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Review

Renin angiotensin aldosterone inhibition in the treatment of cardiovascular disease

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ABSTRACT

A collective century of discoveries establishes the importance of the renin angiotensin aldosterone system in maintaining blood pressure, fluid volume and electrolyte homeostasis via autocrine, paracrine and endocrine signaling. While research continues to yield new functions of angiotensin II and angiotensin-(1–7), the gap between basic research and clinical application of these new findings is widening. As data accumulates on the efficacy of angiotensin converting enzyme inhibitors and angiotensin II receptor blockers as drugs of fundamental importance in the treatment of cardiovascular and renal disorders, it is becoming apparent that the achieved clinical benefits is suboptimal and surprisingly no different than what can be achieved with other therapeutic interventions. We discuss this issue and summarize new pathways and mechanisms effecting the synthesis and actions of angiotensin II. The presence of renin-independent non-canonical pathways for angiotensin II production are largely unaffected by agents inhibiting renin angiotensin system activity. Hence, new efforts should be directed to develop drugs that can effectively block the synthesis and/or action of intracellular angiotensin II. Improved drug penetration into cardiac or renal sites of disease, inhibiting chymase the primary angiotensin II forming enzyme in the human heart, and/or inhibiting angiotensinogen synthesis would all be more effective strategies to inhibit the system. Additionally, given the role of angiotensin II in the maintenance of renal homeostatic mechanisms, any new inhibitor should possess greater selectivity of targeting pathogenic angiotensin II signaling processes and thereby limit inappropriate inhibition.

Contents

Abbreviations: ACE, angiotensin converting enzyme; ACE 2, angiotensin converting enzyme 2; Ang I, angiotensin I; Ang II, angiotensin II; Ang-(1–12), angiotensin-(1–12); Ang-(1–7), angiotensin-(1–7); Ang-(1–9), angiotensin-(1–9); AGT, angiotensinogen; ANRI, angiotensin receptor neprilysin inhibitor; ASO, antisense oligonucleotide; BigAng 25, big angiotensin 25; CVD, cardiovascular disease (s); DRI, direct renin inhibitor; LCZ696, sacubitril-valsartan; HF, heart Failure; MRA, mineralocorticoid receptor antagonist; MrgD, mas-related G-protein coupled receptor member D; NP, natriuretic peptides; NPRA, atrial natriuretic peptide receptor; NEP, neprilysin; RAAS, renin angiotensin aldosterone system.

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1. Introduction

In the face of profound advances in the biomedical sciences, preventive health care approaches, education, and socioeconomic improvements, deaths due to cardiovascular disease (CVD) are globally on the rise when compared with mortality rates 25 years ago [1]. In the USA, rates of middle-aged white non-Hispanic men and women have shown a significant rise in all-cause mortality [2] that may be attributed in part to the impact of societal stresses on cardiovascular health. Roth et al. [1] documented recently that ischemic heart disease remains the leading cause of death worldwide accounting for almost half of the increase in the number of cardiovascular deaths. The 2017 American Heart Association (AHA) update shows heart failure (HF) rates increasing to 800,000 new cases over the last five years [3]. The AHA's update report specifies that the number of people with heart failure (HF) diagnosis is expected to rise by 46 percent by 2030 [3], which computes to eight million HF patients. Disentangling the numerous factors influencing these statistics is outside the objectives of this review article. These data, however, underline the existence of a real disconnect among scientific advances in cardiovascular disease mechanisms, the development of new medicines to halt disease processes, and the void for a more aggressive implementation of health care resources across all segments of the American population.

An emerging illustration of the disconnect in translating scientific knowledge with continual discovery processes in drug development is applicable to heart medicines where a significant impasse has occurred since the introduction of angiotensin II (Ang II) receptor blockers (ARBs) [4,5]. While efforts to surpass the benefits achieved with ARBs through the development of the direct renin inhibitor aliskiren did not meet expectations [6–8], the combination of valsartan with an inhibitor of endopeptidase 24-11 (neprilysin) has shown promise in reducing HF progression when compared with the standard of care [8,9]. Nevertheless, even this new angiotensin receptor-neprilysin combination inhibitor showed limited superiority over conventional angiotensin converting enzyme (ACE) inhibitor therapy [9].

Since the first demonstration of the impact of ACE inhibition on hypertensive patients with the orally active agent teprotide [10], accelerated research efforts by academic investigators and pharmaceutical companies through a 27 years' period brought about the introduction of eleven drugs targeting ACE, nine compounds acting as selective orally active blockers of the Ang II type 1-receptor (ARBs), and one direct renin inhibitor [11]. Mineralocorticoid receptor antagonists were added to this armamentarium to improve efficacy in situations such as primary aldosteronism and resistant hypertension [12]. These remarkable clinical translation achievements are the corollary of a voluminous research literature documenting the importance of the renin angiotensin aldosterone system (RAAS) as a key contributor to the development and progression of cardiovascular disease [13]. Ang II modulation of cellular inter- and intracellular signaling mechanisms participating in growth, cell-to-cell communication, immunity, lipid peroxidation, and insulin resistance plays a fundamental role in cardiovascular pathology.

It is not the scope of this article to review the literature on Ang II physiological mechanisms. Likewise, this review does not intend to address the clinical literature that justifies the use of RAAS inhibitors as the cornerstone of cardiovascular disease therapies. This review addresses emerging limitations behind the translational disconnect between what has been learned in the laboratory setting regarding Ang II roles in cardiovascular disease progression and the real-world effectiveness of RAAS inhibitors in halting or reversing clinical events. Instead, we will underscore one potential explanation for the fact that clinical outcome studies using a direct renin inhibitor, ACE inhibitors or ARBs have demonstrated benefits that are less than what would have been expected. Those wishing to delve more deeply on the arguments presented in this review can access the enclosed references [14–21].

2. Biotransformation pathways of angiotensins. Current concepts

Since the original recognition of renin, angiotensinogen (AGT), and ACE as the critical proteins contributing to Ang II formation, impressive advances in the understanding of the role of this system in both physiology and pathology unmasked that this hormonal system was constituted by a network of proteins, peptides, and receptors more complex than anticipated.

Fig. 1 shows the currently accepted multi-pathway processing steps leading to the generation of the main functionally active peptides Ang-(1–9) [22,23], Ang II, Ang-(1–7) [24,25], and their respective derivatives Ala^1-Ang II [26] and alamandine [Ala^1-Ang-(1–7)] [27]. Critical angiotensins forming substrates are AGT and the shorter AGT derived sequences, angiotensin-(1–25) (BigAng 25) [28] and angiotensin-(1–12) [Ang-(1–12)] [29]. Processing of AGT by renal renin may be particularly important within the circulation and the renal medulla [30–32], whereas non-renin pathways may be more actively engaged in forming Ang II in tissues such as the heart [33,34]. The discovery of the two alternate Ang II-forming substrates, Ang-(1–25) and Ang-(1–12), invigorated the concept that mechanisms of angiotensin peptide formation in organs and cells may not follow the biochemical processing documented in the circulation. In keeping with this interpretation, tissue Ang II formation from either Ang-(1–25) or Ang-(1–12) appears to be primarily due to chymase (EC 3.4.21.39), a member of the serine family of proteinases that are abundantly present in mast cells [35–38]. There are no definitive studies addressing the enzymatic pathway accounting for Ang-(1–12) and Ang-(1–12) generation from AGT. A preliminary report from our laboratory implicates kallikrein or an aprotinin-sensitive enzyme for the cleavage of AGT into Ang-(1–12) [39]. While the potential contribution of Ang-(1–25) as an Ang II forming substrate is confined to one published paper where the substrate was identified from the urine of normal subjects [28], more extensive research on Ang-(1–12) has led to the conclusion that this extended form of angiotensin I (Ang I) is truly a functionally endogenous Ang II generating substrate that is predominantly expressed in tissues serving as an intracrine source for direct Ang II production [40]. Ang-(1–12) expression and content is augmented in the heart of spontaneous hypertensive rats (SHR) [41], the left ventricle of rats expressing the human AGT gene [42], and the enlarged left atrial appendage of subjects with left heart disease and left atrial enlargement [43]. Additional studies document Ang-(1–12) as a source for Ang II actions in modulating

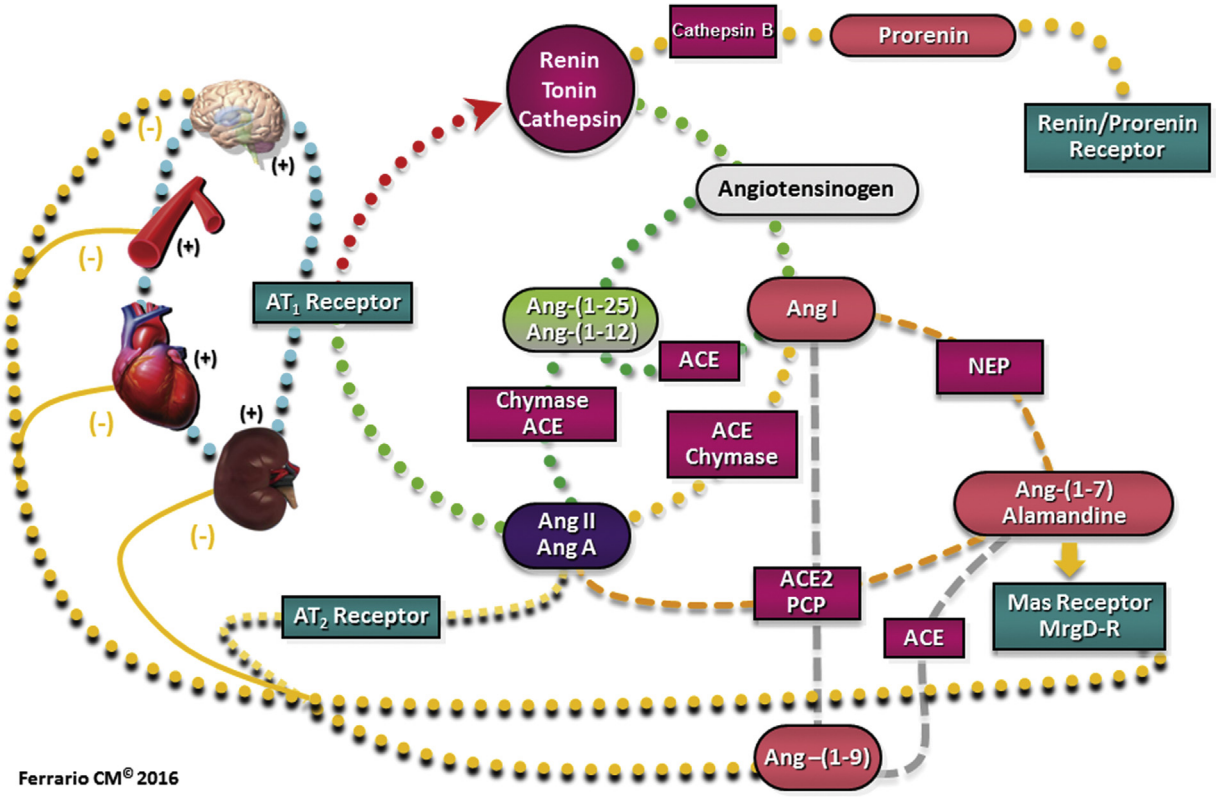

Fig. 1. Schematic diagram of currently characterized biotransformation pathways accounting for the formation of the biological active peptides Ang-(1–9), Ang II, and Ang-(1–7). Peptides with substitution of aspartic to alanine in position 1 of the Ang II and Ang-(1–7) molecules should be viewed as secondary processing pathways.

baroreflexes [44], central sympathetic outflow [45], and augmenting cardiac contractility through altering the electrophysiological properties of the myocytes [46]. Additional studies provide evidence for a tonic role of Ang-(1–12) in the central regulation of blood pressure through the demonstration that cerebrospinal fluid (CSF) delivery of an Ang-(1–12) antibody reduced the magnitude of hypertension in transgenic rats expressing the Ren-2 gene in their genome [47] while Ang-(1–12) injected into the arcuate nuclei of the hypothalamus caused a robust hypertensive response associated with increased splanchnic nerve sympathetic discharges [48]. As illustrated in Fig. 1, Ang II formation from Ang-(1–12) represents a non-renin dependent pathway [34,49]. Ang-(1–12) affinity for chymase is several orders of magnitude higher than for ACE [40]; studies of Ang-(1–12) metabolism in plasma membranes isolated from human left atrial [50] or left ventricular tissues [51] showed chymase as the primary Ang II forming enzyme. A robust but often neglected literature implicates chymase as the primary Ang II forming enzyme from Ang I in humans [35–37,52]. This is of considerable importance as it explains in part the relatively lesser efficacy of ACE inhibitors in suppressing Ang II levels during chronic treatment with these agents [53,54].

A third enzymatic pathway is constituted by the mono carboxypeptidase angiotensin converting enzyme 2 (ACE2) which shows less than 50% amino acid homology with ACE and is insensitive to blockade with ACE inhibitors [55–57]. ACE2 hydrolyzes Ang I into Ang-(1–9) and Ang II into Ang-(1–7) [58]. ACE2 role as a pivot point regulating the formation of the cardio-renal protective peptides Ang-(1–9) and Ang-(1–7), in part through lowering the concentrations of Ang I and Ang II, respectively, may represent a critical step in modulating Ang II actions in the etiopathogenesis of cardiovascular disease [59].

Since the original description of Ang-(1–7) biological activity [60], multiple studies now confirm the existence of an intrinsic arm within the RAAS in which the heptapeptide acts to oppose the vasoconstrictor, trophic, proliferative, and pro-thrombotic Ang II actions. Seminal studies by Ferrario and collaborators on Ang-(1–7) provided the basis for the inclusion of Ang-(1–7) as a counterregulatory arm of the RAAS (reviewed in [61]) and identified neprilysin (E.C. 3.4.24.11) [62], prolyl endopeptidase (E.C. 3.4.21.26), and later ACE2 (EC:3.4.17.23) as Ang-(1–7)-forming enzymes from Ang I [63,64]. Definitive studies demonstrating reduced Ang-(1–7) in essential hypertension [65], the contribution of Ang-(1–7) to the antihypertensive action of ACE inhibitors [66], and its participation in reparative left ventricular remodeling during post-myocardial infarction are reviewed elsewhere [25,39,59,61].

Ang II and Ang-(1–7) biological activity is mediated through the coupling of the peptides to the G-couple receptor proteins –AT_1, AT_2, mas, and the mas-related G protein-coupled receptor-member D (MrgD) receptors [67–72]. Although AT_1 receptors exhibit a wide tissue distribution, expression and function of these proteins have been best studied in cardiovascular, renal, and the peripheral and the central nervous systems. Non-peptide ARBs act as specific AT_1 receptor blockers in the vascular system, adrenal cortex, and the kidneys although losartan, its active metabolite EXP3174 [73,74] and irbesartan [75,76] also act as partial antagonists of thromboxane A2 receptors (TxA2). Likewise, telmisartan behaves as a partial agonist of the peroxisome proliferator-activated receptor gamma (PPAR-γ) [77] while the uricosuric effects of losartan through blockade of the renal tubular uric acid transporter [78–80] are credited with broadening the therapeutic effectiveness of this agent and compensating for the mild hyperuricemia associated with chronic diuretic therapy. Ang II binding to AT_1 receptors stimulates Gq/11 and Gi/o proteins leading to Ca^{2+} signal [81]. Signaling mechanisms mediated by Ang II binding to AT_2 receptors are less defined. Carey's review [82] reports that binding of Ang II to AT_2 receptors results in the activation of phosphotyrosine phosphatase and

Table 1
Reported Side Effects of FDA Approved Renin Angiotensin Aldosterone System Inhibitors.

Drug Class	Reported Adverse Effects[1]
Angiotensin Converting Enzyme Inhibitors [Available in the US are: benazepril (Lotensin™), captopril (Capoten™), enalapril (Vasotec™, Epaned™), fosinopril (Monopril™), lisinopril (Prinivil™, Zestril™), moexipril (Univasc™), perindopril (Aceon™), quinapril (Accupril™), ramipril (Altace™), trandolapril (Mavik™)]	Dried cough (5%–25% of subjects), hyperkalemia, dizziness (lightheadedness or faintness upon rising), headache, drowsiness, diarrhea, low blood pressure, weakness, loss of taste (salty or metallic taste), and rash. Chest pain, increased uric acid levels, sun sensitivity, and increased BUN and creatinine levels have been reported. More serious but rare side effects include kidney failure, allergic reactions (angioedema), a decrease in white blood cells, pancreatitis, and liver dysfunction.
Aldosterone Receptor Antagonists [Available in the US are: eplerenone (Inspra™) and spironolactone (Aldactone™)]	Acne, alopecia, edema, gender dysphoria (amenorrhea, breast enlargement in men), heart failure, hypertension, hirsutism, hypokalemia. Side effects are less severe with eplerenone.
Angiotensin Receptor Blockers [Available in the US are: candesartan (Atacand™), eprosartan (Teveten™), irbesartan (Avapro™), losartan (Cozaar™), olmesartan (Benicar™), telmisartan (Micardis™), valsartan (Diovan™), and azilsartan (Edarbi™).	Headache, fainting, dizziness, nasal congestion, diarrhea, back pain, leg pain. Angioedema and hyperkalemia reported rarely.
Direct Renin Inhibitors [Available in the US is: aliskiren (Tekturna™)]	Side effects comparable to those encountered with ARBs. Diarrhea, however, reported more frequently.
Angiotensin receptor neprilysin inhibitor (ARNI) [Available in the US is sacubitril/valsartan (Entresto™)]	Hypotension, hyperkalemia, cough, dizziness, and rarely kidney failure.

[1]-Prescribing information may be consulted for detailed explanation of side-effects.

consequent inhibition of kinase p 42 and p 44 mitogen-activated protein (MAP) kinases. Ang-(1–7) binding to the mas receptor leads to inhibition of serum-stimulated ERK1/2 MAP kinase activity [83,84]. In an experimental HF model, Ang-(1–7) improved intracellular Ca^{++} mobilization through activation of the mas-related nitric oxide-bradykinin pathway [85]. More recently, elegant experiments by Tezner et al. [72] demonstrate that Ang-(1–7) binding to the MrgD receptor activates the Gαs/AC/cAMP pathway leading to an increase in PKA activity and CREB phosphorylation. Importantly, this study provided definitive evidence that PD123319 is not a selective AT_2 receptor antagonist [72].

3. Benefits and pitfalls of renin angiotensin aldosterone system inhibition

With more than half a century of experience in the use of therapies that are directed to inhibit Ang II actions, ACE inhibitors and ARBs have become an indispensable prescription for the treatment of essential hypertension, progression of chronic renal disease, post-myocardial infarction, congestive heart failure, and type 2 diabetes mellitus. The inclusion of aldosterone receptor antagonists to this therapeutic armamentarium is generally restricted to the management of resistant hypertension [86–88]. A summary of adverse side effects associated with these agents are documented in Table 1. Given that Ang II and Ang-(1–7) should be viewed as pleiotropic hormones, it is not surprising that pharmacological approaches designed to suppress the ACE/Ang II/AT_1 axis or activate the ACE2/Ang-(1–7)/mas axis are being explored in a variety of other human diseases [89].

The wide use of these medications has provided the opportunity to evaluate these agents' true benefits in reducing coronary heart disease, stroke, HF, cardiovascular and all-cause mortality in randomized controlled outcome trials and post-surveillance studies. An emerging literature questions, however, whether the benefit of target organ protection and reduction of cardiovascular risk associated with blockade of RAAS components is achieving what would have been predicted from the voluminous literature that establishes that dysregulation of this system is an obligatory fundamental factor of the mechanisms accounting for target organ damage and cardiovascular-mediated clinical events. The idea that excessive RAAS hyperactivity is optimally inhibited by combining different RAAS inhibitors [90–93] has instead led to worsening, rather than improvement, of clinical outcomes despite apparent benefits in reduction of surrogate measures like hypertension and proteinuria [94–96]. Preclinical studies also demonstrate a critical role of Ang II in the pathogenesis of atherosclerosis [97], however, limited clinical evidence of the antiatherogenic effects of Ang II blockade is available [15,98–100]. Likewise, a report that included 24 trials with 198,275 patient years of follow-up found that RAAS inhibition showed superiority only when compared to placebo but not with active controls in patients with stable coronary heart disease [15]. This conclusion is reminiscent of the report made by the Blood Pressure Lowering Treatment Trialists' Collaboration group who reported no evidence for differences among drug classes for major cardiovascular events [101]. While many arguments may be posited as to the reasons for this disconnect, we have proposed that incomplete blockade of Ang II pathological actions is due to the failure of RAAS inhibitors to access intracellular proteins accounting for canonical and non-canonical mechanisms of Ang II formation [19–21,39].

4. Direct renin inhibitors: an incomplete story

AGT cleavage by renin, considered the rate-limiting step in Ang II generation, is a logical step to inhibit RAAS. Pepstatin was the first synthetic renin inhibitor to be considered for potential therapeutic actions [102]. These early studies led to the development of a series of first-generation agents that required parenteral administration and showed limited activity in healthy volunteers [103,104]. Although orally active compounds like enalkiren, remikiren and zankiren were developed, their clinical potential were not pursued as they had poor bioavailability, short half-life, and weak antihypertensive activity [105]. A more sophisticated structure-based design approach led to the synthesis of aliskiren fumarate, the first non-peptide direct renin inhibitor with favorable pharmacokinetic properties [106]. Aliskiren was approved in 2007 by the FDA and the Europe Middle East and Africa (EMEA) regulatory bodies for the treatment of hypertension, either as a monotherapy or in combination with other antihypertensive agents [107].

A key therapeutic rationale for aliskiren was to achieve complete RAAS inhibition in patients receiving ACE inhibitors or ARBs. It is well documented that following ACE inhibitor treatment there

can be reactive increases in compensatory pathways leading to plasma Ang II returning to pretreatment levels or higher [108]. Likewise, aldosterone breakthrough, observed with ACE or ARB therapy [109–111], may be in part due to adrenal AT_2 receptor activation [112,113] or Ang III non-Ang II receptor stimulation [114]. Increases in plasma renin concentration following therapy with ACE inhibitors or ARBs may in itself be a cardiovascular risk factor [115–117].

Indeed, with aliskiren added to the antihypertensive standard of care, the compensatory rise in plasma renin activity was neutralized suggesting that better RAAS suppression could be now realized [118] and further reductions of blood pressure were observed when combined with other antihypertensives such as ACE inhibitors or ARBs [91,118,119]. These data corroborated and extended earlier studies of Menard and colleagues [90,120] who demonstrated incomplete RAAS suppression with a single agent. Additionally, such data highlight the complexity of RAAS and the existence of non-canonical pathways that contribute to RAAS.

Better end organ protection in patients with kidney disease, HF, and atherosclerosis, independent of blood pressure reductions, is a significant unmet medical need. Hence, ineffective and/or insufficient inhibition of tissue Ang II activity at cardiovascular and renal sites was the biologic rationale used to evaluate aliskiren as an add-on therapy in patients with HF or diabetic kidney disease [121]. The concept that tissue or local Ang II production exerts pathophysiologic effects independent of systemic RAAS had been well established before the development of aliskiren [122]. Implicit in this view was that ACE inhibitors (or ARBs) exert some of their protective effects in tissue independent of blood pressure lowering, however, such effects are incomplete [123].

Initial clinical studies evaluating aliskiren as an add-on to ACE inhibitor or ARB therapy demonstrated beneficial effects on surrogate endpoints, such as reductions in blood pressure and proteinuria. Additionally, adverse effects such as hyperkalemia, renal impairment or hypotension were sufficiently low as to not cause concern. Despite these early positive results, larger trials with longer treatment duration and hard cardiovascular or renal outcomes showed no clinical utility, in fact, adverse effects were observed [124–126]. An experimental study suggested that the antihypertensive response produced by concomitant blockade of both renin and Ang II triggers significant renal injury due to loss of autoregulatory capacity [127]. Currently the use of aliskiren in combination to an ACE inhibitor or ARB is proscribed with no further plans of development.

An understanding of the clinical failures of aliskiren has remained elusive. It is tempting to speculate that combination treatment of aliskiren and ARB revealed a unique and deleterious profile of renin inhibition [128]. Preclinical studies have demonstrated renal accumulation of aliskiren [129,130], which could promote a discordance between renal tissue versus circulating RAAS suppression [131]. In support of this concept, VTP-27999, a more potent renin inhibitor, produced greater renin inhibition that paradoxically resulted in extrarenal RAAS stimulation in healthy volunteers [132]. Consistent with these data are the observations that aliskiren results in a ~2-fold greater increase in plasma renin levels compared to equivalent blood pressure lowering doses of an ACE inhibitor or an ARB [107].

It may be concluded that the therapeutic index of renin inhibition is no better compared to an ACE inhibitor or ARB, and that all therapies have the propensity to inappropriately suppress RAAS when used in combination. Given the strength of the evidence of synergy when combining RAAS blockers to beneficially impact hypertension, HF and kidney disease [90–93], a hypothesis can be formulated that the therapeutic goal of RAAS blockade should be to maximally limit pathogenic Ang II signaling without disrupting renal homeostatic processes. Hence, that aggressive RAAS inhibition has not demonstrated clinical utility may be a failure to maximally inhibit RAAS without provoking renal complications. As previously discussed, non-canonical pathways of pathogenic Ang II generation and signaling underscore the challenges of effective RAAS inhibition as combinations of RAAS inhibitors could in theory offer better efficacy, but also produce a significant renal safety hazard.

Despite the evidence that intrarenal Ang II contributes to hypertension or renal disease [31,133], renal homeostatic functions required for maintenance of renal blood flow and GFR are in part regulated by Ang II [134,135]. That all RAAS components have been identified throughout the entire nephron is suggestive of an essential role of intrarenal RAAS for volume and electrolyte homeostasis [136].

It is well established that RAAS blockage presents a particular risk-to-benefit analysis in regards to renal impairment [137], and that such risks are amplified in the setting of salt-restriction/dehydration [138–140], in the elderly [141], or in patients with diabetes, heart or renal disease [142]. Because Ang II has divergent activities on promoting hypertension and disease as well as maintaining essential renal homeostatic mechanisms, the conflicting results obtained to-date underscore the need to better understand the role of intrarenal RAAS. Such insights could lead the way to the development of a superior inhibitor capable of preserving essential renal Ang II activities while inhibiting pathogenic Ang II signaling.

5. Angiotensin converting enzyme inhibitors

ACE inhibitors are the mainstay of cardiovascular disease treatment and are prescribed for the treatment of hypertension, myocardial infarction, left ventricular dysfunction, HF, diabetic mellitus, and renal insufficiency [143]. The relatively benign side effect profile of ACE inhibitors are summarized in Table 1. The potency of ACE inhibition is influenced by the drug's affinity to interact with the zinc (Zn^{++}) ligand of the ACE [144]. There are three distinct chemical classes of ACE inhibitors. Sulfhydryl containing ACE inhibitors (i.e., captopril) bind strongly with the Zn^{++} ligand but disulphide formation limits their half-life. Drugs containing a carboxyl group constitute most ACE inhibitors. These agents bind to side chains of the enzyme within the active moiety for improved potency and duration of action [144]. A third group of drugs composed of phosphorus-containing ACE inhibitors is represented by fosinopril [145,146]. Although direct ACE inhibitors comparisons among the available agents are rare, lisinopril, perindopril, and quinapril may be favored because of their prolonged half-life and greater lipophilicity [147]. As reviewed elsewhere [18], evidence from large clinical trials document a beneficial effect of ACE inhibitors in retarding HF progression and repeat hospitalizations, adverse cardiac remodeling and increased survival post myocardial infarction, vascular disease secondary to atherosclerosis or hypertension, and chronic renal disease including diabetic nephropathy.

While the antihypertensive effects of these drugs are proven and many studies have confirmed their ability to acutely suppress the conversion of Ang I into Ang II, a consistent suppression of tissue or plasma Ang II concentrations has not been demonstrated [53]. While an ACE escape mechanism has been suggested to account for the recovery of Ang II [148], little attention has been paid to the multiple studies showing that chymase, rather than ACE, is the main Ang II-forming enzyme from either Ang I or Ang-(1–12) in humans in tissues like the heart and vascular wall [20,35–39,52]. Studies by Wei et al. [149] in ACE knockout mice and those of Ahmad et al. [40,50,51,150] and Ferrario et al. [42] in rats expressing the human AGT gene demonstrate a critical role of chymase as a tissue Ang II forming enzyme. Alternate enzymatic pathways may also contribute to Ang II generation. According

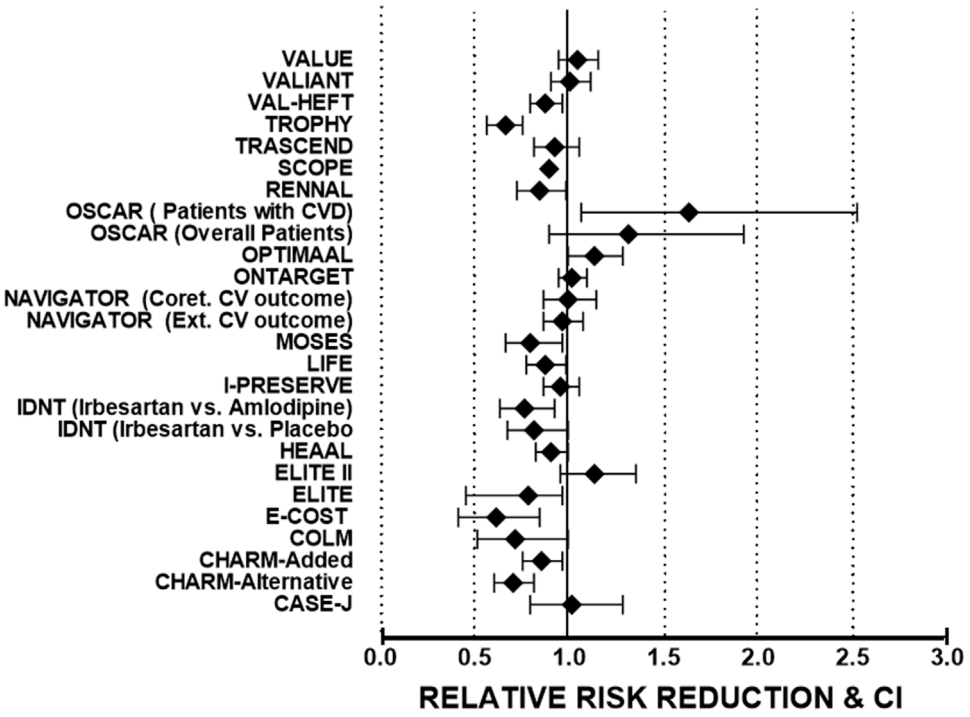

Fig. 2. Relative risk and 95% confidence intervals of the effect of Ang II receptor blockers on primary cardiac end points of large randomized clinical trials. Acronyms are: CHARM-Alternative, Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity [164]; CHARM-Added, Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity [165]; ELITE, Evaluation of Losartan in the Elderly Study [272]; ELITE II, the Losartan Heart Failure Survival Study (Evaluation of Losartan in the Elderly Study) [273]; HEAAL, Heart failure Endpoint evaluation of Ang II Antagonist Losartan [158]; I-PRESERVE, Irbesartan in Heart Failure with Preserved Ejection Fraction Study [169]; LIFE, Losartan Intervention For Endpoint reduction Study [157]; ONTARGET, The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial [274]; OPTIMAAL, Optimal Trial in Myocardial Infarction with the Ang II Antagonist Losartan [275]; TRASCEND, Telmisartan Randomized Assessment Study in ACE Intolerant subjects with cardiovascular Disease [274]; TROPHY, Trial of Preventing Hypertension [162]; VAL-HEFT, Valsartan Heart Failure Trial [159]; VALIANT, Valsartan in Acute Myocardial Infarction trial [163]; VALUE, Valsartan Antihypertensive Long-term Use Evaluation study [161].

to Husain et al. [151] and Dive et al. [152] characterization of a novel inhibitor of the N-terminal active site of ACE suggested the existence of a Ang II-forming metalloproteinase enzyme distinct from both ACE and chymase. No further data exist as to the potential chemical nature and function of this enzyme.

Differences in expression and Ang II-forming enzyme affinity as a function of tissue compartment and species may explain the finding that increased plasma Ang II levels are present in 50 percent of ACE inhibitor treated subjects [54]. The apparent limited ability of ACE inhibitors to maintain a consistent suppression of plasma and tissue Ang II levels in part explains why re-analysis of clinical benefits associated with ACE inhibition from robust meta-analysis of the currently reported clinical trials documents a higher than expected residual risk of clinical events [18]. As reviewed in Reyes et al. [21], the relative risk reduction (RR) achieved with ACE inhibitors for the treatment of hypertension, post-myocardial infarction, and HF averaged 27% in major clinical trials. In keeping with these findings, Baker's et al. [14] analysis of 7 clinical studies that included 32,559 participants showed a RR of 0.87 [95% CI, 0.81–0.94] and 0.83 [CI, 0.73–0.94] for total mortality and nonfatal myocardial infarction, respectively. That means that the absolute benefit of these treatments benefited no more than 17% of treated patients. Similar conclusions were reported by van Vark et al. [153] who found the hazard ratio for ACE inhibitor treated all-cause mortality from hypertensive subjects to average 0.90 (CI, 0.84–0.97). Therefore, the residual risk associated with ACE inhibitors across all examined trials remains unacceptably high. A detailed analysis of the impact of ACE inhibitors on all-cause mortality, cardiovascular mortality, myocardial infarction, stroke, and the composite of myocardial infarction and stroke showed that the number of patients needed to be treated to prevent one event ranged from 67 to 409 [17]. Zanchetti and collaborators have provided a detailed analysis of the significance of the residual risk in treated hypertensive patients [154].

6. Angiotensin receptor blockers

The theoretical rationale for a more specific blockade of Ang II pathological actions through the binding of non-peptide antagonists to the AT_1 receptor accounted for the introduction of ARBs to the antihypertensive prescription armamentarium in 1995 [67]. These drugs ability to achieve their clinical goals bypassing the limitations of an ACE escape phenomena and non-ACE sources of Ang II formation was viewed as a definitive advantage. This is despite their effect to dramatically increase blood Ang II levels due to blockade of AT_1-mediated receptor internalization [13]. The proven ability of ARBs to elicit minimal or essentially non-clinically relevant side effects has been an added advantage of these agents (Table 1). All eight approved ARBs are selective ligands of AT_1 receptors and in pharmacological studies showed significant potency in their ability to cause a rightward shift of the dose-response curve to Ang II [67]. Differences in the ability of ARBs to reduce the maximal response *in-vitro* has led to their subclassification as possessing surmountable or insurmountable antagonism [155]. The clinical impact of these pharmacological ligand-interactions in terms of the drugs ability to achieve lasting antihypertensive effects remains unproven. Large clinical trials utilizing losartan [156–158], valsartan [159–163], candesartan [164–167], irbesartan [168,169], telmisartan [94,96] and olmesartan [170] have proven their ability to control blood pressure in hypertensive patients, reduce stroke-risk, decrease HF hospitalizations, and improve the prognosis of diabetes nephropathy. A composite of key clinical trials RR and confidence intervals is documented in Fig. 2. From the analysis of the 26 trials presented in Fig. 2, the pooled RR reduction averaged 0.93 (C.I.

0.84–1.01). These data demonstrate a relatively small benefit of ARB in the prevention or treatment of clinical events or superiority over either ACE inhibitors or other therapies. On the other hand, only the Losartan Intervention For Endpoint Reduction in Hypertension (LIFE) trial suggests a potential for superiority over other treatments. The extensive data gathered from the investigation of 9124 hypertensive patients with electrocardiographic evidence of left ventricular hypertrophy in the LIFE trial documented that for the comparable antihypertensive actions of the two active treatment arms, those randomized to the losartan-based therapy showed a 13% lower RR of primary cardiovascular events and 25% smaller RR of fatal and non-fatal strokes [157]. Similarly, superior outcomes over conventional therapy were documented in the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) Study [156] and the Irbesartan Diabetic Nephropathy Trial (IDNT) [168] in subjects with type 2 diabetic nephropathy (Fig. 2). As concluded by Düsing [18,171], improved safety and enhanced tolerability over other therapies may be the greatest clinical advantage of this drug class. However, some have questioned whether ARBs show equivalent efficacy when compared with ACE inhibitors [172]. In our minds, such lackluster and/or nonexistent efficacy improvements beyond ACE inhibitors does not negate the role of RAAS in the etiopathogenesis of cardiovascular disease. The small effect of ARBs is suggestive of intracellular sites of Ang II activity that would be largely unopposed [19,20,173–175]. That ARBs induce compensatory pathways that increase circulating Ang II as well as increased expression of downstream metabolites like Ang-(1–7) [13,59] underscore the complexity of understanding the mechanisms that limit their efficacy.

7. Mineralocorticoid receptor antagonists (MRA)

The introduction of spironolactone, the first mineralocorticoid receptor antagonist (MRA), culminated efforts of multiple investigators who in the 1950's were preoccupied with exploring the relationship between aldosterone and sodium metabolism [176,177]. Cranston et al. [178] first report of the modest antihypertensive actions of spironolactone initiated further interest in exploring the role of aldosterone as a causative mechanism of essential hypertension leading Conn to propose that primary aldosteronism could explain between 15 and 25% of the cause of essential hypertension [179]. Comprehensive updates on the mechanism of action and indications of MRA are published [12,119]. The side effects associated with the use of these MRAs are shown in Table 1. Both spironolactone and the newer MRA eplerenone are frequently prescribed in combination with other antihypertensive agents for the treatment of resistant hypertension or HF [180,181]. The increased selectivity for mineralocorticoid receptors (MR) of a new nonsteroidal MRA, finerenone (BAY 94-8662), is the current focus of an aggressive program seeking to assess the efficacy of this third generation MRA on HF, chronic kidney disease, and diabetic nephropathy [182–185]. Finerenone acts as a full antagonist of the MR and shows an even accumulation of the drug in the heart and kidney contrasting with the much larger kidney accumulation of spironolactone and eplerenone.

Emerging strategies to counteract the hypertensive and profibrotic actions of aldosterone are being explored through the development of drugs that inhibit the activity of aldosterone synthase, the enzyme that represents the rate limiting step of aldosterone production [119,186,187]. The advantage of aldosterone synthase inhibitors (ASI) over MRA is that MRA do not block non-genomic actions of aldosterone [119]. In addition, blockade of aldosterone synthesis obviates the reactive increase in MRA-induced aldosterone [119]. The aldosterone synthase inhibitor, LCI699 has been reported to decrease plasma and urine aldosterone concentrations, increases PRA, and prevents target organ damage [188,189]. As reviewed by Oparil and Schmieder [119], disappointing results obtained in phase II clinical trials, including minimal blood pressure reductions to an escape phenomena, resulted in discontinuing the first orally active ASI.

8. Angiotensin receptor neprilysin inhibitor (ARNI)

The combination of the neprilysin inhibitor sacubitril with valsartan, although a combination therapy receiving much attention due to its effects on natriuretic peptides, is included in this review by virtue of its AT_1 receptor blocking component and the potential effects of sacubitril on angiotensin metabolism. While LCZ696 (sacubitril/valsartan) has been approved for the treatment of HF, the vasodilator effects of this combination therapy as an antihypertensive agent remain unappreciated due to its sponsor's focus on HF. Nevertheless, following the first report of the pharmacological actions of LCZ696 by Gu and colleagues [190], a PubMed search reveals 260 publications on this drug to-date.

Neprilysin, or neutral endopeptidase (NEP), catalyzes the degradation of key peptide hormones that regulate cardiovascular and renal homeostasis. NEP actions in angiotensin metabolism include degradation of Ang II and Ang-(1–7), activities that would be expected to produce opposing effects on vasomotor tone and blood pressure [63,191]. However, it is the proteolysis of natriuretic peptides (NPs) by NEP that has garnered much interest. The three members of this family are atrial (ANP), brain or B-type (BNP) and C-type (CNP). ANP and BNP bind to the atrial natriuretic peptide receptor (NPRA), a guanylyl cyclase-coupled receptor located in the vasculature and kidneys. Activation of this receptor increases cGMP leading to vasodilation, natriuresis and diuresis [192,193]. CNP is specific for NPRB, also a guanylyl cyclase-coupled receptor; however, the significance of NPRB activation in the context of the cardiovascular system is less certain. Expression and release of ANP and BNP from cardiomyocytes is increased during heart wall stress and hypertrophy, common HF features. Their activation promotes blood pressure and volume reductions that act to counteract the increased cardiac wall stress. Such effects represent a counterregulatory system to oppose the actions of Ang II. Therefore, maintaining elevated levels of ANP and BNP via inhibition of NEP are an attractive strategy for combating the undesirable effects of inappropriate RAAS activation.

Candoxatril, the first NEP inhibitor evaluated in the clinic, produced dose-dependent increases in ANP and natriuresis in healthy volunteers [194]. Since these encouraging results did not translate to any benefit in patients with hypertension or heart failure, further drug development was halted [195]. An additional failure of another NEP inhibitor, ecadotril, demonstrated the challenges of targeting NEP [196]. In this study, ecadotril was given at four dose levels in HF patients with systolic dysfunction receiving an ACE inhibitor. In support of target engagement, plasma and urinary cGMP increased in a dose-dependent manner. However, ANP levels were not significantly changed [196]. Surrogates of HF suggested no beneficial effects of treatment; in fact, there was a discordance in mortality of more deaths with ecadotril treatment compared to placebo. Additionally, there was a suggestion of drug-induced aplastic anemia which was hypothesized to be due to toxicity of the thioester group of ecadotril.

NEP has broad proteolytic activity beyond natriuretic peptide regulation. NEP also degrades Ang II, renal Ang-(1–7), bradykinin, substance P, adrenomedullin, glucagon, vasoactive intestinal peptide, and amyloid-β [191]. Therefore, NEP inhibition would be predicted to increase some peptides that would counteract the protective effects of increasing NPs or elicit responses that compromise safety. Hence the rationale of combining a NEP inhibitor with either

a ACE inhibitor or an ARB is an appropriate strategy. The first therapy tested with such properties was omapatrilat, which had dual actions to inhibit both ACE and NEP [197–199]. Unlike the previous clinical results with NEP inhibition alone, omapatrilat had potent anti-hypertensive effects that were superior relative to ACE inhibitor treatment [197] and that were accompanied by increased Ang-(1–7) urinary excretion [199]. Additional encouraging signs of improved efficacy compared to the standard of care in HF [200] provided the rationale to test omapatrilat in a large HF outcome trial which demonstrated no benefit compared to enalapril [201]. Worryingly, a reported increase in the occurrence and severity of angioedema halted further drug development. This was considered a consequence of increased bradykinin due to omapatrilat's inhibition of ACE, NEP and aminopeptidase. Considering the poor risk-to-benefit ratio, further clinical development of omapatrilat was discontinued [202].

Combining a NEP inhibitor with an ARB, instead of an ACE inhibitor, had the appeal of having less of an effect to exacerbate the untoward effects associated with ACE inhibitors and led to the development of LCZ696 (Entresto®, sacubitril valsartan), a first-in-class combined NEP inhibitor and ARB. Clinical studies demonstrated LCZ696 to be superior to valsartan for blood pressure lowering [203] and HF amelioration [204,205] without evidence of adverse safety or tolerability [206]. These encouraging results supported the evaluation of LCZ696 compared to enalapril in an 8000 patient outcome study in HF with reduced ejection fraction. The Prospective Comparison of the Angiotensin Receptor–Neprilysin Inhibitor [ARNI] with ACEI [Angiotensin-Converting– Enzyme Inhibitor] to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial (PARADIGM-HF) was powered to determine an effect on the primary composite endpoint of death from cardiovascular causes or first hospitalization for HF following 34 months of treatments [207]. However, after a mean patient follow-up of 27 months, the PARADIGM-HF data monitoring committee recommended early termination of the trial for efficacy [207]. LCZ696 reduced the primary composite endpoint by 21.8% and all-cause mortality by 16%. Such improvements were unprecedented, as they were of the same magnitude of protection observed in the initial studies that established ACE inhibitors as the gold standard in HF treatment [208]. Nevertheless, the authors of this study do not elaborate on the fact that the difference in the reduction of the primary event between HF patients assigned to the enalapril and LCZ696 arms of the study was a mere 4.7% [207]. These effects were consistent across all prespecified subgroups. Although LCZ696 was associated with a higher proportion of patients with hypotension and non-serious angioedema, there was a reduced incidence of renal impairment, hyperkalemia, and cough with LCZ696 treatment [207]. Importantly, the occurrence of serious angioedema was unchanged between both groups.

Entresto® was approved by the FDA in July 2015 for the treatment of HF with reduced ejection fraction and recently was given Class I recommendation authorizing its use as the standard of care. Its efficacy in HF with preserved ejection fraction is currently underway in a 4000+ patient outcome trial (PARAGON-HF). Additionally, the drug sponsor recently announced an effort to evaluate its efficacy and safety in over 40 ongoing and planned clinical trials (FortiHFy program), which would make it the largest industry-sponsored HF clinical program to date. One area of particular concern is any effect of Entresto® to contribute to Alzheimer disease (AD), as animal models demonstrate a role of neprilysin to degrade pathogenic amyloid-β [209]. Current clinical assessments of changes in pathogenic amyloid-β [210] or dementia-related events [211] with Entresto® have not revealed a safety concern; however, longer follow-up studies are still warranted to exclude such concerns.

9. Alternative approaches to RAAS blockade

9.1. Angiotensinogen antisense

Linkage and genetic association studies have suggested an association between AGT and hypertension [212,213]. Common variants within the AGT promoter region and post-translational redox modifications of AGT have been shown to modulate the substrate and be associated with hypertension and hypertensive-related diseases [214–216]. Experimental studies have demonstrated a relationship between plasma AGT levels and hypertension, with seminal work demonstrating that plasma AGT and blood pressure are elevated in transgenic mice with increasing amounts of AGT [217].

Despite the biological rationale of targeting AGT, the substrate has not been a target of traditional small molecule inhibitor approaches, as downstream proteases and/or receptors are much more 'druggable'. Antisense is especially well-suited for such targets, and given the primacy of AGT as the key RAAS substrate, there were early efforts to antisense AGT. Reports of blood pressure lowering following antisense oligonucleotide (ASO) AGT treatments were initially reported from Phillips and co-workers [218–220]. These early reports used unmodified phosphodiester or phosphorothioate linked oligodeoxynucleotides targeting the AUG start codon to inhibit translation initiation, a commonly used early antisense design method. A single dose administration of ASO was administered into the lateral ventricles of the brain and resulted in relatively modest (~30%) but significant AGT reductions within the hypothalamus [220]. Impressive mean arterial pressure reductions, approaching 40 mm Hg, followed AGT ASO administration. Similar doses of the AGT ASO given IV for systemic exposure did not have any effect on blood pressure [221].

With the success of targeting central AGT expression, methods to enable ASO liver delivery to reduce systemic AGT were described. Various strategies were employed, such as liposomal formulation with viral agglutinins [222], liposomal formulation alone [221], asialoglycoprotein-poly(L)lystine-ASO complexes [223–225] and adeno-associated viral (AAV) based [226]. Collectively these reports demonstrate that ASO-mediated systemic reductions of AGT can reduce blood pressure in hypertensive rats. The complexity of these formulations, challenges of AAV-based gene therapy and the requirement of IV administration are significant barriers to translate these methods into clinical approaches for hypertension management. Additionally, the therapeutic effect of these methods was relatively modest, with reports showing only 40–50% maximal reductions of plasma AGT. Major limitations inherent in these methods were (1) the identification of active sequences, (2) the oligonucleotide chemistry and (3) an understanding of the antisense mechanisms.

As stated earlier, early antisense strategies to inhibit translation initiation by targeting the AUG initiation codon were commonly used [227]. Early on this was an attractive strategy as it only required knowledge of the gene sequence at a limited site. However, more potent methods of gene inhibition had been described that utilized RNase H-mediated RNA cleavage of ASO-RNA duplexes [228,229]. The advantages of RNase H-dependent approaches were both mechanistic and practical; for example, RNA could be measured (e.g. by PCR) to determine ASO activity. With the ability to use higher-throughput methods to screen for active ASOs, RNase H-active ASOs are amenable to much larger screens of ASOs such that hundreds (or more) of prospective sequences can be evaluated. Such screening is critical for the identification of ASOs with acceptable tolerability and potency. Although RNase-H active ASOs were used in some reports, the screen used to identify active sequences was inadequate. For example, only 3 AGT ASOs were evaluated [222,223] which is insufficient given our experience.

Another important limitation was the oligonucleotide chemistry. The phosphorothioate (PS) backbone modification described in these reports was critical in the early development of ASOs and allowed for improved nuclease resistance and increased binding to plasma proteins [229]. Further improvements in sugar modifications, applied at the opposite ends of the ASO to create 'gapmers', have provided the most value in improving the pharmacological properties of ASOs. Such sugar modifications improve potency resulting in AGT reductions of up to 90% [230–232]. Finally, oligonucleotide modifications to elicit argonaute 2-mediated RNA cleavage, used in all small interfering RNA (siRNA) approaches, offers another potent mechanism of inhibiting AGT [233]. Thus, ASO gapmer and siRNA methods offer the most potent mechanisms of RNA-based therapeutics currently available. Early development programs have been described using both platforms [234–236]. Such therapeutic approaches offer a unique means of RAAS blockade as compensatory feedback and non-canonical pathways of Ang II generation and signaling may not limit therapeutic efficacy to the same extent that they do with ACE inhibitors and/or ARBs. Safety studies will be required to ensure that the more complete suppression of Ang II via AGT inhibition does not result in dysregulation of renal Ang II homeostatic processes.

9.2. Angiotensin II vaccines

Endogenous immuno-neutralization of circulating Ang I or Ang II has been studied as an alternate single or adjuvant therapy for hypertension. As reviewed by Oparil and Schmieder [119], vaccines directed to block Ang II have been relatively effective clinically and no evidence has been obtained as to their efficacy and ability to produce sustained antihypertensive responses that are accompanied by reduction in clinical events.

9.3. Activators of AT_2 receptors or the ACE2/Ang-(1–7)/mas receptor axis

The characterization of ACE2 as a pathway for Ang II degradation and the observation that significant cardiac dysfunction was associated with ACE2 gene suppression in mice [55,237,238] allowed skeptic investigators to accept the existence of an endogenous system in which Ang-(1–7) represented an internal feedback mechanism for limiting Ang II hyperactivity [24,25,59,61]. These contributions also stimulated the development of AT_2 receptor agonists as a potential approach to compensate for Ang II actions.

Compound 21 (C21) is the first non-peptide agonist of the AT_2 receptor that is investigated as a potential antihypertensive compound [239–241]. Vasorelaxant and potent natriuretic actions of C21 in experimental models of hypertension failed to be associated with sustained blood pressure reductions [242–244] unless concomitant AT_1 receptor blockade is included in the study. The absence of robust and sustained antihypertensive actions may limit the future clinical development of AT_2 receptor agonists.

More intensive approaches have been applied to drugs augmenting the activity of the ACE2/Ang-(1–7)/mas receptor axis. These approaches focus on facilitating the cardiorenal protective actions of Ang-(1–7) through enhancing Ang II metabolism by ACE2 [245], facilitating conversion of Ang I into Ang-(1–9), or both. Clinical experience with human recombinant ACE2 (hrACE2) is limited to studies in normal healthy volunteers [246] and an ongoing clinical trial involving patients with acute respiratory distress syndrome (Clinical Trial Identifier NCT01597635). In healthy volunteers, administration of hrACE2 was associated with no changes in blood pressure and significant decreases in plasma Ang II levels; changes in plasma Ang-(1–7) levels were inconsistent [246].

Protecting or extending the bioavailability and half-life of Ang-(1–7) is another approach that is being investigated clinically as a critical body of experimental research suggest it as a viable avenue for drug development. Strategies include: a)- Ang-(1–7) encapsulation in hydroxy-propyl-β-cyclodextrin (HP-β-CD/Ang1-7); and b)- preventing Ang-(1–7) enzymatic degradation via inclusion of a thioether bridge to the peptide [247]. Clinical evidence for a beneficial effect of augmenting Ang-(1–7) activity has been negative.

10. Summary and conclusions

Björn Folkow, the notable Swedish physiologist, first called attention to the importance of *"adaptive changes of vascular structure"* as a mechanism contributing to the increased vascular resistance of essential hypertension [248,249]. The increased vascular resistance reflects an adaptive structural change in precapillary resistance vessels to the increased load. Vessel thickening augments their reactivity to neurohormonal stimuli as well as altering the ratio between the thickness of the vessel wall and its lumen. The adaptive structural response of resistance vessels to elevated blood pressure may limit their maximal vasodilator response, as documented in experimental [248] and clinical studies [250–253]. The combined contributions of vascular hypertrophic remodeling, increased vascular stiffness and vascular endothelial dysfunction over a long time period may explain the less than optimal efficacy of current treatments with drugs that inhibit the expression or action of Ang II. On the other hand, the common clinical experience that combining RAAS agents with another agent from a different drug class achieves superior antihypertensive effects suggests otherwise [92]. On an aggregate, laboratory research and genome approaches continue to implicate a causal role of excess neurohormonal drive in the pathogenesis of CVD. Pleiotropic Ang II actions in cardiac and vascular remodeling, increased neurogenic drive, stimulation of immune adaptive processes, build-up of radical oxygen species, release of thrombogenic factors, and extracellular matrix remodeling, provide compelling evidence to its contribution to the myriad of etiopathogenetic mechanisms of CVD. In accepting this evidence, we are faced with the issue of what is the cause of the disconnect between the science behind the functions of the RAAS and the clinical outcomes of preventing its blockade.

While discussion of these issues may raise as much ire as disturbing a hornet's nest, there are indeed two major possible explanations that need to be considered. First, tissue mechanisms associated with the cardiac and vascular adaptive response to hypertension, coronary heart disease and HF may be associated with or caused by activation of intracrine mechanisms of Ang II formation and action [20,21,173,174,254–257]. Biochemical mechanisms for angiotensin generation and receptor signaling are present within the cellular environment including nuclei and mitochondria [258–260]. As reviewed by Kumar et al. [173] direct evidence for intracrine activity is inferred by the demonstration that intracellular dialysis of Ang II, Ang-(1–7), or renin in cardiac myocytes is associated with changes in junctional conductance. In keeping with this interpretation, intracellular delivery of Ang-(1–12) altered the excitability of WKY cardiac myocytes, an effect that could be prevented by administration of chymostatin or valsartan [46]. Several studies have documented no changes in cardiac Ang II content during chronic inhibition of ACE or AT_1 receptor blockade [19,20,261,262]. We have proposed that these data suggest a failure ACE inhibitors, ARBs and renin inhibitors to reach the intracellular site(s) at which Ang II is generated [20,21]. Second, multiple studies have documented that chymase rather than ACE is the major Ang II forming enzyme from either Ang I [36,52,263] or, more recently, Ang-(1–12) [33,40,50]. Thus, pathogenic non-canonical paracrine and intracrine mechanisms of Ang II are unaffected by the current standard of care [19].

While the clinical importance of these alternate Ang II mechanisms remains to be precisely documented, it is evident that a more promising drug development program should be based on creating drugs that can neutralize intracellular formation or action of Ang II. Wei et al. [264] reported improved left ventricle function, decreased adverse cardiac remodeling, and improved survival of hamsters treated with combined ACE and chymase inhibition in a model of post myocardial infarction. In addition, a strong body of experimental evidence demonstrates robust antiarrhythmic effects of chymase inhibition [265,266] while additional studies reported beneficial effects of chymase inhibition in reversing vascular atherosclerosis and adverse cardiac remodeling [267–271]. The relevance of chymase in CVD will be tested in an ongoing clinical study evaluating the chymase inhibitor BAY1142524 in a post-myocardial infarction setting (CHIARA MIA 2).

Such pathologic actions of Ang II must be weighed against the essential role of Ang II to preserve renal homeostatic functions. As with any therapy, there is an inherent risk-to-benefit ratio defining the therapeutic index of a RAAS inhibitor. Thus, one of the many challenges of RAAS drug discovery will be to find new methods to inhibit this system which result in therapies with greater efficacy and no compromise in safety.

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