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Viewpoint

β-Adrenergic Receptor Blockers in Hypertension

Sheldon W. Tobe, MD, MScCH (HPTE), FRCPC, FACP, FASH

Aboriginal and Rural Health Research, Northern Ontario School of Medicine, Division of Nephrology, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada

β-Blockers have been used widely since the 1970s in the treatment of hypertension. In recent years, however, the use of β-blockers as an initial therapy in the treatment of hypertension has been challenged. The reasons for this controversy and the rationale for keeping β-blockers as a recommended treatment for hypertension are discussed in the articles in this supplement to the *Canadian Journal of Cardiology (CJC)*.

β-Blockers are efficacious in the management of hypertension,[1] but they are also known for their adverse effects on glucose metabolism and insulin levels. Insulin resistance in hypertension is associated with reduced skeletal muscle blood flow and reduced insulin-mediated glucose utilization.[2] Insulin resistance in obesity is also caused in part by decreased muscle blood flow and reduced glucose utilization.[3] Nonvasodilating β-blockers reduce muscle blood flow and impair insulin sensitivity.[4] Vasodilating β-blockers might counteract insulin resistance by increasing muscle blood flow, thus restoring glucose utilization. Improved insulin sensitivity was demonstrated for carvedilol in a comparison with metoprolol[5] and nebivolol compared with atenolol.[6] These effects might be important from a hemodynamic perspective, as described by Messerli and Grossman when they compared carvedilol with nonvasodilating β-blockers: "By shifting the hemodynamic profile from a pattern of normal cardiac output and high vascular resistance to a pattern of low cardiac output and high vascular resistance, traditional β-blockers make the hypertensive patient hemodynamically older and may accelerate the biological clock."[7] The vasodilating β-blockers might thus offer a potential advantage in the management of hypertension.

The effect on central hemodynamics, as described by Messerli and Grossman[7] for nonvasodilating β-blockers, would be expected to lead to a lack of effect on central blood pressure, particularly in older patients. Lack of improvement in central blood pressure is theorized to be at least in part responsible for the higher risk of stroke found in outcome trials with β-blockers compared with other antihypertensive agents in older patients.[8] As is pointed out in many of the articles included in this supplement of the *CJC*, the role of β-blockers in hypertension has been debated hotly since the publication of a meta-analysis on the subject by Lindholm et al. in 2005.[8] After this publication, β-blockers were relegated to fourth-line therapy by the National Institute for Health and Clinical Excellence on the management of hypertension from the United Kingdom,[9] and maintained only as a possible choice for antihypertensive treatment by the European Society of Hypertension,[10] and the Eighth Joint National Committee for hypertension in the United States.[11] Having chaired the Canadian Hypertension Education Program (CHEP) guidelines process for 5 years until 2012, I personally believed that there was a need to explain why Canadian hypertension guidelines continue to recommend β-blockers for the initial management of hypertension in patients younger than the age of 60 years, and as part of combination therapy in hypertensive patients who require more than 1 agent. The release in Canada of nebivolol, a new vasodilatory β-blocker, provided the stimulus to review the β-blocker class in antihypertensive therapy. For this supplement of the *CJC*, volunteer experts and participants in Canadian clinical practice guidelines groups, such as CHEP, were invited to write targeted review articles to inform clinicians managing hypertension in understanding how to use this class of antihypertensive agent confidently and safely.

Dr Pierre Larochelle, who is the immediate past President of Hypertension Canada, together with his colleagues review 30 years of β-blocker clinical trials for hypertension, starting with the seminal β-blocker studies and concluding with a description of the major meta-analyses of the hypertension literature.[12] Dr Ross Feldman, past Chair of CHEP and the first President of Hypertension Canada, has summarized the physiology and pathophysiology of β-blockers, including data from his own research.[13] Dr Luc Poirier, who is presently Chair of the CHEP, provides a clinical pharmacologist's review of the mechanism and actions of β-blockers and the heterogeneity within the class.[14] In addition to variability in their durations of action, the various β-blockers have different properties. These properties affect how they will be used by clinicians managing patients with different conditions, including ischemic heart disease, heart failure, and hypertension. These properties include water or lipid solubility, the potency and selectivity of blockade of the β_1 receptor, and other β receptors, the ability of the molecule to stimulate β-adrenergic receptors (intrinsic sympathomimetic activity) and vasodilatory activity (a table showing the properties of the commonly used β-blockers is presented in the article by Larochelle et al.[12]).

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Corresponding author: Dr Sheldon W. Tobe, Department of Medicine, University of Toronto, Dialysis Division of Nephrology, Suite A240, Sunnybrook Health Sciences Centre, 2075 Bayview Ave, Toronto, Ontario M4N 3M5, Canada. Tel.: +1-416-480-6901; fax: +1-416-480-6940.
E-mail: sheldon.tobe@sunnybrook.ca
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Dr Jonathan Howlett, known for his role in heart failure guidelines, reviews nebivolol and the literature describing its use in hypertension and in heart disease.[15] The article by Drs Kuyper and Khan[16] updates a previous meta-analysis performed by Khan and McAlister from 2006,[17] which motivated the CHEP position on recommending β-blockers as initial therapy for hypertension therapy in patients younger than 60 years of age, in response to the meta-analysis by Lindholm et al. a year earlier.[8] Their updated meta-analysis was carried out to determine if the efficacy of β-blockers in hypertension could be stratified according to atenolol vs nonatenolol agents in patients younger than the age of 60 and in older patients. The role of β-blockers in atrial fibrillation and heart failure is discussed by Drs Paul Dorian and Paul Angaran, who review the role of β-blockers in atrial fibrillation, in the context of comorbidities, including hypertension.[18] The article by Richards and Tobe describes how β-blockers can be combined with other antihypertensives to achieve synergy.[19] Dr Luc Trudeau clearly summarizes the literature on central blood pressure using data from beta blocker studies to illustrate the principles.[20]

β-Blockers remain part of our armamentarium for the management of hypertension. The vasodilating β-blockers have a theoretical advantage over the nonvasodilating β-blockers. By preserving muscle blood flow, they should improve the surrogate outcomes of insulin resistance and central blood pressure. Unfortunately, clinical outcome studies of vasodilating β-blockers compared with other antihypertensive agents and with the nonvasodilating β-blockers in the management of hypertension are lacking. Because of this lack of evidence, vasodilating β-blockers are not mentioned specifically as a subclass in the CHEP hypertension recommendations. The theoretical advantages of vasodilating β-blockers should motivate the organization of prospective clinical trials to determine whether the use of vasodilating β-blockers is associated with hard outcome differences compared with nonvasodilating β-receptor antagonists.

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