzyme inhibitor; NYHA = New York Heart Association; Prev. = Prevention; Treat. = Treatment. CIBIS-II = Cardiac Insufficiency Bisoprolol Study-part II; CONSENSUS = Cooperative North Scandinavian Enalapril Survival Study; COPERNICUS = Carvedilol Prospective Randomised Cumulative Survival trial; EPHESUS = Eplerenone’s Neurohormonal Efficacy and Survival Study; MERIT = Metoprolol CR/XL Randomized Intervention Trial in Heart Failure; RALES = Randomized Aldactone Evaluation Study; SOLVD = Studies Of Left Ventricular Dysfunction.

![Figure 2](image2.png)

**Figure 2.** The cumulative effects of triple therapy with angiotensin-converting enzyme inhibitors, beta-blockers, and aldosterone antagonists over two years showing the potential number of lives saved over two years. These studies also showed a reduction in hospitalization and an improvement in patients’ symptoms amongst survivors.
fail to operate in a conventional manner once patients develop HF (24). Hypertension is consistently associated with a better prognosis in patients with HF and provides an additional substrate for the actions of triple therapy (25). The lack of evidence for and potential futility or dangers of aspirin therapy in patients with HF are widely known, yet cardiologists refuse to give up old habits (3,4). Hypercholesterolemia is also associated with a better outcome either because it is a marker of an intrinsically better prognosis or because it provides cardiovascular protection in this setting (5,6,26). If the former is true, lipid-lowering therapy could still be an important adjunctive treatment for many patients with HF and coronary disease. If the latter is true then lipid-lowering therapy is not only adding to wasteful polytherapy but may also have an adverse effect on patient outcome (5). The large post–infarction trials effectively excluded HF, as evidenced by the low annual mortality in these studies (about 2% per annum) (2,27). Three large studies of statins in patients at increased risk of developing HF, one in older patients and two in patients with hypertension, showed no effect of statins on mortality or chronic disability, further suggesting that such treatment may be futile for patients with HF (2). Two large placebo-controlled trials examining the effects of statins in over 10,000 patients with HF and coronary disease are now underway and will provide evidence for the safety and efficacy of statins (2).

Misuse of pharmacotherapy is not the only or, indeed, most expensive problem. Many cardiologists recommended angiography as part of the investigation of HF (28). However, there is no evidence that revascularization, even for hibernating or ischemic myocardium, improves patient outcome; therefore, investigation of coronary disease should usually be confined to patients with angina intractable to medical management (29). Two large randomized-controlled outcome studies are underway investigating the safety and efficacy of revascularization for patients with HF (29). Their results should be awaited before jumping to expensive investigations and potentially deleterious or futile interventions. For now, there is more evidence in favor of interventions such as enhanced external counterpulsation than for angioplasty or coronary bypass grafting in patients with HF and coronary disease (30,31). There is growing evidence that a range of implantable devices may be useful for the management of HF, although the issue of patient selection to ensure cost-effectiveness is unresolved (32). Although electrophysiologists may be the most appropriate specialists to implant devices, it may be more appropriate for HF physicians to select patients and provide continuing medical management.

The growing complexity of selecting and monitoring treatment for HF due to left ventricular systolic dysfunction means that it is difficult to disseminate best medical practice to all health professionals who might encounter such patients. A network of family physicians supported by HF specialists (possibly recruited from amongst cardiologists, geriatricians, primary care physicians, or nurses) who could evaluate new patients, reevaluate them regularly, and manage them when they require admission to hospital may be the most, and possibly only, effective option. The support of physicians with expertise in the care and rehabilitation of frail elderly patients will be essential. Depending on the level of nonspecialist support, a specialist could support a case–load of 200 to 500 patients. Assuming a prevalence of HF due to left ventricular systolic dysfunction of 1%, any community of >20,000 people might require the support of at least one HF specialist, 20 to 50 such specialists would be required per million population, translating to between 10,000 to 20,000 specialists in the U.S. or about 1,500 to 3,000 in the UK. The complexity and arguments in favor of specialist management of left ventricular systolic dysfunction contrast starkly with the lack of such arguments for “diastolic” HF, which is equally common but for which a specialist role is distinctly unproved, so far (33).

Braunstein et al. (15) have highlighted the high prevalence and prognostic associations of noncardiac comorbidities in patients with HF. The study does not provide information on how these comorbidities should be managed. According to current evidence, it seems more appropriate for HF specialists to be educated in the key aspects of the management of common comorbid medical conditions, resorting to specialist advice where evidence of real benefit exists, rather than to try to educate all physicians about how to manage HF well. The current disorganized state of affairs in which no group has been allowed to properly champion the needs of victims of HF, the most common malignant disease in Europe and North America (34), should not be allowed to persist. Patients need coordinated services, with clear management plans that serve their needs and offer society value—for money. Too many “cooks” will ensure that effective policy and management decisions are not made.

Reprint requests and correspondence: Dr. John G. F. Cleland, Castle Hill Hospital, University of Hull, Castle Hill Road, Kingston–Upon–Hull, Cottingham HU16 5JQ, United Kingdom. E-mail: J.G.Cleland@medschool.hull.ac.uk.

REFERENCES


