One Size Fits Some

One Size Fits All

The advent of angiotensin-converting enzyme inhibitors and β-blockers impacted heart failure therapeutics1,2 in a truly revolutionary way. They are recommended across all New York Heart Association classes for the management of patients with heart failure with reduced ejection fraction (EF).3 Although β-blockers have not been critically examined in patients with class I symptoms, we accept the notion that for these 2 classes of drugs, one size truly does fit all. We argue about dose, not whether we should use the drugs.4,5 We can also debate the duration of treatment in patients who have normalized their EF and the likelihood of recurrence of heart failure if those medications are stopped. Fundamentally, the importance of blockade of the renin–angiotensin system and adrenergic stimulation are fully accepted concepts that apply in young and old, symptomatic and asymptomatic, borderline low and very low EF, left ventricular failure and biventricular failure, in the presence of comorbidities and in otherwise healthy patients.

One Size Fits Some

For all other drug classes, guideline recommendations are driven almost entirely by the inclusion and exclusion criteria used in randomized, placebo-controlled clinical trials. Of course, there is a counter argument, partly based on our concept of number needed to treat. The vast majority of patients who have implantable defibrillators implanted for primary prevention does not gain any survival advantage, suggesting that EF as a discriminatory variable is not sufficient. The problem of course is that a myriad of risk stratification studies have failed to convince clinicians and guideline committees that additional screening helps: we remain unconvinced that modalities like T-wave alternans, signal-averaged ECG, or echocardiographically defined dyssynchrony improve our ability to discern risk. Similarly, the nonresponse rate to biventricular pacing is clinically recognized and much debated, although perhaps less so when we are more stringent in evaluating the ECG (left bundle branch block with QRS >150 ms). Still, not all fine-tuning of indications works; for example, the PROSPECT study failed when we are more stringent in evaluating the ECG (left bundle branch block with QRS >150 ms). Still, not all fine-tuning of indications works; for example, the PROSPECT study failed to identify echocardiographic measures of dyssynchrony to inform patient selection.6 This dilemma raises an issue about how we can best improve on the identification of potential responders to specific therapies and how aggressively we should seek to modify best practice to better direct therapies to patients most likely to benefit.

We have recently considered at least one approach that adds a potential layer of refinement to a new guideline and to the concept that one size fits some. Specifically, we argue...
that in the case of ivabradine, a single heart rate (HR) determination may be too crude and potentially inadequate for the selection of patients.

The Case of Ivabradine
Elevated resting HR has been established as a risk factor in chronic heart failure.\(^1\) The SHIFT trial investigated the therapeutic benefit of HR lowering with ivabradine in combination with maximally tolerated β-blocker therapy on cardiovascular outcomes.\(^9\) Patient enrollment required a basal HR ≥70 beats per minute confirmed with a 12-lead ECG after at least 5-minute rest on 2 consecutive visits. At each follow-up, HR assessment was performed in the same manner. Although this approach is reasonable in clinical trial screening and now forms the basis of its indication and Guideline position,\(^10\) this type of assessment may not be a reliable measure of overall HR control because of the transient nature of the measurements. Thus, we propose that using rate histograms derived from implantable defibrillators and cardiac resynchronization devices for HR assessment before and after ivabradine has been prescribed and used by the patient.

The percentages of patients in the SHIFT trial with a cardiac resynchronization therapy and implantable cardioverter-defibrillator were 1% and 3%, respectively, whereas the frequency of cardiac rhythm device use in the United States is significantly higher.\(^11\) Given the current status of device software, we posited that evaluation of HR trends would be feasible, allow for greater discrimination in candidate selection, and provide a more sophisticated gauge of response. Specifically, we have used plots of HR trends and rate histograms from device interrogations to assess HR before and after treatment.

Figures 1 and 2 show the averaged ventricular rate trend line and histograms of 2 typical patients, each with implantable cardioverter-defibrillators from the same manufacturer; medication compliance was confirmed by queries to the patients’ pharmacies. There is a notable decline in baseline HR at a date corresponding to the start of therapy (Figure 1). The baseline histograms demonstrate a predominant baseline HR of >70 beats per minute; with ivabradine, the ventricular rate in each case shifts leftward (Figure 2). Although the start dates for drug initiation are not precisely contemporaneous with the initial date of the second histogram detection period in each set, they are separated in both cases by <1 week.

This analysis is limited to qualitative assessment because, according to the device manufacturer, the current status of interrogation software does not permit download of the precise average heart rate and confidence intervals for each histogram bar during patient assessment in the clinic setting. Nevertheless, we propose that a qualitative assessment of HR trends adds potential value to the identification of responders beyond what a simple clinic measurement of HR can provide. This refinement may identify some patients who are more tachycardic than appreciated based on a single office-based HR measurement and are therefore candidates for ivabradine.

At the same time, it may be less imperative to treat patients who have 1 or 2 readings of tachycardia (HR >70 beats per minute) but demonstrate a left shifted histogram. The next logical question: can the HR histogram be used as a qualitative (or with better analytics a quantitative) tool to maximize outcomes? Although an additional clinical trial or observational data may be required to assess whether this augmented selection algorithm identifies patients most likely to benefit from ivabradine, it is logical to assume that the histogram, as a variant of an area under the curve for HR, will be more discriminating than isolated HR measurements.

One Size Fits a Few
The population of patients undergoing placement of a left ventricular assist device or heart transplant serves as the most extreme example wherein an intervention is limited to patients within a narrowly defined range of illness. Although differences in threshold for left ventricular assist device implant and transplant listing may exist by center, and arguments persist about intervening too early or too late, the consistent message is that for these approaches to work, the patient must fall within a very narrow phenotypic bandwidth. The reason for this is in part because of the invasive nature of the procedures and the cost, as well as the need for focused commitment of both patient and provider team to maximize benefit while minimizing potential harm.

Concluding Thoughts
Because heart failure therapeutics have matured, the concept that one size fits all may be increasingly viewed through the lens of historical perspective.\(^1\)\(^2\) For the nonexpert in the field, we have gained enormous traction with the argument that angiotensin-converting enzyme inhibitors/angiotensin receptor blockers and β-blockers are for all patients (who can tolerate them). Setting aside the ongoing debate with angiotensin receptor/neprilysin inhibition,\(^12\)\(^13\) once we consider the use
of other interventions, we are increasingly fitting a therapy to patient phenotype, rather than genotype. For now and perhaps for the foreseeable future, that is an appropriate and acceptable response to the precision medicine mandate. The issue is whether we can further improve on the one size fits some meme, with more sophisticated means of capturing the patient phenotype that could plausibly benefit and thereby refine our treatment paradigms and improve care. This is not a call for additional subgroup analyses; they have limitations.14 Rather, as in the case with ivabradine, we should try to deliver as much precision as we can to our list of indications (and contraindications), thereby maximizing benefit without exposing patients to undue costs and potential harm.

Disclosures

Dr Hauptman is an advisor to Amgen, Relypsa, BioControl Medical, St. Jude Medical, and Sensible Medical; a participant on Speaker Bureaus with Amgen, Otsuka, and Relypsa; and an investigator with Alnylam Pharmaceuticals and the NHLBI. The other authors report no conflicts.

References


KEY WORDS: algorithms • angiotensin-converting enzyme inhibitors • genotype • heart rate • ivabradie • precision medicine
Variations on a Precision Medicine Theme: One Size Fits Some
Paul J. Hauptman, Timothy A. Gong and Andrija Vidic

Circ Heart Fail. 2016;9:
doi: 10.1161/CIRCHEARTFAILURE.116.003021
Circulation: Heart Failure is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2016 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-3289. Online ISSN: 1941-3297

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://circheartfailure.ahajournals.org/content/9/8/e003021

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published
in Circulation: Heart Failure can be obtained via RightsLink, a service of the Copyright Clearance Center, not
the Editorial Office. Once the online version of the published article for which permission is being requested is
located, click Request Permissions in the middle column of the Web page under Services. Further information
about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation: Heart Failure is online at:
http://circheartfailure.ahajournals.org//subscriptions/