

Therapeutic Class Overview

Angiotensin II Receptor Blockers (ARBs)-Single Entity Agents

Therapeutic Class

- Overview/Summary:** The angiotensin II receptor blockers (ARBs) are Food and Drug Administration (FDA) approved to treat hypertension, to reduce the risk of cardiovascular death and heart failure hospitalization in patients with heart failure, to treat diabetic nephropathy with elevated serum creatinine and proteinuria in patients with type 2 diabetes and hypertension, to reduce the risk of stroke in patients with hypertension and left ventricular hypertrophy, cardiovascular risk reduction in patients unable to take angiotensin converting enzyme (ACE) inhibitors and to reduce the risk of cardiovascular mortality in clinically stable patients with left ventricular failure or left ventricular dysfunction following myocardial infarction.¹⁻⁹ The renin-angiotensin-aldosterone system (RAAS) is the most important component in the homeostatic regulation of blood pressure.^{10,11} Excessive activity of the RAAS may lead to hypertension and disorders of fluid and electrolyte imbalance.¹² Renin catalyzes the conversion of angiotensinogen to angiotensin I. Angiotensin I is then cleaved to angiotensin II by ACE. Angiotensin II can increase blood pressure by direct vasoconstriction and through actions on the brain and autonomic nervous system.^{10,12} In addition, angiotensin II stimulates aldosterone synthesis from the adrenal cortex, leading to sodium and water reabsorption. Angiotensin II exerts other detrimental cardiovascular effects including hypertrophy and remodeling.^{10,11} The RAAS plays an important role in the development and progression of heart failure.² ACE inhibitors block the conversion of angiotensin I to angiotensin II, and also inhibit the breakdown of bradykinin, a potent vasodilator associated with dry cough.¹⁰⁻¹³ Since angiotensin II may also be generated through other pathways that do not depend upon ACE (e.g., chymase), blockade of angiotensin II by ACE inhibitors is incomplete.^{10,11} The ARBs block the angiotensin II receptor subtype AT₁, preventing the negative effects of angiotensin II regardless of origin. The ARBs have not been shown to affect bradykinin. Currently, losartan and eprosartan (600 mg strength) are the only agents in the class that are available generically. Azilsartan (Edarbi[®]), the newest ARB, was approved by the FDA in 2011 for the treatment of hypertension.

Table 1. Current Medications Available in Therapeutic Class¹⁻⁹

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Azilsartan (Edarbi [®])	Hypertension	Tablet: 40 mg 80 mg	-
Candesartan (Atacand [®])	Hypertension, heart failure (NYHA Class II to IV)*	Tablet: 4 mg 8 mg 16 mg 32 mg	-
Eprosartan (Teveten [®])	Hypertension	Tablet: 400 mg 600 mg	✓ #
Irbesartan (Avapro [®])	Hypertension, diabetic nephropathy in patients with type 2 diabetes mellitus and hypertension [†]	Tablet: 75 mg 150 mg 300 mg	-
Losartan (Cozaar [®])	Hypertension, diabetic nephropathy in patients with type 2 diabetes mellitus and hypertension [†] , reduction in the risk of stroke in patients with hypertension and left ventricular hypertrophy [‡]	Tablet: 25 mg 50 mg 100 mg	✓
Olmесartan (Benicar [®])	Hypertension	Tablet: 5 mg 20 mg	-

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Telmisartan (Micardis®)	Hypertension, cardiovascular risk reduction in patients unable to take ACE inhibitors [§]	40 mg Tablet: 20 mg 40 mg 80 mg	-
Valsartan (Diovan®)	Hypertension, heart failure (NYHA Class II to IV) , post-myocardial infarction [¶]	Tablet: 40 mg 80 mg 160 mg 320 mg	-

ACE inhibitor=angiotensin converting enzyme inhibitors, NYHA=New York Heart Association

*To reduce the risk of cardiovascular death and heart failure hospitalization in patients with left ventricular systolic dysfunction. Candesartan has an added effect on these outcomes when used with an angiotensin converting enzyme inhibitor.

†Reduces the rate of progression to nephropathy in patients with elevated serum creatinine and proteinuria (>300 mg/day).

‡There is evidence that this benefit does not apply to African American patients.

§Reduction of risk of myocardial infarction, stroke or cardiovascular death in patients 55 years of age and older at high risk of developing major cardiovascular events. Use of telmisartan with an angiotensin converting enzyme inhibitors is not recommended.

Consider using an angiotensin converting enzyme inhibitors first.

|| Reduction in heart failure hospitalizations. There is no evidence that valsartan provides added benefit when used with adequate doses of an angiotensin converting enzyme inhibitors.

¶In clinically stable patients with left ventricular failure or dysfunction following myocardial infarction, to reduce the risk of cardiovascular mortality.

Generic available in 600 mg strength only

Evidence-based Medicine

- Clinical trials have demonstrated the safety and efficacy of the angiotensin II receptor blockers (ARBs) in the treatment of hypertension, diabetic nephropathy, heart failure, post-myocardial infarction, reducing cardiovascular risk and reducing the risk of stroke in patients with left ventricular hypertrophy.¹⁴⁻⁶⁵
- Head-to-head trials of agents in the class have failed to consistently demonstrate the “superiority” of one ARB over another for their respective indications.^{14-16,21,22,24,27,46} Comparisons between the ARBs and angiotensin converting enzyme inhibitors have generally demonstrated comparable efficacy between medication classes in the treatment of hypertension, heart failure, post-myocardial infarction, reducing cardiovascular risk and diabetic nephropathy.^{19,23,25,28,35-37,39,40,44,45,49}

Key Points within the Medication Class

- According to Current Clinical Guidelines:
 - Treatment guidelines for hypertension recommend the use of angiotensin II receptor blockers (ARBs) in hypertensive patients with certain compelling indications including heart failure, left ventricular hypertrophy, chronic kidney disease and diabetes.⁶⁶⁻⁶⁸
 - Treatment guidelines for the management of stable angina recommend ARBs in patients with hypertension and those who have an indication for an angiotensin converting enzyme (ACE) inhibitor but are intolerant to them, who have heart failure or who have had a myocardial infarction and have a left ventricular ejection fraction of ≤40%.⁶⁹
 - Treatment guidelines for the management of unstable angina/non-ST elevation myocardial infarction recommend the use of ARBs in patients who are intolerant to ACE inhibitors and who have had a myocardial infarction or have clinical or radiological signs of heart failure or a left ventricular ejection fraction of ≤40%.^{70,71} Similarly, guidelines for the management of ST-elevation myocardial infarction recommend ARBs in patients who are intolerant to ACE inhibitors and have heart failure or who have a left ventricular ejection fraction of ≤40%.^{72,73}
 - The National Institute for Health and Clinical Excellence recommends that ARBs be reserved for patients post-myocardial infarction who are intolerant to ACE inhibitor therapy. Routine use of ARBs after a myocardial infarction is not recommended.⁷⁴
 - Treatment guidelines for the management of heart failure recommend ARBs, specifically losartan and irbesartan, in patients with type 2 diabetes mellitus and nephropathy who are at

- risk for the development of heart failure. ARBs are recommended in patients intolerant to ACE inhibitors who have cardiac structural abnormalities or remodeling who have not developed heart failure symptoms, especially in patients with reduced left ventricular ejection fraction and a history of myocardial infarction. Individual ARBs may be considered as initial therapy instead of an ACE inhibitor in patients with heart failure who have had a myocardial infarction and in patients with chronic heart failure and systolic dysfunction.⁷⁵⁻⁷⁸
- Treatment guidelines for the management of hypertension in patients with diabetes recommend a regimen including either an ACE inhibitor or an ARB. If one class is not tolerated the other should be tried. In patients with type 2 diabetes, hypertension, macroalbuminuria and renal insufficiency, ARBs have been shown to delay the progression of nephropathy.⁷⁹
 - Other Key Facts:
 - Clinical trials have demonstrated the safety and efficacy of the angiotensin II receptor blockers (ARBs) for their respective Food and Drug Administration approved indications.
 - In general, clinical guidelines recommend the use of an ARB in patients who are intolerant to angiotensin converting enzyme (ACE) inhibitors, or as first line alternatives to ACE inhibitors.
 - Losartan and eprosartan (600 mg strength) are the only generic ARBs currently available.

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