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REVIEW

Personalized medicine and treatment approaches in hypertension: current perspectives

James Brian Byrd

Division of Cardiovascular Medicine,
Department of Medicine, University
of Michigan, Ann Arbor, MI, USA

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Correspondence: James Brian Byrd
Division of Cardiovascular Medicine,
Department of Medicine, University
of Michigan, 20-209W North Campus
Research Complex, 2800 Plymouth Road,
Ann Arbor, MI 48109-2800, USA
Tel +1 734 998 7991
Fax +1 855 230 1379
Email jbbyrd@umich.edu

Abstract: In the US, hypertension affects one in three adults. Current guideline-based treatment of hypertension involves little diagnostic testing. A more personalized approach to the treatment of hypertension might be of use. Several methods of personalized treatment have been proposed and vetted to varying degrees. The purpose of this narrative review is to discuss the rationale for personalized therapy in hypertension, barriers to its development and implementation, some influential examples of proposed personalization measures, and a view of future efforts.

Keywords: hypertension, blood pressure, personalized medicine

Introduction

More than a global epidemic, hypertension is in fact the leading risk factor for the global burden of disease, according to the World Health Organization.[1] Current guidelines for the diagnosis and treatment of hypertension offer convenient heuristics for clinicians. However, these algorithms are not highly personalized to the pathophysiology of individual patients. Though greater personalization of hypertension treatment might be valuable, this "hypothesis" is too vague to be tested experimentally. What is meant by "personalization"? What type of value should personalization offer, and what costs are reasonable to buy greater personalization? Since no series of experiments could refute the possibility that some type of personalization would add some kind of value, attempts to understand personalized medicine must focus on specific, testable propositions. This narrative review highlights rationales for personalized hypertension care, influential personalization frameworks, limitations of these frameworks or their vetting, and future directions suggested by the current state of knowledge.

Rationale for personalized medicine in the treatment of hypertension

A logical starting point in considering personalized medicine in hypertension is to ask whether it is desirable. Francis Collins (director of the National Institutes of Health [NIH]) and Margaret Hamburg (former commissioner of the US Food and Drug Administration [FDA]) have written eloquently about the promise of personalized medicine.[2] They highlight the way in which the genomic era has positioned medicine for successful personalization efforts. Since that article was written, genetic, genomic, transcriptional, and proteomic methods continue to evolve and to provide profound insights into pathophysiology. Turner et al elaborated additional thoughtful rationales for personalized medicine, specifically in the field of hypertension.[3] The authors

highlighted the intuitive appeal and the opportunity to benefit the individual patient maximally.

Personalized medicine for hypertension can be viewed in terms of predicting which drug will lower blood pressure (BP) most effectively in an individual. Another way to think of the problem is the inverse: personalized medicine to avoid patient-specific risks for adverse effects of drugs[4] or drugs that predictably lack efficacy. Along these lines, well-described problems with adherence provide additional impetus to personalize the treatment of hypertension. Hypertension imposes an unparalleled burden of disease around the globe,[1] yet adherence to antihypertensive medications is poor.[5–7] A common problem, poor adherence is associated with a lack of improvement in cardiovascular risk.[5] Though most adverse events due to antihypertensive medications are not life-threatening, these experiences can contribute to cardiovascular morbidity and mortality by virtue of decreasing adherence. The ability to predict adverse events or lack of efficacy in an individual patient would facilitate efforts to improve adherence.

Barriers to personalized therapy for hypertension

It is logical to assume that the rise of systems biology and the resulting novel biological insights will result in more personalized treatment of hypertension. However, there are significant barriers to overcome along the way. The translation of novel mechanistic insights into clinical algorithms depends upon painstaking and expensive clinical investigation. In addition, substantial resources will be required to overcome the natural tendency to do things as they have been done in the past.

Costs of developing and evaluating personalized medicine approaches in hypertension

A proposed personalization method would theoretically require a clinical trial to demonstrate persuasively benefit above current guideline-based therapy, though less stringent evidence might be acceptable.[8] Science is an iterative process, and there will be failed personalized medicine efforts on the way to successful ones. To the extent that diagnostic methods predictive of response are developed in nonhuman species, the failure rate will be higher by virtue of species differences. To view a drug as "safe and effective" for all patients with a broadly defined indication, such as hypertension, is antithetical to personalized medicine. Consider, however, the position of a company developing a new drug for hypertension. What incentive exists for the company to define who will not benefit from the drug? In some situations, there may be a clear answer: a companion diagnostic

test in which the company has a stake. In other situations, the answer is less clear. Despite hurdles, the field of oncology has demonstrated that with sufficient investment of resources, it is possible to implement personalized medicine approaches in the clinic (eg, GTPase KRas [*KRAS*]-mutation testing/ cetuximab treatment[9] or HER2 testing/trastuzumab[10] treatment). For the most part, the insights used to personalize oncologic treatment are currently inapplicable in hypertension. With rare exceptions,[11,12] models of hypertension have not involved somatic mutations, which have been integral to oncology's personalized medicine successes.

Barriers to adoption of personalized medicine in hypertension

Successfully developing and vetting a novel approach to personalized treatment of hypertension does not ensure its widespread adoption. Law et al performed a seminal meta-analysis showing similar effectiveness of common antihypertensive medication classes in clinical trial populations.[13] The investigators proposed a population-level "polypill" strategy for cardiovascular treatment based on age, rather than more personalized risk-factor analysis. Their argument is appealing, and has generated some misplaced skepticism of personalized medicine. Law et al's meta-analysis by no means precludes important, predictable individual differences in responsiveness to medication classes or susceptibility to adverse events. Indeed, their findings are compatible with continued strong interest in personalized treatment of hypertension. The most tractable form of personalized therapy for hypertension would not focus on forecasting distant future cardiovascular events (ie, improved risk-factor analysis). Rather, personalized treatment of hypertension would be most readily facilitated by the ability to anticipate drug response or adverse effects (responsiveness/tolerability). More successful BP lowering in individuals would in fact facilitate Law et al's goal of lowering the average BP in the population.

There is good reason to believe that predictable differences in responsiveness to antihypertensive medications exist. Common genetic variants affect the pharmacokinetics and pharmacodynamics of some antihypertensive drugs, eg, β-blockers[14] and hydralazine.[15] Moreover, there are distinct subsets of hypertensive pathophysiology. For example, at least some patients with primary hypertension have a decreased plasma volume compared to normotensive individuals.[16] However, patients with mineralocorticoid-induced hypertension, eg, primary aldosteronism, have expanded plasma volume. This fundamental and reproducible physiologic difference would be expect to have implications for treatment response. However, convenient and accurate

markers of plasma volume are not available in the clinic, with plasma renin activity (PRA) coming closest to this goal (in patients without concomitant heart failure). The field of hypertension awaits the development of clinically applicable phenotyping methods permitting strong inferences about pathophysiology and expected treatment response. The development of such tests depends upon the training of a cadre of sophisticated clinician–scientists interested in these issues. Cold Spring Harbor is now publishing a new journal focused solely on personalized medicine. Engagement from this premier research organization on this topic is likely to help stimulate rigorous research. In summary, therapeutic equivalence between various types of antihypertensive drugs cannot be presumed at the level of the individual, despite meta-analyses showing similar mean BP reduction and event reduction with different drugs at the population level.

Influential approaches to personalizing drug therapy in hypertension

The value of any specific approach to personalized medicine is not self-evident, but is a proposition to be tested. Previous attempts to personalize the treatment of hypertension illuminate potentially promising avenues, as well as pitfalls.

Aldosterone measurement

Personalized therapy is conditioned upon identifying a trait or group of traits differentiating the response of individual patients. Therefore, diagnostic testing is at the center of the personalized medicine movement. In 1954, scientists working in the chemical division of Merck & Co reported the isolation of aldosterone,[17] previously known as electrocortin. Conn reported the discovery of primary aldosteronism shortly thereafter – in 1955.[18] By 1960, Laragh et al had demonstrated that aldosterone was not consistently elevated in hypertension,[19] and eventually primary aldosteronism was deemed rare. The development of the aldosterone-to-renin ratio described herein gave new life to the idea that primary aldosteronism is common.[20] Aldosterone can increase in response to PRA, or due to primary aldosteronism. These situations would be treated differently, and thus measuring aldosterone in isolation is not an attractive method of personalizing antihypertensive medication therapy.

Renin profiling

PRA played a key evolutionary role in maintaining intravascular volume in an environment with scant sources of dietary sodium. PRA's role in the regulation of BP and response to medications was explored in seminal work by Laragh, Sealey, and many colleagues over several decades. An excellent summary of some of the most important findings was published in 2011.[21] An appealing and influential model of antihypertensive medication treatment informed by renin profiling emerged from this work. Egan et al compared renin profile-guided treatment to clinical judgment not informed by PRA in a randomized clinical trial in uncontrolled but treated hypertensive patients. The intention-to-treat analysis included 77 patients, and the findings indicated equal or better BP control using renin profiling.[22] An additional randomized trial of renin profiling has been completed (https://clinicaltrials.gov/ct2/show/NCT00834600); the results have not yet been published.

Aldosterone-to-renin ratio

PRA and aldosterone are regulated by several variables, and their relationship to each other may be more informative than either measurement alone. The ratio is used to diagnose primary aldosteronism, but is not recommended for widespread screening in patients with hypertension in US or European hypertension guidelines.

Single-nucleotide polymorphism and haplotype approach to pharmacogenomics

Seminal work done by Geller et al has elucidated a series of rare monogenic forms of hypertension.[23–26] However, the contribution of common genetic variants, such as single-nucleotide polymorphisms (SNPs), to hypertension is complex and subtle. Genome-wide association studies have supported the prediction that SNPs have a small effect on physiology compared to rare disease-causing mutations. Therefore, attempts to predict response to medications using SNPs require large sample sizes and are unlikely to find effect sizes of clinical significance. After a series of small studies suggested that a particular insertion/deletion polymorphism in the *ACE* gene was informative, the GenHAT study examined the relationship between the *ACE* insertion/deletion polymorphism, treatment response in hypertension, and coronary heart disease. This study of 37,939 patients with hypertension demonstrated persuasively that there was no effect of insertion/deletion polymorphism on treatment response or coronary heart disease.[27] Although many SNP-association studies have been performed in hypertension, SNP-association studies have come under criticism for poor reproducibility and potential for bias,[28] and this mode of scientific inquiry has largely been abandoned. Table 1 highlights several genetic polymorphisms that have been intensively investigated as potential predictors of antihypertensive drug response.

Table 1 Summary of candidate gene pharmacogenetics studies using antihypertensive medications

Gene	Protein	Alleles or locus	Study	Drug	Study population	Finding
ACE	Angiotensin I-converting enzyme					
		ACE insertion/ deletion polymorphism	Ueda et al[35]	Enalapril	Normotensive men (n=23)	Variant was informative regarding pressor response to angiotensin I
		ACE insertion/ deletion polymorphism	Harrap et al[36]	Perindopril	Hypertensive or nonhypertensive patients with a history of cerebrovascular disease (n=5,688)	Variant was not associated with BP response
		ACE insertion/ deletion polymorphism	Arnett et al[27]	Lisinopril	Hypertensive patients aged 55 years or older with one or more risk factors for cardiovascular disease (n=37,939)	Variant was not associated with BP response
CYP2D6	Cytochrome P450, family 2, subfamily D, polypeptide 6					
		CYP2D6*3, *4, *6	Wuttke et al[37]	Metoprolol	German patients reported by their physicians as having had a pronounced adverse event related to metoprolol (n=24)	Poor metabolizers were overrepresented among patients with pronounced adverse events compared to a general population
		CYP2D6*3–*10, *41, and duplications	Fux et al[38]	Metoprolol	Patients treated with metoprolol irrespective of indication (n=121)	CYP2D6 genotype was not significantly associated with metoprolol adverse effects
		CYP2D6*3, *4, *5, *6	Rau et al[39]	Metoprolol	β-blocker-naïve patients with a cardiovascular indication for metoprolol (n=232)	Metoprolol lowered heart rate, DBP, and mean arterial pressure significantly more in poor metabolizers compared to non-poor metabolizers
ADRB1	β₁-adrenergic receptor					
		Arg389Gly (rs1801253)	O'Shaughnessy et al[40]	Atenolol or bisoprolol	Cohort 1, untreated hypertensive patients (n=92, atenolol); cohort 2, untreated hypertensive patients (n=55, bisoprolol)	Variant did not affect hemodynamic response to chronic β-blockade
		Arg389Gly (rs1801253)	Liu et al[41]	Metoprolol	Healthy men (n=8)	Homozygosity for ADRB1 Arg389 alleles predicted response to metoprolol
		Arg389Gly (rs1801253)	Sofowora et al[42]	Atenolol	Healthy men and women (n=34)	Variant was associated with variation in sensitivity to atenolol
		Arg389Gly (rs1801253) and Ser49Gly (rs1801252)	Johnson et al[43]	Metoprolol	Hypertensive men and women (n=40)	Variants in ADRB1 were informative regarding BP response to metoprolol

(Continued)

Table 1 (*Contiuned*)

Gene	Protein	Alleles or locus	Study	Drug	Study population	Finding
		Arg389Gly (rs1801253) and Ser49Gly (rs1801252)	Karlsson et al[44]	Atenolol	Hypertensive patients with left ventricular hypertrophy (n=101)	Variants did not exert a major effect on BP response to atenolol
		Arg389Gly (rs1801253) and Ser49Gly (rs1801252)	Liu et al[45]	Metoprolol	Men and women with essential hypertension (n=61)	Variants in *ADRB1* were informative regarding BP response to metoprolol
		Arg389Gly (rs1801253) and Ser49Gly (rs1801252)	Kumar et al[46]	Metoprolol	Healthy males (n=41)	Variants did not exert an effect on BP response to exercise during treatment with metoprolol
		Arg389Gly (rs1801253) and Ser49Gly (rs1801252)	Suonsyrjä et al[47]	Bisoprolol	Moderately hypertensive men (n=233)	Variants did not exert a major effect on BP response to bisoprolol
		Arg389Gly (rs1801253) and Ser49Gly (rs1801252)	Filigheddu et al[48]	Atenolol	Never-treated essential hypertension patients (n=340)	Variants did not exert an effect on BP response to atenolol
ADRB2	β_2-adrenergic receptor					
		Gly16Arg (rs1042713)	Suonsyrjä et al[47]	Bisoprolol	Moderately hypertensive men (n=233)	Variants did not exert an effect on BP response to bisoprolol
		Cys19Arg (rs1042711), Gly16Arg (rs1042713), and Gln27Glu (rs1042714)	Filigheddu et al[48]	Atenolol	Never-treated essential hypertension patients (n=340)	Variants did not exert an effect on BP response to atenolol
		rs2053044	Anthony et al[49]	Ramipril	Participants in the African American Study of Kidney Disease (n=336)	Variant was associated with time to BP control assessed by mean arterial pressure
GRK4	G protein-coupled receptor kinase 4					
		Arg65Leu (rs2960306), Ala142Val (rs1024323), and Ala486Val (rs1801058)	Vandell et al[50]	Atenolol Candesartan,	Patients with mild-to-moderate hypertension (n=768)	A variant diplotype was associated with DBP lowering during exposure to atenolol

(*Continued*)

Table 1 (*Continued*)

Gene	Protein	Alleles or locus	Study	Drug	Study population	Finding
		Arg65Leu (rs2960306), Ala142Val (rs1024323), and Ala486Val (rs1801058)	Sanada et al[51]	Losartan, telmisartan, or valsartan	Patients with essential hypertension (n=829)	The 142V allele was informative regarding decrease in SBP during exposure to ARBs
NEDD4L	Neural precursor cell expressed, developmentally downregulated 4-like, E3 ubiquitin protein ligase					
		rs4149601	Luo et al[52]	Hydrochlorothiazide	Patients with hypertension (n=833) compared to normal controls (n=853, case-control study)	Allele was associated with BP response to hydrochlorothiazide
		rs4149601	Svensson-Färbom et al[53]	A thiazide diuretic or β-blocker	Patients with hypertension (DBP >100 mmHg, n=1,863)	In patients treated with β-blocker or diuretic monotherapy, allele associated with SBP and DBP reduction
		rs4149601, rs292449, rs1008899, and rs75982813	McDonough et al[54]	Hydrochlorothiazide	Patients with-mild-to moderate hypertension (n=768)	Significant associations or trends were found between each of the four variants and response to hydrochlorothiazide in whites; no associations were found with respect to response to atenolol

Abbreviations: BP, blood pressure; DBP, diastolic BP; SBP, systolic BP; ARBs, angiotensin-receptor blockers.

Genome-wide association approach to pharmacogenomics

There are reasons to doubt whether the DNA sequence can powerfully predict response to antihypertensive drugs. Specifically, the invariant nature of the DNA sequence means that environmental influences on BP response are not accounted for by sequence analysis. The GENRES randomized, placebo-controlled, crossover trial was published earlier this year.[29] The study was informed by a genome-wide association study, and suggested a possible relationship between nephrosis (*NPNS1*) gene variants and response to an angiotensin-receptor antagonist – losartan. In addition, evidence was found supporting two other genes' (*ALDH1A3* and *CLIC5*) influence on BP response to hydrochlorothiazide.

Hemodynamic assessments

Arterial stiffness has been proposed as a parameter that might permit personalized selection of antihypertensive medications. Protogerou et al analyzed arterial stiffness by pulse-wave velocity in a randomized, double-blind, clinical trial comparing atenolol to perindopril/indapamide. They found that baseline pulse-wave velocity predicted response to antihypertensive medication.[30]

Personalized medicine and current hypertension guidelines

To the extent that guideline-based treatment of hypertension has been personalized in the US, it has been on the basis of phenotypes perceived as requiring no testing (eg, race) and phenotypes requiring simple diagnostic testing (eg, chronic kidney disease and diabetes). The most recent Joint National Committee (JNC) discussion of routine diagnostic testing in hypertension was published just 2 years after the human genome was decoded.[31] JNC 7 recommended a modest degree of personalization, using methods more than 40 years old (12-lead electrocardiography, urinalysis, blood glucose,

hematocrit, serum potassium, creatinine, calcium, fasting lipoprotein profile). In contrast, the document written by the JNC 8 committee did not offer an update regarding diagnostic testing, although its recommendations assume a knowledge of whether the patient has chronic kidney disease or diabetes.[32] The European Society of Hypertension guidelines suggest that laboratory investigation of hypertension proceed from "the most simple to more complicated ones".[33] In summary, current hypertension guidelines emphasize simplicity and pragmatism in diagnostic testing.

Emerging approaches to personalized medicine in the treatment of hypertension

Future approaches to the personalization of hypertension treatment will likely focus less on the DNA sequence and more on variables that can change over time. The DNA sequence is static throughout life, but the emergent effect of the DNA sequence and the environment on BP is dynamic, changing throughout life. Looking further downstream from the DNA at quantifiable, emergent determinants of BP and drug response will likely prove more useful. For example, Qi et al recently showed a relationship between activation of the renin–angiotensin–aldosterone system (RAAS) or exogenous administration of aldosterone and the presence of subunits of the epithelial sodium channel in urinary extracellular vesicles.[34] Therefore, a new means of evaluating the RAAS may have arrived, and with it a host of questions that were intractable in the past. Whether these extracellular vesicles are participating in a new form of endocrine signaling is unknown, and is an area of intense investigation. Moreover, we are witnessing the emergence of clinical "-omics" approaches that will reflect physiological states influenced by the environment, rather than static genomic information. The fields of epigenomics, metabolomics, proteomics, transcriptomics, and lipidomics are likely to yield data useful in personalizing treatment of hypertension.

Conclusion

No approach to the personalization of hypertension therapy has been demonstrated to have unequivocal value, yet spectacular recent advances in the ability to measure human physiology open a window of opportunity to move beyond the current state of affairs toward personalized medicine in hypertension. Personalized therapy for hypertension appears to be in its infancy. Because of the clear promise of improved health if progress is made, the NIH and FDA have devoted significant resources to fostering personalized medicine. Additional government investment in personalized hypertension care appears well justified in view of hypertension's prime role in deaths and disability around the globe compounded by well-known medication-intolerance issues leading to poor adherence. The field of hypertension awaits the development of clinically feasible phenotyping methods that allow clinicians to draw strong inferences about pathophysiology.

Disclosure

The author reports no conflicts of interest in this work.

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