OPTUMRx

Therapeutic Class Overview
Angiotensin II Receptor Blockers (ARBs)

INTRODUCTION

- Approximately 121.5 million American adults are living with some form of cardiovascular (CV) disease (congestive heart disease, heart failure, stroke, and hypertension) according to the American Heart Association (AHA) Heart Disease and Stroke Statistics 2019 update *(Benjamin et al 2019).* Cardiovascular disease accounts for an estimated 840,678 deaths in the US annually and is the leading cause of death globally.
- The estimated prevalence of heart failure (HF) is 6.2 million for Americans aged ≥ 20 years. Projections show that the prevalence of HF will increase 46% from 2012 to 2030, resulting in > 8 million people ≥ 18 years of age with HF (*Benjamin et al 2019*).
- Hypertension (HTN) is an independent risk factor for CV disease and increases the mortality risks of CV disease and other diseases *(Benjamin et al 2019).* The 2017 American College of Cardiology (ACC)/AHA clinical practice guideline defines HTN as blood pressure (BP) ≥ 130/80 mm Hg (*Whelton et al 2018).* Nearly half of American adults (46%) have HTN based on this definition.
- Lowering of BP has been shown to reduce the risk of fatal and nonfatal CV events including stroke and myocardial infarctions (MIs). Lipid control, diabetes mellitus (DM) management, smoking cessation, exercise, weight management, and limiting sodium intake may also reduce CV risk *(Benjamin et al 2019).*
- Numerous classes of antihypertensives are available to reduce BP. Some examples of antihypertensives include diuretics, angiotensin converting enzyme inhibitors (ACE-Is), angiotensin II receptor blockers (ARBs), beta blockers, and calcium channel blockers (CCBs). Selection of antihypertensive therapy for a specific patient is determined by patient characteristics such as ethnic group, and the presence of compelling indications such as HF, DM, chronic kidney disease (CKD), history of stroke or MI, and risk factors for coronary heart disease (CHD). Some patients require 2 or more antihypertensives from different pharmacological classes to achieve BP control *(Go et al 2014, Weber et al 2014, Whelton et al 2018).*
- In general, guideline-recommended BP goals in hypertensive adults range from < 130/80 mm Hg to < 140/90 mm Hg *(Arnett et al 2019, de Boer et al 2017, Whelton et al 2018).*
  - Blood pressure goals for older patients have long been a point of debate. The SPRINT trial followed patients ≥ 50 years with high BP and increased CV risks under intense hypertensive treatment (with a systolic blood pressure [SBP] goal of < 120 mm Hg) compared to standard HTN treatment (with an SBP goal of < 140 mm Hg) over a period of 3.2 years. The trial ended early; however, results demonstrated a reduced primary composite outcome of MI, acute coronary syndrome (ACS), stroke, HF, or CV death driven mainly by reduced HF events and CV death with intense treatment compared to standard treatment. The SPRINT trial pointed to potential clinical benefits associated with more intensive treatment in certain patients, although early termination of the trial and variations in the BP-measurement technique employed have called into question the generalizability of the results *(SPRINT Research Group 2015).*
  - A recent guideline from the American College of Physicians (ACP) and the American Academy of Family Physicians (AAFP) on treatment of HTN in adults aged ≥ 60 years recommends standard and intense SBP treatment goals of < 150 mm Hg and < 140 mm Hg, respectively, with more intense BP reduction reserved for patients with a history of stroke or transient ischemic attack *(Qaseem et al 2017).*
- The cardinal symptoms of HF are dyspnea and fatigue. HF leads to exercise intolerance, fluid retention, pulmonary congestion, and peripheral edema, often resulting in hospitalization (*Yancy* et al, *2013*).
- There are 2 forms of HF:
  - Heart failure with reduced ejection fraction (HFrEF) or systolic HF: ejection fraction (EF) ≤ 40%
  - Heart failure with preserved ejection fraction (HFpEF) or diastolic HF: EF ≥ 50%
- Recent guideline updates from the ACC/AHA/Heart Failure Society of America (HFSA) state that in patients with chronic symptomatic HFrEF New York Heart Association (NYHA) Class II or III who tolerate an ACE-I or ARB, replacement by an angiotensin receptor and neprilysin inhibitor (ARNI), such as sacubitril/valsartan, is recommended to further reduce morbidity and mortality (*Yancy et al 2016, Yancy et al 2017*).

- Sacubitril/valsartan is usually administered in place of an ACE-I or other ARB; although, the role for the management of HF is not as well established as ACE-Is or other ARBs. Based on study data, there is minimal evidence of benefits and harms in the following populations: very elderly patients, African Americans, NYHA Class I or IV, patients with low BP or co-morbid HTN refractory to treatment, and patients with HFpEF. Further studies are warranted in these groups.
- This review includes the ARBs, the ARB combination products, and the only approved ARNI (sacubitril/valsartan). ARBs work primarily through reduction of systemic vascular resistance as a result of selective antagonism of angiotensin II at the angiotensin II AT1 receptor. Angiotensin II is the primary vasoactive hormone.
  - The ARBs are Food and Drug Administration (FDA)-approved to treat HTN. Some ARBs have additional indications for HF, diabetic nephropathy, or CV risk reduction in certain high-risk populations.
  - The ARB combinations are products that combine an ARB with a diuretic (ie, chlorthalidone, hydrochlorothiazide [HCTZ]), a beta blocker (ie, nebivolol), and/or a CCB (ie, amlodipine) in a fixed-dose formulation. By combining agents from different classes, these combination products are meant to increase the effectiveness of antihypertensive therapy through complementary mechanisms of action while minimizing the potential for dose-related adverse effects. All ARB combination products are FDA-approved for the treatment of HTN. Losartan/HCTZ is also indicated to reduce the risk of stroke in patients with HTN and left ventricular (LV) hypertrophy.
  - Sacubitril/valsartan is indicated to reduce the risk of CV death and hospitalization for HF in patients with chronic HFrEF.
- Medispan classes: Angiotensin II Receptor Antagonists; Antihypertensive Combinations - ARB/CCB combinations, beta blocker/ARB combination, ARB/thiazide and thiazide-like combinations, and ARB/CCB/thiazide combinations; Cardiovascular Agents, ARNI – Angiotensin II receptor antagonist/neprilysin inhibitor combination

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Single-Entity ARBs	
Atacand (candesartan)	✔
Avapro (irbesartan)	✔
Benicar (olmesartan)	✔
Cozaar (losartan)	✔
Diovan (valsartan)	✔ *
Edarbi (azilsartan)	-
eprosartan	✔ †
Micardis (telmisartan)	✔
ARB/Diuretic Combinations	
Atacand HCT (candesartan/hydrochlorothiazide)	✔
Avalide (irbesartan/hydrochlorothiazide)	✔
Benicar HCT (olmesartan/hydrochlorothiazide)	✔
Diovan HCT (valsartan/hydrochlorothiazide)	✔
Edarbyclor (azilsartan/chlorthalidone)	-
Hyzaar (losartan/hydrochlorothiazide)	✔
Micardis HCT (telmisartan/hydrochlorothiazide)	✔
ARB/Beta Blocker Combinations	
Byvalson (valsartan/nebivolol) ‡	-
ARB/CCB Combinations	
Azor (olmesartan/amlodipine)	✔
Exforge (valsartan/amlodipine)	✔
Twynsta (telmisartan/amlodipine)	✔
ARB/CCB/Diuretic Combinations	
Exforge HCT (valsartan/amlodipine/hydrochlorothiazide)	✔
Tribenzor (olmesartan/amlodipine/hydrochlorothiazide)	✔
ARB/Neprilysin inhibitor Combination	

Drug	Generic Availability
Entresto (sacubitril/valsartan)	-

Abbreviations: ARB = angiotensin II receptor blocker; CCB = calcium channel blocker
*Prexxartan (valsartan) oral solution was FDA-approved in December 2017; however, it has been discontinued.
†Branded Teveten (eprosartan) is no longer marketed.
‡In December 2018, Allergan announced that it would be discontinuing Byvalson (*FDA Drug Shortages 2019*).

(Drugs@FDA 2019, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2019)

INDICATIONS

Table 2. FDA-approved indications for single-entity ARBs

Indication	Atacand (candesartan)	Avapro (irbesartan)	Benicar (olmesartan)	Cozaar (losartan)	Diovan (valsartan)	Edarbi (azilsartan)	eprosartan	Micardis (telmisartan)
Hypertension in adults	✔	✔	✔	✔	✔	✔	✔	✔
Hypertension in children ages 1 to < 17 years	✔							
Hypertension in children ages 6 to 16 years			✔	✔	✔			
Treatment of diabetic nephropathy in hypertensive patients with type 2 DM, an elevated serum creatinine, and proteinuria		✔		✔				
Heart failure (NYHA Class II to IV) in adults	✔				✔			
Reduction in the risk of stroke in patients with hypertension and LV hypertrophy				✔				
Post-MI: Reduction of cardiovascular mortality in clinically stable patients with LV failure or LV dysfunction					✔			
Cardiovascular risk reduction in patients 55 years of age or older at high risk of developing major cardiovascular events who are unable to take ACE-Is								✔

Abbreviations: ACE-I = angiotensin converting enzyme inhibitor; LV = left ventricular; MI = myocardial infarction; NYHA = New York Heart Association

(Prescribing information: Atacand 2018, Avapro 2018, Benicar 2017, Cozaar 2018, Diovan 2017, Edarbi 2016, eprosartan 2014, Micardis 2018)

Table 3. FDA-approved indications for combination products containing ARBs

Drug	Hypertension	Reduction in the Risk of CV Death and HF Hospitalization in Patients with Chronic HF and Reduced EF	Reduction in the Risk of Stroke in Patients with Hypertension and Left Ventricular Hypertrophy
ARB/Diuretic Combinations			
Atacand HCT (candesartan/hydrochlorothiazide)	✔*	-	-
Avalide (irbesartan/hydrochlorothiazide)	✔†	-	-
Benicar HCT (olmesartan/hydrochlorothiazide)	✔*	-	-

Drug	Hypertension	Reduction in the Risk of CV Death and HF Hospitalization in Patients with Chronic HF and Reduced EF	Reduction in the Risk of Stroke in Patients with Hypertension and Left Ventricular Hypertrophy
Diovan HCT (valsartan/hydrochlorothiazide)	✔ †	-	-
Edarbyclor (azilsartan/chlorthalidone)	✔ †	-	-
Hyzaar (losartan/hydrochlorothiazide)	✔ ‡	-	✔ §
Micardis HCT (telmisartan/hydrochlorothiazide)	✔ *	-	-
ARB/Beta Blocker Combination			
Byvalson (valsartan/nebivolol)	✔ *	-	-
ARB/CCB Combinations			
Azor (olmesartan/amlodipine)	✔ †	-	-
Exforge (valsartan/amlodipine)	✔ †	-	-
Twynsta (telmisartan/amlodipine)	✔ †	-	-
ARB/CCB/Diuretic Combinations			
Exforge HCT (valsartan/amlodipine/hydrochlorothiazide)	✔ *	-	-
Tribenzor (olmesartan/amlodipine/hydrochlorothiazide)	✔ *	-	-
ARB/Neprilysin inhibitor Combination			
Entresto (sacubitril/valsartan)		✔ ‖	

Abbreviations: ARB = angiotensin II receptor blocker; CCB = calcium channel blocker; CV = cardiovascular; EF = ejection fraction; HF = heart failure

*This fixed-dose combination is not indicated for initial therapy.

†Indicated to treat HTN in patients not adequately controlled on monotherapy or as initial therapy in patients who are likely to need multiple drugs to achieve their BP goals.

‡The fixed-dose combination is not indicated for initial therapy, except when the HTN is severe enough that the value of achieving prompt BP control exceeds the risks of initiating combination therapy in these patients.

§There is evidence that this benefit does not extend to African American patients.

‖NYHA Class II to IV

(Prescribing information: Atacand HCT 2018, Avalide 2018, Azor 2017, Benicar HCT 2017, Byvalson 2019, Diovan HCT 2015, Edarbyclor 2016, Entresto 2018, Exforge 2015, Exforge HCT 2015, Hyzaar 2018, Micardis HCT 2018, Tribenzor 2017, Twynsta 2018)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

Single-Entity ARBs

- ARBs have demonstrated efficacy for the treatment of HTN in adults. A Cochrane systematic review of 46 randomized, placebo-controlled trials evaluated the BP lowering ability of 9 different ARBs (N = 13,451) in patients with a baseline BP of 156/101 mm Hg. On average, SBP was lowered by 8 mm Hg and diastolic blood pressure (DBP) by 5 mm Hg with maximum recommended doses of ARBs. No clinically meaningful differences within the ARB class were observed in the reduction of BP *(Heran et al 2008).* A systematic review and network meta-analysis of 36 RCTs evaluated the comparative effectiveness of ARBs (versus another ARB, HCTZ, or placebo) in lowering BP and CV event rates (including MI, stroke, cardiovascular mortality, and all-cause mortality) in patients with hypertension. BP reduction and CV event rates were found to be similar among all ARBs assessed, and the authors concluded that evidence is not sufficient to show differences in reduction of blood pressure or CV disease among members of the ARB drug class (*Tsoi et al 2018*).

  - Meta-analyses have shown that ACE-Is and ARBs have similar long-term effects on BP *(Sanders et al 2011, Savarese et al 2013).* Additionally, a Cochrane review involving 11,007 subjects with primary HTN found no evidence of a difference in total mortality or CV outcomes for ACE-Is in comparison to ARBs (*Li 2014*).
- Telmisartan is indicated to reduce CV risk in patients unable to take ACE-Is. The ONTARGET trial compared telmisartan and ramipril monotherapy and in combination with each other and demonstrated no significant difference between any groups in death from CV causes, MI, stroke, or hospitalization for HF *(ONTARGET Investigators 2008).* In the TRANSCEND trial, no significant difference was observed between telmisartan and placebo in death from CV causes, MI, stroke, or HF hospitalizations. The composite endpoint of death from CV causes, MI, and stroke occurred in significantly fewer patients in the telmisartan group, but this significance was lost after adjustment for multiplicity of comparisons and overlap with the primary outcome *(Foulquier et al 2014, TRANSCEND Investigators 2008)*.
- Losartan is indicated to reduce the risk of stroke in patients with HTN and LV hypertrophy. The efficacy of losartan was demonstrated in the LIFE trial and its corresponding sub-analyses. Losartan was compared to therapy with atenolol. Results demonstrated a 24.9% relative risk reduction for stroke in patients treated with losartan-based regimens compared to atenolol-based regimens *(Dahlöf et al 2002)*. However, a post-hoc analysis in African American patients showed an increase in the composite of CV death, MI, and stroke with losartan compared to atenolol *(Julius et al 2004)*.
- Candesartan and valsartan are indicated to treat HF. Trials demonstrated the efficacy of candesartan alone and in combination with ACE-I therapy compared to placebo in reducing the risk of all-cause mortality, CV death, and/or HF hospitalization *(McMurray et al 2003, Pfeffer et al 2003b, Yusuf et al 2003)*. When compared to enalapril in the RESOLVD trial, candesartan was not significantly better in improving 6-minute walking distance, NYHA functional class, or quality of life *(McKelvie et al 1999)*. Losartan was compared to captopril in patients with HF, and no significant difference was observed in renal function or all-cause mortality *(Pitt et al 1997, Pitt et al 2000)*. However, there was a significantly lower risk of sudden death and resuscitated cardiac arrest with losartan *(Pitt et al 2000)*. The Val-HeFT trial showed no significant difference in all-cause mortality between valsartan and placebo. However, the valsartan group demonstrated a significant improvement in NYHA functional class, HF hospitalizations, morbidity, and mortality *(Cohn et al 2001)*.
- Valsartan is indicated to reduce CV mortality in patients with post-MI LV failure or dysfunction. The VALIANT trial compared valsartan with captopril and combination therapy with valsartan plus captopril. No significant differences in all-cause mortality, CV death, reinfarction, or HF hospitalization were observed between monotherapy groups or combination therapy compared to captopril monotherapy *(Pfeffer et al 2003a)*. Losartan has also been evaluated in patients post-MI compared to and in combination with captopril. Results were similar to those of the VALIANT trial *(Dickstein et al 2002)*.
- Irbesartan and losartan are indicated for the treatment of diabetic nephropathy in patients with type 2 DM and HTN. However, clinical benefit in diabetic nephropathy has been shown with other ARBs, including candesartan, losartan, telmisartan, and valsartan *(Barnett et al 2004, Galle et al 2008, Hou et al 2007, Mogensen et al 2000, Viberti et al 2002)*.
- The ORIENT and ROADMAP studies followed patients with DM and compared the effects of olmesartan versus placebo. Outcomes demonstrated a higher rate of death from CV causes in both trials compared to placebo. This finding contradicts outcomes of other studies that include ARBs and/or olmesartan. A number of factors may have contributed to these outcomes including concomitant medications, patients with higher CV risks, and other potential confounders. Further studies in diabetic patients are needed to validate findings *(Haller et al 2011, Imai et al 2011)*.
- Studies have demonstrated that the combination of 2 inhibitors of the renin angiotensin-aldosterone system (RAAS), including an ACE-I with an ARB, provides no renal or CV benefits, with an increase in significant adverse events, particularly in patients with DM and/or renal insufficiency. Most notably, patients receiving combination therapy had increased rates of hyperkalemia, hypotension, and renal dysfunction. All agents in the class have safety warnings against combined use *(Fried et al 2013, ONTARGET Investigators 2008, Parving et al 2012, Pfeffer et al 2003a, Sakata et al 2015)*.

Combination Products Containing ARBs

- Clinical trials assessing the combination ARBs in the treatment of HTN have demonstrated that, in general, dual therapy combinations of ARBs plus a diuretic (either HCTZ or chlorthalidone) or amlodipine achieve greater reductions in BP and higher BP control rates compared to monotherapy regimens of ARBs, amlodipine, or diuretics *(Chrysant et al 2004, Chrysant et al 2008, Derosa et al 2014, Destro et al 2008, Flack et al 2009, Littlejohn et al 2009, Neutel et al 2006, Neutel et al 2008, Neutel et al 2012, Philipp et al 2007, Sachse et al 2002, Salerno et al 2004, Sharma et al 2007a, Sharma et al 2012, Waeber et al 2001, Zhu et al 2012)*. A meta-analysis by Conlin et al found that combination therapy

with ARBs and HCTZ resulted in substantially greater reductions in SBP and DBP compared to ARB monotherapy *(Conlin et al 2000)*.

- Trials assessing triple therapy regimens with an ARB, amlodipine, and HCTZ demonstrate significantly greater BP reductions with triple therapy compared to combination and monotherapy *(Calhoun et al 2009a, Calhoun et al 2009b, Destro et al 2010, Ohma et al 2000, Wright et al 2011)*.
- The safety and efficacy of nebivolol/valsartan 5/80 mg was based on a double-blind, placebo-controlled, parallel-group, dose-escalating, Phase 3, randomized controlled trial in 4,159 patients with Stage 1 or 2 HTN. Patients were randomized to 1 of 4 treatment arms (with a total of 7 dose groups plus placebo): (1) nebivolol/valsartan (5/80 mg, 5/160 mg, or 10/160 mg); (2) nebivolol monotherapy (5 mg or 20 mg); (3) valsartan monotherapy (160 mg or 320 mg); or (4) placebo. All treatment was administered in fixed doses once per day for 4 weeks; doses were then doubled for weeks 5 to 8 of treatment. Compared to placebo, nebivolol/valsartan 5/80 mg significantly lowered SBP by 8.3 mmHg and DBP by 7.2 mmHg, monotherapy with nebivolol 5 mg lowered SBP by 4.7 mmHg and DBP by 4.4 mmHg, and monotherapy with valsartan 80 mg lowered SBP by 5.4 mmHg and DBP by 3.9 mmHg after 4 weeks of treatment. Higher doses of the combination did not lead to further clinically meaningful reductions in BP. No adverse events were observed more frequently with nebivolol/valsartan compared to placebo. As anticipated with beta blocker and ARB therapy, serious adverse reactions such as hypotension or hyperkalemia may occur *(Giles et al 2014)*.
- Head-to-head trials have not consistently demonstrated superiority of one ARB combination product over another *(Ambrosioni et al 2010, Bobrie et al 2005, Cushman et al 2012, Derosa et al 2014, Fogari et al 2006, Lacourcière et al 2003, Ohma et al 2000, Sharma et al 2007b, Toh et al 2016, White et al 2008, Wright et al 2011)*.
- The efficacy and safety of sacubitril/valsartan were evaluated in the PARADIGM-HF trial. (*McMurray et al 2014*). A total of 8,442 patients were randomized head-to-head to enalapril 10 mg twice daily or sacubitril/valsartan 97/103 mg twice daily.
- In the PARADIGM-HF trial, the following results were demonstrated after 2.25 years of treatment:
  - CV mortality: The absolute risk was 3.1% less for sacubitril/valsartan-treated patients than those treated with enalapril (risk reduction [RR], 20%; hazard ratio [HR], 0.8; 95% confidence interval [CI], 0.71 to 0.89; P < 0.001; number needed to treat [NNT], 32; 95% CI, 22 to 62).
  - HF hospitalization: The absolute risk was 2.8% less for sacubitril/valsartan-treated patients than those treated with enalapril (RR, 21%; HR, 0.79; 95% CI, 0.71 to 0.89; P < 0.001; NNT, 36; 95% CI, 21 to 77).
  - Combined measure of CV mortality or HF hospitalization (primary endpoint): The absolute risk was 4.7% less for sacubitril/valsartan-treated patients than those treated with enalapril (RR, 20%; HR, 0.8; 95% CI, 0.73 to 0.87; P < 0.001; NNT, 22; 95% CI, 15 to 35).
  - Symptomatic relief: Kansas City Cardiomyopathy Questionnaire (KCCQ) scores were utilized to measure a patient's physical functioning, symptoms, and quality of life (range, 0 to 100 points) with higher scores indicating better health status. At 8 months, scores significantly improved by 1.64 points favoring sacubitril/valsartan over enalapril (P = 0.001). There are different approaches to determining clinical significant KCCQ scores. Based on the varied approaches, clinically significant changes in KCCQ scores have ranged from a difference of 5-point to 10-point declines. In trials, changes of 4 points have been noted in stable HF patients; therefore, the 1.6-point difference in KCCQ for sacubitril/valsartan may not have resulted in an enhanced quality of life when compared to those treated with enalapril regardless of statistical significance (*Green et al 2000, Cardiovascular Outcomes 2008*).
- *Packer et al* published a follow-up analysis of the PARADIGM-HF trial, which outlined the incremental effects of sacubitril/valsartan over enalapril for those with non-fatal progression of HF in surviving patients.
  - Data demonstrated that sacubitril/valsartan-treated patients had slower progression of clinical deterioration compared to enalapril-treated patients in many endpoints that are markers for HF progression (ie, intensified outpatient therapy, emergency department visits, number of hospitalizations, etc.). However, sacubitril/valsartan was not significantly different from enalapril in the number of hospitalized days per admission per patient or in patients requiring cardiac resynchronization therapy, ventricular assist device implants, or a heart transplant (*Packer et al 2015*).
- A separate analysis of the PARADIGM-HF trial reported results for additional composite endpoint rates:
  - CV mortality, HF hospitalization, MI, stroke, and resuscitated sudden death: 24.3% with sacubitril/valsartan vs 28.4% with enalapril (HR, 0.83; 95% CI, 0.76 to 0.90; P < 0.001).
  - CV mortality, non-fatal MI, unstable or other hospitalized angina, or percutaneous or surgical coronary revascularization: 17.1% with sacubitril/valsartan vs 20.3% with enalapril (HR, 0.83; 95% CI, 0.75 to 0.92; P < 0.001) (*Mogensen et al 2017*).

- The 5-year estimated NNT was analyzed for the overall PARADIGM-HF cohort. The 5-year NNT for sacubitril/valsartan compared to enalapril for the primary outcome (CV death or HF hospitalization) and all-cause mortality was 14 and 21, respectively, in the overall cohort (*Srivastava et al 2018*).
- *Lewis et al* published an analysis focused specifically on the health-related quality of life outcomes in PARADIGM-HF. Consistent with the main publication, small but statistically significant improvements in KCCQ scores were reported. At 8 months, the sacubitril/valsartan group noted improvements versus the enalapril group in both KCCQ clinical summary score (CSS) (+0.64 vs -0.29; P = 0.008) and KCCQ overall summary score (OSS) (+1.13 vs -0.14; P < 0.001). Additionally, at 8 months, the proportion of patients with a clinically significant improvement (≥ 5-point increase) in KCCQ score was slightly greater with sacubitril/valsartan vs enalapril (34.5% vs 33.4% for OSS and 32.8% vs 32.6% for CSS) and the proportion with deterioration (≥ 5-point decrease) was less with sacubitril/valsartan versus enalapril (27.2% vs 30.5% for OSS and 27.2% vs 31.2% for CSS). Trends were similar through the 36-month time period but were not statistically significant at some later time points; the ability to draw conclusions is limited by the low completion rate of 29% at 36 months (*Lewis et al 2017*).
- *Chandra et al* examined the effects of sacubitril/valsartan on physical and social activity limitations in patients with HF in a secondary analysis of the PARADIGM-HF trial. Patients receiving this therapy had significantly better adjusted change scores in most physical and social activities at 8 months and during 36 months as compared to patients given enalapril. The largest improvements were in household chores (adjusted change score difference, 2.35; 95% CI: 1.19 to 3.50; P < 0.001) and sexual relationships (adjusted change score difference, 2.71; 95% CI, 0.97 to 4.46; P = 0.002) (*Chandra et al 2018*).
- Based on a cohort analysis of data from the run-in period of PARADIGM-HF, a total of 2,079 patients (19.8%) discontinued treatment with sacubitril/valsartan and were identified as not tolerating treatment. A total of 55% of patients who withdrew from therapy discontinued due to adverse effects (53.7% during phase 1 of the run-in period with enalapril and 56.1% during phase 2 of the run-in period with sacubitril/valsartan).
  - According to the analysis, an increased risk of discontinuation of either drug during run-in was associated with patients with a low estimated glomerular filtration rate (adjusted odds ratio [OR], 1.49; 95% CI, 1.35 to 1.65), HF due to ischemic cause (adjusted OR, 1.25; 95% CI, 1.13 to 1.39), higher N-terminal pro-B-type natriuretic peptide (adjusted OR, 1.2 per log increment; 95% CI, 1.14 to 1.26), and lower systolic BP (adjusted OR, 1.11 per 10 mmHg decrease; 95% CI, 1.07 to 1.14).
  - In patients tolerant to enalapril, an increased risk of sacubitril/valsartan discontinuation was associated with lower DBP (adjusted OR, 1.19 per 10 mm Hg decrease; 95% CI, 1.11 to 1.27).
  - The most common adverse effects for enalapril and sacubitril/valsartan were hypotension (24.7% vs 29.8%, respectively), hyperkalemia (29.4% vs 22.5%, respectively), and worsening renal function (30.6% vs 31.6%, respectively). Of note, angioedema occurred in 0.2% of patients entering the run-in period; however, taking into account the baseline group, this may be lower than observed in a real world setting (*Desai et al 2016*).
- Sacubitril/valsartan was compared to enalapril in patients with HFrEF hospitalized for acute decompensated HF in the multicenter, randomized PIONEER-HF study. Change from baseline to weeks 4 and 8 in the primary endpoint, time-averaged proportional change in N-terminal pro-B-type natriuretic peptide (NT-proBNP), was greater with sacubitril/valsartan compared to enalapril (percent change, -46.7% vs -25.3%; ratio of change with sacubitril/valsartan vs enalapril, 0.71; 95% CI, 0.63 to 0.81). Rates of safety outcomes, including worsening renal function, hyperkalemia, and symptomatic hypotension, were not significantly different between groups. Sacubitril/valsartan also reduced the risk of composite of death, rehospitalization for HF, left ventricular device implantation, and inclusion on heart transplantation list (HR, 0.54; 95% CI, 0.37 to 0.79); however, this was an exploratory endpoint *(Velazquez et al 2018).*
- As part of the post-marketing requirements for sacubitril/valsartan, a clinical trial evaluating cognitive effects was required. This trial is not anticipated to be completed until October 2021 (*FDA approval letter 2015*). However, an analysis of cognitive-related events in HFrEF trials was conducted. Based on a search of adverse event reports, dementia-related adverse effects were similar for enalapril and sacubitril/valsartan for both the narrow (0.36% vs 0.29%, respectively; HR, 0.73; 95% CI, 0.33 to 1.59) and broad search terms (2.3% vs 2.48%, respectively; HR, 1.01; 95% CI, 0.75 to 1.37). PARADIGM-HF patients were followed for a median of 2.25 years (upper range to 4.3 years); however, longer term follow-up may be warranted in order to detect any potential impacts on cognition (*Cannon et al 2016*).

CLINICAL GUIDELINES

- The 2017 ACC/AHA guideline for the prevention, detection, evaluation, and management of high BP in adults *(Whelton et al 2018)* offers updated classifications of HTN and goals of treatment (see Table 4).

Table 4. Classification of BP measurements

BP Category	BP	Treatment or follow-up
Normal	SBP < 120 mm Hg *and* DBP < 80 mm Hg	▪ Evaluate yearly; lifestyle changes are recommended
Elevated	SBP 120 - 129 mm Hg *and* DBP < 80 mm Hg	▪ Evaluate in 3 to 6 months; lifestyle changes are recommended
HTN stage 1	SBP 130 - 139 mm Hg *or* DBP 80 - 89 mm Hg	▪ Assess the 10-year risk for heart disease and stroke using the ASCVD risk calculator. ▪ If ASCVD risk is < 10%, lifestyle changes are recommended. A BP target of < 130/80 mm Hg may be reasonable. ▪ If ASCVD risk is > 10%, or the patient has known CVD, DM, or CKD, lifestyle changes and 1 BP-lowering medication are recommended. A target BP of < 130/80 mm Hg is recommended.
HTN stage 2	SBP ≥ 140 mm Hg *or* DBP ≥ 90 mm Hg	▪ Lifestyle changes and BP-lowering medication from 2 different classes are recommended.

Abbreviations: ASCVD = atherosclerotic cardiovascular disease, BP = blood pressure, CKD = chronic kidney disease, CVD = cardiovascular disease, DBP = diastolic blood pressure, DM = diabetes mellitus, HTN = hypertension, SBP = systolic blood pressure

  - In patients with stage 1 HTN, it is reasonable to initiate therapy with a single antihypertensive agent. In patients with stage 2 HTN and BP more than 20/10 mm Hg higher than their target, 2 first-line agents of different classes should be initiated.
    - First-line antihypertensive agents include thiazide diuretics, CCBs, and ACE-Is or ARBs.
    - Diuretics, ACE-Is, ARBs, CCBs, and beta-blockers have been shown to prevent CVD compared with placebo.
      - ACE-Is were notably less effective in preventing HF and stroke compared with CCBs in black patients. ARBs may be better tolerated than ACE-Is in black patients, with less cough and angioedema, but they offer no proven advantage over ACE-Is in preventing stroke or CVD in this population; thiazide diuretics (especially chlorthalidone) or CCBs are the best initial choice for single-drug therapy in this population.
    - ARBs are reasonable if an ACE-I is not tolerated for treatment of HTN for those with CKD stage 3, or for stage 1 or 2 with albuminuria.
- The 2019 ACC/AHA guideline on the primary prevention of CVD recommends using BP-lowering medications in hypertensive adults: with an estimated 10-year ASCVD risk ≥ 10% and a SBP ≥ 130 mm Hg or DBP ≥ 80 mmHg; with diabetes and a BP > 130/80 mm Hg; or with an estimated 10-year ASCVD risk < 10% and a SBP ≥ 140 mm Hg or DBP ≥ 90 mmHg (*Arnett et al 2019*). A target BP of < 130/80 mmHg is recommended for most patients.
- The American Diabetes Association position statement on DM and HTN *(de Boer et al 2017)* recommends that most patients with DM and HTN be treated to a goal BP of < 140/90 mm Hg. Lower BP targets such as < 130/80 mm Hg may be appropriate for individuals at high risk of CVD.
  - Treatment for HTN should include drug classes demonstrated to reduce CV events in patients with DM: ACE-Is, ARBs, thiazide diuretics, or dihydropyridine CCBs.
  - Patients with BP ≥ 160/100 mm Hg should have prompt initiation of 2 drugs or a single-pill combination of drugs demonstrated to reduce CV events in patients with DM.
  - An ACE-I or ARB, at the maximum tolerated dose indicated for BP treatment, is the recommended first-line treatment for HTN in patients with DM and urine albumin-to-creatinine ratio ≥ 30 mg/g creatinine.

- The American Academy of Pediatrics clinical practice guideline for high BP in children and adolescents *(Flynn et al 2017)* recommends that the treatment goal with nonpharmacologic and pharmacologic therapy should be a reduction in SBP and DBP to < 90th percentile and < 130/80 mm Hg in adolescents ≥ 13 years old.
  - In hypertensive children and adolescents who have failed lifestyle modifications, clinicians should initiate pharmacologic treatment with an ACE-I, ARB, long-acting CCB, or thiazide diuretic.
  - Children and adolescents with CKD, HTN, and proteinuria should be treated with an ACE-I or ARB.
- Various other guidelines and position statements place ARBs as first-line therapy in patients with DM and microalbuminuria; with stable CAD and HTN; and after an MI. ARBs have demonstrated clinical benefit and reductions in morbidity and mortality in these populations *(Amsterdam et al 2014, Go et al 2014, Rosendorff et al 2015, Weber et al 2014).*
  - Due to differences in the activity of the RAAS, ARBs are often less effective as HTN monotherapy in black patients (African or Caribbean descent). Alternative first-line options for these patients include CCBs and thiazide diuretics *(Weber et al 2014).*
- HF guidelines recommend evidence-based maximally tolerated doses of ACE-Is or ARBs, and beta blockers and/or diuretics, as needed, for first-line treatment in patients with HFrEF (NYHA Class I to IV; Stage C) (*Yancy et al 2013, Yancy et al 2016, Yancy et al 2017).*
- Key recommendations from the 2016 and 2017 Focused Update of the ACC/AHA/HFSA HF guidelines related to ACE-Is, ARBs, and ARNI in Stage C HFrEF include the following (*Yancy et al 2016, Yancy et al 2017):*
  - The clinical strategy of inhibition of the RAAS with ACE-Is or ARBs or ARNI in conjunction with evidence-based beta blockers, and aldosterone antagonists in selected patients, is recommended for patients with chronic HFrEF to reduce morbidity and mortality. (Sacubitril/valsartan is recommended with a lower level of evidence than ACE-Is and ARBs.)
  - The use of ACE-Is is beneficial for patients with prior or current symptoms of HFrEF to reduce morbidity and mortality.
  - The use of ARBs to reduce morbidity and mortality is recommended in patients with prior or current symptoms of chronic HFrEF who are intolerant to ACE-Is because of cough or angioedema.
  - In patients with chronic symptomatic HFrEF NYHA Class II or III who tolerate an ACE-I or ARB, replacement by an ARNI is recommended to further reduce morbidity and mortality.
  - ARNI therapy should not be administered concomitantly with ACE-Is or within 36 hours of the last dose of an ACE-I.
  - ARNI therapy should not be administered to patients with a history of angioedema.

SAFETY SUMMARY

- In July 2018, the FDA first issued a recall of several valsartan products that exceeded acceptable levels of a probable carcinogen, N-nitrosodimethylamine (NDMA). In October 2018, the presence of another impurity, N-nitrosodiethylamine (NDEA), was also discovered in certain valsartan products. Since then, voluntary recalls of other valsartan-, losartan-, and irbesartan-containing products have been announced due to nitrosamine impurities. NDMA is also found in water and certain foods, and has been shown to increase risk of cancer in animal studies. To provide context on the risk, the FDA has stated that if 8,000 people took 320 mg daily of the recalled valsartan for 4 years, one additional cancer case may occur over the course of the 8,000 people's lifetimes. To mitigate potential drug shortages, the FDA has announced interim limits for the nitrosamine impurities in ARBs, temporarily allowing distribution of medications that have between 0.96 and 9.82 parts per million of NDMA, to help ensure that an adequate supply is available on the market. In March 2019, the FDA announced that it expects that adequate supplies of losartan without nitrosamine impurities will be available in approximately 6 months. The FDA website is maintaining an updated list of recalled products and should be consulted to determine if a specific manufacturer and lot is recalled. *(FDA drug safety alert 2019)*.

Boxed Warnings

- Use during pregnancy should be avoided. When pregnancy is detected, ARBs should be discontinued as soon as possible. Drugs that act directly on the RAAS can cause injury and death to the developing fetus.

Contraindications

- ARBs are contraindicated in patients with DM who are also receiving Tekturna (aliskiren) therapy.
- ARB combinations containing diuretics (ie, HCTZ, chlorthalidone) are contraindicated in patients with anuria.
- Nebivolol/valsartan is additionally contraindicated in patients with severe bradycardia, heart block greater than first degree, cardiogenic shock, decompensated cardiac failure, sick sinus syndrome (unless a permanent pacemaker is in place), and severe hepatic impairment.

- Sacubitril/valsartan is contraindicated in patients with a history of angioedema related to previous ACE-I or ARB therapy, concomitant use with aliskiren in patients with diabetes, or ACE-Is in all patients. Sacubitril/valsartan should not be administered within 36 hours of switching from or to an ACE-I.

Warnings and Precautions

- In general, ARBs have warnings for fetal toxicity, hypotension (especially in volume- or salt-depleted patients), impaired renal function, and hyperkalemia/electrolyte imbalances. Treatment should be discontinued when pregnancy is detected.
  - Candesartan and olmesartan have warnings for morbidity in infants < 1 year of age.
  - Olmesartan has a unique warning for sprue-like enteropathy, which is manifested by severe, chronic diarrhea with substantial weight loss.
  - Telmisartan has a unique warning for use in patients with impaired hepatic function, as it is eliminated mostly by biliary excretion.
- Diuretics (ie, HCTZ, chlorthalidone) may alter glucose tolerance and raise levels of cholesterol, triglycerides, and serum uric acid levels (which may precipitate gout). Diuretics may cause elevations of serum calcium and monitoring is recommended in patients with hypercalcemia.
  - HCTZ may also cause an idiosyncratic reaction resulting in acute transient myopia and acute angle-closure glaucoma.
  - Thiazide diuretics have been reported to cause exacerbation or activation of systemic lupus erythematosus.
- Nebivolol has warnings for abrupt cessation of therapy, cardiac failure, bronchospastic diseases, thyrotoxicosis, and peripheral vascular disease.
- Amlodipine has warnings for increased angina and acute myocardial infarction, and hepatic impairment.
- Sacubitril/valsartan has additional warnings for angioedema, hypotension, a risk of decreased or impaired renal function in susceptible patients, and hyperkalemia.

Adverse Effects

- Common adverse effects with ARBs include hypotension, dizziness, back pain, and headache.
  - The most common adverse reaction with azilsartan is diarrhea.
- The CCB amlodipine may cause peripheral edema.
- The most common adverse effects reported (incidence ≥ 5%) with sacubitril/valsartan include hypotension, hyperkalemia, cough, dizziness, and renal failure. With regard to hypotension, a recent Institute for Safe Medication Practices (ISMP) Quarter Watch reported that many patients initiating therapy on sacubitril/valsartan experienced significant complications ranging from dizziness to blackouts and other consequences serious enough to require hospitalization (*ISMP Quarter Watch 2017*).
- The FDA has required post-marketing studies for sacubitril/valsartan in order to assess the incidence of angioedema in patients of African or Caribbean descent (Black patients) and the risk of cognitive dysfunction in HF patients with HFpEF (*FDA approval letter 2015*). Postmarketing reports include hypersensitivity, including rash, pruritus, and anaphylactic reactions.
- Experts have raised questions regarding the potential for impact on cognitive dysfunction due to the mechanism of action of sacubitril/valsartan, particularly in patients with Alzheimer's disease. The concern is specifically around the sacubitril component and issues with neprilysin inhibition in the brain. Theoretically, neprilysin inhibition could lead to amyloid deposits, which has been linked to dementia.
- According to pharmacodynamic studies, sacubitril/valsartan 400 mg (2 x 97/103 mg tablets) once daily increased cerebrospinal fluid amyloid-β ($A\beta_{1-38}$) concentrations after 2 weeks in healthy patients. Also, the active metabolite (LBQ657) does minimally cross the blood brain barrier. The clinical relevance of increased concentrations is unknown (*Vodovar et al 2015*).

Important Drug Interactions

- Dual blockade of the RAAS with ACE-Is, ARBs, or aliskiren is associated with increased risks of hypotension, hyperkalemia, and changes in renal function (including acute renal failure).
  - Most patients receiving the combination of 2 RAAS inhibitors do not obtain any additional benefit compared to monotherapy.
  - Avoid use of aliskiren with ARBs in patients with renal impairment (glomerular filtration rate < 60 mL/min).

- In patients who are elderly, volume-depleted (including those on diuretic therapy), or with compromised renal function, concomitant use of non-steroidal anti-inflammatory agents (NSAIDs) with ARBs may result in deterioration of renal function, including acute renal failure. The antihypertensive effect of ARBs may be attenuated by NSAIDs.
- Concomitant use of ARBs and potassium-sparing diuretics (eg, spironolactone, amiloride, triamterene) can increase the risk of hyperkalemia.
- ARBs may increase serum lithium concentration; lithium levels should be monitored.
- Concurrent administration of the bile acid sequestering agent, colesevelam hydrochloride, reduces the systemic exposure and peak plasma concentration of olmesartan.
- Concomitant use of telmisartan and ramipril is not recommended due to increased exposure to ramipril and ramiprilat.
- HCTZ absorption is impaired in the presence of anionic exchange resins (ie, cholestyramine and colestipol resins).
- Concomitant use of HCTZ with carbamazepine has been associated with an increased risk for symptomatic hyponatremia.
- Nebivolol should not be used with cytochrome P450 (CYP) 2D6 inhibitors.
- Amlodipine should not be coadministered with doses higher than 20 mg of simvastatin per day.
- Exposure to amlodipine is increased with CYP3A4 inhibitors.

DOSING AND ADMINISTRATION

- In general, the safety and efficacy of ARBs have not been established in severe hepatic impairment.
- ARB combination products containing diuretics are not recommended in patients with severe renal impairment.
- Some ARB combination products are not recommended as initial therapy in patients with hepatic impairment because the recommended ARB starting dose is not available in the fixed-dose combination product.
- ARB combination products containing amlodipine are not recommended as initial therapy in elderly patients or patients with severe hepatic impairment because the recommended amlodipine starting dose of 2.5 mg is not available in the fixed-dose combination product.

Table 5. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Single-Entity ARBs				
Atacand (candesartan)	Tablets	Oral	HTN: Once or twice daily HF: Once daily	Initiate with 8 mg once daily in moderate hepatic impairment.
Avapro (irbesartan)	Tablets	Oral	Once daily	
Benicar (olmesartan)	Tablets	Oral	Once daily	
Cozaar (losartan)	Tablets	Oral	Once daily	Initiate with 25 mg once daily in mild to moderate hepatic impairment.
Diovan (valsartan)	Tablets	Oral	HTN: Once daily HF/post-MI: Twice daily	Safety and efficacy not established in severe renal impairment
Edarbi (azilsartan)	Tablets	Oral	Once daily	
eprosartan	Tablets	Oral	Once or twice daily	Max 600 mg per day in moderate or severe renal impairment
Micardis (telmisartan)	Tablets	Oral	Once daily	
ARB/Diuretic Combinations				
Atacand HCT (candesartan/hydrochlorothiazide)	Tablets	Oral	Once daily	
Avalide (irbesartan/hydrochlorothiazide)	Tablets	Oral	Once daily	

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Benicar HCT (olmesartan/hydrochlorothiazide)	Tablets	Oral	Once daily	
Diovan HCT (valsartan/hydrochlorothiazide)	Tablets	Oral	Once daily	
Edarbyclor (azilsartan/chlorthalidone)	Tablets	Oral	Once daily	
Hyzaar (losartan/hydrochlorothiazide)	Tablets	Oral	Once daily	
Micardis HCT (telmisartan/hydrochlorothiazide)	Tablets	Oral	Once daily	
ARB/Beta Blocker Combinations				
Byvalson (valsartan/nebivolol)	Tablets	Oral	Once daily	Not recommended in moderate to severe hepatic impairment or severe renal impairment.
ARB/CCB Combinations				
Azor (olmesartan/amlodipine)	Tablets	Oral	Once daily	
Exforge (valsartan/amlodipine)	Tablets	Oral	Once daily	
Twynsta (telmisartan/amlodipine)	Tablets	Oral	Once daily	
ARB/CCB/Diuretic Combinations				
Exforge HCT (valsartan/ amlodipine/hydrochlorothiazide)	Tablets	Oral	Once daily	
Tribenzor (olmesartan/ amlodipine/hydrochlorothiazide)	Tablets	Oral	Once daily	
ARB/Neprilysin inhibitor Combination				
Entresto (sacubitril/valsartan)	Tablets	Oral	Twice daily	Reduce initial dose for: • ACE-I/ARB naïve • Prior low dose of ACE-I/ ARB before initiating sacubitril/valsartan • Severe renal or moderate hepatic impairment

Abbreviations: ACE-I = angiotensin converting enzyme-inhibitor; ARB = angiotensin II receptor blocker; CCB = calcium channel blocker; HF = heart failure; HTN = hypertension; MI = myocardial infarction
See the current prescribing information for full details

CONCLUSION

- The single-entity and combination ARB products are FDA-approved for the treatment of HTN, and most are generically available. Some ARBs have additional indications for HF, diabetic nephropathy, or CV risk reduction in certain high-risk populations.
- Evidence-based guidelines recognize the important role ARBs play in the treatment of HTN and other CV and renal diseases. The current ACC/AHA guidelines recommend a BP goal of < 130/80 mm Hg for most patients *(Arnett et al 2019, Whelton et al 2018)*.
- ARBs have demonstrated efficacy in lowering SBP and DBP in patients with HTN.
  - Head-to-head trials have not consistently demonstrated superiority of one ARB compared to another.
  - Clinical trials assessing the ARB combination products in the treatment of HTN have demonstrated that, in general, dual therapy combinations of ARBs plus either HCTZ, nebivolol, or amlodipine achieve greater reductions in BP and higher BP control rates compared to monotherapy regimens. Head-to-head trials have not consistently demonstrated superiority of one combination product over another.
  - ARBs have generally demonstrated comparable efficacy to ACE-Is across indications.

- Studies have demonstrated that the combination of 2 inhibitors of the RAAS, including an ACE-I with an ARB, provides no renal or CV benefits and increased risk of adverse events, including hyperkalemia, hypotension, and renal dysfunction. All agents in this class have safety warnings against combined use.
- All ARBs have a boxed warning for use in pregnancy and are contraindicated in patients with DM who are also receiving aliskiren therapy. Other warnings include hypotension, renal failure, and hyperkalemia.
- Common adverse effects of ARBs include hypotension, dizziness, back pain, and headache.
- Current guidelines recommend ARBs as a first-line therapy for patients with HTN, DM with microalbuminuria, stable CAD with HTN, and post-MI *(Amsterdam et al 2014, de Boer et al 2017, Go et al 2014, Rosendorff et al 2015, Weber et al 2014, Whelton et al 2018).*
  - Due to differences in the activity of the RAAS, ARBs are often less effective as HTN monotherapy in black patients; CCBs and thiazide diuretics should be used as first-line options in these patients.
- Recent guideline updates from the ACC/AHA/HFSA state that in patients with chronic symptomatic HFrEF NYHA Class II or III who tolerate an ACE-I or ARB, replacement by an ARNI is recommended to further reduce morbidity and mortality (*Yancy et al 2016, Yancy et al 2017*).

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