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BLOOD PRESSURE MONITORING AND MANAGEMENT (JOHN COCKCROFT, SECTION EDITOR)

Personalized Medicine and the Treatment of Hypertension

Sarah Melville[1,2] · James Brian Byrd[3]

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Abstract

Purpose of Review The purpose of this review is to discuss the implications of personalized medicine for the treatment of hypertension, including resistant hypertension.

Recent Findings We suggest a framework for the personalized treatment of hypertension based on the concept of a trade-off between simplicity and personalization. This framework is based on treatment strategies classified as low, medium, or high information burden personalization approaches. The extent to which a higher information burden is justified depends on the clinical scenario, particularly the ease with which the blood pressure can be controlled.

Summary A one-size-fits-many treatment strategy for hypertension is efficacious for most people; however, a more personalized approach could be useful in patients with subtypes of hypertension that do not respond as expected to treatment. Clinicians seeing patients with unusual hypertension phenotypes should be familiar with emerging trends in personalized treatment of hypertension.

Keywords Personalized medicine · Population health · Blood pressure · Hypertension · Resistant hypertension · Primary aldosteronism

Introduction

After centuries of identifying characteristics of patients that foreshadow prognosis and help inform treatment, this strategy has been named: precision, individualized, or personalized medicine. This approach to medicine emphasizes that patients with the same disease are nonetheless different from one another and thus respond differently to the same treatment. In a challenge to this seemingly obvious view, John Snow and others working in the field of epidemiology have demonstrated that highly effective interventions can be undertaken without knowing individual patients' traits. Providing clean water solves cholera epidemics, irrespective of the personal characteristics of the patients who had been infected by cholera. This population-based approach to medicine emphasizes that some of the most potent interventions are broadly effective, requiring little or even no information about individuals. The success of public health interventions that do not involve personalized medicine alongside the increasing availability of technologies that could help personalize care raises the question to what extent will personalizing the treatment of hypertension impact the health of patients. The purpose of this paper is to discuss current and emerging options for the personalization of hypertension and whether there is sufficient data to understand their role vis-a-vis less personalized one-size-fits-many approaches.

Elevated blood pressure continues to be the leading risk factor for death and disability [1] and is predicted to still be the leading risk factor in 2040 [2]. Even per the higher blood pressure threshold for diagnosis used in the USA until 2017, hypertension affects about a billion people globally [3, 4]. The new, lower BP threshold for diagnosis in the 2017 ACC/AHA guidelines [5] further increases the

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✉ James Brian Byrd
jbbyrd@med.umich.edu

[1] CardioVascular Research New Brunswick, Saint John Regional Hospital, HHN, Saint John, Canada

[2] IMPART Investigator Team Canada, Saint John, New Brunswick, Canada

[3] Department of Internal Medicine, Division of Cardiovascular Medicine, University of Michigan Medical School, 5570C MSRB II, 1150 West Medical Center Drive, SPC 5678, Ann Arbor, MI 48109-5678, USA

prevalence of hypertension [6]. In the USA, blood pressure is at goal in only 53% of treated hypertensive patients per this new definition of hypertension [6]. Whether personalization is the key to greater health benefit compared to simpler one-size-fits-many interventions is debated. We review recent studies bearing on personalized treatment of hypertension and propose a means of resolving the tension between the benefits of simplicity and the benefits of personalization when treating hypertension.

A Framework for Understanding Personalized Treatment of Hypertension

In general, there is a trade-off between simplicity and the incorporation of rich information about individuals in clinical decision-making. More personalized treatment strategies create the most value for patients in whom simple strategies with low information burden prove ineffective. To the extent that the added complexity of additional information increases the likelihood of good decision-making and improved outcomes, the added complexity can be worthwhile. As complexity grows with a given personalization approach, handling the complexity without increasing the calculation burden on the clinician becomes imperative. Therefore, as illustrated in Fig. 1, we suggest that efforts to personalize treatment of hypertension are rational when a simpler, one-size-fits-many approach is unsuccessful. For example, the Birmingham Hypertension Square [7] is an easily remembered proposed algorithm premised on just a few pieces of information about patients. Other very low information burden treatment strategies such as non-pharmacologic methods of hypertension control with lifestyle modifications and regular physical activity [8] are efficacious for some people. In contrast, genomic-based approaches to personalization of treatment could be highly complex and computationally expensive. Our review of the literature is framed around this concept of trading simplicity for detailed patient information when treating hypertension and when this trade-off might increase efficacy.

Handling more information places a burden on clinicians. More complicated approaches to predicting antihypertensive drug response raise two practical questions: (1) does the benefit of predicting these responses exceed the costs of collecting and analyzing large amounts of data? and (2) does the strategy make sense from the perspective of caring for individuals, the population, or both? The answers depend on the benefits of using the "right" medication. Resistant hypertension, defined as above-goal BP despite concurrent use of three antihypertensive drug classes in the setting of good adherence [9], is a good example of a situation in which poorly chosen medications can contribute to ongoing problems, risks, and frustrations. Patients with resistant hypertension are at increased risk of adverse outcomes compared with patients with non-resistant hypertension [10]. Moreover, resistant hypertension is often caused by primary aldosteronism [11], with pathophysiology strongly suggesting use of a particular drug class, mineralocorticoid receptor antagonists. Even in patients with resistant hypertension who do not appear to have overt primary aldosteronism, mineralocorticoid receptor antagonists are often effective [12••]. Yet, not all cases of resistant hypertension are related to mineralocorticoid receptor activation. Mineralocorticoid receptors are grossly underused in resistant hypertension [13]. It is,

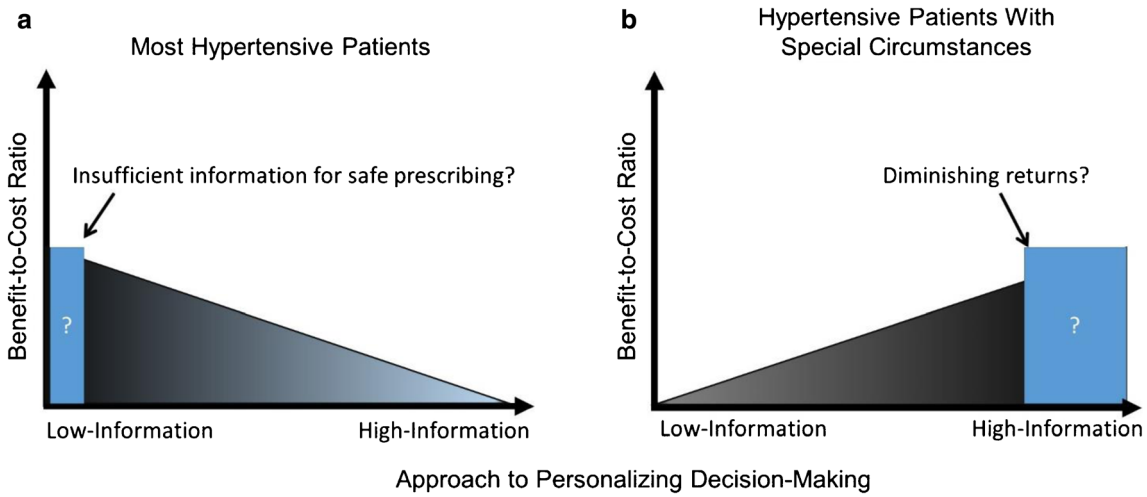

Fig. 1 **a** Low information burden personalized medicine approaches can be adequate for treatment efficacy (e.g., one-size-fits-many). In some cases, however, the low information burden approaches to treatment do not provide effective results, so **b** reasonable higher information burden personalized medicine approaches should be considered

therefore, a case in which personalization of the treatment to the patient might be worth considerable effort.

Low Information Burden Personalization Approaches

The decision whether to lower the blood pressure is the initial opportunity to personalize the treatment of hypertension. The HOPE-3 trial [14] tested the hypothesis that lowering blood pressure in a broad population of people at moderate risk for cardiovascular events would reduce events compared to placebo. The trial did not provide evidence for this hypothesis; there was a significant benefit in the patients with highest tertile of blood pressure, but not the overall study population. Although the study clearly was designed to evaluate a one-size-fits-many approach, the results support the idea that some information about the patient is important in choosing whether to treat. Results of the HOPE-4 trial will likely be released in early 2019. This trial in 30 communities with 1376 participants in Colombia and Malaysia in participants randomized to usual care or an intervention package included a combination antihypertensive and cholesterol-lowering medication [15]. The results will shed further light on the benefits of a relatively impersonal, one-size-fits-many approach to prevention of cardiovascular disease.

With respect to which drug should be used, a variety of low information burden personalization approaches have been proposed. A single parameter such as sex [16] or ancestry [17] has been proposed to be useful for personalizing hypertension care. For example, in the treatment of primary aldosteronism, eplerenone is better tolerated in men than is spironolactone, which has antiandrogenic adverse effects [16]. Other simple parameters such as age can be useful. For example, the Birmingham Hypertension Square [7] updated to include newer information indicating spironolactone as fourth-line antihypertensive medication [12••, 18] is a reasonable personalization approach in theory. Whether it confers any advantages in practice has not yet been evaluated rigorously. However, rigorous evaluation of a one-size-fits-many approach to BP lowering has been undertaken. In a study of 700 patients from urban hospital clinics in Sri Lanka, patients with mild to moderate hypertension treated with a low fixed-dose combination pill of three antihypertensive drugs were more likely to achieve their target blood pressure after 6 months than patients receiving usual care [19••].

Another low information burden approach to personalizing hypertension treatment studied for decades is renin profiling, discussed in a prior review [20]. Although this review focuses primarily on more recent approaches, there is some support in the literature for using renin profiling [21]. However, one of the key clinical trials (NCT00834600) appears never to have been published as discussed elsewhere [20], leaving open questions about the usefulness of the approach. Combining renin and aldosterone to screen for primary aldosteronism is useful in certain populations and is recommended in the ACC/AHA 2017 Hypertension Guidelines [5] and the Endocrine Society guidelines on primary aldosteronism [22].

Novel approaches to predicting response to antihypertensive medications in resistant hypertension are being developed. For example, Luther [23••] and colleagues have explored mass spectrometric measurement of extracellular vesicle-shuttled proteins to predict response to mineralocorticoid receptor antagonists. Byrd and colleagues have measured mRNA transcripts in the human urine supernatant to detect mineralocorticoid receptor activation [24••]. This approach lends itself to future pharmacotranscriptomic studies, in which RNA transcripts are assayed to predict drug response and titrate drug doses.

Not only does personalized medicine have potential for guiding drug treatment of hypertension, but it might also be useful in selecting patients for other treatments. For example, should catheter-based renal denervation eventually be approved by the US FDA, the question of the proper patients in whom it will be effective will be of keen interest. After an initial neutral sham-controlled RCT [25], recent clinical trials reported that renal denervation could reduce systolic blood pressure to an extent in certain patients [26–28]. There remain many unknowns about this procedure such as for whom this treatment would be most appropriate as well as any possible long-term effects of the treatment. For a review of some of the emerging considerations, see a recent review by Rimoldi and colleagues [29]. It is not yet possible to categorize how information-intensive personalized selection of patients for renal denervation would be, since this science remains in its infancy.

Medium Information Burden Personalization Approaches

A recent highly novel effort to personalize the treatment of hypertension was introduced by Laffin et al. [30••]. Their approach compares a person to the average participant actually enrolled in the Systolic Blood Pressure Intervention Trial (SPRINT) [31], in recognition of the possibility that a person who meets entry criteria might be different from most people eventually enrolled. As clinical trial data sharing becomes more common [32, 33], we anticipate an increase in the number of novel proposals for treatment of hypertension personalized according to calculations based on commonly collected laboratory and demographic data. Computational approaches to predict response to drug treatment using a medium information burden are already proliferating. For example, patients' laboratory values have been used to predict the outcomes of thiopurine treatment in patients with inflammatory

bowel disease [34••]. The same approach could be studied in predicting response to antihypertensive medications.

Efforts are underway to identify sets of single nucleotide polymorphisms that can be combined to forecast response to hydrochlorothiazide and chlorthalidone [35, 36••]. Whether this medium information burden personalization approach is superior to renin profiling in predicting drug response is unknown. Moreover, whether predictions of response to first-line drugs will improve patient outcomes will require additional large, randomized, prospective studies. These trials will need to be strategy trials comparing the use of these personalization methods to standard care. Strategy trials are challenging for a variety of reasons including strong clinician preferences diminishing enthusiasm for enrolling patients, as well as difficulties in blinding. Nonetheless, more strategy trials are needed to demonstrate value of personalized treatment of hypertension.

High Information Burden Personalization Approaches

While the diagnosis of hypertension can be made with a sphygmomanometer, some rare subtypes are best identified using genetic testing for mutations of large effect size. Whether treatment of common forms of hypertension could be improved by genomics-based personalization efforts has been tested in various proof-of-principle studies. Simple, low information burden approaches involving one or two polymorphisms do not appear to be promising for hypertension pharmacogenomics since the effect size is very small [37]. Combining large numbers of loci to make a pharmacogenomics score is computationally feasible as demonstrated by the rise of gene risk scores [38, 39]. However, the value of a polygenic score to predict response to antihypertensive medications remains untested.

A strong emerging trend is to use machine learning models to make predictions based on many clinical characteristics mined from the electronic health record. Although we are not aware of these approaches being used to predict response to antihypertensive medications, this likely will occur. Since machine learning models must be trained on data, one of the key challenges is access to high-quality data sets with interpretable and reliable outcome data. Data quality within the electronic health record is a major concern, as well. In addition, models premised on a large number of clinical variables may be fragile when some of the data is missing for a given patient. Finally, approaches for prospectively validating these techniques as useful in improving patient outcomes will need to be developed since the considerations are likely somewhat different from typical randomized, controlled trials.

Personalized Blood Pressure Goals

We have discussed several approaches to personalizing the choice of antihypertensive treatment. It is also important to consider the extent to which BP goals should be personalized. Clinical hypertension guidelines are general recommendations and require clinicians to use appropriate judgment, as well as to make treatment decisions for each patient based on individual characteristics and circumstances. The clinical guidelines are based on a treat-to-target strategy stratified by patient characteristics. Further personalization of BP goals based on an individual assessment of overall cardiovascular disease risk has been proposed [40••]. However, there are no clinical trial data directly comparing individualized risk-based blood pressure goals with treating to a standard blood pressure target [41].

Perspectives on Personalized Medicine for Hypertension Treatment

In patients in whom the common first-line drugs as suggested by the guidelines are not effective when combined rationally in a 3-drug regimen, the causes of apparent treatment resistant hypertension and the possibility of secondary hypertension need to be assessed so treatment can be individualized accordingly. In addition to the several future directions outlined above, we might well see an increase in N-of-1 trials to assess randomized treatment effects in individual patients [42]. In the final analysis, we do not anticipate that personalization *or* a one-size-fits-many approach will be proven best, but rather we expect a variety of approaches to co-exist, to be called upon when most useful.

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Compliance with Ethical Standards

Conflict of Interest SM has no conflict of interest to declare and is supported via funding from the New Brunswick Health Research Foundation (NBHRF) (Operating Grant: Health Research Value Demonstration Initiative [HRVDI]) provided directly to professional supervisors, Keith R. Brunt, PhD (IMPART investigator team Canada) and Sohrab Lutchmedial, MD, FRCP(C) (CardioVascular Research New Brunswick, Saint John Regional Hospital, Horizon Health Network). JBB is funded by the National Institutes of Health award 5K23HL128909.

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