Use of biomarkers in the evaluation and treatment of hypertensive patients

Gemma Currie, MBChB; Christian Delles, MD*

Institute of Cardiovascular and Medical Sciences, University of Glasgow, UK

Institute of Cardiovascular and Medical Sciences
BHF Glasgow Cardiovascular Research Centre
University of Glasgow
126 University Place
Glasgow, G12 8TA
Scotland, UK

G Currie: Phone: +44 (141) 330 5189
Fax: +44 (141) 330 3360
e-mail: Gemma.Currie@glasgow.ac.uk

C Delles: Phone: +44 (141) 330 2749
Fax: +44 (141) 330 3360
e-mail: Christian.Delles@glasgow.ac.uk

* Corresponding author

Key words

Biomarkers; Hypertension; Imaging; Prevention; Pathophysiology; Target organ damage

Abstract

The current definition of hypertension is based on blood pressure values, and blood pressure also drives treatment decisions, is the most important treatment monitoring tool and helps estimating risk of hypertension related organ damage. In an era of precision medicine additional biomarkers are needed in the diagnosis and management of patients with hypertension. In this review we outline the areas in which functional, imaging and circulating biomarkers could help in a more individualised definition of hypertension and associated risk. We will cover biomarkers for diagnosis; of pathophysiology and prediction of hypertension; response to treatment, organ damage; and to monitor treatment. A clear focus is on the vasculature, the heart and the kidneys, whereas we see a need to further develop biomarkers of cerebral function in order to diagnose cognition deficits and monitor changes in cognition in the future to support addressing the growing burden of hypertension associated vascular dementia.

Introduction

Hypertension affects approximately one third of the population worldwide and its prevalence is continuously increasing [1, 2]. Hypertension is a major risk factor for cardiovascular morbidity and mortality in both sexes. Despite the availability of efficient and well tolerated antihypertensive medication for many decades the prevalence of uncontrolled hypertension remains alarmingly high [3]. Although even patients with controlled hypertension appear to be at higher cardiovascular risk than healthy control subjects, the cardiovascular risk in those with uncontrolled or difficult to control hypertension is particularly high [4].

Strategies to reduce the global burden of hypertension and associated cardiovascular diseases include primary prevention by addressing lifestyle factors, aggressive blood pressure-lowering therapy and prevention and treatment of target organ damage. In a highly prevalent condition such as hypertension a combination of broad and simple treatment aimed at all patients as well as targeted approaches aimed at individual patients appears most promising. In this review we will discuss how biomarkers can help in our understanding of the pathophysiology of hypertension, guide therapeutic approaches and monitor treatment success. We will not be able to provide a comprehensive review of all such biomarkers. Instead, we would like to give an overview of the multiple roles that biomarkers can play in hypertension and illustrate these roles with key examples.

The NIH Biomarker Definitions Working Group defines a biomarker as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention" [5]. Characteristics that derive from imaging studies or other investigations are included in this definition and are often more important in clinical practice than circulating biomarkers. Although many of the biomarkers used in hypertension simultaneously evaluate multiple aspects of disease we will discuss these aspects separately in this review (Figure).

The definition of hypertension is based on a value that can be measured: blood pressure [6, 7]. Blood pressure is indeed the universal biomarker for hypertension. It can be objectively measured, defines the condition, guides therapeutic approaches and is routinely used to assess responses to a therapeutic intervention. However, there are areas where additional biomarkers are urgently needed. For example, biomarkers can help us understand the complex pathophysiology and hence pave the way to development of novel therapeutic strategies; identify individuals requiring more intensive treatment; gauge compliance with treatment; and identify secondary forms of hypertension.

Diagnostic biomarkers in hypertension

With the definition of hypertension being based on blood pressure it is difficult to imagine which other factors could improve, redefine or even replace the current diagnostic criteria for the condition. We will draw some scenarios that highlight the shortcomings of a purely blood pressure-based definition of hypertension and how additional biomarkers could provide further insights. We will focus on primary hypertension as the role of biomarkers in the diagnosis of secondary forms of hypertension is clinically established and already part of current [7, 8].

Dimensions of blood pressure

Traditionally hypertension has been defined based on office blood pressure readings. In recent years the role of out-of-office blood pressure readings in the form of ambulatory blood pressure monitoring (ABPM) and home (self) blood pressure monitoring has been recognised [9]. More frequent blood pressure readings especially in the form of out-of-office readings allowed the recognition of blood pressure variability as a new marker of cardiovascular risk. Increased blood

pressure variability, both in the short term (as derived for example from ABPM) and in the long term (for example visit-to-visit variability) has been found to be a risk factor for cardiovascular, particularly for cerebrovascular, events independent of the level of blood pressure [10] and could be a specific therapeutic target [11]. Another novel blood pressure modality is central blood pressure. Whilst peripheral blood pressure (for example in the brachial artery where it is most commonly measured) is highly correlated with central blood pressure (*i.e.* blood pressure in the aorta and carotid arteries) in larger cohorts [12] substantial differences between central and peripheral blood pressure in individual patients have been described. A range of non-invasive devices have been developed that derive central blood pressure from peripheral readings and features of the pulse waveform, and normal values for central blood pressure have been established [13]. Nevertheless, there remains controversy surrounding use of central blood pressure in the diagnosis and treatment of hypertension [14, 15]. It is clear, however, that antihypertensive medication can have different effects on peripheral and central blood pressure [16] and assessing haemodynamic features beyond the traditional measurement of brachial blood pressure is an attractive concept for the management of hypertension.

Independent of the method of assessment the threshold for definition of hypertension is a matter of ongoing debate. Fuelled by the recognition that (apart from very low blood pressure) there is a continuous relationship between level of blood pressure and cardiovascular risk [17] and recent trial evidence of better outcomes in those treated to lower targets [18] there is now debate regarding whether the 140/90 mmHg threshold can still be recommended for diagnosis of hypertension and as a therapeutic target [19]. With limited resources available and potential risks associated with too great a reduction in blood pressure, at least in some groups of patients [20, 21], more precise diagnosis and risk stratification of individuals are warranted.

In summary, whilst hypertension continues to be defined as raised blood pressure the phenotype "blood pressure" has evolved considerably in recent years. Not all of these developments

have been integrated into clinical practice guidelines which are directed towards the vast majority of patients with hypertension who are managed in general practice. However, in an attempt to deliver individualised therapies in the future, deeper characterisation of hypertension and the phenotype "blood pressure" is required.

Biomarkers of pathophysiology

Genetic aspects and "omics"

Genetic components of hypertension have been reviewed extensively elsewhere [22].The genome remains stable throughout life and therefore offers the potential to detect increased risk already at very early stages and before disease develops. Throughout life the relationship between genotype and phenotype can be modified, for example by interaction with environmental factors [23], providing the rationale for studies into gene expression and gene regulation as biomarkers of hypertension. Transcriptomic profiles that characterise hypertension in rodent models have been established [24] and first data in human kidneys point towards differences in the expression of the gene encoding renin between hypertensive and normotensive individuals [25]. Studies into the regulation of gene expression and in particular into microRNAs are of interest in this context [26]. A recent example shows that circulating levels of miR-181a are a surrogate for renal miR-181a expression where it colocalises with renin particularly in collecting ducts and that this microRNA is differentially regulated between hypertensive and normotensive subjects [27].

There is therefore great hope that "higher" omics technologies including transcriptomics, proteomics and metabolomics will provide additional and more precise data to describe exactly the position of an individual on their path to development of disease. As yet there are, however, only limited data available that specifically address hypertension, in part because of the difficulties

disentangling blood pressure from its consequences including target organ damage. Nevertheless, some metabolites such as hexadecanedioate have been found to be differentially regulated in hypertension [28] and the potential of proteomics to impact on cardiovascular health and disease has recently been defined [29]. In specific hypertensive conditions such as pre-eclampsia a wealth of proteomic and metabolomic data are available that provide some insights into the pathogenesis that could also inform our understanding of essential hypertension and other vascular diseases [30-32].

Renal aspects and the sympathetic nervous system

There is a particularly close relationship between hypertension and renal function. Hypertension can damage the kidneys and thus affect renal function. On the other hand, any changes in glomerular filtration rate or tubular reabsorption of water and salt are associated with altered renal pressure natriuresis. Thereby a range of signalling pathways including the RAAS, the sympathetic nervous system (SNS), reactive oxygen species (ROS), the endothelin system, natriuretic hormones, inflammatory cytokines and nitric oxide are all linked to hypertension [33]. Renal function in its own right and factors contributing to renal dysfunction could play a role as biomarkers of hypertension.

In this context we would like to draw attention to the revived interest in the role of the SNS in the pathogenesis of hypertension, in part fuelled by the initially promising data on renal sympathetic denervation to treat patients with resistant hypertension [34]. There is no doubt that SNS activity is increased in patients with hypertension but conventional biomarkers such as 24-hour urinary catecholamine excretion are not suited to reliably reflect this. More sophisticated techniques such as measurement of noradrenaline spillover and of muscle sympathetic nerve activity may be required to accurately describe SNS activity although some information can derive from markers such as heart rate and plasma noradrenaline levels [35]. The disappointing results of a recent large randomised

clinical trial into renal sympathetic denervation [36] has opened discussions not only into the technical aspects of the procedure but also into identification of those patients who could benefit from sympathetic denervation. In this context biomarkers including markers of SNS activity could play a role [37] to explain why some patients experience substantial blood pressure reductions with this procedure [38].

Another recent development that is not directly related to the kidneys but challenges our concepts of the kidneys as the main player in electrolyte and in particular in sodium balance is the discovery of the skin and more generally, of the (extrarenal) interstitium as an organ that is critically involved in sodium storage and regulation [39]. Whilst opening new insights in the role of sodium in the development of hypertension and its interaction with the immune system [40] these findings also define interstitial sodium content as a new biomarker that can be measured by magnetic resonance imaging [41], is increased in hypertension [42], can be modified *e.g.* by exercise [43] and be a treatment target *e.g.* using haemodialysis in patients with end-stage renal failure [44]; thereby fulfilling all the criteria of a biomarker [5].

Markers of vascular dysfunction

The relationship between hypertension and vascular function and structure is equally strong. Again, hypertension can cause vascular damage but altered vascular function and structure are also critically involved in the pathogenesis of hypertension. This relates to both the small [45, 46] and the large vessels [46]. From a biomarker perspective vascular phenotypes are particularly attractive for the precise assessment of blood pressure, detection of hypertension-related damage and for monitoring of treatment success. However, recent developments in circulating biomarkers of vascular function should be highlighted here as they provide insights into the pathophysiology of hypertension.

Microparticles are small fragments of membrane released from eukaryotic cells that play a role as biomarkers of cell activation and stress as well as biovectors that transmit signals between cells and between organs [47, 48]. In the context of hypertension microparticles that derive from endothelial cells are of particular interest. Differences in numbers and composition of endothelial cell derived microparticles have been demonstrated between hypertensive and normotensive individuals [49] and antihypertensive and lipid-lowering therapies have been shown to change microparticle function [50]. Pre-eclampsia has been subject to a relatively large number of microparticle studies [51, 52] providing evidence for their role as mediators of the rapidly developing systemic endothelial dysfunction and hypertension in this condition. Microparticles are probably a prime example of novel biomarkers that provide insight into the pathophysiology of hypertension and vascular dysfunction but are not yet ready for clinical application. This is due to ongoing discussions about their precise definition; technical challenges related to their measurement; absence of standardised protocols; and lack of clinical data providing evidence for a role of microparticles in the management of hypertension over and above measurement of blood pressure.

There is also development in the discovery of novel vasoactive substances that could serve as biomarkers of hypertension and other cardiovascular diseases in the future. Without going into any detail we would like to highlight that advances in technology and especially in mass spectrometry have made it possible to screen for and detect such novel substances and have led to the identification of Angiotensin A [53] and more recently of Vasoconstriction-Inhibiting Factor [54] as novel players in the balance between vasoconstriction and vasorelaxation. Other factors including arginine vasopressin and its inert prosegment copeptin have been found to be associated with essential hypertension [55] and pre-eclampsia [56, 57] but the clinical relevance remains to be determined.

Oxidative stress and inflammation

In addition to principles that affect specific organs such as the kidneys or the vasculature there are pathophysiological mechanisms of a more general nature that are critically involved in the development of hypertension. The contribution of reactive oxygen species (ROS) to the pathogenesis of endothelial dysfunction but also the development of advanced structural changes such as increased vascular stiffness and atherosclerosis is well established [58]. Beyond the vasculature altered ROS production plays a crucial role in the kidneys and only recently the contribution of site specific expression of sources of ROS such as nicotinamide adenine dinucleotide phosphate reduced oxidase 5 (Nox5) in the kidneys has been recognised [59]. From a biomarker perspective ROS are attractive as oxidative stress has been found to be involved in all stages of the cardiovascular continuum, from early asymptomatic disease to advanced organ damage [60]. The comprehensive assessment of a complex phenomenon such as oxidative stress is challenging and multiple biomarkers have to be employed. There is evidence that hypertension is associated with increased levels of markers of oxidative stress that reflect different sources and actions of ROS [61] but given the complex nature of oxidative stress we do not believe that such markers add substantially to the management of patients with hypertension at this point in time. Assessment of markers of oxidative stress can, however, shed light on the mechanisms that link traditional and novel risk factors such as chronic inflammation to the development of cardiovascular diseases.

Similarly, there has been considerable progress in our understanding of the interplay between inflammation and vascular disease in recent years, and immune mechanisms are among the most promising targets for novel therapeutic approaches in hypertension [62]. Like oxidative stress, inflammation is a complex phenomenon and the immune system contains too many components to be represented fully by single biomarkers. Nevertheless, simple biomarkers of inflammation such as C-reactive protein are indeed raised in patients with hypertension; these data have been recently reviewed elsewhere [63].

Rather than going into further detail of biomarkers of oxidative stress and inflammation we would like to mention briefly the role of uric acid as biomarker of hypertension. Uric acid is an attractive biomarkers as it can be measured easily and as part of routine clinical biochemistry. Uric acid affects endothelial function by mechanisms involving oxidative stress and inflammation and the epidemiological basis for an association between raised uric acid levels and hypertension and its cardiovascular complications is robust [64-67]. Uric acid has the potential to add to risk stratification and serve as a therapeutic target. In the context of uric acid as biomarker of pathophysiology it is interesting to note that uric acid-lowering therapy in obese adolescents with prehypertension resulted in significant reductions of blood pressure and systemic vascular resistance [68]. These individuals are young and do not have established vascular disease or hypertension and the concept of interfering with a pathogenetic factor at an early stage of disease is attractive. Whether uric acid can play a role as a therapeutic target in established hypertension remains to be determined. Recent data using a propensity-matched design in adults with hypertension suggest that exposure to allopurinol indeed reduces rates of stroke and cardiac events and provide a basis for the design of prospective clinical trials [69].

Biomarkers to predict development of hypertension

It appears plausible that biomarkers associated with the pathophysiology of hypertension can provide information about development of hypertension in individuals who are (still) normotensive. A cluster of clinical risk factors including diabetes, obesity and smoking are known to be associated with a higher risk of developing hypertension [70] but additional biomarkers could help to restratify this risk and identify those who could benefit most from strategies of primordial prevention. First and foremost one might think of genetic factors, and as outlined above there is some potential that genomic information could identify those at higher risk – with the caveats of gene-environment

interaction and modulation of transcription and translation by other factors to be taken into account.

Within the circulating biomarkers and biomarkers in urine there are data on a cluster of markers including C-reactive protein, fibrinogen, plasminogen activator inhibitor-1, aldosterone, renin, B-type natriuretic peptide, N-terminal proatrial natriuretic peptide, homocysteine and urinary albumin:creatinine ratio that are associated with incident hypertension [71]. Other studies have found associations between incident hypertension and parathyroid hormone [72], cardiac troponin T [73], plasma bicarbonate [74], uric acid [75], insulin sensitivity [76], lipoprotein particle size and subclass concentration [77] and vitamin D [78] – to name a few.

Clearly these associations are of interest but most of the above data require further replication and validation in independent cohorts. And even if confirmed, the therapeutic options to prevent hypertension are currently limited. Studies in patients with prehypertension have shown that pharmacological treatment can delay the onset of overt hypertension [79, 80] but true primordial prevention is currently out of reach. It is possible, however, that precise definition of altered biomarker profiles in individual patients can identify dysregulated pathways which could be subject to specific preventative therapies instead of the currently employed "general" antihypertensive agents.

Biomarkers to predict treatment response

The effect of individual antihypertensive agents in patients with hypertension is difficult to predict. Whilst overall systolic blood pressure reductions of 5 to 10 mmHg per antihypertensive agent can be expected the individual response varies. Biomarkers could help to predict blood pressure response and thereby avoid cycling through classes of antihypertensive agents in order to

find the right drug for a given patient. A very simple algorithm based on age and ethnic background of a patient remains the foundation of the National Institute for Health and Care Excellence (NICE) guidelines in the UK [https://www.nice.org.uk/guidance/cg127. Accessed 12 March 2016]. Age and ethnicity serve as surrogates for renin and thereby RAAS activity and allocate RAAS blockers to those in whom the system is more active [81]. This crude strategy has recently been confirmed in the PATHWAY-2 Trial where the blood pressure-lowering effect of spironolactone was greatest in patients with high levels of plasma renin [82].

Other strategies to predict treatment response are based on haemodynamic profiles and basically address the fact that vasoconstriction and cardiac output/volume overload contribute to varying extents across patients with hypertension and could direct therapy preferentially to vasodilators and diuretics, respectively. Small and short-term studies have shown that an individualised treatment with antihypertensive agents tailored towards haemodynamic profiles can improve blood pressure control [83] or reduce adverse events at similar blood pressure control compared to conventional treatment algorithms [84].

Some elements of individual responses to antihypertensive therapy will be independent of the current state of the organism and can be predicted by genetic factors. However, unlike other cardiovascular conditions where pharmacogenetic studies have demonstrated genetically determined differences in the metabolism and thereby efficacy of *e.g.* clopidogrel and warfarin [85], pharmacogenetics currently plays less of a role in hypertension. Antihypertensive agents are generally well tolerated, affect multiple pathophysiological principles and are thereby less likely influenced in their action by specific genetic variants. Some evidence for specific gene variants being associated with blood pressure-lowering effects have, however, already been reported [86], and whether other genetic variants such as those in the *UMOD* gene predict treatment response will have to be subject of future clinical studies. A promising concept to identify people who more likely

respond to certain classes of antihypertensive lies in the study of associations between treatment response and a large number of genetic variants in the sense of pharmacogenomics [87, 88].

Biomarkers to assess complications of hypertension

There is a continuous relationship between BP and cardiovascular events [17]. In contrast, the correlation between level of blood pressure and level of organ damage, *e.g.* degree of increased left ventricular mass, is less close than expected given the causal relationship between blood pressure and left ventricular hypertrophy [89]. Additional biomarkers therefore offer the potential to reclassify individuals especially in the intermediate risk categories into higher or lower risk of organ damage than estimated from blood pressure alone. Providing information independent of blood pressure and other risk factors is one of the key requirements for a biomarker that could serve as risk stratification tool. A recent example specifically in the area of hypertension is the above mentioned finding that blood pressure variability is an independent risk factor particularly for stroke – independent of the level of blood pressure [10]. Similar data exist for vascular phenotypes such as arterial stiffness [90] and circulating biomarkers [71] although the latter only moderately improve prediction of events compared to traditional risk factors including blood pressure.

It would be beyond the scope of this paper to comprehensively review the assessment of target organ damage in people with hypertension. Instead, we would like to focus on assessment of early stages of hypertension-related organ damage including subclinical vascular, cardiac and renal phenotypes and mention briefly the cerebral consequences of hypertension. We will not systematically review the state-of-the-art but rather point towards some of the recent developments (Table).

Vascular damage

There is agreement in clinical guidelines that assessment of vascular structure and function has the potential to support risk estimation and to guide therapeutic decisions [7]. It is often a cascade from endothelial dysfunction as the earliest marker of vascular damage to increased vascular stiffness and atherosclerotic burden that describe a continuum of changes in the vasculature in response to hypertension. In turn, these changes can also develop in parallel with increased blood pressure or even contribute causally to its development. Statements outlining clinical characterisation of vascular phenotypes comprehensively [91] or focussing on specific aspects such as endothelial dysfunction [92] are available. Advanced phenotyping techniques such as pulse wave analysis or measurement of pulse wave velocity do not yet play a role in clinical practice although they may help in the assessment of individual patients with difficult-to-control hypertension [38].

We would like to take the opportunity to highlight two recent developments that have the potential to change the assessment of vascular function in the future. First, there has been considerable progress in the development of tools to characterise the retinal microvasculature. Where traditional methods such as fundoscopy or simple retinal photography only provide information on vascular structure there are now techniques such as Scanning Laser Doppler Flowmetry that can within seconds assess structure [93] but also provide information on perfusion and changes in perfusion in response to experimental stimuli such as nitric oxide synthase inhibition or pharmacological treatment [94]. It remains to be determined whether such tools will be available for screening of patients with hypertension in the future and whether they will provide information in addition to traditional fundoscopy and inform treatment decisions.

Second, although a large number of circulating biomarkers are available that provide information about certain aspects of vascular function and structure there is clearly no single biomarker that assesses the state of the vasculature comprehensively and can thereby routinely

inform clinical practice. Markers of endothelial cell function and activation such as E-selectin [95] and fibrinogen [96] and markers of inflammation such as C-reactive protein [95, 97] have all been found to be related to some but not all vascular properties and they cannot replace other tools in research or clinical practice [98]. There is hope, however, that novel large-scale biomarker experiments based on proteomics and metabolomics can lead to more comprehensive insights into the vasculature by assessing and integrating the information from hundreds and thousands of features (peptides, proteins, metabolites) [29]. We have recently described the vascular proteome of a diabetic mouse model [99] and are currently working on the integration of preclinical and clinical proteomic data in order to develop novel biomarkers of vascular disease that could be applied to patients with hypertension [http://www.sysvasc.eu. Accessed 12 March 2016] and similar activities are underway in other laboratories [29].

Cardiac damage

Whilst cardiac conditions can cause changes in blood pressure, high blood pressure also affects the heart. Among the subclinical changes in cardiac function and structure are impaired diastolic filling of the left ventricle and left ventricular hypertrophy, respectively. Especially for the latter there is evidence that it is an independent risk factor for cardiovascular events [100], can respond differently to different blood pressure lowering agents [101] and can be a treatment target in its own right [102, 103]. Screening methods with ECG based indices of left ventricular hypertrophy are commonly recommended [7] whereas more sophisticated methods that involve echocardiography or cardiac magnetic resonance imaging (MRI) require expert skills and are relatively costly.

This is where circulating biomarkers could play a role in early detection of cardiac damage. There is evidence for markers of collagen turnover [104], brain natriuretic peptides [105-107] and

cardiac troponins [107] to be associated with cardiac damage and/or adverse outcome independently of blood pressure but the incremental value over blood pressure, traditional risk factors and simple screening tests such as ECG currently appears too small to justify their use in routine clinical practice. Multidimensional biomarkers that are based on omics techniques have again the potential to overcome the limitations of single biomarkers and there is already some evidence that proteomic signatures associated with early functional cardiac changes are predictive of development of overt heart failure [108]. Clearly such approaches are not yet ready for the clinic but with technology developing so rapidly omics based biomarkers may not only get more precise but also less expensive in the near future [29].

Renal damage

Guidelines recommend serum creatinine and estimated glomerular filtration rate to assess renal excretory function and urinary albumin excretion as biomarker of (early) renal damage [7], and there is evidence that cystatin C could provide additional information also with regard to cardiovascular and risk prediction [109]. These are well established screening tools but as with all screening markers there is a balance between sensitivity and specificity that cannot be optimal for both. Neither are these markers specific for hypertension-related renal damage nor are they sensitive enough to detect the very early stages of renal disease. Whilst this may not be a problem for the majority of patients with uncomplicated hypertension there are patients where more detailed information about renal function is required.

Novel imaging biomarkers such as MRI based arterial spin labelling (ASL) [110] and Blood Oxygenation Level-Dependent (BOLD) MRI [111] provide deep insight into renal perfusion and oxygenation, respectively, that have the potential to inform diagnostic and therapeutic decisions. The future will show whether such tools will play a role in the management of patients with

hypertension or whether they will remain restricted to research applications or to primary kidney disease. The possibility to use BOLD MRI for the diagnosis of renal artery stenosis [112], however, demonstrates how such techniques could find their way into clinical practice in hypertension.

Similarly, out of the large number of circulating biomarkers of that have for example been studied in diabetic nephropathy [113] none currently play a role in clinical practice in hypertension. It is again the perspective to miniaturise (multiplex) such assays in order to provide a comprehensive characterisation of an individual patient's renal phenotype that could be important in future precision medicine. And as above, proteomic approaches in plasma [114] and urine [115] have yielded first promising results that may extend to early detection of renal damage, prediction of progression rate of renal failure and monitoring of therapeutic approaches [116].

Cerebral damage

Most of the efforts in hypertension management have focussed on acute cerebral events, where the association between blood pressure and stroke is epidemiologically robust [17], pathophysiologically evident [117] and may have therapeutic consequences regarding the choice of the best antihypertensive agents for at-risk patients [118]. In recent years an additional focus on the association between blood pressure and cognition has developed, and strategies to reduce the increasing prevalence of dementia are urgently needed. Epidemiologic evidence points towards an association between hypertension and cerebral microvascular damage that is a surrogate of vascular dementia [119]. It appears plausible that appropriate blood pressure control can reduce the damage to the cerebral vasculature and thus help to combat dementia [120]. However, especially in the elderly tight blood pressure control can be associated with side effects including falls [21] and cerebral hypoperfusion [121] that pose challenges on antihypertensive therapy.

Biomarkers to identify early stages of cerebral damage are urgently needed. The gold standard methods of assessing white matter lesions by MRI [122] and positron emission tomography [123] are associated with high costs and is restricted to specialist centres and therefore not suitable as screening and monitoring tool. In recent years, a number of surrogate biomarkers of white matter lesions, altered cerebral perfusion and cognitive decline have been studied but despite being a global health challenge this area of research is still underdeveloped. There is, however, evidence on a correlation between aortic stiffness and cognition [124] and advanced retinal imaging may provide deep insight into the cerebral microvasculature [94, 125]. Out of the circulating biomarkers we would just like to highlight recent findings on the correlation between ubiquitin C-terminal hydrolase-L1 levels and cerebral white matter lesions [126] and specifically in hypertension, circulating vascular cell adhesion molecule-1 can provide information on cerebral blood flow and may be identify those at highest risk of falls [127]. Of all possible organ damage related with hypertension we see the most urgent need for studies into biomarkers of cognition where available data that could inform therapeutic decisions are lacking behind the rapid increase in prevalence of dementia.

Biomarkers to monitor therapy

Blood pressure is not only the universal biomarker of hypertension it is also the target of therapeutic approaches in patients with hypertension. Lowering blood pressure has been found to reduce cardiovascular risk [128, 129]. This effect is largely independent of the individual factors contributing to the pathogenesis of hypertension, and even in patients with secondary forms of hypertension stenosis unspecific blood pressure lowering therapy confers survival benefit compared to no treatment.

We expect that blood pressure reduction will remain the main goal of antihypertensive therapy in the foreseeable future. However, there may be opportunities for “disease modifying” therapies that address specific pathophysiological factors such as inflammation and oxidative stress that require careful characterisation and monitoring based on biomarker profiles. Such treatments would then not in the first instance address the symptom “blood pressure” but counteract the primary causes of hypertension and thereby lead to reduction of blood pressure in the longer term. Such effects have already been shown in patients with autoimmune diseases treated with anti-inflammatory agents such as infliximab [130]. Similarly, it may be possible in patients with hypertension to focus on prevention of organ damage for example by introducing specific cardioprotective therapies leading to regression of left ventricular hypertrophy independent of blood pressure. It will be difficult to prove a clinical benefit of such strategies and to dissect blood pressure lowering effects from organ specific effects of therapeutic agents but if at any point in the future such strategies will be tested it is clear that biomarkers will play a crucial role in characterisation and monitoring of patients.

Conclusions

Blood pressure is currently the best biomarker in the management of patients with hypertension but provides no insights into the pathogenesis, extent of hypertension-related organ damage and may not be the best tool to monitor therapeutic success. Novel imaging modalities and circulating biomarkers as well as better understanding of blood pressure modalities such as central blood pressure and blood pressure variability will in the future help to individualise preventative and therapeutic strategies in patients with hypertension. Blood pressure will not be replaced by other biomarkers of hypertension in the foreseeable future but could be complemented by biomarkers that provide additional information and this inform more precise medicine.

Acknowledgements

Our work is supported by collaborative project grants from the European Commission "EU-MASCARA" (grant agreement 278249), "sysVASC" (grant agreement 603288), "HOMAGE" (grant agreement 305507) and "PRIORITY" (grant agreement 279277). Icons in the figure were made by Freepik from www.flaticon.com.

Table

	Imaging / Structure	Imaging / Function	Circulating
Vascular	**Carotid Ultrasound** Pulse wave velocity **Retinal imaging / fundoscopy**	Flow-mediated dilatation Peripheral arterial tonometry Pulse wave analysis Pulse wave velocity Retinal Scanning Laser Doppler Flowmetry	Adhesion molecules Markers of inflammation Markers of collagen turnover Markers of oxidative stress
Cardiac	**Echocardiography** Cardiac MRI	**Echocardiography** Cardiac MRI **ECG**	**Cardiac troponins** **Natriuretic peptides** Markers of collagen turnover Proteomic markers
Renal	**Ultrasound** **MRI** **MR angiography**	**Doppler Ultrasound** Arterial spin labelling MRI Blood oxygenation level dependent MRI	**Albuminuria** **Serum creatinine /eGFR** Cystatin C Proteomic markers
Cerebral	MRI	MRI	Adhesion molecules

	Positron emission tomography	Markers of neuronal damage
	Cognitive function tests	

Examples of biomarkers to assess hypertension associated damage of the vasculature, the heart, the kidneys and the brain. Markers in **bold** are currently recommended for clinical use whereas markers in regular font are mainly used in research and are not in general clinical care of patients with hypertension. ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; MR, magnetic resonance; MRI, magnetic resonance imaging.

Figure legend

Transition from normal blood pressure to hypertension and hypertension associated organ damage.

The figure illustrates factors involved in the pathogenesis of hypertension and the effects of hypertension on the vasculature, heart, kidneys and the brain. Being primarily a vascular disorder, there is overlap between the effects on organs. For example cerebrovascular disease / stroke and dementia could feature both under vascular and cerebral damage. Biomarkers described in this review can inform all steps in this figure from explaining pathophysiology to assessment of organ damage and provide tools to direct preventative and therapeutic approaches.

BP, blood pressure; cIMT, carotid intima-media thickness; CKD, chronic kidney disease; CV, cardiovascular; EF, ejection fraction; ESRD, end-stage renal disease; LVH, left ventricular hypertrophy; RAAS, renin-angiotensin-aldosterone system; TIA, transient ischaemic attack.

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