

Therapeutic Class Overview

Angiotensin II Receptor Blockers (ARBs)

INTRODUCTION

- Approximately 126.9 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 2021 update (Virani et al 2021). Cardiovascular disease accounts for an estimated 868,662 deaths in the US annually and is the leading cause of death globally.
- The estimated prevalence of heart failure (HF) is 6 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 (Virani et al 2021).
- Hypertension (HTN) is an independent risk factor for CV disease and increases the mortality risks of CV disease and other diseases (Virani et al 2021). The 2017 American College of Cardiology (ACC)/AHA clinical practice guideline defines HTN as a blood pressure (BP) $\geq 130/80$ 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 (Virani et al 2021).
- 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, Unger et al 2020, 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 HTN 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 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) $\leq 40\%$
 - Heart failure with preserved ejection fraction (HFpEF) or diastolic HF: EF $\geq 50\%$
- HF guidelines recommend evidence-based maximally tolerated doses of ACE-Is/ARBs/ARNIs, and/or beta-blockers with 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; Maddux et al 2021).
- Sacubitril/valsartan is administered in place of an ACE-I or other ARB; although, its 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]) 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 adults with chronic HF and for the treatment of symptomatic HF with systemic left ventricular systolic dysfunction in pediatric patients 1 year of age and older.
- Medispan classes: Angiotensin II Receptor Antagonists; Antihypertensive Combinations - ARB/CCB combinations, 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)	-
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/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

([Drugs@FDA 2021](#), [Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2021](#))

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

Indication	Atacand (candesartan)	Avapro (irbesartan)	Benicar (olmesartan)	Cozaar (losartan)	Diovan (valsartan)	Edarbi (azilsartan)	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 2020, Avapro 2020, Benicar 2019, Cozaar 2020, Diovan 2021, Edarbi 2020, Micardis 2020)

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

Drug	Hypertension	Reduction in the Risk of CV Death and HF Hospitalization in Adults with Chronic HF	Reduction in the Risk of Stroke in Patients with Hypertension and Left Ventricular Hypertrophy	Symptomatic HF in pediatric patients ≥ 1 year
ARB/Diuretic Combinations				
Atacand HCT (candesartan/hydrochlorothiazide)	✓ *	-	-	-
Avalide (irbesartan/hydrochlorothiazide)	✓ †	-	-	-
Benicar HCT (olmesartan/hydrochlorothiazide)	✓ *	-	-	-
Diovan HCT (valsartan/hydrochlorothiazide)	✓ †	-	-	-
Edarbyclor (azilsartan/chlorthalidone)	✓ †	-	-	-

Drug	Hypertension	Reduction in the Risk of CV Death and HF Hospitalization in Adults with Chronic HF	Reduction in the Risk of Stroke in Patients with Hypertension and Left Ventricular Hypertrophy	Symptomatic HF in pediatric patients ≥ 1 year
Hyzaar (losartan/hydrochlorothiazide)	✓ †	-	✓ §	-
Micardis HCT (telmisartan/hydrochlorothiazide)	✓ *	-	-	-
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/Nepriylsin 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.

|| Benefits are most clearly evident in patients with LVEF below normal. LVEF is a variable measure, so use clinical judgment in deciding whom to treat.

(Prescribing information: Atacand HCT 2020, Avalide 2020, Azor 2020, Benicar HCT 2020, Diovan HCT 2020, Edarbyclor 2020, Entresto 2021, Exforge 2021, Exforge HCT 2021, Hyzaar 2020, Micardis HCT 2020, Tribenzor 2020, 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 (vs 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

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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, Salerno et al 2004, Sharma et al 2007a, Sharma et al 2012, 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).
- Head-to-head trials have not consistently demonstrated superiority of one ARB combination product over another (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 clinically 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 HF with reduced ejection fraction (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 2019*).
- Sacubitril/valsartan was FDA-approved in October 2019 for pediatric patients at least 1 year of age with HF due to systemic left ventricular systolic dysfunction based on 12-week data from the PANORAMA-HF trial. PANORAMA-HF is a randomized, double-blind trial comparing sacubitril/valsartan to enalapril in pediatric patients with NYHA Class II to IV HF. In an interim analysis, plasma NT-proBNP level change from baseline to 12 weeks was assessed in 110 patients, and there was no significant difference between groups (44% reduction with sacubitril/valsartan and 33% with enalapril). However, because these reductions in NT-proBNP were similar or larger than what was seen with adult patients in PARADIGM-HF and those patients had improved outcomes, it was considered reasonable to infer improved cardiovascular outcomes in pediatric patients (*Entresto prescribing information 2021, Shaddy et al 2017*).
- The PARAGON-HF trial evaluated sacubitril-valsartan efficacy in 4,822 patients with HF with preserved ejection fraction (HFpEF) ($\geq 45\%$), NYHA class II to IV HF, elevated levels of natriuretic peptides, and structural heart disease. This double-blind trial randomly assigned patients to sacubitril-valsartan (target dose, 97 mg sacubitril and 103 mg of valsartan twice daily) or valsartan (target dose, 160 mg twice daily). The primary outcome was a composite of total hospitalization for HF and death from CV causes. Results did not find a significantly lower rate of the composite primary endpoint with sacubitril-valsartan compared with valsartan alone (rate ratio, 0.87; 95% CI, 0.75 to 1.01; $p = 0.06$) (*Solomon et al 2019*). Additionally, the incidence of death from CV causes (8.5% sacubitril-valsartan vs 8.9% valsartan; HR 0.95; 95% CI, 0.79 to 1.16) and total hospitalizations for HF (690 vs 797; rate ratio, 0.85; 95% CI, 0.72 to 1.00) were not significantly different between the groups.
- 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 (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	<ul style="list-style-type: none"> Evaluate yearly; lifestyle changes are recommended
Elevated	SBP 120 - 129 mm Hg and DBP < 80 mm Hg	<ul style="list-style-type: none"> Evaluate in 3 to 6 months; lifestyle changes are recommended
HTN stage 1	SBP 130 - 139 mm Hg or DBP 80 - 89 mm Hg	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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 (*American Diabetes Association 2021, de Boer et al 2017*) recommends that patients with DM and HTN be treated to a goal BP of at least < 140/90 mm Hg. Target BPs should be individualized, and 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 \geq 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 \geq 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 \geq 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, Unger et al 2020*).
 - 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 combination therapy with a CCB plus thiazide diuretic or CCB plus ARB (*Unger et al 2020*).
- HF guidelines recommend evidence-based maximally tolerated doses of ACE-Is/ARBs/ARNIs, and/or beta-blockers with 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, Maddux et al 2021*).
- Key recommendations from the 2021 update to the 2017 ACC expert consensus decision pathway for optimization of HF treatment include (*Maddux et al 2021*):
 - In a patient with new-onset Stage C HFREF, an ACE-I/ARB/ARNI or beta-blocker should be started. In some cases, an ACE-I/ARB/ARNI and a beta-blocker can be started at the same time. Regardless, both classes of agents should be up-titrated to the maximum tolerated or target doses in a timely fashion.
 - In patients without prior exposure to an ACE-I or ARB, recent data, along with aggregate clinical experience, suggest that directly initiating ARNI therapy, rather than a pretreatment period ACE-I or ARB, is a safe and effective strategy.
 - ARNI therapy should not be administered concomitantly with ACE-Is or within 36 hours of the last dose of an ACE-I. This delay is not required when switching from an ARB to ARNI therapy.
 - ARNI therapy should not be administered to patients with a history of angioedema.
 - ARNI therapy may exert a more noteworthy effect on BP when compared with ACE-Is/ARBs; therefore, in patients with borderline BP, careful administration and follow-up are advised.

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, FDA drug shortages 2021*).

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

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- 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.
- 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.
 - **HCTZ is associated with an increased risk of non-melanoma skin cancer.**
- 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.
- 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, colestevam 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.
- 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	
Micardis (telmisartan)	Tablets	Oral	Once daily	
ARB/Diuretic Combinations				
Atacand HCT (candesartan/hydrochlorothiazide)	Tablets	Oral	Once daily	
Avalide (irbesartan/hydrochlorothiazide)	Tablets	Oral	Once daily	
Benicar HCT (olmesartan/hydrochlorothiazide)	Tablets	Oral	Once daily	
Diovan HCT (valsartan/hydrochlorothiazide)	Tablets	Oral	Once daily	
Edarbyclor (azilsartan/chlorthalidone)	Tablets	Oral	Once daily	

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Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Hyzaar (losartan/hydrochlorothiazide)	Tablets	Oral	Once daily	
Micardis HCT (telmisartan/hydrochlorothiazide)	Tablets	Oral	Once daily	
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: <ul style="list-style-type: none"> • 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.
- Sacubitril/valsartan is FDA-approved for HF and is the sole agent in this class approved for HF in pediatric patients.
- 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 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 increases the 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, Unger et al 2020, Whelton et al 2018*).

- Due to differences in the activity of the RAAS, ARBs are often less effective as HTN monotherapy in black patients; alternative first-line options for these patients include combination therapy with a CCB plus thiazide diuretic or CCB plus ARB.
- HF guidelines recommend evidence-based maximally tolerated doses of ACE-Is/ARBs/ARNIs, and/or beta-blockers with diuretics, as needed, for first-line treatment in patients with HF_{rEF} (NYHA Class I to IV; Stage C) (Yancy *et al* 2013, Yancy *et al* 2016, Yancy *et al* 2017; Maddux *et al* 2021).
- Key recommendations from the 2021 update to the 2017 ACC expert consensus decision pathway for optimization of HF treatment include (Maddux *et al* 2021):
 - In a patient with new-onset Stage C HF_{rEF}, an ACE-I/ARB/ARNI or beta-blocker should be started. In some cases, an ACE-I/ARB/ARNI and a beta-blocker can be started at the same time. Regardless, both classes of agents should be up-titrated to the maximum tolerated or target doses in a timely fashion.
 - In patients without prior exposure to an ACE-I or ARB, recent data, along with aggregate clinical experience, suggest that directly initiating ARNI therapy, rather than a pretreatment period ACE-I or ARB, is a safe and effective strategy.

REFERENCES

- American Diabetes Association. Cardiovascular disease and risk management: standards of medical care in diabetes: 2021. *Diabetes Care*. 2021;44(Suppl 1):S125-S150.
- Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;130:e344-426.
- Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2019;74(10):e177-232.
- Atacand HCT [package insert], Baudette, MN: ANI Pharmaceuticals; Inc.; May 2020.
- Atacand [package insert], Baudette, MN: ANI Pharmaceuticals, Inc.; June 2020.
- Avalide [package insert], Bridgewater, NJ: Sanofi-Aventis U.S. LLC; December 2020.
- Avapro [package insert], Bridgewater, NJ: Sanofi-Aventis U.S. LLC; December 2020.
- Azor [package insert], Basking Ridge, NJ: Daiichi Sankyo Inc.; October 2020.
- Barnett AH, Bain SC, Bouter P, et al; Diabetics Exposed to Telmisartan and Enalapril Study Group. Angiotensin-receptor blockade versus converting-enzyme inhibition in type 2 diabetes and nephropathy. *N Engl J Med*. 2004 Nov 4;351(19):1952-1961.
- Benicar HCT [package insert], Basking Ridge, NJ: Daiichi Sankyo Inc.; May 2020.
- Benicar [package insert], Basking Ridge, NJ: Daiichi Sankyo; October 2019.
- Bobrie G, Delonca J, Moulin C, et al. A home blood pressure monitoring study comparing the antihypertensive efficacy of two angiotensin II receptor antagonist fixed combinations. *Am J Hypertens*. 2005;18:1482-1488.
- Calhoun D, Crikelair N, Yen J, et al. Amlodipine/valsartan/hydrochlorothiazide triple combination therapy in moderate/severe hypertension: secondary analyses evaluating efficacy and safety. *Adv Ther*. 2009a;26(11):1012-1023.
- Calhoun D, Lacourcière Y, Chiang Y, et al. Triple antihypertensive therapy with amlodipine, valsartan, and hydrochlorothiazide - a randomized clinical trial. *Hypertension*. 2009b;54:32-39.
- Cannon JA, Shen L, Jhund PS, et al; for the PARADIGM-HF investigators. Dementia-related adverse events in PARADIGM-HF and other trials in heart failure with reduced ejection fraction. *Eur J Heart Fail*. 2017;19(1):129-137.
- Cardiovascular Outcomes, Inc. Kansas City Cardiomyopathy Questionnaire. <http://cvoutcomes.org/topics/3038>. Accessed May 12, 2021.
- Chandra A, Lewis EF, Claggett BL, et al. Effects of sacubitril/valsartan on physical and social activity limitations in patients with heart failure: a secondary analysis of the PARADIGM-HF trial. *JAMA Cardiol*. 2018;3(6):498-505.
- Chrysant SG, Melino M, Karki S, et al. The combination of olmesartan medoxomil and amlodipine besylate in controlling high blood pressure: COACH, a randomized, double-blind, placebo-controlled, 8-week factorial efficacy and safety study. *Clin Ther*. 2008;30(4):587-604.
- Chrysant SG, Weber MA, Wang AC, et al. Evaluation of antihypertensive therapy with the combination of olmesartan medoxomil and hydrochlorothiazide. *Am J Hypertens*. 2004;17(3):252-259.
- Cohn JN, Tognoni G; Valsartan Heart Failure Trial Investigators. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. *N Engl J Med*. 2001;345(23):1667-1675.
- Conlin PR, Spence JD, Williams B, et al. Angiotensin II antagonists for hypertension: are there differences in efficacy? *Am J Hypertens*. 2000;13(4 Pt 1):418-426.
- Cozaar [package insert], Whitehouse Station, NJ: Merck & Co. Inc.; June 2020.
- Cushman WC, Bakris GL, White WB, et al. Azilsartan medoxomil plus chlorthalidone reduces blood pressure more effectively than olmesartan plus hydrochlorothiazide in stage 2 systolic hypertension. *Hypertension*. 2012;60(2):310-318.
- Dahlöf B, Devereux RB, Kjeldsen SE, et al; LIFE Study Group. Cardiovascular morbidity and mortality in the Losartan Intervention For End point reduction in hypertension study (LIFE): a randomized trial against atenolol. *Lancet*. 2002;359(9311):995-1003.
- de Boer IH, Bangalore S, Benetos A, et al. Diabetes and hypertension: a position statement by the American Diabetes Association. *Diabetes Care*. 2017;40:1273-1284.
- Derosa G, Cicero AF, Carbone A, et al. Results from a 12 months, randomized, clinical trial comparing an olmesartan/amlodipine single pill combination to olmesartan and amlodipine monotherapies on blood pressure and inflammation. *Eur J Pharm Sci*. 2014;51:26-33.
- Desai AS, Solomon S, Claggett B, et al. Factors associated with noncompletion during the run-in period before randomization and influence on the estimated benefit of LCZ696 in the PARADIGM-HF trial. *Circ Heart Fail*. 2016;9(6):e002735.

- Destro M, Crikelair N, Yen J, et al. Triple combination therapy with amlodipine, valsartan and hydrochlorothiazide vs dual combination therapy with amlodipine and hydrochlorothiazide for stage 2 hypertensive patients. *Vasc Health Risk Manag.* 2010;6:821-827.
- Destro M, Luckow A, Samson M, et al. Efficacy and safety of amlodipine/valsartan compared to amlodipine monotherapy in patients with stage 2 hypertension: a randomized, double-blind, multicenter study: the EX-EFFeCTS study (abstract). *J Am Soc Hypertens.* 2008;2(3):294-302.
- Dickstein K, Kjekshus J; OPTIMAAL Steering Committee of the OPTIMAAL Study Group. Effects of losartan and captopril on mortality and morbidity in high-risk patients after acute myocardial infarction: the OPTIMAAL randomised trial. Optimal Trial in Myocardial Infarction with Angiotensin II Antagonist Losartan. *Lancet.* 2002;360(9335):752-760.
- Diovan HCT [package insert], East Hanover, NJ: Novartis; August 2020.
- Diovan [package insert], East Hanover, NJ: Novartis; April 2021.
- Drugs@FDA: FDA approved drug products. Food and Drug Administration website. <https://www.accessdata.fda.gov/scripts/cder/daf/>. Accessed May 12, 2021.
- Edarbi [package insert], Atlanta, GA: Arbor Pharmaceuticals, Inc.; March 2020.
- Edarbyclor [package insert], Atlanta, GA: Arbor Pharmaceuticals, Inc.; March 2020.
- Entresto [package insert], East Hanover, NJ: Novartis AG; February 2021.
- Exforge HCT [package insert], East Hanover, NJ: Novartis Pharmaceuticals Corporation; February 2021.
- Exforge [package insert], East Hanover, NJ: Novartis Pharmaceuticals Corporation; April 2021.
- Flack JM, Calhoun DA, Satlin L, et al. Efficacy and safety of initial combination therapy with amlodipine/valsartan compared to amlodipine monotherapy in black patients with stage 2 hypertension: the EX-STAND study. *J Hum Hypertens.* 2009;23(7):479-489.
- Flynn JT, Kaelber DB, Baker-Smith CM, et al. Clinical practice guideline for screening and management of high blood pressure in children and adolescents. *Pediatrics.* 2017;140(3):e20171904.
- Fogari R, Zoppi A, Mugellini A, et al. Hydrochlorothiazide added to valsartan is more effective than when added to olmesartan in reducing blood pressure in moderately hypertensive patients inadequately controlled by monotherapy. *Adv Ther.* 2006;23(5):680-695.
- Food and Drug Administration (FDA) Drug Shortages. Current and Resolved Drug Shortages and Discontinuations Reported to FDA. https://www.accessdata.fda.gov/scripts/drugshortages/dsp_ActiveIngredientDetails.cfm?Al=Nebivolol+Hydrochloride+and+Valsartan+%28BYVALSAN%29+Tablets&st=d&tab=tabs-2. Accessed May 12, 2021.
- Food and Drug Administration approval letter. Novartis Pharmaceuticals Corp: NDA 207 620. July 7, 2015. http://www.accessdata.fda.gov/drugsatfda_docs/applletter/2015/207620Orig1s000ltr.pdf. Accessed May 12, 2021.
- Food and Drug Administration. FDA updates and press announcements on angiotensin II receptor blocker (ARB) recalls (valsartan, losartan and irbesartan). November 13, 2019. Food and Drug Administration website. <https://www.fda.gov/Drugs/DrugSafety/ucm613916.htm>. Accessed May 12, 2021.
- Foulquier S, Böhm M, Schmieder R, et al. Impact of telmisartan on cardiovascular outcome in hypertensive patients at high risk: a telmisartan randomized assessment study in ACE intolerant subjects with cardiovascular disease subanalysis (TRANSCEND). *J Hypertens.* 2014;32(6):1334-1341.
- Fried LF, Emanuele N, Zhang JH, et al. Combined angiotensin inhibition for the treatment of diabetic nephropathy (VA NEPHRON-D). *N Engl J Med.* 2013;369(20):1892-1903.
- Galle J, Schwedhelm E, Pinnetti S, et al for the VIVALDI Investigators. Antiproteinuric effects of angiotensin receptor blockers: telmisartan versus valsartan in hypertensive patients with type 2 diabetes mellitus and overt nephropathy. *Nephrol Dial Transplant.* 2008;23(10):3174-3183.
- Go AS, Bauman M, King SM, et al. An effective approach to high blood pressure control: A Science Advisory from the American Heart Association, the American College of Cardiology, and the Centers for Disease Control and Prevention (AHA/ACC/CDC). *Hypertension.* 2014;63(4):878-885.
- Green C, Porter C, Bresnahan D, et al. Development and evaluation of the Kansas City Cardiomyopathy Questionnaire: a new health status measure for heart failure. *J Am Coll Cardiol.* 2000;35:1245-1255.
- Haller H, Ito S, Izzo JL, et al. Olmesartan for the delay or prevention of microalbuminuria in Type 2 Diabetes. *N Engl J Med.* 2011;364(10):907-917.
- Heran BS, Wong MMY, Heran IK, Wright JM. Blood pressure lowering efficacy of angiotensin receptor blockers for primary hypertension. *Cochrane Database of Systematic Reviews.* 2008;4:CD003822. doi: 10.1002/14651858.CD003822.pub2.
- Hou FF, Xie D, Zhang X, et al. Renoprotection of optimal antiproteinuric doses (ROAD) study: a randomized controlled study of benazepril and losartan in chronic renal insufficiency. *J Am Soc Nephrol.* 2007;18(6):1889-1898.
- Hyzaar [package insert], Whitehouse Station, NJ: Merck & Co. Inc.; August 2020.
- Imai E, Chan JC, Ito S, et al. Effects of olmesartan on renal and cardiovascular outcomes in type 2 diabetes with overt nephropathy: a multicenter, randomized, placebo-controlled study. *Diabetologia.* 2011;54(12):2978-2986.
- Julius S, Alderman MH, Beevers G, et al. Cardiovascular risk reduction in hypertensive black patients with left ventricular hypertrophy: the LIFE study. *J Am Coll Cardiol.* 2004;43(6):1047-1055.
- Lacourcière Y, Gil-Extremera B, Mueller O, et al. Efficacy and tolerability of fixed-dose combinations of telmisartan plus HCTZ compared to losartan plus HCTZ in patients with essential hypertension. *Int J Clin Pract.* 2003;57(4):273-279.
- Lewis EF, Claggett BL, McMurray JJ, et al. Health-related quality of life outcomes in PARADIGM-HF. *Circ Heart Fail.* 2017;10(8). pii: e003430.
- Li EC, Heran BS, Wright JM. Angiotensin converting enzyme (ACE) inhibitors versus angiotensin receptor blockers for primary hypertension. *Cochrane Database Syst Rev.* 2014;(8):CD009096. doi: 10.1002/14651858.CD009096.pub2.
- Littlejohn T, Majul C, Olvera R, et al. Results of treatment with telmisartan-amlodipine in hypertensive patients. *J Clin Hypertens (Greenwich).* 2009;11(4):207-213.
- Maddux TM, Januzzi JL, Allen LA. 2021 update to the 2017 ACC expert consensus decision pathway for optimization of heart failure treatment: answers to 10 pivotal issues about heart failure with reduced ejection fraction: a report of the American College of Cardiology Solution Set Oversight Committee. *J Am Coll Cardiol.* 2021;77(6):772-810.
- McKelvie RS, Yusuf S, Pericak D, et al. Comparison of candesartan, enalapril, and their combination in congestive heart failure: randomized evaluation of strategies for left ventricular dysfunction (RESOLVD) pilot study. The RESOLVD Pilot Study Investigators. *Circulation.* 1999;100(10):1056-1064.
- McMurray JJ, Ostergren J, Swedberg K, et al; CHARM Investigators and Committees. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-Added trial. *Lancet.* 2003;362(9386):767-771.

- McMurray JJ, Packer M, Desai AS, et al; for the PARADIGM-HF Investigators and Committees. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med*. 2014;371(11):993-1004.
- Micardis HCT [package insert], Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc.; August 2020.
- Micardis [package insert], Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals; July 2020.
- Mogensen CE, Neldam S, Tikkanen I, et al. Randomised controlled trial of dual blockade of renin-angiotensin system in patients with hypertension, microalbuminuria, and non-insulin dependent diabetes: the candesartan and lisinopril microalbuminuria (CALM) study. *BMJ*. 2000;321(7274):1440-1444.
- Mogensen UM, Kober L, Kristensen SL, et al; for the PARADIGM-HF Investigators and Committees. The effects of sacubitril/valsartan on coronary outcomes in PARADIGM-HF. *Am Heart J*. 2017;188:35-41.
- Neutel JM, Franklin SS, Lapuerta P, et al. A comparison of the efficacy and safety of irbesartan/HCTZ combination therapy with irbesartan and HCTZ monotherapy in the treatment of moderate hypertension. *J Hum Hypertens*. 2008;22(4):266-274.
- Neutel JM, Franklin SS, Oparil S, et al. Efficacy and safety of irbesartan/HCTZ combination therapy as initial treatment for rapid control of severe hypertension. *J Clin Hypertens (Greenwich)*. 2006;8(12):850-857.
- Neutel JM, Mancía G, Black HR, et al for the TEAMSTA Severe HTN Study Investigators. Single-pill combination of telmisartan/amlodipine in patients with severe hypertension: results from the TEAMSTA severe HTN study. *J Clin Hypertens (Greenwich)*. 2012 Apr;14(4):206-215.
- Ohma KP, Milon H, Valnes K. Efficacy and tolerability of a combination tablet of candesartan cilexetil and hydrochlorothiazide in insufficiently controlled primary hypertension—comparison with a combination of losartan and hydrochlorothiazide. *Blood Press*. 2000;9(4):214-220.
- ONTARGET Investigators. Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med*. 2008;358(15):1547-1559.
- Orange Book: Approved drug products with therapeutic equivalence evaluations. Food and Drug Administration website. <https://www.accessdata.fda.gov/scripts/cder/ob/index.cfm>. Accessed May 12, 2021.
- Packer M, McMurray J, Desai AS, et al. Angiotensin receptor neprilysin inhibition compared with enalapril on the risk of clinical progression in surviving patients with heart failure. *Circulation*. 2015;131(1):54-61.
- Parving H, Brenner BM, McMurray JJ, et al. Cardiorenal end points in a trial of aliskiren for type 2 diabetes (ALTITUDE). *N Engl J Med*. 2012;367(32):2204-2213.
- Pfeffer MA, McMurray JJ, Velazquez EJ, et al; Valsartan in Acute Myocardial Infarction Trial Investigators. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. *N Engl J Med*. 2003a;349(20):1893-1906.
- Pfeffer MA, Swedberg K, Granger CB, et al; CHARM Investigators and Committees. Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-Overall programme. *Lancet*. 2003b;362(9386):759-766.
- Philipp T, Smith TR, Glazer R, et al. Two multicenter, 8-week, randomized, double-blind, placebo-controlled, parallel-group studies evaluating the efficacy and tolerability of amlodipine and valsartan in combination and as monotherapy in adult patients with mild to moderate essential hypertension. *Clin Ther*. 2007;29(4):563-580.
- Pitt B, Poole-Wilson PA, Segal R, et al. Effect of losartan compared to captopril on mortality in patients with symptomatic heart failure: randomized trial—the Losartan Heart Failure Survival Study ELITE II. *Lancet*. 2000;355(9215):1582-1587.
- Pitt B, Segal R, Martinez FA, et al. Randomised trial of losartan versus captopril in patients over 65 with heart failure (Evaluation of Losartan in the Elderly Study, ELITE) *Lancet*. 1997;349(9054):747-752.
- Qaseem A, Witt TJ, Rich R, et al. Pharmacologic treatment of hypertension in adults aged 60 years or older to higher versus lower blood pressure targets: a clinical practice guideline from the American College of Physicians and the American Academy of Family Physicians. *Ann Intern Med*. 2017;166(6):430-437.
- Rosendorff C, Lackland DT, Allison M, et al. Treatment of hypertension in patients with coronary artery disease: a scientific statement from the American Heart Association, American College of Cardiology, and American Society of Hypertension (AHA/ACC/ASH). *J Am Coll Cardiol*. 2015;65(18):1998-2038.
- Sakata Y, Shiba, Takahashi J, et al. Clinical impacts of additive use of olmesartan in hypertensive patients with chronic heart failure: the supplemental benefit of an angiotensin receptor blocker in hypertensive patients with stable heart failure using olmesartan (SUPPORT) trial. *Eur Heart J*. 2015;36(15):915-923.
- Salerno CM, Demopoulos L, Mukherjee R, et al. Combination angiotensin receptor blocker/hydrochlorothiazide as initial therapy in the treatment of patients with severe hypertension. *J Clin Hypertens (Greenwich)*. 2004;6(11):614-620.
- Sanders GD, Coeytaux R, Dolor RJ, et al. Angiotensin-converting enzyme inhibitors (ACE-Is), angiotensin II receptor antagonists (ARBs), and direct renin inhibitors for treating essential hypertension: an update. Comparative Effectiveness Review No. 34. (Prepared by the Duke Evidence-based Practice Center under Contract No. 290-02-0025.) AHRQ Publication No. 11-EHC063-EF. Rockville, MD: Agency for Healthcare Research and Quality. June 2011.
- Savarese G, Costanzo P, Cleland JG, et al. A meta-analysis reporting effects of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in patients without heart failure. *J Am Coll Cardiol*. 2013;61(2):131-142.
- Shaddy R, Canter C, Halnon N, et al. Design for the sacubitril/valsartan (LCZ696) compared with enalapril study of pediatric patients with heart failure due to systemic left ventricle systolic dysfunction (PANORAMA-HF study). *Am Heart J*. 2017;193:23-34.
- Sharma A, Bagchi A, Kinagi S, et al. Results of a comparative, phase III, 12-week, multicenter, prospective, randomized, double-blind assessment of the efficacy and tolerability of a fixed-dose combination of telmisartan and amlodipine versus amlodipine monotherapy in Indian adults with stage II hypertension. *Clin Ther*. 2007a;29(12):2667-2676.
- Sharma AM, Bakris G, Neutel JM, et al. Single-pill combination of telmisartan/amlodipine versus amlodipine monotherapy in diabetic hypertensive patients: an 8-week randomized, parallel-group, double-blind trial. *Clin Ther*. 2012;34(3):537-551.
- Sharma AM, Davidson J, Koval S, et al. Telmisartan/hydrochlorothiazide versus valsartan/hydrochlorothiazide in obese hypertensive patients with type 2 diabetes: the SMOOTH study. *Cardiovasc Diabetol*. 2007b;6:28.
- Solomon SD, McMurray JJV, Anand IS, et al for the PARAGON-HF Investigators and Committees. Angiotensin-neprilysin inhibition in heart failure with preserved ejection fraction. *N Engl J Med*. 2019;381(17):609-620.
- SPRINT Research Group. A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med*. 2015;373(22):2103-2116.

- Srivastava PK, Claggett BL, Solomon SD, et al. Estimated 5-year number needed to treat to prevent cardiovascular death or heart failure hospitalization with angiotensin receptor-neprilysin inhibition vs standard therapy for patients with heart failure with reduced ejection fraction: an analysis of data from the PARADIGM-HF trial. *JAMA Cardiol.* 2018;3(12):1226-1231.
- Toh N, Ishii K, Kihara H, et al; Effect of ARB/Diuretics on Diastolic Function in Patients with Hypertension 2 (EDEN2) trial investigators. Effect of diuretic or calcium-channel blocker plus angiotensin-receptor blocker on diastolic function in hypertensive patients. *Circ J.* 2016;80(2):425-434.
- TRANSCEND Investigators. Effects of the angiotensin-receptor blocker telmisartan on cardiovascular events in high-risk patients intolerant to angiotensin-converting enzyme inhibitors: a randomized controlled trial. *Lancet.* 2008;372(9644):1174-1183.
- Tribenzor [package insert], Basking Ridge, NJ: Daiichi Sankyo Inc.; October 2020.
- Tsoi B, Akioyamen LE, Bonner A, et al. Comparative efficacy of angiotensin II antagonists in essential hypertension: systematic review and network meta-analysis of randomised controlled trials. *Heart Lung Circ.* 2018;27(6):666-682.
- Twynsta [package insert], Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals Inc.; November 2018.
- Velazquez EJ, Morrow DA, DeVore AD, et al; PIONEER-HF Investigators. Angiotensin-neprilysin inhibition in acute decompensated heart failure. *N Engl J Med.* 2019;380(6):539-548.
- Unger T, Borghi C, Charchar F, et al. 2020 International Society of Hypertension global hypertension practice guidelines. *J Hypertens.* 2020;38(6):982-1004.
- Viberti G, Wheeldon NM; MicroAlbuminuria Reduction With VALsartan (MARVAL) Study Investigators. Microalbuminuria reduction with valsartan in patients with type 2 diabetes mellitus: a blood pressure-independent effect. *Circulation.* 2002;106(6):672-678.
- Virani SS, Alonso A, Aparicio HJ, et al. Heart disease and stroke statistics – 2021 update: a report from the American Heart Association. *Circulation.* 2021;143(8):e254-e743.
- Vodovar N, Paquet C, Mebazaa A, et al. Neprilysin, cardiovascular, and Alzheimer's diseases: the therapeutic split? *Eur Heart J.* 2015; 36(15):902-905.
- Whelton PK, Carey RM, Aronow WS, et al. 2017 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. *Hypertension.* 2018;71(6):e13-e115.
- White WB, Murwin D, Chrysant SG, et al. Effects of the angiotensin II receptor blockers telmisartan versus valsartan in combination with hydrochlorothiazide: a large, confirmatory trial. *Blood Press Monit.* 2008;13(1):21-27.
- Wright RF, Duprez D, Purkayastha D, et al. Combination angiotensin-receptor blocker (ARB)/calcium channel blocker with HCTZ vs the maximal recommended dose of an ARB with HCTZ in patients with stage 2 hypertension: the Exforge as compared to losartan treatment in stage 2 systolic hypertension (EXALT) study. *J Clin Hypertens (Greenwich).* 2011;13(8):588-597.
- Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *J Card Fail.* 2017;23(8):628-651.
- Yancy CW, Jessup M, Bozkurt B, et al. 2016 ACC/AHA/HFSA Focused Update on New Pharmacological Therapy for Heart Failure: An Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure. *Circulation.* 2016;134(13):e298.
- Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA Guideline for the Management of Heart Failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol.* 2013;62(16):e147-239.
- Yusuf S, Pfeffer MA, Swedberg K, et al; CHARM Investigators and Committees. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. *Lancet.* 2003;362(9386):777-781.
- Zhu DL, Bays H, Gao P, et al. Efficacy and tolerability of initial therapy with single-pill combination telmisartan/hydrochlorothiazide 80/25 mg in patients with grade 2 or 3 hypertension: a multinational, randomized, double-blind, active-controlled trial. *Clin Ther.* 2012;34(7):1613-1624.

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