Hypertension

REVIEW

Angiotensinogen Reconsidered: Evolving Perspectives in Hypertension Research

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ABSTRACT: Hypertension is the leading modifiable risk factor for cardiovascular disease, stroke, chronic kidney disease, and premature mortality. Although AGT (angiotensinogen) is a central component of the renin-angiotensin-aldosterone system, it was historically viewed primarily as a biochemical substrate rather than an active regulator of blood pressure and received less attention as a therapeutic target in hypertension compared with downstream renin-angiotensin-aldosterone system components such as angiotensin-converting enzyme and angiotensin II receptors. However, emerging evidence highlights its dynamic, tissue-specific role in blood pressure regulation and its responsiveness to metabolic, hormonal, and inflammatory stimuli. This narrative review examines the molecular biology, structure-function relationships, and regulatory mechanisms of AGT, including genetic variants such as M235T and −6G>A, which contribute to interindividual and population-level susceptibility to hypertension. We further explore AGT's pathogenic role in salt-sensitive hypertension, obesity-related inflammation, and renin-angiotensin-aldosterone system escape phenomena. Recent translational advances, including RNA-based therapeutics such as small interfering RNAs (zilebesiran) and antisense oligonucleotides (tonlamarsen), demonstrate promising blood pressure reductions and favorable safety profiles in clinical trials. AGT also shows potential as a biomarker for hypertensive nephropathy and treatment responsiveness. This review underscores the value of AGT as an upstream therapeutic target and diagnostic marker, offering new avenues for precision medicine and long-acting strategies in the management of both conventional and resistant hypertension while possibly addressing medication adherence-related obstacles.

Key Words: angiotensinogen ■ hypertension ■ inflammation ■ obesity ■ risk factors

Almost one-third of people worldwide suffer from hypertension (1.39 billion individuals), which is a major modifiable risk factor for heart failure, stroke, atherosclerotic cardiovascular disease, CKD, and early mortality.[1]

AGT (angiotensinogen), the obligate precursor of all angiotensin peptides, occupies a central position within the renin-angiotensin-aldosterone system (RAAS) and exerts substantial influence over pathway activity.[2] Conventionally, AGT was regarded as a passive substrate; however, it is increasingly recognized that AGT is not an inert substrate but a dynamically regulated determinant of RAAS activity, with tissue-specific expression and regulation that may contribute to blood pressure (BP) control, particularly under pathophysiological conditions where RAAS activation is amplified.[3,4]

In addition, under pathological conditions, genomic variations in the *AGT* gene, such as M235T and −6G>A, as well as epigenetic and hepatic regulatory mechanisms influenced by environmental factors like inflammation, oxidative stress, and salt intake, result in elevated AGT expression and an increased risk of hypertension.[5,6] Rising circulating AGT levels are independently associated with higher systolic and diastolic BP, even after adjusting for renin or aldosterone levels.[4]

Current antihypertensive drugs primarily target downstream RAAS components, such as ACE (angiotensin-converting enzyme) and AT_1 (angiotensin II type 1) receptors, to lower BP and decrease the risk of major adverse cardiovascular events.[7] However, hypertension control rates remain poor, and clinical challenges remain, including treatment-resistant hypertension, patient drug response variability, and medication adherence issues related to lifelong polypharmacy.[8] Accordingly, preclinical and early phase clinical trials demonstrate notable and sustained reductions in BP, as well as favorable safety and pharmacokinetic profiles, for novel therapeutic approaches that inhibit the

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Nonstandard Abbreviations and Acronyms

ACE	angiotensin-converting enzyme
AGT	angiotensinogen
Ang I	angiotensin I
Ang II	angiotensin II
AOPP	advanced oxidation protein product
ARB	angiotensin receptor blocker
ASGPR	asialoglycoprotein receptor
ASO	antisense oligonucleotide
AT1	angiotensin II type 1
BP	blood pressure
CKD	chronic kidney disease
GWAS	genome-wide association studies
IL-6	interleukin-6
MESA	Multi-Ethnic Study of Atherosclerosis
NGAL	neutrophil gelatinase-associated lipocalin
RAAS	renin-angiotensin-aldosterone system
SBP	systolic blood pressure
siRNA	small interfering RNA
SNP	single-nucleotide polymorphism
STIM1	stromal interaction molecule-1
TNF-α	tumor necrosis factor-α

synthesis of AGT, such as small interfering RNAs (siRNAs) and antisense oligonucleotides (ASOs) that specifically silence AGT mRNA in hepatocytes.[9,10] Both use RNA degradation pathways to alter the expression of AGT. While siRNAs direct RNA-induced silencing complex-mediated degradation in the cytoplasm through Ago2-dependent slicing, ASOs enlist RNase-H1 to cleave target mRNA in the nucleus.[11]

This review aims to fill a critical gap in the understanding of the AGT in the pathophysiology and treatment of hypertension. Despite its central role in RAAS biology, there is new evidence on its intricate and underappreciated regulatory mechanisms, as well as its potential as a novel therapeutic target. It focuses on the dynamic role of AGT in the molecular regulation of BP, genetic contributions to the risk of hypertension, and associated pathophysiological mechanisms. We further investigate the clinical importance of AGT by assessing its usefulness as a biomarker, examining evidence on therapeutics that target and lower AGT, and highlighting ongoing studies, knowledge gaps, and potential directions for precision medicine and innovative treatments for hypertension.

MOLECULAR BIOLOGY OF AGT

The AGT gene is 13 kilobases long, with 4 introns and 5 exons, and is located on chromosomes 1q42–43 in humans.[2] The AGT protein, a 55 to 60 kDa glycoprotein that functions as renin's primary substrate, is produced and initiates the RAAS cycle.[2] Ang I (Angiotensin I) is produced when renin breaks down AGT, and the ACE subsequently converts it to Ang II (angiotensin II). Ang II is a strong vasoconstrictor. It increases BP and triggers an increase in aldosterone production by the adrenal cortex. Aldosterone acts on the kidney to promote sodium retention and intravascular volume expansion, which completes the traditional RAAS pathway, maintaining vascular tone and fluid-electrolyte balance.[7]

The transcription of the AGT gene is controlled by a variety of stimuli including glucocorticoids, estrogen, and cytokine-responsive sites, such as those impacted by IL-6 (interleukin-6) and TNF-α (tumor necrosis factor-α).[12] Thyroid hormones, dexamethasone, and synthetic estrogens such as ethinyl estradiol are further modulators that affect tissue-specific AGT synthesis in the liver, adipose tissue, kidneys, and brain.[12]

Mechanisms of posttranscriptional control also play a role, particularly through the elements of the 3′ untranslated region, which impact the stability of mRNA and the efficiency of translation.[3]

This careful control helps the body respond to physiological and pathological changes. For instance, inflammation and hormone signals can increase AGT levels in the liver and other areas, which directly affect vascular tone and sodium balance.[3,8,12] Plasma AGT levels and diastolic BP are positively correlated, indicating that differences in RAAS components may explain 15% to 20% of interindividual BP variability in the general population.[13] Although AGT circulates at much higher absolute concentrations than renin, plasma levels are near the Km of renin, such that renin is not fully substrate-saturated. Consequently, modest increases in AGT can significantly enhance angiotensin generation and raise BP.[13,14].

MOLECULAR STRUCTURE AND FUNCTION OF THE AGT PROTEIN

Renin cleaves the essential N-terminal peptide sequence of the AGT protein, a globular-shaped secretory α2-globulin, to initiate RAAS activation.[2,3] The resulting des (Ang I)-AGT was once believed to be biologically inactive, but it is now understood to have additional regulatory roles unrelated to angiotensin synthesis.[3,8] Evidence indicates that des(Ang I)-angiotensinogen plays a role in physiological processes such as liver steatosis, adipose tissue growth, and angiogenesis inhibition, underscoring its significance beyond Ang II synthesis.[15]

Structural and crystallographic studies indicate that glycosylation and redox conditions, which might serve as checkpoints for renin binding and enzymatic activity, influence conformational changes that impact the accessibility of the renin cleavage site inside AGT.[3]

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Although the liver is the primary location for AGT synthesis, the presence of local paracrine and autocrine RAAS axes is supported by extrahepatic production in adipose tissue, renal proximal tubules, vascular endothelium, and the central nervous system.[3,16] AGT levels in plasma typically exceed the Michaelis-Menten constant (Km) for renin, indicating that changes in AGT levels have a direct impact on Ang I availability and the activation of RAAS that follows.[16]

Because elevated AGT levels result in higher Ang II production even in the presence of reduced renin activity, experimental models suggest that AGT abundance can individually cause RAAS activation. In patients treated with ACE inhibitors, AGT overexpression may sustain residual angiotensin II synthesis through ACE-independent pathways, contributing to so-called RAAS escape.[7,15,16] Experimental data demonstrate that alternative proteases such as chymase can generate angiotensin II from angiotensin I or angiotensin$^{1-12}$ within cardiac and vascular tissues, thereby bypassing ACE and promoting persistent tissue RAAS activation.[15,16] In contrast, angiotensin receptor blockers (ARBs) block AT_1 receptor signaling irrespective of the angiotensin II source and may permit preferential activation of AT_2 receptors, which exert vasodilatory and protective effects.[17,18] Although conventional RAAS inhibition may prevent this ACE-independent Ang II generation, it may nevertheless lead to persistent hypertension and cardiac remodeling.[15]

These molecular dynamics demonstrate AGT's critical regulatory function in the RAAS and validate its potential as an upstream therapeutic target.[7,9,10] As illustrated in Figure 1, AGT overexpression initiates a cascade of downstream events, ranging from renal sodium retention to vascular remodeling, that collectively contribute to hypertension and end-organ damage.

GENETIC VARIANTS OF AGT AND HYPERTENSION RISK

Single-nucleotide polymorphisms (SNPs), GWAS (genome-wide association studies), and functional genomic models, demonstrate that AGT is linked to the pathogenesis of hypertension through genetic mechanisms.

Single-Nucleotide Polymorphisms

Among the most extensively investigated AGT variants is the M235T (rs699) variant, a missense polymorphism located in exon 2 of the AGT gene. Across multiple populations, the methionine-to-threonine substitution has been associated with higher plasma AGT concentrations and elevated BP.[13,19] The promoter variant −6G>A (rs5051), which is in strong linkage disequilibrium with the 235T allele, enhances hepatic AGT transcription and likely accounts for much of the functional signal attributed to M235T.[19] Additional variants, including rs4762 (T174M) and rs5051 (−6G>A), are frequently linked to increased plasma AGT levels, hypertension, and cardiovascular disease, although the most consistent epidemiological and functional evidence implicates rs699.[15] Notably, carriers of the 235T allele often exhibit a more pronounced hypertensive phenotype and greater dietary salt sensitivity.

A Copenhagen City Heart Study analysis, which included 9100 participants, assessed the relationship between the M235T and T174M polymorphisms and high BP. A higher risk of high BP was linked to the TT genotype, and there was a statistically significant difference in plasma AGT levels between 235T homozygotes and 235M carriers in both men and women.[20] Furthermore, in a recent prospective pilot study of 95 hypertensive Jordanians, variability in the BP–lowering response to valsartan was associated with the AGT M235T genotype, along with age, height, and sex, underscoring the role of genetic and demographic factors in personalized antihypertensive therapy.[21]

Other regulatory SNPs, such as G–217A and A–20C, are located in the 5 upstream promoter region and affect transcriptional regulation through altered binding of hepatocyte nuclear factors and estrogen response elements.[22,23] These changes affect AGT production differently depending on the tissue and hormones present, leading to variations in BP between individuals and populations. Significantly, the influence of AGT variants may differ by ethnicity and sex, further highlighting their complexity, as shown in Table 1.[24]

Apart from the extensively studied M235T and promoter variations, other polymorphisms, like T174M (Exon 2), are linked to preeclampsia because of potential impacts on protein conformation.[25] In certain groups, preeclampsia risk is increased by −217A>G, which increases AGT transcription in hepatic and placental tissues.[26] AGT, ACE, and AT1R variant combinations also synergistically increase RAAS activation, raising the risk of severe preeclampsia and early onset hypertension, according to gene-gene interaction studies.[27]

GWAS and Population Genetics

Large-scale GWAS strongly support the role of AGT in controlling BP. The MESA (Multi-Ethnic Study of Atherosclerosis) cohort shows clear links between different versions of the *AGT* gene and both systolic and diastolic BP in various ethnic groups.[28] Simultaneously, a GWAS found *cis*-acting SNPs close to the AGT promoter were responsible for 20% to 30% of the heritability of plasma AGT levels, making AGT one of the most potent genetic regulators of its own expression.[29] These variations were linked to characteristics of intermediate BP in addition to affecting AGT plasma concentrations. In addition, studies

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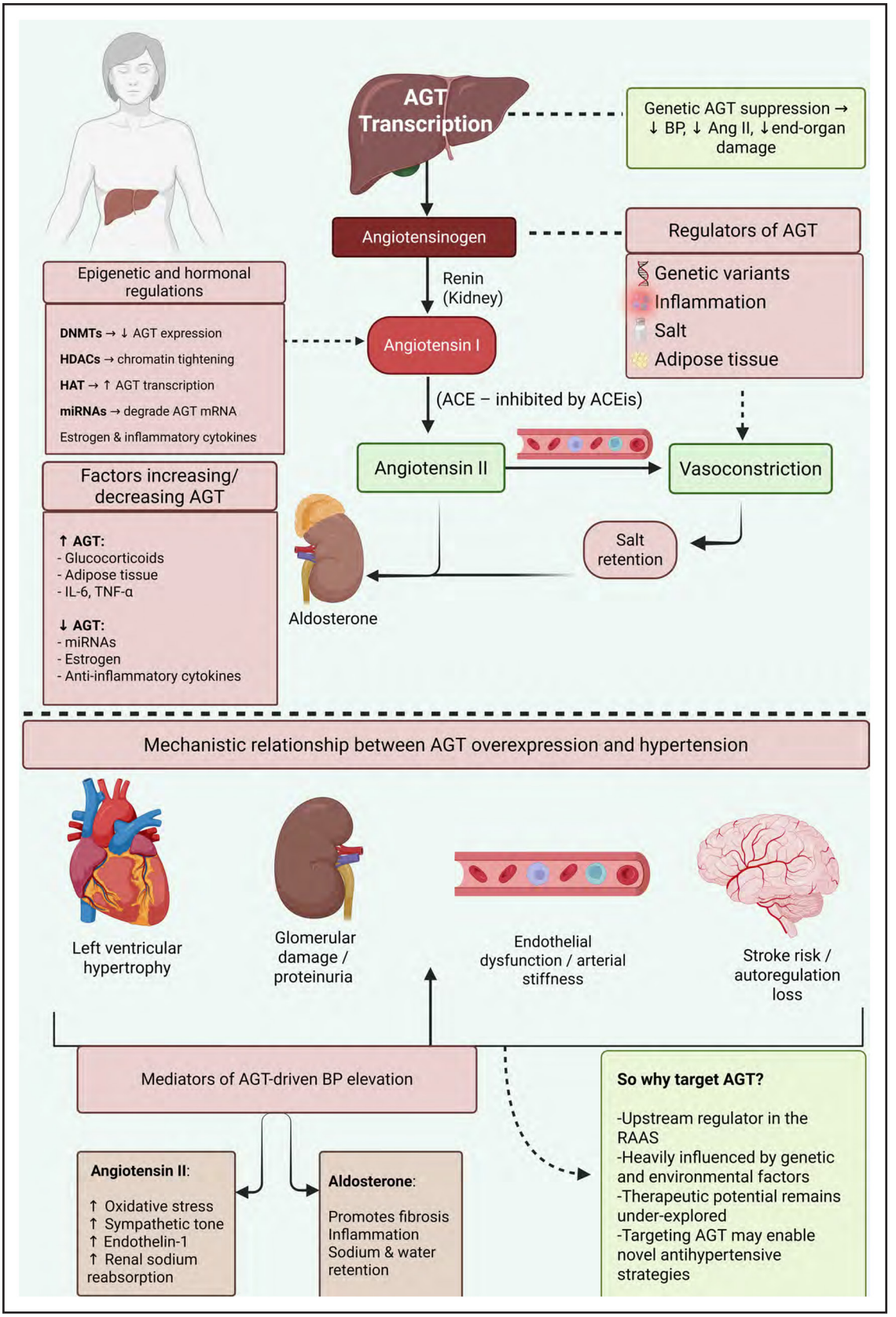

Figure 1. Mechanistic role of AGT (angiotensinogen) in hypertension: regulatory factors, pathways, and end-organ impact.
Ang II indicates angiotensin II; BP, blood pressure; DNMT, DNA methyltransferase; HAT, histone acetyltransferase; HDAC, histone deacetylase; IL-6, interleukin-6; miRNA, MicroRNA; RAAS, renin-angiotensin-aldosterone system; and TNF-α, tumor necrosis factor-alpha.

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Table 1. Key Angiotensinogen (AGT) Polymorphisms and Their Clinical Impact on Hypertension and Preeclampsia

Polymorphism	Location	Effect on AGT	Associated phenotypes	Study population(s)
M235T (rs699)	Exon 2	↑ AGT expression and plasma levels	Hypertension, preeclampsia	European, Asian, African, Indian, Iranian
−6G>A (rs5051)	Promoter	↑ Promoter activity; linked to M235T	Hypertension, preeclampsia	Various
−20A>C	Promoter	May affect transcription factors binding; more data is needed	Hypertension (inconsistent data)	Small cohorts; unclear
−217A>G	Promoter	↑ Placental/liver AGT transcription	Preeclampsia	Iranian, Black, White
T174M	Exon 2	Less studied; more data is needed	Preeclampsia (limited data)	Limited population data
AGT+ACE+AT1R combo	Multiple genes	Synergistic increase in RAAS activation	Severe preeclampsia, early onset HTN	Indian and Chinese women

Adapted from references.[12,15,17–21] AGT indicates angiotensinogen; RAAS, renin-angiotensin-aldosterone system; HTN, hypertension, ↑, increased; and ↓, decreased.

found strong links between different *AGT* changes and BP traits, especially in salt-sensitive populations. These studies also found that individuals with *AGT* risk alleles respond less to ACE inhibitors, suggesting that understanding these genes could help tailor treatment for high BP.[30]

Functional Genomics and Therapeutic Validation

Significant drops in intrarenal Ang II levels and systemic BP are seen in experimental investigations employing liver-specific Agt knockout mice, confirming the causative function of hepatic AGT protein in BP maintenance.[13,31] Other studies support these findings by deleting the enhancer regions of the Agt gene in mice using CRISPR/Cas9. The regulatory significance of AGT expression control in the pathophysiology of hypertension was further supported by the complete resistance of mice with specific enhancer deletions to salt-sensitive hypertension under high-salt settings.[32]

PATHOPHYSIOLOGICAL ROLE OF AGT IN HYPERTENSION

Through complex tissue-specific and systemic mechanisms, AGT is thought to be more than just a quiet precursor in the RAAS; it plays an active role in the pathophysiology of hypertension. A significant body of research demonstrates that pro-hypertensive inflammatory, hormonal, and metabolic signals, irrespective of standard downstream RAAS components, have an impact on AGT levels.[8,33]

Overexpression of AGT, Obesity, and Inflammation

An essential factor in regulating AGT levels is adipose tissue, particularly visceral fat. AGT mRNA is increased in adipocytes, and both body mass index and circulatory AGT levels positively correlate with its expression.[8] IL-6 and TNF-α are 2 cytokines that mediate the inflammation linked to obesity, which further stimulates AGT synthesis in the liver and adipose tissues.[8] This local overproduction stimulates sympathetic activation, salt retention, and vasoconstriction by elevating systemic Ang II.[8] Increased BP in experimental mouse models with overexpression of adipose-specific AGT highlights the direct hypertensinogenic activity of this gene.[31,34]

Salt Sensitivity and Intrarenal AGT

The kidney's expression of AGT is significant in salt-sensitive hypertension. In the tubular environment, intrarenal AGT operates locally to elevate Ang II, where it enhances sodium reabsorption by activating the Na^+/H^+ exchanger and epithelial sodium channels.[16] Conversely, hepatic AGT mostly maintains circulating levels. Even when systemic renin activity is reduced, animal studies demonstrate that high-salt diets increase intrarenal AGT mRNA, which may suggest a renin-independent amplification loop.[16,32] This intrarenal RAAS overactivity is a feature of salt-sensitive hypertension and is associated with salt-responsive increases in BP in human populations.[8]

Estrogen and Sex-Specific Effects

The AGT promoter region contains estrogen-responsive regions, which demonstrate that estrogen has a significant impact on AGT expression.[17] Some of the reported variation between men and women in the prevalence and severity of hypertension may be due to sex-specific differences in AGT expression and function.[8,18] Because higher circulating AGT concentrations are a result of elevated estrogen levels during pregnancy, this regulatory axis is fundamental. When maladaptive, estrogen-induced elevation of hepatic AGT may lead to gestational hypertension and partially account for the physiological plasma volume expansion seen during pregnancy.[6,17,25]

AGT as RAAS Escape's Central Amplifier

Because of compensatory or chronic overexpression of AGT, pharmacological blockage of the RAAS with

ACE inhibitors or ARBs frequently fails to suppress the system entirely.[4,7,33] Particularly in organs like the kidney and heart, residual AGT can act as a rate-limiting factor for ongoing Ang II synthesis due to this RAAS escape phenomenon.[33] The inability to fully suppress AGT within tissue-specific RAAS pathways highlights its role as a central amplifier of hypertensive signaling. AGT integrates hormonal, inflammatory, and epigenetic inputs, sustaining local RAAS activation and contributing to the pathophysiology of hypertension, as illustrated in Figure 1.

ANGIOTENSINOGEN LEVELS AND HYPERTENSION: A LONGSTANDING ASSOCIATION WITH CLINICAL EVIDENCE

Plasma AGT levels are elevated in individuals with hypertension compared with normotensive controls, as demonstrated by several cross-sectional and case-control studies. One of the latest evidence, from a cross-sectional study of 64 newly diagnosed, treatment-naïve obese hypertensive men and 40 obese normotensive controls who underwent 24-hour ambulatory BP monitoring,[35] plasma AGT levels were significantly higher in the hypertensive group and independently associated with elevated 24-hour systolic BP, diastolic BP, and pulse pressure, even after adjusting for age and plasma Ang II. This indicates a potential role for AGT in BP regulation beyond downstream RAS components.

Similarly, in a large cross-sectional analysis from the MESA cohort involving 5786 participants without clinical cardiovascular disease at baseline, plasma AGT levels were measured to evaluate their relationship with BP and hypertension across sex and ethnic groups.[4] The study found that women had significantly higher AGT levels than men across all ethnicities, with the highest levels observed in White participants and the lowest in Chinese participants. After adjusting for relevant covariates, higher AGT levels were associated with higher systolic BP (SBP) and diastolic BP and increased odds of prevalent hypertension. In men not taking RAAS-blocking medications, a 1 SD increase in AGT was associated with a 2.61 mm Hg increase in SBP, compared with 0.97 mm Hg in women. While these associations were moderated by ACE inhibitor or ARB use, the relationship between AGT and BP remained statistically significant in most subgroups. However, the study did not find a significant association between AGT levels and incident hypertension after adjustment.

In a 2025 retrospective study assessing novel biomarkers for hypertensive nephropathy, urinary AGT levels were significantly elevated in patients with hypertensive nephropathy compared with both hypertensive patients without nephropathy and healthy controls. AGT concentrations demonstrated a strong positive correlation with traditional markers of renal impairment, including serum creatinine, blood urea nitrogen, and uric acid, and were inversely correlated with estimated glomerular filtration rate.[36] Logistic regression identified urinary AGT as an independent risk factor for hypertensive nephropathy (odds ratio [OR], 1.436 [95% CI, 1.183–1.742]; $P<0.05$). Although AGT alone demonstrated good diagnostic performance (area under the curve [AUC], 0.807; specificity: 100%), its sensitivity was moderate (51.7%). When combined with other biomarkers, namely serum STIM1 (stromal interaction molecule-1), AOPPs (advanced oxidation protein products), and urinary NGAL (neutrophil gelatinase-associated lipocalin), the diagnostic accuracy markedly improved (AUC, 0.973), showing that AGT's value may come as part of an integrated biomarker strategy for early hypertensive nephropathy detection.

AGT DYNAMICS IN DIFFERENT FORMS OF HYPERTENSION

The regulation of AGT in different hypertensive states is incompletely understood. While most evidence links chronic hypertension to elevated plasma and tissue AGT, far less is known about its role in acute severe BP elevations or acute severe hypertension. In contrast, pregnancy-related hypertension and preeclampsia have been more directly studied.

Pregnancy and Preeclampsia

Plasma AGT rises during normal pregnancy under estrogenic influence, but its alteration in preeclampsia remains controversial, with some contemporary views suggesting that placental factors and AT1 receptor autoantibodies are more central drivers than systemic RAAS activation or AGT elevation.[37] In a pilot study of 17 preeclamptic and 17 normotensive pregnant women, total plasma AGT levels were unchanged, but the proportion of oxidized AGT was significantly higher in preeclampsia and correlated with BP, implicating oxidative modification of AGT in the pathophysiology.[38] As discussed above, genetic variants such as the M235T polymorphism in the AGT gene are linked to increased plasma AGT levels and heightened risk of preeclampsia,[6] further supporting the relationship.

In contrast, the evidence on urinary AGT levels in preeclampsia is relatively more limited and inconsistent across the studies.[39] For example, urinary AGT/creatinine ratios were higher in pregnancy than in nonpregnant controls in a study of 90 women, but slightly lower in preeclampsia compared with normal pregnancy, while still correlating positively with BP and proteinuria, indicating that intrarenal RAS activation might contribute to disease severity.[40]

Acute Severe Hypertension (Previously Hypertensive Urgency and Emergencies)

In a matched case-control study of 75 patients with malignant hypertension between 1995 and 2005, compared with 150 hypertensive and 150 normotensive controls, the AGT M235T TT genotype in White individuals was strongly associated with malignant hypertension.[41] Within this malignant cohort, TT carriers also had worse renal dysfunction and more microangiopathic hemolysis.[41] Direct in vivo or clinical evidence of rapid AGT modulation during episodes of hypertensive urgency and emergencies is limited. Understanding whether AGT alters transiently in these settings could clarify its role in acute pathophysiological responses.

POTENTIAL OF ANGIOTENSINOGEN AS A DIAGNOSTIC/PROGNOSTIC BIOMARKER

As outlined above, AGT holds promise as a diagnostic and prognostic biomarker because, as the sole precursor to all angiotensin peptides, its levels reflect upstream activation of the renin-angiotensin system. Elevated AGT concentrations, whether in plasma or urine, are associated with hypertension and its severity, renal injury, and cardiovascular disease, while genetic variants like M235T further support its role in identifying individuals at increased risk for these conditions. Despite its central role, AGT is not currently widely used as a clinical biomarker, partly due to overlapping influences from other RAAS components and confounding variables, including renin levels and sodium intake. Beyond these confounding factors, although AGT measurement is technically feasible with stable and reproducible assays (eg, ELISA), its current clinical use is limited by assay accessibility and complexity, lack of standardization, and insufficient validation. From an analytical perspective, wider adoption of AGT as a clinical biomarker will require greater assay standardization. Current assays differ in the epitope(s) recognized and whether they quantify intact AGT, des(Ang I)-AGT, or total AGT, and there are no universally accepted calibration standards or cutoff values across platforms.[42] Preanalytical factors such as fasting status, time of day, posture, sodium intake, and concomitant use of RAAS inhibitors or diuretics might possibly introduce biological and analytical variability, particularly in patients with chronic kidney disease (CKD) or resistant hypertension, where volume status and RAAS activation are labile. Potential intraindividual variability over time and the lack of harmonized reference ranges across sex, ethnicity, and kidney function strata further complicate the interpretation of single measurements and serial monitoring. A key unresolved question is whether plasma or urinary AGT provides sufficient incremental predictive value beyond established markers to justify routine measurement. Most available studies have not systematically evaluated the added prognostic contribution of AGT on top of BP, estimated glomerular filtration rate, albuminuria, and traditional cardiovascular risk factors using discrimination and reclassification metrics. In CKD and resistant hypertension, where biomarker burden is already high, it will be important to demonstrate that AGT meaningfully improves risk stratification or treatment selection, for example, by identifying patients at the highest risk of renal progression or those most likely to benefit from intensive RAAS blockade or AGT-targeted therapies. Prospective cohorts and intervention trials incorporating AGT into multivariable risk models will be essential to clarify its clinical utility.

CONVENTIONAL ANTIHYPERTENSIVES EFFECT ON ANGIOTENSINOGEN

The impact of conventional antihypertensives on AGT levels is limited. ACE inhibitors suppress angiotensin II formation, which disrupts the negative feedback on renin secretion, leading to increased renin levels and a compensatory rise in hepatic AGT production.[43] ARBs, by blocking AT1 receptors, similarly enhance renin release and may indirectly stimulate AGT expression. The impact of β-blockers on AGT varies: by dampening sympathetic stimulation, they can lower renin output and potentially reduce AGT synthesis,[44] though findings are inconsistent across different agents. Calcium channel blockers do not directly influence the RAAS and potentially exert minimal effect on AGT,[45] with any changes likely resulting from secondary hemodynamic shifts. Diuretics, through plasma volume reduction, activate the RAAS, increasing renin secretion and potentially upregulating AGT as part of a physiological attempt to reestablish fluid homeostasis.

NOVEL THERAPEUTIC APPROACHES TARGETING AGT

The key therapeutic approaches, mechanisms, and comparative advantages of targeting AGT in hypertension management are summarized in Table 2.

AGT-Targeting siRNA

Zilebesiran is a GalNAc-conjugated siRNA designed to selectively silence the AGT gene in hepatocytes.[9] The GalNAc moiety facilitates targeted delivery via high-affinity binding to the ASGPR (asialoglycoprotein receptor), which is abundantly expressed on hepatocytes. Upon receptor-mediated endocytosis, the siRNA is internalized and incorporated into the RNA-induced silencing complex.[46] Guided by sequence complementarity, the RNA-induced silencing complex-loaded antisense

Table 2. Comparison of AGT-Targeted Therapies, Renin Inhibitors, and ACE Inhibitor/ARBs on RAAS Modulation and Clinical Outcomes

Effect/ parameter	AGT-targeted therapies	Direct renin inhibitors	ACE inhibitor and ARBs (grouped)
Mechanism of action	Lowers angiotensinogen substrate → blocks the entire RAAS cascade upstream	Inhibits the renin enzyme → reduces angiotensin I formation	Blocks ACE enzyme or angiotensin II receptor → inhibits angiotensin II effects downstream
Effect on angiotensin II levels	Marked reduction due to substrate depletion	Decreased, but compensatory, renin increment can limit the effect	ACE inhibitor: decreased angiotensin II; ARBs: angiotensin II may increase due to feedback
Renin feedback/ compensation	Reduced renin levels due to less substrate	Increased renin activity due to feedback	Increased renin and angiotensin II levels due to feedback
Aldosterone suppression	Upstream inhibition: Reduces angiotensin II formation at the source, resulting in significant aldosterone suppression	Generally lowered due to reduced angiotensin II production	Reduce angiotensin II activity, leading to initial aldosterone suppression.
	Blunted feedback: low AGT levels limit renin activity, preventing aldosterone escape	Suppression can be incomplete or variable because of compensatory mechanisms and possible aldosterone escape	Increased renin and angiotensin II (in ARBs) may trigger aldosterone escape
	Sustained action: long-acting RNA-based therapies ensure persistent suppression of aldosterone production		
Blood pressure control	Potentially more consistent and long-lasting control, yet more evidence required from clinical trials	Effective, but may be limited by feedback	Effective but subject to escape phenomena and variable control
Tissue-specific RAAS inhibition	Possible, with targeted delivery to the kidney, adipose, and brain	Systemic only	Systemic only
Duration of effect	Long-acting (weeks to months with RNA therapies)	Short-acting (daily dosing)	Short-acting (daily dosing)
Renoprotection and proteinuria	Promising benefits from local RAAS suppression	Monotherapy is less effective than ACE inhibitor/ARBs for renal outcomes	Proven benefit in reducing proteinuria and slowing CKD progression
		No clear evidence of superior long-term renoprotection in large trials	
Impact on fibrosis/inflammation	Strong theoretical and preclinical antifibrotic potential via upstream angiotensin II suppression	Preclinical studies show attenuation of cardiac and renal fibrosis	Well-established antifibrotic effects via inhibition of angiotensin II-mediated profibrotic pathways
	May surpass ACE inhibitor/ARBs by reducing local tissue RAAS activity more completely	Clinical evidence is limited; no consistent antifibrotic benefit in large human trials	Long-term use slows structural remodeling in the heart and kidneys
	Animal models show reduced renal, cardiac, and adipose fibrosis		Considered the standard of care for antifibrotic RAAS intervention
Side effect profile	Under investigation, likely fewer off-target effects	Hyperkalemia, hypotension risk	ACE inhibitor: cough, angioedema risk; ARBs: generally well tolerated
Limitations	Current studies are limited to preclinical and early phase clinical trials	Traditional approaches inhibit specific steps further downstream in the RAAS cascade, rather than targeting AGT at the upstream level Conventional therapies targeting the RAAS cascade are susceptible to RAAS escape	
	The long-term safety profile and potential adverse events have yet to be fully evaluated		
	Patients with chronic hypertension often face challenges adhering to daily oral regimens, making compliance a significant barrier to effective blood pressure control Standard therapies, such as ACE inhibitors, affect both systemic and local RAAS pathways, potentially leading to adverse effects including cough, hyperkalemia, and angioedema		
	The risks associated with AGT suppression during acute stress or physiological challenges remain unclear		
	AGT-targeting therapies are currently administered via subcutaneous or intravenous injection, restricting their accessibility to hospital settings		
Advantages	Antisense oligonucleotides (ASOs) and small interfering RNAs (siRNAs) silence AGT at the transcript level, targeting an upstream component of the RAAS cascade	They demonstrate well-established efficacy in reducing arterial blood pressure and cardiovascular morbidity and mortality	
	These therapies offer a prolonged duration of action, with dosing intervals ranging from monthly to every 6 months, helping to overcome compliance issues—a major barrier in hypertension management	They exhibit a relatively rapid pharmacodynamic response, suitable for acute blood pressure management	

(*Continued*)

Table 2. Continued

Effect/ parameter	AGT-targeted therapies	Direct renin inhibitors	ACE inhibitor and ARBs (grouped)
	Oral bioavailability allows for ease of administration		
	They hold potential for personalization, as treatment can be tailored to individuals with high-risk genotypes or elevated plasma AGT levels, advancing the field of precision medicine		
	Generic formulations contribute to cost-effectiveness and broad population access		
	RNA-based therapeutics targeting AGT are designed to selectively reduce hepatic AGT production, minimizing effects on renal and central nervous system RAAS activity and potentially lowering the risk of off-target adverse events	They confer end-organ protection, including cardioprotective and nephroprotective effects, and improve outcomes in patients with comorbid diabetes	
	Their pharmacokinetics, safety profiles, and adverse event management are well characterized in clinical practice		
	They are endorsed by international clinical guidelines for the management of hypertension, heart failure, and chronic kidney disease		

ACE indicates angiotensin-converting enzyme; AGT, angiotensinogen; ARB, angiotensin II receptor blocker; CKD, chronic kidney disease; RAAS, renin-angiotensin-aldosterone system; and RNA, ribonucleic acid.

(guide) strand of siRNA binds to AGT mRNA, promoting its endonucleolytic cleavage and degradation.[46] This posttranscriptional gene silencing significantly reduces hepatic AGT synthesis, leading to decreased systemic levels of AGT, the precursor of angiotensin I and II, thereby attenuating activation of the RAAS.[46] By targeting AGT at its hepatocytes specifically, zilebesiran offers a durable and upstream mechanism for sustained BP reduction (Figure 2). In clinical studies, zilebesiran produced dose-dependent reductions in circulating AGT of ≈70% to 85%, with sustained suppression lasting up to 6 months, indicating substantial but incomplete inhibition of functional plasma AGT.[9,47]

The KARDIA-1 phase 2 randomized trial evaluated zilebesiran in adults with mild to moderate hypertension. Subcutaneous doses of 150 to 600 mg administered every 3 or 6 months significantly reduced 24-hour ambulatory systolic BP at 3 months compared with placebo, with reductions up to 16.7 mm Hg. Zilebesiran was generally well tolerated; most adverse events were mild, including injection site reactions and mild hyperkalemia.[47]

Furthermore, the phase 2 KARDIA-2 randomized clinical trial highlights the potential of zilebesiran as an important add-on therapy for patients with inadequately controlled hypertension.[48] In this context, a single subcutaneous dose of zilebesiran was evaluated as add-on therapy in 663 patients with inadequately controlled hypertension despite stable treatment with either indapamide, amlodipine, or olmesartan.[48] Three months after treatment, zilebesiran significantly reduced 24-hour mean ambulatory SBP compared with placebo across all cohorts: by −12.1 mm Hg with indapamide, −9.7 mm Hg with amlodipine, and −4.5 mm Hg with olmesartan.[48] Similarly, while mild hyperkalemia, hypotension, and acute kidney injury occurred more frequently with zilebesiran, most events were self-limited.[48]

The top-line results of the phase 2 KARDIA-3 trial were presented at the European Society of Cardiology's Congress in August 2025. The data are not formally published yet. Overall, findings on zilebesiran's efficacy and safety as a novel AGT-lowering strategy for BP control among patients on single standard antihypertensive agents, yet the long-term impact of the treatment, including cardiovascular outcomes, and potential adverse events in larger populations remain to be elucidated. There is a phase 3 cardiovascular outcomes trial planned (REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT07181109).

As a novel biologic agent, zilebesiran may pose challenges related to cost-effectiveness, insurance coverage, and patient access following approval. In addition, given its mechanism of action within the RAAS, concomitant use of zilebesiran with ACE inhibitors, ARBs, potassium-sparing diuretics, or NSAIDs may carry a theoretical risk, particularly in patients susceptible to renal impairment; however, further evidence is needed to clarify the safety and clinical relevance of such combinations.

AGT-Targeting Antisense Oligonucleotides

Antisense inhibition of AGT has been studied for over 20 years, with early preclinical evidence showing that AGT-targeting antisense RNA reduced BP and AGT expression in hypertensive murine animal models.[49]

A recent preclinical study evaluated hepatocyte-targeted GalNAc-conjugated ASOs in LDL receptor−/− hypercholesterolemic mice (n=~10–15/group) fed a Western diet for 12 weeks.[50] Weekly subcutaneous AGT ASOs (1–5 mg/kg) significantly reduced plasma AGT, lowered systolic BP, and attenuated atherosclerotic lesion area in a dose-dependent manner.[50] Compared with losartan (15 mg/kg per day), AGT ASOs achieved greater renin upregulation and BP reduction, with similar antiatherosclerotic effects.[50] In addition, AGT ASOs, but not losartan, reduced liver steatosis, suggesting Ang II-independent metabolic benefits of hepatic AGT suppression.

REVIEW

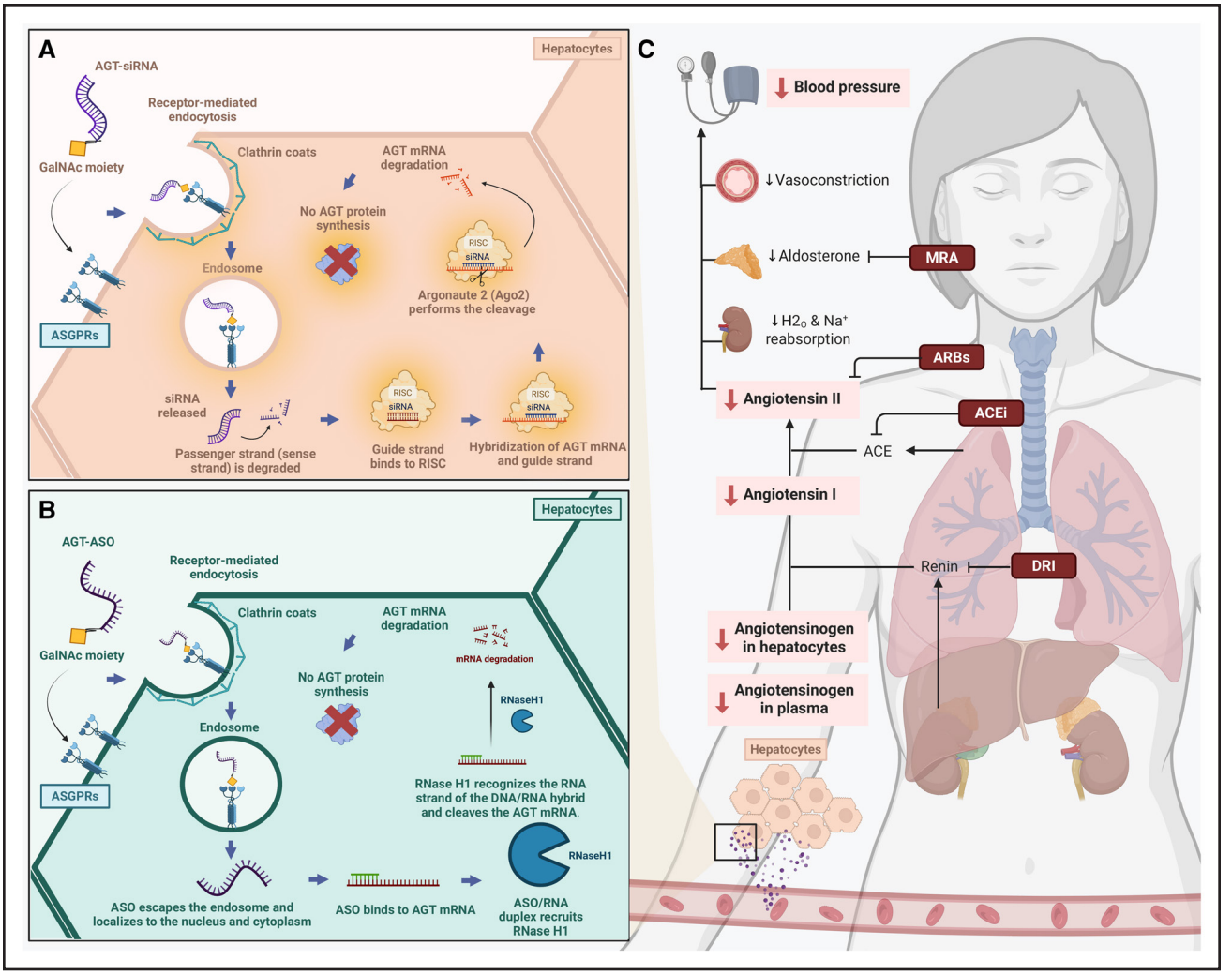

Figure 2. Mechanisms of AGT (angiotensinogen) gene silencing by small interfering RNA (siRNA) and antisense oligonucleotides in hepatocytes.
This figure illustrates the cellular mechanisms by which AGT expression is inhibited using siRNA (**A**) and antisense oligonucleotides (ASO; **B**), both of which are conjugated to GalNAc for targeted delivery to hepatocytes via ASGPR-mediated endocytosis. siRNA-mediated silencing involves incorporation into the RNA-induced silencing complex (RISC) complex and cleavage of AGT mRNA by Ago2, while ASOs hybridize with AGT mRNA and recruit RNase H1 for targeted degradation. **C**, Shows the downstream physiological effects of reduced AGT production, including decreased formation of angiotensin peptides and subsequent lowering of blood pressure, as well as targeting by conventional antihypertensives.

In recent years, there has been growing emphasis on generating clinical evidence to evaluate the safety and efficacy of AGT-targeting ASOs in humans. A GalNAc-conjugated antisense oligonucleotide targeting hepatocyte-derived AGT, IONIS-AGT-LRx, represents a novel, hepatocyte-targeted approach to RAAS inhibition evaluated for safety, pharmacodynamics, and antihypertensive potential in early phase randomized, double-blind, placebo-controlled clinical trials. A study assessed IONIS-AGT-LRx across 3 trials: 1 phase 1 in healthy volunteers and 2 phase 2 trials in hypertensive patients (monotherapy n=25; add-on therapy n=26).[10] Weekly subcutaneous 80 mg dosing for 6 to 8 weeks led to significant reductions in plasma AGT (−54% to −67%, $P<0.001$) with no serious adverse events or significant effects on potassium, renal, or liver function. BP reductions were observed (SBP −8 to −12 mm Hg; diastolic BP −1 to −6 mm Hg), though not statistically significant, potentially due to small sample sizes.[10]

Another small trial evaluated ION904, a next-generation GalNAc-conjugated ASO targeting hepatic AGT, in a phase 1 single-ascending dose study (n=56) and a phase 2 pilot trial in hypertensive patients (n=48).[51] Monthly subcutaneous dosing over 3 months produced up to 86% plasma AGT reduction ($P=0.001$) with no serious adverse events, hyperkalemia, renal or hepatic dysfunction, or thrombocytopenia.[51] Though not powered for efficacy, 42% of treated subjects achieved ≥10 mm Hg SBP reduction versus 30% in the placebo group. There is also an ongoing trial of ION904 (otherwise known as

tonlamarsen) among patients with uncontrolled hypertension that is ongoing (REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT06864104).

A phase 2 pilot study randomized 26 patients with uncontrolled hypertension on 2 to 3 medications (including ACE inhibitor/ARB) to weekly subcutaneous IONIS-AGT-LRx (80 mg) or placebo for 8 weeks. The AGT inhibitor achieved a 67.4% AGT reduction versus 3.4% with placebo ($P<0.001$). Mean SBP/diastolic BP reductions were −12/−6 mm Hg versus −5/−1 mm Hg with placebo, and more patients on IONIS-AGT-LRx achieved BP targets (SBP ≤140 mm Hg: 50% versus 25%; diastolic BP ≤80 mm Hg: 56% versus 12.5%). No safety concerns or RAAS-related on-target effects were observed.[52]

A systematic review and meta-analysis included 4 randomized controlled trials (n=512) evaluating injectable AGT inhibitors (Zilebesiran and IONIS-AGT-LRx) versus placebo in hypertensive patients.[53] AGT inhibitors significantly reduced plasma AGT (mean differences [MD] −77.9%), systolic BP (MD −14.2 mm Hg), and diastolic BP (MD −8.5 mm Hg) without increasing serious adverse events, hyperkalemia, hypotension, or discontinuation.[53] Injection site reactions were more frequent (RR 5.86), but overall tolerability was favorable, supporting AGT inhibition as an effective, long-acting antihypertensive strategy.[53]

Overall, these results support the potential of AGT-targeting ASOs as a safe, durable upstream RAAS inhibitor. The mechanism of AGT-targeting ASOs is shown in Figure 2.

Other Potential Strategies

A preclinical study used the CRISPR-Cas9 system to partially disrupt the AGT gene in the liver of spontaneously hypertensive rats, aiming for long-term BP control.[32] In both young (5-week) and adult (12-week) spontaneously hypertensive rats (n=4–5/group), a ≈40% reduction in hepatic AGT led to significant, sustained BP reduction for up to 1 year. Plasma angiotensin I and II levels dropped, renin activity remained intact, and the physiological response to sodium depletion and furosemide was preserved. The effect was also observed in normotensive rats.[32] These findings suggest that a one-time gene-editing approach could durably control hypertension without impairing stress responses in the preclinical context.

Another preclinical study demonstrated that immunoneutralization of human angiotensin$^{1-12}$ lowers BP in a transgenic hypertensive rat model, suggesting a novel therapeutic approach,[54] although there is currently no direct evidence supporting the neutralization of AGT itself as an effective antihypertensive strategy or whether it is practically feasible.

Overall, while early phase studies of siRNA and ASO therapies targeting hepatic AGT have demonstrated promising and durable reductions in BP with generally favorable safety profiles, several uncertainties remain. The long-term physiological consequences of sustained upstream RAAS suppression have not been defined, particularly in relation to adaptive pathways, renal hemodynamics, and electrolyte homeostasis, and the immunogenicity and reversibility of nucleic acid-based agents warrant further study given their prolonged pharmacodynamic effects. In addition, the slow offset of gene-silencing therapies may limit the ability to rapidly de-escalate RAAS inhibition in clinical scenarios such as acute kidney injury, hypovolemia, or pregnancy, and it is unclear whether partial renin escape, chymase-mediated angiotensin II formation, or other aldosterone regulatory mechanisms emerge during chronic AGT depletion. Finally, whether reductions in BP achieved through upstream AGT inhibition translate into improved cardiovascular outcomes remains to be established, and dedicated phase 3 outcome trials will be essential for determining net clinical benefit and identifying which patient populations are most likely to benefit.

THERAPEUTIC POTENTIAL OF AGT INHIBITION IN RESISTANT HYPERTENSION

Resistant hypertension is clinically defined as BP that remains above the recommended target, generally ≥140/90 mm Hg, or ≥130/80 mm Hg in patients with comorbid conditions such as diabetes or CKD, despite adherence to a regimen of 3 antihypertensive agents from different classes, one of which must be a diuretic, all administered at maximally tolerated or optimal doses.[55] The definition also encompasses individuals whose BP is controlled but who require 4 or more antihypertensive medications to achieve normotension, so-called controlled resistant hypertension. Before establishing the diagnosis, it is imperative to exclude pseudo-resistance, including factors such as inaccurate BP measurement, poor medication adherence, the white coat effect, and secondary causes of hypertension.[56]

Resistant hypertension affects ≈10% to 20% of individuals with hypertension and is associated with worse cardiovascular and renal outcomes.[57] Given the high prevalence and poor outcomes associated with resistant hypertension, AGT-targeted therapies may offer a novel avenue to improve BP control and mitigate organ damage by offering many system-specific or patient-oriented treatment options.

Resistant Hypertension Due to CKD

Urinary AGT has been shown to dynamically reflect renal structural changes and predict acute kidney injury-to-CKD progression, with sustained elevation correlating

with renal fibrosis.[58] Similarly, another study used renal tubule–specific Agt knockout mice (RT-Agt$^{-/-}$) in both Akita and streptozotocin-induced diabetic models to demonstrate that intrarenal RAS inactivation attenuates diabetic kidney disease progression via modulation of glomerular hemodynamics and SGLT2 expression, supporting AGT-targeted strategies as potential therapies for CKD-associated resistant hypertension.[59] In a multicenter, prospective, single-arm study of 205 patients with overt proteinuria treated with valsartan, baseline urinary AGT and its reduction over 24 weeks independently predicted both short- and long-term antiproteinuric response, highlighting the potential of AGT as a biomarker and therapeutic target in proteinuric kidney disease.[60] In a rat model of protein overload-induced nephropathy, proteinuria significantly upregulated renal AGT expression in proximal tubules, promoting local angiotensin II generation and contributing to tubulointerstitial injury, highlighting AGT's key role in mediating proteinuria-driven kidney damage.[61] Together, these findings suggest that targeting AGT could be highly beneficial in CKD by not only serving as a dynamic biomarker for early detection and monitoring of disease progression but also by disrupting the intrarenal RAAS activation that drives hypertension and tubulointerstitial fibrosis.

Obesity-Associated Resistant Hypertension

In human adipose tissue from obese individuals, AGT expression was confirmed at both mRNA and protein levels, indicating that adipocytes may locally produce AGT-derived peptides, potentially linking adipose RAAS activity to obesity-related metabolic dysregulation.[62] In a transgenic mouse model, adipose-specific overexpression of AGT promoted adipocyte hypertrophy and obesity. These effects were reversed by AT2 receptor deletion, although AT2 deficiency exacerbated AGT-induced hypertension via increased renin expression, highlighting AGT's dual role in obesity and BP regulation.[63] Obesity also promotes systemic inflammation and sympathetic nervous system overactivity, both of which stimulate RAAS activation.[64,65] In normotensive individuals, especially those with a family history of hypertension, plasma AGT levels were positively correlated with body mass index, leptin, and BP, suggesting that adipose-derived AGT may contribute to obesity-related hypertension risk even in early, prehypertensive stages.[66] AGT-targeted therapy is especially appealing in this context as it addresses both the metabolic and hormonal drivers of resistant hypertension.

Vascular Remodeling and Resistant Hypertension

Studies using multiple genetically modified mouse models, including Tsukuba hypertensive mice transgenic for human AGT and renin, Agt hypomorphic mice with reduced plasma AGT, LDL receptor deficient mice, and mice with adult onset Agt knockdown via antisense oligonucleotides, consistently demonstrate that AGT promotes atherosclerosis independently of plasma cholesterol.[8] Vascular inflammation promotes atherosclerosis through a positive-feedback loop in which locally produced angiotensin II induces interleukin-6 synthesis, which in turn stimulates hepatic AGT production via the JAK/STAT3 pathway, amplifying vascular RAAS activity and inflammation, suggesting that targeting this axis may reduce atherosclerosis, even though specific studies on AGT are lacking.[67] Hence, targeting AGT can prevent or reverse maladaptive vascular remodeling and improve BP control.

Several important limitations should be acknowledged in the current clinical evidence supporting AGT-targeted therapies. Most available studies are early phase trials with relatively small sample sizes and short follow-up durations, limiting the assessment of long-term efficacy and safety. BP reduction has been the primary surrogate end point, while effects on hard cardiovascular and renal outcomes remain unknown. In addition, heterogeneity in background antihypertensive therapy, dosing regimens, and patient populations complicates cross-trial comparisons and generalizability. Finally, the long-term consequences of sustained upstream RAAS suppression, including potential effects on electrolyte balance, renal hemodynamics, and compensatory pathways, require careful evaluation in larger, adequately powered, outcome-driven trials.

FUTURE DIRECTIONS IN AGT-TARGETED HYPERTENSION THERAPY

Although multiple avenues for AGT-targeted research exist, several appear particularly actionable and hypothesis-driven. First, integrating AGT-lowering agents with established cardiometabolic therapies, such as SGLT2 (sodium-glucose co-transporter 2) inhibitors or GLP-1 (glucagon-like peptide-1) receptor agonists may leverage complementary mechanisms in patients with obesity, CKD, or resistant hypertension. Second, genotype- and phenotype-guided treatment strategies could enable precision AGT inhibition in defined subgroups. Finally, prospective studies incorporating AGT into risk stratification and treatment algorithms may clarify patient selection and inform future clinical trials.

Multi-Omic Drug Discovery and Precision Targeting

The future of AGT-targeted hypertension therapy lies at the intersection of precision medicine and systems biology. Multi-omic approaches offer promising avenues for deeper mechanistic insights and therapeutic innovation.

Stratifying patients based on AGT genotypes may allow for the rational use of gene-silencing agents like antisense oligonucleotides or siRNAs in genetically susceptible subpopulations. For instance, a case-control study investigated 4 AGT gene SNPs (rs2004776, rs3789678, rs5051, rs7079) in isiXhosa-speaking South Africans, which found no significant association between these polymorphisms and hypertension, highlighting the importance of population-specific genetic studies for informing precision medicine and preventing ineffective or unnecessary genetically targeted therapies.[68,69] Epigenomic mechanisms, particularly DNA methylation and histone modifications in hepatocytes and adipocytes, regulate AGT expression in response to environmental and hormonal cues such as salt intake, aldosterone, and angiotensin II.[12,70,71] In a recent transgenic mouse study, a high-salt diet increased human AGT gene expression through DNA demethylation and enhanced transcription factor binding, with the Hap-I risk haplotype showing stronger epigenetic and transcriptional changes than Hap-II, revealing salt-sensitive regulatory mechanisms of hypertension.[72] Overall, these dynamic changes contribute to the pathogenesis of salt-sensitive hypertension and cardiovascular disease.

On the transcriptomic level, understanding tissue-specific AGT expression dynamics under hypertensive stressors, such as in obesity, may refine the timing and targeting of RNA-based therapies.[73] Proteomic profiling of AGT variants and their posttranslational modifications could inform the rational design of monoclonal antibodies and aptamers, especially in patients exhibiting aberrant AGT stability or cleavage kinetics. For example, a study demonstrated that a monoclonal antibody targeting human angiotensin$^{1-12}$ effectively neutralized its vasoconstrictor effects, reduced arterial pressure in transgenic hypertensive rats, and showed potential as a novel therapeutic approach by blocking non-renin-dependent pathways of angiotensin II generation.[54] A recent fluorescence-based biosensing study employing G-quadruplex aptamer-conjugated magnetic beads for the sensitive detection of AGT at the cellular level suggests the potential for future development of AGT-targeting aptamers not only for diagnostics but also for therapeutic inhibition in renin-angiotensin system–related diseases.[74] Finally, combining AGT-targeted approaches with agents like SGLT2 inhibitors or GLP-1 receptor agonists, particularly in patients with concurrent metabolic dysregulation, represents a synergistic strategy worth evaluating.

Nonhepatic AGT Targeting

Neuron-specific overexpression of AGT in mice reveals that brain-derived AGT contributes to central BP regulation and enhances salt appetite.[75] Indeed, Cre-LoxP-based studies further demonstrate that brain-specific AGT and renin expression elevate brain Ang II levels, enhance sympathetic activity and energy expenditure, and implicate central Ang II in regulating peripheral functions, including sodium balance and metabolic rate.[76] Thus, brain-targeted AGT suppression could modulate central RAS activity while sparing peripheral hemodynamics.

Adipose-derived AGT plays a paracrine role in linking obesity to metabolic hypertension through local Ang II production and inflammation. In aP2-Agt transgenic mice, adipocyte AGT overexpression induced systemic insulin resistance and glucose intolerance via NADPH (Nicotinamide adenine dinucleotide phosphate) oxidase and NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) activation,[77] ultimately impairing glucose uptake in skeletal muscle. Adipose-specific AGT knockout models showed reduced adipose inflammation and enhanced glucose tolerance without affecting body weight, partly by enhancing stromal vascular cell metabolism.[78] These results highlight adipose AGT as a paracrine driver of obesity-related metabolic dysfunction and hypertension, and a potential therapeutic target.

AGT, also synthesized by proximal tubular cells, contributes to intrarenal Ang II formation, sodium retention, and tubulointerstitial fibrosis.[79,80] Proximal tubule–specific AGT overexpression in mice, and upregulation of PT-derived AGT, induced salt-sensitive hypertension independent of systemic RAS activation.[81] Under physiological conditions, the liver remains the dominant source of circulating AGT and renal angiotensin II.[82] However, under pathological conditions, including hypertension, diabetes, CKD, and states of inflammation and oxidative stress, proximal tubular AGT expression is markedly upregulated and may substantially contribute to intrarenal RAAS activation.[16,59,79–81] Indeed, the selective knockout of Agt in the proximal tubule did not alter renal AGT, angiotensin II concentrations, kidney morphology, BP, or sodium elimination.[82] Further investigation is required to understand the therapeutic value of kidney-targeted AGT inhibition.

ONGOING TRIALS

The recent wave of clinical trials targeting AGT reflects a growing shift toward upstream inhibition of the RAAS. Multiple agents employing nucleic acid-based strategies, such as antisense oligonucleotides and small interfering RNAs, are currently under evaluation across diverse clinical settings. Trials in phase 2 or later are listed in Table 3. There are multiple phase 1 studies completed or ongoing of nucleic acid-based therapeutics, including: ART101, GW906, and SYH2062.

CONCLUSIONS

AGT occupies a central yet historically underappreciated position within the RAAS cascade and the broader pathophysiology of hypertension. Far from being a passive

Table 3. Summary of Key Ongoing Phase 2 or Later Clinical Trials of Drugs Targeting Angiotensinogen

Clinical trial number	Title	Status	Study design	Population description	Intervention and exposure	Primary outcome(s)
NCT07181109	Zilebesiran in Patients With Hypertension Not Adequately Controlled and With Either Established Cardiovascular Disease or High Risk for Cardiovascular Disease (ZENITH)	Recruiting	Phase 3, randomized, double-blind, placebo-controlled	Anticipated enrollment of 11 000 participants Has established CVD (defined as coronary, cerebrovascular, or peripheral artery disease) or high risk for CVD Has treated hypertension on stable therapy with at least 2 standard of care antihypertensive medications, one of which must be a thiazide, thiazide-like, or loop diuretic	300 mg zilebesiran subcutaneously (SC) once every 6 mo compared with placebo	Time to First Occurrence of a Composite end point of Cardiovascular Death, Nonfatal Myocardial Infarction, Nonfatal Stroke, or HF Event (Hospitalization for HF or Urgent HF Visit)
NCT06864104	A Study to Investigate Tonlamarsen for the Treatment of Adults With Uncontrolled Hypertension (KARDINAL)	Enrollment completed	Phase 2, randomized, double-blind, placebo-controlled	Enrollment of 206 participants Has uncontrolled hypertension while receiving between 2 and 5 antihypertensive medications prescribed for hypertension	90 mg of tonlamarsen will be administered subcutaneously every 4 wk during the randomized part of the study	Co-primary of AGT lowering and office systolic BP lowering after 20 wk
NCT06857955	A Study to Identify an Optimal Dose of QCZ484 in Mild to Moderate Hypertensive Patients	Recruiting	Phase 2, randomized, double-blind, placebo-controlled	Anticipated enrollment of 380 participants Hypertension treatment naive or on maximum 2 anti-HTN medications and able to undergo washout for 4 wk Mean sitting systolic BP ≥140 mm Hg measured by office BP and mean 24 h systolic BP ≥130 mm Hg and <160 mm Hg measured by ABPM	Various doses of QCZ484	Change from baseline at Month 3 in mean 24 h systolic BP by ABPM

ABPM indicates ambulatory blood pressure monitoring; AGT, angiotensinogen; BP, blood pressure; CVD, cardiovascular disease; HF, heart failure; and HTN, hypertension.

substrate, AGT is a dynamically regulated determinant of RAAS activity with tissue-specific effects that are modulated by genetic, hormonal, metabolic, and inflammatory cues. Advances in molecular and functional studies have strengthened evidence of AGT's role, not only as a determinant of interindividual BP variation but also as a mediator of target-organ damage in hypertensive disease states. The development of nucleic acid-based therapeutics, such as zilebesiran and tonlamarsen targeting hepatic AGT synthesis, has opened a transformative frontier in hypertension treatment, offering sustained, upstream RAAS suppression with promising efficacy and safety. These novel modalities may prove particularly beneficial in patient populations with resistant hypertension, CKD, and obesity-related metabolic dysfunction, where conventional therapies often fall short, yet the efficacy in larger populations and long-term adverse events remain to be elucidated. In addition, AGT's utility as a diagnostic and prognostic biomarker, particularly in urine and plasma, might possibly offer opportunities for earlier detection, risk stratification, and personalized treatment. Looking ahead, integrating AGT-targeted interventions with multi-omic profiling and advanced delivery technologies may open a new era of precision hypertension therapy. Continued clinical trials and mechanistic studies will be critical to translating these advances into widespread clinical practice, potentially redefining hypertension management across diverse patient populations.

ARTICLE INFORMATION

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The figures were crafted at biorender.com.

Data Availability

No original data were generated during the study. All the data are available in the literature and cited in the article.

Author Contributions

M. Kanbay was responsible for conceptualization, methodology, writing—review and editing, and supervision. M. Guldan contributed to conceptualization, methodology, investigation, and writing—original draft, visualization. L. Ozbek contributed

to conceptualization, methodology, investigation, writing—original draft, and visualization. R. Al-Shiab contributed to the writing—original draft, investigation, and visualization. L.J. Laffin contributed to writing—review and editing, and critical revision of the article.

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