



Vascular 2013

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Revisiting β -Blockers for the Treatment of Uncomplicated Hypertension

Montreal - The Canadian Hypertension Education Program (CHEP) continues to be the only program globally that annually reviews, updates and re-examines the hypertension literature to provide Canadian practicing physicians with optimal guidance in managing their patients. CHEP recommendations are predominantly class-based, with five different classes of drugs forming the basis of initial treatment following lifestyle modifications. A possible challenge with class-based recommendations is that not all medications within the class produce the same pharmacodynamic effects. For example, CHEP guidelines suggest that β -blocker use in the uncomplicated patient should be reserved for those less than 60 years of age. However, as reported at this year's meeting, newer β -blockers show differences in efficacy, tolerability and ancillary properties relative to traditional β -blockers and may fulfill an important niche in the treatment paradigm.

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Early outcome trials conducted in patients with hypertension on β -blockers demonstrated positive outcomes in terms of reduction in MI, stroke and cardiovascular events (MRC Study *BMJ* 1985;291:97-104; IPPSH Study *J Hypertension* 1985;3:379-82). Yet over the last number of years, the use of these agents as first-line monotherapy may have been limited, likely due to the less favourable adverse event profile associated with traditional β -blockers. Moreover, both the 2013 Canadian Hypertension Education Program (CHEP) and the European Society of Hypertension (ESH) recommend β -blockers as first-line agents in patients with uncomplicated hypertension. The CHEP algorithm for treating the uncomplicated hypertensive patient suggests a target blood pressure (BP) of <140/90 mmHg, first through lifestyle modifications, and then with initial drug therapy using a thiazide or thiazide-like diuretic, angiotensin-converting-enzyme (ACE) inhibitor, angiotensin receptor blocker, long-acting calcium channel blocker or β -blocker.

Re-Analysis of the β -blocker Trials

In 2005, a large meta-analysis of 13 randomized controlled β -blocker trials by Lindholm et al. (*Lancet* 2005; 366:1545-53) suggested that β -blockers were associated with an increased risk of stroke when compared to other antihypertensives. However, there was no difference in myocardial infarction or mortality risk. In 2006, Khan and McAlister (*CMAJ* 2006; 174:1737-42) re-examined the β -blocker studies and divided the patient groups by age (<60 and \geq 60 years) for their meta-analysis. Versus placebo, β -blockers demonstrated a positive outcome on the composite end point (death, myocardial infarction and stroke) in patients <60 years of age. In patients \geq 60 years, the trend was for benefit vs placebo, but statistical significance was not reached. When compared to other antihypertensives, β -blockers demonstrated similar efficacy improving outcomes in younger patients, but not in older patients, where the collective data pointed to an excess risk of stroke. It is on the basis of these meta-analyses that the CHEP guidelines limit the recommendation of β -blockers as first-line monotherapy in the treatment of uncomplicated hypertension to those <60 years

of age. Interestingly, in the β -blocker review by Lindholm et al. above, atenolol was the β -blocker in 14 of the 18 studies analyzed, encompassing 86% of the β -blocker patient cohort in the meta-analysis. This raises the potential question as to whether the guideline recommendations are weighted towards concern for the use of atenolol in older (\geq 60 years) hypertensives vs β -blockers in general.

β -blocker Pharmacology

It is important to note that both the CHEP and ESH guidelines make their recommendations based on class of drug, not individual drug. β -blockers are a heterogeneous class, with some demonstrating non-selectivity for the β -receptor (nadolol, propranolol), others demonstrating selectivity for the β_1 -receptor (acebutolol, atenolol, bisoprolol, metoprolol, nebivolol), while others have α_1 - and β -adrenergic antagonist activity (carvedilol, labetalol). Even amongst the β_1 -selective blockers as stated, the rank order of selectivity is greatest for nebivolol and least for acebutolol. (Mason et al. *J Cardiovasc Pharmacol* 2009;54:123-8). The mechanism of action of the β -blockers is not completely understood but involves reduction in cardiac output, inhibition of the renin angiotensin system, decrease in plasma volume, decrease in peripheral resistance, decrease in norepinephrine release and CNS effects, among others (Frishman et al. *J Clin Hypertension* 2011; 13:649-53). Accordingly, some of these mechanistic effects may explain some of the untoward effects of traditional β -blockers, including bradycardia, AV block, bronchospasm, depression, fatigue, sexual dysfunction, decreased insulin sensitivity and lipid profile disturbances. Considering the distribution of β_1 - and β_2 -receptors and their subsequent pharmacodynamic actions, β_1 -selective antagonists seem preferable for treating patients with hypertension, and as such, became increasingly more utilized in hypertension trials as they became available.

Advances in β -blockers

Newer β -blockers are much more β_1 -selective than atenolol and may show other advantageous pharmacological properties, such as vasodilation, which may result in hemodynamic benefits

for patients. Nitric Oxide (NO) has long been studied in the regulation of peripheral arteriolar tone which is implicated in a number of cardiovascular and non-cardiovascular diseases (*Front Physiol* 2013 Nov 6;4:321). Nebivolol, which is highly β 1-selective, has also been shown to enhance NO release from human endothelial cells (Mason et al. *Circ* 2005;112:3795-801).

The effects of atenolol on vascular smooth muscle (endothelium) have been studied by Schiffrin and colleagues. They have demonstrated that atenolol exhibits less endothelium-dependent relaxation than losartan and nifedipine GITS (Gastro-Intestinal Therapeutic System) (Schiffrin et al. *Circ* 2000;101:1653-9; *J Hypertension* 1996;14:1247-55). These studies suggest that different β -blockers have different effects on endothelial function and NO release.

Hypertension Treatment in the Younger (<60 years) Hypertensive

It is well known that the prevalence of hypertension increases with age and most hypertension studies are often in older (>55 years) patients.

Focusing on the younger patient and during the Clinical/Outcomes/Population Research track at this year's Canadian Hypertension Congress (CHC), Dr. Bobby Khan from the Atlantic Vascular Research Foundation presented results of an 8 week study of 641 mild to moderate hypertension patients, age range 18-55 years; mean age 45 (Giles et al. *J Clin Hypertens* 2013;15:687-93). In their study the nebivolol treated group had greater reductions in DBP -11.8 mmHg vs -5.5 mmHg, SBP -13.7 mmHg vs -5.5 mmHg than placebo treated patients with an overall response rate of 72.8% vs 47.9% respectively. This β -blocker "has properties that improve nitric oxide bioavailability which may suggest some of its impact on vasodilation ... and provides the benefits we would like to see in improving vascular health," said Dr. Khan. Adverse event rates were similar between the β -blocker and placebo (34.7% and 32.2% respectively).

Considering the meta-analyses of Drs. Khan and McAlister from the previous page, there appears to be a place for the use of β -blockers in the younger uncomplicated hypertensive patient. In addition to BP control and other comorbidities, medication side effects should be taken into account when considering the appropriate patient for β -blocker therapy. With significant heterogeneity within the β -blocker class of drugs, tailoring therapy to particular patients and utilizing newer agents may offer another alternative to other first-line treatments.

Draft 2014 CHEP Recommendations

The 2014 Draft CHEP Recommendations were presented as part of CHC program. This year's update and debate focused on re-examining previous clinical trials and modifying recommendations based on another look at this existing data.

For example, although the use of low dose acetylsalicylic acid in hypertensive patients older than 50 years of age has been recommended to reduce overall risk, a re-review of the HOT study (*Lancet* 1998; 351(9118):1755-62) downgraded the evidence from class A to B. In previous guidelines, target blood pressure in the very elderly (≥ 80 yrs) uncomplicated hypertensive was relatively stringent (<140 mmHg systolic). Based on a re-review of the HYVET trial (*N Engl J Med* 2008; 358:1887-98) which demonstrated a benefit in treating the very elderly with the thiazide-like diuretic indapamide, this recommendation was reworded to make the systolic target (<150 mmHg) align more closely with the trial. "Currently, and as of last year, based on the results of the HYVET trial we made a recommendation to relax the systolic blood pressure target in individuals over the age of 80 years and it was relaxed to a systolic target of less than 150," said Dr. Raj Padwal, Director of the Hypertension Clinic, University of Alberta.

Moreover, both the CHEP and ESH hypertension guidelines suggest that many hypertensive patients will require two or more first line agents to control their blood pressure. One useful combination is a long acting calcium channel blocker and beta blocker. In a study presented at this meeting by Rizk and Mahmoud they showed that nifedipine sustained release 10 mg b.i.d. plus metoprolol 25 mg o.d. had a therapeutic efficacy of 96.7% whereas nifedipine alone was 73.3% efficacious (Abstract ACS 14).

A new recommendation, for patients with established coronary disease and hypertension, was put forward with respect to exerting caution in achieving systolic blood pressure targets so as not to allow diastolic pressure to drop below 60 mmHg due to concerns with exacerbating ischemia.

Summary

Both the CHEP and the ESH guidelines continue to support a role for β -blockers in the treatment of hypertension as first line, in patients younger than 60 years of age, and as dual, triple or quadruple therapy in patients of all ages. However, β -blockers are a heterogeneous class of medications and all members of the class may not provide similar benefits in all hypertensive patients. \square

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