Contemporary Management of Hypertension in Adults and Review of New Cardiovascular Medications

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Relevant Financial Disclosure(s)

Candace Becker

- I have nothing to disclose

Objectives

- Review ACC/AHA guidelines for medication management of hypertension (HTN)
- List drug classes, mechanism of action, and caveats for specific populations
- Share ACC Late Breaking Clinical Trial (LBCT) Data to include new cardiovascular(CV) medications and new uses

JACC JOURNALS

ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines

2017

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Definition and causes of hypertension (HTN)

Blood Pressure Categories

American Heart Association | American Stroke Association

BLOOD PRESSURE CATEGORY	SYSTOLIC mm Hg (upper number)		DIASTOLIC mm Hg (lower number)
NORMAL	LESS THAN 120	and	LESS THAN 80
ELEVATED	120 – 129	and	LESS THAN 80
HIGH BLOOD PRESSURE (HYPERTENSION) STAGE 1	130 – 139	or	80 – 89
HIGH BLOOD PRESSURE (HYPERTENSION) STAGE 2	140 OR HIGHER	or	90 OR HIGHER
HYPERTENSIVE CRISIS (consult your doctor immediately)	HIGHER THAN 180	and/or	HIGHER THAN 120

- Environmental risk factors
- Overweight and obesity
- Sodium intake
- Potassium level
- Physical fitness
- Alcohol
- Secondary HTN
- Genetic predisposition

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Prevalence

- In 2010, HTN was the leading cause of death and disability-adjusted life years worldwide.
- In the US, HTN accounted for more cardiovascular disease (CVD) deaths than any other modifiable CVD risk factor, second only to cigarette smoking as a preventable cause of death for any reason.
- 23,272 US National Health and Nutrition Examination Survey (NHANES) participants, >50% of deaths from coronary heart disease (CHD) and stroke occurred among individuals with HTN.
- Because of the high prevalence of HTN and its associated increased risk of CHD, stroke, and end-stage renal disease (ESRD), the population-attributable risk of these outcomes associated with HTN is high.
  - In the ARIC (Atherosclerosis Risk in Communities) study, 25% of the CV events (CHD, coronary revascularization, stroke, or heart failure) were attributable to HTN.
  - In the Northern Manhattan study, the percentage of events attributable to HTN was higher in women (32%) than in men (19%) and higher in blacks (36%) than in whites (21%).
  - In 2012, HTN was the second leading assigned cause of ESRD (secondary to diabetes), and accounted for 34% of incident ESRD cases in the US population.

Fixed and modifiable risk factors

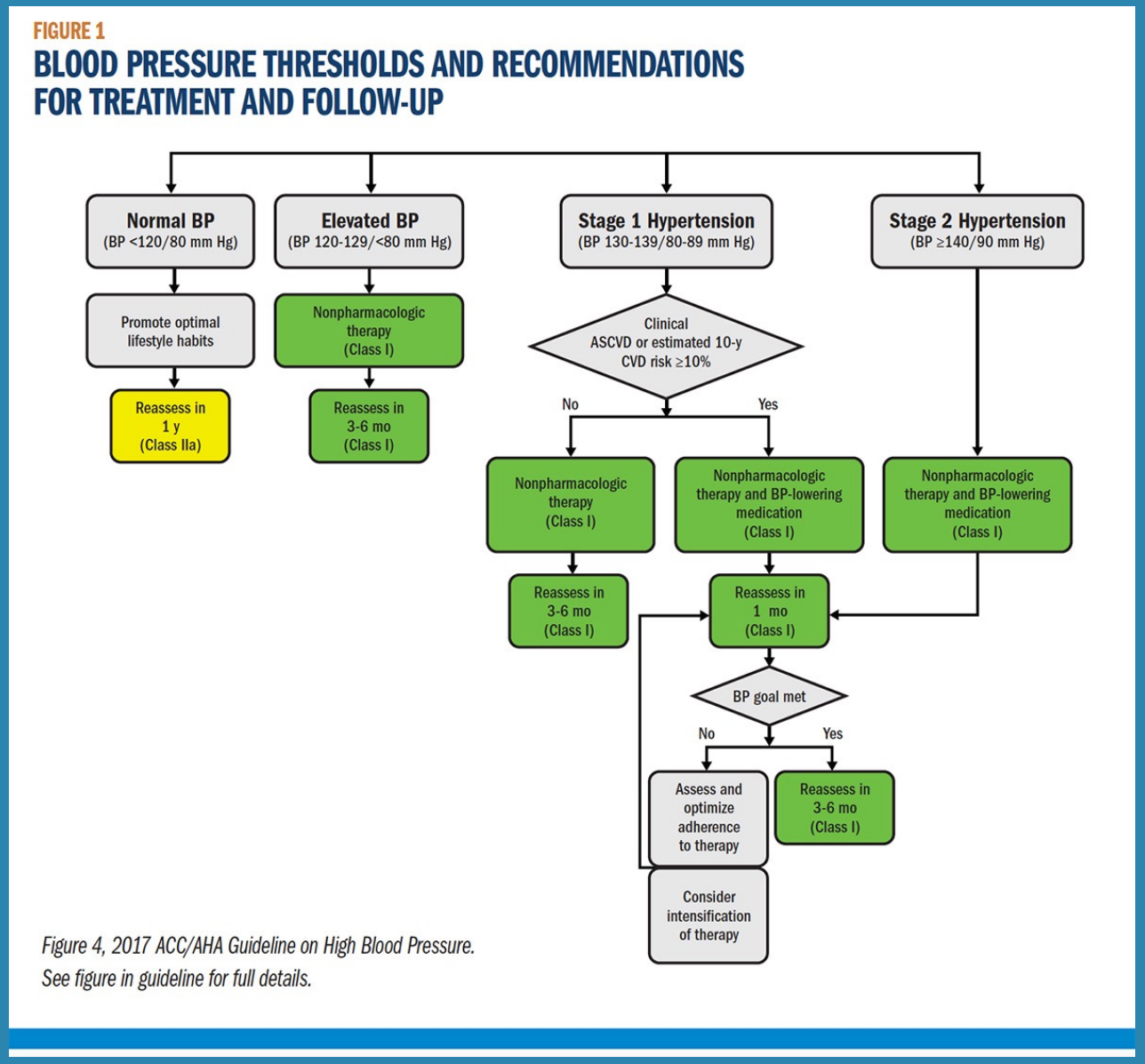
Table 5. CVD Risk Factors Common in Patients With Hypertension

Modifiable Risk Factors*	Relatively Fixed Risk Factors†
Current cigarette smoking, secondhand smoking	CKD
	Family history
Diabetes mellitus	Increased age
Dyslipidemia/hypercholesterolemia	Low socioeconomic/educational status
Overweight/obesity	Male sex
Physical inactivity/low fitness	Obstructive sleep apnea
Unhealthy diet	Psychosocial stress

*Factors that can be changed and, if changed, may reduce CVD risk.

†Factors that are difficult to change (CKD, low socioeconomic/educational status, obstructive sleep apnea[S2.4-12]), cannot be changed (family history, increased age, male sex), or, if changed through the use of current intervention techniques, may not reduce CVD risk (psychosocial stress).

CKD indicates chronic kidney disease; and CVD, cardiovascular disease.



ACC/AHA Guidelines on High Blood Pressure

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Recommendations for drug therapy initiation

- Fist prevent, treat and delay onset
- Drug therapy with established CVD and BP >130/80 mmHg
- Estimated 10 year risk of atherosclerotic CVD of >10%
  - https://tools.acc.org/ascvd-risk-estimator-plus/#!/calculate/estimate/
- SBP > 140 and/or DBP > 90 regardless of calculated CV risk
- Initial therapies include at least one or more of the four major classes:
  - ACE-I, ARB
  - Thiazide
  - CCB
  - BB (if history IHD or HF, AF, pregnancy, hyperthyroid

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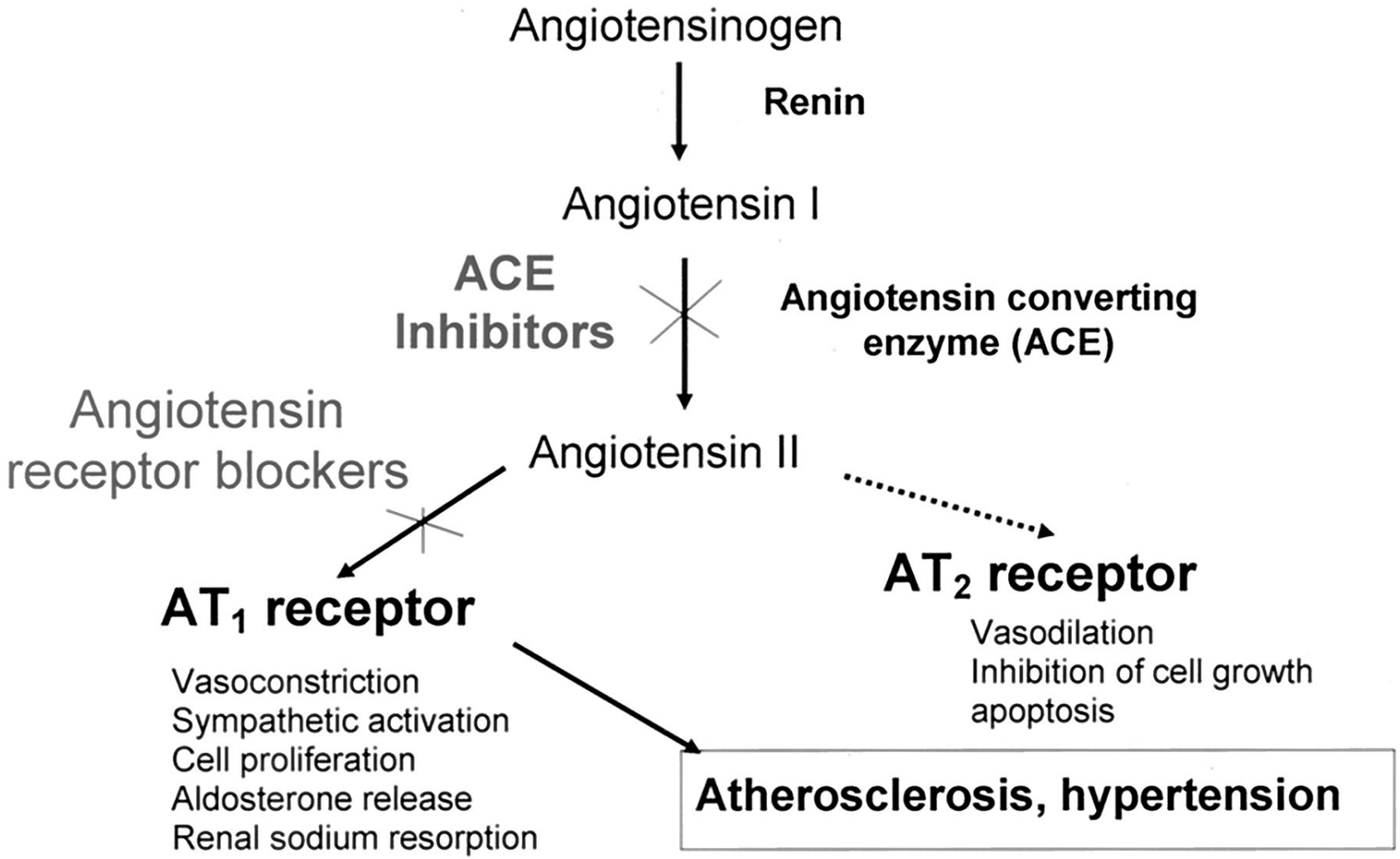
Angiotensin converting enzyme inhibitors (ACE-i)

- prils

-MOA: block angiotensin I conversion to angiotensin II thus inhibiting vasoconstriction

ACE inhibitors	Benazepril	10–40	1 or 2	Do not use in combination with ARBs or direct renin inhibitor. There is an increased risk of hyperkalemia, especially in patients with CKD or in those on K^+ supplements or K^+-sparing drugs. There is a risk of acute renal failure in patients with severe bilateral renal artery stenosis. Do not use if patient has history of angioedema with ACE inhibitors. Avoid in pregnancy.
	Captopril	12.5–150	2 or 3	
	Enalapril	5–40	1 or 2	
	Fosinopril	10–40	1	
	Lisinopril	10–40	1	
	Moexipril	7.5–30	1 or 2	
	Perindopril	4–16	1	
	Quinapril	10–80	1 or 2	
	Ramipril	2.5–20	1 or 2	
	Trandolapril	1–4	1	

ACE-I Mechanism of action (MOA)

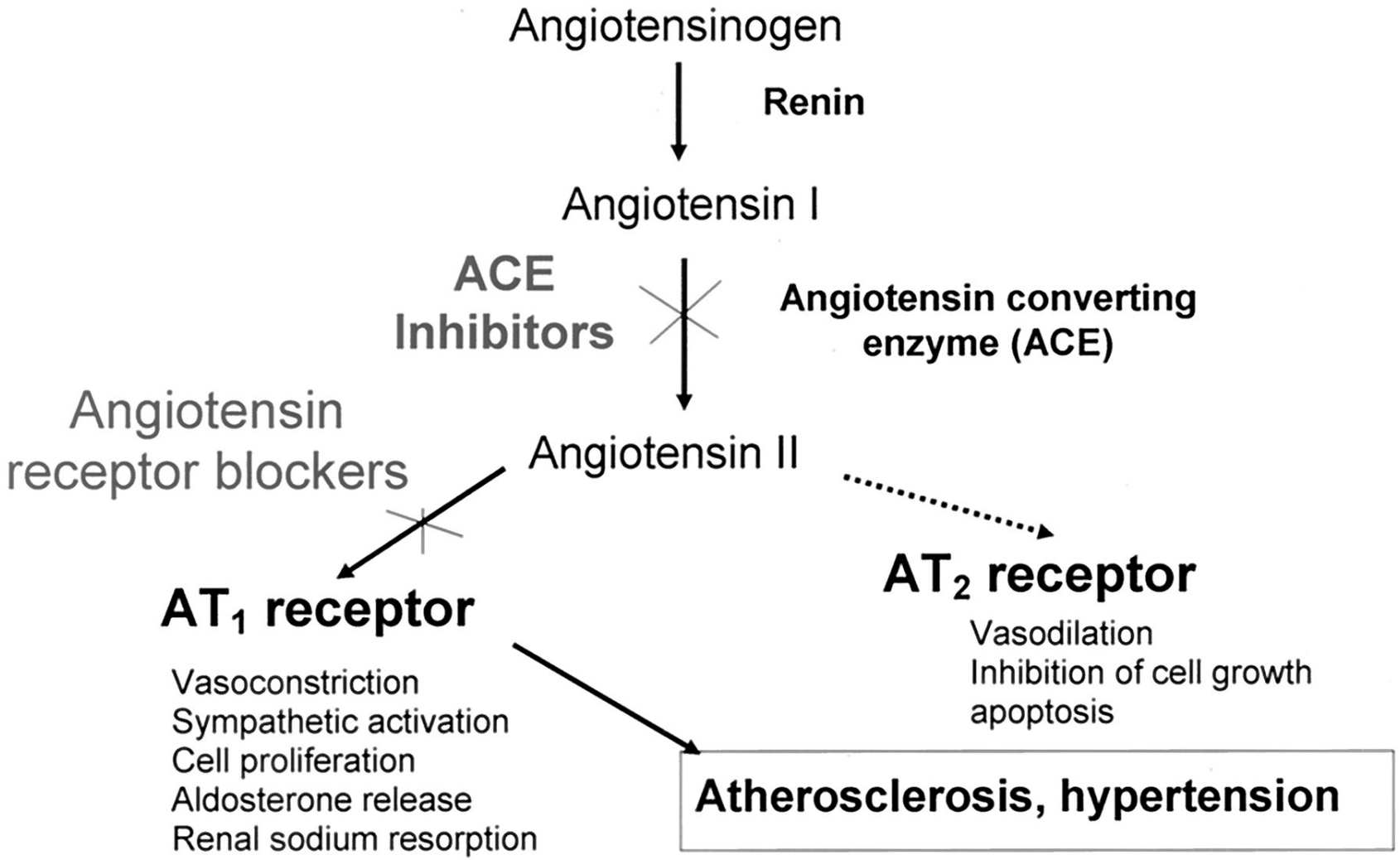


Angiotensin receptor blockers (ARB)

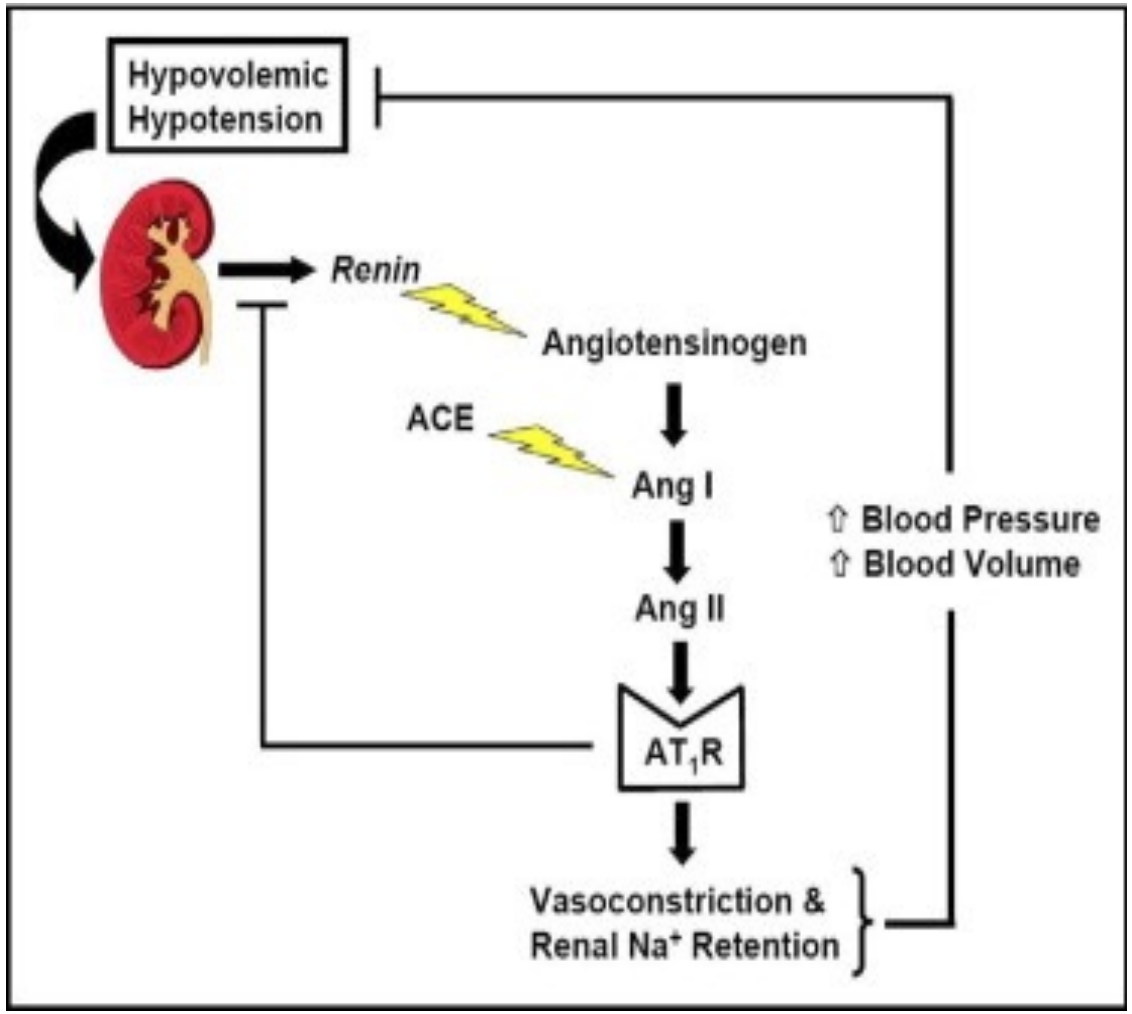
- -sartans
- Block AT1 receptor, inhibiting vasoconstriction, sympathetic activation, aldosterone release and renal sodium resorption

ARBs	Azilsartan	40–80	1	Do not use in combination with ACE inhibitors or direct renin inhibitor. There is an increased risk of hyperkalemia in CKD or in those on K^+ supplements or K^+-sparing drugs. There is a risk of acute renal failure in patients with severe bilateral renal artery stenosis. Do not use if patient has history of angioedema with ARBs. Patients with a history of angioedema with an ACE inhibitor can receive an ARB beginning 6 weeks after ACE inhibitor is discontinued. Avoid in pregnancy.
	Candesartan	8–32	1	
	Eprosartan	600–800	1 or 2	
	Irbesartan	150–300	1	
	Losartan	50–100	1 or 2	
	Olmesartan	20–40	1	
	Telmisartan	20–80	1	
	Valsartan	80–320	1	

ARBs MOA


Angiotensinogen
Renin
Angiotensin I
ACE Inhibitors
Angiotensin converting enzyme (ACE)
Angiotensin receptor blockers
Angiotensin II
AT1 receptor
Vasoconstriction
Sympathetic activation
Cell proliferation
Aldosterone release
Renal sodium resorption
AT2 receptor
Vasodilation
Inhibition of cell growth
apoptosis
Atherosclerosis, hypertension

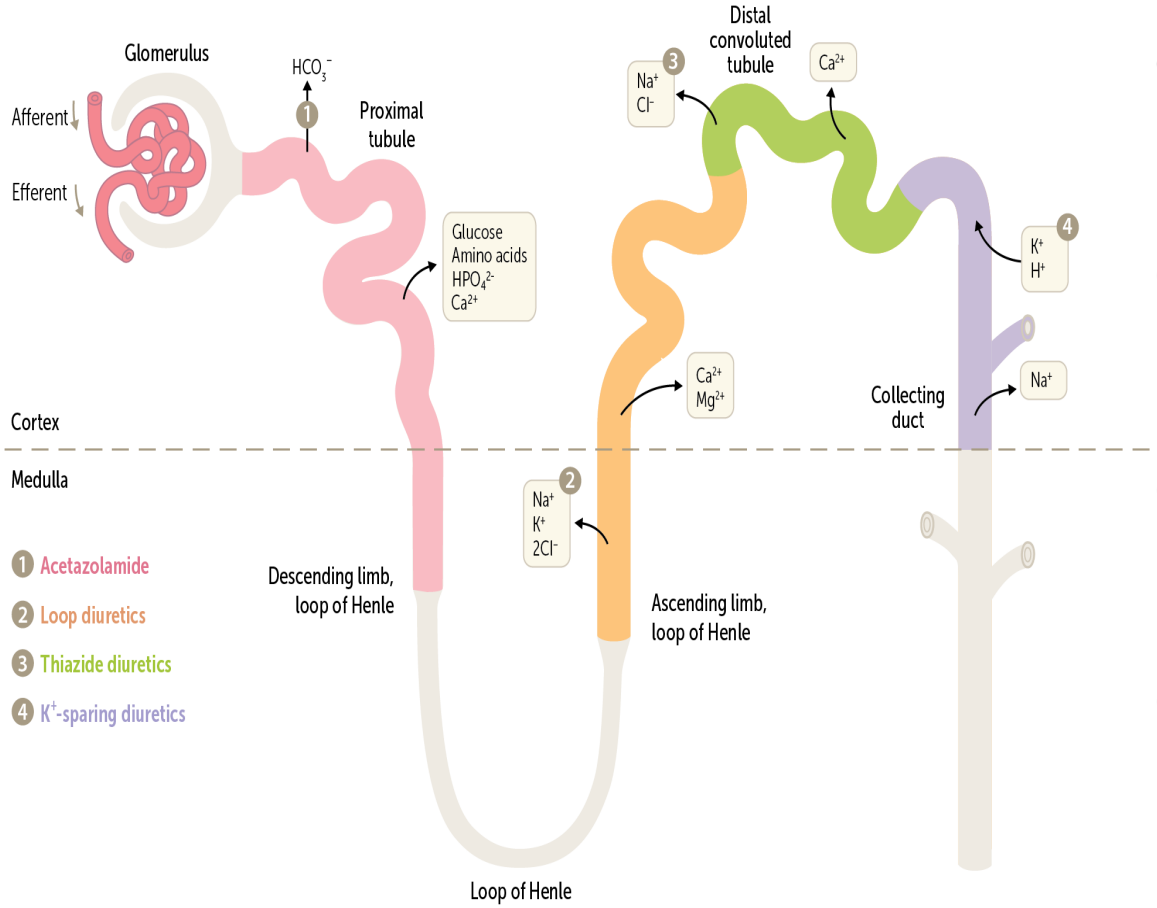
Direct renin inhibitor - Aliskiren



Direct renin inhibitor	Aliskiren	150–300	1	• Do not use in combination with ACE inhibitors or ARBs. • Aliskiren is very long acting. • There is an increased risk of hyperkalemia in CKD or in those on K^+ supplements or K^+-sparing drugs. • Aliskiren may cause acute renal failure in patients with severe bilateral renal artery stenosis. • Avoid in pregnancy.

Thiazide or thiazide type diuretics

- Inhibit absorption of sodium from distal tubules
- Decreased extracellular fluid thus decreased venous return, increased renin release, decreased CO and increased total peripheral resistance

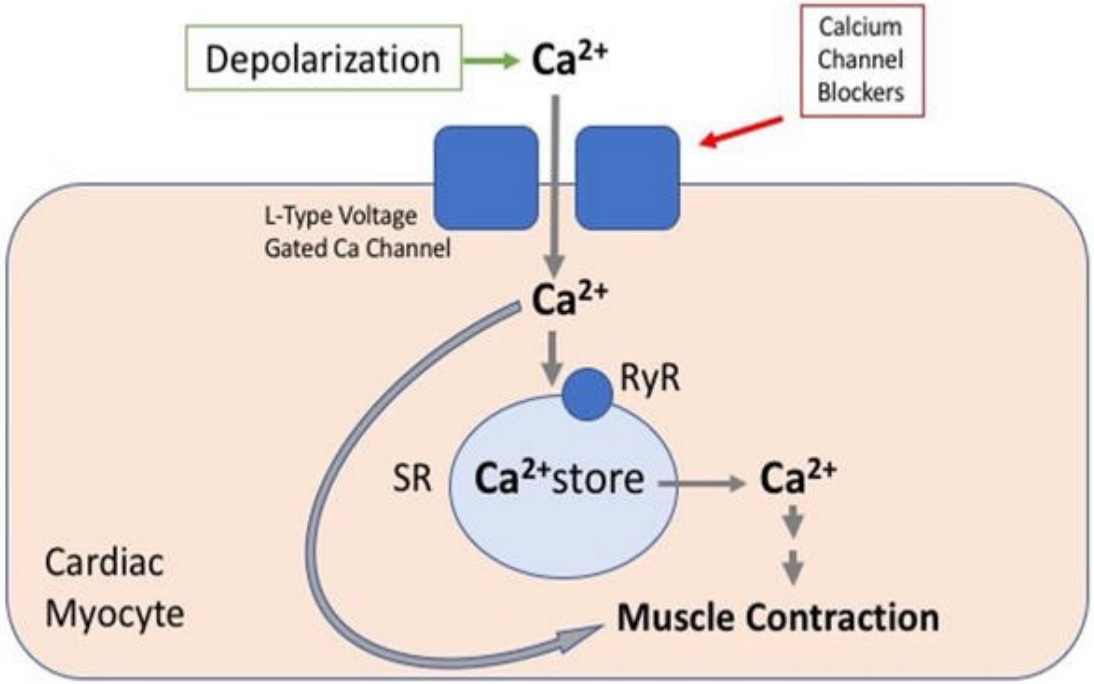


Chlorthalidone	12.5–25	1
Hydrochlorothiazide	25–50	1
Indapamide	1.25–2.5	1
Metolazone	2.5–5	1

- Chlorthalidone is preferred on the basis of prolonged half-life and proven trial reduction of CVD.
- Monitor for hyponatremia and hypokalemia, uric acid and calcium levels.
- Use with caution in patients with history of acute gout unless patient is on uric acid–lowering therapy.

Calcium channel blockers - nondihydropyridines

- Block calcium channels in myocardium
  - reduce heart rate and contractions
  - vasodilate



Diltiazem ER	120–360	1
Verapamil IR	120–360	3
Verapamil SR	120–360	1 or 2
Verapamil-delayed onset ER	100–300	1 (in the evening)

- Avoid routine use with beta blockers because of increased risk of bradycardia and heart block.
- Do not use in patients with HF*r*EF.
- There are drug interactions with diltiazem and verapamil (*CYP3A4* major substrate and moderate inhibitor).

Calcium channel blockers - dihydropyridines

- Block calcium channels found on smooth muscle cells or arterial blood vessels

CCB—dihydropyridines	Amlodipine	2.5–10	1
	Felodipine	2.5–10	1
	Isradipine	5–10	2
	Nicardipine SR	60–120	2
	Nifedipine LA	30–90	1
	Nisoldipine	17–34	1

- Avoid use in patients with HF*r*EF; amlodipine or felodipine may be used if required.
- They are associated with dose-related pedal edema, which is more common in women than men.

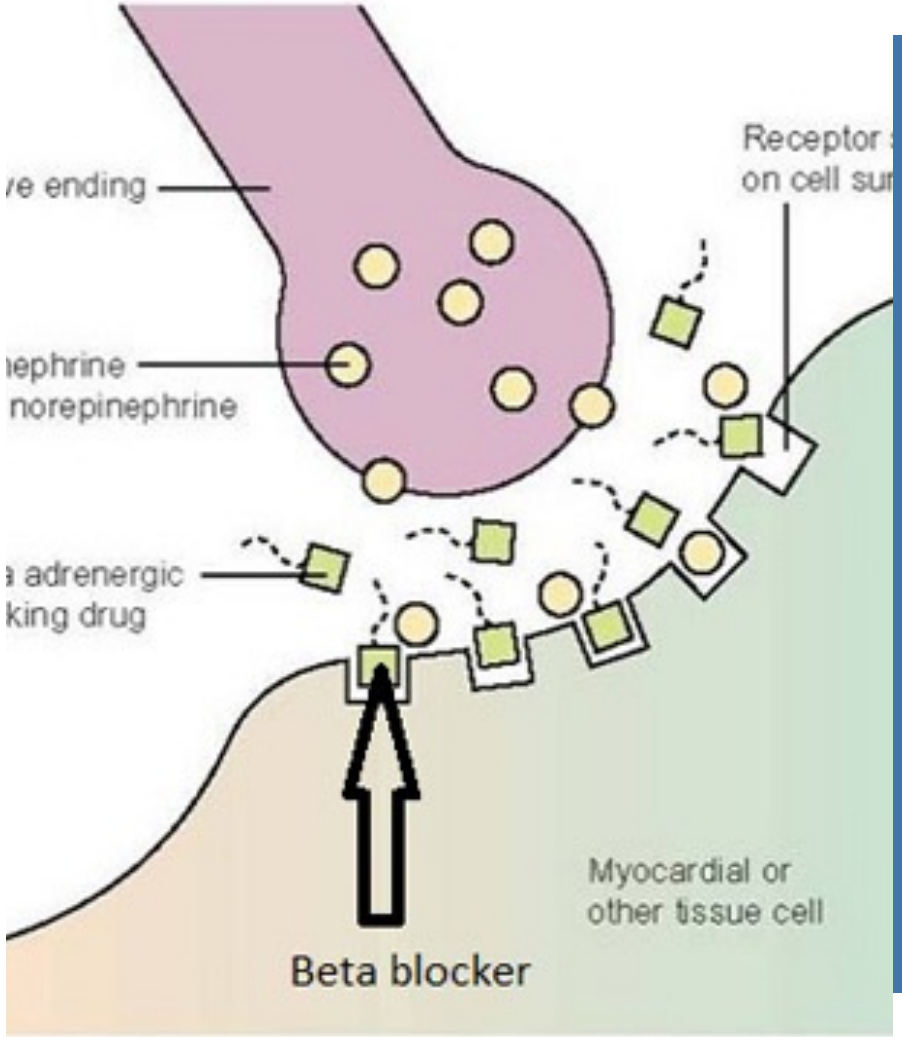
Beta-blockers (BB)

- - lol
- MOA – competitive antagonists to catecholamines on heart
  - Decreased HR ad contractility >>Decrease myocardial O2 consumption

Beta blockers—cardioselective	Atenolol	25–100	2	Beta blockers are not recommended as first-line agents unless the patient has IHD or HF. These are preferred in patients with bronchospastic airway disease requiring a beta blocker. Bisoprolol and metoprolol succinate are preferred in patients with HF*r*EF. Avoid abrupt cessation.
	Betaxolol	5–20	1	
	Bisoprolol	2.5–10	1	
	Metoprolol tartrate	100–200	2	
	Metoprolol succinate	50–200	1	
Beta blockers—cardioselective and vasodilatory	Nebivolol	5–40	1	Nebivolol induces nitric oxide–induced vasodilation. Avoid abrupt cessation.
Beta blockers—noncardioselective	Nadolol	40–120	1	Avoid in patients with reactive airways disease. Avoid abrupt cessation.
	Propranolol IR	80–160	2	
	Propranolol LA	80–160	1	
Beta blockers—intrinsic sympathomimetic activity	Acebutolol	200–800	2	Generally avoid, especially in patients with IHD or HF. Avoid abrupt cessation.
	Penbutolol	10–40	1	
	Pindolol	10–60	2	
Beta blockers—combined alpha- and beta-receptor	Carvedilol	12.5–50	2	Carvedilol is preferred in patients with HF*r*EF. Avoid abrupt cessation.
	Carvedilol phosphate	20–80	1	
	Labetalol	200–800	2	

Beta-blockers: selective vs non-selective and MOA

- Selective – B1 cardioselective
  - Atenolol
  - Metoprolol tartrate
  - Bisoprolol
  - Nebivolol
  - Esmolol



- Nonselective – B1 and B2 blockade
  - Propranalol
  - Nadolol
  - Timolol

Progression and types of BB

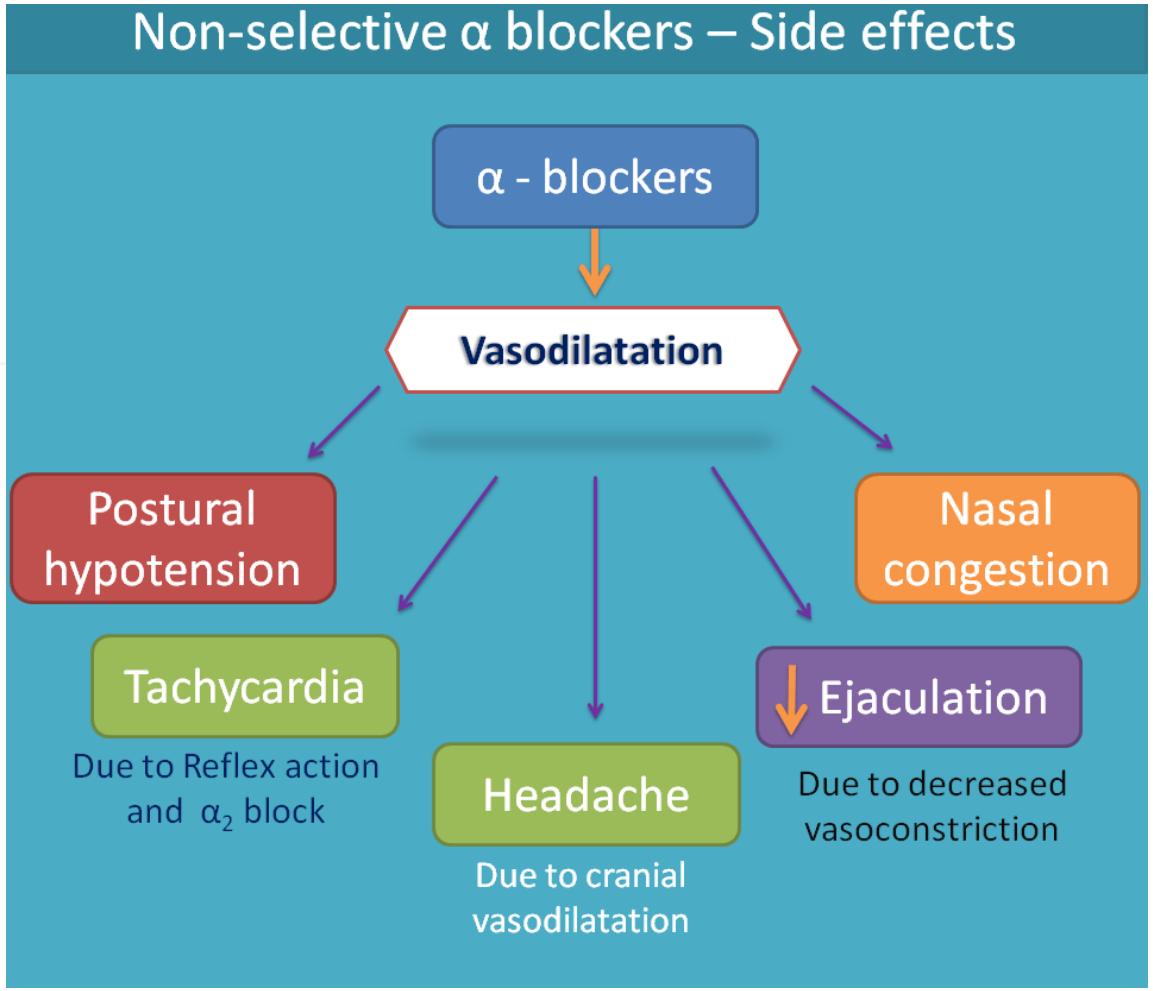
DR GIRISH WARU CCMP BJ MEDICAL PUNE

BETA ADRENERGIC BLOCKERS (BB)

First generation Non selective BB	Second gen. B 1 Selective BB (cardioselective)	Third generation Non selective (Alpha + beta)	Third generation B 1 Selective BB With vasodilator
पाणी थंडा नही सब पी लो P T N S P L	आज आपको बडा इनाम मिला A A B E M	कार लेंगे C L	बेटा नही चाहिये B N C
Propranolol	Atenolol	Carvedilol	Betaxolol
Timolol	Acebutolol	Labetalol	Nebivolol
Nadolol	Bisoprolol		Celiprolol
Sotalol	Esmolol		
Pindolol	Metoprolol		
Levobunolol			

Alpha blockers

Alpha-1 blockers	Doxazosin	1–16	1	• These are associated with orthostatic hypotension, especially in older adults. • They may be considered as second-line agent in patients with concomitant BPH.
	Prazosin	2–20	2 or 3	
	Terazosin	1–20	1 or 2	
Central alpha$_2$-agonist and other centrally acting drugs	Clonidine oral	0.1–0.8	2	• These are generally reserved as last-line because of significant CNS adverse effects, especially in older adults. • Avoid abrupt discontinuation of clonidine, which may induce hypertensive crisis; clonidine must be tapered to avoid rebound hypertension.
	Clonidine patch	0.1–0.3	1 weekly	
	Methyldopa	250–1000	2	
	Guanfacine	0.5–2	1	



Direct vasodilators

Direct vasodilators	Hydralazine	100–200	2 or 3	• These are associated with sodium and water retention and reflex tachycardia; use with a diuretic and beta blocker.
	Minoxidil	5–100	1 -3	• Hydralazine is associated with drug-induced lupus-like syndrome at higher doses. • Minoxidil is associated with hirsutism and requires a loop diuretic. Minoxidil can induce pericardial effusion.

Secondary agents

Diuretics—loop	Bumetanide	0.5–2	2	• These are preferred diuretics in patients with symptomatic HF. They are preferred over thiazides in patients with moderate-to-severe CKD (e.g., GFR <30 mL/min).
	Furosemide	20–80	2	
	Torsemide	5–10	1	
Diuretics—potassium sparing	Amiloride	5–10	1 or 2	• These are monotherapy agents and minimally effective antihypertensive agents. • Combination therapy of potassium-sparing diuretic with a thiazide can be considered in patients with hypokalemia on thiazide monotherapy. • Avoid in patients with significant CKD (e.g., GFR <45 mL/min).
	Triamterene	50–100	1 or 2	
Diuretics—aldosterone antagonists	Eplerenone	50–100	1 or 2	• These are preferred agents in primary aldosteronism and resistant hypertension. • Spironolactone is associated with greater risk of gynecomastia and impotence as compared with eplerenone. • This is common add-on therapy in resistant hypertension. • Avoid use with K^+ supplements, other K^+-sparing diuretics, or significant renal dysfunction. • Eplerenone often requires twice-daily dosing for adequate BP lowering.
	Spironolactone	25–100	1	

Combination therapy

Combination type	Examples
ACE inhibitors and calcium channel blockers	Amlodipine–benazepril, enalapril–felodipine
ACE inhibitors and diuretics	Lisinopril–hydrochlorothiazide
Angiotensin II antagonists and diuretics	Losartan–hydrochlorothiazide
Beta blockers and diuretics	Bisoprolol–hydrochlorothiazide
Centrally acting drug and diuretic	Methyldopa–hydrochlorothiazide
Diuretic and diuretic	Triamterene–hydrochlorothiazide

Abbreviation: ACE, angiotensin-converting enzyme.

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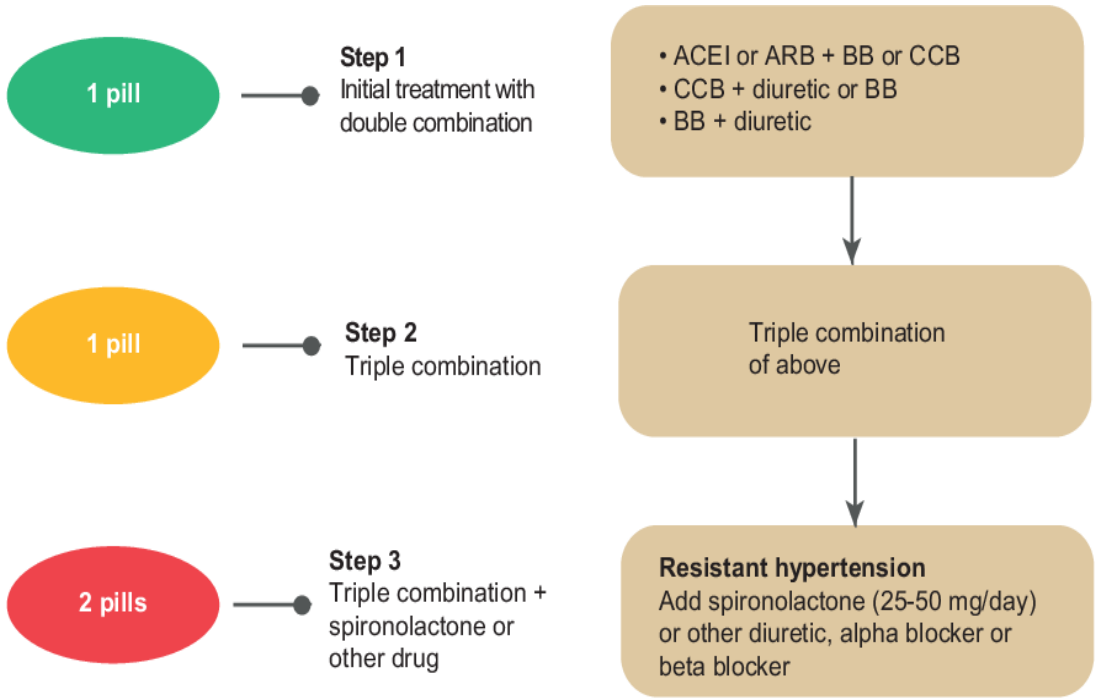
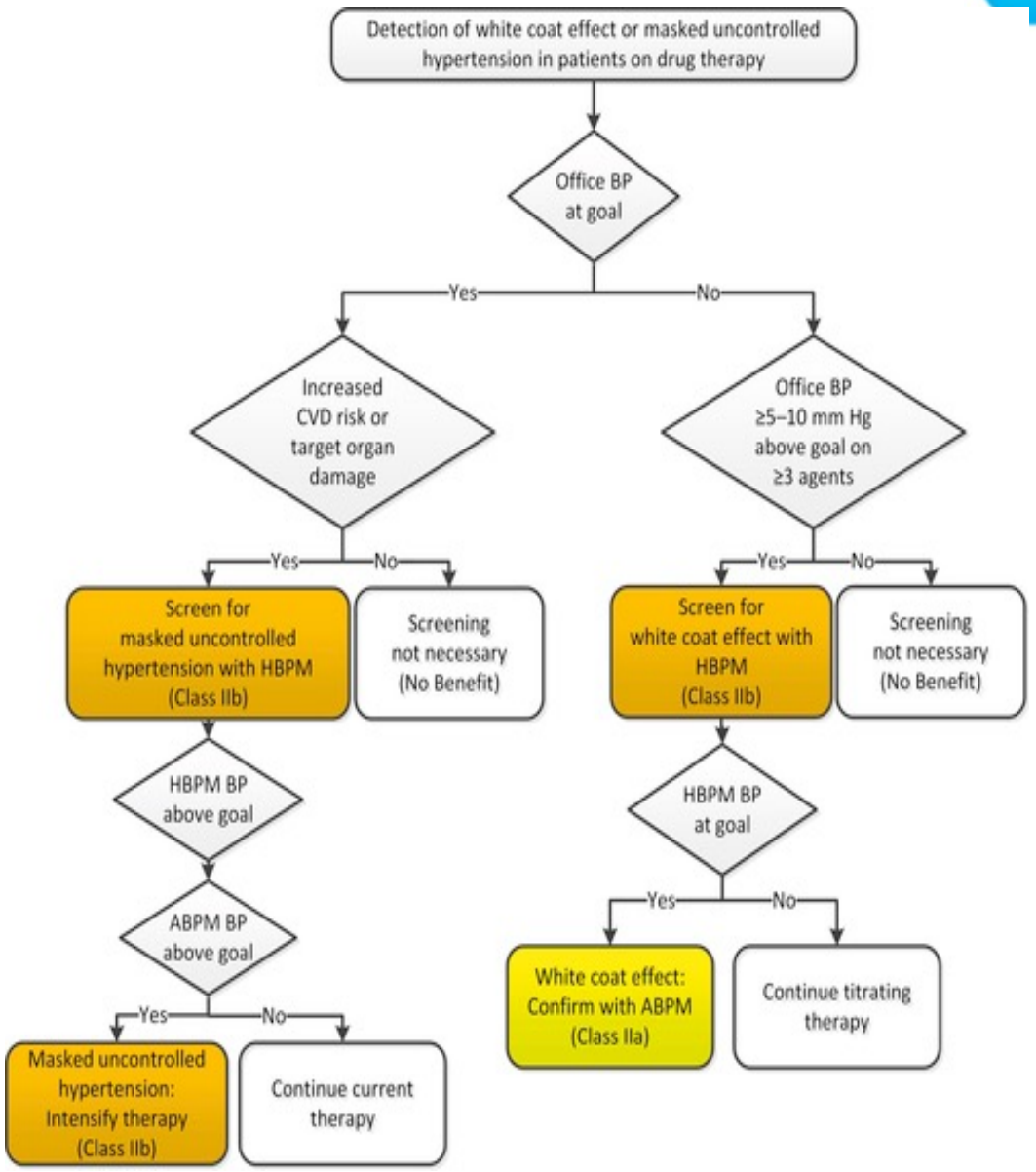
Step approach to combination therapy



Whitecoat Syndrome



What new in hypertensive management?

- Zilebesiran is an investigational RNA interference agent targeting angiotensinogen (AGT), a hormone produced predominantly in the liver that contributes to blood pressure regulation.
- A single injection of the experimental medication zilebesiran was safe and effective in reducing systolic blood pressure in people with mild-to-moderate high blood pressure for up to six months, as detailed in the Phase 2 of the KARDIA study, reported as late-breaking science today at the American Heart Association's Scientific Sessions 2023.

What new in hypertensive management?

- Lorundrostat: Aldosterone synthase inhibitor.
  - novel class of antihypertensive that decreases body's production of aldosterone.
  - Medicines currently available for patients block the receptor for aldosterone, but aldosterone can still be circulating and have a negative impact on patients.
  - Up to 25 percent of all people with hypertension exhibit abnormal aldosterone levels.

What new in hypertensive management?

- Esaxerenone : nonsteroidal mineralocorticoid receptor (MR) antagonists
  - high potency and selectivity for MR compared with spironolactone and eplerenone
  - strong blood pressure-lowering effect in hypertensive animals
  - effective and well-tolerated MRB in Japanese hypertensive patients
- SGLT2 inhibitor : inhibit sodium-glucose transport in proteins in the nephron
  - effectively reduces 24-h BPs including nighttime and morning BPs
  - aminopeptidase A inhibitor has central effects on vasopressin, a combined endothelin A and B receptor blocker, and an aldosterone synthase inhibitor devoid of glucocorticoid activity.
  - For patients with type 2 diabetes mellitus and hypertension with a low risk of genital infection, SGLT2i should be considered as an adjuvant drug for a first-line antihypertensive regimen. (NIH, 2023)

ACC 2024 Late-breaking clinical trials

Empagliflozin After Acute Myocardial Infarction: Results of the **EMPACT-MI Trial**

- **Method:** event-driven, double-blind trial, conducted from December 2020 to March 2023 at 451 sites in 22 countries, randomly assigned 6,522 patients (median age 63 years, 24.9% women, 83.6% White, 1.4% Black, 12.8% Asian) who had been hospitalized for acute MI and were at risk for HF with newly reduced left ventricular ejection fraction (LVEF) or congestion or both to either 10 mg daily of empagliflozin or a placebo in addition to standard care within 14 days of admission. At baseline, 78.4% of patients had an LVEF ≤45%, and 57.0% had signs or symptoms of congestion that resulted in treatment during the index hospitalization.
- **Results:** first hospitalization for HF or death from any cause, the composite primary endpoint, occurred in 267 patients (8.2%) in the empagliflozin group and 298 patients (9.1%) in the placebo group during the median follow-up of 17.9 months. The two groups had incidence rates of 5.9 and 6.6 events, respectively, per 100 patient-years (hazard ratio [HR], 0.90; 95% CI, 0.76-1.06; p=0.21).
- Secondary endpoints, total number of hospitalizations for HF or death from any cause occurred in 317 cases in the empagliflozin group and 385 in the placebo group (rate ratio [RR], 0.87; 95% CI, 0.68-1.10). Total number of nonelective cardiovascular hospitalizations or death from any cause were 666 and 730, respectively (RR, 0.92; 95% CI, 0.78-1.07). Total number of nonelective hospitalizations for any cause or death from any cause were 998 and 1,138 (RR, 0.87; 95% CI, 0.77-1.0), and total number of hospitalizations for MI or death from any cause were 276 and 274 (RR, 1.06; 95% CI, 0.83-1.35).

The SGLT2 inhibitor empagliflozin did not lower the risk of a first hospitalization for heart failure (HF) or death from any cause among patients with an increased risk for HF following acute myocardial infarction (MI)

ACC 2024 Late-breaking clinical trials

CSL112 (Apolipoprotein A-I) Infusions and Cardiovascular Outcomes in Patients With Acute Myocardial Infarction (ApoA-I Event Reducing in Ischemic Syndromes II **AEGIS-II) Trial**

- **Method**: phase 3, multicenter, double-blind, randomized, placebo-controlled, parallel-group trial investigating the efficacy and safety of CSL112 compared to placebo among high-risk acute MI participants. Eligibility criteria include age ≥ 18 years with type 1 (spontaneous) MI, evidence of multivessel stable coronary artery disease, and presence of diabetes requiring pharmacotherapy, or ≥2 of the following: age ≥ 65 years, prior MI, or peripheral artery disease. 18,218 participants randomized 1:1 to receive 4 weekly infusions of CSL112 6 g or placebo, initiated prior to or on the day of discharge and within 5 days of first medical contact. The primary outcome is the time to first occurrence of the composite of CV death, MI, or stroke through 90 days. Key secondary outcomes include the total number of hospitalizations for coronary, cerebral, or peripheral ischemia through 90 days and time to first occurrence of the composite primary outcome through 180 and 365 days.
- **Results:** incidence of cardiovascular death or any type of MI was numerically lower in the CSL112 group throughout follow-up: HR, 0.91 at 90 days; HR, 0.89 at 180 days, and HR, 0.92 at 365 days. For the composite of cardiovascular death and non-type 2 MI, which the authors noted may not be affected by plaque stabilization, HRs were 0.91, 0.87 and 0.91 at days 90, 180 and 365, respectively.

ACC 2024 Late-breaking clinical trials

ULTIMATE-DAPT: Ticagrelor monotherapy following one month of dual antiplatelet therapy (DAPT) outperforms 12-month DAPT (aspirin and ticagrelor) post PCI

- placebo-controlled trial, conducted at 58 medical centers in China, Pakistan, Italy and the U.K., randomized 3,400 patients who had undergone DAPT for one month following PCI for an acute coronary syndrome (ACS) and had no adverse cardiovascular or bleeding events to either continuing DAPT or switching to ticagrelor and a placebo for 11 months. All patients had participated in the IVUS-ACS randomized trial, and all patients and staff interacting with the patients were blinded to the randomized assignment in the present study. Their median age was 62 years, most were men (74%) and Chinese (88%), and most (70%) had single-vessel disease. Transradial access was used in 97% of patients.
- Results showed that the primary endpoint of clinically relevant bleeding (BARC 2, 3 or 5) at one year occurred in 4.6% of patients continuing DAPT and 2.1% of patients on ticagrelor monotherapy (hazard ratio [HR], 0.45; 95% CI, 0-30-0.66; p<0.0001). The composite primary endpoint of major adverse cardiovascular events and cerebrovascular (MACCE) events showed no significant difference between groups, with 3.7% of patients who continued DAPT and 3.6% of those taking ticagrelor monotherapy experiencing such events (HR, 0.98; 95% CI, 0.69-1.39; p for noninferiority <0.0001; p for superiority =0.89). No significant interactions were seen across the 12 prespecified subgroups for clinically relevant bleeding or MACCE.

ACC 2024 Late-breaking clinical trials

Comparison of an "Inclisiran First" Strategy With Usual Care in Patients With Atherosclerotic Cardiovascular Disease: Results From the **VICTORION-INITIATE Randomized Trial**

Inclisiran is a novel small interfering RNA therapy that inhibits the production of the PCSK9 protein. Inclisiran is currently FDA approved as an adjunct to statin therapy in patients with clinical ASCVD or heterozygous FH who require additional LDL-lowering

- **Method**: prospective, parallel-group study, conducted at 45 sites in the U.S., randomized 450 adult patients (30.9% women, 12.4% Black, 15.3% Hispanic) with LDL-C ≥70 mg/dL or non–HDL-C ≥100 mg/dL and fasting triglycerides <500 mg/dL to either usual care or usual care plus immediately initiating inclisiran 284 mg at Days 0, 90 and 270 ("inclisiran first"). Laboratory assessments were performed on Days 0, 90, 180, 270 and 330. The mean baseline LDL-C was 97.4 mg/dL.
- **Results**: primary endpoint of percentage change in LDL-C from baseline at Day 330 was a 60% reduction in the inclisiran first group compared with 7% in the usual care group. Statin discontinuation rates, a co-primary endpoint, were 6% and 16.7% in the inclisiran first group and usual care group, respectively, which the authors noted was noninferior.
- Furthermore, the goal LDL-C <70 mg/dL was achieved by 81.8% of the inclisiran first group vs. 22.2% in the usual care group. And more patients in the inclisiran first group than the usual care group reached an LDL-C <55mg/dL (71.6% vs. 8.9%).

ACC 2024 Late-breaking clinical trials

Once-weekly Semaglutide in Patients With Heart Failure With Preserved Ejection Fraction, Obesity and Type 2 Diabetes: Main Results From the **Step-HFpEF Dm Trial**

- **Method:** Enrollment of patient with LVEF ≥45%, NYHA functional class II–IV, Kansas City Cardiomyopathy Questionnaire clinical summary score (KCCQ-CSS) <90 points, 6-minute walk distance >100 m, Type 2 DM diagnosed ≥90 days prior to screening with HbA_{1c} ≤10%, and ≥1 of the following:
  - Elevated LV filling pressures (invasively measured)
  - Elevated natriuretic peptide levels and structural echocardiographic abnormalities
  - HF hospitalization (previous 12 months) and ongoing requirement for diuretics and/or structural echocardiographic abnormalities
- Patients were randomized in a 1:1 fashion to once weekly subcutaneous semaglutide (n = 310) or matching placebo (n = 306) for 52 weeks. Semaglutide treatment was initiated at a dose of 0.25 mg once weekly for the first 4 weeks, and the dose was escalated every 4 weeks with the aim of reaching the maintenance dose of 2.4 mg by week 16. Total randomized participants: 616; Median duration of follow-up: 52 weeks; Median patient age: 69 years; Percentage female: 44%
- **Results:** among obese patients with HFpEF and type 2 DM, once weekly subcutaneous semaglutide was superior to placebo in improving body weight and patient-oriented QoL outcomes at 52 weeks.

ACC 2024 Late-breaking clinical trials

Zilebesiran in Combination With a Standard-of-care Antihypertensive in Patients With Inadequately Controlled Hypertension: Primary Results From the Phase 2 **Kardia-2 Study**

Zilebesiran is a subcutaneously injected RNA interference agent that targets hepatic synthesis of angiotensinogen (AGT), which is the most upstream precursor of all angiotensin peptides.

- **Method**: Randomized, Parallel, Blinded, Placebo, Phase 2 study in patients with uncontrolled hypertension. Randomized to zilebesiran vs. placebo after a run-in period where they received indapamide 2.5 mg daily, or amlodipine 5 mg daily, or olmesartan 40 mg daily. Total number of enrollees: 1,500; Duration of follow-up: 6 months; Mean patient age: 59 years; Percentage female: 43%; Percentage with diabetes: 23%. Subjects must have untreated systolic blood pressure 155-180 mm Hg, or treated systolic blood pressure 145-180 mm Hg
- **Results**: The primary outcome, change from baseline to 3-month 24-hour mean ambulatory systolic blood pressure, was -12.1 mm Hg in the indapamide group for zilebesiran vs. placebo ($p < 0.001$), -9.7 mm Hg in the amlodipine group for zilebesiran vs. placebo ($p < 0.001$), and -4.0 mm Hg in the olmesartan group for zilebesiran vs. placebo ($p = 0.036$). The blood pressure difference was sustained to 6 months in the indapamide and amlodipine groups.
- Secondary outcomes: Change from baseline to 3-month office systolic blood pressure: -18.5 mm Hg in the indapamide group for zilebesiran vs. placebo ($p < 0.001$), -10.2 mm Hg in the amlodipine group for zilebesiran vs. placebo ($p < 0.001$), and -7.0 mm Hg in the olmesartan group for zilebesiran vs. placebo ($p < 0.001$)

ACC 2024 Late-breaking clinical trials

Efficacy and Safety of Olezarsen in Patients With Hypertriglyceridemia and High Cardiovascular Risk: Primary Results of the **BRIDGE-TIMI 73a Trial**

Ligand-conjugated antisense (LICA) medicine is an investigational drug designed to inhibit the production of apoC-III

- **Method**: Phase 3, multi-center, randomized, double-blind, placebo-controlled study in up to approximately 390 participants. Participants will be randomized to receive olezarsen or placebo in a 53-week treatment period. The length of participation in the study will be approximately 78 weeks, which includes an up to 12-week screening period, a 53-week treatment period, and a 13-week post-treatment evaluation period or transition to open-label extension (OLE) study with up to 1-year treatment.
- **Results:** Monthly administration of subcutaneous olezarsen substantially reduced triglyceride levels compared with placebo among patients with predominantly moderate hypertriglyceridemia and elevated CV risk, according to new phase 2 data.” Additionally, “the investigational therapy...had effects on lipid measures beyond triglycerides, with meaningful reductions in apolipoprotein B and non-HDL cholesterol

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Lerodalcibep compared with placebo among patients with increased risk of cardiovascular disease (CVD).

Lerodalcibep blocks pro-protein convertase subtilisin/kexin type 9 (PCSK9) binding to low-density lipoprotein (LDL)-receptors, thus preventing receptor degradation, which enhances LDL-C clearance and lowering of LDL-C levels.

- **Method**: Randomized, Parallel, Blinded, Placebo controlled in Patients with established or at high risk for CVD. Randomized to lerodalcibep 300 mg dose in 1.2 mL subcutaneous injection (n = 615) vs. placebo (n = 307). Total number of enrollees 922, 52 week follow up, mean age 65, percentage female 47%, percentage DM 45%
- **Results**:The primary outcome, change in LDL-C at 52 weeks, was -56.3% in the lerodalcibep group vs. -0.14% in the placebo group ($p < 0.001$).
- Secondary outcomes: Patients achieving ≥50% reduction in LDL-C: 94% with lerodalcibep vs. 19% with placebo, ≥1 adverse event leading to study drug withdrawal: 4.2% with lerodalcibep vs. 4.6% with placebo, change in apolipoprotein B at 52 weeks: -43% for lerodalcibep vs. placebo, change in lipoprotein(a) at 52 weeks: -33% for lerodalcibep vs. placebo

ACC 2024 Late-breaking clinical trials

Plozasiran (ARO-APOC3), An Investigational RNAi Therapeutic, Reductions in APOC-3 and Triglycerides (TG) in Patients With Severe Hypertriglyceridemia (SHTG), **SHASTA-2**

Apolipoprotein C-III (APOC3) inhibits triglyceride clearance by reducing lipoprotein lipase–mediated hydrolysis and hepatocyte uptake of triglyceride-rich lipoproteins. ARO-APOC3, a hepatocyte-targeting RNA interference therapeutic, inhibits APOC3 messenger ribonucleic acid expression, lowering triglyceride levels.

- **Method:** double-blind, phase 2b, placebo-controlled, dose-ranging trial tested the effectiveness and safety of plozasiran as an add-on to existing lipid-lowering treatment in patients with severe hypertriglyceridemia. A total of 229 patients (55 years old, 78% men, 90% White) were enrolled in eight countries. The majority of enrolled patients had at least three of the following risk factors: elevated risk for or history of cardiovascular disease, diabetes, low HDL-C and high body mass index.
- Patients were randomized to one of four groups. Three groups received two injections of plozasiran at one of three doses (10 mg, 25 mg or 50 mg); the fourth group received two injections of a placebo. The first injection was given on day one and the second at week 12.
- **Results**: reduced triglyceride levels significantly without causing any significant safety concerns in patients with severely elevated triglyceride levels at risk for developing acute pancreatitis, according to results from the SHASTA 2 study presented during a Late-Breaking Clinical Trial session at ACC.24.

ACC 2024 Late-breaking clinical trials

Effect of Edetate Disodium Based Chelation Infusions on Cardiovascular Events in Post-MI Patients With Diabetes: The **TACT2 Trial**

- **Methods:** The double-blind factorial trial, conducted at 88 sites across the U.S. and Canada, randomized 959 patients (median age 67, 26.9% women, 61.5% Non-Hispanic White) with diabetes (>90% with type 2) and prior MI to either weekly edetate disodium infusions or a placebo for 40 weeks. In the treatment group, 68% of participants received all 40 infusions; 78% received at least 20.
- **Results:** at a median follow-up of 48 months, there was no significant difference between the two groups in terms of the primary composite endpoint: death from any cause, MI, stroke, coronary revascularization or hospitalization for unstable angina occurred in 35% of patients in both groups (hazard ratio, 0.93; 95% CI, 0.76-1.16; p=0.53).

ACC 2024 Late-breaking clinical trials

Long-term Beta-blocker Treatment After Acute Myocardial Infarction and Preserved Left Ventricular Ejection Fraction: The **REDUCE-AMI Trial**

- **Method**: parallel-group, open-label trial, conducted from September 2017 through May 2023 at 45 centers across Sweden, Estonia and New Zealand randomly assigned 5,020 patients (median age 65, 22.5% women) with acute MI who had participated in the SWEDEHEART registry, undergone coronary angiography and had an LVEF ≥50% to long-term treatment with one of two beta-blockers – metoprolol or bisoprolol (median dose of metoprolol 100 mg and bisoprolol 5 mg) or to no beta-blocker treatment.
- **Results:** at a median follow-up of 3.5 years, the primary composite endpoint of death from any cause or new MI occurred in 199 (7.9%) of patients in the beta-blocker group and 208 (8.3%) of patients in the no-beta-blocker group (hazard ratio, 0.96; 95% CI, 0.79-1.16; p=0.64).

ACC 2024 Late-breaking clinical trials

Benzodiazepine-free Cardiac Anesthesia For Reduction of Postoperative Delirium **(B-Free)**: A Multi-centre Randomized Cluster Crossover Trial

- **Method**: Cluster, crossover, randomized study of patient undergoing cardiovascular surgery were randomized to restrictive benzodiazepine use (n = 9,827) vs. liberal benzodiazepine use (n = 9,941). Total number of enrollees: 19,768; duration of follow-up: in-hospital; mean patient age: 65 years; percentage female: 27%
- **Results**: primary outcome, delirium within 72 hours, was 14.0% in the restrictive group vs. 14.9% in the liberal group (p = 0.07).
- Secondary outcomes: *Excluding patients who received benzodiazepine within 24 hours prior to surgery:* Delirium within 72 hours was 13.7% in the restrictive group vs. 14.9% in the liberal group (p = 0.01).

ACC 2024 Late-breaking clinical trials

A Selective Aldose Reductase Inhibitor (at-001) For the Treatment of Diabetic Cardiomyopathy: Primary Results of the Phase 3 Randomized Controlled **ARISE-HF Study**

Aldose reductase (AR) catalyzes the first and rate-limiting step in the polyol pathway, and AR inhibition has been shown to reduce diabetic complications, including DbCM in animal models and in patients with DbCM

- **Method**: Phase 3 randomized, placebo-controlled, double blind, global clinical study to investigate the efficacy of AT-001 (1000 mg twice daily [BID] and 1500 mg BID) in 675 T2DM patients with DbCM at high risk of progression to overt HF. ARISE-HF assesses the ability of AT-001 to improve or prevent decline in exercise capacity as measured by functional capacity (changes in peak oxygen uptake [peak VO_2]) over 15 (and possibly 27) months of treatment. Additional endpoints include percentage of patients progressing to overt HF, health status metrics, echocardiographic measurements, and changes in cardiacbiomarkers.
- **Results**: Treatment with AT-001, a highly selective aldose reductase inhibitor, had no significant effect on exercise capacity as measured by peak oxygen uptake (VO2) among individuals with diabetic cardiomyopathy (DbCM)

Questions?

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