REPORT 1 OF THE COUNCIL ON SCIENCE AND PUBLIC HEALTH (I-14)
Genomics in Hypertension: Risk Prediction and Treatment
(Reference Committee K)

EXECUTIVE SUMMARY

Objectives. One in three adults has hypertension, a major risk factor for cardiovascular disease, stroke and kidney failure. Hypertension is responsible for half of all cardiovascular-related mortalities and is present in approximately 50 percent of patients with coronary artery disease and 70 percent of those with stroke. Hypertension's serious burden of disease has led to intensive efforts to identify undiagnosed hypertension and control it. Since hypertension is partially hereditary, research examining the genetic factors that contribute to it is underway, along with an exploration of translating genetic information into tools that better identify who is at risk for hypertension before it develops and predict what therapies will be most effective for each individual. The Council on Science and Public Health initiated this report to examine current knowledge about the genetic factors relevant to the control of hypertension and emerging genomic-based diagnostic and therapeutic tools.

Data Sources. Literature searches were conducted in the PubMed database for English-language articles published between 2004 and 2014 using the search terms "hypertension" and "blood pressure" with the terms "genomic," "genetic," "personalized medicine," "pharmacogenomic," and "family history." To capture reports not indexed on PubMed, a Google search was conducted using the same search terms. Additional articles were identified by manual review of the references cited in these publications.

Results. Dozens of gene variants have been identified that are associated with blood pressure control, partially explaining the heritability of blood pressure. Genetic tests aimed at enhancing the prediction of hypertension and associated cardiovascular events have been developed. Although the tests are significantly associated with changes in blood pressure, hypertension incidence, stroke, and coronary heart disease, they do not appear to add utility to risk prediction based on factors like obesity and prehypertension. Despite a relatively standardized approach to treating hypertension, variability in response to antihypertensive medications is common. Genetic variations are thought to partially explain this variability, and pharmacogenomic evaluation has been suggested as a potential method by which the most effective antihypertensive could be selected for each patient.

Conclusions. The state of genomic-based diagnosis and treatment of hypertension is still in its infancy, but important discoveries are being made that may partially explain some of the variation in individual risk and response to antihypertensive medications. With continued discovery of genetic variants, genetic tests could become useful in predicting hypertension before it manifests. In the meantime, family history is a valuable tool for predicting those who may be at risk. Although no clinical practice guidelines recommend genotyping before initiating antihypertensive therapy, an awareness of the pharmacogenomic factors affecting response to antihypertensive agents is important for anticipating varying responses to prescribed medications and altering treatment when blood pressure levels are not satisfactorily lowered. Clinical trials designed to reduce heterogeneity among study populations will aid in the interpretation of results and applicability to patient care.

REPORT OF THE COUNCIL ON SCIENCE AND PUBLIC HEALTH

CSAPH Report 1-I-14

Subject: Genomics in Hypertension: Risk Prediction and Treatment

Presented by: Stuart Gitlow, MD, Chair

Referred to: Reference Committee K
(Hugh Taylor, MD, Chair)

BACKGROUND

One in three adults in the United States (about 77 million) has hypertension, a major risk factor for cardiovascular disease, stroke and kidney failure.[1] Hypertension is responsible for half of all cardiovascular-related mortalities[1] and is present in approximately 50 percent of patients with coronary artery disease and 70 percent of those with stroke.[2,3] Its financial burden in the U.S. is nearly $50 billion annually, including health services, medications, and missed days of work.[1] This burden of disease has led to intensive efforts to identify undiagnosed hypertension and control it. The American Medical Association has partnered with the Department of Health and Human Service's Million Hearts® initiative, Johns Hopkins Medicine's Armstrong Institute for Patient Safety and Quality and the Johns Hopkins Center to Eliminate Cardiovascular Health Disparities to make a measureable impact on the number of patients with uncontrolled hypertension.

The biological pathways underlying blood pressure control are complex, and incompletely understood. Additionally, variation in risk factors and response to antihypertensive medications among individuals is common. A great deal of research aiming to understand the underlying causes and optimal treatments is ongoing. This research includes efforts to uncover the genetic factors contributing to hypertension, along with the possibility of translating genetic information into tools that better identify who is at risk before it develops and predict what therapies will be most effective for each individual. The Council on Science and Public Health initiated this report to examine current knowledge about the genetic factors relevant to the control of hypertension and emerging genomic-based diagnostic and therapeutic tools.

METHODS

Literature searches were conducted in the PubMed database for English-language articles published between 2004 and 2014 using the search terms "hypertension" and "blood pressure" with the terms "genomic," "genetic," "personalized medicine," "pharmacogenomic," and "family history." These searches were intended to identify the involvement of genetics in the control of blood pressure, contribution to hypertension, risk assessment, and therapeutic management. To capture reports not indexed on PubMed, a Google search was conducted using the same search terms. Additional articles were identified by manual review of the references cited in these publications.

RISK FACTORS

Action of the AMA House of Delegates 2014 Interim Meeting: Council on Science and Public Health Report 2 Recommendations Adopted as Amended, and Remainder of Report Filed.

A number of risk factors for the development of hypertension have been identified including age, ethnicity, family history and genetic factors, lower education and socioeconomic status, greater weight, lower physical activity, tobacco use, psychosocial stressors, sleep apnea and dietary factors, e.g., dietary fats, higher sodium intake, lower potassium intake and excessive alcohol intake.[1] These risk factors increase the relative risk of developing hypertension by about 1.5-6-fold.[4,5] Individual risk for hypertension and its eventual development is dependent on the risk factors present and their combined effects. Many risk factors, such as weight, physical activity, tobacco use and dietary intake are modifiable and can attenuate or amplify the risk conferred non-modifiable risk factors.[6]

Family History as a Risk Factor

Data supporting a role for the genetic control of blood pressure comes from family and twin studies. The heritability of blood pressure is approximately 30-60 percent,[7] meaning that 30-60 percent of hypertension risk can be explained by additive genetic factors.[8,9] Family history can therefore be a valuable indicator of an individual's chance of developing hypertension.[10] Individuals that have one or both parents with hypertension have an approximately 1.5-2.5-fold greater risk of developing hypertension themselves.[11-13] This risk rises to as much as 6.2-fold in individuals whose parents both experienced hypertension before the age of 55 years.[11,12] These risk increases are independent of other behavioral risk factors that tend to be shared among families, like physical activity levels, dietary intake patterns and alcohol consumption.

GENE DISCOVERY EFFORTS

Studies demonstrating the heritability of blood pressure and family history as a risk factor have prompted intensive efforts to discover gene variants that contribute to hypertension. Early efforts to identify hypertension-causing gene variants were dominated by linkage and association mapping studies, i.e., studies designed to map genetic regions and gene variants that are shared among individuals and families with hypertension.[14,15] These were successful in identifying variants that alone are sufficient to cause rare monogenic hypertension syndromes such as familial hyperaldosteronism and congenital adrenal hyperplasia, but the studies were underpowered to detect common gene variants with smaller contributions to hypertension that, in combination, are likely to cause hypertension in a much larger proportion of the population.[14-18]

Newer genomic technologies have enabled the rapid scanning of the genome for single-nucleotide variations associated with common, complex conditions. Termed "genome-wide association studies," or GWAS, the studies use statistical algorithms to detect association between a certain phenotype and genetic variants.[19] Several GWAS have been undertaken to identify variants contributing to hypertension. To date, more than 40 variants affecting blood pressure have been identified, but none, individually or in combination, are thought to explain more than 1-2% of systolic and diastolic blood pressure variance.[14] This translates into approximately 1 mmHg for systolic blood pressure and 0.5 mmHg for diastolic blood pressure.[20] Although these increases are small, modest increments in population systolic and diastolic blood pressure are associated with substantial increases in cardiovascular disease risk and mortality.[21-24] Nonetheless, a great deal of work remains to identify other variants involved in blood pressure control.

The issue of GWAS detecting only a small proportion of the heritability of common, complex diseases has led to the term "missing heritability" and speculation about how to detect and explain the remaining heritability.[25] Predictions about what constitutes missing heritability include undiscovered rare variants that have large effect sizes, undetected structural variants such as

insertions and deletions, epigenetic effects like imprinting, and unknown gene-environment interactions.[14,25-27]

RISK PREDICTION USING GENOMICS

The identification of genetic variants affecting blood pressure has led to the development of genetic tests aimed at enhancing the prediction of hypertension and associated cardiovascular events in individual patients. These tests assess genotype at several variant locations associated with blood pressure control, and then return a genetic risk score (GRS) based on the variants that are present. GRSs evaluated to date are significantly associated with changes in blood pressure, hypertension incidence, stroke, and coronary heart disease, even after the effects of traditional risk factors are accounted for.[20,28,29] The relative weight of the GRS's ability to predict hypertension is similar to that of type 2 diabetes or positive family history of hypertension, but less than that of obesity or prehypertension.[28] Although studies so far have been unable to show that use of a GRS improves risk classification beyond the presence of other risk factors, a closer look at gene variant combinations has yielded promising results. For example, in those carrying a combination of variants that results in the highest GRS range, risk for coronary heart disease is increased by 60-70 percent.[30]

Some potential for GRS utility exists in younger age groups that may not yet exhibit other risk factors. In a study of children, adolescents and teens of European ancestry, a GRS predicted increased risk of adult hypertension and coronary heart disease independently of a family history of hypertension.[31,32] Similar results were observed among the more ethnically diverse population of the Bogalusa Heart Study.[31]

Modulating Genetic Risk and Risk Perception

Like many complex diseases, the development of hypertension is the result of a combination of inherited genetic factors and environmental/behavioral risks. Although the genetic variants identified thus far contribute only a small proportion to hypertension risk, emerging evidence suggests that their effects can be magnified or attenuated by interaction with non-genetic risk factors. For example, the heritability of blood pressure appears to be modulated by body-mass index (BMI). Generally speaking, heritability increases as BMI increases.[33] The physiological mechanisms underlying this relationship are not fully understood, but are thought to be a function of the increased inflammation, insulin resistance, and hormonal changes associated with obesity that can cause changes in gene expression.[33] Similarly, dietary intake patterns associated with obesity are thought to result in epigenetic modifications that can alter gene expression.[34,35] Socioeconomic factors like literacy, income and educational attainment also have been shown to modulate the effect of hypertension gene variants. The mechanisms by which these interactions are mediated are unclear but are hypothesized to depend on the genes' pleiotropic involvement in pathways controlling learning, memory and addiction behaviors.[36-39]

Apart from risk modulation due to changes in gene expression, studies are exploring how risk perception among individuals may change and potentially affect behavior. One trial currently underway is testing changes in risk perception and understanding of a series of genetic test results for participants with hypertension who receive in-person genetic counseling versus those that do not.[40] The goal is to determine whether, in patients with a chronic disease like hypertension, genetic counseling affects how risk and personal control are perceived and how health behavior may be impacted.

GENOMIC APPLICATIONS IN TREATMENT

Although comorbidities and other patient characteristics must be considered when choosing an anti-hypertensive therapy, the treatment of hypertension usually begins with a thiazide diuretic, calcium channel blocker (CCB), angiotensin-converting enzyme (ACE) inhibitor or an angiotensin receptor blocker (ARB).[41,42] In African-Americans, the recommended first-line therapy is a thiazide or CCB.[42] A second drug from a different class is commonly recommended if blood pressure control is not achieved with one drug.[41,42] β-blockers are often prescribed to treat hypertension, but they are no longer recommended as a first-line therapy due to mixed findings about their ability to reduce cardiovascular death, myocardial infarction and stroke.[41] As many as 16 million patients report taking antihypertensive medication,[43] and several antihypertensives were among the top 100 prescribed drugs in the United States last year.[44]

Despite a recommended standard approach to pharmacologic treatment of hypertension, patient response is often variable and suboptimal. The response rate to any given antihypertensive is about 50 percent,[45-46] and aside from age and race, there are few reliable predictors of the most effective antihypertensive therapy for each patient.[45,47] Genetic variations are thought to partially explain the variability in response, and pharmacogenomic evaluation has been suggested as a potential method by which the most effective antihypertensive could be selected for each patient.[45] Below, selected pharmacogenomic study results are briefly summarized for several antihypertensive drug classes.

Thiazides

Thiazide diuretics target the sodium-chloride transporter in the distal renal tubule, increasing excretion of sodium, chloride and potassium. Substantial variation in response to thiazides has been observed among patients, with a growing body of evidence suggesting that certain genetic polymorphisms influence response. Several genetic variants affecting response to hydrochlorothiazide have been identified in clinical trial populations.[48] For example, carriers of a variant in the *α-adducin* gene appear to have a greater decrease in systolic and diastolic blood pressure in response to hydrochlorothiazide than do non-carriers.[48] Further, in *α-adducin* variant carriers, thiazide therapy is associated with a more substantial reduced risk of combined myocardial infarction and stroke than are ACE inhibitors, CCBs, β-blockers or other vasodilators.[49] The *α-adducin* variant is estimated to be present in 30-60 percent of the population, depending on ethnicity,[50] potentially explaining a portion of the observed patient variability in thiazide response, and pointing to a possible opportunity to better target thiazide therapy.

Angiotensin-Converting Enzyme Inhibitors

ACE inhibitors, which suppress the renin-angiotensin-aldosterone system by inhibiting formation of angiotensin II, have been used for many years in the treatment of hypertension, heart failure, myocardial infarction, renal failure and diabetic nephropathy, and have been shown to significantly reduce mortality related to cardiovascular disease.[51] However, nearly 20% of patients discontinue ACE inhibitor therapy due to adverse drug reactions,[52] two of which are a dry, persistent cough and the more serious angioedema, a quickly developing inflammation in the dermis, subcutaneous tissue, mucosa and submucosal tissues.[53] A number of studies have identified a gene variant that is associated with a 2-4-fold increase in ACE inhibitor-induced angioedema in carriers.[53-55] Additionally, a GWAS identified 16 and 41 variants in African-Americans and Europeans, respectively, that are moderately associated with ACE inhibitor-induced angioedema.[56] Similarly, a study examining ACE inhibitor-induced cough revealed a significant association with a variant in the gene encoding the angiotensin-converting enzyme itself, occurring with greater frequency in Asian populations than in Caucasian populations.[57] Subgroup analyses revealed that in those recessive for the variant and over age 60 years, ACE inhibitor-induced cough was more than twice

as likely to occur.[57] The angioedema and cough results may contribute to efforts to identify which patients will experience adverse reactions when taking ACE inhibitors, but since they were primarily derived from small studies, further research is required to determine whether testing patients for variants before prescribing ACE inhibitors is clinically warranted.

Calcium Channel Blockers

CCBs have been a recommended first-line therapy for hypertension and reduction of cardiovascular risks for a number years, although their efficacy varies from one patient to another.[46] To explore the basis of this variability, a pharmacogenomic risk score was developed using three gene variants that were identified as being associated with poor cardiovascular outcomes in patients being treated with CCBs or β-blockers, with one point assigned for each homozygous variant they carried.[58] In patients with a pharmacogenomic risk score of zero or 1, meaning they were not homozygous for any variant or were homozygous for only one variant, respectively, CCB treatment was associated with an approximately 40% reduced risk for adverse cardiovascular outcomes.[58] In those with a score of 2 or 3, meaning that they were homozygous for two or three variants, respectively, CCB treatment was associated with an approximately 30% increased risk.[58] The same relationship was not seen in patients treated with β-blockers, suggesting that in those with a higher pharmacogenomic risk score, CCB therapy should be avoided.

Angiotensin Receptor Blockers

ARBs modulate the renin-angiotensin-aldosterone system by reducing the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking its binding to the angiotensin-1 receptor. They also are used often in patients who cannot tolerate ACE inhibitor-induced cough.[59] Although research into the pharmacogenomic effects of ARBs is sparse, results suggest that patients carrying certain genetic variants may respond better to ARBs than those who do not carry the variants. In a small study comparing systolic and diastolic levels in Japanese patients taking ARBs, those carrying certain sets of variants had lower systolic and diastolic values than those who did not carry the variants.[60] Further studies are needed to determine whether this result will be consistently observed among other ethnicities and in larger clinical trial populations.

β-Blockers

Although β-blockers are no longer recommended as a first-line therapy to treat uncomplicated hypertension, they are still used by millions of patients and often prescribed when comorbidities such as arrhythmia, coronary artery disease, angina, migraines, and some types of congestive heart failure are present. Several β-blockers are metabolized by the cytochrome P450 2D6 (CYP2D6) enzyme, which is subject to altered activity when mutations in the gene encoding it are present. For example, studies have demonstrated that in patients carrying mutations that reduce the activity of CYP2D6 (poor metabolizers), the metabolism of metoprolol is reduced.[61,62] In poor metabolizers, β-blocker therapy results in a greater heart rate reduction than in normal (extensive) metabolizers. However, metoprolol's effect on blood pressure response does not appear to be different in poor metabolizers, and a difference in adverse event rates has not been observed.[63-66] Since other β-blockers are not metabolized by CYP2D6 as extensively as metoprolol, it is unlikely that mutations in the gene encoding CYP2D6 would affect their efficacy or toxicity.[67]

Several drugs act as potent inhibitors of CYP2D6 activity, altering the pharmacokinetics of drugs metabolized by CYP2D6. The drug labeling for metoprolol, nebivolol, carvedilol and propranolol notes that co-administration of drugs inhibiting CYP2D6 activity may increase toxicity and adverse

events due to increased plasma levels of the β-blocker.[68-71] Drugs such as bupropion, fluoxetine, paroxetine, and quinidine are strong inhibitors of CYP2D6.[72]

DISCUSSION AND FUTURE PERSPECTIVES

The physiological control of blood pressure is complex, but continued identification of associated gene variants has contributed to increased understanding of the biological pathways involved and the factors that lead to hypertension. Although the genetic variants discovered so far appear to contribute only a small proportion to the overall risk for hypertension, much thought and effort is being directed toward identifying variants that may contribute to the "missing heritability." Recent discoveries in genomic architecture, such as the effects of imprinting, along with a better understanding of the interaction between inherited and behavioral risk factors, hold promise for filling the heritability gap.

A key problem complicating the interpretation of hypertension clinical trial results is the variability of the phenotype. Blood pressure levels measured in clinical trial participants can be affected by a number of factors. These include the type of measurement method (home or ambulatory devices, physician office measurement, other retail or pharmacy devices) and the time of the day during which the measurements are taken. Inaccuracies in self-reported information are often present. Additionally, the use of antihypertensive medications prior to the trial and their long-term effects on blood pressure levels may skew blood measurements during the trial.[48] Since even small changes in blood pressure levels can impact cardiovascular outcomes, heterogeneity in the trial population can lead to results that are difficult to interpret and apply to clinical care. For genomic research, the detection of variants that contribute to a small proportion of total blood pressure control is difficult if the clinical trial population is not simultaneously large and free of heterogeneity.[14] To improve the quality of information from clinical trials, many calls for the incorporation of methods to reduce heterogeneity have been made.[14,29,48]

The state of genomic-based diagnosis and treatment of hypertension is still in its infancy, but important discoveries are being made that may partially explain some of the variation in individual risk and response to antihypertensive medications. In particular, GRSs developed to date are about as good as other risk factors at predicting hypertension. With continued discovery of genetic variants, it is not unreasonable to think that the GRSs will improve and could become a valuable tool in predicting hypertension before it manifests. In the meantime, physicians should be aware that a large proportion of blood pressure variability is genetic, and that a family history is a valuable tool for predicting those who may be at risk. Likewise, although no clinical practice guidelines recommend genotyping before initiating antihypertensive therapy, an awareness of the pharmacogenomic factors affecting response to antihypertensive agents is important for anticipating varying responses to prescribed medications and altering treatment when blood pressure levels are not satisfactorily lowered. Tools to aid in prescribing decisions are especially needed since many patients must take multiple antihypertensive medications to achieve blood pressure control, increasing the risk for adverse events and drug interactions.

With continued improvements in clinical trial design, discovery of genetic variants not yet known to control blood pressure, and application of new findings to targeted antihypertensive therapy, the potential to improve prevention and treatment of hypertension and reduce adverse cardiovascular events is promising.

RECOMMENDATIONS

The Council on Science and Public Health recommends that the following recommendations be adopted and the remainder of the report be filed.

1. Our American Medical Association encourages continued research on the genetic control of blood pressure, including in pediatric populations, and the development of genomic-based tools that may assist health professionals in better predicting risk and targeting therapy for hypertension. (New HOD Policy)

2. Our AMA supports the view that hypertension clinical trial designs should attempt to reduce phenotypic heterogeneity in order to improve the quality and interpretation of results. (New HOD Policy)

Fiscal note: Less than $500.

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