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HYPERTENSION AND THE HEART (B UPADHYA, SECTION EDITOR)

Does the Naked Emperor Parable Apply to Current Perceptions of the Contribution of Renin Angiotensin System Inhibition in Hypertension?

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Abstract

Purpose of Review To address contemporary hypertension challenges, a critical reexamination of therapeutic accomplishments using angiotensin converting enzyme inhibitors and angiotensin II receptor blockers, and a greater appreciation of evidence-based shortcomings from randomized clinical trials are fundamental in accelerating future progress.

Recent Findings Medications targeting angiotensin II mechanism of action are essential for managing primary hypertension, type 2 diabetes, heart failure, and chronic kidney disease. While the ability of angiotensin converting enzyme inhibitors and angiotensin II receptor blockers to control blood pressure is undisputed, practitioners, hypertension specialists, and researchers hold low awareness of these drugs' limitations in preventing or reducing the risk of cardiovascular events. Biases in interpreting gained knowledge from data obtained in randomized clinical trials include a pervasive emphasis on using *relative risk reduction* over *absolute risk reduction*. Furthermore, recommendations for clinical practice in international hypertension guidelines fail to address the significance of a *residual risk* several orders of magnitude greater than the benefits. We analyze the limitations of the clinical trials that have led to current recommended treatment guidelines. We define and quantify the magnitude of the *residual risk* in published hypertension trials and explore how activation of alternate compensatory bioprocessing components within the renin angiotensin system bypass the ability of angiotensin converting enzyme inhibitors and angiotensin II receptor blockers to achieve a significant reduction in total and cardiovascular deaths. We complete this presentation by outlining the current incipient but promising potential of immunotherapy to block angiotensin II pathology alone or possibly in combination with other antihypertensive drugs.

Summary A full appreciation of the magnitude of the *residual risk* associated with current renin angiotensin system-based therapies constitutes a vital underpinning for seeking new molecular approaches to halt or even reverse the cardiovascular complications of primary hypertension and encourage investigating a new generation of ACE inhibitors and ARBs with increased capacity to reach the intracellular compartments at which Ang II can be generated.

Keywords Angiotensin II · Angiotensin-(1–12) · Angiotensin converting enzyme · Angiotensin receptor blockers · Hypertension clinical trials · Residual risk · Blood pressure · Renal disease · Immunotherapy · Monoclonal antibodies

Abbreviations

ACCOMPLISH	Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension
ACE	Angiotensin converting enzyme
AGT	Angiotensinogen
ALLHAT	Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial
ANBP2	Second Australian National Blood Pressure Study
Ang II	Angiotensin II
Ang-(1−12)	Angiotensin-(1–12)

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Ang-(1–7)	Angiotensin-(1–7)
ARBs	Ang II receptor blockers
ASCOT BPLA	Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm
ASO	Antisense oligonucleotides
AT1-R	Type I Ang II receptor
CAGR	Compound annual growth rate
CAPPP	Captopril prevention project
CASE-J Ex	Candesartan Antihypertensive Survival Evaluation in Japan extension
COLM	Combination of OLMesartan
CVD	Cardiovascular disease
E-COST	Efficacy of Candesartan on Outcome in Saitama Trial
EUROPA	European trial on reduction of cardiac events with perindopril in stable coronary artery disease
HIJ-CREATE	Heart Institute of Japan Candesartan Randomised Trial for Evaluation in CAD
HOPE	Heart Outcomes Prevention Evaluation
HYVET	Hypertension in the Very Elderly Trial
JMIC-B	The Japan Multicenter Investigation for Cardiovascular Diseases-B
LDL	Low-density lipoprotein
LIFE	Losartan Intervention for Endpoint Reduction
mAb	Monoclonal antibody
MOSES	Morbidity and Mortality After Stroke, Eprosartan Compared With Nitrendipine for Secondary Prevention

Introduction

Hans Christian Andersen's *The Naked Emperor* tale illustrates a situation wherein most observers share a collective ignorance of an obvious fact. In the context of this presentation, we address the belief that medications preventing angiotensin II (Ang II) formation or its binding to the type I Ang II receptor (AT_1-R) are highly efficacious in preventing cardiovascular and total mortality [1•].

Although the ability of direct renin inhibitors (DRI), angiotensin converting enzyme (ACE) inhibitors, and Ang II receptor blockers (ARBs) to control blood pressure is without questioning, in-depth analysis of the results obtained in randomized clinical trials (RCT) and large meta-analysis [2] reveals their limitations in reducing cardiovascular events when a critical appraisal of the *absolute* and *residual risks* obtained in clinical trials are critically reexamined.

The cornerstone of evidence-based medicine relies upon the conclusions obtained in large clinical trials. The information furnished by well-conducted RCT in the treatment of CVD determines treatment recommendations in international guidelines and influences the direction of basic science research. RCT expresses the efficacy of medical intervention in terms of *relative risk reduction* (an estimate of the percentage of baseline risk that is removed because of the new therapy) and *absolute risk reduction* (the proportion of patients who are spared the adverse outcome by receiving the new medication rather than the control therapy) [3]. In the past, international guidelines focused on documenting the *absolute risk* [4••]. Increased influence of commercial entities in financing RCT and the fact that *absolute risk* did not always translate into clinical effectiveness [5] favored the use of *relative risk reduction* as the basis for establishing therapeutic efficacy [6, 7•]. The pitfalls regarding the common use of *relative risk reduction* versus *absolute risk* are stressed by the Blood Pressure Lowering Treatment Trialists' Collaboration [8, 9•, 10] and underscored in a meta-analysis that included 67,475 individuals from 11 RCTs and 26 randomized groups [9•]. This later study showed that blood pressure control for five years in 1000 patients assigned to different levels of predicted *absolute risk* prevented 14 (95% CI: 8–21), 20 (95% CI: 8–31), 24 (95% CI: 8–40), and 38 (95% CI: 16–61) cardiovascular events, respectively [9•]. These data contrast with the larger numerically value of the reported *relative risk reduction* in RCT [4••, 11].

The *Residual Risk* in Primary Hypertension

Cardiologists pioneered assessing the *residual risk* in explaining the probability of vascular events in patients with adequate control of proatherogenic factors [12, 13••]. According to Vanuzzo [13••], "the *residual CVD risk* is the risk of CVD events persisting despite treatment for or achieving targets for risk factors such as low-density lipoprotein (LDL) cholesterol, blood pressure, and glycemia." Unfortunately, the investigation of the *residual risk* to explain the limited efficacy of antihypertensive medications remains underrecognized. The term *residual risk* is not found in the 55 pages of the joint ACC/AHA Hypertension guidelines [14], while the concept of the *residual risk* is briefly mentioned in the 2020 International Society of Hypertension global hypertension practice guidelines [15].

Figure 1 illustrates the main components of the *residual risk* and the critical contribution of excess RAS activity in contributing to hypertension pathogenesis**.** Lifestyle changes such as sedentarism, salt [16], and alcohol intake, obesity, tobacco smoking, atherogenic dyslipidemia [increased blood concentrations of small, dense LDL particles, decreased high-density lipoprotein (HDL) particles, increased triglycerides, inadequate blood pressure control [poor choice of antihypertensive medications, resistant hypertension, adherence to therapy [17]], chronic systemic inflammation

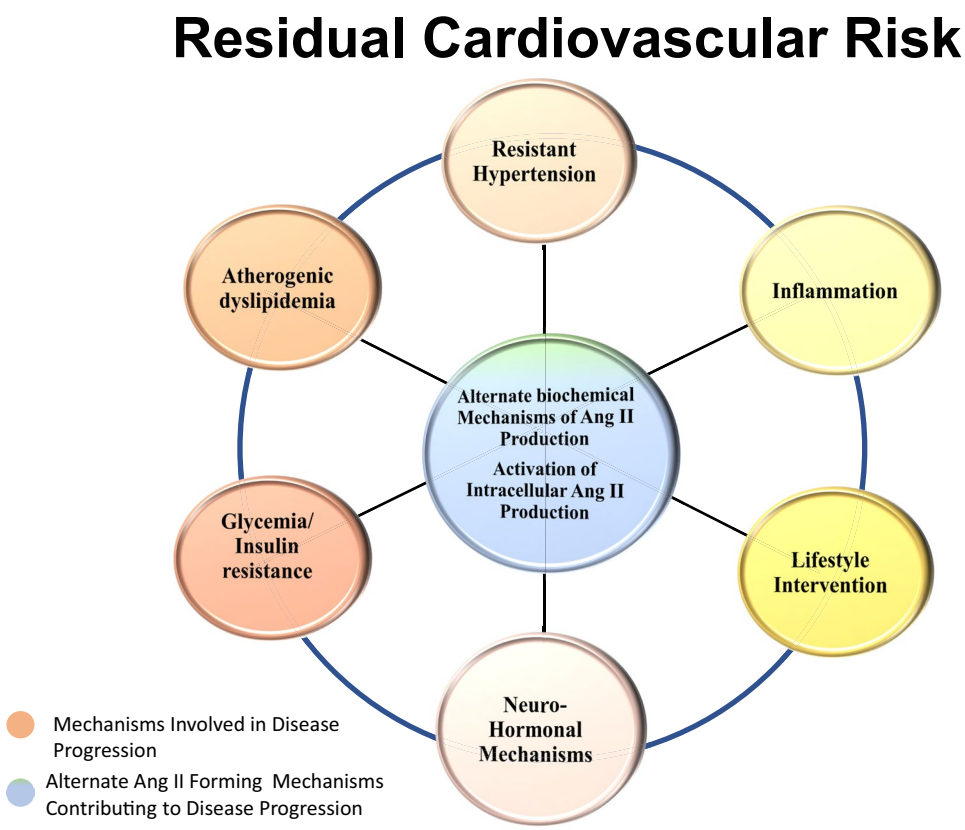


Fig. 1 Composite diagram of a central role of the renin angiotensin system in contributing to the lifetime residual risk in primary hypertension

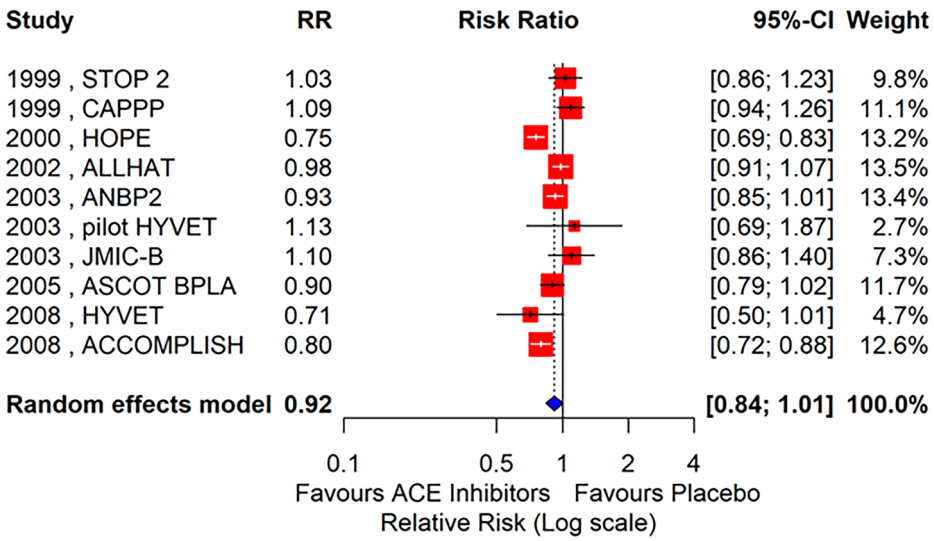
[18–21], neuro-hormonal activation (increased sympathetic nerve activity [22, 23], and the metabolic derangement brought about by type 2 diabetes, and insulin resistance [24] contribute to the disease process. The importance of addressing the contribution of blood pressure-independent mechanisms was documented in the STENO-2 trial [25]. In this RCT, co-treatment of multiple risk factors reduced the risk of cardiovascular and microvascular events by almost 50 percent [25].

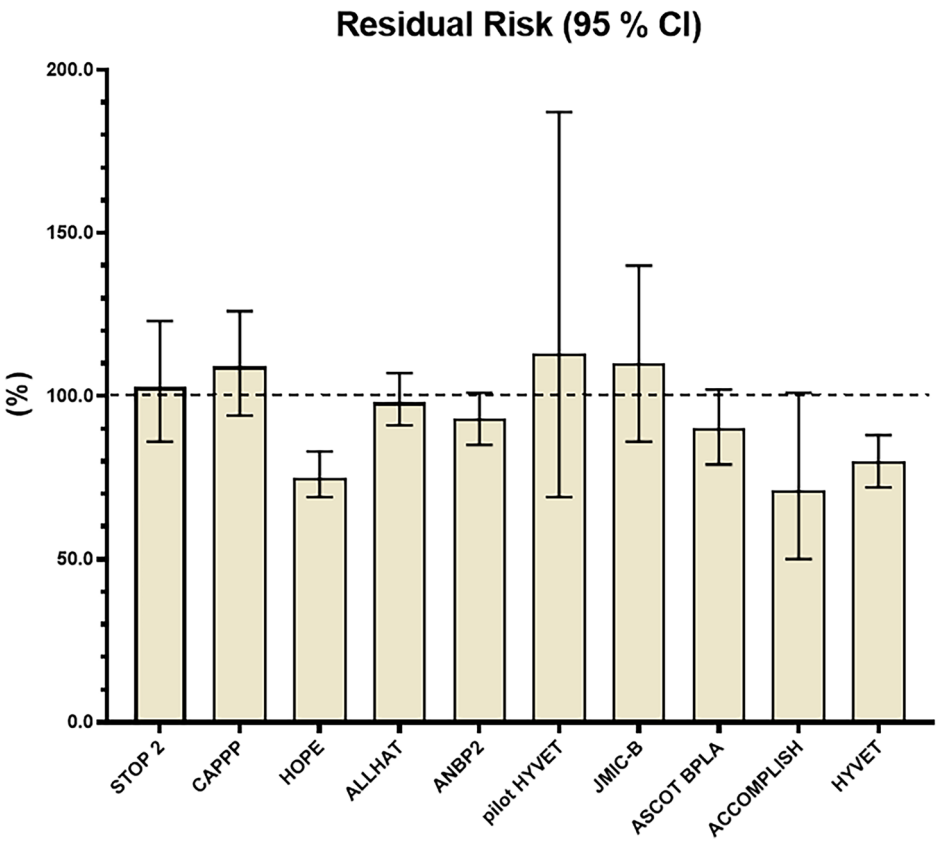
The Renin Angiotensin System and the *Residual Risk*

A considerable amount of knowledge from both clinical and experimental research implicates a primary contribution of the RAS to the pathogenesis of primary hypertension [26•]. These accomplishments have translated into making ACE inhibitors and ARBs a cornerstone of treating cardiovascular and renal disease patients [1•]. Nevertheless, their proven ability to control blood pressure obscures a suboptimal long-term efficacy in halting or avoiding cardiovascular events [27]. We [28, 29, 30••, 31, 32], Dusing [33, 34••], and others [9•, 11, 13••, 35, 36, 37•, 38] have independently addressed the limited efficacy of ACE inhibitors and ARBs in reducing the magnitude of clinical events in treated hypertensives. Brugts et al. [37•] analyzed the impact of RAS inhibitors on all-cause mortality and major cardiovascular events in hypertension. Their study included seven trials using ACE inhibitors as the active treatment and 11 other trials using ARBs. All-cause mortality incidents were reduced by approximately 10% in patients medicated with ACE inhibitors and not in patients medicated with ARBs. On the other hand, cardiovascular mortality was not different in patients medicated with RAS inhibitors compared to control medications [37•].

Figures 2 and 3 contrast the magnitude of the *relative risk* reduction versus the *residual risk* in the primary endpoint reported in major hypertension clinical trials using ACE inhibitors or ARBs. The pooled *relative risk reduction* of the primary endpoint in 10 hypertension clinical trials using ACE inhibitors versus conventional therapy averaged 8%, representing a *residual risk* of 92% (Fig. 2). In addition, in eight of the ten studies illustrated in Fig. 2, the upper limit of the confidence interval includes or crosses (1.0). This finding indicates insufficient evidence to conclude that ACE therapy is better than conventional therapy in reducing the primary endpoint. A similar compilation of the impact of ARBs in 11 clinical trials documents a polled *relative risk reduction* of 10% and a *residual risk* amounting to 90% (Fig. 3). As with the data obtained from ACE inhibitor trials (Fig. 2), the null hypothesis (i.e., no differences between the

ANGIOTENSIN CONVERTING ENZYME INHIBITORS





◂**Fig. 2** Forest plot of the reported *relative risk* (RR) (*top panel*) and calculated *residual risk* (*bottom panel*) of hypertension trials comparing ACE inhibitors to conventional therapy. Values are expressed as means ± 95% Confidence Intervals. Data are abstracted from the data reported in STOP 2: β-blockers (atenolol, metoprolol, pindolol, and amiloride versus enalapril or lisinopril). The primary endpoint was fatal stroke, fatal myocardial infarction, and other fatal cardiovascular diseases [120]. CAPPP: captopril versus conventional antihypertensive therapy (diuretic, β-blockers). Primary endpoint: composite of fatal and nonfatal myocardial infarction, stroke, and other cardiovascular deaths [121]. HOPE: ramipril versus placebo. Primary outcome was a composite of myocardial infarction, stroke, or death from cardiovascular causes [122]. ALLHAT: lisinopril vs chlorthalidone or amlodipine. Primary outcome: combined fatal coronary artery disease or non-fatal myocardial infarction [123]. ANBP2: enalapril or other ACE inhibitor vs hydrochlorothiazide or other diuretic. Primary outcome was difference in the total number of cardiovascular events between the two treatment groups [124]. Pilot HYVET: lisinopril or other ACE inhibitor vs bendroflumethiazide (or other diuretic) or no treatment. Primary outcome was differences in mortality from all causes between the groups [125]. JMIC-B: ACE inhibitor vs nifedipine retard. Primary endpoint was overall incidence of cardiac events and coronary interventions [126]. ASCOT BPLA: amlodipine ± perindopril vs atenolol ± bendroflumethiazide. Primary endpoint was non-fatal myocardial infarction and fatal coronary artery disease [127]. ACCOMPLISH: benazepril combined with amlodipine versus benazepril combined with hydrochlorothiazide. Primary endpoint was composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, hospitalization for angina, resuscitation after sudden cardiac arrest, and coronary revascularization [128]. HYVET: indapamide ± perindopril vs placebo in octogenarian hypertensive individuals. Primary endpoint was either fatal or non-fatal strokes [129]. The random effect meta-analysis model was used to compute an overall pooled *relative risk* ratio. The weighted mean difference across the two groups was computed to estimate the pooled size effect. The 95% CI was calculated using Wilson method. Statistical heterogeneity was tested by Cochran's Q statistics and a value of $I2 \geq 75\%$ was considered an indication of high heterogeneity. Publication bias was investigated using Deek's test. The statistical significance was set at a p value < 0.05. The analyses were performed by using R Studio version 1.3.1056, R 4.0.3 with "metafor" packages

two arms of the study) in the confidence interval is present in eight of the 11 clinical trials. This further analysis stresses that the *residual risk* in patients treated with ACE inhibitors or ARBs is eight to ten times higher than the benefit.

Defying Attempts to Untie the Gordian Knot

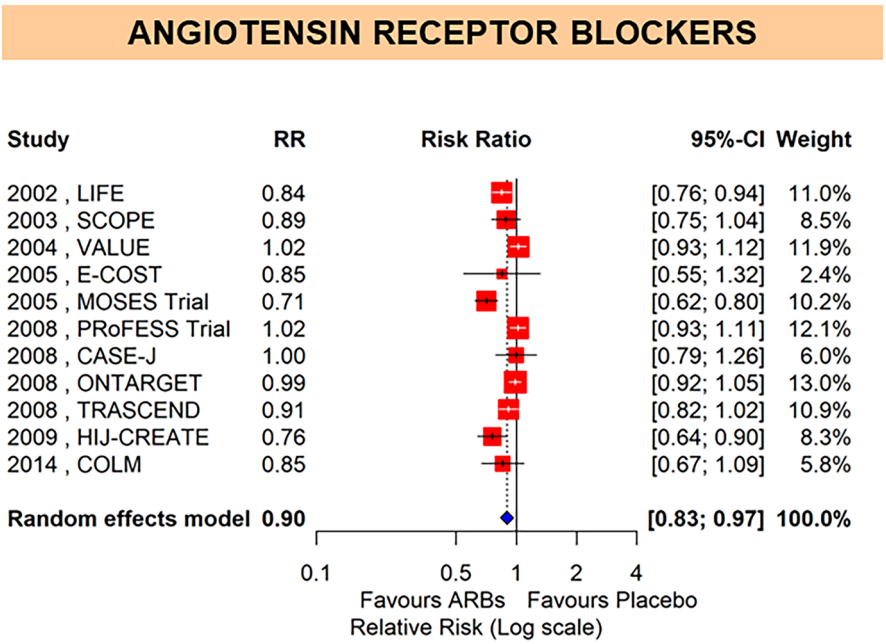
Given the monumental genetic, molecular, physiological, and clinical evidence for critical participation of Ang II in the pathogenesis of CVD, it is paradoxical that the long-term effects of RAS-based therapies fall short of expectations. While environmental and phenotypic factors, as outlined in Fig. 1, contribute to limiting the benefits of these agents in preventing clinical events, there is only a marginal improvement in the *residual risk* by including hypertension trials in which patients receive concomitant therapies with statins and antiplatelet agents [39, 40].

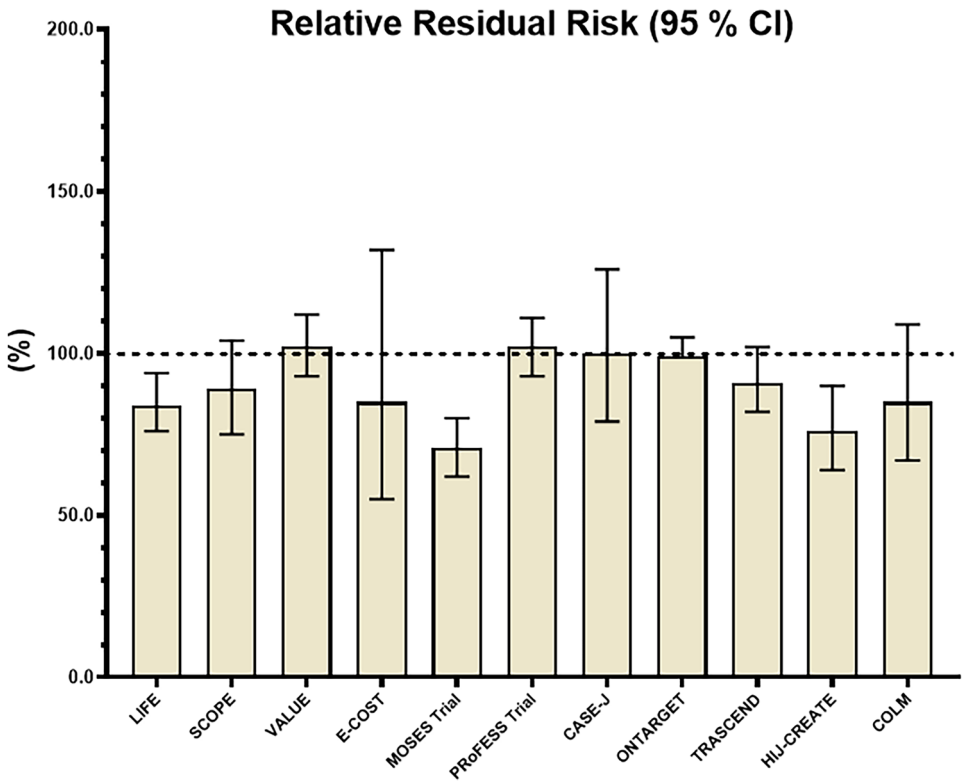
Failure to translate basic research evidence into clinical outcomes may include the following: the greater rigor of the procedures used in animal experimentation, the intervening effect of genetic and metabolic cofactors differences between laboratory animals and humans, suboptimal dosing of RAS inhibitors, treatment adherence, and a limited understanding regarding how age and andropause/menopause [41] influences therapeutic responses. Often, recommended therapeutic dosing of medications in humans ignores the impact of a 100-fold difference in body surface area (BSA) between rodents and humans [42, 43].

We have suggested that the long-term therapeutic efficacy of ACE inhibitors and ARBs is influenced by the activation of alternate enzymatic mechanisms leading to Ang II production, the inability of these drugs to reach intracellular sites at which Ang II can be generated, or both [44•]. As early as 1982, Biollaz et al. [45] demonstrated an "escape mechanism" of ACE enzymatic activity in patients medicated with enalapril to explain the restoration of plasma Ang II levels in the presence of complete suppression of plasma ACE enzymatic activity. Because the "ACE escape" phenomenon is based on the presence of normal to high circulating Ang II during long-term ACE inhibition, the term does not differentiate whether the restoration of plasma Ang II concentrations is due to reactivation of ACE gene expression or the emergence of alternate non-canonical ACE-independent pathways for Ang II production [46–48]. This second possibility is strengthened by the demonstration that a greater blood pressure reduction can be achieved by the addition of ARB to an ACE inhibitor [49, 50] or a DRI to an ARB [51, 52].

Convincing literature reveals the existence of tissue-generating angiotensins through enzymatic pathways that depart from renin/ACE-dependent mechanisms. Among the proteases that can generate Ang II, the serine protease chymase (EC 3.4. 21.39) shows a high and specific ability to generate Ang II in tissues. A comprehensive discussion of chymase biological actions in tissue remodeling and heart disease has been reviewed recently [53••]. The data demonstrates compartmentalization of Ang II synthesis by different enzymatic pathways in the interstitial and intravascular spaces (Fig. 4 and reference [54•]).

Since the original discovery of chymase's specificity and catalytic activity for Ang I into Ang II hydrolysis in human cardiac membranes [55], its importance in blood pressure regulation and adverse cardiovascular remodeling continues to be underappreciated [56, 57, 58•, 59]. Opposing arguments against a chymase role in the pathogenesis of CVD, as advocated by Danser and colleagues [58•], are deeply flawed because they ignore chymase contribution as an intracellular Ang II forming enzyme [60, 61•, 63••]. Intracellular Ang II generation, found in cardiac, renal, and vascular endothelial cells, stimulates remodeling of the extracellular





matrix [64]. In humans, chymase activity and expression are increased in the enlarged left atrial of patients with a diagnosis of mitral valve disease, persistent atrial fibrillation, and the post-operative pericardial fluid of patients undergoing open heart surgery [64, 65•, 66, 67•, 68]. Furthermore, renin [69•] and cathepsin D [70] are implicated in the intracellular hydrolysis of angiotensinogen (AGT) into Ang I, while chymase accounts for 90% of the cardiac Ang II forming activity [62, 71, 72].

As discussed by us elsewhere [53••], a reluctance to accept a critical role of chymase in human diseases is based on the unproven idea that pharmacological blockade of AT_1-R would be sufficient to prevent pathological consequences of Ang II production escaping ACE inhibition. The

◂**Fig. 3** Forest plot of the reported *relative risk* (RR) (*top panel*) and calculated *residual risk* (*bottom panel*) of hypertension trials comparing ARBs to other antihypertensive therapies. Data are abstracted from the reported primary endpoint of LIFE: losartan ± hydrochlorothiazide vs atenolol ± hydrochlorothiazide. Primary endpoint was cardiovascular events (death, myocardial infarction, or stroke [130]). SCOPE: candesartan vs placebo. Primary endpoint was major cardiovascular events, a composite of cardiovascular death, non-fatal stroke and non-fatal myocardial infarction [131]. VALUE: valsartan vs amlodipine. Primary endpoint was superiority of the valsartan-based treatment in reduction of cardiac morbidity and mortality among high cardiovascular risk patients [132]. E-COST: candesartan versus conventional therapy other than ACE inhibitors. Primary endpoint was hospitalization due to stroke, myocardial infarction, and congestive heart failure [133]. MOSES: eprosartan vs nitrendipine. Primary endpoint was composite of total mortality and all cardiovascular and cerebrovascular events [134]. PRoFESS: telmisartan vs placebo. Primary endpoint was recurrent stroke [135]. CASE-J: candesartan vs amlodipine. Primary endpoint was first fatal/non-fatal cardiovascular event [136]. ONTARGET: ramipril versus telmisartan and their combination. Primary endpoint was death from cardiovascular causes, myocardial infarction, stroke, or heart failure hospitalization [137]. TRASCEND: telmisartan vs placebo. The primary outcome was the composite of cardiovascular death, myocardial infarction, stroke, or hospitalization for heart failure [138]. HIJ-CREATE: candesartan vs non-ARB. Primary endpoint was occurrence of a first major adverse cardiovascular event [139]. COLM: olmesartan combined with a calcium channel blocker versus a diuretic. Primary endpoint was a composite of cardiovascular morbidity and mortality [140]. Statistical procedures as described in Fig. 2 legend

limited efficacy of ACE inhibitors and ARBs to ameliorate clinical events does not support this idea. New research identifies chymase in Ang II generation from a novel extended form of Ang I—named angiotensin-(1–12) [Ang-(1−12)] [73••, 74]—in normal and diseased human atrial and ventricular tissues [65•, 67•, 68, 75••, 76, 77•], and the blood of primary hypertensive patients naïve or not naïve to antihypertensive medications [78•, 79••]..

The characterization of Ang-(1−12) as a renin-independent Ang II forming substrate (Fig. 4) and our references [44•, 80] explain a surge in circulating Ang II levels in patients medicated with ACE inhibitors [81, 82]. Although Ang-(1−12) seems to be preferentially converted to Ang II by ACE in the circulation [83], chymase hydrolyzes Ang-(1−12) directly into Ang II in the human and rodent hearts [65•, 76, 77•] and the rat bone marrow [84]. The clinical importance of Ang-(1−12) as an alternate Ang II forming pathway has gained importance with the demonstration of increased circulating levels of the substrate in primary hypertensive patients [78•, 79••] and the findings that a monoclonal antibody (mAb) directed against the human Ang-(1−12) C-terminus induces a sustained fall in the elevated blood pressure of transgenic rats with the genetic expression of the human AGT gene in their genome [85••]. The discovery of Ang-(1–12) as an endogenous Ang II-forming substrate reveals a new avenue for developing antihypertensive and cardioprotective therapies that may obviate known shortcomings of current chemical inhibitors while improving patient adherence, a significant problem with antihypertensive therapy [86]. Recent data strengthens how the circulating and paracrine/intracrine systems interact with each other. While the presence of catalytic enzymes cleaving AGT in cellular cytosolic and nuclear compartments seems not to be disputed, less clear is whether the formation of angiotensin peptides results from the metabolism of intracellularly formed AGT or its uptake from the interstitium. Pulgar et al. [87•] showed that AGT is internalized by a non-AT_1-R-dependent pathway in human retinal pigment cells, extending a previous demonstration by us of increased cardiac myocyte uptake of Ang-(1−12) in SHR [88]. These data establish a route for processing internalized AGT into Ang II by chymase, dismissing the faulty argument that chymase has no function in Ang II generation in the rodent and human heart [58•].

Emerging evidence of the limited efficacy of RAS chemical inhibitors to halt disease progression and increased awareness of suboptimal adherence to antihypertensive therapy has brought about the development of molecular interventions capable of modulating or inhibiting gene expression through transcriptional or translational repression. Two different approaches targeting hepatic AGT are currently being tested. One approach uses antisense oligonucleotides (ASO) to suppress the expression of hepatic AGT [89–92, 93••], capitalizing on the early and generally forgotten work of Ian Phillips and colleagues [94] a quarter of a century ago. The other strategy focuses on the repression of hepatic AGT translation through synthesizing small interfering RNA (siRNA) [95–99, 100••, 101, 102••, 103–105]. Both approaches seem to exert suppression of circulating AGT associated with a decrease in blood pressure. While a detailed analysis of the data derived from preclinical and phase I and phase II trials using AGT siRNAs or AGT ASO is outside the scope of this review, the apparent benefits of these procedures in avoiding the need for the daily administration of medications and increasing tolerability may lead to better blood pressure control and adherence to therapy. Nevertheless, a precautionary note has been levied by us [106•] because no information exists regarding the long-term consequences of suppressing the non-angiotensin protein component of AGT protein—des-(Ang I)-AGT [107, 108, 109••]—that is linked to angiogenesis and tumorigenicity [110, 111•, 112].

The discovery of Ang-(1−12) as an alternate non-renin-dependent source for direct Ang II generation suggested the possibility of using immunotherapeutic approaches to prevent the conversion of the Ang-(1−12) substrate into Ang II. The demonstration of a heightened level of plasma Ang-(1−12) in untreated primary hypertension [78•, 85••] stimulated a proof-of-concept study in which a specific mAb directed against the human C-terminus of the dodecapeptide

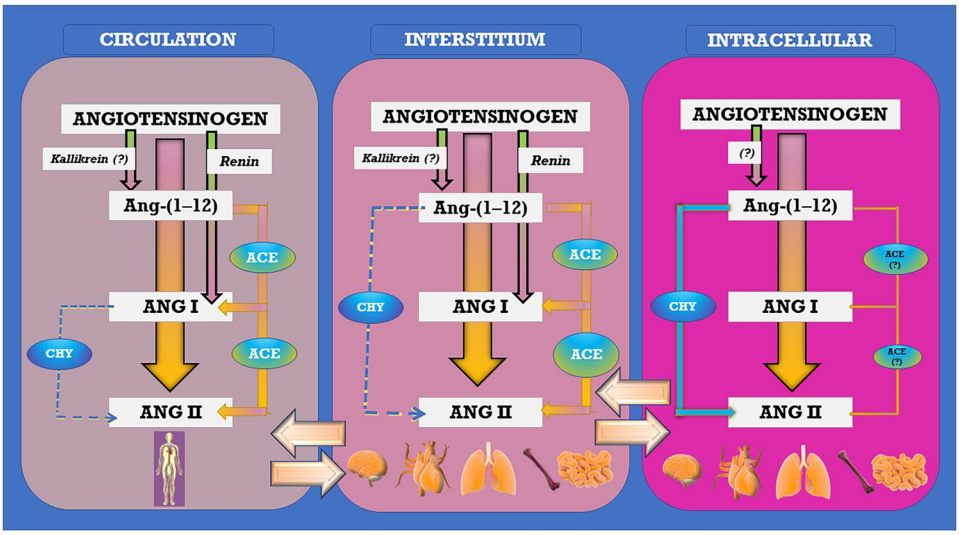


Fig. 4 Contrasting biotransformation pathways for angiotensin II (Ang II) generation in blood, the extracellular interstitium, and the intracellular compartments. Pulmonary epithelial and vascular endothelium ACE are primarily responsible for hydrolyzing Ang-(1−12) into Ang I and Ang II in the circulatory compartment [83]. ACE contribution wanes as the primary source for Ang-(1−12) metabolism in the interstitial space. Within the cell, Ang-(1−12) is converted to Ang II directly as Ang I is essentially not present [65•, 75••, 77•]. Abbreviations as defined in text

counteracted the constrictor activity of generated Ang II and induced a sustained fall in the elevated blood pressure of transgenic rats expressing the human AGT [85••]. The data obtained in this study demonstrate a significant ability of the h-Ang-(1–12) mAb to induce a vasodilator action in isolated perfused carotid artery rings and systemic circulation [85••]. Further work is necessary to determine the long-term effect of Ang-(1−12) immunoneutralization in the control of blood pressure. Nevertheless, the proven specificity of the h-Ang-(1–12) mAb in terms of blocking the catalytic site of the substrate to the actions of ACE and chymase renders this approach beneficial in terms of avoiding problems arising from interfering with the non-angiotensin coding sequence of AGT [106•].

Conclusions

"The emperor has no clothes describes a situation in which people are afraid to criticize something or someone because the perceived wisdom of the masses is that the thing or person is good or important" (https://www.bookbrowse.com/expressions). The applicability of this tale to the topic of this review is a literary license highlighting the general acceptance of the superior properties of ACE inhibitors and ARBs not only in undeniable efficacy in controlling blood pressure but their overestimated efficacy in reducing clinical events and cardiovascular and total mortality. Identifying a *residual risk* many orders of magnitude greater than the *relative risk reduction* in landmark hypertension trials using these drugs yields a different conclusion. This issue, addressed in the past by other investigators [13••, 30••, 33, 113, 114] and the Blood Pressure Trialists [7•, 115, 116], remains unappreciated. Health research dissemination of risk information in *relative risk* is misleading because it compares the same risk of events in another group [3].

Since the original characterization of angiotensin-(1–7) [Ang-(1–7)] by Ferrario's laboratory [117, 118, 119••] as a biologically active peptide functioning to oppose the vasoconstrictor and growth-promoting actions of Ang II, the biochemical physiology of the RAS revealed a complex non-linear system where alternate biotransformation pathways not involving renin or ACE participate in the regulation of arterial pressure, tissue perfusion, and cellular homeostasis. Although the efficacy of chemical drugs to oppose the hydrolytic activity of renin, ACE, or prevent Ang II binding to AT_1-R is now established, their effectiveness in halting adverse cardiovascular remodeling and cardiovascular mortality may be limited because of their lack of access to the cellular compartments where intracrine processing of AGT occurs. Novel strategies suppressing hepatic AGT synthesis or expression or preventing Ang-(1−12) metabolism with a specific mAb/nanobody [85••] create a new opportunity to advance the pharmacotherapy of hypertension treatment and possibly other diseases in which angiotensins play a contributory role.

We hope that the data reviewed here will foster a greater understanding of the limitations of current RAS-based therapies in hypertension, stimulate further research in seeking molecular approaches to halt or even reverse the cardiovascular complications of primary hypertension, and encourage investigating a new generation of ACE inhibitors and ARBs with increased capacity to reach the intracellular compartments at which Ang II can be generated.

Author Contribution All authors contributed equally to the conception of the review and approved the version submitted here.

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Compliance with Ethical Standards

Conflict of Interest The authors declare no competing interests.

Human and Animal Rights Studies from the authors' laboratory discussed in this review article comply with ethical standards and had prior approval by the Wake Forest University internal animal and human review boards.

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- • Of importance
- •• Of major importance

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