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Treatment of Hypertension in 2016 – Role of Beta Blockers

Medical Science

KEYWORDS :

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Preface

Use of beta blockers (BB) to treat hypertension started in the 1960's, as these agents had enormous improvement in terms of adverse effects over the existing antihypertensive drugs in vogue at that time, such as ganglionic blockers, guanethidine, or methyldopa. However, since the introduction of newer classes of antihypertensive drugs, such as diuretics, calcium channel blockers (CCBs),angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs), BB have been subjected to a more stringent scrutiny and their performance is usually compared with these new agents. The BB are still preferred in hypertensive patients who have suffered from myocardial infarction (MI), or other forms of IHDs, and HF due to systolic dysfunction, but not in hypertensive patients without comorbidities. Beta-blockers are usually avoided in patients suffering from bronchial asthma, or with airway hyper-reactivity. Their use as first-line therapy for hypertension first came under criticism in the 1990's when it was shown by meta-analyses of clinical trials that BB did not significantly reduce cardiac and all-cause mortality. Propranolol showed little benefit against stroke and none on coronary events in elderly patients. Beta-blockers were also found less effective in lowering systolic blood pressure (SBP) and diastolic blood pressure (DBP) in hypertensive patients than those treated with ACEIs, ARBs, and CCBs, and significantly less patients continued their treatment with BB. Several recent meta-analyses have questioned the usefulness of BB as the primary tools to treat hypertension.[1] The purpose of this review is to determine the current consensus, or at least the difference of opinions of various investigators regarding the use of BB in the treatment of hypertension.

2. Why Are Beta-Blockers Less Effective in the Prevention of Cardiovascular Events Than Other Antihypertensive Agents.

Prichard classified beta-blockers into three types according to their beta1-selectivity and vasodilatory potential . An additional classification is lipophilic or hydrophilic beta-blockers. Atenolol is a beta1-selective agent, and it has been widely used as the control drug in large randomized prospective controlled trials of newer antihypertensive agents such as CCB and ACEI or ARB.[2] Table 1 summarizes the plausible reasons why beta-blockers are considered to be relatively ineffective for the prevention of cardiovascular events .

Table 1: Plausible reasons for beta-blockers being relatively ineffective for the prevention of cardiovascular events & stroke.

Less effective lowering of the blood pressure

Visit-to-visit blood pressure instability

Less effective lowering of the central blood pressure

Less effective regression of the left ventricular hypertrophy

Unfavorable metabolic effects

Less effective vascular protection

Reduced drug compliance

In the Anglo-Scandinavian Cardiac Outcomes Trial- Blood Pressure Lowering Arm (ASCOT-BPLA) study, blood pressure values were lower in those allocated to the CCB based regimen as compared to those allocated to the BB based regimen throughout the trial period .[2] Recently, Webb et al. reported a meta-analysis in which they described visit-to-visit blood pressure instability in patients receiving BB treatment , and also that this instability was associated with an increased risk of stroke . Atenolol was used in the ASCOT-BPLA study, and not only the analysis conducted by Webb et al. but also that conducted by Rothwell et al. involved the use of atenolol. Some studies demonstrated that once-daily atenolol does not provide adequate blood pressure control during the night-time and early morning periods because of its pharmacokinetic profile and half-life . These drug profiles of atenolol may be the cause for its relatively weak blood pressure-lowering effect and the blood pressure instability. On the other hand, metoprolol or bisoprolol have been shown to be more effective in sustaining 24-hour and early morning BP reductions as compared with atenolol .Central (aortic and carotid) blood pressure is pathophysiologically more relevant than the peripheral pressure in the pathogenesis of cardiovascular disease. Augmentation index (AI), a marker of the interaction of incident pressure wave and reflected pressure wave, was significantly and inversely related to heart rate due to an alteration in the relative timing of the reflected pressure wave . BB reduce the heart rate and decrease AI, which reduces their efficacy in reducing the central blood pressure as compared to other antihypertensive agents . In their meta-analysis, Fagard et al. reported that BB exert a relatively weak effect in causing regression of the left ventricular mass . In Fagard et al.'s review, atenolol was used in about 70% of the study subjects prescribed BB and no study involving the use of vasodilatory BB was included. Recently, the advantages of nebivolol, a vasodilatory BB, over conventional agents in reducing the central blood pressure and inducing regression of the left ventricular mass have been reported . Compared with atenolol, nebivolol exerts a more favorable effect on 24-hour blood pressure profile . Furthermore, nebivolol and telmisartan, an angiotensin II receptor blocker, decreased the left ventricular mass to a similar degree. Shahin et al. reported that angiotensin-converting enzyme inhibitors improve endothelial function and are superior antihypertensive agents as compared to CCB & BB .However, in all of the studies cited in their meta-analysis, atenolol had been used as the BB. In contrast to atenolol, carvedilol and nebivolol have shown to improve the endothelial function. While the meta-analysis conducted by Messerli et al. reported the unfavorable effects of BB on the metabolic profiles, this analysis did not include studies in which vasodilatory BB had been used . More recent studies

have reported the relatively less harmful effects of vasodilatory BB on the metabolic profiles and also on weight gain . As described above, new generations of BB, such as the long-acting and/or vasodilatory BB may overcome the relatively weak effect of beta-blockers in preventing cardiovascular events.[3]

Concerns about Recent Meta-Analyses.

A Cochrane Collaboration analysis conducted by Wiysonge et al., which was a representative analysis to evaluate the usefulness of BB in the management of hypertension, suggested that first-line beta-blocker use was not as good as other classes of antihypertensive drugs to decrease the mortality or morbidity . In his review, there is some doubt about the suitability of atenolol as a first-line antihypertensive drug (used in 60 -70% subjects), because of its low lipophilic profile and relatively weak effect on cardiovascular protection .[3] The MAPHY study demonstrated the significantly lower risk for coronary events in patients on metoprolol, a lipophilic BB, as compared to those on diuretics . The usefulness of lipophilic BB for the prevention of cardiovascular events is still under debate . The meta-analysis conducted by Wiysonge et al. (total number of analyzed subjects, 91561) reported the higher risk for cardiovascular events in patients on BB as compared to those on diuretics. However, the number of study subjects prescribed metoprolol included in their metaanalysis was 7663 (8.4%). On the other hand, the metaanalysis conducted by Turnbull et al. (total number of study subjects for the comparison of the outcomes of major cardiovascular events (ACEI or CCB vs BB) was 14583, demonstrated no evidence of any difference in the effect between BB and other classes of antihypertensive agents in preventing major cardiovascular events . This meta-analysis included two studies in which metoprolol alone was used in the BB arm and two other studies in which Bisoprolol was used as one of the BB in the beta-blocker arm. The number of study subjects prescribed metoprolol included in this meta-analysis was 1062 (13.5%). Thus, the meta-analysis conducted by Turnbull et al. might have included a lower number of subjects prescribed atenolol and higher number of study subjects prescribed metoprolol, as compared to the meta-analysis conducted by Wiysonge et al. . Then, recently, Turnbull et al. suggested that lipophilic BB may be preferable to hydrophilic BB for reducing the mortality in patients with coronary artery disease , though lipophilic β-blockers are associated with an increased risk of depressive symptoms . Lindholm et al. reported that the differential effects between nonatenolol BB and other antihypertensive drugs on the risk of major cardiovascular events could not be fully evaluated because of the small number of studies including subjects prescribed nonatenolol BB. Anyhow, atenolol is one of the most widely used BB, and more than 50% of the data in previous metaanalyses were derived from subjects prescribed atenolol. A meta-analysis to examine the effects of lipophilic and/or vasodilatory beta-blockers on the risk of major cardiovascular events is proposed.[4]

4. Vasodilatory Beta Blockers in Treating Hypertension

Vasodilatory beta blockers like carvedilol, nebivolol & labetalol decrease blood pressure largely through reducing systemic vascular resistance, while maintaining cardiac output. The benefits of peripheral vasodilation contribute to reduced cardiac afterload and preload, lack of adverse effects on lipid and glucose metabolism, and possible reversal of adverse arterial remodeling. Arterial remodeling (stiffness) may increase distal wave reflection of blood back to the aorta, which augments the outgoing central systolic pulsewave from the heart, thus increasing central aortic pressure. Reversal of arterial remodeling may thereby lower central aortic pressure. By lowering blood pressure in a more physiologically relevant manner, vasodilatory beta blockers may be a more appropriate therapy for hypertension compared with traditional BB.[5]

5.Use of Beta Blockers in Patients With Hypertension and Other Compelling Indications

The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure recommends BB for the treatment of hypertension, particularly in patients with certain compelling indications, such as high coronary disease risk, diabetes and heart failure, or in patients who have experienced myocardial infarctions. In these particular conditions, the effects of BB on the myocardium itself may provide benefits beyond lowering blood pressure.[1]

Coronary artery disease: Coronary artery disease is characterized in part by reduced myocardial oxygen supply when demand is high. Reduction of blood pressure, heart rate, and myocardial oxygen demand in patients with coronary artery disease reduces ischemia and lowers the risk for cardiovascular events.The American Heart Association recommends a stricter adherence to blood pressure goal for patients diagnosed with coronary artery disease, with conditions considered coronary artery disease risk equivalents (i.e., carotid artery disease, peripheral artery disease, abdominal aortic aneurysm), or at high risk for developing coronary artery disease (10-year Framingham risk score 10%). Treatment of coronary artery disease with BB is recommended by several guidelines because BB not only reduce blood pressure but also decrease myocardial oxygen demand. However, the effects of nonvasodilating BB on hyperemic coronary blood flow are variable, which may or may not increase coronary flow reserve. Reduction of coronary flow reserve via increased coronary blood flow at rest or decreased hyperemic coronary blood flow is an independent, negative factor for mortality in patients with coronary artery disease. Because of amelioration of rest and hyperemic coronary blood flow, vasodilatory BB may be a better option than traditional BB in patients with high coronary artery disease risk. It should be noted, however, that no vasodilating BB currently have an indication for the treatment of chronic stable angina in patients with coronary artery disease.[4]

Post–myocardial infarction: According to American Heart Association guidelines, BB are recommended in hemodynamically stable hypertensive patients after myocardial infarction. The value of BB in patients after myocardial infarction has been established in the Beta Blocker Heart Attack Trial (BHAT; propranolol), the Gothenburg metoprolol trial, the Norwegian timolol trial, and the Carvedilol Post-Infarct Survival Control in LV Dysfunction (CAPRICORN) trial. Among the vasodilatory BB, only carvedilol is indicated for use in patients with post–myocardial infarction left ventricular dysfunction.[5]

Heart failure: Heart failure is a serious natural progression of uncontrolled hypertension. Beta blockers, specifically carvedilol, bisoprolol & metoprolol succinate , improve outcomes in patients with systolic heart failure by inhibiting the negative effects associated with sympathetic nervous system activation. Benefits of BB therapy in this patient population include reducing the risk for death and reducing symptoms, improving clinical status, and improving overall patient well-being. Moreover, recent clinical evidence suggests that the risk for mortality and rehospitalization are significantly lower in patients with heart failure who continue BB therapy after hospital discharge com-

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pared to patients not continuing BB treatment.[5]

Diabetes: Although traditional BB have been effective in patients with diabetes, the adverse metabolic and lipid consequences raised some concerns. The new-onset diabetes risk with traditional BB in clinical trials is variable, depending on dose, treatment duration, and patient age. A recent meta-analysis by Bangalore et al of 12 trials involving 94,492 patients with hypertension reported a 44% increased new-onset diabetes risk with pooled data of the traditional BB, atenolol and propranolol compared with placebo. When compared with thiazide diuretics, atenolol, metoprolol, and propranolol were associated with a 26% lower new-onset diabetes risk . Compared with CCBs and ACE inhibitors or ARBs, BB based therapy (atenolol, metoprolol, and any BB and diuretic together) increased the new-onset diabetes risk by 21% and 23%, respectively. However, several limitations should be considered when evaluating the results of this meta-analysis: marked heterogeneity was present in the comparisons and the diagnostic diabetes criteria were not uniform across the trials, making it difficult to compare incidence rates accurately. In contrast, vasodilatory _ blockers such as carvedilol and nebivolol have shown neutral or beneficial effects on metabolic parameters in patients with diabetes and hypertension .In the Glycemic Effect in Diabetes Mellitus: Carvedilol-Metoprolol Comparison in Hypertensives (GEMINI) trial (carvedilol demonstrated efficacy in reducing blood pressure comparable to the traditional BB metoprolol tartrate , without adversely affecting glycemic control . In a subgroup analysis in another trial, glycosylated hemoglobin was significantly reduced from baseline with nebivolol (n = 1,485; 6.93% vs 6.68% after treatment, p =0.001). There was also a significant decrease from baseline in fasting glucose. These results suggest a lack of adverse effect on glycemic control with nebivolol; however, interpretation is limited by the open label study design that did not include a placebo or active comparator.[1]

6.Beta-blockers versus diuretics. Diuretics have been an integral part of antihypertensive therapy and their effectiveness is still without doubt, but with negative effects on patient's metabolic profile. Both thiazide diuretics and BB increase diabetes risk, but their combined use is frankly diabetogenic. Messerli et al raised the question if BB were useful as first-line antihypertensive therapy in the elderly, and they later reported that BB with diuretics, in fact, resulted in a worse outcome than the use of diuretics alone. Thiazide diuretics reduce the risk of stroke more than BB but are associated with increased insulin-resistance, and the risk of gout.[2]

7 .Beta-blockers versus renin-angiotensin inhibitors.The control rate of SBP and DBP in mild-to-moderately hypertensive middle-aged and elderly patients was significantly higher after a 12-week treatment with lisinopril than with atenolol. Whereas after a 3-year follow-up, both ramipril and metoprolol significantly decreased MAP, and showed no significantly different effects on renal function, albuminuria, and left ventricular mass index in patients with hypertension. In the PROBE trial, both nebivolol and ramipril significantly decreased left ventricular mass and mass index in hypertensive patients with left ventricular hypertrophy. However, the effect of nebivolol was significantly better than ramipril. In combination with lisinopril, nebivolol significantly lowers DBP in stage II diastolic hypertension compared with placebo, nebivolol, or lisinopril alone. Nebivolol was however, equally effective in reducing central systolic and DBP, peripheral PP, and the augmentation index. Perindopril and metoprolol-treatment for 6 months also showed no significantly different effects on aortic elasticity in patients with pre-hypertension. Metoprolol and valsartan also showed comparable effects on endothelial function and carotid artery elasticity, and reducing BP in mildly hypertensive patients. However, metoprolol was more effective in reducing 24-hour MAP without affecting artery stiffness than candesartan after the repair of aorta coarctation in hypertensive patients. Nebivolol is equally effective as valsartan in hypertensive patients with obstructive sleep apnea, but reduces HR significantly more than valsartan, which could be beneficial for certain patients.[4]

8.Beta-blockers versus calcium channel blockers. In the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA), compared with atenolol, the amlodipine treatment of hypertension reduced the relative risk of cardiovascular events (non-fatal MI, fatal CHD) by 17% in patients older than 65 years, and 15% in those younger than 65 years. The events were higher in older patients and thus benefit was more significant in these patients. The amlodipine-treated group also showed lower BP within-individual visit-to-visit, and 24-hour ambulatory blood pressure monitoring (ABPM) variability in SBP which also decreased, whereas variability in the atenolol-treated group increased over time. The lower variability in the amlodipine group was partly credited for the reduced risk of stroke in this group. The same ASCOT trial also showed a significant reduction in total cardiovascular events and procedures in a subgroup of patients with diabetes mellitus, and a significantly lower carotid SBP, a significant independent predictor of left ventricular mass index, in amlodipine-treated group than in atenolol group, despite no significant differences in brachial pressure.[3]

9.*Beta-blocker combinations*. Multidrug treatment is required in many patients with uncontrolled hypertension. However, the order of initiation and addition has been studied by many researchers to show a greater BP-lowering response than when the order was switched, indicating the importance of the order. In various dose combinations, atenolol with amlodipine was significantly more effective in lowering SBP and DBP, and more patients achieved target BP than patients treated with monotherapy with either drug. Atenolol with aliskiren was also more effective in lowering SBP and DBP than aliskiren alone, and patients with high baseline plasma renin activity (PRA) registered a significant drop in PRA in atenolol-treated stage I-II hypertensive patients. The Combination Therapy of Hypertension to Prevent Cardiovascular Event (COPE) Trial evaluated combinations of calcium channel blocker benidipine with an ARB, a BB, or a thiazide diuretic in hypertensive patients to achieve target BP and prevent cardiovascular events. All combinations were similarly effective. Combining atenolol with nitrendipine significantly increases body weight and fasting blood glucose level in overweight and obese hypertensive patients, which needs to be controlled with metformin. A fixed dose combination of metoprolol extended release with amlodipine was as effective, and well tolerated as a combination of losartan and amlodipine in reducing both SBP and DBP. However, combining carvedilol extended release with lisinopril was not superior to monotherapy with the either drug, except in high dose combinations, despite producing additional reduction in 24-hour mean DBP. Adding nebivolol to resistant stage I-II hypertensive patients undergoing antihypertensive therapy significantly improves the response and control rate.

Carvedilol in combination with lisinopril significantly improved endothelial function in hypertensive obese patients compared with a combination of hydrochlorothiazide and

lisinopril, though oxidative stress was not significantly affected by either treatment. In diabetic hypertensive patients receiving a renin-angiotensin blocker, addition of carvedilol results in a significant reduction in triglycerides, total cholesterol, and non-HDL cholesterol levels, whereas addition of metoprolol caused an increase in both triglycerides and non-HDL cholesterol levels, and a decrease in LDL and HDL cholesterol levels. Addition of carvedilol butnot metoprolol to high-risk diabetic African-American patients, who had persistent microalbuminuria despite receiving ACEI treatment, improves endothelial function and reduced microalbuminuria. A study judging the effectiveness of various antihypertensive drug classes showed that the average reduction in SBP achieved over a 24 hour period in descending order was: 10.3 (9.9-10.8) for ARBs; 9.2 (8.6-9.9) for BB ; 8.5 (7.9-9.0) for ACEIs; 8.8 (8.3-9.2) for CCBs; and 8.8 (8.3-9.4) for diuretics. The percentage of patients reporting adverse effects attributable to treatment in descending order was: 9.9 for diuretics; 8.3 for CCBs; 7.5 for BB; 3.9 for ACEIs; and 0 for ARBs. The annual drug cost using standard doses was estimated to be the highest for ARBs, followed by ACEIs, CCBs, BB, and diuretics. A similar conclusion was reached after a meta-analysis of randomized controlled clinical trials by the Blood Pressure Lowering Treatment Trialists' Collaboration, who stated that there is little evidence from these overviews to support the preferential choice of particular drug classes for the prevention of cardiovascular events when choosing combinations for treating hypertension.[5]

CONCLUSION : In conclusion, it is our view that Beta blockers may no longer be the undisputed leader, however they still hold a special place in the treatment of cardiovascular diseases, including hypertension due to their costeffectiveness, and a reasonable adverse effects profile. While there are differences of opinion regarding their preference based on meta-analyses of clinical trials, there is still no unequivocal evidence against their use in all types of clinical situations encompassing hypertension. The reality of modern hypertension treatment is that most patients will require multiple drugs to achieve blood pressure goals. In patients with co-morbidities that necessitate more aggressive goals, combination therapy will likely be essential. For many of these patients, including those with diabetes or high coronary artery disease risk, BB are a beneficial, guideline-recommended treatment option. They are still regarded as utmost useful for patients with IHD & heart failure, but more important is the individualization of therapy. Third generation vasodilating Beta blockers have many advantages over the first and second generation BB, due to their unique properties and better effects on metabolic profile, and should be preferred whenever possible. Nevertheless, more comparative clinical trials involving third generation Beta blockers and other classes of antihypertensive agents would be required to have a better understanding regarding the current role of Beta blockers in the treatment of hypertension. Therefore, when addressing the question of Beta blockers' role in hypertension, the answer lies not in global generalizations but in assessing individual patients and specific Beta blocking agents.

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