Chapter 9

Clinical Outcomes with Bisoprolol and Amlodipine: Current Status and Future Prospects

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Both β-blockade and calcium channel blockade has been shown to improve clinical outcomes in hypertension and other cardiovascular conditions. Most people with hypertension receive combination antihypertensive therapy, and β-blockers and calcium channel blockers will play an important role in the combination regimens of many patients with hypertension.

Introduction

The goal of antihypertensive treatment is to reduce the risk of the long-term, adverse cardiovascular outcomes associated with high blood pressure (BP), such as myocardial infarctions (MIs), strokes, and chronic kidney disease, among others. Chapter 1 of this book details the association between hypertension and its cardiovascular complications. The purpose of this chapter is to review the strengths and limitations of β-blockers

and calcium channel blockers (CCBs) with regard to improving clinical outcomes in people with hypertension.

Clinical evidence for improved clinical outcomes with β-blockers and CCBs

β-blockers (including bisoprolol)

β-blockers in hypertension

Bisoprolol has never been evaluated in a randomised outcome trial in people with hypertension. Accordingly, this section will review the evidence for the effects of β-blockers as a class on outcomes in populations with hypertension, followed by a summary of indirect evidence relating to bisoprolol itself and cardiovascular outcomes.

Multiple meta-analyses have compared β-blockers with placebo (or no treatment) or members of other antihypertensive classes and Table 1 shows recent examples of these, published since 2015 [1–7]. Overall, there is clear evidence for a reduction in the risk of major adverse cardiovascular events and other adverse outcomes with β-blockers versus placebo or no treatment. Evidence for an effect on mortality was conflicting, and several analyses suggested that CCBs were more effective in preventing strokes than β-blockers (although β-blockers themselves reduced the risk of stroke compared with placebo). Another meta-analysis, not shown in Table 1, showed that members of any class of antihypertensive agent reduced the risk of stroke in patients at high risk of adverse cardiovascular outcomes (mostly due to the presence of pre-existing cardiovascular disease) [8].

There was no significant difference in effects on all-cause or cardiovascular mortality, or all-cause or cardiovascular hospitalisation between bisoprolol (highly selective β_1-adrenoceptor blocker) and nebivolol (a "third generation" β_1-adrenoceptor blocker, i.e. with additional vasodilator actions) in a head-to-head randomised comparison involving 1 year of treatment [9]. Consistent with these findings, a large database analysis found no significant differences in the risk of acute MI, stroke

Table 1 Overview of large, recent meta-analyses that compared the effects of β-blockers with placebo or no treatment, or members of other antihypertensive classes.

Author [Ref]	Trials	Patients	Main findings
Thomopoulos et al [1]	67	68,478	Benefit vs. placebo[a] for stroke (RR 0.77 [0.61 to 0.97]), HF (RR 0.57 [0.35 to 0.91]), stroke + CHD (RR 0.84 [0.74 to 0.95]), stroke + CHD + HF (RR 0.78 [0.64 to 0.96]) in populations with hypertension; no significant effect vs. placebo[a] on CHD or CV or all-cause mortality.
Wiysonge et al [2,3]	4[b]	23,613	β-blockers were more effective vs. placebo[a] for CVE (RR 0.88 [0.79 to 0.97]) and stroke (RR 0.80 [0.66 to 0.96]); no significant benefit for all-cause mortality or CHD. CCBs more effective vs. β-blockers for preventing stroke (RR 1.07 [1.0 to 1.14]), CVE (RR 1.18 [1.08 to 1.29]) and all-cause mortality (RR 1.07 [1.0 to 1.14]); no significant difference for CHD. RAAS blockers more effective vs. β-blockers for preventing stroke (RR 1.30 [1.11 to 1.53]); no significant benefit for all-cause mortality, CVE or CHD. No significant difference between β-blockers and diuretics for all outcomes.
Emdin et al [4]	45[c]	100,354	Similar effects of members of different antihypertensive classes on outcomes in people with T2D except for apparent benefit for CCBs on stroke (higher risk with β-blocker), and lower risk of HF with diuretics or ARBs.
Ettehad et al [5]	123	613,815	β-blockers were less effective than other antihypertensive classes for prevention of MACE, stroke, and renal failure. Calcium channel blockers were superior to other drugs for the prevention of stroke.
Thomopoulos et al [6]	50	247,006	β-blockers were less effective for reducing stroke vs. CCBs, ARBs or all RAAS blockers (there was no comparison between β-blockers and ACEI). No significant differences between β-blockers and other antihypertensive classes or effects on CHD, HF, stroke + CHD, stroke + CHD + HF, CV mortality, or all-cause mortality.
Vögele et al [7]	5[d]	8,019	No significant difference between β-blockers and placebo[a] on a composite outcome of death, MI or stroke (RR 0.89 [0.75–1.05]). Benefit for β-blockers vs. placebo[a] on nonfatal stroke (RR 0.78 [0.63 to 0.98]) and HF (RR 0.54 [0.37 to 0.81]); no difference for death or nonfatal MI. β-blockers less effective than other antihypertensive classes (pooled) for nonfatal stroke (RR 1.18, [1.07–1.30]); no difference for death, nonfatal MI, HF.

[a]Or no treatment. [b]Evaluations of β-blockers vs. placebo or no treatment for the first-line treatment of hypertension. [c]Studies in people with type 2 diabetes. [d]Evaluated effects in patients aged ≥65 y. ACEI: angiotensin-converting enzyme inhibitors; ARB: angiotensin receptor blockers; CCB: calcium channel blocker(s); CHD: coronary heart disease; CV: cardiovascular; CVE: CV events; HF: heart failure; MACE: major adverse cardiac events; MI: myocardial infarction; RAAS: renin-angiotensin-aldosterone system; Ref: reference; RR: risk ratio; T2D: type 2 diabetes; vs.: versus; y: year. Numbers in square parentheses are 95% confidence intervals.

or hospitalisation for heart failure between two third-generation β-blockers (nebivolol and carvedilol) and atenolol, a cardioselective β-blocker with lower selectivity for β_1- versus β_2-adrenoceptors than bisoprolol (see Chapter 4 of this book for a discussion of cardioselectivity) [10]. Evidence for an additional beneficial effect on clinical outcomes associated with the additional vasodilator properties (stimulation of nitric oxide production for nebivolol and α-adrenoceptor blockade for carvedilol) is lacking [11, 12].

β-blockers in other cardiovascular diseases

The clinical evidence for improved clinical outcomes with β-blockers in patients with stable heart failure or ischaemic heart disease (IHD) is well established [12]. Indeed, β-blockers are recommended as part of the therapeutic regimen for these patients in international guidelines [13–15].

The evidence base for bisoprolol in the management of heart failure was established by the three randomised Cardiac Insufficiency Bisoprolol Study (CIBIS) trials [16–18]. CIBIS I demonstrated symptomatic improvement in patients with heart failure randomised to bisoprolol or to placebo, but had insufficient power to evaluate effects on hard clinical endpoints [16]. CIBIS II was larger, and demonstrated statistically and clinically significant improvements for bisoprolol versus placebo in all-cause mortality (hazard ratio [HR] 0.66, 95% confidence interval [95% CI] 0.54 to 0.81, $p<0.0001$) and sudden deaths (HR 0.56 [95% CI 0.39 to 0.80], $p=0.0011$) [17]. These were interim findings, as the study was stopped early, as routine data monitoring indicated that its primary endpoint (reduction in mortality) had been met. Finally, CIBIS III demonstrated that clinical outcomes did not differ importantly whether bisoprolol was administered before or after an angiotensin converting enzyme (ACE) inhibitor [18].

Meta-analysis supports the benefit of β-blockers in patients with IHD, including after application of percutaneous coronary intervention and in patients receiving an ACE inhibitor [19–23]. The Total Ischemic Burden Bisoprolol Study involved randomisation of 330 patients with stable angina, a positive exercise test and ≥2 documented episodes of

myocardial ischaemia during the previous 2 days to bisoprolol or nifedipine (a short-acting CCB) [24, 25]. Patients randomised to bisoprolol versus nifedipine demonstrated fewer episodes of ischaemia and a lower risk of a composite cardiac outcome at 1 year.

Amlodipine

Amlodipine in hypertension

Table 2 summarises three major randomised cardiovascular outcomes trials that evaluated amlodipine in patients with hypertension [26–29]. All of these trials enrolled populations at elevated cardiovascular risk due to the presence of hypertension and one or more risk factors for adverse cardiovascular outcomes.

The large **Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) trial** randomised more than 30,000 people with hypertension to amlodipine, a thiazide diuretic, or an ACE inhibitor [26]. There were no significant differences between treatments in the incidence of the primary cardiovascular endpoint in ALLHAT.

The Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial involved randomisation of a hypertensive patient population to either amlodipine or to an angiotensin receptor blocker (ARB), valsartan [27]. There was no significant difference between treatments in the incidence of the primary composite cardiovascular endpoint at the end of the trial. However, there were fewer MIs in the amlodipine versus valsartan groups (HR 1.19, p=0.02), with a trend towards a lower risk of stroke with amlodipine (HR 1.15, p=0.08). Differences in BP lowering between the study arms, in particular during the first year, has been advanced as a possible explanation for these observations [30].

The Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA) was a randomised comparison of the effects on clinical outcomes of treatment based on amlodipine versus atenolol in high-risk hypertensive subjects [28]. This trial differed from ALLHAT and VALUE, as an element of combination therapy was factored into the design of the study: patients uncontrolled on

Table 2 Principal randomised evaluations of the effects of amlodipine on clinical outcomes.

Trial (year[a])	Study arms	Follow-up (y)[b]	Primary outcome	Main findings
ALLHAT (2002) [10] (N=33,357)	Amlodipine Chlorthalidone Lisinopril[c]	4.9	Composite: fatal CHD + nonfatal MI	No significant differences in the primary outcome (RR vs chlorthalidone was 0.98 [0.90 to 1.07] for amlodipine and 0.99 [0.91 to 1.08] for lisinopril. Also no differences between groups for mortality (secondary outcome).
VALUE (2004) [27] (N=15,245)	Amlodipine Valsartan	4.5	Cardiac morbidity/ mortality[f]	No difference overall between treatment groups for the primary endpoint (HR 1.04 [94 to 1.15]). An apparent early excess of MI events in the valsartan arm is unexplained but has been attributed to slower BP lowering vs amlodipine.
ASCOT-BPLA (2005) [28] (N=19,257)	Amlodipine[d] Atenolol[d]	5.5[e]	Composite: fatal CHD + nonfatal MI	Trend in favour of amlodipine- vs atenolol-based therapy for primary outcome (HR 0.90 [79 to 1.02]). Benefit for amlodipine in terms of fewer strokes (HR 0.77 [0.66 to 0.89]), total CV events and procedures (HR 0.84 [0.78 to 0.90]), and deaths (HR 0.89 [0.81 to 0.99]).
ACCOMPLISH (2008) [29] (N=11,506)	Amlodipine Hydrochloro-thiazide (each added to benazepril)	3 y	Composite: CV death, MI, stroke, other cardiac morbidity[g]	Benefit for amlodipine for primary endpoint (HR 0.80 [0.72 to 0.90]) and secondary composite of CV death, MI or stroke (HR 0.79 [0.67 to 0.92]).

[a]Of main publication. [b]Mean or median. [c]A doxazosin arm was discontinued during the study and will not be discussed here. [d]Perindopril could be added to amlodipine and bendro-flumethiazide to atenolol, as required. [e]Trial terminated prematurely as recommended by routine trial data monitoring. [f]Interventional procedures, hospitalisation for heart failure, nonfatal MI, fatal CHD. [g]Primary composite was CV death, nonfatal MI, nonfatal stroke, hospitalisation for angina, resuscitation after sudden cardiac arrest, coronary revascularisation.
BP: blood pressure; CHD: coronary heart disease; CV: cardiovascular; HR: hazard ratio; MI: myocardial infarction; RR: relative risk; y: year. Numbers in square parentheses are 95% confidence intervals.

amlodipine or atenolol could receive additional per-protocol treatment with perindopril or a thiazide diuretic, respectively. The trial was terminated early due to a likelihood of benefit in the amlodipine arm; while the reduction in the primary endpoint with amlodipine did not achieve statistical significance, there were benefits for amlodipine versus atenolol in multiple secondary cardiovascular outcomes.

The Avoiding Cardiovascular Events Through Combination Therapy in Patients Living With Systolic Hypertension (ACCOMPLISH) trial was a randomised comparison of two antihypertensive combination regimens (amlodipine or a thiazide diuretic added to an ACE inhibitor in high-risk hypertensive patients) [29]. Amlodipine-based treatment was associated with a lower risk of a broad primary cardiovascular composite outcome as well as a secondary composite that resembles the primary outcome used in the other trials discussed here (cardiovascular death + nonfatal MI or stroke).

Accordingly, amlodipine was equivalent to, or superior to, other evidence-based treatments for hypertension for improving long-term clinical outcomes. Meta-analyses suggest comparable efficacy for CCBs versus other antihypertensive classes in reducing the risk of major adverse cardiovascular outcomes, with a greater effect on stroke compared with other antihypertensive classes, as described above [2–6]. A meta-analysis published in 2014 that included these and smaller trials shows that the risk of most adverse clinical outcomes was lower or similar for amlodipine compared with a β-blocker or diuretic, or with an ACE inhibitor or ARB [31].

Amlodipine in other cardiovascular diseases

Several outcomes trials have evaluated amlodipine in patients with stable coronary artery disease, and these are reviewed briefly below.

The Comparison of Amlodipine vs Enalapril to Limit Occurrences of Thrombosis (CAMELOT) study compared the effectiveness of these agents with placebo for reducing the risk of cardiovascular events over 2 years of treatment in 1,991 patients with angiographically documented coronary artery disease [32]. The broad primary endpoint employed by this trial included cardiovascular death,

nonfatal MI, resuscitated cardiac arrest, coronary revascularisation, hospitalization for angina or for congestive heart failure, stroke, transient ischemic attack, or peripheral vascular disease. The frequency of the primary endpoint was reduced during treatment with both amlodipine (HR 0.69 [95% CI 0.54 to 0.88]) and enalapril (HR 0.85 [95% CI 0.67 to 1.07]), with no significant difference between treatments (HR 0.81 [95% CI 0.63 to 1.04]). There was a trend towards slowing of atherosclerosis regression in the amlodipine group, compared with the other treatments.

The Prospective Randomized Evaluation of the Vascular Effects of Norvasc Trial (PREVENT) was a randomised, placebo-controlled trial in 825 patients with angiographically confirmed coronary artery disease [33]. The study was designed to test the hypothesis that treatment with amlodipine might slow the progression of coronary atherosclerosis, determined using quantitative angiography. The primary endpoint (change in coronary luminal diameter) was not met in this study, although there was significant reduction of atherosclerosis progression for amlodipine versus placebo when measured using ultrasound techniques. There was also no difference between treatments for mortality or major adverse cardiovascular events. However, there were fewer episodes of angina or heart failure, or of revascularisation procedures, in the amlodipine versus placebo group.

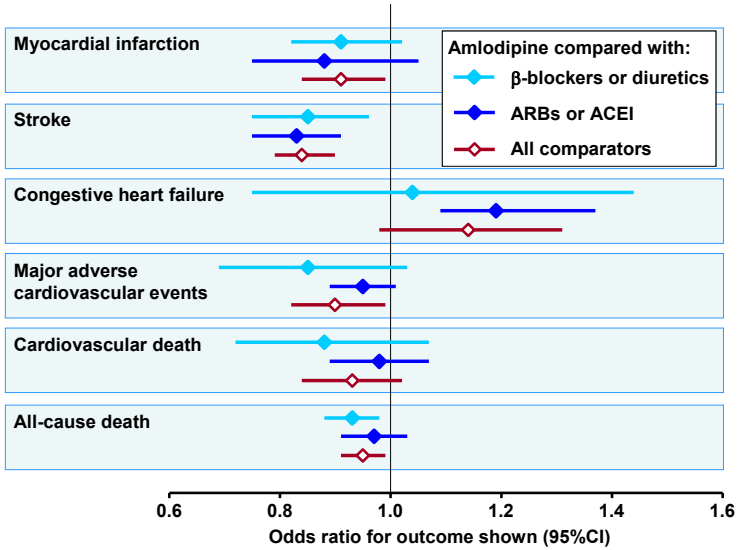
The Coronary AngioPlasty Amlodipine REStenosis Study (CAPARES) study evaluated the rate of restenosis following percutaneous transluminal coronary angioplasty (PTCA) in a population of 661 patients randomised to amlodipine or placebo [34]. The primary endpoints were loss in minimal lumen diameter (quantitative coronary angiography) and a major adverse cardiovascular events composite of death, MI, coronary artery bypass graft surgery and repeat PTCA, measured during the 4 months following the original PTCA procedure. There was no difference between treatments for the angiographic outcome, but there was a clinical benefit for amlodipine versus placebo in terms of reduced need for repeat PTCA (relative risk ratio [RRR] 0.45 [95% CI 0.22 to 0.91]), and a reduced frequency of the cardiovascular composite outcome (RRR 0.65 [95% CI 0.43 to 0.99]).

An outcomes trial was conducted in patients with severe heart failure—**the Prospective Randomized Amlodipine Survival Evaluation (PRAISE)** [35]. A total of 1153 patients with left ventricular ejection fraction (LVEF) <30% were randomised to amlodipine or placebo, in addition to their usual therapy, for 6–33 months. The risk of the primary cardiovascular composite outcome (death or hospitalisation for coronary events) was reduced by 16% (95% CI 10 to 24) for amlodipine versus placebo. A subgroup analysis suggested that benefit was only seen in patients with heart failure of non-ischaemic aetiology, with no significant effect in patients with heart failure of ischaemic aetiology. A second study (**PRAISE-2**) tested this hypothesis by randomising a population of 1,654 patients with non-ischaemic cardiomyopathy and LVEF <30% to amlodipine or placebo for a median of 33 months [36]. In this trial, there was no benefit for amlodipine versus placebo (HR 1.09 [95% CI 0.92 to 1.29]). The effects of amlodipine therefore, appear to be neutral in patients with heart failure [36].

The clinical evidence base for bisoprolol and amlodipine—limitations and future prospects

Guidelines have downgraded the place of β-blockers as a class in the management of hypertension in recent years, and these agents are favoured for use in patients with special indications for their use, such as heart failure or IHD [13]. The effects of combination therapy approaches on hypertension-mediated clinical outcomes remains largely unstudied, especially with regard to the β-blocker class. For example, the ASCOT-BPLA [28] and ACCOMPLISH [29] trials, described above, were cardiovascular outcomes trials that set out to evaluate antihypertensive combinations. Both evaluated amlodipine in combination with an ACE inhibitor, but only ASCOT-BPLA included a β-blocker, atenolol, that has lower β_1-adrenoceptor selectivity (cardioselectivity) than bisoprolol. Indeed, the ASCOT-BPLA trial was described by one of its principal investigators as a comparison of “older” and “newer”

Figure 1 Comparison of clinical outcomes for amlodipine versus other antihypertensive agents from a meta-analysis.



Odds ratios <1 indicate lower frequency/risk for amlodipine vs. comparator. ARB: angiotensin receptor blocker; ACEI: angiotensin-converting enzyme inhibitor; CI: confidence interval. Drawn from data presented in reference [31].

antihypertensive therapies [37], a strategy which seemed likely to preclude evaluation of β-blockers in combination with "newer" antihypertensive therapies.

The reduction in emphasis on the use of the β-blocker class in people with hypertension is due to a perception of lower efficacy in reducing hypertension-mediated target organ damage, associated in turn with a lesser effect of β-blockers on central BP, compared with some other antihypertensive classes [13, 38, 39]. However, consideration of the clinical pharmacology of antihypertensive agents as though given as monotherapy is discordant with the call from the current European guideline for the management of hypertension for the use of combination antihypertensive therapy from the time of diagnosis of hypertension [13]. Complementary mechanisms of action of components of combination regimens can, in principle, provide complementary mechanisms of cardiovascular protection. For example, a study in hypertensive patients showed that addition

of amlodipine to bisoprolol markedly reduced both central BP and pulse pressure, in addition to brachial BP, thus overcoming one of the clinical limitations of β-blockade when used as monotherapy [40].

Current European guidelines for the management of hypertension are very clear in their recommendation that most people with hypertension who require pharmacotherapy should receive rational combination treatments, rather than monotherapy [13]. In future, the therapeutic evaluation of antihypertensive treatments should focus more strongly on comparing rational antihypertensive combinations with complementary mechanisms of action, rather than monotherapies. This approach would build on the substantial evidence base for improved outcomes that we have with existing antihypertensive agents, in a way that reflects more closely actual current practice in the management of hypertension.

Conclusions

Bisoprolol and amlodipine have been in clinical use for the management of hypertension (and other cardiovascular conditions) for decades, and their efficacy and safety profiles when used as monotherapy are well understood. These drugs have complementary mechanisms of action and have each been shown to improve clinical outcomes in this population. This combination, prescribed appropriately and supported by delivery within a single tablet, has a place in the management of hypertension.

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