Review Article

Historical, present, and emerging biomarkers in hypertension: a narrative review

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Background and Objective: Hypertension is the leading risk factor for morbidity and mortality worldwide and it is projected that by the year 2025, 1.5 billion adults across the globe will have hypertension. This review will discuss the evidence and applicability of numerous blood biomarkers studied (historical, present, and emerging) to better understand the pathophysiology, diagnosis, progression, therapeutic modalities, and efficacy of hypertension.

Methods: We utilized internet-based search engines including PubMed, Google scholar, and EBSCO to identify articles of interest. The search was conducted starting between January 1, 2022 to July 30, 2022 and included all publications in English. The last database search was performed on July 30, 2022. A combination of the following MeSH terms were used: "biomarkers, hypertension", "hypertension", "genetic, epigenetic biomarkers", "biomarkers in hypertension". We used studies of multiple designs including basic science research, as well as prospective and retrospective cohort clinical studies.

Key Content and Findings: Several hypertension-related biomarkers have been proposed and examined over the decades. These include components of the renin-angiotensin-aldosterone system (RAAS), such as plasma renin activity (PRA) and aldosterone, and components of the sympathetic nervous system, such as norepinephrine. Components of either or both systems are logical biomarker candidates since they play a significant role in the physiology of blood pressure regulation and the pathophysiology of hypertension. Other biomarkers studied include the albumin/creatinine ratio, a measure reflecting renal function/dysfunction, C-reactive protein (CRP), a measure reflecting inflammation, and pro-brain natriuretic peptide, a measure reflecting cardiac function and sodium and water homeostasis. Lastly, we included emerging biomarkers including adrenomedullin, and genetic/epigenetic biomarkers. While no biomarker has been found which can be applied to all patients with hypertension, their use in specific cases, particularly in the assessment of global cardiovascular risk is promising.

Conclusions: In the future, emerging biomarkers such as members of the calcitonin gene-related peptide (CGRP) superfamily such as adrenomedullin and CGRP, as well as others currently in early research stages may help in the identification of persons at heightened risk for the development of hypertension and/or those with hypertension who may be at higher risk for target organ damage. In addition, the use of biomarkers could assist in monitoring responses to non-pharmacologic and pharmacologic treatment in those with newly diagnosed and established hypertension.

Keywords: Biomarkers; hypertension; pathophysiology

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Introduction

Hypertension is the leading risk factor for morbidity and mortality worldwide (1), and by the year 2025, it is projected that 1.5 billion adults across the globe will have hypertension (2). Beyond the significant disease burden associated with hypertension, there is a sizable economic impact, the true value of which is difficult to precisely measure. For these reasons, continued efforts to identify strategies to prevent and adequately manage hypertension are of top priority.

Traditionally, hypertension has been defined in terms of sustained derivations in blood pressure beyond the norm. While the specific blood pressure threshold at which hypertension is defined is based on the measured systolic and diastolic blood pressure (mmHg), the blood pressure threshold for the diagnosis of hypertension varies based on the specific hypertension guideline used. The most used diagnosis of hypertension in adults without known cardiovascular disease, diabetes mellitus, chronic kidney disease, or high cardiovascular risk is sustained blood pressure greater than or equal to 140 mmHg systolic or 90 mmHg diastolic. It is well established that chronic elevations in blood pressures translates to an increased risk of cardiovascular complications and death (3).

While conventional practice focuses heavily on blood pressure, blood pressure alone may not universally address other relevant questions or factors necessary for the effective and individualized treatment of hypertension. Specifically, blood pressure alone may fail to recognize and predict pre-existing, imminent, or incident hypertension-induced end-organ damage. One potential method to help augment our perception of risk associated individuals with hypertension is the use of existing and emerging biomarkers.

In the clinical context, a biomarker is a measurable indicator of some biological state or condition which may correlate with a patient's clinical symptoms, diseased diagnosis, and or disease progression and outcomes. Some specific biomarkers have been recognized as predictors of relevant clinical outcomes such as brain natriuretic peptide for detecting heart failure exacerbations and troponin for detecting myocardial infarctions (4-7). Multiple biomarkers for hypertension have been studied over the past years and some may shed light on the underlying processes involved in the development and progression of hypertension. However, to date, many of these biomarkers have not received widespread acceptance or become part of everyday clinical practice. While many of these biomarkers are related to hypertension some of their derangements may represent conditions that may produce hypertensive states such as renal failure, diabetes mellitus, or conn syndrome. However, given the increasing prevalence of hypertension and its disease burden globally, it is time to re-examine this approach.

In this narrative review, we will discuss the evidence and applicability of numerous clinical blood and urinary biomarkers studied (historical, present, and emerging) to better understand the pathophysiology, diagnosis, progression, therapeutic modalities, and efficacy of hypertension which is summarized in *Table 1*. We present the following article in accordance with the Narrative Review reporting checklist (available at https://jlpm.amegroups.com/article/view/10.21037/jlpm-22-27/rc).

Methods

We utilized internet-based search engines including PubMed, Google scholar, and EBSCO to identify articles of interest. The search was conducted starting between January 1, 2022 to July 30, 2022 and included all publications in English. A combination of the following MeSH terms were used: "biomarkers, hypertension", "hypertension", "genetic, epigenetic biomarkers", "biomarkers in hypertension". Based on the title and abstract, articles were selected and after reading the full texts and assessing the quality of the texts, we eventually ended up including them on this topic. Articles were restricted to those published in English irrespective of the date of publication if the publication was deemed to be of high clinical or historical relevance. We used studies of multiple designs including basic science research, as well as prospective and retrospective cohort clinical studies. The quality of the studies was assessed by three researchers (HM, JS, and DJD) (*Table 2*).

Historical and established biomarkers in hypertension detection, treatment, and prognosis

Several hypertension-related biomarkers have been proposed and examined over the decades. Some established biomarkers include components of the renin-angiotensin-aldosterone system (RAAS), such as plasma renin activity (PRA) and aldosterone, and components of the sympathetic nervous system, such as norepinephrine. Components of either or both systems are logical biomarker candidates since they play a key role in the physiology of blood pressure

Table 1 Individual biomarkers and the diagnostic and therapeutic roles they play in EH

Biomarkers	Diagnostic value	Therapeutic implications
Present biomarkers		
PRA	Allows identification of hypertension subtypes of low renin and high renin hypertension	Low renin hypertension may respond better to diuretics or calcium channel blockers, whereas high renin hypertension may respond better to RAAS blockers, such as angiotensin converting-enzyme inhibitors or ARBs when each agent is used as monotherapy
Aldosterone	Identifies hypertension with suppressed PRA and inappropriately high aldosterone levels, such as in primary or secondary hyperaldosteronism	Suppressed PRA and high aldosterone hypertension may respond better to MRA, such as spironolactone
Norepinephrine	Allows identification of hypertension mediated by increased sympathetic nervous activity	Due to paucity of data on its predictive and prognostic value, routine measurement of norepinephrine in hypertension is not commonplace except when the diagnosis of pheochromocytoma is suspected
Historical biomarkers		
Albumin/creatinine ratio	Allows identification of individuals at risk for hypertension and/or renal disease	Further studies are needed to determine the applicability in everyday practice however measurement of UACR has shown promising results in the identifying individuals at the highest risk of developing hypertension and to be beneficial in the overall risk of the development and/or progression of renal disease in hypertension and diabetes
Markers of inflammation (CRP and IL-6)	Allows identification of individuals at risk for hypertension	Due to paucity of data on the predictive and prognostic value, routine serologic measurement and therapeutic implication of CRP and IL-6 are not commonplace in patients with hypertension
PAI-1	Several studies have shown that PAI-1 levels precede the onset of hypertension which could be used in identification of individuals at risk for hypertension	Further studies are required to fully understand the therapeutic implications
Emerging biomarkers		
Adrenomedullin	Allows identification of individuals at risk for hypertension and response therapy	Higher serologic levels of adrenomedullin are found in patients with vascular failure and should be considered as a target for testing and therapy of hypertension, however, further prospective studies are needed to confirm this applicability
CGRP	Further studies are required to fully understand the diagnostic implications of CGRP in hypertension	Currently, CGRP antagonist therapy is only used in the treatment of migraine. Further studies are required to fully elucidate the usefulness of CGRP as an agonist as a novel therapeutic agent for cardiovascular disorders including hypertension
Hs-cTnT	Identifies individuals at risk for hypertension	Higher serologic hs-cTnT is associated with hypertension and risk of left ventricular hypertrophy which allows identifying individuals at risk for hypertension and offering the opportunity for more intensive preventive and/or earlier pharmacologic treatment strategies
NT-proBNP	Allows risk stratification and monitoring of therapeutic response in patients with hypertension	Patients with high NT-proBNP are at risk for hypertension and successful blood pressure treatment reduces NT-proBNP which subsequently lowers the risk of cardiovascular disease

Table 1 (*continued*)

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Biomarkers	Diagnostic value	Therapeutic implications
AGT	Several haplotypes of *AGT* gene were found to have association with hypertension pathogenesis however further studies are needed to fully elucidate specific haplotypes that would be used in general population	Further studies are required to fully understand the therapeutic implications
NPPA	Polymorphisms of coding gene for NPPA has been associated with the susceptibility to hypertension however further prospective studies are needed to associate which NPPA SNPs are truly related to hypertension	Further studies are required to fully understand the therapeutic implications
SCNN1A	Several studies showed a significant association of *SCNN1A* marker rs13306613 with diastolic blood pressure and *SCNN1B* marker rs12447134 with systolic blood pressure however further studies are needed to identify the true causal variants	Further studies are required to fully understand the therapeutic implications
ADRB2	Further research is still warranted to elucidate the role of the multiple polymorphisms within the *ADRB2* gene in the mechanism of hypertension and its diagnostic values	Further studies are required to fully understand the therapeutic implications
miRNAs	Further studies are required to fully understand the diagnostic implications of miRNAs in hypertension	Further studies are required to fully understand the therapeutic implications

EH, essential hypertension; PRA, plasma renin activity; CRP, C-reactive protein; IL-6, interleukin 6; PAI-1, plasminogen activator inhibitor-1; CGRP, calcitonin gene-related peptide; hs-cTnT, high-sensitivity cardiac troponin T; NT-proBP, N-terminal pro-B-type natriuretic peptide; AGT, angiotensinogen; NPPA, natriuretic peptide A; SCNN1A, sodium channel epithelial 1 subunit alpha; ADRB2, β2-adrenergic receptor; miRNAs, microRNAs; SNPs, single-nucleotide polymorphisms; RAAS, renin-angiotensin-aldosterone system; ARBs, angiotensin receptor blockers; MRA, mineralocorticoid antagonists; UARC, urinary albumin/creatinine ratio.

Table 2 The search strategy summary

Items	Specification
Date of search	January 1, 2022 to July 30, 2022
Databases and other sources searched	PubMed
Search terms used	("Biomarkers" [MeSH]) AND "hypertension" [MeSH]
	"Hypertension" [MeSH]
	("genetic" [MeSH]) AND "epigenetic" [MeSH] ("biomarkers" [MeSH]) AND "hypertension" [MeSH]
	"Biomarkers in hypertension" [MeSH]
Timeframe	May 5, 1974 to September 14, 2021
Inclusion and exclusion criteria	Articles were restricted to those published in English irrespective of the date of publication if the publication was deemed to be of high clinical or historical relevance. We used studies of multiple designs including basic science research, as well as prospective and retrospective cohort clinical studies
Selection process	It was conducted independently by Hata Mujadzic, Jamario Skeete, Donald J. DiPette; data selection is the intersection of the search of three authors

regulation and the pathophysiology of hypertension. While no biomarker has been found which can be applied to all patients with hypertension, their use in specific cases, such as in resistant hypertension patients where evaluation for hyperaldosteronism or pheochromocytoma is well known. Other historical biomarkers studied include the urinary albumin/creatinine ratio (UACR), a measure reflecting renal function/dysfunction and the serologic agents C-reactive protein (CRP). While these biomarkers are commonly used in other diseases, they were historically thought to be of use as biomarkers in hypertension. In this narrative review we will discuss the evidence and applicability of some of the most studied biomarkers (historical, present) to better understand the pathophysiology, diagnosis, progression, therapeutic modalities, and efficacy of hypertension.

Present biomarkers

PRA

The RAAS plays a crucial role in regulating renal, cardiac, and vascular physiology, as well as blood pressure homeostasis. Numerous common pathologic conditions are caused by its activation, including hypertension, heart failure, and kidney disease (8). After renin cleaves the substrate angiotensinogen (AGT), it releases angiotensin I, an inactive peptide. The endothelial angiotensin-converting enzyme (ACE) present in the lung converts angiotensin I into angiotensin II. Angiotensin II is activated by ACE which leads to vasoconstriction and sodium retention, resulting in an increase in blood pressure.

PRA, a clinical marker of renin levels, is a biomarker that has been studied for several decades in regard to pathologic, prognostic, and therapeutic implications in individuals and populations with hypertension. From a pathogenic standpoint, PRA levels can be used to divide hypertension into two categories; low renin or high renin hypertension (9). Of these two categories, low renin hypertensive states seemingly have more diagnostic implications, and may point to the presence of sodium/salt sensitivity of blood pressure as well as conditions such as resistant hypertension, primary hyperaldosteronism, Liddle syndrome, congenital adrenal hyperplasia, and other less common disease states.

Importantly, PRA has been used to predict the blood pressure response to specific single medication (monotherapy) pharmacologic anti-hypertensive treatment options. Laragh *et al.* described that patients with hypertension with a PRA <0.65 ng/mL/hour (low renin, salt-sensitive hypertension) have predominantly sodium/volume-dependent hypertension and are likely to respond with a greater blood pressure reduction to diuretics (later calcium channel blockers as well), whereas those with PRA ≥0.65 ng/mL/hour (high renin, salt-resistant hypertension) have predominantly vasoconstriction-dependent hypertension and would likely respond better to RAAS-inhibitors that either block angiotensin II formation (ACE inhibitors), block its action [angiotensin receptor blockers (ARBs)], or decrease renal renin release (β-blockers) (10). However, Weintraub *et al.* in their post hoc analysis of the ValVET study showed that PRA is not a useful diagnostic or therapeutic guide in elderly hypertension individuals due to wide variations in baseline values and complex responses to therapy (11). Lastly, the more recent study of Mehanna *et al.* assessed the PRA's clinical utility after categorizing baseline PRA (12). They found that Americans of European ancestry with PRA <0.65 ng/mL/hour had a greater decrease in systolic blood pressure to chlorthalidone than metoprolol (by −15.9 mmHg, P<0.0001), whereas those with PRA ≥0.65 ng/mL/hour had a greater decrease in systolic blood pressure to metoprolol than chlorthalidone (by 3.3 mmHg, P=0.04). Based on this data, it could be deduced that PRA could predict the systolic blood pressure response to certain therapeutic strategies among Americans of European ancestry. However, this association between systolic blood pressure and PRA was not observed among Americans of African ancestry, thereby limiting its universal applicability. Further complicating the use of PRA in pharmacologic anti-hypertensive therapy is the observation that once two anti-hypertensive agents from complementary pharmacologic classes are used together for example a RAAS (ACE inhibitor or ARB) inhibitor and a thiazide or thiazide-like diuretic or calcium channel blocker, the blood pressure is lowered equally in hypertensive individuals with low or high PRA levels and in patients across wide demographic populations such race, ethnicity, sex, salt-sensitivity, and age. As such, further prospective studies are needed to evaluate the use of this biomarker to initiate or intensify blood pressure therapy and to better define whether its use in clinical practice would be useful (12).

Aldosterone

Mineralocorticoids like aldosterone, a component of the RAAS, play a vital role in blood pressure hemostasis but also may be associated with the pathogenesis of hypertension in some individuals through abnormally elevated levels of

aldosterone through its direct tissue effects and/or resultant salt and water retention.

As a trigger for aldosterone production and renin, under normal physiologic conditions exhibit a linear relationship between both. However, deviations in this relationship (blood aldosterone: renin ratio), provide information about pathophysiologic causes of hypertension and allows the selection of appropriate therapeutic interventions, in appropriate instances. There is a subset of hypertensive individuals who fail to experience the anticipated changes in aldosterone when changing their sodium intake. In such individuals, diuretics are less effective than ACE inhibitors (RAAS inhibition) because they have normal/high renin levels. In others with suppressed PRA and high aldosterone levels, such as in primary or secondary hyperaldosteronism including resistant hypertension, may respond better to mineralocorticoid antagonists (MRA), such as spironolactone.

In patients with essential hypertension (EH), aldosterone testing is not yet proven to be a biomarker for initiation or intensification of blood pressure therapy. In a recent study by Wang *et al.* has shown that increased serum aldosterone levels do predispose to the development of hypertension which is associated with direct vascular effects as well as sodium retention and/or undetected primary hyperaldosteronism (13). However, in their follow-up study which included 1,456 non- hypertensive individuals with the strongest association of hypertension risk and characteristics of a biomarker approach to predict hypertension, the association between serum aldosterone and incident hypertension was not significant after adjusting for other factors such as UACR, CRP, and plasminogen activator inhibitor-1 (PAI-1). This suggests interactions of aldosterone and other processes including other potential single biomarkers or co-biomarkers. Given this data, a better strategy may be that rather than looking at biomarkers individually, having a multi-biomarker score may predict hypertension with better sensitivity as well as specificity (13). This approach has been used with success in examining multiple cardiovascular risk factors to determine overall cardiovascular risk, for example.

Norepinephrine

With our evolving understanding of the pathologic basis of hypertension, the increasing role of the sympathetic nervous system, through its neurotransmitters, such as norepinephrine, have been considered as potential biomarkers has been investigated. Despite such investigation and study, there are still controversies about whether an actual causal relationship exists between hypertension and norepinephrine.

It is known that sympathetic stimulation is a trophic factor for vascular hypertrophy (14). Consequently, some individuals, particularly those who are young as well as those who experience frequent surges in sympathetic activity may develop hypertension due to vascular remodeling and sustained increased peripheral resistance (15). Additionally, norepinephrine has been implicated in the development of salt-sensitive hypertension due to activation of the sodium chloride cotransporter in the kidneys in some animal models (16).

For these reasons, norepinephrine has been examined as a potential biomarker for the prediction of hypertension. However, the data to support this hypothesis is mixed, with there only being a few studies assessing the predictive power of elevated norepinephrine levels in the development of hypertension, with varying conclusions. On one hand, Böhm *et al.* (17) found that subjects who later developed hypertension had higher resting plasma norepinephrine levels compared with those who remained normotensive during a 7-year follow-up. This association was also noted in long-term studies Flaa *et al.* (18). On the flip side, one study that assessed mental stress-induced blood pressure response together with plasma norepinephrine levels found a relatively weak prediction with future elevations in blood pressure after a follow-up period of 2.5 years (19). Given the paucity of data on the predictive and prognostic value of norepinephrine in the management of hypertension, the routine measurement of norepinephrine or its metabolites is not commonplace in persons with hypertension.

Historical biomarkers

Albumin/creatinine ratio

In the evaluation of hypertension patients, the UACR may play an important role as a biomarker. Using 6,205 normotensive subjects, Takase *et al.* examined whether urinary albumin could predict the development of hypertension and future increases in blood pressure (20). To determine urinary albumin to creatinine concentrations, urine samples were collected. In this study, subjects were followed for a median of 1,089 days after baseline examination to determine whether hypertension developed. At baseline, urinary albumin was in the normal range

(UACR <30 mg/g Cr) in most subjects (97.5%). A total of 1,184 subjects (19.1%) developed hypertension during the follow-up period. It is noteworthy that the authors found the UACR to be an independent predictor of future increases in systolic blood pressure (P<0.01) (20). Another prospective study examined 1,173 individuals without hypertension were at baseline [2005–2008] and again during a follow-up period [2008–2011]. The subjects were classified according to baseline UACR tertiles. During an average of 2.6 years of follow-up, subjects in the higher tertiles of UACR had a higher risk of incident hypertension than those in the lower tertiles (21).

Lastly, a recent study involving 412 normotensive individuals, has shown that subjects with increased UACR (≥5 mg) had a higher risk of incident hypertension than did those with low UACR (<5 mg), irrespective of their backgrounds (22). As a result of this study, it was found that a slight increase in urinary albumin excretion might be a risk factor for hypertension in a community-based Japanese population (22). Furthermore, other studies have found that subclinical abnormalities in the kidneys or endothelium may precede progression to higher blood pressure stages (13,21,23). It will take further studies to determine whether the measurement of UACR, alone or in combination with other markers, can help identify those at greatest risk of developing hypertension.

Markers of inflammation [CRP and interleukin 6 (IL-6)]

Inflammatory mediated alterations in vascular tone and remodeling play a critical role in the development of hypertension (24). It is also important to note that plasma concentrations of inflammatory markers and mediators are increased in some cardiovascular diseases (25,26). These molecules include CRP, adhesion molecules such as vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1) (27,28) chemokines such as monocyte chemoattractant protein-1 (MCP-1), as well as anti-fibrinolytic agents such as PAI-1 (29,30).

As is the case with other biomarkers, defining the utility of CRP and IL-6 in the assessment of persons with hypertension is controversial with mixed results on clinical studies. A study by Wang *et al.* which included 1,456 non-hypertensive individuals showed a strong association of hypertension risk and characteristics of a biomarker approach to predict hypertension (13). They found that out of 9 studied biomarkers, CRP, PAI-1, and the urinary albumin/creatinine were associated with a higher risk of developing hypertension. They proposed this link through several pathophysiological mechanisms, through activation of the renin-angiotensin system since CRP upregulates type 1 angiotensin receptors responsible for angiotensin II mediated vasoconstriction as well as pro-atherogenic actions (13). Furthermore, an additional study showed that CRP is associated with increased systolic blood pressure, pulse pressure, and hypertension (31).

On the other hand, findings of other studies have failed to show the ability of CRP and IL-6 to convincingly predict or detect hypertension. For instance, Sesso *et al.* in their study of 400 females with hypertension and age-matched normotensive control subjects, showed that the ability of either or both IL-6 and CRP to predict hypertension using crude-matched models was lost when multivariate models were applied (30). A subsequent prospective case-control study by Sesso *et al.* assessed the ability of CRP and other plasma inflammatory markers to predict the risk of developing hypertension (32). However, this study also did not demonstrate CRP and IL-6 to statistically predict the development of hypertension in middle-aged and older men, particularly after adjusting for body mass index.

In addition, Davey Smith *et al.* in a recent study, showed that after adjustment for life course confounders and a Mendelian randomization approach, CRP did not appear to predict an elevated blood pressure, and as such, suggested that associations seen in previous studies are a reflection of confounding and reverse causation rather than a causal effect (33).

While the utility of CRP in the evaluation and management of hypertension is less established, the use of this biomarker might be more appropriate for global cardiovascular risk assessment. As such, in 2003, the Centers for Disease Control and Prevention and the American Heart Association (AHA) from the United States introduced CRP as part of the global assessment of cardiovascular risk, a recommendation that has been included in guidelines by the European Society of Cardiology, the Canadian Cardiovascular Society and the American College of Cardiology (34-37).

PAI-1 in EH

PAI-1 is a serine protease inhibitor synthesized by endothelial cells, hepatocytes, vascular smooth muscles, and adipocytes (38). In vascular tissue, it causes accumulation of extracellular matrix and regulates vascular remodeling, while in plasma, it promotes clot formation. Few studies

showed that PAI-1 might be involved in the pathogenesis of hypertension. The levels of plasma PAI-1 in hypertensive individuals have been documented in several cross-sectional studies (39,40).

However, it is believed that hypertension increases PAI-1 levels rather than vice versa due to hypertension-induced shear stress and endothelial activation. Wang *et al.*, in their prospective study of 1,456 patients, suggested that elevated PAI-1 levels precede the onset of hypertension (13). They considered it a multifactorial effect as higher PAI-1 levels reflect endothelial dysfunction, which may precede hypertension. Still, they also found that the RAAS system and CRP induce expression of PAI-1, suggesting a common pathway of these molecules and an implication in the pathogenesis of hypertension. Additionally, a reduced fibrinolytic effect is also seen in metabolic syndrome, raising another possibility that elevated PAI-1 levels reflect metabolic changes such as insulin resistance and diabetes mellitus which also predisposes to hypertension (13).

Additionally, an experimental model of hypertension has shown that increased vascular PAI-1 activity accelerated perivascular and medial fibrosis, whereas suppressed PAI-1 activity protected against these changes (41).

Emerging hypertension biomarkers

In the last decade, several emerging biomarkers have been explored to determine the role that these may play in the management of hypertension. These include members of the calcitonin gene-related superfamily such as adrenomedullin and calcitonin gene-related peptide (CGRP), and the serologic agents, high sensitivity troponin, and N-terminal pro-B-type natriuretic peptide (NT-proBNP).

Adrenomedullin

Central to hypertension, is vascular dysfunction. In 2018, the Physiological Diagnosis Criteria for Vascular Failure Committee of the Japan Society for Vascular Failure proposed new physiological diagnostic criteria for vascular failure, targeting the vascular layers and areas, and assessing endothelial function and arterial stiffness (a marker integrating medial layer function) using universally available diagnostic tools (42). However, until recently, no studies have been done to assess the blood biomarker for the diagnosis of vascular failure.

Promising results have been seen with adrenomedullin, which is a vasoactive peptide initially identified in human pheochromocytomas (43). Through autocrine, paracrine, and endocrine mechanisms, adrenomedullin is a potent vasodilator and angiogenic peptide that protects cardiovascular and renal tissues. It is secreted by a large variety of cells, not only endothelial and vascular smooth muscle cells. Its expression is inducible by shear stress, oxidative stress, and hypoxia (44). Beygui *et al.* showed that genetic variants at the adrenomedullin locus influence adrenomedullin gene expression in monocytes and circulating levels of adrenomedullin affecting vascular tone, primarily of peripheral arteries. This suggests that additional studies will be required to access whether adrenomedullin should be considered as a target for testing and therapy of hypertension (45).

The most recent study from 2021 by Koyama *et al.* investigated the potential of adrenomedullin as a novel biomarker for arterial stiffness causing hypertension compared to high-sensitivity CRP (hs-CRP). Of 2,169 individuals enrolled, adrenomedullin was significantly higher in participants with vascular failure as defined by brachial-ankle pulse wave velocity than control groups, suggesting that adrenomedullin may be useful as a novel biomarker on routine blood examination to assess modifiable cardiovascular risk factors such as hypertension (43). Given these promising and initial results, further prospective studies are required to confirm this applicability in everyday practice.

CGRP

Calcitonin related peptide is a 37 amino acid peptide first identified in 1982 (46). It was later discovered that it acts as a potent vasodilator and has a transmitter role in the peripheral and central nervous system playing a significant role in pain and cardiovascular regulation (47). In 1986, Struthers *et al.* described vasodilatory effects of CGRP with subsequent decrease in blood pressure after IV infusion of CGRP (48). Additional study by Jäger *et al.* demonstrated similar effect with increases of blood flow to skin and brain after administration of CGRP by intravenous infusion (49). Lastly, Kurtz *et al.* demonstrated that CGRP has effects on other organ systems such as kidneys, inducing relaxation and increase in cyclic AMP (cAMP) resulting in increased blood flow and subsequent glomerular filtration (50). The reduction in blood pressure seen by CGRP can be explained via nitric oxide (NO) and endothelium independent or NO and endothelium dependent pathways. Vasodilatory activity of NO and endothelium independent pathway is explained

by binding of CGRP to its receptor which subsequently increases cAMP via G-protein coupled adenylate cyclase that in turn phosphorylates and opens potassium-ATP channels resulting in vascular smooth muscle relaxation (51,52).

Despite its vasodilatory effects, its effects on hypertension gave equivocal results. In patients with hypertension, plasma CGRP was found to be decreased in study by Edvinsson *et al.* (53) unchanged in study by Schifter *et al.* (54) while Masuda *et al.* (55) found that levels of CGRP are higher in people with hypertension. These contradictory findings were thought to be due to differences in sampling as well as due to heterogeneity in duration, severity, and treatment of the varying hypertensive populations studied (56). Interestingly, Masuda *et al.* have shown that patients with secondary hypertension had significant decrease in plasma CGRP levels after adrenalectomy suggesting that CGRP is a compensatory response to elevated blood pressure (55). Additionally, a study carried out by DiPette *et al.* demonstrated that a bolus intravenous injection of α-CGRP at doses of 22, 65, 220, and 2,200 pmol in conscious rats reduced mean blood pressure and increased blood flow and/or peripheral resistance in vital organs, such as the heart in a dose dependent manner (57).

Altogether, these studies emphasize potent effects of CGRP on multiple cardiovascular functions. Currently, CGRP antagonist therapy is only used in the treatment of migraine. However, further studies are needed to fully elucidate the usefulness of CGRP as an agonist as a novel therapeutic agent for cardiovascular disorders, including hypertension and congestive heart failure. Theoretically, CGRP as described above could mediate protective actions however there are many challenges with implementing this to everyday practice. First, it is very short-lived peptide making it difficult to accurately measure and implementing high-performance liquid chromatography or mass spectroscopy to measure CGRP accurately might not be practical in everyday practice. Thus, further studies are needed to enhance the bioactivity of CGRP in circulation via CGRP analogs and novel peptide delivery systems which could lead to potential new medications and/or more accurate serologic or urinary measures of CGRP which may provide more options for hypertension treatment and/or clinical biomarkers.

High-sensitivity cardiac troponin T (hs-cTnT) in EH

Several studies have demonstrated that cTnT is a beneficial biomarker of prognosis in chronic heart failure and in acute coronary syndromes (58-60). However, cTnT levels are undetectable by conventional cTnT assays in most patients presenting with EH and no signs or symptoms of HF. Newly developed high-sensitivity assays can measure low levels of cTnT accurately and with insignificant variation. The association of baseline hs-cTnT with incident diagnosed hypertension was examined in a recent cohort study of 15,792 participants. The study found that hs-cTnT was associated with incident hypertension and left ventricular hypertrophy in an ambulatory population with no history of cardiovascular disease (61).

Even though the exact mechanism linking hs-cTnT to hypertension is unclear, a few points are worth considering. Hypertension develops over time, starting with normotension, abnormal diurnal patterns of blood pressure (nocturnal non-dipping), to pre-hypertension, and finally to clinical hypertension. It is well known that abnormalities in cardiac and vascular structure occur long before clinical hypertension. Thus, these early changes of cardiac structure even prior to developing clinical hypertension could be the explanation for elevated hs-cTnT. Additionally, hs-cTnT and hypertension could be a manifestation of masked hypertension when the patient's office blood pressure level is within the normal range, but home readings are in the hypertensive range. Thus, elevated hs-cTnT may be useful in identifying individuals at risk for hypertension and offering the opportunity for more intensive preventive and/or earlier pharmacologic treatment strategies.

NT-proBNP

As a consequence of volume overload and pressure overload, ventricular myocardium is primarily responsible for the production of natriuretic peptides such as the BNP hormone and its inactive N-terminal fragment (NT-proBNP) (62). BNP acts on distant tissues and causes diuresis, vasodilatation, and decreased renin and aldosterone secretion. Nonetheless, there is evidence of a relationship between blood pressure, blood pressure variation, and natriuretic peptide expression. A recent small study of 98 patients with asymptomatic EH and 24-hour ambulatory blood pressure mentoring showed that patients with hypertension and abnormal circadian blood pressure variation have higher natriuretic peptide levels than those with normal variation (P<0.0005) (63).

It is not clear why these peptide levels are increasing, but it might be caused by a faster diastolic filling time,

and this could be used for risk stratification in persons with hypertension. The Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) randomized a subset of 6,549 patients at risk with no history of coronary heart disease to either atenolol-based or amlodipine-based blood pressure-lowering treatment (64). During a follow-up period of 5.5 years, 485 cardiovascular disease cases were accrued and matched with 1,367 controls. NT-proBNP was measured at baseline and 6 months into the trial. In a multivariable regression analysis, a 1-mm Hg increase in the SD of systolic blood pressure was associated with a 2% increase in baseline NT-proBNP (P<0.0001). NT-proBNP was reduced by 36.5% (P=0.0001) with amlodipine treatment. The risk of cardiovascular disease was lower among amlodipine recipients whose NT-proBNP was below the median (61 pg/mL) at the end of the 6-month period [odds ratio (OR), 0.58; 95% confidence interval (CI), 0.37–0.91] after adjusting for confounders, including baseline NT-proBNP and blood pressure (64).

Genetic and epigenetic biomarkers

In EH, alleles in polygenes may alter the function and expression of encoded proteins, creating ends-phenotypes that complicate into hypertension. Discoveries of genetic and epigenetic mechanisms have related several pathologies, including cardiovascular disease to genetic and epigenetic dysregulation. These emerging biomarkers that may in the future receive approval are a common topic nowadays. Technological advances and big data analysis have revealed novel disease mechanisms and targets, allowing for more personalized treatment and diagnosis of hypertension in the future. As such pharmacogenetics and pharmacoepigenetics make it possible to predict drug response and develop tailored therapies on differences in epigenetics in each patient. Similarly, epigenetic biomarkers have emerged as a promising tool for diagnosing and prognosis cardiovascular diseases. However, in order to determine with certainty which genetic/epigenetic biomarkers are reliable for clinical routine, multiple studies with a large sample population are needed. In this narrative review, we also discussed the most well-studied genetic/epigenetic biomarkers and their controversy aiming to improve the diagnosis, prognosis, and therapy in hypertensive patients.

AGT

AGT was the first candidate gene linked to EH and remains one of the most closely studied genes for this illness (65). In humans, the AGT gene is part of the serpin gene family. It extends only 12 kb with a total of 5 exons on chromosome 1 (1q42-q43). Having a diverse range of cell specificities, it is found in many tissues, including the liver, adipose tissue, heart, vessel wall, brain, and kidney (66). The AGT enzyme is a substrate to renin, one of the enzymes in the RAAS, which cleaves N-terminal amino acids of mature AGT secreted by hepatocytes. A first cleavage occurs via renin, released from juxtaglomerular cells, to yield angiotensin I decapeptide, followed by ACE to yield angiotensin II octapeptide. In the RAAS cascade, the enzymatic reaction renin-AGT controls plasma AGT levels and is crucial to blood pressure control (65). Several polymorphisms have been found in the gene's 5' flanking region, exons, and introns, which implicate this gene in EH (65). Moreover, Zhao *et al.* demonstrated that the nucleotide nucleotides *20, *17, *517, and *792 of AGT play a significant role in the pathogenesis of high blood pressure (67). Other studies have also found a correlation between plasma AGT levels, anti-AGT antibodies, and AGT transgene injections with blood pressure (68-70). As a result of these studies, the AGT gene has become a perfect marker for studying its haplotype association with hypertension pathogenesis. This was supported by a study that identified 44 single-nucleotide polymorphisms (SNPs) in the AGT gene and assembled a complete haplotype map with six major haplotypes of AGT in both whites and Japanese, although their frequency varied dramatically between the two populations (71). Additionally, Zhu *et al.* analyzed the haplotype of each gene of the RAAS in black and white hypertensive populations (71,72). Further analysis was conducted with individual SNPs and haplotype blocks and several SNPs in the AGT gene were associated with hypertension, but no particular haplotype was found to be at risk for transmission distortion (71). A study of ACE interaction with haplotype blocks of AGT in a Taiwanese population reported contrary results (73). Lastly, a more recent study by Purkait *et al.* (74) performed SNPs analysis and possible haplotypes across the AGT promoter and gene region in 414 subjects (256 hypertensive cases and 158 controls). A-152G, rs5050, A-20C, and rs4762 and rs699 in exon2 all showed a stronger positive association with hypertension than rs11568020 or rs5050. Also, 3 haplotypes (H4, H7, and H8) showed a stronger positive association with hypertension. H2 haplotypes were associated with a protective effect against hypertension. It is difficult to interpret how these associations occur. However, the results of these studies suggest that haplotypes are associated with

hypertension.

Natriuretic peptide A (NPPA)

An important member of the natriuretic peptide system, atrial natriuretic peptide (ANP) might contribute to the development of hypertension which has been discussed above. Polymorphisms of its coding gene—NPPA—have also been associated with the susceptibility to hypertension (75-77). The NPPA gene variant rs5068, located at the NPPA gene, has been found to be associated with hypertension at a genome-wide significance of 1×10^{-8} (78). Zhang *et al.* in their prospective study of 736 patients suggested that a common NPPA SNPs rs5063 was associated with serum ANP levels and ANP was prospectively associated with hypertension in the Chinese Han population (79). Li *et al.* in their prospective study showed that DNA methylation of the 9 CpGs at the NPPA promoter was decreased in Chinese adults with hypertension and as such aberrant DNA methylation of the *NPPA* gene may participate in the mechanisms of hypertension (80). The results of these studies, however, suggest that more prospective studies are needed to associate which NPPA SNPs are truly related to hypertension.

Sodium channel epithelial 1 subunit alpha (SCNN1A)

Due to its effect on sodium balance, the kidney is an important organ in blood pressure regulation. Sodium reabsorption and excretion in the kidney are controlled by the epithelial sodium channel (ENaC), located at the distal nephron (81,82). There are three homologous subunits of ENaC, encoded by SCNN1A, SCNN1B, and SCNN1G, respectively. It is mainly found in the luminal membranes of connecting tubule cells and in principle cells of collecting ducts (83). Studies have shown that rare changes in the *SCNN1B* or *SCNN1G* genes are responsible for Liddle's syndrome, an inherited disease causing early-onset hypertension (84,85). Furthermore, Kakizoe *et al.* found that salt-sensitive hypertension and organ damage are associated with inappropriate ENaC expression and activation in Dahl salt-sensitive rats (86). In spite of inconsistent results, *SCNN1B* and *SCNN1G* genes are implicated in the physiological variation of systolic blood pressure (87,88). As such, in the future, the association between ENaC variants and EH should be studied more closely. Additionally, a prospective study by Liu *et al.* (89) showed investigated associations of *SCNN1A*, *SCNN1G*, and *SCNN1B* genes with systolic blood pressure, diastolic blood pressure, and mean arterial pressure (MAP) using both single-marker and gene-based analyses in 2,880 Han Chinese participants. They found a significant association of *SCNN1A* marker rs13306613 with diastolic blood pressure and *SCNN1B* marker rs12447134 with systolic blood pressure. In addition, 5 SNPs in *SCNN1G* and 4 SNPs in *SCNN1B* achieved nominal significance for systolic blood pressure, diastolic blood pressure or MAP under the additive model. Gene-based results showed significant associations of *SCNN1G* and *SCNN1B* with blood pressure levels. As such, it is imperative to replicate these findings in different populations and conduct additional functional studies in order to identify the true causal variants.

β2-adrenergic receptor (ADRB2)

As a candidate gene for EH, the *ADRB2* gene has been extensively researched, but no consensus has been reached across different ethnicities. Researchers have found that ADRB2 polymorphisms may affect EH and noncardiovascular diseases. Molecular studies have extensively examined the role of ADRB2 in hypertension. Studying SNPs in the coding region, researchers found that the SNPs Arg16→Gly (rs1042713, A46G), Gln27→Glu (rs1042714, C79G), and Arg16→Gly + Gln27→Glu, in comparison to wild-type ADRB2, have normal agonist binding and functional coupling to stimulation of adenylyl cyclase activity (90). *In vivo*, it has been reported that both polymorphisms could contribute to enhanced vascular reactivity to isoproterenol in vessel capacitance which may influence blood pressure. Previous studies have examined the association between the A46G, C79G, and C-47T polymorphisms and EH risk (91). There were several studies that found no association between them (92-99). However, there are varying opinions regarding the allele associated with hypertension or related traits (100-103). A study has reported an increased risk for EH in Japanese when carrying the GG46 genotype (100). However, the GG46 genotype was also suggested to protect the Yi minority of Chinese against EH in another study on East Asian populations (104,105). Earlier studies by Lou and colleagues showed that A46G polymorphism G allelic frequency was significantly higher in hypertensive subjects (P=0.011; OR, 1.287; 95% CI, 1.059–1.565) than in controls. Based on stratification analyses by obesity, the propensity of hypertension was higher in those with the

A46G polymorphism (GG *vs.* AG *vs.* AA: P<0.001; OR, 1.645; 95% CI, 1.258–2.151). There was a significant interaction between A46G genotype and body mass index on EH risk. Neither the C-47T nor C79G polymorphisms were associated with EH risk (106). It still remains to be determined what role the polymorphisms in the ADRB2 gene play in EH.

MicroRNAs (miRNAs)

There are a number of systems in the body that function to maintain blood pressure homeostasis. In fact, miRNAs are short endogenous conserved ncRNAs that regulate gene expression programs. miRNAs play an important role in the regulation of gene expression programs that underlie normal and pathological cellular processes, including cardiovascular diseases. There is evidence that miRNAs are involved in cellular processes such as differentiation, growth, and metabolism (107). MiRNAs are non-coding, post-transcriptional miRNAs that are 18–25 nucleotides long, and their dysregulation is linked to the development of cancer, EH, and endothelial dysfunction (108-111). Since miRNAs are found in body fluids and their expression is altered in high blood pressure, they have been investigated as potential biomarkers for hypertension. Kontaraki *et al.* (112) in their study focused on the expression of has-miR-9 and has-miR-129 in peripheral blood in normotensive compared to hypertensive subjects. There was a lower expression of both miRNAs in those with high blood pressure, and they were positively correlated with pulse pressure. The miR-9 level correlated positively with left ventricular mass as well. In hypertension, these miRNAs may act as indicators of advanced tissue damage (112). The miRNA expression in whole-plasma samples of six healthy individuals and six hypertensive Chinese individuals was examined using microarrays, which revealed three miRNAs that were up-regulated in hypertension included hsa-miR-425, hsa-miR-505, and hsa-miR-210. A similar pattern of findings was observed in two other cohorts (11 healthy subjects, 20 pre-hypertensive subjects, and 19 hypertensive subjects, and 91 healthy subjects, and 101 hypertensive subjects) (113). In all three cohorts, hypertensive patients had consistently higher miR-505 levels. Through its regulation of the gene for fibroblast growth factor 18 (FGF18), this miRNA has been found to play a role in angiogenesis by inhibiting endothelial cell migration and tube formation (113). Lastly, Matshazi *et al.* (114) in their most recent study using quantitative reverse transcription-polymerase chain reaction, evaluated the expression levels of miR-126-3p, 30a-5p, 182-5p, 30e-3p, and 1299 in the whole blood of 1456 participants. It was discovered that expression of miR-126-3p and 182-5p was significantly higher in known hypertensives when compared to both screen-detected hypertensives and normotensives, and also between screen-detected hypertensives and normotensives. The expression of miR-126-3p, 182-5p, and 30a-5p was also significantly correlated with known hypertension. At the moment, this field is still in its infancy, which may change in the future. It would be useful to have larger sample sizes and to improve the methodology, such as by identifying markers that would be useful as targets for the diagnosis of hypertension as well as the development of miRNA-based treatments (114).

Conclusions

The role of biomarkers in the pathophysiologic process and management of hypertension continues to be an area of active research. While no biomarker has been found which can be applied to all patients with hypertension, their use in specific cases, particularly in the assessment of global cardiovascular risk is promising. In the future, emerging biomarkers such as adrenomedullin, as well as others currently in early research stages may help in the identification of persons at heightened risk for the development of hypertension and/or those with hypertension who may be at higher risk for target organ damage. In addition, the use of biomarkers could assist in monitoring responses to non-pharmacologic and pharmacologic treatment in those with newly diagnosed or established hypertension. The goal of identifying and employing biomarkers clinically is to increase the hypertension control rates to decrease the disease burden such as the increased morbidity and mortality in persons with hypertension, world-wide.

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