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Deposited on: 15 February 2017

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Genomics and precision medicine for clinicians and scientists in hypertension. ¹

Authors: Anna Dominiczak, Christian Delles and Sandosh Padmanabhan

Short: Genomics and Precision Medicine

Word Count: 2500

Address of corresponding author

Professor Anna Dominiczak
BHF Glasgow Cardiovascular Research Centre
Institute of Cardiovascular and Medical Sciences
University of Glasgow
126 University Pl
Glasgow
G12 8TA

Tel: +44 141 330 2738
Fax: +44 141 330 5440
email: Anna.Dominiczak@glasgow.ac.uk

¹ This is a summary of the lecture AD presented at the AHA Council for Hypertension Annual Meeting in 2016.
In 1903 Sir William Osler wrote “the good physician treats the disease; the great physician treats the patient who has the disease”. These words ring very true in 2016 as we approach the era of precision or stratified medicine. The precision or stratified medicine (we are going to use these terms interchangeably) is based on identifying subgroups of patients with distinct mechanisms of disease and particular responses to treatments. This allows us to identify and develop treatments that are effective for particular groups of patients. Ultimately precision medicine will ensure that the right patient gets the right treatment at the right time. The above definition broadly follows suggested definition published by the UK Medical Research Council (http://www.mrc.ac.uk/research/initiatives/stratified-medicine/). We can therefore summarise the promise of precision medicine as being able to remove non-responders and toxic responders prior to prescribing medication and to treat with a given drug only responders and patients not predisposed to toxicity.

Such approaches are very well developed in cancer medicine with several examples of successful precision medicine applications in breast, prostate, ovarian, colon and pancreatic cancer \(^1\text{-}^6\) and this list is by no means complete. Cardiovascular medicine in general and hypertension in particular both lag behind oncology in this respect.

However, there are examples from rare monogenic syndromes, where a single genetic mutation explains the entire pathophysiology of severe, early onset hypertension as well as dictating perfect pharmacogenetics-led prescription \(^7\text{-}^8\). These syndromes include the Glucocorticoid Remediable Aldosteronism, Liddle’s Syndrome and pseudohypoaldosteronism type II to name just a few. In these
syndromes glucocorticoids, amiloride and thiazide diuretics, respectively are the pharmacogenetics-led prescriptions, based on our detailed understanding of the genetic pathophysiology of each syndrome. It is much more difficult to apply similar principles to the much more common primary or essential hypertension and yet the current approach of prescribing the same or nearly the same treatment for all is not sustainable long-term. The methodology, which has brought significant progress in genomics of hypertension is the genome wide association study (GWAS). In a classic GWAS thousands of patients and controls are included in a three-phase design, where data from the discovery cohort are first reproduced and then validated on separate, large cohorts of cases and controls. The GWAS requires 500,000-2,500,000 markers, known as single nucleotide polymorphisms (SNPs) with a good genome-wide coverage. The “hits” are presented in a format called a Manhattan plot with p values of $10^{-8}$ or below normally considered to achieve a genome-wide significance.

Several GWAS have been published followed by well-designed meta-analyses. The early GWAS for hypertension within the Wellcome Trust Case-Control Consortium was negative most likely due to inclusion of hypertensive subjects in the control group, although other causes such as lack of power and relatively low number (500,000) of SNPs should also be considered. The first successful GWAS meta-analysis included some 200,000 subjects and identified 29 genomic regions associated with blood pressure (BP) sub-phenotypes and hypertension as a binary trait. The contribution of each individual SNP was approximately 1 mmHg for systolic and 0.5 mmHg for diastolic BP. The weighted genetic risk scores (GRS),
which were calculated for all 29 SNPs, showed highly significant associations with coronary heart disease, left ventricular hypertrophy and stroke but not with markers of renal function. The quality and the breadth of phenotyping in these very large, multi-centre studies is not perfect, with the limited number of BP and other phenotypes used. It is possible that the relative deficiency of more difficult to measure renal biomarkers have led to weaker risk scores related to kidney function.

Further data with potential clinical significance have been generated by even larger meta-analyses published recently. In one of these studies, Surendran et al. genotyped nearly 350,000 individuals to identify 30 new blood pressure or hypertension-associated risk loci. These analyses provide insights into the pathophysiology of hypertension thus highlighting new potential for precision medicine and for druggable targets. The second study by Ehret et al. performed association analyses on 340,000 individuals and identified 66 loci; of which 17 were novel, involved in BP regulation. The 66 index SNPs combined in a risk score showed comparable effects in nearly 65,000 individuals from non-European descent. Similarly to previous studies, 66-SNP GRS was significantly associated with target organ damage in multiple tissues but with minor effects in the kidney. The third study by Liu et al. identified 31 new loci, which were enriched for known variants for cardiometabolic traits. In addition, blood pressure associations at 39 previously published loci were confirmed. These large meta-analyses have increased the number of loci associated with BP regulation to 120 with 3.5% of the trait variance now explained.
In parallel experiments, functional data of potential clinical significance have been published using smaller but perfectly selected and phenotyped cohorts. One good example here is the GWAS of blood pressure extremes, which identified variants in the uromodulin gene (\textit{UMOD}) associated with hypertension \cite{18}. The special feature of this study was the selection of 2000 so called hypercontrols, subjects who had BP below 120/80 mmHg and were free from cardiovascular events during 10 year follow-up \cite{19}. The uromodulin gene and protein are selectively expressed in the thick ascending loop of Henle (Figure 1), the part of the nephron responsible for 25% of sodium reabsorption in the kidney \cite{8,18,20,21}. Experiments with \textit{Umod} knock-out mice showed not only a highly significant BP difference between the \textit{Umod}+/+ and \textit{Umod}−/− mice but also revealed that the knock-out mice are unable to increase their BP in response to 2% NaCl \cite{21}. Trudu et al \cite{22} performed elegant experiments, which showed that \textit{UMOD} polymorphisms are associated with a differential BP response to loop diuretics (the specific blocker of the main sodium channel in the thick ascending limb of the loop of Henle, NKCC2) in patients with essential hypertension \cite{22}. GWAS studies have been fruitful in discovering novel and robust associations with common traits. However, major challenges exist in identifying causal variants and demonstrating their functional mechanisms together with clinical translation. The novel implication from studies of Padmanabhan et al \cite{18,20,21} and Trudu et al \cite{22} is that based on \textit{UMOD} rs13333226 genotype, there are two strata of hypertensive patients. The high-UMOD group (AA genotype) has increased UMOD excretion, greater salt sensitivity, hypertension, normal estimated glomerular filtration rate (eGFR) and greater BP response to loop diuretics. The low-UMOD group has decreased UMOD excretion, salt resistance increased eGFR, increased proximal tubular reabsorption of Na⁺ (possibly related to increased GFR), a poor BP response
to loop diuretics and a diminished function of NKCC2. These two contrasting strata present an opportunity for hypertension precision medicine. Volume overload is one of underlying causes for uncontrolled hypertension and yet loop diuretics, which are the most effective diuretics, are rarely used in hypertension without edema, heart failure or chronic kidney disease. A prospective genotype directed trial of a long-acting loop diuretic, torasemide in uncontrolled hypertensive patients will confirm or refute the hypothesis that the AA – high UMOD genotype patients are good responders to loop diuretics. It will simultaneously confirm that the UMOD-NKCC2 interaction is one of the mechanisms of salt-sensitivity. This precision medicine trial has been recently funded by the British Heart Foundation (CS.16/1/31878). Other areas for clinical and preclinical mechanistic studies include hepsin, the newly discovered protease that cleaves UMOD from its glycoprophosphatidylinositol (GPI) anchor, other transporters that may influence NKCC2 function – ROMK, Na+/K+ATPase or chloride channels; tubulo-glomerular feedback or other proteins. This molecular context of UMOD function is depicted in Figure 1.

Whilst this and other similar studies are in progress, it is important to recognise that in addition to generating evidence for stratified or precision therapy, it is essential to show that the stratifier demonstrates increased cost-effectiveness, and improved quality of care.

Dzau et al 25 analysed data from the Health Economics Medical Innovation Simulation, a pre-existing health simulation model, to assess the benefits and cost of personalized precision medicine innovations that would potentially improve identification and screening of presymptomatic, high risk patients. They calculated health generated value expressed as quality-adjusted life years (QALYs). The QALY
concept is being widely used in health economic modelling as it measures the effects of disease burden on quantity (life span) and quality of life. These measurements modelled over nearly a 50 year period, showed that even a 10% reduction in one of the six diseases - cancer, diabetes, heart disease, stroke, lung disease and hypertension could potentially save between $33 to $114 billion, in the form of longer and healthier lives (Figure 2). Hypertension and heart disease demonstrate the greatest value, primarily due to their high prevalence. It is clear from this modelling that with 10% incidence reduction for hypertension, the value of health is identical to similar incidence reduction in cancer. Even more striking are data that could be generated with 50% incidence reduction, where value of health for hypertension is almost double of the same value modelled for cancer. These are very important considerations for policy makers in health systems around the world.

We believe that precision medicine as applied to cardiovascular disease in general and hypertension in particular is here to stay. It will require major national and international collaborations between clinical academic centres, health systems and industry. One excellent example of such national effort is the Scottish Ecosystem for Precision Medicine (http://www.imperial.ac.uk/media/imperial-college/institute-of-global-health-innovation/Precision_Medicine_Report.pdf). Using excellent and Scotland-wide electronic health records together with highly collaborative four clinical academic centres and the National Health Service (NHS) free at the point of delivery, we are able to jointly create an excellent system to tackle multiple chronic diseases and cancer with precision medicine tools. Other examples include the UK Catapult for Precision Medicine (http://pm.catapult.org.uk) and President Obama’s Precision Medicine initiative in the United States.
In summary, the time is right for hypertension researchers to develop precision medicine tools for patients with essential or primary hypertension. These tools will be heavily based on genomics, at least initially, but there is growing evidence that other omics, including transcriptomics, proteomics and metabolomics will be increasingly used in combination with whole genome sequencing to facilitate disease stratification, early diagnostics and the precision prevention of hypertension and its complications.

**Funding**

A. Dominiczak has funding from the Scottish Ecosystem for Precision Medicine. C. Delles is funded by EU-MASCARA” (grant agreement 278249). S.Padmanabhan is funded by the MRC (MR/M016560/1, The AIM-HY Study) and the British Heart Foundation (PG/12/85/29925, CS/16/1/31878, and BHF Centre of Research Excellence Award (RE/13/5/30177, A. Dominiczak and C. Delles). MRC/BBSRC Glasgow Molecular Pathology Node (MR/N005813/1, A. Dominiczak).

**Disclosures**

Anna Dominiczak: Editor-In-Chief of Hypertension. Christian Delles and Sandosh Padmanabhan are both Hypertension Editorial Board Members.


9. WTCCC. Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. *Nature*. 2007;447:661-678.


Figure Legends

**Figure 1.** Molecular context of *UMOD* in the thick ascending limb of loop of Henle cells. *UMOD* indicates the uromodulin gene, ClC-Ka indicates chloride channel protein class Ka; Clc-Kb, chloride channel protein class Kb; E.R., endoplasmic reticulum; GPI, glycosylphosphatidylinositol; NKCC2, Na⁺ K⁺ 2Cl⁻ cotransporter 2; and ROMK, renal outer medullary potassium channel. Reprinted from “Uromodulin, an emerging novel pathway for blood pressure regulation and hypertension” by Padmanabhan et al, Hypertension 2014;64:918. Copyright 2014 by Wolters Kluwer Health. Reprinted with permission

**Figure 2.** Value of health from hypothetical personalised and precision medicine prevention innovation at two levels of incidence reduction in six diseases in the USA ($ billions). Value of health is measured in the quality–adjusted life-years (QALYs), which estimates the effects of disease burden on the quantity (life span) and quality of life. Reprinted from “Aligning incentives to fulfil the promise of personalised medicine” by Dzau et al, Lancet 2015;385:2118.Copyright 2015 by Elsevier. Health. Reprinted with permission
Cumulative value of additional quality-adjusted life-years generated (2012–60, valued at US$100,000 each)

Value of health (US$ billions)

<table>
<thead>
<tr>
<th>Disease</th>
<th>10% Incidence Reduction</th>
<th>50% Incidence Reduction</th>
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<tbody>
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<td>Cancer</td>
<td>70</td>
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<tr>
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