This review evaluates the current position of calcium channel blockers (CCB) in antihypertensive treatment in the light of three major comparative studies and two extensive meta-analyses. The latter both show that CCB are equivalent to conventional (initial β-blocker or diuretic therapy) when total and cardiovascular mortality are the end points. Divergent points between the meta-analyses include stroke and myocardial infarction (MI). One meta-analysis compared CCB with conventional therapy, to find a small 13% reduction in stroke and a small, nonsignificant 12% increase in MI. The other meta-analysis found a 26% increase in MI when CCB were compared with all other therapies including the angiotensin converting enzyme (ACE) inhibitors. This increase was most robust ($P < .001$) when comparing CCB with ACE inhibitors, consonant with proposed protective effects of ACE inhibitors on cardiovascular risk. At present, only the comparison of CCB with conventional therapy, and not that with ACE inhibitors, rests on secure comparative data. When cost is compelling, conventional therapy is less expensive. For the individual patient, issues of quality of life (for example, impotence with diuretics and β-blockers) might be decisive. Nonetheless, β-blockers are preferred in postinfarct patients or in those with heart failure or unstable angina (a contraindication to dihydropyridines in the absence of β-blockade). In others, the benefits of only a borderline stroke reduction with CCB versus an equally borderline increase in MI should be evaluated for each individual patient, taking into account the age group and the patient’s preferences. In conclusion, overall CCB are neither better nor worse than conventional therapy, allowing for possible small differences in stroke and MI. The ACE inhibitors may protect better, although data are incomplete. Am J Hypertens 2001;14:1074–1081 © 2001 American Journal of Hypertension, Ltd.

Key Words: Calcium channel blockers, mortality, meta-analyses, stroke, myocardial infarction.

Calcium channel blockers (CCB) are powerful antihypertensive agents. Until recently, however, there have been no trials showing efficacy of CCB in reducing outcome measures such as stroke and heart disease. A promising start was that a placebo-controlled trial in the elderly with isolated systolic hypertension was stopped because of the marked reduction in stroke.$^1$ Furthermore, development of dementia was lessened.$^2$ Nonetheless, efficacy of any group of drugs does not necessarily equal safety. The latter may be defined as the absence of significant adverse effects when the drug is used with due regard for its known contraindications.$^3$ In the case of CCB, there have been concerns expressed that these agents may have inherent safety problems, such as increases of myocardial infarction, cancer, and gastrointestinal bleeding. Although the latter two fears have not been substantiated,$^3$ the possible relationship of CCB use to acute myocardial infarction (MI) remains controversial.$^4$ Recently, the results of three large outcome studies, and two comprehensive meta-analyses have appeared.$^5$–$^9$ The purpose of this review is to reevaluate the safety and efficacy of CCBs as antihypertensives in light of these new studies.

Calcium Channel Blockers: Do They Decrease Mortality in Hypertension?

To achieve a decrease of mortality by any antihypertensive requires a very large trial or a high-risk population, or a meta-analysis on several trials.$^{10}$ Considering the high-risk elderly population, the Systolic Hypertension in Europe study$^1$ was stopped prematurely because of the large effect of the CCB nitrindipine, whereas there was only a trend toward a mortality reduction. In the diabetic subgroup,
prospective, randomized, open, blinded endpoints; BP

more in the Systolic Hypertension in China study, 12 ni-
reduction versus that of placebo,13 two-thirds of the pa-
population, in the only trial that gave a clear-cut mortality
that of conventional therapy. When considering the elderly
1). In each case, the mortality in the CCB group equaled
SIGHT), and Nordic Diltiazem study (NORDIL) (Table
Intervention as a Goal in Hypertension Treatment (IN-
Trial in Old Patients with Hypertension-2 study (STOP-2),
this supposition comes from three recent trials: Swedish
reduce mortality in hypertension. Additional evidence for
fedipine tablets gave a clear reduction in overall mortality,
First, comparing
Comparators
Comparators
DHP; conventional
therapy; ACE inhibitors
2196, 2213, 2205,
respectively
76 years
PROBE (prospective,
randomized, open,
blinded-endpoint)
Endpoints clearly defined
pretrial
Nonblinded drugs
194/98
159/80, 158/81, 159/81
Up to 6 years
Fatal stroke, fatal MI, and
other fatal CV disease
Similar in all groups

Table 1. Key features of recent large outcome trials comparing CCB with other agents in hypertension

<table>
<thead>
<tr>
<th></th>
<th>STOP-25</th>
<th>NORDIL6</th>
<th>INSIGHT7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comparators</td>
<td>DHP; conventional therapy; ACE inhibitors</td>
<td>CCB (diltiazem); conventional therapy</td>
<td>CCB (nifedipine); K-retaining diuretic</td>
</tr>
<tr>
<td>Numbers in trial, CCB vs non-CCB</td>
<td>2196, 2213, 2205, respectively</td>
<td>5410, 5471, respectively</td>
<td>3157, 3164, respectively</td>
</tr>
<tr>
<td>Mean age at start</td>
<td>76 years</td>
<td>60 years</td>
<td>Most 60–70 years</td>
</tr>
<tr>
<td>Trial design</td>
<td>PROBE (prospective, randomized, open, blinded-endpoint)</td>
<td>PROBE</td>
<td>Double-blind, prospective, dynamic randomized</td>
</tr>
<tr>
<td>Strong points of study</td>
<td>Endpoints clearly defined pretrial</td>
<td>Endpoints clearly defined pretrial; best BP control, most on single agent</td>
<td>High diuretic dose allowed</td>
</tr>
<tr>
<td>Weak points of study</td>
<td>Nonblinded drugs</td>
<td>Nonblinded drugs</td>
<td></td>
</tr>
<tr>
<td>Mean initial BP</td>
<td>194/98</td>
<td>174/106</td>
<td>173/99</td>
</tr>
<tr>
<td>Mean final BP</td>
<td>159/80, 158/81, 159/81</td>
<td>155/88, 149/87</td>
<td>138/82</td>
</tr>
<tr>
<td>Duration (approximate)</td>
<td>Up to 6 years</td>
<td>Up to 5 years</td>
<td>At least 3 years</td>
</tr>
<tr>
<td>Primary endpoint(s)</td>
<td>Fatal stroke, fatal MI, and other fatal CV disease</td>
<td>All stroke (fatal and nonfatal), all MI, all other CV death</td>
<td>Total morbidity: stroke, subarachnoid hemorrhage, MI, heart failure, death of cerebrovascular or CV origin including sudden cardiac death</td>
</tr>
<tr>
<td>Major results</td>
<td>Similar in all groups</td>
<td>Similar in both groups</td>
<td>Similar in both groups</td>
</tr>
</tbody>
</table>

CCB = calcium channel blockers; STOP-2 = Swedish Trial in Old Patients with Hypertension-2 study; NORDIL = Nordic Diltiazem study; INSIGHT = Intervention as a Goal in Hypertension Treatment; DHP = dihydropyridines; ACE = angiotensin converting enzyme; PROBE = prospective, randomized, open, blinded endpoints; BP = blood pressure (in mm Hg); MI = myocardial infarction; CV = cardiovascular.

there was, however, a clear mortality reduction.11 Furthermore in the Systolic Hypertension in China study,12 nifedipine tablets gave a clear reduction in overall mortality, again in an elderly population. These are suggestive evidence for the hypothesis that calcium channel blockers can reduce mortality in hypertension. Additional evidence for this supposition comes from three recent trials: Swedish Trial in Old Patients with Hypertension-2 study (STOP-2), Intervention as a Goal in Hypertension Treatment (INSIGHT), and Nordic Diltiazem study (NORDIL) (Table 1). In each case, the mortality in the CCB group equaled that of conventional therapy. When considering the elderly population, in the only trial that gave a clear-cut mortality reduction versus that of placebo,13 two-thirds of the patients received combined β-blocker plus low-dose diuretic therapy after starting on one of these agents. The conventional group in STOP-2 and in NORDIL were similarly treated. If conventional therapy reduces mortality,11 then CCB do likewise.

What Do the Recent Meta-Analyses Teach Us?

Blood Pressure Lowering Treatment Trialists

This trial compared the results with different antihypertensives in 37,872 patients in eight trials.9 First, comparing ACE inhibitors and CCB separately with placebo, they provide strong evidence of benefits of each type of drug on stroke and major cardiovascular events, with ACE inhibitors additionally decreasing coronary heart disease (Table 2). Thus, when compared with placebo, CCB reduced stroke by 39% (confidence intervals [CI] 0.44 to 0.85), major cardiovascular events by 28% (CI, 0.59 to 0.87) and cardiovascular deaths also by 28% (CI, 0.52 to 0.98). They also found that CCB, when specifically compared with “conventional” (diuretic- or β-blocker–based therapy), gave the same incidence of major cardiovascular events, cardiovascular death, and total mortality. The CCB apparently reduced stroke by 13% (CI, 0.77 to 0.98) and increased coronary heart disease by 12% (CI, 1.00 to 1.26). Yet all of these confidence intervals stretch close to unity. In general there were few differences between the dihydropyridines (DHP) such as nifedipine and amlodipine and the non-DHP. The specific virtue of this meta-analysis is that it was prospectively started in 1995 by the principal investigators of the major trials then in progress. This procedure avoided one of the major problems of a retrospective meta-analysis—namely selection bias—resulting from the subjective judgment of which trials to include and which to exclude. This study also has the authoritative backing of the World Health Organization and International Society of Hypertension. The major defect is the grouping together of trials with totally different cardiovas-
cicular inclusion criteria, for example hypertension and coronary artery disease. This incongruity fortunately does not affect the comparison of CCB with conventional agents in hypertension.

**Pahor et al Meta-Analysis**

This study on 27,743 individuals in nine trials compares longer-acting CCB with all other antihypertensive drugs not only in the three major trials shown in Table 1, but also in several smaller trials. One strength of this study is its comprehensive nature. Another is the viewpoint of a group of a meta-analysis critically depends on the quality of the studies deemed to be eligible for that meta-analysis: “Trials with major design flaws carry little or no weight.” If the major issue is the effect of different antihypertensives on outcome measures, then it is crucial that these should be clearly defined. In STOP-2, NORDIL, and INSIGHT there were exact and detailed definitions of stroke, myocardial infarction, and heart failure. In INSIGHT, an independent critical events committee assessed all end points according to prespecified criteria. These therefore become the major studies, on a total of 21,611 patients v 27,743 in the Pahor et al meta-analysis, so that the minor studies included by Pahor et al cover 6,132 individuals. In MIDAS (Multicenter Isradipine Diuretic Atherosclerosis Study) clinical end points were not predefined. In Cardiovascular Study in the Elderly (CASTEL) the only predefined end points were total and cardiovascular mortality, with others not listed in the trial protocol. The Pahor meta-analysis also relies on the Appropriate Blood Pressure Control in Diabetes (ABCD) study, where the outcome data have had to be revised, and on the Fosinopril versus Amlodipine Cardiovascular Events Trial (FACT) which was an open label study without clearly predetermined outcome end points.

**Can the Two Major Meta-Analyses Be Reconciled?**

First, both studies remind us of the importance of outcome studies, not just blood pressure (BP) reduction, in the evaluation of antihypertensive agents. Second, and most importantly, it needs to be reemphasized that both studies show that CCB have an effect on total and cardiovascular mortality similar to other agents, strongly suggesting the importance of BP reduction on these outcomes. Why then the differences? An important difference between the two

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**Table 2. Major differences between two recent meta-analyses comparing CCB with other therapies in hypertension**

<table>
<thead>
<tr>
<th></th>
<th>Pahor et al, 2000</th>
<th>BP Trialists, 2000</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Authors</strong></td>
<td>Seven academics from three USA universities</td>
<td>Committee of 54 academicians under the aegis of the WHO-International Society of Hypertension</td>
</tr>
<tr>
<td><strong>Type of study</strong></td>
<td>Retrospective</td>
<td>Prospective</td>
</tr>
<tr>
<td><strong>Entry point</strong></td>
<td>All trials on hypertension meeting criteria</td>
<td>All trials from initiation of study</td>
</tr>
<tr>
<td><strong>Comparators</strong></td>
<td>All non-CCB results taken together; small separate comparisons</td>
<td>Separate comparison of CCB with conventional therapy and with ACE inhibition</td>
</tr>
<tr>
<td><strong>Number of trials</strong></td>
<td>Nine</td>
<td>Seven</td>
</tr>
<tr>
<td><strong>Numbers in study</strong></td>
<td>27,743</td>
<td>23,454 CCB v conventional; 4871 CCB v ACE inhibitors</td>
</tr>
<tr>
<td><strong>Major result</strong></td>
<td>Total and CV mortality unchanged</td>
<td>Total and CV mortality unchanged</td>
</tr>
<tr>
<td><strong>CV outcomes</strong></td>
<td>MI 26% (CI 1.11–1.43); CHF 25% (CI 1.07–1.46); stroke unchanged (odds ratio 0.90; CI 0.80–1.02)</td>
<td>NS MI 12% (CI 1.00–1.26); NS CHF12% (CI 0.95–1.33)</td>
</tr>
</tbody>
</table>

WHO = World Health Organization; CHF = congestive heart failure; NS = nonsignificant; CI = confidence interval; ↑ = increase; ↓ = decrease; other abbreviations as in Table 1.
studies is that the Pahor et al study does not compare CCB with each of the other classes individually, but with all the others taken as a group. Looking at the data in this way, CCB give a modest but detectable 26% increase in MI, without any compensatory benefits. However, this result is in contrast to that of the BP Trialists, in which CCB, when compared with conventional therapy by β-blockers or diuretics, give only a modest nonsignificant increase in coronary events, and a small statistically significant decrease in stroke. Different comparators explain different conclusions. The BP Trialists found that when CCB were separately compared with ACE inhibitors, there were no differences in stroke, but coronary heart disease was modestly decreased by 19% in the ACE inhibitor group (CI, 0.68 to 0.97). Thus, adding in the ACE inhibitor group to conventional therapy as in the Pahor et al study, would first tend to reduce the benefit of CCB on stroke and, second, to magnify the adverse effect of CCB on MI. Thus, a reasonable hypothesis is that, in the Pahor et al meta-analysis, it is the more favorable outcome data with ACE inhibitors, not with diuretics or β-blockers that tip the scales against the CCB. This proposal is supported by their subgroup analysis, in which the most robust change is the increase of MI (P < .001) when CCB are compared with ACE inhibitors, whereas versus conventional therapy the confidence intervals either overlapped or were close to unity. Choice in BP treatment is essentially between specific agents—that is, the prescriber must decide whether the specific first-line drug is to be a CCB, conventional therapy by a diuretic or a β-blocker, an ACE inhibitor, or another type of agent. Therefore, the BP Trialists are adopting a situation closer to clinical reality in comparing CCB specifically with two of the other choices available.

The ACE inhibitors, as a group, may confer cardiovascular protection beyond BP reduction. This challenging hypothesis receives support both from the Heart Outcomes Prevention Evaluation (HOPE) study, and from the retrospective analysis, over many years, of the Glasgow Blood Pressure Clinic. In the latter preliminary study, at apparently equal degrees of BP reduction, ACE inhibitors were better than calcium blockers in reducing coronary artery disease and overall mortality. Direct comparative randomized studies essentially only stem from one trial, STOP-2, with supportive data from McInnes et al and ABCD favoring the hypothesis that ACE inhibitors are better than CCB in reducing cardiovascular morbidity but not mortality. Nonetheless, direct comparisons are few and limited in number, so data from large prospective trials in progress are awaited.

Thus, the common point of these two meta-analyses lies in the similar total and cardiovascular mortality and the divergent points lie in the inclusion by Pahor et al of ACE inhibitor data together with conventional therapy, thereby weakening the effect of CCB on stroke found by the BP Trialists and strengthening the borderline adverse effect on MI.

### Assessement of Proposed Relatively Small Stroke Reduction and Similar Increase in Myocardial Infarction Associated With CCB Therapy

The possibility of changes in stroke and MI is supported by two other meta-analyses, both of which focus on the three major trials that were large, randomized, blinded, and with clearly predefined outcome measures. These could be regarded as grade A trials. In our study (submitted for publication), when compared with conventional therapy, CCB reduced nonfatal stroke by an average of 25% (CI, 0.65 to 0.86, P = .001) and increased nonfatal acute MI by 18% (CI, 1.11 to 1.38, P = .036). The lower P value with stroke may give it the greater significance, especially when corrected for multiple comparisons. Also of interest is another meta-analysis that shows a reduction of stroke (15%) versus an increase (20%) in MI. Thus, a consistent finding in all four meta-analyses is the small increase in MI approximately balanced by less stroke, when comparing CCB versus conventional therapy. Again, note the relative statistical weakness of such data.

Nonetheless, the consistency of the data on stroke and nonfatal MI leads to—but does not prove—a hypothesis that these may be real changes. The CCB could have two types of effects that produce stroke. First, they reduce carotid atherosclerosis as in Verapamil in Hypertension and Atherosclerosis Study (VHAS), in Borhani, and in the Prospective Randomized Evaluation of the Vascular Effects of Norvasc Trial (PREVENT). Second, they have platelet inhibitor qualities acting on a different site from aspirin and, therefore, may have antithrombotic qualities that could help to prevent stroke. Regarding the proposed increase of MI, the simplest explanation would be that CCB, as a group, increase adrenergic stimulation. This increase is especially found with the DHP, and even agents such as amlodipine and slow-release nifedipine are capable of such an increase. In the one of the major studies (NORDIL), diltiazem, a non-DHP, was used. It would be expected that chronic diltiazem would decrease in plasma catecholamines. However, for most of the NORDIL study, the short-acting form of diltiazem was used, which increases plasma catecholamine levels. Taking the situation in which there is a brisk and rapid increase in catecholamines, as when capsular nifedipine is given to patients with unstable angina, there is an increase in MI that is avoided by combination with β-blockade, with the combination being beneficial. Therefore, there is suggestive evidence that adrenergic stimulation by CCB tends to increase MI, compared with conventional therapy. On the hand ACE inhibitors, besides having antiadrenergic effects, directly inhibit the coagulation system.
Table 3. Contraindications to the use of CCB as first-line antihypertensive therapy

<table>
<thead>
<tr>
<th>Condition</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart failure with hypertension</td>
<td>Although amlodipine may have neutral effect, other non-CCB such as diuretics, ACE inhibitors, and ( \beta )-blockers all benefit heart failure.</td>
</tr>
<tr>
<td>Post–myocardial infarct with hypertension</td>
<td>DHP CCB lack the supportive data of ( \beta )-blockers and ACE inhibitors; non-DHP seem safe; verapamil has data for protection.</td>
</tr>
<tr>
<td>African Americans with proteinuria &gt;300 mg/day</td>
<td>AASK trial stopped, amlodipine arm. DHP CCB may not be used without ( \beta )-blocker; non-DHP may be used.</td>
</tr>
<tr>
<td>Unstable angina with hypertension</td>
<td></td>
</tr>
</tbody>
</table>

DHP = dihydropyridine; other abbreviations as in Tables 1 and 2.

**Some Benefits and Defects of CCB Therapy**

**Benefits**

Are there other benefits of CCB therapy, besides the possibility of stroke reduction? First, they act soon, which is useful to convince the patient that BP can be controlled, thereby gaining the patient’s confidence. Second, they often bring down the BP in otherwise refractory cases. Third, they may be used as initial therapy in salt-sensitive African American patients, who may not respond to initial single therapy with \( \beta \)-blockers or ACE inhibitors (for reservations emanating from the African-American Study of Kidney Disease and Hypertension (AASK) study, see later here). Fourth, CCB may be especially useful in selected patients with stable effort angina. Fifth, they are often required in combination therapy to reduce BP to the new low limits now being suggested, especially in diabetic patients. Sixth, they have antihypertensive effects that are less influenced by indomethacin than in the case of an ACE inhibitor.

**Known Defects**

What are the disadvantages of CCB therapy? These agents, especially the dihydropyridine group, when given in high doses, often have nuisance side effects such as headache and ankle swelling that make it relatively common for patients to withdraw. Nonetheless, in mild hypertension, amlodipine in a low dose of 5 mg was the best tolerated of the five types of agents used, including a \( \beta \)-blocker and a diuretic. Next, there are some important situations in which CCB should not be used by preference as initial antihypertensive therapy (Table 3). First, in postinfarct patients, there are no trials favoring the use of DHP. Non-DHP may be different, with good data for verapamil and lesser data for diltiazem. Second in heart failure, there are no data favoring CCB. Third, in renal disease and in diabetic patients with nephropathy, ACE inhibitors may be preferred, as will now be discussed.

**Renal Disease**

Regarding hypertensives with overt proteinuria, there is a caution in an African American (and probably patients of African descent elsewhere) on the basis of preliminary results of the AASK Study. The amlodipine arm of this study was stopped because of worsening renal function but the ACE inhibitor and \( \beta \)-blocker arms continued in those with proteinuria >300 mg/day. Here there is a pathophysiologic basis for preferring ACE inhibitors, which reduce both afferent and efferent arteriolar tone, whereas the DHP CCB tend to reduce only the afferent tone with risk of increasing intraglomerular hypertension and worsening proteinuria. Nonetheless, there is no evidence for a blanket contraindication to DHP in hypertensive patients with proteinuria. Of note, in INSIGHT, proteinuria of \( \geq 0.5 \) g/24 h was one the possible entry criteria to the trial. It was the diuretic rather than the CCB group that had more withdrawals because of impaired renal function (4.6% withdrawal in the diuretic group, 1.8% in the CCB group, \( P < .0001 \)). Of note, the combination of ACE inhibitors and CCB may reduce proteinuria better than either alone.

**Diabetic Hypertensive Patients**

First, in diabetic hypertensive patients with nephropathy, similar hemodynamic arguments indicate a preference for the use of ACE inhibitors or for angiotensin receptor blockers (“sartans”) in these circumstances. However, direct comparative data are lacking, and the first comparative study in diabetic nephropathy will be between the CCB amlodipine and the angiotensin receptor blocker irbesartan. Second, in elderly diabetics (presumably without overt nephropathy), MI was more decreased with ACE inhibitors than with CCB. Also of note, in another trial on diabetic hypertensive subjects, an ACE inhibitor was more effective than a DHP in decreasing MI. Thus, ACE inhibitors rather than CCB should be first line choice in diabetic patients, especially those with nephropathy. However, these are not arguments to abandon initial CCB for initial conventional therapy in diabetic patients. Conventional and CCB therapy could not be distinguished in elderly diabetic patients in STOP-2, or in the subgroup analysis of Pahor et al. The CCB-based therapy was particularly effective in elderly diabetic patients. These arguments become academic with the new low BP aims
fewer metabolic side effects with a CCB than with diuretics

Low-dose diuretics are well authenticated to reduce all major outcomes when compared with placebo yet there is only one large comparative study of diuretic versus CCB therapy. The INSIGHT study compared long-acting nifedipine in an initial dose of 30 mg daily with a thiazide-potassium–retaining combination diuretic in an initial dose of 25 mg hydrochlorothiazide with 5 mg amiloride daily (equivalent to one half a tablet of Moduretic). Doses could be doubled if needed. The diuretic group showed an increased blood sugar and uric acid, matched by increased development of diabetes and of gout. In INSIGHT, the diuretic treatment group also had more hypokalemia, hypernatremia, hyperuricemia, hypoglycemia, and renal impairment than did the CCB group. Hypokalemia occurred in 6.2% of the diuretic-treated group and 1.9% of the nifedipine group, even though a potassium-retaining agent was used. Hypokalemia even of mild degree may be more serious than previously considered. In the Systolic Hypertension in the Elderly Program (SHEP) study diuretic therapy, even with relatively low doses of chlorthalidone such as 12.5 and 25 mg, was associated with increased hypokalemia and a decreased cardiovascular benefit of treatment. It should, moreover, be noted that in the INSIGHT study the thiazide dose was allowed to go up to 50 mg, which is “high” by current standards. In a meta-analysis that separately considered low-dose and high-dose diuretic therapy versus β-blocker therapy, only low-dose diuretics clearly reduced mortality. However, in these trials the majority received therapy in addition to the diuretic; in INSIGHT it was usually monotherapy.

individualized and patient-guided choice

There may be different principles of choice for different needs. In a cost-conscious community, issues of individualized therapy may well be less important than the overall benefit of BP reduction, whether by conventional therapy or by more modern therapy including CCB. The initial choice of a low-dose diuretic would be evidence based, often then going on to combination therapy. Coming to the individual, I propose that choice between CCB and conventional treatment by a β-blocker or diuretic could be put to the patient, who should be given the information that overall mortality is equally reduced by both therapies, and that there is some evidence of decreased stroke and increased MI with CCB. Several complex considerations come into the overall choice (Table 4). Even low-dose diuretics have potential problems, including impotence, less effect in middle-aged patients, and hypokalemia. For a middle-aged active man, risk of impotence or loss of exercise capacity with β-blockers may be decisive factors. Furthermore, β-blockers do not prevent coronary disease. For someone at high cardiovascular risk, an ACE inhibitor should be initiated on the basis of the HOPE study.

For an elderly person, systolic BP—a determinant of stroke—is better reduced by CCB or diuretics than by ACE inhibitors or β-blockers. At equal BP reductions, decreased stroke may outweigh increased risk of coronary heart disease. We know how to prevent MI, and with risk factor calculations widely available, the small increase of risk of coronary heart disease with CCB could be factored in and fully countered by attention to lifestyle, better BP control, or diet and statin-induced cholesterol lowering. There is also much known about the management of acute MI and remodeling. By contrast, once brain cells are dead, there is little to be done. Stroke aftermath is a major problem in our aging population, and if CCBs reduce this
even marginally better than conventional therapy, that is important.

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