β blockers in hypertension and cardiovascular disease

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This review provides practical pointers on the use of β blockers for the non-specialist clinician

β blockers are useful in managing angina and reducing mortality after myocardial infarction and in heart failure. They probably reduce cardiovascular events in high risk surgery and retard the progression of atherosclerosis. In younger patients, β blockers should remain first line antihypertensives, together with diuretics, calcium channel blockers, angiotensin converting enzymes, and adrenergic receptor binders; choice depends on the individual case.

Not all β blockers are equivalent in cardiovascular protective effects, and atenolol seems inferior to other antihypertensive drugs in reducing stroke and total mortality. Recent publications have found that β blockers are less effective than other antihypertensive drugs in preventing cardiovascular outcomes in hypertensive patients.[1-3] In interpreting the new data, it is important to integrate these new results with previous trials and meta-analyses.

Are β blockers less protective in hypertensive patients?

Results of ASCOT-BPLA (the Anglo-Scandinavian cardiac outcomes trial—blood pressure lowering arm) suggest that atenolol may be only marginally inferior to amlodipine.[1] Its main lesson is that blood pressure must be tightly controlled, and patients taking β blockers (and diuretics) must be monitored so that cardiovascular risk factors are not adversely altered.

Sources and selection criteria

The references in the ASCOT trial,[1] recent meta-analyses of treatment with β blockers,[2 3] and guidelines of hypertension societies (Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7), British Hypertension Society, World Health Organization, European Society of Hypertension–European Society of Cardiology) were supplemented with a PubMed search using the keywords "clinical trial", "beta-blockers", "hypertension", and "cardiovascular outcomes".

ASCOT-BPLA randomised 19 257 high risk people with hypertension to amlodipine (adding perindopril) or atenolol (adding bendroflumethiazide). After 5.5 years, the primary end point, non-fatal myocardial infarction and cardiovascular death, was similar in the two groups (relative risk 0.90, 95% confidence interval 0.79 to 1.02; P=0.11). Several measures were lower with amlodipine: coronary end point (8% *v* 9%; 0.87, 0.79 to 0.96; P=0.007), stroke (3% *v* 4%; 0.77, 0.66 to 0.89; P=0.0003) and mortality (8% *v* 9%; 0.89, 0.81 to 0.99; P=0.02). Patients taking amlodipine had significantly lower blood pressure, as well as higher HDL (high density lipoprotein) cholesterol, and lower body mass index and concentrations of triglyceride, creatinine, and glucose. Multivariate adjustment for all these differences abolishes the difference in the cardiovascular event rate of the two groups.[4]

Thus, rather than showing the inferiority of atenolol, ASCOT-BPLA shows the importance of rigorously controlling blood pressure and other risk factors to reduce clinical cardiovascular disease. Although statistically significant, the 1% reduction in coronary event, stroke, and total mortality is not inspiring; the number needed to treat (NNT) for a year to prevent one cardiovascular event is 220, and to prevent one death is 650.[w1] With diuretic antihypertensive therapy to prevent heart failure NNT=48, and for the reduction in mortality with β blockers after myocardial infarction NNT=25-80.[w2 w3]

Meta-analyses

Two large meta-analyses also question the value of β blockers in cardiovascular protection of hypertensive patients.[2 3] These show that atenolol is inferior in reducing stroke and mortality, but non-atenolol β blockers may be equivalent to other antihypertensive drugs.

Carlberg reviewed the effects of atenolol on cardiovascular outcomes in hypertensive patients aged 52-70 who were followed up for 4.6 years. In four studies comparing atenolol with placebo (6825 patients) there was no difference in total mortality (relative risk 1.01, 0.89 to 1.15), cardiovascular mortality (0.99, 0.83 to 1.18), myocardial infarction (0.99, 0.83 to 1.19), and stroke (0.85, 0.72 to 1.01). In five studies comparing atenolol with other antihypertensive agents (17 671

References w1-w24 are on bmj.com

patients), despite equivalent reduction in blood pressure, atenolol treatment was associated with higher total mortality (1.13, 1.02 to 1.25), cardiovascular mortality (1.16, 1.00 to 1.34), and stroke (1.30, 1.12 to 1.50).

Lindholm's meta-analysis was more comprehensive, reviewing 13 trials (105 951 patients) comparing β blockers with other antihypertensives and seven trials (27 433 patients) comparing β blockers with placebo. Overall, β blockers were inferior to other antihypertensives in preventing stroke (1.16, 1.04 to 1.30), but the results were different for atenolol and non-atenolol β blockers (table 1). Compared with other antihypertensive drugs, atenonol was associated with higher risk of stroke (1.26, 1.15 to 1.38) and total mortality (1.08, 1.02 to 1.14). Non-atenolol β blockers were not inferior to other antihypertensives in preventing stroke (1.20, 0.30 to 4.71), myocardial infarction (0.86, 0.67 to 1.11), and total mortality (0.89, 0.70 to 1.12).

Atenolol

The different pharmacokinetic properties of atenolol and non-atenolol β blockers may account for their different cardiovascular protective effects in older hypertensive patients. Good data now show that atenolol is inferior, but the data are not conclusive enough to require using a substitute in all patients. Before starting or continuing with atenolol, though, a cautious clinician would ask whether another β blocker could be used. Atenolol is hydrophilic, has minimal hepatic metabolism, and is excreted in the urine; its long half life allows once daily dosage.[w4] It is inexpensive and has little interaction with drugs that are metabolised in the liver; these features account for its popularity. However, its pharmacokinetic profile can be disadvantageous in older patients with renal impairment, which slows clearance of atenolol.[w5]

Do β blockers have any role in cardiovascular disease?

Although the value of β blocker use in early myocardial infarction is controversial, β blockade clearly reduces adverse events in secondary prevention after infarction.[w6] Reviewing 31 trials (24 974 patients), Freemantle found that treatment with β blockers after infarction significantly reduced mortality (relative risk 0.77, 0.69 to 0.85).[5] All β blockers did not behave similarly; mortality was reduced with acebutolol (607 patients; 0.49, 0.25 to 0.93), metoprolol (5772 patients; 0.80, 0.66 to 0.96), propranolol (5785 patients; 0.71, 0.59 to 0.85), and timolol (2084 patients; 0.59, 0.46 to 0.77). No mortality reduction was seen with atenolol (1.02, 0.52 to 1.99). The NNT over two years to reduce one death with β blockers after infarction is 42; it compares favourably with treatment with antiplatelets (NNT=153) and statins (NNT=94).

Table 1 | Incidence of stroke and myocardial infarction and total mortality in hypertensive patients[3]

Outcome	Relative risk (95% CI) with β blockers *v* other antihypertensive drugs
Stroke:	
Atenolol	1.26 (1.15 to 1.38)
Other β blockers	1.20 (0.30 to 4.71)
Myocardial infarction:	
Atenolol	1.05 (0.91 to 1.21)
Other β blockers	0.86 (0.67 to 1.11)
Total mortality:	
Atenolol	1.08 (1.02 to 1.14)
Other β blockers	0.89 (0.70 to 1.12)

Good evidence exists for reduction in symptoms of angina and also for an antiatherosclerotic effect with β blockers.[6] By influencing the pathophysiology of atheroma progression they may improve prognosis. BCAPS (the β blocker cholesterol lowering asymptomatic plaque study) studied 793 patients with asymptomatic carotid plaques over 36 months, randomising them to placebo, fluvastatin 40 mg, or long acting metoprolol 25 mg. Progression of atheroma was assessed by measuring carotid intima-media thickness. Compared with placebo, metoprolol significantly reduced the rate of plaque progression over 18 months (difference 0.058 mm/year; P=0.004) and over 36 months (0.023 mm/year; P=0.014). In patients taking metoprolol, total mortality and cardiovascular events were significantly lower than in those not taking β blockers (8 *v* 19; P=0.031).

β blockers improve prognosis in patients with all grades of symptomatic heart failure. Recent evidence suggests that β blockers are equivalent to angiotensin converting enzyme inhibitors as initial drugs in treating heart failure.[w8] Bisoprolol, metoprolol, and carvedilol all reduce mortality in heart failure.

CIBIS-II (the cardiac insufficiency bisoprolol study II) randomised 2647 patients with ejection fraction <35% and New York Heart Association (NYHA) class III or IV to bisoprolol or placebo, with the primary end point of total mortality.[7] The trial was terminated after 1.3 years, when it showed that bisoprolol reduced mortality significantly (11.8% *v* 17.3%; relative risk 0.66, 0.54 to 0.81; P<0.0001). It also significantly reduced total hospitalisation (0.80, 0.71 to 0.91; P=0.0006) and death from cardiovascular causes (0.71, 0.56 to 0.90; P=0.0049).

MERIT-HF (metoprolol CR/XL randomised intervention trial in congestive heart failure) involved 3391 patients (NYHA classes II to IV, ejection fraction 40%).[8] When the trial was terminated after one year, metoprolol clearly reduced total mortality (7.2% *v* 11.0%; 0.66, 0.53 to 0.81; P<0.0001) as well as cardiovascular mortality (0.62, 0.50 to 0.78), sudden death (RR 0.59, 0.45 to 0.78), and death from heart failure (0.51, 0.33 to 0.79). A carvedilol trial involving 1094 patients also showed highly significant reduction in total mortality (3.2% *v* 7.8%; 0.35, 0.20 to 0.61; P0.001).[w7]

More impressive was COPERNICUS (the carvedilol prospective randomised cumulative survival study), which enrolled 2289 ill patients (NYHA class IV, ejection fraction 25%).[9] After 10.4 months, carvedilol markedly reduced overall mortality (130 *v* 190 deaths; 0.65, 0.52 to 0.81; P=0.0014), as well as death or admission to hospital (0.76, 0.67 to 0.87; P<0.001).

What is still controversial?

Are non-atenolol β blockers (especially metoprolol and bisoprolol) superior to atenolol in preventing adverse cardiovascular outcomes in hypertensive patients?

Are β blockers equivalent to other classes of antihypertensive agents in reducing clinical events in younger patients?

Can β blockers reduce clinical events and improve prognosis in patients with coronary disease?

Will perioperative use of β blockers reduce postoperative cardiovascular morbidity and mortality?

Table 2 | Relative risk of cardiovascular outcomes (death, stroke, or myocardial infarction) in hypertensive patients treated with β blockers[13]

Age at baseline	Relative risk (95% CI) with β blockers
<60 years:	
β blockers *v* placebo	0.86 (0.74 to 0.99)
β blockers *v* other drugs	0.97 (0.88 to 1.07)
≥60 years	
β blockers *v* placebo	0.89 (0.75 to 1.05)
β blockers *v* other drugs	1.06 (1.01 to 1.10)

Is treatment outcome affected by type of β blocker used or age profile of patient?

β blockers do not all produce the same outcome when used in the same clinical condition. A study similar to COPERNICUS but using bucindolol produced results different from those with carvedilol.[10] In 2708 patients (NYHA class III or IV, ejection fraction <35%) after two years, total mortality was not significantly affected by bucindolol (33% with placebo, 30% with bucindolol; 0.90, 0.78 to 1.02; P=0.10). Although many reasons were postulated, the practical message is that some, but not all, β blockers reduce mortality in heart failure.[w9] Thus, in treating heart failure, clinicians should choose only those β blockers that have been shown to be useful. Similarly, in hypertension, myocardial ischaemia, or after myocardial infarction, only those β blockers with good evidence favouring their value should be used.

Older people with hypertension may have a different profile from younger ones.[13] Khan and McAlister reviewed cardiovascular events (stroke, myocardial infarction, and death) in 145 811 patients from 21 hypertension trials (table 2). Among patients under 60 years, β blockers reduced cardiovascular outcomes compared with placebo (19 414 patients; relative risk 0.86, 0.74 to 0.99) and were equivalent to other antihypertensive drugs (30 412 patients; 0.97, 0.88 to 1.07). In patients aged 60 and over, β blockers were equivalent to placebo (8019 patients; 0.89, 0.75 to 1.09) and were less effective in reducing cardiovascular outcomes than other antihypertensive drugs (79 775 patients; 1.06, 1.01 to 1.10). These results are clinically reasonable, since the pathophysiology of hypertension is different in younger and older patients.[14 15]

β blockers may be more useful in younger people with hypertension who have a higher sympathetic drive but essentially normal vascular resistance.[16] Rather than pointing to "the end of β blockers in uncomplicated hypertension," the evidence today suggests that β blockers are efficacious in cardiovascular protection of younger people with hypertension.[w14]

Which β blocker should we use?

Strong evidence from clinical trials shows that bisoprolol, carvedilol, and metoprolol improve prognosis in heart failure, and acebutolol, metoprolol, propranolol, and timolol reduce mortality after myocardial infarction[5 7-9]

Metoprolol and bisoprolol may improve prognosis in patients with coronary artery disease, as some randomised trials have shown they reduce adverse events in stable patients and patients at high risk[6 19 20]

Atenolol has been shown in clinical trials to be inferior to other antihypertensive agents in reducing cardiovascular outcomes (especially strokes); no evidence from clinical trials supports its use after a myocardial infarction or in heart failure[2 3 11 12 w10-w14]

How should β blockers be used?

We must be cautious and objective in interpreting the data on use of β blockers in hypertensive patients. The preference for new drugs sometimes results in an increase in clinical disease, as the COX-2 experience shows.[17 w15 w16] Diuretics were once thought to be unsafe antihypertensives because of the metabolic changes they induce,[w17 w18] but ALLHAT (the antihypertensive and lipid lowering treatment to prevent heart attack trial) showed that their cardiovascular protection in hypertension equals or surpasses that conferred by newer drugs.[18] Diuretics are especially useful in stroke prevention, and a meta-analysis by Psaty (42 clinical trials, 192 478 patients) found that all antihypertensive drugs are inferior to diuretics in reducing cardiovascular events.[w19 w20]

The need to choose the correct β blocker for the clinical situation must be borne in mind when interpreting the comparative trials of antihypertensive drugs involving β blockers. That β blockers relieve angina has been known since the 1960s.[w21] β blockers clearly reduce mortality in secondary prevention after myocardial infarction.[5] They also reduce cardiovascular events in the preoperative management of high risk ischaemic patients before major vascular surgery.[19] Continuation of bisoprolol for two years after surgery further reduces cardiac death and myocardial infarctions.[20] Metoprolol's antiatherosclerotic effect provides a pathophysiological rationale for the improved prognosis with β blockers in myocardial ischaemia.[6]

β blockers reduce mortality in all classes of heart failure,[w22] but not all β blockers are the same: bucindolol does not produce the same mortality reduction as carvedilol in similar patients.[10] Although β blockers have clear benefit in secondary prevention, they do not affect prognosis when used in early myocardial infarction; the reduction in re-infarction and sudden death is balanced by the increase in heart failure and shock.[5 w6 w23]

The data from trials of atenolol in hypertension are not reassuring. As well as the results of ASCOT-BPLA, atenolol was also shown to be inferior to losartan in the LIFE (losartan intervention for end point reduction in hypertension) study, which found that angiotensin

SUMMARY POINTS

β blockers reduce mortality after a myocardial infarction and improve prognosis in patients with systolic heart failure

They reduce adverse outcomes in perioperative management of high risk patients

In younger hypertensive patients (aged under 60 years), β blockers are equivalent to other antihypertensive agents

β blockers may improve prognosis and favourably retard disease progression in coronary artery disease

Atenolol may be less useful than other β blockers, and other antihypertensive drugs, in reducing cardiovascular disease in hypertensive patients

receptor blockers are especially useful in stroke prevention.[21 w24] Yet, for preventing stroke, an angiotensin receptor blocker was equivalent to a calcium channel blocker in VALUE (the valsartan antihypertensive long-term use evaluation trial), while the angiotensin converting enzyme inhibitor was inferior to diuretic in ALLHAT.[18 22] As there is no evidence that angiotensin antagonists are better at preventing stroke, the results of LIFE must be due to the inferiority of atenolol.

The meta-analysis showing atenolol to be inferior to comparative antihypertensive drugs but non-atenolol β blockers to be equivalent to comparator drugs, is further evidence cautioning against atenolol use in hypertension.[3] The review suggesting that β blockers reduce cardiovascular outcomes in younger but not in older people with hypertension makes a logical point.[13] Younger people with hypertension tend to have a higher sympathetic tone and thus may better respond to β blockade. In older people, β blockers should be avoided unless another clinical condition necessitates their use.

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Additional educational resources

For healthcare professionals

National Collaborating Centre for Chronic Conditions. *Hypertension: management of hypertension in adults in primary care: partial update*. London: Royal College of Physicians, 2006. www.nice.org.uk/CG034guidance

World Health Organization, International Society of Hypertension Writing Group. World Health Organisation (WHO)/International Society of Hypertension (ISH) statement on management of hypertension. *J Hypertens* 2003;21:1983-92.

Guidelines Committee. European Society of Hypertension-European Society of Cardiology guidelines for the management of arterial hypertension. *J Hypertens* 2003;21:1011-53.

Chobanian AV, Bakris GL, Black HR, et al and the National High Blood Pressure Education Program Coordinating Committee. Seventh report of the National Committee on prevention, detection, evaluation, and treatment of high blood pressure. *Hypertension* 2003;42:1206-52.

Information for patients

NICE. Hypertension—information for the public (www.nice.org.uk/CG034publicinfo)

British Blood Pressure Association (www.bpassoc.org.uk)

American Heart Association (www.americanheart.org)

National Heart Lung and Blood Institute (www.nhlbi.nih.gov/health/index.htm)

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