LETTER TO THE EDITOR

Compelling Indications Should be Listed for Individual Beta-Blockers (Due to Diversity), Not for the Whole Class

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1. INTRODUCTION

Beta-blockers (BBs) are an important class of drugs, with numerous indications in cardiology, emergency and general medicine. The indications include heart failure (HF), acute myocardial infarction (AMI), post-MI [1], supraventricular and ventricular arrhythmias, chronic coronary syndrome, systemic arterial hypertension (HTN), hypertrophic cardiomyopathy and aortic aneurysm or dissection. All BBs decrease heart rate (HR) and blood pressure (BP), the major determinants of myocardial oxygen consumption; therefore, myocardial anti-ischemic action is a class effect. On the other hand, it is very important that not all BBs decrease all-cause mortality and sudden death; therefore, their crucial characteristics are not the class effect [2].

2. LITERATURE OVERVIEW

Importantly, not all indications and contraindications are valid for each BB because there is only some degree of uniformity among BBs as a class of drugs [3-5]. Despite their common mechanism of action, BBs show several distinctions regarding specific activities [6]. To start with the basic characteristic of BBs, the effect on HR is stronger for *e.g.* bisoprolol *vs* nebivolol (in the average doses), while the opposite is true for the action on BP.

BBs differ in the degree of preferential affinity for β-adrenergic receptors (β-ARs) that is, in their β1 selectivity (cardioselectivity), the degree of antagonist activity towards β-ARs, pharmacokinetic properties [7] (*e.g.* half-life, lipophilicity, excretion), as well as additional pharmacodynamic properties *e.g.* vasodilating properties [8] (α-receptor blocking property or capability to stimulate nitric oxide production), intrinsic sympathomimetic activity (ISA), membrane stabilizing activities (MSA), inverse agonist [9] and biased agonist activity [10] and evidence-based indication in HF [11].

These specific properties of BBs additionally determine not only their indications [12] but the distinctions in their side effects and contraindications [7]. Administration of an appropriate BB is of importance, according to the main indication (which is supported by evidence and recommended in current guidelines), as well as according to patient's co-morbidities as additional indications [13]. For example, not all BBs have an acute myocardial infarction (AMI) as an evidence-based indication [14]. Moreover, only a few of numerous BBs are recommended for HF with reduced left ventricular ejection fraction (LVEF) [15, 16]. Furthermore, the effect of various BBs on central (aortic) BP is different: vasodilatory BBs (such as carvedilol and nebivolol) decrease it, while the first and the second generation of BBs do not. Therefore, vasodilatory BBs (by decreasing aortic BP) can be expected to better prevent aortic complications (dissection and aneurysm) in patients with Marfan syndrome [17].

Administration of an appropriate BB regarding the specific indication expectedly results in improvement of the patient's condition, which progresses to better adherence, and consequently reduces the chance for BB rebound [13]. Compelling indications for antihypertensives are listed in guidelines [18, 19] and they are very useful to help optimize antihypertensive treatment [19-21].

Having in mind how many differences there are among BBs, it seems logical and practical not to refer to them always as a group, but to individualize the choice for specific indications. The *first* suggestion is to improve the classification of BBs, by incorporating indications for individual BB. For example, for bisoprolol, the numerous indications could include HF, AMI,

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post-MI, chronic coronary syndrome, supraventricular and ventricular arrhythmias, HTN, aortic aneurysm or dissection, hypertrophic cardiomyopathy, *etc*. The *second* suggestion is to improve (some of) the current reports on a specific indication (disease) by listing exactly which BB is indicated. For example, for HF (both with and without preserved LVEF), only 3 BBs (carvedilol, bisoprolol, metoprolol succinate) should be listed according to some guidelines [16] or 4 BBs (the 3 BBs already mentioned plus nebivolol) as recommended by other guidelines [15]. The *third* suggestion is to explain how strong the evidence is for each BB. For example, evidence-based indication (derived from several randomised clinical trials) for a particular BB can be marked as the level of evidence A (LOE-A). Similarly, LOE-C can be used if the indication for another BB as suggested by experts. The additional (*fourth*) suggestion is that in large tables with numerous drugs (such as compelling indications for antihypertensive drugs) when BBs are mentioned, a couple of proper individual examples should be listed in parenthesis. This can help prevent inadequate choices from the BB class (as BBs are very different).

Lists of compelling indications for BBs, or the other way round - list of diseases as indications for a particular BB can help physicians to select the most appropriate BB. Namely, in a paper about tremor, in the part about treatment, instead of (or in addition to) BB, should list "propranolol" (which blocks strongly β2-ARs) and not *e.g*. bisoprolol (because it is a β1-selective BB and therefore not indicated for tremor treatment). Similarly, if the topic is the chronic treatment of ventricular tachycardia in patients with chronic obstructive lung disease, potential mistakes in practice can be avoided if "bisoprolol" is stated instead of BB. Even a better example is the direct comparison between the first BB used (propranolol) and the latest one (nebivolol): propranolol is not β1-selective "cardioselective" and therefore is indicated for tremor, but not in chronic obstructive lung disease, *etc*. while nebivolol is very cardioselective (and has a better metabolic profile as far as glycaemia and cholesterol are concerned) [20]. Moreover, propranolol is not vasodilatory but nebivolol is; propranolol has membrane stabilizing activity, but nebivolol does not [22]; propranolol is not indicated in congestive heart failure while nebivolol is recommended by the European Society of Cardiology (ESC) for heart failure, particularly with preserved ejection fraction (HFpEF) [15]. Indeed, such tables with individual BBs and their compelling indications (with the levels of evidence) are very important and ought to be created by international experts, in the form of position paper/guidelines. Table **1** illustrates the main proposal of the paper and it may serve as a material to initiate this process.

Table 1. Characteristics of some currently used β-blockers.

Name	β1-AR Specificity [23, 24]	ISA Activity / β3 Agonism [25-27]	Lipophilicity [2, 28, 29]	Intensive First-pass Metabolism in the Liver [5]	Vasodilatation [30, 31]	Additional α-AR Blockade [32]	Compelling Indications [27, 33, 34]
Bisoprolol	High	No	Moderate	No	No	No	Supraventricular tachyarrhythmias, Ventricular tachyarrhythmias, HTN, chronic coronary syndrome, heart failure, post-MI
Metoprolol succinate	Moderate- high	No	Moderate	Yes	No	No	HTN, stable angina, post-MI, Supraventricular tachyarrhythmias, Ventricular tachyarrhythmias, Prevention of episodic migraine
Carvedilol	No	No	Moderate/high	Yes	Yes	Yes	HTN, stable angina, heart failure, Post-MI, Supraventricular tachyarrhythmias, Ventricular tachyarrhythmias, Portal hypertensive bleeding (prophylaxis)
Nebivolol	High	β3 agonist	Moderate	Yes	Yes	No	HTN, heart failure
Propranolol	No	No	High	Yes	No	No	Hyperthyroidism, Supraventricular tachyarrhythmias, Ventricular tachyarrhythmias, Essential tremor, Anxiety, Portal hypertensive bleeding (prophylaxis) Prevention of episodic migraine
Atenolol	Moderate/high	No	Low	No	No	No	HTN, chronic coronary syndrome, post-MI, Supraventricular tachyarrhythmias, Ventricular tachyarrhythmias

Abbreviations: Intrinsic sympathomimetic activity (ISA); Adrenergic receptor (AR); Arterial hypertension (HTN); Myocardial infarction (MI).

CONCLUSION

BBs differ within the class in so many ways that it is not only logical but also practical for real-life clinical practice that experts in the field make a list of the compelling indications for individual BBs. The time has come to incorporate our knowledge about BBs into a new approach of presenting these useful and very individual drugs.

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