Variations on a Precision Medicine Theme
One Size Fits Some

Paul J. Hauptman, MD; Timothy A. Gong, MD; Andrija Vidic, DO

Precision medicine, or personalized medicine, refers to the tailoring of therapy to the individual characteristics of patients. It can be applicable to patients with advanced disease and to preventative interventions as well. The impetus for this approach came from sequencing of the human genome and the anticipation that an individual's sequence would inform treatment, aided perhaps by Big Data algorithms. In heart failure, advances in omics have occurred alongside other disciplines but from a practical standpoint, our ability to provide precision medicine remains more or less in the neutral position. In this article, we maintain that despite significant limitations on our ability to use genotyping or Big Data to impact real-world heart failure care in real time, we are in fact practicing a significant degree of precision medicine and can continue to do more of the same with relatively modest changes in approach to practice.

One Size Fits All

The advent of angiotensin-converting enzyme inhibitors and β-blockers impacted heart failure therapeutics[1,2] 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. Mineralocorticoid receptor antagonists are indicated for New York Heart Association classes II, III, and IV but with specific caveats related to renal function and comorbidities. For example, in the post–myocardial infarction setting, mineralocorticoid receptor antagonists are indicated if the event is accompanied by heart failure or the patient has diabetes mellitus. A patient with a creatinine clearance <30 mL/min would not meet criteria nor would a patient with asymptomatic left ventricular dysfunction. The combination of hydralazine and nitrates is indicated for patients with symptomatic heart failure who self-identified as black. Digoxin is indicated for patients who remain symptomatic despite maximal medical therapy. Selection of device therapy is driven mostly by EF and for biventricular pacing by the QRS duration. We have accepted this approach: easy to understand and, to a great degree, true to the original trials that led to approval.

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 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

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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.[7,8] 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

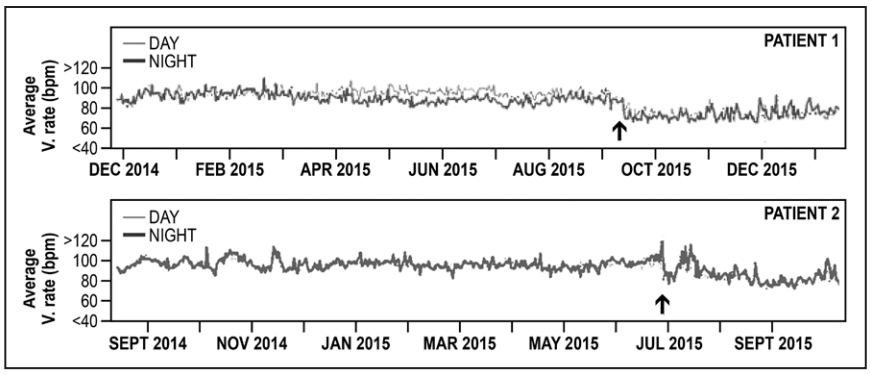

Figure 1. Averaged ventricular rates of 2 patients before and after initiation of ivabradine. Arrow indicates date of initiation of ivabradine.

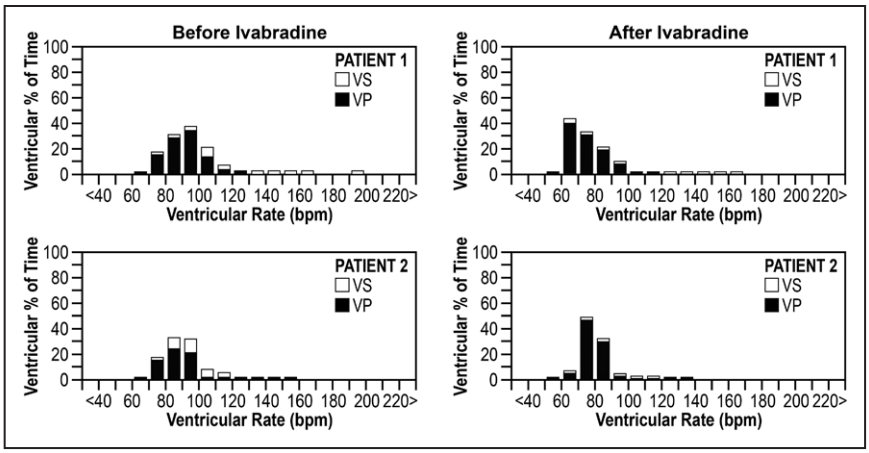

Figure 2. Rate histograms on dates before and after the initiation of therapy. Ivabradine initiated within 1 wk of the start date of the time frame for the second histogram. VP indicates ventricular pacing; and VS, ventricular sensing.

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

1. Swedberg K. From CONSENSUS to SAVE: the early development of inhibition of the renin-angiotensin system in the treatment of chronic heart failure. *J Card Fail*. 2016;22:395–398. doi: 10.1016/j.cardfail.2015.11.007.
2. Goldstein S. The evolution of heart failure therapy in the past sixty years: one man's journey. *J Card Fail*. 2015;21:773–778. doi: 10.1016/j.cardfail.2015.06.005.
3. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, Johnson MR, Kasper EK, Levy WC, Masoudi FA, McBride PE, McMurray JJ, Mitchell JE, Peterson PN, Riegel B, Sam F, Stevenson LW, Tang WH, Tsai EJ, Wilkoff BL; American College of Cardiology Foundation; American Heart Association Task Force on Practice Guidelines. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2013;62:e147–e239. doi: 10.1016/j.jacc.2013.05.019.
4. Packer M, Poole-Wilson PA, Armstrong PW, Cleland JG, Horowitz JD, Massie BM, Rydén L, Thygesen K, Uretsky BF. Comparative effects of low and high doses of the angiotensin-converting enzyme inhibitor, lisinopril, on morbidity and mortality in chronic heart failure. ATLAS Study Group. *Circulation*. 1999;100:2312–2318.
5. Wikstrand J, Hjalmarson A, Waagstein F, Fagerberg B, Goldstein S, Kjekshus J, Wedel H; MERIT-HF Study Group. Dose of metoprolol CR/XL and clinical outcomes in patients with heart failure: analysis of the experience in metoprolol CR/XL randomized intervention trial in chronic heart failure (MERIT-HF). *J Am Coll Cardiol*. 2002;40:491–498.
6. Chung ES, Leon AR, Tavazzi L, Sun JP, Nihoyannopoulos P, Merlino J, Abraham WT, Ghio S, Leclercq C, Bax JJ, Yu CM, Gorcsan J 3rd, St John Sutton M, De Sutter J, Murillo J. Results of the Predictors of Response to CRT (PROSPECT) trial. *Circulation*. 2008;117:2608–2616. doi: 10.1161/CIRCULATIONAHA.107.743120.
7. Lechat P, Hulot JS, Escolano S, Mallet A, Leizorovicz A, Werhlen-Grandjean M, Pochmalicki G, Dargie H. Heart rate and cardiac rhythm relationships with bisoprolol benefit in chronic heart failure in CIBIS II trial. *Circulation*. 2001;103:1428–1433.
8. Böhm M, Swedberg K, Komajda M, Borer JS, Ford I, Dubost-Brama A, Lerebours G, Tavazzi L; SHIFT Investigators. Heart rate as a risk factor in chronic heart failure (SHIFT): the association between heart rate and outcomes in a randomised placebo-controlled trial. *Lancet*. 2010;376:886–894. doi: 10.1016/S0140-6736(10)61259-7.
9. Swedberg K, Komajda M, Böhm M, Borer JS, Ford I, Dubost-Brama A, Lerebours G, Tavazzi L; SHIFT Investigators. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. *Lancet*. 2010;376:875–885. doi: 10.1016/S0140-6736(10)61198-1.
10. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Colvin MM, Drazner MH, Filippatos G, Fonarow GC, Givertz MM, Hollenberg SM, Lindenfeld J, Masoudi FA, McBride PE, Peterson PN, Stevenson LW, Westlake C. 2016 ACC/AHA/HFSA focused update on new pharmacological therapy for heart failure: an update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America [published online ahead of print May 20, 2016]. *J Card Fail*. 2016. doi:http://dx.doi.org/10.1016/j.cardfail.2016.07.001.
11. Blair JE, Zannad F, Konstam MA, Cook T, Traver B, Burnett JC Jr, Grinfeld L, Krasa H, Maggioni AP, Orlandi C, Swedberg K, Udelson JE, Zimmer C, Gheorghiade M; EVEREST Investigators. Continental differences in clinical characteristics, management, and outcomes in patients hospitalized with worsening heart failure results from the EVEREST (Efficacy of Vasopressin Antagonism in Heart Failure: Outcome Study with Tolvaptan) program. *J Am Coll Cardiol*. 2008;52:1640–1648. doi: 10.1016/j.jacc.2008.07.056.
12. Packer M. Love of angiotensin-converting enzyme inhibitors in the time of cholera. *JACC Heart Fail*. 2016;4:403-408.
13. Feldman A. Neprilysin inhibition in the time of precision medicine. *JACC Heart Fail*. 2016;4:400-414.
14. Vidic A, Chibnall JT, Goparaju N, Hauptman PJ. Subgroup analyses of randomized clinical trials in heart failure: facts and numbers [published online ahead of print June 22, 2016]. *ESC Heart Fail*. doi: 10.1002/ehf2.12093.

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