Canadian Journal of Cardiology 35 (2019) 539–543

Training/Practice
Contemporary Issues in Cardiology Practice

Switching Between β-Blockers: An Empiric Tool for the Cardiovascular Practitioner

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ABSTRACT

β-Blockers are a cornerstone of therapy for cardiovascular disease, but their clinical benefits are not consistent across the class and specific agents are preferred for certain indications. Further, when prescribed, a patient's clinical status might change, requiring the cardiologist to switch to an alternate agent. Examples of such scenarios include the development or a worsening of chronic noncardiac diseases (eg, hyperthyroidism, renal failure), new cardiac-related disease (eg, heart failure, atrial fibrillation), or practical/safety issues (eg, pregnancy, cost, side effects). However, guidelines on how to best switch to a different β-blocker are lacking. Additionally, most hospital-based formularies and guidelines do not provide recommendations around common challenges, like medication intolerance or adjustments for acute illness. We present a practical approach to switching between commonly prescribed β-blockers, which considers drug interchangeability for various indications, rationale for switching, necessary initial adjustments to dose/frequency, and differences in target/maximal doses.

RÉSUMÉ

Les bêtabloquants sont la pierre angulaire du traitement des maladies cardiovasculaires, mais les bienfaits cliniques varient d'un bêtabloquant à l'autre, certains agents étant préférables aux autres pour certaines indications. En outre, il est possible que l'état clinique du patient change une fois un agent prescrit, ce qui pousserait le cardiologue à prescrire un agent de substitution. Parmi les scénarios possibles, notons l'apparition ou l'aggravation d'une maladie chronique non cardiaque (p. ex., hyperthyroïdie, insuffisance rénale) ou d'une nouvelle maladie cardiaque (p. ex., insuffisance cardiaque, fibrillation auriculaire), ou la présence de problèmes pratiques ou liés à l'innocuité (p. ex., grossesse, coûts, effets indésirables). Or, il n'existe pas de lignes directrices sur la meilleure façon de passer d'un bêtabloquant à un autre. De plus, la plupart des listes de médicaments et des lignes directrices des hôpitaux ne fournissent pas de recommandations sur les difficultés fréquentes, comme les intolérances aux médicaments ou les ajustements à faire en cas de maladie aiguë. Nous présentons une démarche pratique de substitution entre des bêtabloquants couramment prescrits qui tient compte de l'interchangeabilité des médicaments pour diverses indications, de la raison de la substitution, des ajustements initiaux nécessaires de la dose et de la fréquence, ainsi que des différences dans les doses cibles ou maximales.

β-Blockers are a routine part of cardiovascular care, but their mechanisms of action, metabolism, off-target effects, and indication vary according to agent. At a basic level, most β-blockers are classified by β-1, β-2, or non-selective β-receptor affinity. However, a mechanistic basis for the lack of a "class effect" is elusive, and β-receptor selectivity alone does not appear to be the unifying explanation. As such, clinicians need to know the most evidence-based β-blocker for common and rare conditions, irrespective of theoretical mechanism, including those extending beyond cardiovascular disease. Herein, we discuss a practical, empiric approach to selecting an initial β-blocker, and switching between agents on the basis of the primary cardiac problem, existing comorbidities, and acuity of presentation.

Cardiac Indications for β-Blockers

The most frequently encountered condition for which robust evidence for β-blocker therapy exists is heart failure with reduced ejection fraction, which includes carvedilol, bisoprolol, and metoprolol succinate. In contrast, bucindolol did not reduce mortality, and metoprolol tartrate was inferior

Received for publication December 21, 2018. Accepted January 24, 2019.

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See page 543 for disclosure information.

https://doi.org/10.1016/j.cjca.2019.01.013

Table 1. Commonly used β-blockers, their dosing and frequency regimen, and indications

β-blocker	Route	Frequency	Starting dose, mg/kg/d	Typical adult starting dose	Maximum dose, mg/kg/d	Typical adult maximal dose	Equivalent daily dose	Specific cardiac indications	Common noncardiac indications	Additional considerations
Acebutolol	PO	OD or BID	1	200-400 mg divided OD or BID	20	600 mg BID	200 mg/d	HTN,* stable CAD	Hyperthyroidism (although other agents preferred)	> 100 mg/d unlikely to offer further antihypertensive benefit; higher doses often needed for angina
Atenolol	PO	OD or BID	0.5	25-50 mg OD	2	200 mg OD	50 mg/d	HTN,* MI, stable CAD	Hyperthyroidism (second-line)	Not recommended in pregnancy > 100 mg/d unlikely to offer further antihypertensive benefit
Bisoprolol	PO	OD	0.04	1.25-2.5 mg OD	0.14	20 mg OD	5 mg/d	HFrEF, arrhythmia, HTN (second-line)*		May use up to 20 mg OD for hypertension; Target dose for HFrEF: 10 mg OD
Carvedilol	PO	BID	0.1	3.125 mg BID	0.7	50 mg BID	25 mg/d	HFrEF, HTN (second-line),* MI with EF < 40%	Esophageal varices (second-line)	Target dose in HFrEF: 50 mg BID
Labetalol	PO	BID (for large doses may divide TID or QID)	3	100 mg BID	10	800 mg TID	200 mg/d	HTN in pregnancy, HTN crisis	Subarachnoid hemorrhage	Safe in pregnancy
Metoprolol	PO/I.V.	Depends on formulation	1	12.5-25 mg BID	6 (up to 400 mg/d)	200 mg BID	100 mg/d 50 mg BID	HTN,* HFrEF, arrhythmia, MI, stable CAD	Migraine (second-line), hyperthyroidism (second-line)	Safe in pregnancy, only succinate formulation indicated in HFrEF
Nadolol	PO	OD	0.6	40 mg OD	3.4	320 mg OD	80 mg/d	HTN,* CAD, arrhythmia, long QT syndrome	Esophageal varices; migraine	
Nebivolol	PO	OD	0.07	5 mg OD	0.6	40 mg OD	10 mg/d	HFrEF, HTN (second-line)		Useful in severe bronchospasm
Propranolol	PO/I.V.	Depends on formulation	1	40 mg BID	5	40 mg QID (arrhythmia) or 80 mg QID (angina)	80 mg/d	Arrhythmia, long QT syndrome, HTN,* obstructive hypertrophic cardiomyopathy, stable CAD, MI	Hyperthyroidism; antipsychotic-induced akathisia (second-line), essential tremor, migraine, performance anxiety, esophageal varices	Superior to metoprolol in arrhythmic storm, used for hyperthyroidism in pregnancy

Sotalol	PO	BID	1	40-80 mg BID	4	160 mg BID	80 mg/d	Arrhythmia, HOCM, ARVC		Useful in AF or VT with EF > 35% Assess baseline QTc and creatinine before initiation; adjust dose for renal impairment
Esmolol	I.V.	Continuous infusion	1 (bolus); 0.05 infusion	500 μg/kg load, then 50 μg/kg/min infusion	0.2	200 μg/kg/min	N/A	Intraoperative arrhythmia or arrhythmia in shock	Hyperthyroidism	Rapid onset and offset are ideal in the critical care setting

Equivalent daily dose is on the basis of an approximate conversion between the commonly prescribed doses for each type of β-blocker. Data are derived from Lexicomp.com, PrescribersLetter.com, BC Children's & Women's Hospital Pharmacy Formulary, Vancouver General Hospital Pharmacy Formulary, and Kaiser Permanente Formulary.

AF, atrial fibrillation; ARVC, arrhythmogenic right ventricular cardiomyopathy; BID, twice daily; CAD, coronary artery disease; EF, ejection fraction; HFrEF, heart failure with reduced ejection fraction; HOCM, hypertrophic obstructive cardiomyopathy; HTN, hypertension; I.V., intravenous; MI, myocardial infarction; N/A, not applicable; OD, once daily; PO, by mouth; QID, 4 times daily; TID, twice daily; VT, ventricular tachycardia.

* Although certain β-blockers are approved as first- or second-line antihypertensive agents, contemporary guidelines do not support the use of β-blockers as a first-line option for primary HTN.

to carvedilol in the **C**arvedilol **o**r **M**etoprolol **E**uropean **T**rial (COMET),[1] although the use of lower doses of metoprolol, and shorter-acting formulation might be confounders, highlighting the issue of interchangeability. In other common cardiac problems, like hypertension, atrial fibrillation, and coronary artery disease, β-blocker efficacy appears to exhibit a class effect. Although guidelines do not stipulate a specific agent, only certain types are preferred, because of historical trends and approved indications. Additionally, in some conditions, like hypertension, a β-blocker as first-line therapy is discouraged for patients older than 60 years, although this generalization might not apply in certain settings.[1] In rarer, but potentially more lethal conditions, the β-blocker subtype is important. For channelopathies,[2] like long QT syndrome, nadolol is the most effective agent, followed by bisoprolol and propranolol, which are supported by less robust evidence. In contrast, metoprolol is likely an inferior agent.[2] Table 1 shows the commonly prescribed β-blockers and their indications.

Noncardiac Comorbidities Requiring β-Blockers

Another common situation is the coexistence of a noncardiac condition necessitating β-blockade. These include hyperthyroidism, migraine, tremor, anxiety, and esophageal varices. In each condition, only certain β-blockers have been studied and/or are approved for use (Table 1), and understanding the disease-specific target is important. For example, in the setting of esophageal varices, the potent β-2 antagonism of nadolol causes splanchnic vasodilation and reduces portal pressure. Further, it is not hepatically cleared, making it ideal for cirrhosis. As evidence advances, the preferred β-blocker might also change. Promising data show that carvedilol, a commonly used nonselective β-blocker in cardiac patients, might improve outcomes in patients with cirrhosis and portal hypertension.[3] These advancements are important for the cardiologist to know, because many patients have comorbidities requiring medications traditionally indicated in cardiac disease. Other off-target factors, like blood-brain barrier permeability, theoretically also play a role in β-blocker interchangeability.[1] In neurocognitive diseases, such as depression or dementia, choosing a nonlipophilic agent that cannot cross into the brain is advisable to minimize possible neuropsychiatric side effects (Table 2). Pregnancy represents a unique challenge because of the predisposition to hypotension and increased volume of distribution, necessitating regular dosage increases throughout gestation, especially for hydrophilic agents. Labetalol and metoprolol are safe in pregnancy, although in the absence of hypertension, labetalol might be poorly tolerated. Of note, atenolol is not recommended because it readily crosses the placenta. Metoprolol is reasonable for all other indications, except channelopathy.[2] In this setting, propranolol, a closer equivalent to nadolol, is well described in long QT syndrome,[2] and has safety data[4] from its use in hyperthyroidism during pregnancy.

Interchangeability of Dose, Frequency, and Route

Although switching β-blockers in the outpatient setting is relatively simple, it might represent a period of increased vulnerability, because inadvertent under- or over-dosing could

Table 2. Properties of commonly prescribed β-blockers according to subtype

β-Blocker	Target(s)	Primary clearance by organ system	Lipophilicity	Sympathomimetic activity	Cost
Acebutolol	β-1	Mainly renal	Moderate	Yes*	$
Atenolol	β-1	Renal	Low	No	$
Bisoprolol	β-1	Renal and hepatic	Moderate	No	$
Carvedilol	β-1, β-2, and α-1, nitric oxide-producing	Hepatic	Moderate	No	$$
Labetalol	β-1, β-2, and α-1	Mainly hepatic	Low	No	$$
Metoprolol	β-1, some β-2 at high dose	Mainly hepatic	High	No	$
Nadolol	β-1 and β-2	Renal	Low	No	$$
Nebivolol	Highly β-1 selective, nitric oxide-producing	High interpatient variability; dose adjust for hepatic and renal impairment	Moderate	No	$$$
Propranolol	β-1 and β-2	Hepatic, renal impairment might increase systemic exposure to propranolol	High	No	$
Sotalol	β-1 and β-2, K^+ channel	Renal	Low	No	$
Esmolol	β-1	Hydrolysis of esterase in red blood cells	Low	No	$$$$

Data are derived from Lexicomp.com, and https://pubchem.ncbi.nlm.nih.gov.

*Sympathomimetic agonism could theoretically be proarrhythmic and/or worsen heart failure with reduced ejection fraction.

lead to destabilization. A framework to minimize these challenges is presented in Table 1, which was extrapolated using data from various hospital formularies, pharmacokinetic properties, and our own clinical experience. Of the many theoretical properties of β-blockers (Table 2), only a few have practical relevance. Carvedilol has α-1 blockade effects that lead to vasodilation and additional blood pressure-lowering. Acebutolol has intrinsic sympathomimetic activity, which might worsen heart failure with reduced ejection fraction, as seen with bucindolol. Nebivolol, the most β-1-selective agent, is useful in the setting of intolerable bronchospasm, although it is costly and has fewer indications. Although opting for a more β-1-selective agent might decrease β-2-related side effects, when the ratio of β-1 to β-2 occupancy of an agent exceeds 100, there is probably little to be gained from a tolerability perspective, by selecting an agent with a higher ratio. Long-acting formulations are preferred because they improve adherence and minimize fluctuations in β-blockade. Bisoprolol's high β-1 selectivity, broad range of indications, long duration of action, moderate lipophilicity, and a stable volume of distribution, makes it one of the best options in our experience.

Switching agents in the setting of acute illness might be more difficult. Initially, patients might require a dose reduction or temporary discontinuation depending on their presentation. If a β-blocker switch is needed and the previous β-blocker was withheld for $>$ 48 hours, we recommend starting the new agent at a low dose. However, it is inadvisable to completely withhold a chronic β-blocker unless the circumstances are extreme (eg, shock requiring vasopressors) because of chronic β-adrenergic receptor upregulation causing rebound tachycardia and hypertension. If the β-blocker was not withheld, switching to an equivalent dose can be facilitated by regular monitoring of vital signs, allowing for rapid and safe titration. In some settings, an acute presentation might necessitate urgent switches between β-blockers. For example, incessant ventricular tachycardia responds better to propranolol in the first 48 hours compared with metoprolol on the basis of randomized data.[5] Similarly, in cases of refractory arrhythmia and shock, esmolol is preferred because of its intravenous formulation and short half-life.

Factors related to drug metabolism and clearance might also influence the need to switch agents. Atenolol, nadolol, and sotalol are predominantly renally cleared, and should be adjusted on the basis of creatinine clearance (Table 2). If another less renally cleared β-blocker is equally beneficial, switching agents early in the course of renal disease is recommended, because of the higher risk of acute kidney injury in this population, leading to rapid accumulation. Three β-blockers are largely hepatically cleared: carvedilol, metoprolol, and propranolol. Carvedilol is contraindicated in patients with severe liver disease, whereas metoprolol and propranolol can be used cautiously. Bisoprolol is the only commonly used β-blocker with dual hepatic and renal clearance, making it a practical choice for those with a predisposition to kidney and/or liver disease.

Limitations

Although β-blockers have been extensively studied over the past half-century, many notable limitations exist in this area. The randomized trials often used nonequivalent comparator arms (as seen in COMET[1]), which might create false dichotomies between β-blocker agents. There are also often disparities between a proposed pharmacologic mechanism *in vitro* and the observed effect in humans. Poorly understood mechanisms might account for some of these differences, like variable blockade of presynaptic adrenoreceptors. This article provides an empiric synthesis of data deemed to be most useful at the bedside for clinical decision-making, and does not represent a comprehensive literature review, or discussion of molecular mechanisms and pharmacologic properties of the various β-blocker agents. Although this article focuses on the issue of β-blocker switching, many concepts also directly apply to the choice of initial β-blocker, such as cardiac and noncardiac disease-specific indications.

Conclusions

β-Blockers are a cornerstone of cardiovascular therapy. Despite this, switching agents is often necessary and challenging, because of the variety of indications for the various

β-blockers. Where robust evidence does not exist, switching should be on the basis of practical considerations and proposed equivalent doses, as outlined in Tables 1 and 2. Clinicians should be aware of the pharmacologic properties of the common β-blockers, their β-receptor affinities, and cardiac and noncardiac indications, so as to provide the patient with the most practical and evidence-based choice of agent. At our institutions, empiric guidelines, like the one proposed in this article, are available within the hospital formulary. These practical tools are most useful when they are easily accessible to the busy clinician, and we suggest that embedding them within the electronic health record or in the clinical setting for point of care use are key to their success.

Funding Sources

Dr Krahn is supported by the Heart and Stroke Foundation (G-14-0005732), Canadian Institute of Health Research (343256), and serves as the Sauder Family and Heart and Stroke Foundation Chair in Cardiology, and the Paul Brunes Chair in Heart Rhythm Disorders.

Disclosures

The authors have no conflicts of interest to disclose.

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