First Line Drugs in Chronic Stable Effort Angina—The Case for Newer, Longer-Acting Calcium Channel Blocking Agents

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The American College of Cardiology-American Heart Association Committee recommends first line beta-adrenergic blocking agents for chronic stable effort angina. This article reassesses some critical evidence that is new or could have been neglected by the Committee. In particular, the putative role of calcium channel blocking agents (CCBs) is reexamined. Additional evidence is culled from articles not cited by the Committee, together with added reference to recent trials. Safety, side-effects and tolerability are issues that are evaluated. Mortality data are reviewed with the aid of a meta-analysis of all placebo-controlled trials on long acting CCBs. The advice of the committee may need to be reconsidered in view of recent evidence on the tolerability and benefits in hypertension of newer, longer-acting, second-generation CCBs. Of the older agents, verapamil has been shown to be the best with regard to safety and efficacy. Especially in the elderly, angina is often associated with hypertension, with evidence showing dihydropyridine CCBs and beta-adrenergic blocking agents to be similarly effective. Beta-blockers may have undesirable side effects such impotence and impaired exercise ability, despite their proven protective effects in postinfarct patients and in heart failure. The choice of drug should be keyed to the needs and the pathophysiology of the individual patient. (J Am Coll Cardiol 2000;36:1967–71) © 2000 by the American College of Cardiology

Americans are prone to believe the advice of institutional authorities.

John Seabrook,
New Yorker, Nov 8, 1999.

Recently the American College of Cardiology/American Heart Association (ACC/AHA) guidelines for the treatment of chronic angina strongly suggested that beta-adrenergic blocking agents should be the agents of first choice in the management of angina, both in the text and in an accompanying eye-catching diagram (1). The ACC/AHA guidelines base their preference for beta-blocker therapy on two pieces of evidence: first, the proven life-saving qualities of beta-blockers in postinfarct patients, which leaves open the question of how to handle those who are not postinfarct, and, second, by extrapolation from the supposed effects of these agents in hypertension, where the guidelines believe that beta-blockers, but not calcium channel blockers (CCBs), reduce mortality. I agree with the first of these statements, but otherwise I believe that the advice is overstated. The guidelines are largely based on clinical trial data from the 1980 to the early 1990 eras and do not adequately take into account evidence from the newer long-acting CCBs as exemplified by amlodipine. Among the older agents, the guidelines also do not sufficiently acknowledge that verapamil gives postinfarct protection.

I shall argue that the evidence is that: 1) Both beta-blockers and CCBs are equally effective as antianginals. 2) Regarding mortality in chronic effort angina, beta-blockers reduce mortality in postinfarct and heart failure patients, but there are no data showing that either beta-blockers or CCBs reduce mortality in chronic effort angina. 3) In hypertension beta-blockers and new generation CCBs are equally effective in reducing hard end points. 4) There is no good evidence to show that beta-blockers are better tolerated than the newer CCBs, with a suggestion of the reverse if amlodipine were to be considered. Finally I shall provide evidence for the long-term safety of long-acting CCBs. At the same time, it must be acknowledged that there have been serious problems with the early generation and short-acting CCBs, specifically with instant-release nifedipine (2,3).

Situations in which beta-blockers are clearly the first choice. There are two such situations in which beta-blockers are clearly the first choice, as will be argued. The first of those situations would be in postinfarct patients, and the second would be in those with overt heart failure. Only the former situation is considered in the guidelines.

Postinfarct beta-blockers versus CCBs. After infarction and in the prestatin era, the incidence of effort angina varied from about 20% to 55% (4). There is increasing evidence that beta-blockers give postinfarct protection with a mortality reduction, coming both from meta-analyses of ran-
 Calcium Blockers as First Line Drugs in Effort Angina

Abbreviations and Acronyms
ACC = American College of Cardiology
ACE = angiotensin-converting enzyme
AHA = American Heart Association
CAPARES = Coronary AngioPlasty Amlodipine REStenosis Study
CCB = calcium channel blocking agent
CHD = coronary heart disease
DAVIT = DAnish Verapamil Infarct Trial
DHP = dihydropyridine
PRAISE = Prospective Randomized Amlodipine Survival Evaluation
PREVENT = Prospective Randomized Evaluation of the Vascular Effects of Norvasc Trial
STOP = Swedish Trial in Old Patients

When treating heart failure with angina, an important aim is to treat the heart failure as well as possible, as left ventricular cavity dilation increases the myocardial oxygen demand. Increasingly, beta-blockers are being used in heart failure, now on the basis of trials showing a clear mortality reduction (11,12). About half the patients in these trials had ischemic heart failure, so that the percent with angina must have been relatively high although not stated. Regarding calcium antagonists, in the Prospective Randomized Amlodipine Survival Evaluation (PRAISE) (13), amlopidine did not improve mortality in the subgroup with angina, whereas it did in the subgroup with hypertension. Only if there is persistent hypertension despite the combined use of diuretics, an angiotensin-converting enzyme (ACE) inhibitor and a beta-blocker, is there a good case for adding a CCB. At present in the U.S. there is only one beta-blocker that is licensed for heart failure, and that is carvedilol. In the U.K., but not in the U.S., it is also licensed for angina.

Evidence from hypertension: the agents are equal. “Beta-blockers reduce mortality and morbidity among patients with hypertension,” according to the ACC/AHA Guidelines. This statement is widely quoted but is not necessarily accurate. In fact the analysis by Psaty and Curt Furbeg as published in JNC VI shows that beta-blockers do not reduce mortality in hypertension, nor do these agents reduce coronary heart disease although they do reduce stroke and heart failure (14). In the Controversies series in the Journal of the American Medical Association, Psaty et al. (15) state that drug treatment with beta-blocker therapy has thus far failed to prevent coronary heart disease (CHD). This opinion confirms that of Hansson in 1987, that “three large trials have failed to show a beta-blocker-derived protective effect against CHD in hypertensive patients” (16). There have been only a few head-to-head comparisons of beta-blockers versus low-dose diuretics in hypertension. For example, in the Medical Research Council trial of hypertension, the beta-blockers were no better than placebo in preventing coronary disease, whereas low-dose diuretics were effective (17). The earlier Medical Research Council trial on younger patients showed equal effects on coronary disease in these two types of agents but used high-rather than low-dose diuretics. High-dose diuretics as a group do not protect against coronary disease (14). Another trial, sometimes quoted to support an effect of beta-blockers on coronary disease in hypertensives (18), compared beta-blockers with all nonbeta-blocker therapies (19). In fact, total diuretic use was high in both groups, being 67% in the beta-blocker and 82% in the nonbeta-blocker group.

Calcium channel blockers, on the other hand, have evidence in their favor, being specifically effective in reducing all major cardiac events and angina in elderly patients with systolic hypertension although without any effect on mortality, except in the diabetic subgroup (20,21).

However, such indirect comparisons are imperfect, and the gold standard in reaching valid conclusions is a randomized controlled trial. Swedish Trial in Old Patients (STOP) 2 is a landmark trial on 6,614 hypertensive patients (22). It compares outcome data over a mean of five years in this advanced age population (average: 76 years), CCBs and conventional therapy (diuretics or beta-blockers or both). Therefore, it is blood pressure reduction, per se, which is overriding in conferring benefit, not the agent initially chosen. Of note though, the CCBs used were long-acting preparations of felodipine and isradipine, not amlopidine. Nonetheless, the principle of dihydropyridine (DHP) CCBs having equal effects on mortality as conventional agents is likely to hold for the long-acting DHPs
that were not tested. Thus, presently available hypertension trials with new information on the DHP-type CCBs provide no reason for the prior choice of beta-blockers over CCBs, as argued by the Guidelines.

The Stanford meta-analysis: does tolerability tip the scales? These ACC/AHA recommendations are based on the same trials that are summarized in the meta-analysis from Stanford (23). This meta-analysis proposes equal antianginal efficacy and equal safety for the two types of agents. Regarding efficacy, beta-blockers were borderline better at reducing anginal attacks, and CCBs were better at prolonging the exercise time, but the statistics were marginal with \( p = 0.05 \) in each case, and nitrate use was similar. Given this virtual equality, the meta-analysis goes on to claim that beta-blockers become the agents of choice because they were better tolerated. However, this judgement is based largely on the poor tolerability of nifedipine, especially in the short-acting form. Figure 4 of the meta-analysis illustrates these points (23). The better tolerability of a beta-blocker at equal antianginal efficacy is also confirmed in a more recent trial that compared felodipine with metoprolol (24).

Yet with amlodipine the situation may be different. Its binding site to the calcium channel has unique properties when compared with all the other DHPs (25). It has slower onset and offset kinetics and a much longer inherent half-life than other CCBs. In a large hypertension trial over four years, amlodipine was the best tolerated of the agents compared with an alpha-blocker, a beta-blocker, a diuretic and an ACE-inhibitor (26). In three relatively small comparative studies with beta-blockers, amlodipine was better tolerated (27–29). In the Prospective Randomized Evaluation of the Vascular Effects of Norvasc Trial (PREVENT), amlodipine given to patients with coronary angiographic disease had reduced outcome measures after three years (30). In the Coronary Angio-Plasty RESTenosis Study (CAPARES) (31), amlodipine was started 2 weeks before percutaneous transluminal coronary angioplasty and reduced repeat percutaneous transluminal coronary angioplasty and composite major clinical events. Such data do not exist for beta-blockers.

Verapamil and diltiazem are known to be well-tolerated, except for constipation with verapamil. However, diltiazem, in my view, lacks the same outcome data that verapamil has, and there is some indication that it is not as safe as verapamil (32). Verapamil gives a better overall quality of life than does propranolol (33). As noted in the Guidelines, beta-blockers are the cause of several side-effects such as fatigue, impaired exercise ability and erectile dysfunction. The latter is especially undesirable because it may lead to the use of Viagra, with the real risk of dangerous interactions with nitrates. Only atenolol, and not long-acting nifedipine, reduced testosterone levels over 24 weeks, and this agent gave more sexual dysfunction (34). In another study with sexual intercourse as an end point, atenolol caused a sustained depression (35). In a four-year study on mildly hypertensive middle-aged men, amlodipine gave no more sexual problems than did placebo (36). The beta-blocker used in that study, acebutolol, was atypical in that it has intrinsic sympathomimetic activity and is not licensed for use in angina in the U.S., so that direct comparisons with amlodipine cannot be made.

Safety issues: mortality studies. Ever since the adverse meta-analysis of Furberg et al. (2), the CCBs have been under a cloud. It is often forgotten that, as originally published, there were considerable arithmetical errors in the tables, that all the studies focussed on short-acting nifedipine or nicardipine and that the links to mortality were at doses of short-acting nifedipine of more than 80 mg per day. Since then the mortality risk for CCBs as a group has been discounted by observational studies, showing either the safety of long-acting CCBs (37) or the neutrality of CCBs in hypertension when compared with other agents, as in the Framingham study (38). There are good data from an important observational study in the very elderly showing that, from the mortality point of view, even short acting verapamil is as safe as beta-blockade, whereas short-acting nifedipine is associated with an increased mortality, with short-acting diltiazem somewhere in between (32). Pharmacokinetically, short-acting verapamil has a long-acting metabolite, norverapamil, so that it actually falls into the category of medium- or long-acting CCB (39).

Beta-blockers also have not been without safety problems. In prospective observational study on 12,550 hypertensive patients over six years, those taking beta-blockers had a 28% higher risk of developing diabetes, whereas those taking CCBs had no increase in that risk (40).

To examine the mortality risk, I have grouped all the studies that I could find in which a medium- or long-acting CCB was compared with placebo and in which there was a cardiovascular end point (Table 1). From this point of view, “short” acting verapamil is regarded as having a medium or long duration of action (39). I have excluded the studies reported by Furberg et al. (2), which all relate to short acting DHPs, chiefly capsular nifedipine. The result is that there is a total mortality reduction of 20% (\( p = 0.012 \)). If two studies from China are included, being placebo-controlled, although using sequential rather than random allocation, then the reduction in mortality is 23% with \( p < 0.001 \). These conclusions must be tempered with reservation because of the heterogeneous nature of the trials grouped together. Yet the overall message is that mortality tends to decrease rather than increase, contrary to the original proposal in the meta-analysis that focused on short-acting nifedipine (2).

Caveats. Practice in the management of CHD is rapidly changing with the widespread use of statins and now prophylactic ACE inhibitors, as well as increasing percutaneous interventions under cover of the new platelet glycoprotein IIIb/IIa receptor blockers. Furthermore, a Mediterranean diet can reduce total postinfarct mortality (41). The demographics of angina are also changing with a greater number of elderly patients, often hypertensive and sometimes diabetic, in whom CCBs, but not beta-blockers, have evidence in their favor in placebo-controlled trials (17,20,21). There is an increasing
emphasize on global risk factor prevention including blood pressure control, aggressive lipid lowering, dietary and lifestyle changes. Against this background, current comparisons between beta-blockers and CCBs must necessarily rest on information already gathered, when overall practice in effort angina was different. Thus, prospective, properly powered, random-ized trials between these agents are ideally required in this new era.

Another important issue is cost. The newer generation CCBs are, on the whole, relatively expensive. By contrast, generic verapamil or diltiazem or metoprolol or atenolol are relatively cheap.

Proposal. Therefore, I feel that an open mind should be kept and that there are equal arguments for either beta-blockers or CCBs in chronic effort angina, providing that there is neither prior infarction nor current heart failure. Rather, the choice can be made depending on the patient and the heart. Thus, in an active middle-aged man in whom exercise training and preserved sexual function are important, there are good arguments for starting with a well-tolerated CCB such as amlodipine or one of the non-DHPs. For predominant ischemia, the combination of a long-acting DHP with a beta-blocker (27,42) or long-acting verapamil might be better (43). For a black hypertensive patient with angina and proteinuria, a beta-blocker is better (African American Study of Kidney Disease). It is reassuring that the CCBs, as a group, do not adversely affect all-cause mortality when compared with placebo (44–53) nor when compared with beta-blocker-diuretic therapy in hypertension, but, in a patient with impaired regional contraction and a depressed ejection fraction, such considerations get overridden, and beta-blockers become the agents of choice.

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