Review

β-Blockers in Hypertension: Studies and Meta-analyses Over the Years

Pierre Larochelle, MD, PhD,a Sheldon W. Tobe, MD, MScCH (HPTE), FRCPC, FACP, FASH,b and Yves Lacourcière, MDc

a Institut de recherches cliniques de Montréal, Montréal, Québec, Canada
b Aboriginal and Rural Health Research, Northern Ontario School of Medicine, Division of Nephrology, Sunnybrook Hospital, University of Toronto, Toronto, Ontario, Canada
c Centre hospitalier universitaire de Québec, Quèbec City, Quèbec, Canada

ABSTRACT

β-Blockers are among the most commonly used medications in the treatment of hypertension. However, 45 years after their initial indication for that treatment, their place in the treatment of hypertensive patients is under evaluation and their usefulness has been questioned based on evidence from meta-analyses of clinical trials. The β-blocker class consists of various agents with diverse pharmacokinetic and pharmacodynamic properties including lipo- and hydrophilicity, duration of action, intrinsic sympathomimetic activity, vasodilation, and metabolism linked to genetic polymorphisms. Because of their various properties, some β-blockers are indicated for cardiovascular conditions such as angina, rate control of atrial fibrillation, chronic heart failure, and because they are also indicated for other conditions such as thyrotoxicosis and even migraine and essential tremor, they are very useful in hypertensive patients with these other comorbidities. After publication of the meta-analysis by Lindholm in 2005, the role of β-blockers for the management of hypertension has come under question, and some guidelines groups no longer recommend them as initial therapy. However, a meta-analysis by Khan and McAlister in 2006 supported the Canadian approach to the use of β-blockers as the initial therapy for the management of hypertensive patients younger than the age of 60. A further meta-analysis by Kuyper and Khan in this Canadian Journal of Cardiology supplement brings more clarity to the issue. In this article, we will briefly review the pharmacokinetic and pharmacodynamic properties of this drug class (for a detailed review please see the article by Poirier and Tobe in this supplement to the Canadian Journal of Cardiology) and the major studies that are used in the meta-analysis.

β-Blockers have different pharmacodynamic and pharmacokinetic properties (see Table 1). Some β-blockers can be more selective for the β1 receptor and some can be described to have a property of intrinsic sympathomimetic activity on the β-receptor. They can be vasodilating with β-adrenergic blocking properties (labetolol/carvedilol) or with an increased production of nitric oxide (nebivolol). The metabolism can be influenced by genetic polymorphisms as has been demonstrated for metoprolol, nebivolol, and carvedilol. They can have various degrees of lipophilicity, allowing entry to the central nervous system and greater side effects. Their metabolism affects the route of elimination with the lipophilic agents metabolized by the liver and their excretion potentially slowed by hepatic congestion with congestive heart failure.

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Corresponding author: Dr Pierre Larochelle, Institut de recherches cliniques de Montréal, 110 ouest, av. des Pins, Montréal, Québec H2W 1R7, Canada. Tel.: +1-514-987-5550; fax: +1-514-987-5744.
E-mail: pierre.larochelle@ircm.qc.ca
See page S21 for disclosure information.
and after myocardial infarction, and other indications such as migraine and essential tremor. There have been more than 17 large trials influencing the recommendations on the use of these agents in the treatment of hypertension. The results of these trials initially led to the widespread recommendation for the use of β-blockers in the management of hypertension. However, the recent multiple meta-analyses using these trials have raised a controversy on their place in that treatment. The Canadian Hypertension Education Program recommendations have included β-blockers as a first-line treatment option for patients younger than 60 years of age based on the evidence from these large trials, and this has been supported by 2 of the meta-analyses. This article reviews these studies to help clinicians better understand the role of β-blockers in managing hypertension.

The hydrophilic agents are typically excreted in the urine as with atenolol and drug levels might increase with lower levels of renal function. Thus, this class of drugs, although defined as β-adrenergic receptor blockers or β-blockers are in fact a diverse group of medications with a wide range of properties differentiating these drugs from each other in the treatment of hypertension.

The β-blockers could therefore be subdivided according to their cardioselectivity, their intrinsic sympathomimetic activity, their vasodilatory properties, and their hydro- or lipophilicity.8

β-Blockers are traditionally thought of for cardiovascular disease because they reduce myocardial oxygen consumption, reduce heart rate, and reduce blood pressure (BP) at rest or at exercise. As such, they are used in the long-term management of angina where they have been shown to be associated with good outcomes although their effect on mortality is questioned.9 They can be combined with long-acting and short-acting nitrates and dihydropyridine calcium channel blockers. They have been reported to significantly reduce the rate of reinfarction and mortality after acute MI.10,11 They are now indicated in the treatment of chronic heart failure from left ventricular systolic dysfunction because of their property of blockade of the neurohormonal activity of the sympathetic system. They have been shown to reduce mortality and produce symptomatic improvements in these patients. β-Blockers produce their effect through competitive inhibition on the effects of catecholamines, which activate the adrenergic receptors.

β-Blockers are commonly used for the treatment of hypertension which is still one of the major risk factors for cardiovascular and cerebrovascular disease. The most recent data from the study of the Global Burden of Disease,12 evaluating the risks associated with various noncommunicable diseases in all countries, highlights the growing burden of disease attributable to noncommunicable disease. This World Health Organization-sponsored study has reported that high BP is the most common individual risk factor associated with death and the most frequent individual risk factor associated with the burden of disease. The following β-blocker clinical trials have had an effect on the clinical practice guidelines for the use of these agents in hypertension.

Clinical Trials of β-Blockers in Hypertension

There are many trials that have evaluated the effects of various β-blockers on outcomes in patients with hypertension. One of the questions that has been raised since the use of these antihypertensive agents is whether the benefit of their use is from their BP-lowering effect or their mechanism of action or both. This debate is still ongoing but is similar to the debates on the use of calcium channel blockers 15-20 years ago,13 α-receptor blockers 10-15 years ago,14 and the ongoing debate of the mechanism of blockade of the renin-angiotensin system through either the angiotensin II type 1 receptor or the inhibition of the angiotensin-converting enzyme.15,16

The major clinical studies shown in Table 2 were included in most of the meta-analyses on the use of β-blockers. These protocols are important in the understanding of the effect of this class of agents in patients with hypertension. A variety of

Table 1. Pharmacokinetic and pharmacodynamic properties of commonly used β-blockers

<table>
<thead>
<tr>
<th>Property</th>
<th>β1 selectivity (les/more)</th>
<th>Degree of ISA (none/some)</th>
<th>Vasodilatory (yes/no)</th>
<th>Metabolism influenced by genetic polymorphism (yes/no)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrophilic</td>
<td>Nonselective: nadolol, timolol, sotalol, pindolol; selective: atenolol+</td>
<td>None: atenolol, nadolol, timolol, sotalol; some: labetalol</td>
<td>Yes: labetalol; no: atenolol, nadolol, timolol, sotalol</td>
<td>—</td>
</tr>
<tr>
<td>Lipophilic</td>
<td>Nonselective: propranolol; selective: metoprolol+; bisoprolol+; nebivolol++</td>
<td>None: propranolol, metoprolol, bisoprolol, carvedilol, nebivolol; some: acebutolol+; pindolol++</td>
<td>Yes: carvedilol, nebivolol; no: propranolol, metoprolol, bisoprolol, acebutolol, pindolol</td>
<td>Yes: metoprolol,6 nebivolol,6 carvedilol</td>
</tr>
</tbody>
</table>

The + and ++ indicate the relative degree of selectivity or degree of β1 selectivity and ISA.

ISA, intrinsic sympathomimetic activity.

Data from references.5,6
AAS, African American Study of Kidney Disease and Hypertension; ASCOT-BPLA, Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm; CAPP, Captopril Primary Prevention Project; CONVINCE, Controlled Onset Verapamil Investigation of Cardiovascular End Points; ELSA, European Lacidipine Study on Atherosclerosis; HAPPHY, Heart Attack Primary Prevention in Hypertension; HEP, Hypertension in Elderly Patients in Primary Care; INVEST, International Verapamil-Trandolapril Study; IPPSH, International Prospective Primary Prevention Study in Hypertensives; LIFE, Losartan Intervention For Endpoint reduction in Hypertension; MAPHY, Metoprolol Atherosclerosis Prevention in Hypertensives; MRC, Medical Research Council; STOP-2, Swedish Trial in Old Patients with Hypertension-2; STOP-Hypertension, Swedish Trial in Old Patients with Hypertension; UKPDS, UK Prospective Diabetes Study.

Adapted from Kuyper and Khan with permission from Elsevier.

β-blockers were used in these studies: propranolol was used in 1 trial, oxprenolol in 1 trial, pindolol in 2 trials, metoprolol was used in 6 trials, and atenolol in 13 trials, and none used vasodilating β-blockers.

The first major trial on β-blockers was the Medical Research Council trial in the treatment of mild hypertension comparing a thiazide with propranolol and with placebo. The pilot study of this trial ran from 1973 to 1977 in the United Kingdom with 1849 patients, and the main trial was completed in 1985 with publication later in the year with 17,354 patients from the ages of 35 to 64 years followed for 5 years. The aim of this protocol was to determine whether drug treatment of mild hypertension reduced the rate of stroke, coronary events, and death. It also evaluated the cardiovascular protective efficacy of a thiazide or propranolol compared with placebo. The results indicated that active treatment reduced strokes but not coronary events. A secondary analysis reported that thiazides reduced more strokes than β-blockers and that β-blockers appeared to be effective only in hypertensive nonsmokers. All-cause mortality was reduced in men but not in women. One weakness of this study was the presence of normotensive individuals in this trial. The authors report that one-third to half of the patients taking placebo were normotensive during the trial and had a diastolic pressure <90 mm Hg. This very high percentage of normotensive individuals could explain the low number of events and the limited benefit of treatments.

In the subsequent Medical Research Council trial in elderly patients completed in 1991, 4396 patients between the ages of 65 and 74 years were randomized single blind to receive a hydrochlorothiazide-amiloride combination compared with atenolol and matching placebo. The objective was to evaluate if active treatment reduced all-cause mortality and morbidity due to strokes and coronary events. There was a significant reduction in fatal and nonfatal strokes with the active treatment but the reduction in fatal strokes was confined to the diuretic-treated and the reduction in nonfatal strokes was present in both active treatment groups. Coronary events were reduced although not significantly and there was an overall reduction in cardiovascular events by the active treatment mainly attributed to the diuretic agents. All-cause mortality was not significantly reduced. BP was reduced to a greater extent in the diuretic group for the first 3 months of the trial but became similar in the 2 groups with greater add-on supplementation in the β-blocker group. Major weaknesses in this study included 25% of the patients lost to follow-up and more than 50% of patients were not taking any of their randomized treatment at the end of the trial, including 65% allocated to β-blockers.

In the Heart Attack Primary Prevention in Hypertension (HAPPHY) trial, diuretics (benzofurazide or hydrochlorothiazide) were compared with β-blockers (metoprolol or atenolol) in an open randomized trial on coronary artery events and deaths in 6569 patients aged from 40 to 64 years. There were no significant differences in the end points between the 2 groups of drugs. The trial was done only in men and the choice of the treatments after randomization was left open to the various centres. Therefore, the results were allocated to the β-blocker group or to the thiazide group and not a specific agent. The Metoprolol Atherosclerosis Prevention in Hypertensives (MAPHY) trial was a follow-up extension of the HAPPHY trial, including only patients who had been randomized to metoprolol compared with thiazide diuretics. The follow-up median time was 4.2 years and results indicated a lower total and cardiovascular mortality in the group taking the β-blocker. Not all patients were included, and this was an open follow-up of patients allocated to that group.

In the Swedish Trial in Old Patients With Hypertension (STOP-Hypertension) trial, 1627 patients with an average age of 75.7 years and an initial BP of 195/102 mm Hg were randomized to active treatments or a matching placebo. The active treatments were atenolol, metoprolol, pindolol, or hydrochlorothiazide with amiloride, and each participating centre was allowed to use only 1 of the 4 treatments. There was a significant reduction in fatal and nonfatal strokes and cardiovascular mortality but the difference could not be evaluated between the 4 treatment groups. In the STOP-2 trial, 6614 elderly patients between the ages of 70 and 84 years with a baseline BP of 194/98 mm Hg were randomized in a prospective open randomized trial with blinded end points design to 3 treatment groups: conventional therapy (β-blockers with diuretics), angiotensin-converting enzyme inhibitors, and calcium channel blockers. The β-blockers were the same as in the initial STOP study. All 3 treatments groups showed similar efficacy in prevention of cardiovascular end points of cardiovascular mortality and major morbidity

### Table 2. Trials with β-blockers in hypertension

<table>
<thead>
<tr>
<th>Drug</th>
<th>Year</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propranolol</td>
<td>1985</td>
<td>MRC, trial of mild hypertension</td>
</tr>
<tr>
<td>Oxprenolol</td>
<td>1985</td>
<td>IPPSH</td>
</tr>
<tr>
<td>Pindolol</td>
<td>1991</td>
<td>STOP-Hypertension</td>
</tr>
<tr>
<td>Pindolol</td>
<td>1999</td>
<td>STOP-2</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>1987</td>
<td>HAPPHY</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>1988</td>
<td>MAPHY</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>1991</td>
<td>STOP-Hypertension</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>1999</td>
<td>STOP-2</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>1999</td>
<td>CAPPY</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>2002</td>
<td>AASK</td>
</tr>
<tr>
<td>Atenolol</td>
<td>1986</td>
<td>HEP</td>
</tr>
<tr>
<td>Atenolol</td>
<td>1987</td>
<td>HAPPHY</td>
</tr>
<tr>
<td>Atenolol</td>
<td>1991</td>
<td>STOP-Hypertension</td>
</tr>
<tr>
<td>Atenolol</td>
<td>1999</td>
<td>STOP-2</td>
</tr>
<tr>
<td>Atenolol</td>
<td>1992</td>
<td>MRC, treatment of hypertension in older adults</td>
</tr>
<tr>
<td>Atenolol</td>
<td>1999</td>
<td>CAPPY</td>
</tr>
<tr>
<td>Atenolol</td>
<td>1998</td>
<td>UKPDS</td>
</tr>
<tr>
<td>Atenolol</td>
<td>2002</td>
<td>AASK</td>
</tr>
<tr>
<td>Atenolol</td>
<td>2002</td>
<td>ELSA</td>
</tr>
<tr>
<td>Atenolol</td>
<td>2002</td>
<td>LIFE</td>
</tr>
<tr>
<td>Atenolol</td>
<td>2003</td>
<td>INVEST</td>
</tr>
<tr>
<td>Atenolol</td>
<td>2003</td>
<td>CONVINCE</td>
</tr>
<tr>
<td>Atenolol</td>
<td>2005</td>
<td>ASCOT-BPLA</td>
</tr>
</tbody>
</table>
but the results of the effects of β-adrenergic blockers were included in the group of conventional treatment. The results were allocated to either β-blockers or diuretics without actual information on either group and the choice of drugs in the group was not randomized.

In the UK Prospective Diabetes Study (UKPDS) trial, there were 1148 hypertensive patients with type 2 diabetes mellitus with a mean age of 56 years and a mean BP of 160/94 mm Hg of whom 758 were allocated to a tight control of BP using either captopril, an angiotensin-converting enzyme inhibitor, or atenolol. Both treatments were equally effective in reducing BP and also equally effective in reducing macrovascular end points, deaths, MI, and stroke. The sample size, however, was small.

The largest trial that investigated β-blockers, the International Verapamil-Trandolapril Study (INVEST) trial, randomized 22,576 patients with hypertension and coronary artery disease to compare mortality and morbidity (nonfatal MI or stroke, cardiovascular death of all-cause) outcomes in patients treated with a calcium antagonist strategy or a non-calcium antagonist strategy based on atenolol. To reach the target BP of 140/90 or 130/85 for patients with diabetes, trandolapril and/or hydrochlorothiazide were added to the treatments. The average age was 66 years, 30% were older than the age of 70 years, 85% were already taking antihypertensive medication, and the baseline BP was 149/86 mm Hg. The atenolol-based strategy was as effective as the calcium channel blocker-based strategy and proved to be as effective as the other on protection for the mentioned events including cardiac and stroke. This study demonstrated the effectiveness of a strategy based on β-blockers in patients with hypertension and coronary artery disease.

The Losartan Intervention For Endpoint Reduction in Hypertension (LIFE) trial was a double-blind masked randomized parallel group trial in 9193 patients with hypertension and left ventricular hypertrophy and an average age of 60 years (range, 55-80 years). Patients were randomized to an atenolol-based strategy or a losartan-based strategy. Baseline BP was 174/98 and BP decreased significantly, 30/16 mm Hg in both groups. There was a greater reduction in the number of cardiac end points: MI, stroke, and death in the group taking losartan. The angiotensin receptor blocker-based strategy also reduced fatal and nonfatal strokes more than the atenolol-based strategy, and prevented new-onset atrial fibrillation compared with atenolol.

The Controlled Onset Verapamil Investigation of Cardiovascular End Points (CONVINCE) trial was a randomized double parallel group, actively controlled multicentre trial with a follow-up of 5 years. It compared 2 treatment regimens in 16,602 hypertensive patients with 1 additional risk factor on the rate of fatal and nonfatal MI, stroke, and cardiovascular-related deaths, and also tested whether abrogating the early morning increase in BP with a chronobiologically prepared form of verapamil would be more effective. One treatment regimen was based on a controlled-release verapamil and the other on either hydrochlorothiazide or atenolol. Of the 8361 patients randomized to the hydrochlorothiazide with atenolol group, 4482 (53.6%) were preselected to atenolol. The results were unable to demonstrate the equivalence of the verapamil-based antihypertensive regimen compared with a regimen beginning with a diuretic or a β-blocker (based on the upper bound of the 95% confidence intervals for the primary end point not exceeding 1.16—it was 1.18). These data indicated that the effectiveness of the calcium channel blocker in reducing cardiovascular disease was similar but not better than a diuretic- or β-blocker-based treatment. The CONVINCE study was stopped early by the sponsor and the primary event number (stroke, MI, or cardiovascular disease-related death) was 729 compared with the 2024 estimated to be needed. Although more participants had primary events from 6 am until noon, there was no benefit observed during this time period for the chronobiologically correct verapamil.

Finally the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA) trial compared an antihypertensive regimen based on amlodipine with perindopril as required to reach BP targets, with a regimen based on atenolol with bendroflumethiazide and potassium as required. The protocol was stopped prematurely although there was not a significant difference in the combined end points. There was a statistically significant difference in fatal and nonfatal strokes, total cardiovascular events and procedures, and all-cause mortality in favour of the amlodipine with perindopril combination. The amlodipine with perindopril combination prevented more events than the atenolol with diuretic combination.

The Conduit Artery Function Evaluation (CAFE) sub-study assessed central BP indirectly and found lower central pressure in the amlodipine-based therapy group associated with improved outcomes compared with the atenolol-based therapy group. It is not known if the higher central BP with atenolol was due to relative vasoconstriction affecting wave reflection or a slower heart rate delaying the peak of the outgoing pressure wave leading to augmentation of reflected waves.

Meta-analyses of Studies With β-Blockers

In 1998, Messerli et al. conducted the first meta-analysis of studies that compared the use of β-blockers with diuretics in patients with hypertension considered to be elderly (≥60 years of age). Ten protocols were included with 8217 patients taking β-blockers or diuretics and a follow-up of 5 years. In this meta-analysis, both groups of treatments reduced cerebrovascular events but β-blockers did not reduce coronary artery events or mortality. The authors concluded that β-blockers should no longer be first-line therapy for elderly patients.

In 2001, a meta-analysis by Staessen et al. of 9 trials including 62,605 patients concluded that all antihypertensive agents that included the older drugs, diuretics, β-blockers, and newer agents including calcium channel blockers and angiotensin-converting enzyme inhibitors had similar long-term efficacy and safety. The benefit of the BP-lowering accounted for most of the differences in outcomes. However, the results of the trials and BP reductions with β-blockers and diuretics, were analyzed together and no separate results were reported.

In 2005, Lindholm et al. reported a meta-analysis of 13 trials that compared β-blockers with other treatments in 105,951 subjects with primary hypertension and 7 trials that compared β-blockers with placebo or no treatment in 27,433 patients. In the active treatment comparator, there was an
increased risk of stroke with β-blockers compared with other antihypertensive agents. β-Blockers reduced the risk of stroke in the placebo-controlled trials but only by half of what was expected with other agents. In a later publication, the same group of authors attributed the less positive effect of the β-blockers on the specific use of atenolol although no trial has compared the use of atenolol with other β-blockers.

A Cochrane review by Wiysonge et al. in 2012 of 13 protocols with 97,507 patients including 40,245 taking β-blockers, of whom three-quarters were taking atenolol. The comparators were placebo, diuretics, calcium channel blockers, and renin-angiotensin system inhibitors. They concluded that initiating treatment with β-blockers leads to a modest reduction in cardiovascular disease but the quality of the evidence was judged to be low, so that the true effect of β-blockers was possibly substantially different from the estimate found in their review. They also pointed out that further research should explore whether there are differences between β-blockers, focusing on differential effects between younger and older patients.

The most recent meta-analysis is the update in this supplement of the Canadian Journal of Cardiology by Kuyper and Khan of a previous meta-analysis by Khan and McAlister. That analysis included 145,811 participants in 21 hypertension trials and concluded that the use of β-adrenergic blockers in hypertension is associated with a significant reduction in cardiovascular morbidity and mortality in younger patients but should not be considered for first-line therapy in older patients. In this update, the authors sought to compare the efficacy of β-blockers stratified according to atenolol vs non-atenolol β-blockers, and also according to age. They concluded that atenolol and nonatenolol β-blockers decrease cardiovascular end points in young patients, suggesting that age might be a more important factor than the choice of β-blocker. They also concluded that atenolol is not an appropriate choice for uncomplicated hypertension in older hypertensive patients with significantly worse outcomes, although whether this is a class effect or specific to atenolol remains unclear. It is tempting to link the lack of efficacy of β-blockers as initial therapy in the elderly population with hypertension to a lack of lowering of central BP as was found in the CAFE study, but this is only a hypothesis at this time. It is also possible that the adverse metabolic effects of the nonvasodilating β-blockers might be a contributing factor, but this remains to be proven in a hard outcomes study.

The Blood Pressure Lowering Treatment Trialist Collaboration used individual data for their analysis and reported no clear differences between age groups in the effects of lowering BP and no strong evidence that a protective effect against major cardiovascular events could be related to the use of a class of antihypertensive agent.

The Blood Pressure Lowering Treatment Trialist Collaboration evaluated 31 trials and 190,906 participants. However, β-blockers and diuretics were included together as a class of conventional agents. They reported that further analysis was not able to detect differences when β-blockers were considered separately.

The largest meta-analysis was conducted by Law in 2009 in 108 trials with 464,000 patients to determine the quantitative efficacy of different classes of BP-lowering drugs in preventing coronary artery disease and strokes. In their analysis, β-blockers had an improvement beyond what was expected from BP reduction alone in preventing recurrent coronary heart disease events in people when given shortly after a myocardial infarction. According to their analysis, the 5 main classes of antihypertensive drugs (thiazides, calcium channel blockers, β-blockers, angiotensin receptor blockers, and angiotensin-converting enzyme inhibitors) were similarly effective within a few percentage points in preventing coronary heart disease and stroke.

Conclusions

In conclusion, β-adrenergic receptor blockers have been used for more than 45 years in the treatment of hypertension and in various other clinical situations. They have diverse pharmacokinetic and pharmacodynamic properties. The studies included in the various meta-analyses were done from 1973 to 2012 and used a variety of β-blockers in patients young and old with mild to severe hypertension.

The recent meta-analyses which have specifically investigated the effect of β-blockers in the treatment of hypertension have confirmed their efficacy in the reduction of cardiovascular morbidity and mortality but mainly in younger patients and less in older patients, because there is an excess risk of stroke in older patients with β-blockers compared with other antihypertensive agents. The meta-analysis by Kuyper and Khan also concludes that this class of agents decreases cardiovascular end points in younger patients, suggesting that age might be a more important factor than the choice of β-blocker. Atenolol appears not to be an appropriate choice for uncomplicated hypertension with worse outcomes, although whether this a class effect or specific to atenolol remains unclear.

The role of β-blockers was also reviewed recently by Poirier and Lacourcière, who concluded that although β-blockers are clearly effective in reducing BP, the mechanism of action of conventional oral β-blockers, which depend on the reduction of heart rate and cardiac output, might not be optimal because there is lack of effect on peripheral resistance in the short-term. It is tempting to link the lack of efficacy of β-blockers as initial therapy in elderly patients with hypertension to a lack of lowering of central BP as was found in the CAFE study, but this is only a hypothesis at this time. It is also possible that the adverse metabolic effects of the nonvasodilating β-blockers might be a contributing factor, but this remains to be proven in a hard outcomes study.

There are no studies, however, that compared outcomes in the treatment of hypertension with the various subclasses of β-blockers or β-blockers with different properties such as the vasodilating β-blockers.

The Canadian Hypertension Education Program guidelines continue to support the use of β-blockers as initial treatment in patients younger than 60 years of age, and as part of combination therapy, using the evidence available from outcome trials and meta-analyses. There is a lack of data in comparisons of outcomes of different β-blockers and in particular, comparisons of hard cardiovascular outcomes between vasodilating and nonvasodilating β-blockers in hypertension. Unfortunately, no further randomized controlled trials with hard outcomes are planned (based on search of 443 studies on the clinicaltrials.gov Web site, in February 2014 for
hypertension and β-blockers). This leaves clinicians who want to take an evidence-based approach to their use of β-blockers dependent on meta-analyses of older studies, many with weaker methodologies or on studies with surrogate outcomes.

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