Bisoprolol

Essential medicine status ✓

ATC codes: C07AB07

Indication	Essential hypertension ICD11 code: BA00.Z
INN	Bisoprolol
Medicine type	Chemical agent
List type	Core
Additional notes	Atenolol should not be used as a first-line agent in uncomplicated hypertension patients > 60 years
Formulations	Oral > Solid: 1.25 mg ; 5 mg
EML status history	First added in 2011 (TRS 965) Changed in 2015 (TRS 994)
Sex	All
Age	Adolescents and adults
Therapeutic alternatives	carvedilol (ATC codes: C07AG02) atenolol (ATC codes: C07AB03) metoprolol (ATC codes: C07AB02)
Patent information	Patents have expired in most jurisdictions Read more about patents.
Wikipedia	Bisoprolol
DrugBank	Bisoprolol

Summary of evidence and Expert Committee recommendations

In 2011, the Expert Committee changed the nominated beta-blocker in the WHO Model List from atenolol to bisoprolol, partly because use of atenolol was not appropriate in heart failure. The change was implemented for four listings of beta-blockers in the Model List (Section 12.1 Antianginal medicines, Section 12.2 Antiarrhythmic medicines, Section 12.3 Antihypertensive medicines, and Section 12.4 Medicines used in heart failure). The square box listing includes a note that metoprolol and carvedilol are alternatives to bisoprolol (1). This has caused some confusion at the country level where atenolol is widely available and used in practice: WHO has been asked whether countries should stop using atenolol. A review was commissioned from Professor Anthony Smith, University of Newcastle, Callaghan, NSW, Australia, of the role of atenolol in the management of hypertension and heart failure. The review canvassed the key trials and meta-analyses published since 2000. Expert reviews of the commissioned review were prepared by two members of the Expert Committee. Comments were received from Dr Myriam Henkens, International Medical Coordinator, Médecins Sans Frontières. The 2002 LIFE study, which included 9 222 participants, reignited the debate over the role of atenolol in hypertension, reporting a greater incidence of stroke with this beta-blocker compared with losartan (5% losartan versus 7% atenolol; HR 0.75; 95% CI: 0.63–0.89), which contributed to the composite end-point and overall cardiovascular mortality (2). The trial allowed add-on therapy with hydrochlorothiazide and then other antihypertensive agents, however addition of angiotensin-converting-enzyme inhibitors (ACEI), angiotensin II receptor antagonists (AIIRA) and/or beta-blockers was not permitted. A pre-specified subgroup analysis of 1195 patients with diabetes and hypertension from the LIFE trial produced similar findings, with greater stroke incidence in the atenolol group (9% losartan versus 11% atenolol; HR 0.79; 95% CI: 0.55–1.14 (adjusted for degree of left-ventricular hypertrophy and Framingham risk score at randomisation)) (3). The 2003 INVEST multicentre study of hypertension in 22 576 patients with confirmed coronary artery disease found similar blood pressure control and clinical outcomes, including nonfatal stroke, in patients treated with either verapamil or atenolol (with add-on trandolapril

and/or hydrochlorothiazide) (4). The authors concluded that the two treatments were equi-effective. The 2005 ASCOT-BPLA trial of 19 257 patients (aged 49–75 years) with hypertension and at least three other cardiovascular risk factors was stopped ahead of time as the mortality rate in the atenolol group (with add-on thiazide diuretic and potassium (as required)) was higher than in the amlodipine group (with add-on perindopril) (5). However, a subsequent multivariate analysis of the data concluded that there were no statistically significant differences between the treatment groups (6). A 2005 meta-analysis including both LIFE and ASCOT studies concluded that the "effect of beta-blockers is less than optimum with a raised risk of stroke" (RR 1.16; 95% CI: 1.04–1.30, favouring medicine other than atenolol), with no statistically significant differences in all-cause total mortality and myocardial infarction (7). A 2007 Canadian database study observed similar two-year rates of myocardial infarction, unstable angina, stroke or death in cohorts receiving atenolol, ACEI, thiazide diuretics or calcium blockers (total population 19 249 people, average age 60.6 years) (8). Eligible patients were first-time users of antihypertensive treatment as monotherapy. The authors concluded that atenolol was not associated with a significant burden of cardiovascular morbidity or mortality in uncomplicated hypertension. Long-term follow-up of the United Kingdom Prospective Diabetes Study showed no detrimental effects in those initially randomized to beta-blockers; in particular, there was no excess in stroke (9). A 2006 meta-analysis of 21 hypertension trials showed similar efficacy in reduction of cardiovascular events in younger patients treated with betablockers compared with other agents but more composite end-points (death, stroke, myocardial infarction) in patients over 60 years of age (RR 1.12; 95% CI 1.02–1.24) (10). An additional analysis by Khan et al. excluded three studies also excluded by Lindholm et al. (7), generating an excess composite risk in patients over 60 years, driven largely by an excess risk of stroke (RR 1.18; 95% CI 1.07–1.30). A 2009 meta-analysis included 46 trials designed to determine the efficacy of different classes of blood-pressure-lowering drugs in preventing coronary heart disease (CHD) and stroke and to identify which patients should receive treatment. In the trials assessing blood pressure reduction, beta-blockers had the additional effect of preventing recurrent CHD events in patients with a history of CHD (11). This effect was limited to a "few years" after a myocardial event. All classes of blood-pressure-lowering drugs had a similar effect in reducing CHD events and stroke for a given reduction in blood pressure. A 2009 reappraisal of European guidelines by the European Society of Hypertension Task Force noted that reduction in blood pressure is the prime factor in reducing cardiovascular morbidity and mortality and recommended all classes of medicines as first-line therapy (12). In its 2011 guidance on the initial treatment of primary hypertension, the National Institute for Health and Care Excellence (NICE) recommends an ACEI or an AIIRA as first-line therapy in those aged less than 55 years, with a note to consider beta-blockers in younger patients (13). The European Society of Hypertension/European Society of Cardiology 2013 guidelines for the management of arterial hypertension describe compelling (e.g. asthma, grade 2 or 3 atrioventricular block) and possible (e.g. metabolic syndrome, glucose intolerance, athletes/physically active patients, chronic obstructive pulmonary disease) contraindications to beta-blockers as well as the preferred conditions for treatment with beta-blockers (hypertension with previous myocardial infarction, angina pectoris, heart failure, atrial fibrillation). The guidelines also suggest "all-purpose ranking of drugs for general antihypertensive usage is not evidence-based" (14). The US Joint National Committee 2014 guideline for the management of high blood pressure in adults concluded "the panel did not recommend betablockers for the initial treatment of hypertension because in one study (LIFE trial) use of beta-blockers resulted in higher rate of the primary composite outcome of cardiovascular death, myocardial infarction or stroke compared to use of an AIIRA, a finding that was driven largely by an increase in stroke" (15). The 2014 recommendations of the Canadian Hypertension Education Program are for initial treatment with a single thiazide/thiazide-like diuretic, a beta-blocker (in patients aged less than 60 years), or an ACEI. Beta-blockers are not recommended as first-line treatment for uncomplicated hypertension in patients aged 60 years or more (16). The Expert Committee agreed with evidence reviewed in the application, that atenolol should be considered as an appropriate first-line treatment option in hypertension associated with coronary heart disease, especially for treatment initiated after a myocardial infarction and in patients with angina and supraventricular arrhythmias. It is both reasonable and concordant with the evidence to recommend atenolol as a first-line treatment in younger hypertensive patients, perhaps with a cut-off at 60 years, in line with the Canadian and NICE recommendations. However, atenolol is not recommended as first-line treatment for uncomplicated hypertension in patients over the age of 60 years. The Committee acknowledged that atenolol retains a place as add-on, second- or third-line treatment if blood pressure control is not achieved with other antihypertensive agents. The retention of bisoprolol, carvedilol and metoprolol for the management of chronic cardiac failure is in line with the available evidence. While atenolol has been used in heart failure, the major outcome studies (not included in the commissioned review) have been conducted with these three compounds. Atenolol is a beta 1-receptor blocker with a prolonged half-life that allows once daily dosing, which can assist with patient compliance/adherence. It is not significantly metabolized and is therefore not a target for interactions through metabolic pathways. It is lost from the body by renal excretion and must be used with caution in renal impairment. The Committee noted that atenolol is considerably cheaper than bisoprolol, carvedilol and metoprolol. Based on the

evidence presented, therefore, the Expert Committee recommended that atenolol be included as an additional alternative beta-blocker to metoprolol and carvedilol in the note associated with the listing of bisoprolol in Section 12.3, Antihypertensive medicines, of the Model List. The Committee also recommended that the note state that atenolol should not be used as first-line agent for uncomplicated hypertension in patients aged over 60 years. The Expert Committee did not recommend any changes be made to the current listing of bisoprolol in Section 12.4, Medicines used in heart failure, of the Model List. References: 1. The selection and use of essential medicines. Report of the WHO Expert Committee, 2011 (including the 17th WHO Model List of Essential Medicines and the 3rd WHO Model List of Essential Medicines for Children). Geneva: World Health Organization; 2012. (WHO Technical Report Series, No. 965). 2. Dahlof B, Devereux RB, Kjeldsen SE, Julius S, Beevers G, de Faire U, et al. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. Lancet. 2002;359(9311):995-1003. 3. Lindholm LH, Ibsen H, Dahlof B, Devereux RB, Beevers G, de Faire U, et al. Cardiovascular morbidity and mortality in patients with diabetes in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. Lancet. 2002;359(9311):1004-10. 4. Pepine CJ, Handberg EM, Cooper-DeHoff RM, Marks RG, Kowey P, Messerli FH, et al. A calcium antagonist vs a non-calcium antagonist hypertension treatment strategy for patients with coronary artery disease. The International Verapamil-Trandolapril Study (INVEST): a randomized controlled trial. JAMA. 2003;290(21):2805-16. 5. Dahlof B, Sever PS, Poulter NR, Wedel H, Beevers DG, Caulfield M, et al. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. Lancet. 2005;366(9489):895-906. 6. Poulter NR, Wedel H, Dahlof B, Sever PS, Beevers DG, Caulfield M, et al. Role of blood pressure and other variables in the differential cardiovascular event rates noted in the AngloScandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA). Lancet. 2005;366(9489):907-13. 7. Lindholm LH, Carlberg B, Samuelsson O. Should beta blockers remain first choice in the treatment of primary hypertension? A meta-analysis. Lancet. 2005;366(9496):1545-53. 8. Blackburn DF, Lamb DA, Eurich DT, Johnson JA, Wilson TW, Dobson RT, et al. Atenolol as initial antihypertensive therapy: an observational study comparing first-line agents. J Hypertens. 2007;25(7):1499-505. 9. Holman RR, Paul SK, Bethel MA, Neil HA, Matthews DR. Long-term follow-up after tight control of blood pressure in type 2 diabetes. N Engl J Med. 2008;359(15):1565-76. 10. Khan N, McAlister FA. Re-examining the efficacy of beta-blockers for the treatment of hypertension: a meta-analysis. CMAJ. 2006;174(12):1737-42. 11. Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. BMJ. 2009;338:b1665. 12. Mancia G, Laurent S, Agabiti-Rosei E, Ambrosioni E, Burnier M, Caulfield MJ, et al. Reappraisal of European guidelines on hypertension management: a European Society of Hypertension Task Force document. Blood Press. 2009;18(6):308-47. 13. Clinical management of primary hypertension in adults. NICE clinical guidelines [CG127]. London: National Institute for Health and Care Excellence; 2011. Available from: https://www. nice.org.uk/guidance/cg127/resources/guidance-hypertension-pdf. 14. Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Bohm M, et al. 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J. 2013;34(28):2159-219. 15. James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA. 2014;311(5):507-20. 16. Dasgupta K, Quinn RR, Zarnke KB, Rabi DM, Ravani P, Daskalopoulou SS, et al. The 2014 Canadian Hypertension Education Program recommendations for blood pressure measurement, diagnosis, assessment of risk, prevention, and treatment of hypertension. Can J Cardiol. 2014;30(5):485-501.