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THE PRESENT AND FUTURE

REVIEW TOPIC OF THE WEEK

Achieving a Maximally Tolerated β-Blocker Dose in Heart Failure Patients

Is There Room for Improvement?

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ABSTRACT

Heart failure (HF) is associated with significant morbidity and mortality. Although initially thought to be harmful in HF, beta-adrenergic blockers (β-blockers) have consistently been shown to reduce mortality and HF hospitalization in chronic HF with reduced ejection fraction. Proposed mechanisms include neurohormonal blockade and heart rate reduction. A new therapeutic agent now exists to target further heart rate lowering in patients who have been stable on a "maximally tolerated β-blocker dose," but this definition and how to achieve it are incompletely understood. In this review, the authors summarize published reports on the mechanisms by which β-blockers improve clinical outcomes. The authors describe differences in doses achieved in landmark clinical trials and those observed in routine clinical practice. They further discuss reasons for intolerance and the evidence behind using β-blocker dose and heart rate as therapeutic targets. Finally, the authors offer recommendations for clinicians actively initiating and up-titrating β-blockers that may aid in achieving maximally tolerated doses. (J Am Coll Cardiol 2017;69:2542–50) © 2017 by the American College of Cardiology Foundation.

Beta-adrenergic blockade has been a mainstay of therapy in chronic heart failure (HF) with reduced ejection fraction (EF) for more than 2 decades. Despite once being thought too dangerous for use in HF due to negative inotropic effects, β-blocker therapy has consistently been shown to reduce mortality and HF-related hospitalizations (1–6). β-blocker therapy is strongly supported across major consensus recommendation statements in patients with reduced EF (7–10). Recent guidelines recommend consideration of adding a new heart rate–lowering agent, ivabradine, in patients with stable chronic HF with EF ≤35% and sinus rhythm with resting heart rate ≥70 beats/min on guideline-directed medical therapy, "including a beta-blocker at maximally tolerated dose" (11). These guidelines recommend initiation and up-titration of β-blockers to "target doses, as tolerated" before consideration of ivabradine. Unlike β-blockers, ivabradine has not been shown to confer a reduction in all-cause mortality, but does reduce HF hospitalization and HF-related deaths as compared with placebo (12). In an era with a new therapeutic option for heart rate reduction, the question of how to achieve a

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maximally tolerated β-blocker dose is exceedingly relevant for clinicians considering active titration of β-blockers and/or initiation of ivabradine. Despite decades of experience with the use of β-blockers and randomized clinical trials (RCTs) enrolling more than 10,000 patients, optimally defining and achieving a maximally tolerated β-blocker dose remains a clinical challenge.

In this review, we aim to: 1) provide background on proposed β-blocker mechanisms of benefit; 2) describe the current β-blocker doses achieved in practice and compare them with those achieved in landmark β-blocker trials; 3) summarize the evidence supporting β-blocker dose versus heart rate reduction as therapeutic targets; and 4) offer an algorithm for clinicians regarding up-titration of β-blocker therapy.

OVERVIEW OF DATA SOURCES

To identify relevant articles, we searched MEDLINE (via PubMed) for articles from January 1996 to September 2014. We used Medical Subject Headings (MeSH) and key words, focusing on the most relevant terms. The following search terms were used: (beta blockers[tiab] OR "adrenergic beta-antagonists" [pharmacological action] AND "adrenergic beta-antagonists"[Mesh]) AND ("HF"[Mesh] OR "HF"[tiab] OR congestive HF) AND (dose OR dosing OR heart rate OR "dose-response relationship, drug"[Mesh]). We manually searched for pertinent reviews and studies to find additional relevant citations missed in our original search. We imported all citations into an EndNote X7 (Clarivate Analytics, Philadelphia, Pennsylvania) database.

MECHANISMS OF ACTION AND PATHOPHYSIOLOGY OF HF

HF with reduced EF is a progressive, heterogeneous disorder with a complex pathophysiology. Existing evidence on the pathophysiology of HF has been reviewed previously (13). In brief, the HF phenotype may, in part, involve interaction between myocardial injury and left ventricular dysfunction, and compensatory hemodynamic and neurohormonal mechanisms aimed at maintaining cardiac output (13–15). Compensatory mechanisms include activation of the sympathetic nervous system (SNS), renin-angiotensin-aldosterone system (RAAS), and vasodilatory molecules (e.g., natriuretic peptides, prostaglandins, nitric oxide) (14,15). Chronic activation of adrenergic signaling can lead to adverse biological effects, accelerated cardiovascular pathology, and disease progression (14,16). Sympathetic activation may be central to the progression of HF. Current guideline-directed medical therapy targets these compensatory pathways and aims to interfere with the neuroendocrine consequences that develop from their chronic activation (11). Interference with these pathways is postulated as one mechanism of the observed benefits of β-blockers (16).

In general, the pharmacological action of β-blockers is to attenuate SNS activity. Possible mechanisms by which β-blockers improve outcomes include antiarrhythmic effects, slowing detrimental remodeling, decreased myocyte death from catecholamine-induced necrosis, and/or prevention of other detrimental effects of chronic SNS activation, such as increased heart rate (16,17). If general SNS blockade is the key mechanism by which β-blockers provide clinical benefit in HF, it would be expected that a class effect would emerge. However, although selected β-blockers have established a clear mortality benefit in HF with reduced EF (1–6), others demonstrated equivocal results (18,19). Principle characteristics of major β-blocker clinical trials are listed in **Table 1**.

Notable differences in β-blockers clinically used in HF include differences in beta-1 receptor selectivity and/or affinity, presence of alpha-1 receptor antagonism, antioxidant properties, and vasodilating effects (**Table 2**). Genetic variants associated with variability in β-blocker response include polymorphisms in beta-adrenergic receptors, alpha-adrenergic receptors, cytochrome P450 2C6, and norepinephrine transporter (NET) (20,21).

Individual variations in β-blocker pharmacology combined with genetic variance may assist in understanding the variable effectiveness of different β-blockers, and may ultimately enhance our understanding of both dose-related clinical benefit and adverse effects.

WHAT IS A MAXIMALLY TOLERATED DOSE?

Across major β-blocker trials in chronic HF with reduced EF, doses achieved in trial participants generally approached target doses. In the CIBIS (Cardiac Insufficiency Bisoprolol Study) II, bisoprolol dosing was progressively increased from a 1.25-mg starting dose to a 10.00-mg daily target dose (1). Target dose was achieved in 42% of patients, with >50% of patients receiving at least 75% of the target dose during the maintenance phase. In the USCS (U.S. Carvedilol HF Study), study participants were initiated on carvedilol 6.25 mg or 12.5 mg twice daily (2).

ABBREVIATIONS AND ACRONYMS

ARNI = angiotensin receptor-neprilysin inhibitor

COPD = chronic obstructive pulmonary disease

EF = ejection fraction

HF = heart failure

RCT = randomized clinical trial

SNS = sympathetic nervous system