

JOSEF STEHLIK, MD, MPHSection of Heart Failure and
Transplantation, Department of
Cardiovascular Medicine, The Cleveland
Clinic Foundation**DAVID O. TAYLOR, MD**Director, Heart Failure Special Care Unit,
The Cleveland Clinic Foundation

And an ARB makes nine: Polypharmacy in patients with heart failure

*"Ye are charm'd! Ye are charm'd!
and your fragrant sigh
Is health to the bosom on which ye die."
—Lydia H. Sigourney (1791–1865)
With Wild Flowers to a Sick Friend*

BASED ON EVIDENCE from clinical trials, a patient with advanced ischemic cardiomyopathy should be taking eight medications: an angiotensin-converting enzyme (ACE) inhibitor, a beta-blocker, a diuretic, an aldosterone blocker, digoxin, a statin, aspirin, and clopidogrel.

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And now an angiotensin-receptor blocker (ARB) makes nine. In this issue of the *Journal*, Bhakta and Dunlap¹ examine the evidence behind adding an ARB, such as candesartan, to the regimen of patients with heart failure, evidence that includes the results of the recently published Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM) trial.^{2–5}

Although the evidence for using each of these drugs is strong, after reading Bhakta and Dunlap's excellent review it is difficult not to worry about the pitfalls of polypharmacy.

■ ADVANCES IN HEART FAILURE, ONE DRUG AT A TIME

In the last 3 decades, the list of medications for heart failure expanded considerably. Unlike in many other diseases, in which new

treatments often replace the older ones, medical therapy in heart failure has been largely an "add-on" phenomenon.

Digitalis, in use regularly since the late 18th century and as foxglove extract for centuries before, has not been shown to reduce mortality, but it reduces symptoms and hospital readmissions.⁶

Diuretics have been used in heart failure for more than 50 years. Although there have been no randomized controlled trials to assess their effect on morbidity or mortality, they are used widely for volume control and symptom reduction.

Vasodilators. In view of the physiologic abnormalities associated with heart failure, systemic vasodilation was investigated as a potential treatment strategy in a Veterans Administration trial.⁷ Combination therapy with hydralazine and isosorbide dinitrate was shown to improve both mortality and morbidity compared with placebo, in patients already taking diuretics and digoxin.

ACE inhibitors, in a series of trials,^{8–12} decreased the morbidity and mortality rates in a wide spectrum of heart failure patients and were superior to hydralazine and nitrate therapy.¹³ Although it was initially thought that the benefit of ACE inhibitors was due to their vasodilatory properties, it soon became apparent that their effects in heart failure were more complex.

Beta-blockers, previously avoided in heart failure, have become an integral part of its therapy. Deleterious effects of long-term excess sympathetic activity are overcome by

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sympathetic blockade and translate into reduction of morbidity and mortality.^{14–17} However, beta-blockers were added to, rather than compared with, ACE inhibitors.

Aldosterone inhibitors. As evidence emerged regarding the adverse effects of aldosterone in the heart failure syndrome, agents blocking its effects were tested in clinical trials. Two aldosterone receptor blockers have been shown to decrease morbidity and mortality—spironolactone in advanced heart failure,¹⁸ and eplerenone in patients with left ventricular dysfunction after acute myocardial infarction.¹⁹ These favorable effects appear to be independent of the effects of ACE inhibitors and beta-blockers.

ARBs are being assessed in clinical trials.^{2–5,19–23}

Medications for other conditions. Patients with heart failure have a high prevalence of comorbidities: about half of them have coronary artery disease and hypertension, up to a third have diabetes mellitus, dyslipidemia, or atrial fibrillation, 20% have renal impairment, and 15% have cerebrovascular or peripheral vascular disease. Thus, in addition to the drugs they take specifically for heart failure, patients may require a number of additional medications.

■ PROBLEMS OF POLYPHARMACY

While the expanding number of medications gives us more powerful tools in blocking the neurohormonal derangements of heart failure, the resulting polypharmacy poses many clinical challenges.

Side effects and drug interactions. ARBs, ACE inhibitors, and aldosterone blockers all have potassium-sparing effects and can cause increases of serum creatinine. ARBs, ACE inhibitors, and beta-blockers all have antihypertensive effects. While lowering blood pressure is beneficial in many patients, symptomatic hypotension in patients with advanced heart failure often necessitates dose adjustment or withholding of some of the medications. Twenty-four percent of patients receiving candesartan in the CHARM-Added trial discontinued the study drug due to an adverse event. The discontinuation rate in the placebo group was 18%, which points out the

already high adverse event rate of the current combination therapy.

Noncompliance is a burning issue, particularly when therapy consists of multiple medications, multiple daily doses, and frequent adjustments. Though the prospect of formulations that combine two or more of these drugs in one pill seems attractive, this comes at a cost of inconvenience when trying to titrate or hold one drug at a time.

It is important to note that it is not necessarily the high number of medications that correlates with noncompliance,²⁴ but rather the complexity of daily dosing²⁵ and a lack of belief on the part of the patient that the medication is likely to improve his or her current or future health.^{26,27} “Translating” the results of clinical trials to a language understandable to the patient and aiming for a straightforward dosing schedule of all the cardiac and noncardiac medications will improve our chances of achieving a high compliance rate in our heart failure patients.

Medication errors are not uncommon in highly complicated medication regimens. Every hospital admission or prescription refill is a possible risk for medication omission or dose error.²⁸

Dose titration. Heart failure regimens, particularly those containing ACE inhibitors, beta-blockers, and diuretics, require a careful and graded titration to achieve target doses without excess adverse events. For the clinician, this often poses a dilemma and a burden. Although there is evidence that “subtarget” doses of ACE inhibitors^{29,30} and beta-blockers^{31–33} are also beneficial, there still is no clear answer to whether fewer medication classes at the target dose, or a combination of multiple desirable medication classes at a lower dose, is preferable. Addition of ARBs to the heart failure regimen will make this decision even more complex.

Cost of new therapy, in this case added to the cost of current treatment, is always of concern to patients and health care policy-makers. A 30-day supply of 32-mg candesartan tablets currently retails for \$55 to \$70.^{34,35} Extrapolating from contemporary cost data,³⁶ a 19% reduction in hospitalization alone, as shown by the CHARM-Added trial, would translate into an average monthly inpatient

Medical therapy in heart failure has largely been an ‘add-on’ phenomenon

care cost savings of \$94 per patient. While this may represent cost savings for health plans and hospitals, the added medication cost will in many cases be passed directly to the patient. The nine-drug regimen mentioned above would cost approximately \$300 to \$700/month (or \$3,600 to \$8,400/year), depending on the specific drug formulations used.

■ POLYPHARMACY IS HERE TO STAY

The CHARM trial reminds us that despite the evolving surgical treatments and new

advances in the field of pharmacogenomics,^{37,38} polypharmacy is here to stay for the foreseeable future.

The main challenge is to maximize the use of medications documented to improve outcomes while minimizing adverse events. This requires close monitoring and tailoring of the treatment to the individual patient. Heart failure management programs that consist of a team dedicated to the care of patients with this demanding clinical syndrome appear to be the optimal clinical setting to achieve this goal. 

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ADDRESS: David Taylor, MD, Department of Cardiovascular Medicine, F25, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195.