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Beta Blockers in Hypertension— Losing Ground?

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Abstract: Hypertension is a common condition in developed and developing nations, associated with cardiovascular complications and end organ damage, and yet its etiology remains largely elusive. It has long been recognized that satisfactory control of blood pressure reduces cardiovascular complications. Early trials, before the advent of drugs acting on the renin-aldosterone system, (RAS) revealed the three main drug classes (diuretics, beta blockers, calcium antagonists) to be equally effective in reducing cardiovascular morbidity and mortality. However, more recent data comparing these drugs to RAS active compounds showed a clear superiority of the latter. In particular, RAS active drugs were superior to beta blockers in reducing left ventricular hypertrophy, such that they are now recommended as first line treatment for the majority of patients. They have usurped not only beta blockers but also diuretics and calcium antagonists as first line therapy in younger (< 55 years) patients who have “higher renin” hypertension. Beta blockers, however, still have a role in symptom control. In patients with known ischemic heart disease, they remain the drug of choice, even in the presence of diabetes mellitus. The enclosed chart (Fig. 35.1) illustrates the British Hypertension Society and National Institute of Clinical Excellence guideline for management of hypertension and the role of beta blockade. The latter, although “losing ground”, nevertheless remains an effective and integral agent in the physicians armamentarium.

INTRODUCTION

Primary hypertension is a common disorder affecting about 1 billion individuals worldwide. Its prevalence is likely to increase with the increase in elderly population and increasing prevalence of contributing factors such as obesity and physical inactivity.^{1,2}

It is a major risk factor for premature coronary heart disease, stroke, heart failure events and chronic renal insufficiency^{3,4,5} and about 7.1 million deaths per year may be attributed to it. The World Health Organization reports that suboptimal blood pressure levels (> 115 mmHg SBP) may contribute to 49% of ischemic heart disease and 62% of cerebrovascular disease with little variation by sex.¹

Clinical trial evidence has consistently shown reduction in cardiovascular morbidity and mortality with lowering of blood pressure. Treatment of hypertension is associated with reductions in strokes averaging 35 to 40%; myocardial infarction 20 to 25%; and heart failure, > 50%.^{6,7} The treatment of hypertension has evolved over the past few decades in the light of clinical trials. Currently, there are a number of drug classes available for the management of hypertension. About one third of patients could be managed with a single drug with the remainder requiring two or more drug classes in combination.⁸

Different Classes of Antihypertensive Medication

Diuretics have been evaluated in the management of hypertension for over three decades and found to be safe and effective in lowering morbidity and mortality.⁹ Low to medium dose thiazide diuretics are associated with less adverse biochemical derangement^{10,11} and have been shown in randomized trials to reduce cardiovascular morbidity and mortality compared to high dose diuretics.^{12,13}

Aldosterone antagonists reduce cardiovascular morbidity and mortality in patients with congestive heart failure.^{14,15} The combined treatment of a thiazide diuretic and aldosterone antagonist is also effective in lowering blood pressure as well as reducing the risk of hypokalemia and sudden cardiac death.¹⁶

Calcium channel blockers (CCB) are used for the treatment of many cardiovascular conditions including hypertension, angina pectoris and cardiac arrhythmias. Although the short acting CCB were found to increase the risk of myocardial infarction and mortality,^{17,18} recent trials have shown that CCB are safe and effective in reducing cardiovascular mortality and morbidity.^{13,19-21} This class of drugs, however, is less effective than ACE inhibitors and diuretics in preventing heart failure.^{13,22}

Beta blockers reduce morbidity and mortality in patients after myocardial infarction,²³ angina and congestive cardiac failure. Furthermore, they are effective in rate control in patients with tachyarrhythmias, including atrial fibrillation. This was the rationale for its use as first line therapy in secondary prevention of ischemic heart disease in hypertensive patients.²⁴

Beta blockers are as effective as other antihypertensive agents in reducing the blood pressure.^{25,26} However, there is considerable inter-patient variability in the response to any antihypertensive agent, and variables such as race and age have a significant effect on the response to a single agent.²⁷

Overview of Selected Clinical Trials Data

Clinical trial data indicate that at a similar level of blood pressure reduction, most antihypertensive agents provide similar cardiovascular protection. This is well illustrated in major clinical trials such as the UKPDS,²⁸ CAPPP²⁹ and NORDIL.^{6,22} In these trials conventional antihypertensives, such as beta blockers and diuretics, were as effective as newer agents such as calcium channel blockers and angiotensin converting enzyme inhibitors in reducing cardiovascular morbidity and mortality.

Early guidelines and some recent guidelines recommend beta blockers and diuretics as first line treatment in hypertension.^{30,31} However, more recent clinical trial data has shed doubt on the clinical benefit of beta blockers in hypertensive patients when compared to the newer class of drugs acting on the renin-aldosterone system (RAS).

Beta blocker monotherapy does not appear to confer cardiovascular benefits compared to placebo. In the Medical Research Council trial on hypertension in older adults, atenolol and diuretic were effective in reducing blood pressure when compared to placebo. However, atenolol did not show a significant reduction in cardiovascular end points (stroke, coronary heart disease and death) compared to diuretics.⁹

Furthermore, in a systematic review of clinical trial involving beta blockers and diuretics in elderly patients, beta blockers were ineffective in reducing all-cause mortality, cardiovascular mortality and coronary heart disease compared to diuretics.³²

The poor outcome of beta blockers in elderly could be due to differences in the pathophysiology of hypertension in the elderly and the young.³³ Development of diastolic hypertension in the young was closely linked to the increase in peripheral resistance and high body mass index. In contrast, most cases of isolated systolic hypertension in elderly arise de novo and

are closely related to increased arterial stiffness. Thus, beta blockers, which reduce peripheral vascular resistance, may not be the ideal antihypertensive *monotherapy* for elderly patients.^{2,33}

Furthermore, two recent large scale clinical trials failed to show the superiority of beta blockers in preventing major cardiovascular events in patients with hypertension.

The ASCOT-BPLA trial compared an amlodipine based regime with one centered on atenolol. The primary endpoint of nonfatal and fatal myocardial infarction was not significantly lowered in the amlodipine based regimen compared to the atenolol based group. However, all secondary end points (except nonfatal and fatal heart failure) were reduced in the amlodipine based group. Three points are worthy of note:

1. Only 53% of patients achieved the required systolic and diastolic target level.
2. The study population included patients with at least three cardiovascular risk factors thereby selecting those with moderate risk of future cardiovascular events; and
3. No patients with essential hypertension without other risk factors.¹⁹

Trials with RAS Drugs

Left ventricular hypertrophy (LVH) is common in patients with hypertension and is associated with increased cardiovascular morbidity and mortality.^{34,35} The regression of LVH is directly related to the lowering of blood pressure and also to the class of antihypertensive medication. The advent of a new class of drugs, acting on the renin-aldosterone system has advanced the treatment of hypertensive disease. Of particular interest was the observation that these drugs were effective in reducing LVH.

In the LIFE study, Losartan was compared with atenolol in 9193 participants aged 55-80 years with essential hypertension and left ventricular hypertrophy. Losartan prevented more cardiovascular morbidity and death than atenolol for similar reduction in blood pressure. Klingbeil, et al, in their meta-analysis, showed that angiotensin receptor blockers were superior to beta blockers in reducing LVH. The additional beneficial effect of Losartan could be due to reduction of myocardial fibrosis and myocardial stiffness. Thus, the superiority of losartan in the LIFE study is more likely due to its class effect.³⁶⁻³⁸

Left ventricular hypertrophy is also associated with increased risk of sudden cardiac death after accounting for known risk factors.³⁴ Clinical trial evidence indicates that beta blocker monotherapy or, in combination with diuretic, increase sudden cardiac death when compared to calcium channel blocker, ACE inhibitors or potassium sparing diuretics.³⁹ As LVH prevalence increases with age and hypertension, this could mean a larger population of elderly hypertensives could be at risk of sudden cardiac death if treated with beta blocker monotherapy.^{39,40}

Two recent meta-analysis by Caalberg B⁴¹ and Lindholm LH,⁴² failed to show superiority of beta blockers compared to other antihypertensive medication. *The relative risk of stroke was 16% higher for beta blockers, but no difference was noted for myocardial infarctions.* In a meta-analysis by Lindholm, beta blockers were compared in three separate groups:

- i. against placebo
- ii. against other antihypertensive drugs
- iii. beta blockers in mixed trials.

With the exception of treatment against placebo, beta blocker therapy was associated with increased incidence of stroke. In this meta-analysis clinical trials evaluating young and old, individuals were included in the same analysis despite different pathophysiological processes in the two groups. Furthermore, some trials had patients with multiple risk factors for coronary heart disease, thus one would expect more adverse outcome in high risk patients. It should also be noted that some major trials on beta blockers have not been included in the meta-analysis.³³

Beta Blockade as Antihypertensive in Different Age Groups

Some clinical trials have indicated that beta blockers may be effective in reducing cardiovascular mortality and morbidity in young patients with hypertension. The Medical Research Council (MRC) trial assessed the efficacy of diuretic or beta blocker or placebo in reducing the rate of stroke, of death due to hypertension, and of coronary events in men and women between 35 to 64 years. The rate of stroke, coronary events and cardiovascular events were similar in the beta blocker and the diuretics group.¹²

In the Heart Attack Primary Prevention in Hypertension (HAPPY) trial beta blockers and thiazide diuretics had a similar blood pressure reducing effect and had similar efficacy in reducing hypertensive complications including coronary heart disease.⁴³ In their analysis, Furberg, et al,⁴⁴ stated beta blockers to be as effective as diuretics in reducing blood pressure, improving survival and in preventing major morbidity events.

In addition, a case control study showed beta blockers to prevent first events of nonfatal myocardial infarction.⁴⁵ Furthermore, the Metoprolol Atherosclerosis Prevention in Hypertensive Trial (MAPHY), which was the metoprolol arm of the HAPPY study, showed a 25 percent reduction in coronary events with metoprolol compared to thiazide diuretics.⁴⁶

Development of Diabetes Mellitus

The rate of development of new onset diabetes mellitus varies according to the antihypertensive medication used.^{47,48} In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) approximately 10 percent of the total study population developed new onset diabetes mellitus. The risk was higher for diuretics than for ACE inhibitor or calcium channel blocker.¹³ In the LIFE study, atenolol was more frequently associated with new onset diabetes than losartan. Patients with new onset diabetes were three times more likely to develop cardiovascular disease than those free of diabetes mellitus.^{49,50} Thus, beta blocker, in combination with thiazide diuretic, would increase the incidence of new onset diabetes and increase risk of cardiovascular events. However, in a recent meta-analysis, there was no increase in risk in patients who developed new onset diabetes while on chlorthalidone.⁵¹

Hypertension in diabetic individuals markedly increases the risk of, and accelerates cardiovascular disease.⁵² Furthermore, hypertension is closely associated with diabetic renal disease.⁵³ Current guidelines recommend intense blood pressure control in diabetic hypertensive patients.⁵⁴ In most of the large scale trials investigating diabetes and hypertension, intense blood pressure control was achieved only with combination therapy rather than specific monotherapy.⁵⁵ In the UKPDS study atenolol was as effective as captopril in reducing diabetic complications. However in the LIFE study, losartan was found to be superior to atenolol in reducing cardiovascular end points.³⁶ Beta blockers may mask the hypoglycemic symptoms in diabetic patients, but may be less prominent with beta-1 selective drugs.⁵⁶ Carvedilol may have certain advantages compared to other beta blockers in patients with diabetes. In a small scale trial, carvedilol improved glucose and lipid metabolism compared to atenolol.⁵⁷ In the Glycemic Effects in Diabetes Mellitus: Carvedilol-Metoprolol comparison in Hypertensive (GEMINI) trial, carvedilol, in combination with renin-angiotensin system blockade, did not have an effect on glycemic control and there was a low rate of progression to microalbuminuria compared to metoprolol.⁵⁸ Both trials investigating carvedilol were small scale trials and follow up was for a short duration.

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