Therapeutic Class Overview
Angiotensin II Receptor Blockers (ARBs) Single Entity Agents

INTRODUCTION

- Approximately 92.1 million American adults have at least 1 type of cardiovascular disease according to the American Heart Association Heart Disease and Stroke Statistics 2017 update (Benjamin et al, 2017). From 2004 to 2014, mortality associated with cardiovascular disease declined 25.3%.
- An estimated 85.7 million Americans or 34% of US adults aged ≥20 years have high blood pressure (BP). Hypertension is an independent risk factor for cardiovascular disease and increases the mortality risks of cardiovascular disease and other diseases (Benjamin et al, 2017).
- Lowering of BP has been shown to reduce the risk of fatal and nonfatal cardiovascular events including stroke and myocardial infarctions (MI) improving cardiovascular health and reducing cardiovascular risk also includes lipid control, diabetes management, smoking cessation, exercise, weight management, and limited sodium intake (Benjamin et al, 2017).
- 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 (β)-blockers, and calcium channel blockers (CCBs). Selection of an antihypertensive for a specific patient is determined by patient characteristics such as ethnic group, and the presence of compelling indications such as heart failure (HF), diabetes (DM), chronic kidney disease (CKD), prevention of recurrent stroke, post-MI, and patients with high risk for coronary heart disease (CHD). Some patients require two or more antihypertensives from different pharmacological classes to achieve BP control (Go et al, 2013; Weber et al, 2014; James et al, 2013). Blood pressure goals for older patients have been a point of debate. The recent SPRINT trial followed patients ≥50 years with high blood pressure and increased cardiovascular risks under intense-hypertensive treatment (with a goal of 120 mmHg) compared to standard hypertensive treatment (with a goal of 140 mmHg) over the period of 3.2 years. The trial did end early; however, results demonstrated a reduced primary composite of MI, acute coronary syndrome (ACS), stroke, HF, or cardiovascular death driven mainly by reduced HF events and cardiovascular death with intense-treatment compared to standard treatment (goal 140 mmHg). SPRINT has pointed to potential clinical benefits associated with a more intensive treatment in certain patients (SPRINT Research Group, 2015).
- This review will focus on the ARBs which are Food and Drug Administration (FDA) approved to treat hypertension, to reduce the risk of cardiovascular death and heart failure hospitalization in patients with heart failure, to treat diabetic nephropathy with elevated serum creatinine (SCr) and proteinuria in patients with type 2 diabetes and hypertension, to reduce the risk of stroke in patients with hypertension and left ventricular (LV) hypertrophy for cardiovascular risk reduction in patients unable to take ACE-Is, and to reduce the risk of cardiovascular mortality in clinically stable patients with LV failure or LV dysfunction following MI.
- Medispan Therapeutic Class: Angiotensin II Receptor Antagonists

Table 1. Medications Included Within ARB Class Review

Drug	Manufacturer	FDA Approval Date	Generic Availability
ATACAND® (candesartan)	various	06/4/1998	✔
AVAPRO® (irbesartan)	various	09/30/1997	✔
BENICAR® (olmesartan)	various	04/25/2002	✔
COZAAR® (losartan)	various	04/14/1995	✔
DIOVAN® (valsartan)	various	07/18/2001 (tablet)	✔
EDARBI® (azilsartan)	Takeda	02/25/2011	-
MICARDIS® (telmisartan)	various	11/10/1998	✔
TEVETEN®* (eprosartan)	various	12/22/1997	✔

*Brand name eprosartan (TEVETEN) is no longer available.

(Drugs@FDA, 2017; Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, 2017)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	ATACAND (candesartan)	AVAPRO (irbesartan)	BENICAR (olmesartan)	COZAAR (losartan)	DIOVAN (valsartan)	EDARBI (azilsartan)	MICARDIS (telmisartan)	TEVETEN# (eprosartan)
Hypertension in adults – may be used alone or in combination.	✔	✔	✔	✔	✔	✔	✔	✔
Hypertension in children ages 1 to < 17 years – may be used alone or in combination. Lowering BP reduces the risk of fatal and non-fatal cardiovascular events, primarily strokes and MI.	✔							
Hypertension in children ages 6 to 16 years – may be used alone or in combination.			✔	✔	✔			
Treatment of diabetic nephropathy with an elevated SCr and proteinuria (>300 mg/day) in patients with type 2 diabetes and hypertension. In this population, AVAPRO and COZAAR reduce the rate of progression of nephropathy as measured by the occurrence of doubling of SCr or end-stage renal disease (need for dialysis or renal transplantation).		✔		✔				
Heart failure (NYHA Class II to IV) – reduces cardiovascular death and heart failure hospitalization.	✔							
Heart failure (NYHA Class II to IV) in adults - to reduce the risk of hospitalizations for heart failure.					✔			
Reduction in the risk of stroke in patients with hypertension and LV hypertrophy.				✔				
Post MI: In clinically stable patients with LV failure or LV dysfunction following MI, DIOVAN is indicated to reduce cardiovascular mortality.					✔			
Reduction of the risk of MI, stroke, or death from cardiovascular causes in patients 55 years of age or older at high risk of developing major cardiovascular events who are unable to take ACE-Is.*							✔	

Abbrv: ACE=angiotensin converting enzyme, LV=left ventricular, MI=myocardial infarction, NYHA=New York Heart Association, SCr=serum creatinine

*Consider using ACE-I first, and, if it is stopped for cough only, consider re-trying the ACE-I after the cough resolves. Use of telmisartan with an ACE-I is not recommended.

#Brand name eprosartan (TEVETEN) is no longer available.

Note: There is evidence that ARBs have smaller blood pressure effects (as monotherapy) in African American patients.

(Prescribing information: ATACAND, 2016; AVAPRO, 2016; BENICAR, 2016; COZAAR, 2015; DIOVAN, 2017; EDARBI, 2016; eprosartan, 2014; MICARDIS, 2014)

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

CLINICAL EFFICACY SUMMARY

- Clinical trials assessing the single entity ARBs in the treatment of hypertension have demonstrated efficacy in lowering systolic (SBP) and diastolic blood pressure (DBP). Head-to-head trials have not consistently demonstrated superiority of one ARB compared to another (Kakio et al, 2017; White et al, 2011; Bakris et al, 2011; Baguet et al, 2006, Oparil et al, 2001; Brunner et al, 2006; Xi et al, 2008; Xu et al, 2012; Conlin et al, 2000). A meta-analysis by Conlin et al found that the absolute weighted-average reductions in SBP and DBP associated with ARB monotherapy were comparable for all ARBs (Conlin et al, 2000). Published literature comparing therapy with ARBs and ACE-Is has generally demonstrated no significant differences between classes (Karlberg et al, 1999; Ruilope et al, 2001; Li et al, 2014). Comparisons of ARBs with other blood pressure lowering agents have not consistently demonstrated superiority of ARBs over other agents from different classes (Flack et al, 2003; Karotsis et al, 2006; Sanders et al, 2011; van Vark et al, 2012).
- Telmisartan is indicated to reduce cardiovascular 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 cardiovascular causes, MI, stroke or hospitalization for heart failure (ONTARGET Investigators, 2008). The TRANSCEND trial compared telmisartan and placebo and showed no significant difference between groups in death from cardiovascular causes, MI, stroke or heart failure hospitalizations. The composite endpoint of death from cardiovascular 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 (TRANSCEND Investigators, 2008; Foulquier et al, 2014).
- Losartan is indicated to reduce the risk of stroke in patients with hypertension 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 (hydrochlorothiazide could be added to primary regimens if needed for blood pressure control). Results demonstrated a 24.9% relative risk reduction in stroke in patients treated with losartan-based regimens as 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 cardiovascular death, MI and stroke in losartan-treated patients compared to atenolol (Julius et al, 2004).
- Candesartan and valsartan are indicated to treat heart failure. 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, cardiovascular death and/or heart failure hospitalization (Pfeffer et al, 2003a; McMurray et al, 2003; Yusuf et al, 2003). When compared to therapy with enalapril in the RESOLVD trial, candesartan was not significantly better in improving six-minute walking distance, New York Heart Association (NYHA) functional class or quality of life (McKelvie et al, 1999). Losartan has also been evaluated in patients with heart failure and, when compared to captopril, 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 (Pitt et al, 2000). Trials evaluating the efficacy of valsartan compared to placebo in the Val-HeFT trial show no significant difference in all-cause mortality between valsartan and placebo. However, the valsartan group demonstrated a significant improvement in NYHA functional class, heart failure hospitalizations and morbidity and mortality (Cohn et al, 2001).
- Valsartan is indicated to reduce cardiovascular mortality in patients with post-MI with 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, cardiovascular death, reinfarction or heart failure hospitalization were observed between monotherapy groups or combination therapy compared to captopril monotherapy (Pfeffer et al, 2003b). Losartan has also been evaluated in patients post-MI compared to and in combination with captopril. Results are similar to results observed in the VALIANT trial (Dickstein et al, 2002).
- Irbesartan and losartan are indicated for the treatment of diabetic nephropathy in patients with type 2 diabetes and hypertension. However, clinical benefit in diabetic nephropathy has been shown with other ARBs, including candesartan, losartan, telmisartan and valsartan (Mogensen et al, 2000; Hou et al, 2007; Barnett et al, 2004; Galle et al, 2008; Viberti et al, 2002).
- The ORIENT and ROADMAP studies followed patients with diabetes and compared the effects of olmesartan versus placebo. Outcomes demonstrated a higher rate of death from cardiovascular 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 cardiovascular 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 two inhibitors of the renin angiotensin-aldosterone system (RAAS), including an ACE-I with an ARB, provides no renal or cardiovascular benefits, and significant adverse events particularly in patients with diabetes 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, 2003b; Sakata et al, 2015).

SAFETY SUMMARY

- All ARBs have a boxed warning that states that use during pregnancy should be avoided. When pregnancy is detected, discontinue the ARB as soon as possible. Drugs that act directly on the renin-angiotensin system (RAS) can cause injury and death to the developing fetus.
- ARB-containing products should not be administered in combination with aliskiren in patients with diabetes mellitus. All ARBs may cause hypotension in volume- or salt-depleted patients and renal impairment.
- Dual blockade of the RAS with ARBs, ACE-Is, or aliskiren is associated with increased risks of hypotension, hyperkalemia, and changes in renal function (including acute renal failure) compared to monotherapy. Most patients receiving the combination of two RAS inhibitors do not obtain any additional benefit compared to monotherapy. In general, avoid combined use of RAS inhibitors.
- Other warnings and precautions in certain ARBs include electrolyte abnormalities, hypersensitivity reactions, administration in patients with impaired hepatic function, and sprue-like enteropathy.
- Drug interactions with ARB-containing products include lithium (possible increase in lithium levels) and non-steroidal anti-inflammatory drugs (NSAIDs) (reduce ARB effects and increased risk of renal injury or impairment).
- Common adverse events include hypotension, dizziness, headache, rash, pain, and cough.
- Data from one controlled trial (ROADMAP) and an epidemiologic study (ORIENT) have suggested that high-dose BENICAR (olmesartan 40 mg daily) may increase cardiovascular (CV) risk in diabetic patients, but the overall data are not conclusive (Haller et al, 2011; Imai et al, 2011; FDA Drug Safety Communication: Safety Announcement, 2010; Safety Announcement, 2011; Safety Announcement, 2014).

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Dosage Form: Strength	Usual Adult Dose	Usual Pediatric Dose	Administration Considerations
ATACAND (candesartan)	Tablet: 4 mg 8 mg 16 mg 32 mg	Heart failure (NYHA class II to IV)†: Tablet: initial, 4 mg daily; target, 32 mg daily Hypertension: Tablet: initial, 16 mg daily when used as monotherapy in patients who are not volume-depleted; maintenance, 8 to 32 mg/day in 1 to 2 divided doses Volume-depleted patients: administer under close medical supervision and consider a lower dose.	Hypertension (children 1 to <6 years of age): Tablet as oral suspension: initial, 0.2 mg/kg daily; maintenance, 0.05 to 0.4 mg/kg in 1 to 2 divided doses Hypertension (children 6 to <17 years of age and <50 kg): Tablet: initial, 4 to 8 mg daily; maintenance, 2 to 16 mg in 1 to 2 divided doses Hypertension (children 6 to <17 years of age and	Take with or without food. Oral suspension can be prepared from oral tablets.

Drug	Dosage Form: Strength	Usual Adult Dose	Usual Pediatric Dose	Administration Considerations
			>50 kg): Tablet: initial, 8 to 16 mg daily; maintenance, 4 to 32 mg in 1 to 2 divided doses	
AVAPRO (irbesartan)	Tablet: 75 mg 150 mg 300 mg	Diabetic nephropathy in patients with Type 2 diabetes and hypertension‡: Tablet: target, 300 mg daily in patients who are not volume-depleted Hypertension: Tablet: initial, 150 mg daily; maximum, 300 mg daily Volume or salt-depleted patients: initial, 75 mg daily	Safety and efficacy in children have not been established.	Take with or without food.
BENICAR (olmesartan)	Tablet: 5 mg 20 mg 40 mg	Hypertension: Tablet: initial, 20 mg daily when used as monotherapy in patients who are not volume depleted; maximum, 40 mg daily Volume-depleted patients: administer under close medical supervision and consider a lower dose.	Hypertension (children 6 to 16 years of age and 20 to <35 kg): Tablet: initial, 10 mg daily; maximum, 20 mg daily Hypertension (children 6 to 16 years of age and ≥35 kg): Tablet: initial, 20 mg daily; maximum, 40 mg daily	Take with or without food. Oral suspension can be prepared from oral tablets.
COZAAR (losartan)	Tablet: 25 mg 50 mg 100 mg	Diabetic nephropathy in patients with Type 2 diabetes and hypertension‡: Tablet: initial, 50 mg daily; maintenance, dose should be increased to 100 mg daily based on blood pressure response Hypertension (adult): Tablet: initial, 50 mg	Hypertension (children 6 years of age and older): Tablet: initial, 0.7 mg/kg daily (up to 50 mg total) administered as a tablet or suspension‖	Take with or without food. Oral suspension can be prepared from oral tablets.

Drug	Dosage Form: Strength	Usual Adult Dose	Usual Pediatric Dose	Administration Considerations
		daily in patients who are not volume-depleted; maintenance, 25 to 100 mg/day in 1 to 2 divided doses Reduction in the risk of stroke in patients with hypertension and LV hypertrophy§: Tablet: initial, 50 mg daily; maintenance, HCTZ 12.5 mg daily should be added and/or the losartan dose increased to 100 mg daily followed by an increase in HCTZ 25 mg daily based on blood pressure response. Volume-depleted patients: 25 mg daily		
DIOVAN (valsartan)	Tablet: 40 mg 80 mg 160 mg 320 mg	Heart failure (NYHA Class II to IV)#: Tablet: initial, 40 mg twice daily; maintenance, uptitration to 80 to 160 mg twice daily should be done to the highest dose as tolerated; maximum, 320 mg in divided doses Hypertension: Tablet: initial, 80 to 160 mg daily when used as monotherapy in patients who are not volume depleted; maintenance, 80 to 320 mg daily Post-myocardial infarction*: Tablet: initial, 20 mg twice daily; target, 160 mg twice daily	Hypertension (children 6 to 16 years of age): Tablet: initial, 1.3 mg/kg daily (up to 40 mg total); maximum, 2.7 mg/kg (up to 160 mg) daily	Take with or without food. Oral suspension can be prepared from oral tablets. Exposure to valsartan with a compounded suspension is 1.6 times greater than with the tablet. If the suspension is replaced by a tablet, then the dose may have to be increased.
EDARBI (azilsartan)	Tablet: 40 mg 80 mg	Hypertension: Tablet: 80 mg daily; consider 40 mg daily for	Safety and efficacy in children have not been	Take with or without food.

Drug	Dosage Form: Strength	Usual Adult Dose	Usual Pediatric Dose	Administration Considerations
		patients on diuretics or volume- or salt-depleted patients.	established.	
MICARDIS (telmisartan)	Tablet: 20 mg 40 mg 80 mg	Cardiovascular risk reduction in patients unable to take ACE-Is: Tablet: initial, 80 mg daily Hypertension: Tablet: initial, 40 mg daily; maximum, 80 mg daily	Safety and efficacy in children have not been established.	Take with or without food.
TEVETEN¥ (eprosartan)	Tablet: 600 mg	Hypertension: Tablet: initial, 600 mg daily when used as monotherapy in patients who are not volume-depleted; maintenance, 400 to 800 mg/day in 1 to 2 divided doses	Safety and efficacy in children have not been established.	Take with or without food.

Abbrv: ACE-I=angiotensin converting enzyme inhibitor, HCTZ=hydrochlorothiazide, LV=left ventricular, NYHA=New York Heart Association
†To reduce the risk of cardiovascular death and heart failure hospitalization in patients with LV systolic dysfunction. Candesartan has an added effect on these outcomes when used with an ACE-I.
‡Reduces the rate of progression to nephropathy in patients with elevated SCr and proteinuria (>300 mg/day).
§There is evidence that this benefit does not apply to African American patients.
‖Doses above 1.4 mg/kg (or in excess of 100 mg) daily have not been studied.
¶ Reduction of risk of myocardial infarction, stroke or cardiovascular death in patients 55 years of age and older at high risk of developing major cardiovascular events. Use of telmisartan with an angiotensin converting enzyme inhibitor is not recommended. Consider using an angiotensin converting enzyme inhibitor first.
#Reduction in heart failure hospitalizations. There is no evidence that valsartan provides added benefit when used with adequate doses of an ACE-I.
*In clinically stable patients with LV failure or dysfunction following myocardial infarction, to reduce the risk of cardiovascular mortality.
¥ Brand name eprosartan (TEVETEN) is no longer available.

SPECIAL POPULATIONS

Table 4. Special Populations

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy* and Nursing
ATACAND (candesartan)	No dosage adjustment required in the elderly.	Approved for use in children 1 to <17 years of age for the treatment of hypertension. Children <1 year of age must not receive candesartan. Safety and efficacy in children have not been	No dosage adjustment required.	Initiate with 8 mg once daily for patients with moderate hepatic impairment. No recom-mendations for patients for severe hepatic impairment.	Pregnancy Category: D Unknown whether excreted in breast milk; discontinue drug or nursing.

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy* and Nursing
		established for the treatment of heart failure.			
AVAPRO (irbesartan)	No dosage adjustment required in the elderly.	Safety and efficacy in children have not been established.	No dosage adjustment required.	No dosage adjustment required.	Pregnancy Category: D Unknown whether excreted in breast milk; discontinue drug or nursing.
BENICAR (olmesartan)	No dosage adjustment required in the elderly.	Approved for use in children 6 years of age and older. Children <1 year of age must not receive olmesartan.	No dosage adjustment required when CrCL is <40 mL/minute.	No dosage adjustment required.	Pregnancy Category: D Unknown whether excreted in breast milk; discontinue drug or nursing.
COZAAR (losartan)	No dosage adjustment required in the elderly.	Approved for use in children 6 to 16 years of age for hypertension. Not recommended in children <6 years or with GFR <30 mL/min/1.73m^2.	No dosage adjustment required. Children with GFR <30 mL/min/1.73m^2 should not receive losartan as it has not been studied.	The recommended starting dose in mild to moderate hepatic impairment is 25 mg once daily. Not been studied in patients with severe hepatic impairment.	Pregnancy Category: D Unknown whether excreted in breast milk; discontinue drug or nursing.
DIOVAN (valsartan)	No dosage adjustment required in the elderly.	Approved for use in children 6 to 16 years of age for hypertension.	Safety and effectiveness in severe renal impairment (CrCL ≤30 mL/min) have not been established. Children with GFR <30 mL/min/1.73m^2 or those undergoing dialysis should not receive valsartan as it has not been studied.	No dosage adjustment required for mild or moderate hepatic impairment. No dosing recom-mendation for severe hepatic impairment.	Pregnancy Category: D Unknown whether excreted in breast milk; discontinue drug or nursing.

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy* and Nursing
EDARBI (azilsartan)	No dosage adjustment required in the elderly.	Safety and efficacy in children have not been established.	No dosage adjustment required.	No dosage adjustment required for mild or moderate hepatic impairment.	Pregnancy Category: D Unknown whether excreted in breast milk; discontinue drug or nursing.
MICARDIS (telmisartan)	No dosage adjustment required in the elderly.	Safety and efficacy in children have not been established.	No dosage adjustment required.	Initiate therapy at a low dose and titrate slowly.	Pregnancy Category: D Unknown whether excreted in breast milk; discontinue drug or nursing.
TEVETEN[#] (eprosartan)	No dosage adjustment required in the elderly.	Safety and efficacy in children have not been established.	No dosage adjustment required; do not exceed 600 mg daily.	No dosage adjustment required.	Pregnancy Category: D Unknown whether excreted in breast milk; discontinue drug or nursing.

Abbrv: CrCL=creatinine clearance, GFR = glomerular filtration rate
* Pregnancy Category D = Positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may justify the use of the drug in pregnant women despite potential risks.
[#]Brand name eprosartan (TEVETEN) is no longer available.

CONCLUSION

- The ARBs are FDA-approved to treat hypertension, heart failure, to reduce the risk of cardiovascular death and heart failure hospitalization in patients with heart failure, to treat diabetic nephropathy with elevated serum creatinine and proteinuria in patients with type 2 diabetes and hypertension, to reduce the risk of stroke in patients with hypertension and left ventricular hypertrophy, cardiovascular risk reduction in patients unable to take ACE-Is, and to reduce the risk of cardiovascular mortality in clinically stable patients with left ventricular failure or left ventricular dysfunction following myocardial infarction.
- Clinical trials assessing the single entity ARBs in the treatment of hypertension have demonstrated efficacy in lowering SBP and DBP. Head-to-head trials have not consistently demonstrated superiority of one ARB compared to another. Published literature have found efficacy with ARB monotherapy is comparable for all ARBs, and in comparison to ACE-Is, ARBs have generally demonstrated no significant differences between classes.
- Evidence-based guidelines recognize the important role ARBs play in the treatment of hypertension and other cardiovascular and renal diseases. There is no consensus on blood pressure goals for certain populations, such as older patients, patients with diabetes, and/or CKD.
- The guidelines also differ on first-line treatment options in various groups, however ARBs are recommended as a first-line option for many patient populations. The current treatment guidelines do not establish a preference for one ARB over another.
    - ACE-Is or ARBs are recommended as a first-line option in patients with CKD with or without proteinuria, due to its renal protective attributes (Go et al, 2013; James et al, 2013; Mancia et al, 2013; Weber et al, 2014).
    - ARBs are also recommended as a first-line option for patients with hypertension complicated by comorbidities, such as cerebrovascular disease (e.g., stroke), vascular diseases, and diabetes (American Diabetes Association, 2017; Go et al, 2013; James et al, 2013; Mancia et al, 2013; Weber et al, 2014; Rosendorff et al, 2015).
    - ARBs are also recommended as a therapy option in those patients who are intolerant to ACE-Is and have heart failure, are post-myocardial infarction, have stable angina and unstable angina/non-ST elevation myocardial infarction, or in cases of left ventricular dysfunction, unless otherwise contraindicated (Amsterdam et al, 2014;

Fihn et al, 2014; Go et al, 2013; O'Gara et al, 2013; Montalescot et al, 2013; Nishimura et al, 2014; Piepoli et al, 2016; Ponikowski et al, 2016; Roffi et al, 2016; Steg et al, 2012; Stout et al, 2016; Weber et al, 2014; Windecker et al, 2014; Yancy et al, 2013; Yancy et al, 2016; Yancy et al, 2017).

- In black (patients of Caribbean or African descent) hypertensive patients, thiazide-type diuretics or CCBs are generally recommended as first-line therapy, and ARBs may be considered as add-on therapy (James et al, 2013; Weber et al, 2014). However, some guidelines recommend ARBs as a first line treatment option, regardless of race (Go et al, 2013; Rosendorff et al, 2015).
- ARBs are also recommended as a treatment option for patients with coronary artery disease, chronic aortic or mitral regurgitation, and a reasonable option in patients with other cardiac or vascular diseases (Amsterdam et al, 2014; Nishimura et al, 2014; Windecker et al, 2014; Rosendorff et al, 2015).

- Although pharmacokinetic and pharmacodynamic differences exist among ARBs, the clinical relevance of these differences has not been established. Comparative data regarding the ARBs have not demonstrated distinct, clinically significant differences regarding efficacy, safety and tolerability.
- Adverse effects common to all ARBs include hypotension, hyperkalemia, and dizziness (Clinical Pharmacology, 2017).

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