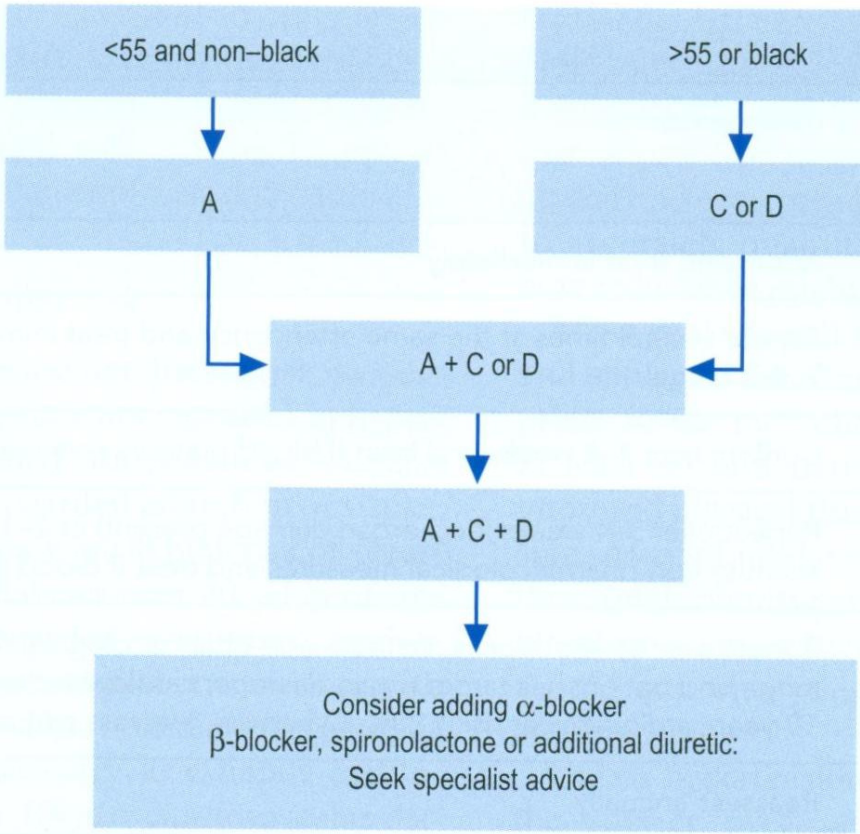

A = ACE inhibitor; C = calcium channel blocker; D = diuretic

Fig. 19.1 Algorithm for drug sequencing in hypertension.

https://basicmedicalkey.com/hypertension-6/

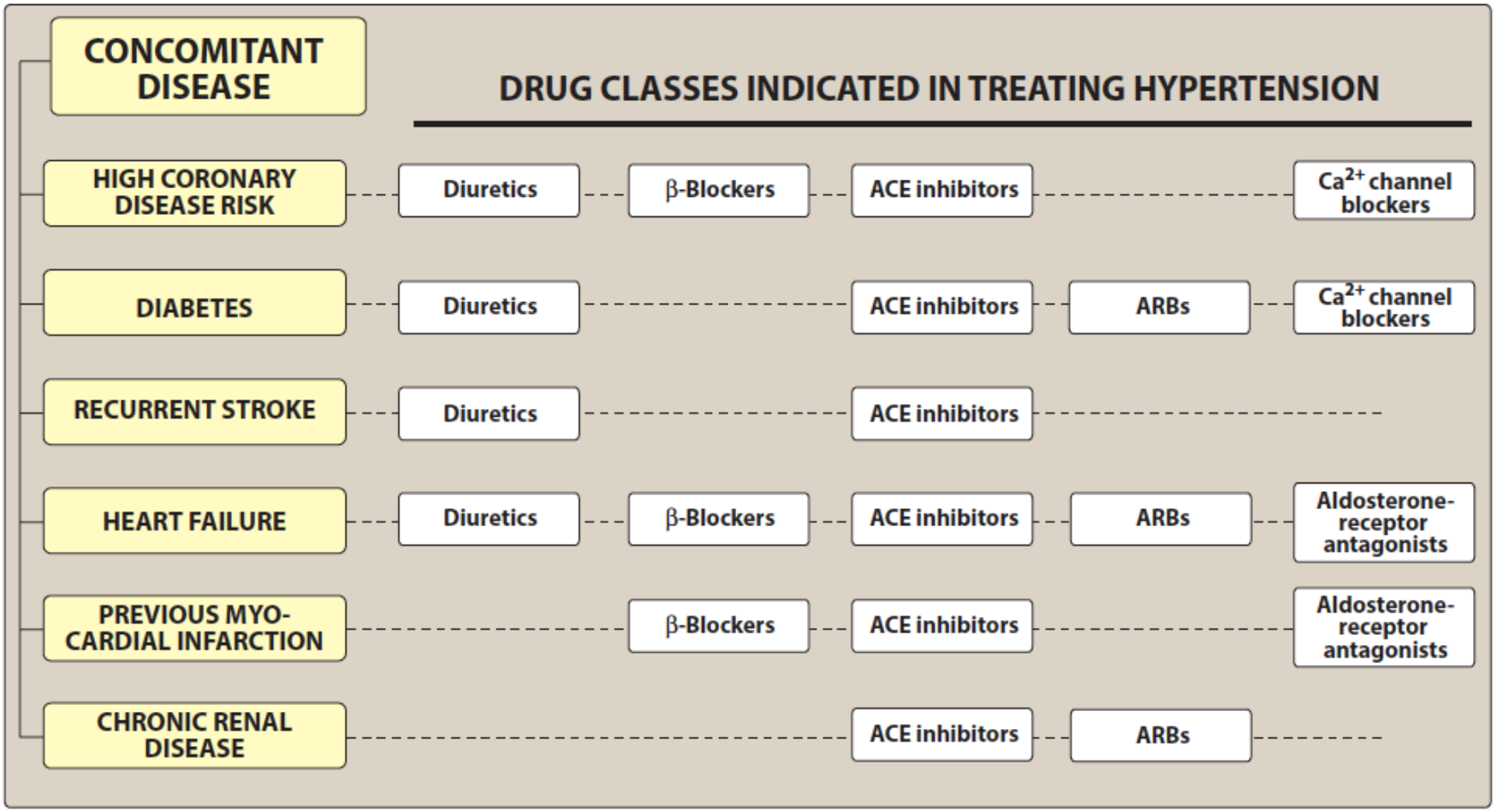

Figure 17.5

Treatment of hypertension in patients with concomitant diseases. [Note: Angiotensin receptor blockers (ARBs) are an alternative to angiotensin-converting enzyme (ACE) inhibitors.]

Lippincott Illustrated reviews Pharmacology, 6th edition, 2015

SUMMARY Drugs Used in Hypertension

Subclass	Mechanism of Action	Effects	Clinical Applications	Pharmacokinetics, Toxicities, Interactions
DIURETICS				
• Thiazides: Hydrochlorothiazide	Block Na/Cl transporter in renal distal convoluted tubule	Reduce blood volume and poorly understood vascular effects	Hypertension, mild heart failure	
• Loop diuretics: Furosemide	Block Na/K/2Cl transporter in renal loop of Henle	Like thiazides • greater efficacy	Severe hypertension, heart failure	See Chapter 15
• Spironolactone • Eplerenone	Block aldosterone receptor in renal collecting tubule	Increase Na and decrease K excretion • poorly understood reduction in heart failure mortality	Aldosteronism, heart failure, hypertension	
SYMPATHOPLEGICS, CENTRALLY ACTING				
• Clonidine, methyl dopa	Activate α_2 adrenoceptors	Reduce central sympathetic outflow • reduce norepinephrine release from noradrenergic nerve endings	Hypertension • clonidine also used in withdrawal from abused drugs	Oral • clonidine also patch • *Toxicity:* sedation • methyldopa hemolytic anemia
SYMPATHETIC NERVE TERMINAL BLOCKERS				
• Reserpine	Blocks vesicular amine transporter in noradrenergic nerves and depletes transmitter stores	Reduce all sympathetic effects, especially cardiovascular, and reduce blood pressure	Hypertension but rarely used	Oral • long duration (days) • *Toxicity:* Reserpine: psychiatric depression, gastrointestinal disturbances
• Guanethidine	Interferes with amine release and replaces norepinephrine in vesicles	Same as reserpine	Same as reserpine	Guanethidine: Severe orthostatic hypotension • sexual dysfunction

Basic and Clinical Pharmacology, Katzung & Trevor, 13th edition

Subclass	Mechanism of Action	Effects	Clinical Applications	Pharmacokinetics, Toxicities, Interactions
α BLOCKERS				
• Prazosin • Terazosin • Doxazosin	Selectively block α_1 adrenoceptors	Prevent sympathetic vasoconstriction • reduce prostatic smooth muscle tone	Hypertension • benign prostatic hyperplasia	Oral • *Toxicity:* Orthostatic hypotension
β BLOCKERS				
• Metoprolol, others • Carvedilol	Block β_1 receptors; carvedilol also blocks α receptors	Prevent sympathetic cardiac stimulation • reduce renin secretion	Hypertension • heart failure	See Chapter 10
• *Propranolol: Nonselective prototype β blocker* • *Atenolol: Very widely used β_1-selective blocker*				
VASODILATORS				
• Verapamil • Diltiazem	Nonselective block of L-type calcium channels	Reduce cardiac rate and output • reduce vascular resistance	Hypertension, angina, arrhythmias	See Chapter 12
• Nifedipine, amlodipine, other dihydropyridines	Block vascular calcium channels > cardiac calcium channels	Reduce vascular resistance	Hypertension, angina	See Chapter 12
• Hydralazine	Causes nitric oxide release	Vasodilation • reduce vascular resistance • arterioles more sensitive than veins • reflex tachycardia	Hypertension • minoxidil also used to treat hair loss	Oral • *Toxicity:* Angina, tachycardia • Hydralazine: Lupus-like syndrome
• Minoxidil	Metabolite opens K channels in vascular smooth muscle			Minoxidil: Hypertrichosis
PARENTERAL AGENTS				
• Nitroprusside • Fenoldopam • Diazoxide • Labetalol	Releases nitric oxide Activates D_1 receptors Opens K channels α, β blocker	Powerful vasodilation	Hypertensive emergencies	Parenteral • short duration • *Toxicity:* Excessive hypotension, shock
ANGIOTENSIN-CONVERTING ENZYME (ACE) INHIBITORS				
• Captopril, many others	Inhibit angiotensin-converting enzyme	Reduce angiotensin II levels • reduce vasoconstriction and aldosterone secretion • increase bradykinin	Hypertension • heart failure, diabetes	Oral • *Toxicity:* Cough, angioedema • hyperkalemia • renal impairment • teratogenic
ANGIOTENSIN RECEPTOR BLOCKERS (ARBs)				
• Losartan, many others	Block AT_1 angiotensin receptors	Same as ACE inhibitors but no increase in bradykinin	Hypertension • heart failure	Oral • *Toxicity:* Same as ACE inhibitors but less cough
RENIN INHIBITOR				
• Aliskiren	Inhibits enzyme activity of renin	Reduces angiotensin I and II and aldosterone	Hypertension	Oral • *Toxicity:* Hyperkalemia, renal impairment • potential teratogen

Basic and Clinical Pharmacology, Katzung & Trevor, 13th edition

Table 2: Names of new drugs designed for new targets

S. No.	Name of drug	Category	Approval	References
1	Sampatrilat	Vasopeptidase inhibitors	Phase 2 and discontinued	17
2	Fasidotril	Vasopeptidase inhibitors	Phase 3 trail	18
4	Gemopatrilat	Vasopeptidase inhibitors	Phase 2 trial and discontinued	19
5	Omapatrilat	Vasopeptidase inhibitors	Phase 3 trial	20
6	Ilepatril	Vasopeptidase inhibitors	Phase 2 trail	21
7	LCZ696 (Valsartan-Sacubitril)	Vasopeptidase inhibitors	2015	22
8	Daglutril	Vasopeptidase inhibitors	Phase 2	23
9	QGC001(RB-150)	Brain RAAS	Phase 2	24
10	Eplerenone	Anti-Aldosterone	2002	25

Yadav Bijay Kumar et al.; 2019, International Journal of Advance Research and Development

Dual Angiotensin Receptor–Neprilysin Inhibitors

NEP (Neprilysin) hydrolyzes atrial natriuretic peptide, brain natriuretic peptide (BNP), C-type natriuretic peptide and, possibly, urodilatin

The effects of NEP inhibition;
Short term; vasodilation, enhanced diuresis, natriuresis and reduced sympathetic tone and aldosterone
Long term; the induction of anti-inflammatory, antifibrotic, and antihypertrophic effects on cardiomyocytes or cardiac fibroblasts in vitro

Dual neprilysin–angiotensin-converting enzyme inhibition with the first representative; omapatrilat lowered BP strongly enough for use in the treatment of patients with hypertension

Increase in the risk of angioedema!!!

Emerging Drug Classes and Their Potential Use in Hypertension
Michel Azizi, Patrick Rossignol, Jean-S.bastien Hulot, Hypertension. 2019;74:1075-1083.

Dual Angiotensin Receptor–Neprilysin Inhibitors

Developing dual ARNIs (angiotensin receptor–neprilysin inhibitors);

The prototype is LCZ696, a single molecule synthesized by the co-crystallization of an ARB (angiotensin receptor blocker), valsartan, and the NEPi prodrug sacubitril (1:1 molar ratio).

Valsartan/sacubitril is approved for the treatment of heart failure with reduced ejection fraction (HFrEF)

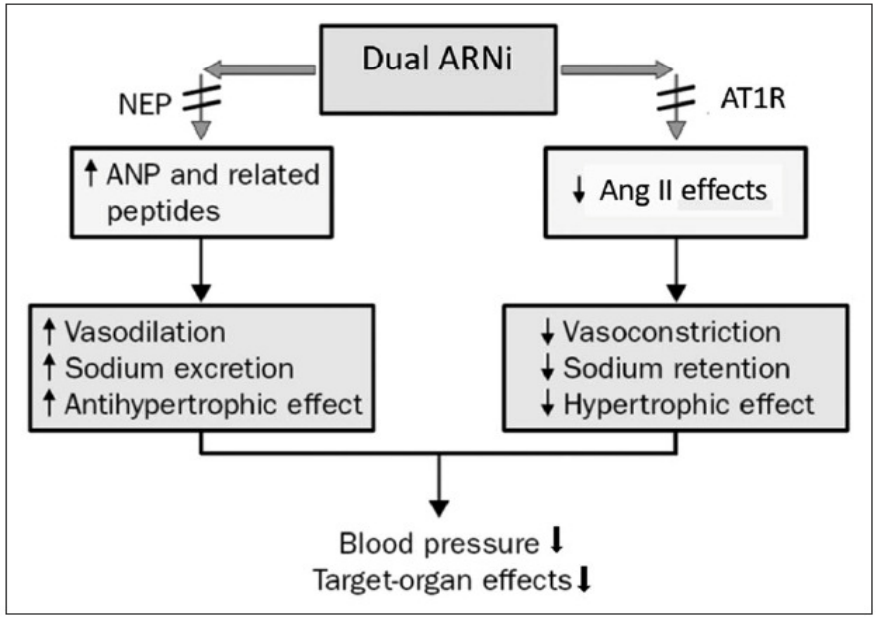

Figure 1. Mechanism of action of the dual ARNI (angiotensin receptor-neprilysin inhibitors). ANP indicates atrial natriuretic peptide; and NEP, neprilysin.

Emerging Drug Classes and Their Potential Use in Hypertension
Michel Azizi, Patrick Rossignol, Jean-S.bastien Hulot, Hypertension. 2019;74:1075-1083.

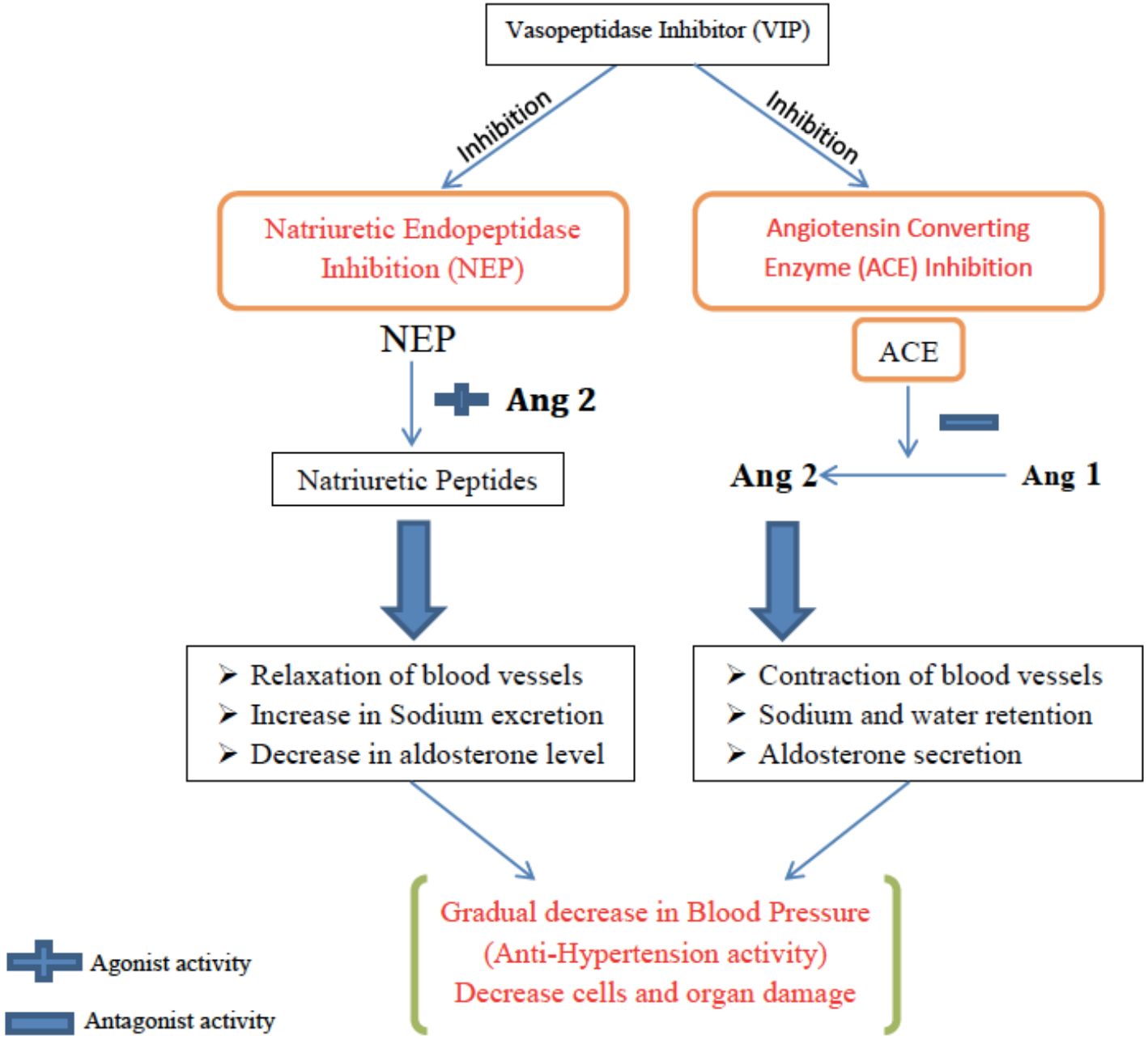

Fig. 1: Role of vasopeptidase inhibitor in hypertension

Yadav Bijay Kumar et al.; 2019, International Journal of Advance Research and Development

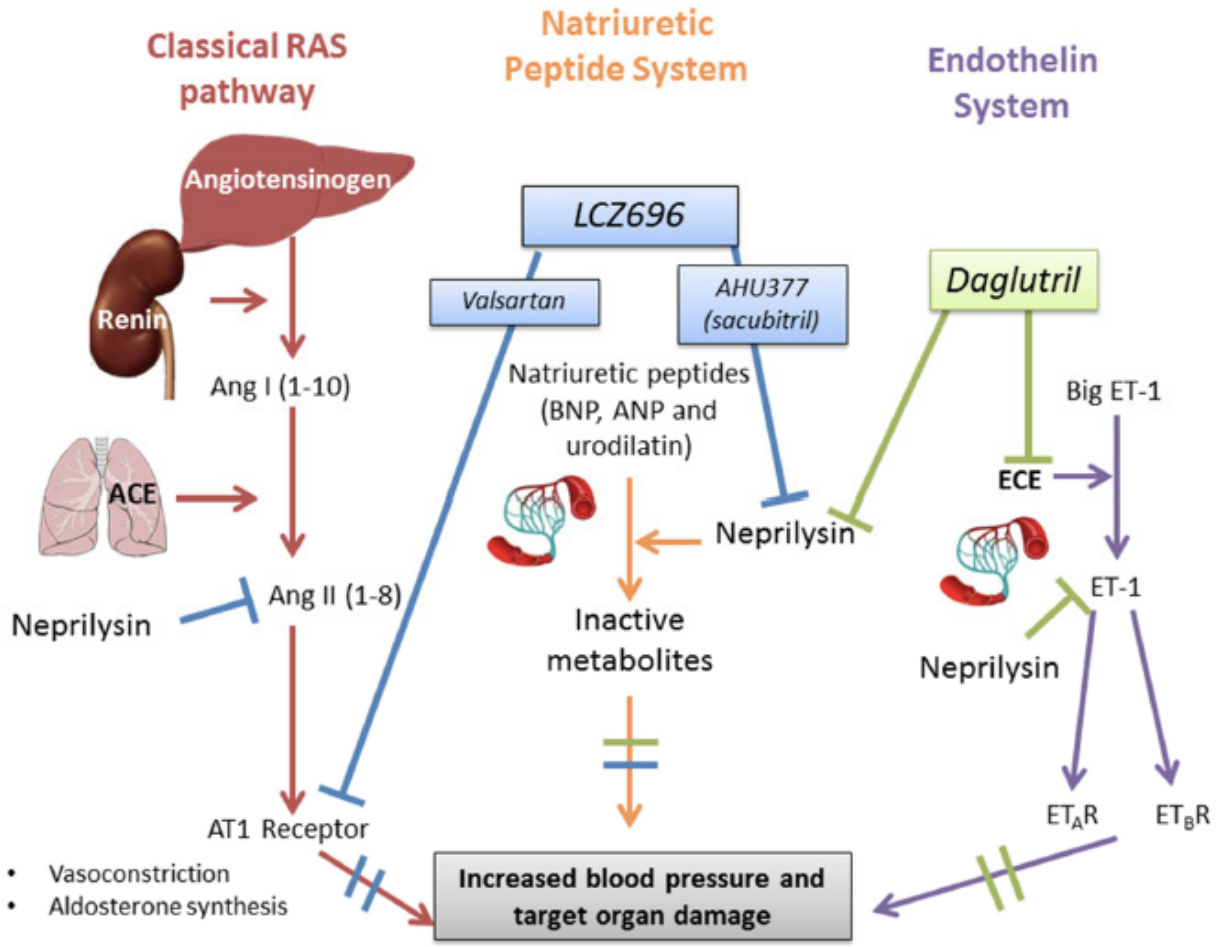

Figure 4. Vasopeptidase inhibitors. Combining an inhibitor of the natriuretic peptide degrading enzyme neprilysin with an angiotensin receptor blocker (ARB) or an endothelin converting enzyme (ECE) inhibitor in the same molecule offers the theoretical advantage of enhancing the favorable vasodilator/natruiretic effects of the natriuretic peptides and reducing the deleterious vasoconstrictor/ proinflammatory effects of angiotensin II (Ang II) and endothelin-1 (ET-1) on blood pressure (BP) and target organ damage. The ARB–neprilysin inhibitor (ARNI), LCZ696, is a single molecule comprising the ARB valsartan and the neprilysin inhibitor pro-drug AHU377 (sacubitril). LCZ696 has been shown to lower BP, particularly in Asian populations, and to prevent death from cardiovascular (CV) causes and hospitalization for heart failure (HF) in patients with reduced left ventricular ejection fraction (LVEF). The ECE–neprilysin inhibitor dagutril has been shown to lower BP in patients with type 2 diabetes mellitus and nephropathy and to reduce pulmonary arterial pressure in patients with HF. Red, classical RAS; orange, natriuretic peptide system; purple, endothelin system; blue, LCZ696; green, dagutril.

Oparil S, Schmieder RE. New approaches in the treatment of hypertension. Circ Res. 2015 Mar 13;116(6): 1074-95.

Soluble Guanylate Cyclase Stimulators

Vericiguat

soluble guanylate cyclase (sGC) stimulator, thereby targeting the NO-sGC-cyclic guanosine monophosphate (cGMP) pathway

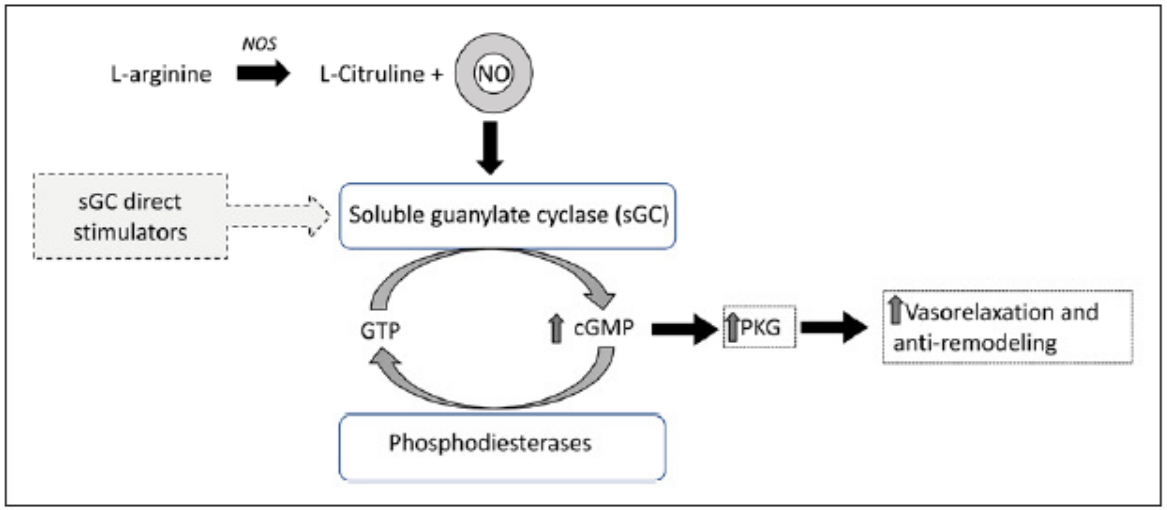

Figure 2. Mechanism of action of the soluble guanylate cyclase (sGC) activators. cGMP indicates cyclic guanosine monophosphate; NOS, nitric oxide synthase; PKG, protein kinase G.

Emerging Drug Classes and Their Potential Use in Hypertension
Michel Azizi, Patrick Rossignol, Jean-S.bastien Hulot, Hypertension. 2019;74:1075-1083.

Nonsteroidal Dihydropyridine-Based Mineralocorticoid Receptor Antagonists

Increased risk of hyperkalemia and worsening renal function with steroidal MRA (mineralocorticoid receptor antagonists), spironolactone and eplerenone, limited use

Development of nonsteroidal dihydropyridine-based third- and fourth-generation MRA; dihydronaphthyridine finerenone (BAY94-8862)

Aldosterone Synthase Inhibitors

MRAs can cause reactive increases in components of the RAAS, particularly aldosterone

Reducing the production of aldosterone, a new class of anti-aldosterone agents, an aldosterone synthase inhibitor (ASI), LCI699

Emerging Drug Classes and Their Potential Use in Hypertension
Michel Azizi, Patrick Rossignol, Jean-S.bastien Hulot, Hypertension. 2019;74:1075-1083.

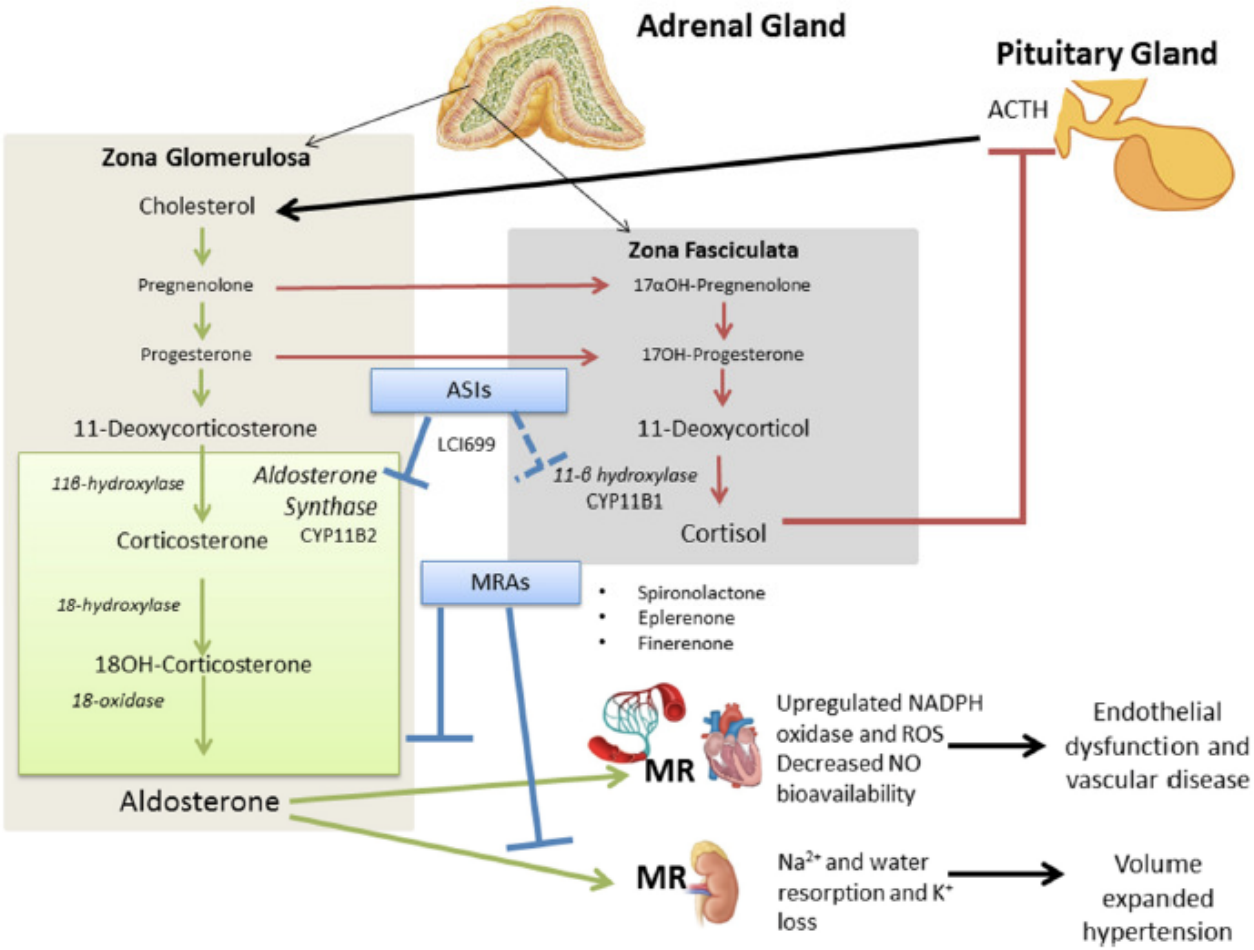

Figure 1. Mechanism of action of anti-aldosterone agents. Aldosterone synthase inhibitors (ASIs), such as LCI699, inhibit the rate limiting step of aldosterone production. Mineralocorticoid receptor agonists (MRAs), such as finerenone, compete for the binding sites of aldosterone and effectively decrease blood pressure and aldosterone-mediated gene transcription. Both approaches have been shown to be useful in treating aldosterone-mediated hypertension and vascular disease. Aldosterone synthesis, green; cortisol synthesis, red; anti-aldosterone drugs, blue.

D

Oparil S, Schmieder RE. New approaches in the treatment of hypertension. Circ Res. 2015 Mar 13;116(6): 1074-95.

Activators of the Angiotensin-Converting Enzyme2/ Angiotensin(1–7)/ MAS Receptor Axis

ACE2 activators
Ang (1–7) analogs
AT2 receptor agonists, peptide and nonpeptide activators of the Mas receptor, and alamandine complexed with cyclodextrin

Ferreira A J, Murça T M, Fraga-Silva R A, Castro C H, Raizada M K and Santos R A 2012 New cardiovascular and pulmonary therapeutic strategies based on the Angiotensin-converting enzyme 2/angiotensin-(1-7)/mas receptor axis *Int. J. Hypertens*. 147825.

Jiang F, Yang J, Zhang Y, Dong M, Wang S, Zhang Q, Liu F F, Zhang K and Zhang C 2014 Angiotensin-converting enzyme 2 and angiotensin 1-7: novel therapeutic targets *Nat. Rev. Cardiol*. **11** 413–26

Centrally Acting Aminopeptidase A Inhibitors

Existence of a functional RAS in the brain, controlling cardiovascular functions, and body fluid homeostasis

An orally active prodrug of EC33 (RB150/QGC001, firabastat)

Inhibits brain APA activity, blocking the formation of brain angiotensin III

(Marc Y, Llorens-Cortes C. The role of the brain renin-angiotensin system in hypertension: implications for new treatment. Prog Neurobiol. 2011;95:89–103.)

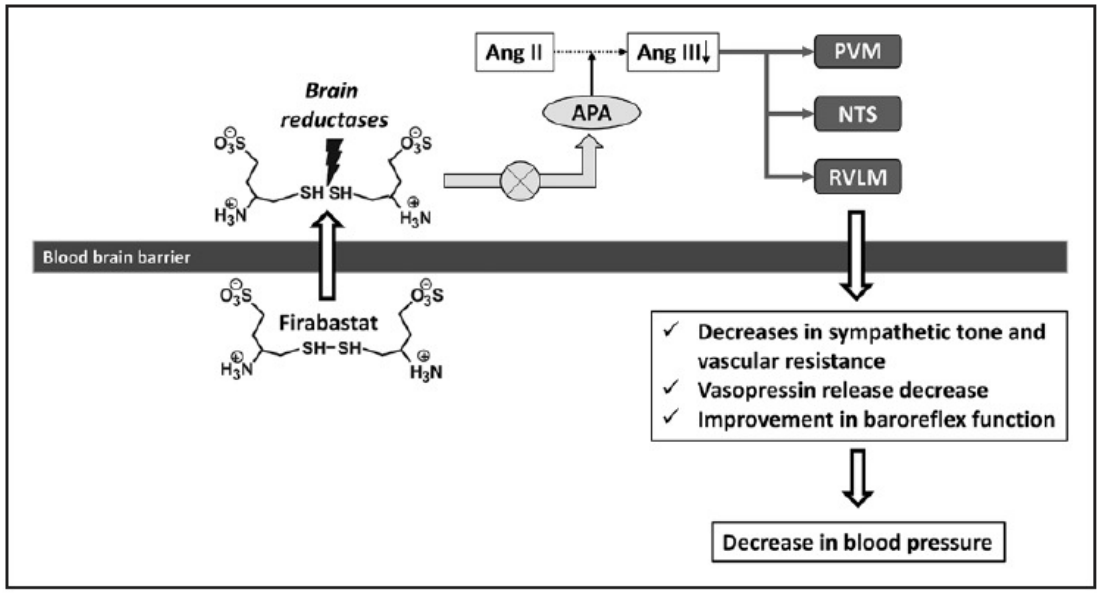

Figure 3. Mechanism of action of the dimer prodrug firabastat. As a dimer, the selective aminopeptidase A (APA) inhibitor EC33 is able to cross the blood-brain barrier and inhibit the APA activity. NTS indicates nucleus tractus solitarii; PVN, paraventricular nucleus; and RVLM, rostral ventrolateral medulla.[78]

Emerging Drug Classes and Their Potential Use in Hypertension
Michel Azizi, Patrick Rossignol, Jean-S.bastien Hulot, Hypertension. 2019;74:1075-1083.

Endothelin Receptor Antagonists

The selective endothelin receptor antagonist, darusentan, a placebo corrected reduction in BP of ~ 11/6 and ~ 18/11 mmHg in phase II and III trials in participants with resistant hypertension

(Black HR, Bakris GL,Weber MA,Weiss R, ShahawyME, Marple R, et al. Efficacy and safety of darusentan in patients with resistant hypertension: results from a randomized, double-blind, placebo- controlled dose-ranging study. J Clin Hypertens (Greenwich). 2007;9(10):760–9.
Weber MA, Black H, Bakris G, KrumH, Linas S,Weiss R, et al. A selective endothelin-receptor antagonist to reduce blood pressure in patients with treatment-resistant hypertension: a randomised, double-blind, placebo-controlled trial. Lancet. 2009;374(9699): 1423–31.)

A phase III placebo-controlled trial for selective ETA receptor antagonist aprocitentan
(PRECISION study ClinicalTrials.gov NCT03541174)

the SONAR study for selective ETA receptor antagonist, atrosentan
(Heerspink HJL, Parving HH, Andress DL, Bakris G, Correa- Rotter R, Hou FF, et al. Atrasentan and renal events in patients with type 2 diabetes and chronic kidney disease (SONAR): a double-blind, randomised, placebo-controlled trial. Lancet. 2019;393(10184):1937–47.)

Azzam O, Kiuchi MG, Ho JK, Matthews VB, Gavidia LML, Nolde JM, Carnagarin R, Schlaich MP. New Molecules for Treating Resistant Hypertension: a Clinical Perspective. Curr Hypertens Rep. 2019 Sep 10;21(10):80.

Natriuretic Peptide Receptor Agonists

Inhibit degradation of endogenous natriuretic peptides for the treatment of HF and refractory or resistant hypertension.

Synthetic natriuretic peptide receptor A (NPR-A) agonist PL-3994

(Sica D, Jordan R, Fischkoff SA. Phase IIa study of the NPR-A agonist, PL-3994, in healthy adult volunteers with controlled hypertension. J Card Fail. 2009;15(6):S67.)

Vasoactive Intestinal Peptide Receptor Agonists

More selective and longer-acting analogue of VIP (PB1046)

dose-dependent effect on BP

(PhaseBio Pharmaceuticals Inc. 2015. PB1046 (Vasomera™) in: clinical development pipeline. Available from: http://phasebio. com/clinical-development-pipeline/vasomera/. Accessed 5 Jun 2019.)

Dopamine β-Hydroxylase Inhibitors

Affect the final step of noradrenaline biosynthesis

Novel, peripherally selective DβH inhibitor, BIA 5-453, renamed as Etamicastat

(Beliaev A, Learmonth DA, Soares-da-Silva P. Synthesis and biological evaluation of novel, peripherally selective chromanyl imidazolethione-based inhibitors of dopamine beta-hydroxylase. J Med Chem. 2006;49(3):1191–7.)

Azzam O, Kiuchi MG, Ho JK, Matthews VB, Gavidia LML, Nolde JM, Carnagarin R, Schlaich MP. New Molecules for Treating Resistant Hypertension: a Clinical Perspective. Curr Hypertens Rep. 2019 Sep 10;21(10):80.

Intestinal Na+/H+ Exchanger 3 (NHE3) Inhibitor

Highly selective NHE3 inhibitor, Tenapanor

Well-tolerated and reducing intestinal sodium absorption in two phase I studies

(Rosenbaum DP, Yan A, Jacobs JW. Pharmacodynamics, safety, and tolerability of the NHE3 inhibitor tenapanor: two trials in healthy volunteers. Clin Drug Investig. 2018;38(4):341–51.)

Azzam O, Kiuchi MG, Ho JK, Matthews VB, Gavidia LML, Nolde JM, Carnagarin R, Schlaich MP. New Molecules for Treating Resistant Hypertension: a Clinical Perspective. Curr Hypertens Rep. 2019 Sep 10;21(10):80.

Sodium-Glucose Cotransporter 2 Inhibitors

Oral hypoglycemic agents, increase the urinary elimination of glucose

Several mechanisms for the antihypertensive actions of SGLT2 inhibitors;

modest diuretic effects, weight loss, and direct vascular effects leading to decreased arterial stiffness and vascular resistance

(Sternlicht H, Bakris GL. Blood pressure lowering and Sodium-Glucose Co-transporter 2 inhibitors (SGLT2is): more than osmotic diuresis. Curr Hypertens Rep. 2019;21:12.)

Azzam O, Kiuchi MG, Ho JK, Matthews VB, Gavidia LML, Nolde JM, Carnagarin R, Schlaich MP. New Molecules for Treating Resistant Hypertension: a Clinical Perspective. Curr Hypertens Rep. 2019 Sep 10;21(10):80.

Vaccines

Recent studies;
AT1 receptor vaccine ATRQβ-001
ATR12181

(Chen X, Qiu Z, Yang S, Ding D, Chen F, Zhou Y, et al. Effectiveness and safety of a therapeutic vaccine against angiotensin II receptor type 1 in hypertensive animals. Hypertension. 2013;61(2):408–16.
Li LD, Tian M, Liao YH, Zhou ZH, Wei F, Zhu F, et al. Effect of active immunization against angiotensin II type 1 (AT1) receptor on hypertension & arterial remodelling in spontaneously hypertensive ats (SHR). Indian J Med Res. 2014;139(4):619–24.)

Molecules Listed as Under Development

B244, undergoing a phase II study in patients with elevated blood pressure (ClinicalTrials.gov NCT02998840)

RMJH-111b (magnesium citrate), a phase I/II safety and tolerability in subjects with essential hypertension, results have not been reported (ClinicalTrials.gov NCT02822222).

SP20203, BAY sGCstim and IT-103, in the development pipeline as of 2018

(Business Wire. 2018. Resistant Hypertension Drug Development Pipeline Study, H1 2018 - ResearchAndMarkets.com. 9 June 2019]; Available from: https://www.businesswire.com/ news/home/20180612006405/en/Resistant-Hypertension-Drug-Development-Pipeline-Study-H1. Accessed 10 Jun 2019.

Azzam O, Kiuchi MG, Ho JK, Matthews VB, Gavidia LML, Nolde JM, Carnagarin R, Schlaich MP. New Molecules for Treating Resistant Hypertension: a Clinical Perspective. Curr Hypertens Rep. 2019 Sep 10;21(10):80.

FDA Approved Drugs

Byvalson (nebivolol and valsartan); Allergan; For the treatment of hypertension, Approved June 2016

Opsumit (macitentan); Actelion Pharmaceuticals; For the treatment of pulmonary arterial hypertension, Approved October 2013

Edarbi (azilsartan medoxomil); Takeda; For the treatment of hypertension, Approved February 2011

Edarbyclor (azilsartan medoxomil and chlorthalidone); Takeda; For the treatment of hypertension, Approved December of 2011

Amturnide (aliskiren + amlodipine + hydrochlorothiazide); Novartis; For the treatment of uncontrolled hypertension, Approved December 2010

Tekamlo (aliskiren + amlodipine); Novartis; For the treatment of hypertension, Approved August 2010

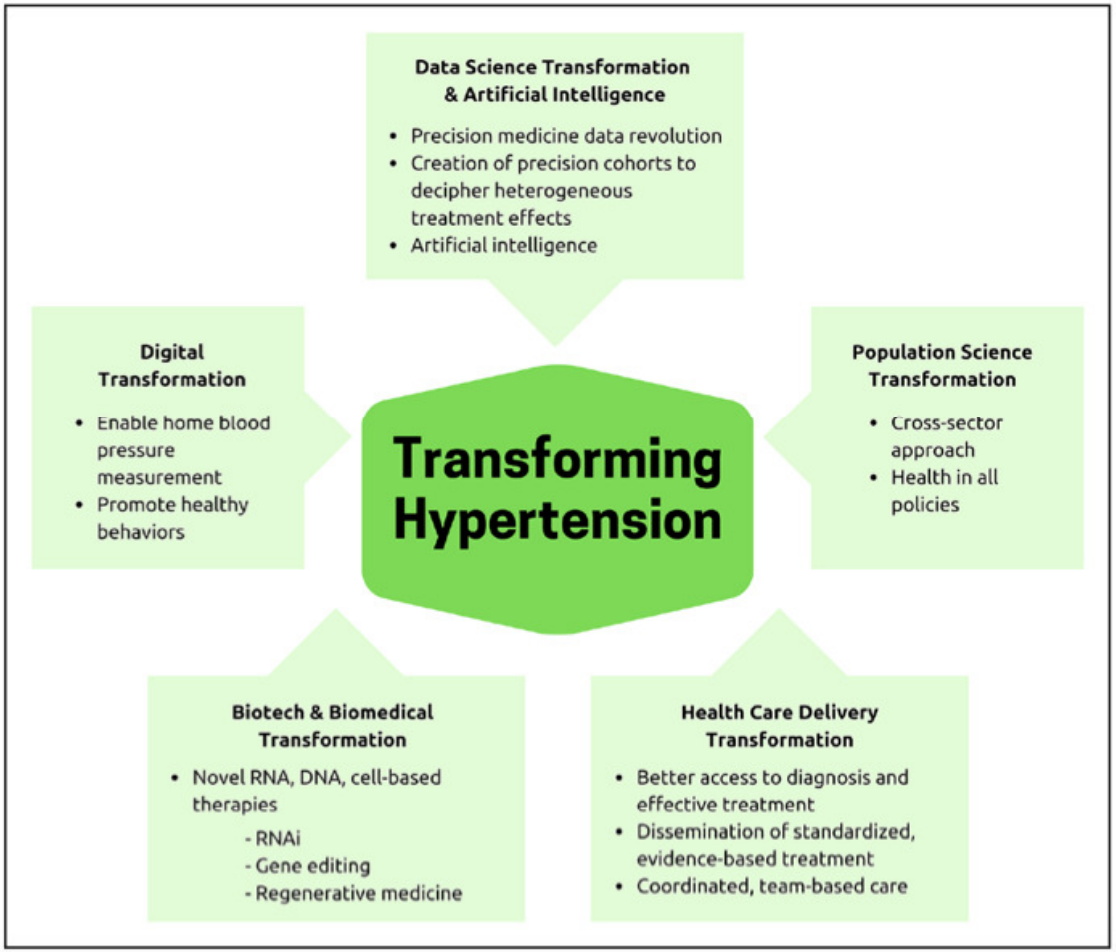

Figure. Hypertension: need for transformation. To control or eliminate hypertension, there is a need for system-wide transformation in research and clinical care as well as the convergence of disciplines. This figure highlights the 5 key areas where progress is needed to advance hypertension control and treatment. Achieving maximum benefit will require convergence of these areas.

Victor J. Dzau, Celynne A. Balatbat Future of Hypertension: The Need for Transformation. Hypertension. 2019;74:450–457