Based on recently published data, are angiotensin-receptor blockers (ARBs) more cardioprotective than angiotensin-converting enzyme inhibitors (ACEIs) for patients with hypertension? And if so, should ARBs be preferred over ACEIs?

Angiotensin-receptor blockers (ARBs) and angiotensin-converting enzyme inhibitors (ACEIs) are commonly used to treat cardiovascular disorders such as hypertension. The eighth report of the Joint National Committee (JNC8) for Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (2014) recommends several first-line classes of drugs to treat hypertension.[1,2] In nonblack patients, JNC8 recommends either a thiazide diuretic, ACEI, ARB, or calcium channel blocker (CCB) alone or in combination. For black patients, a thiazide, CCB, alone or in combination are recommended. JNC8 also recommends an ARB or ACEI alone or in combination with another class for patients with chronic kidney disease (CKD) with or without diabetes. In addition to pharmacotherapy, non-pharmacologic therapy such as lifestyle changes (smoking cessation, healthy diet, physical activity, and control of lipids and glucose levels) are recommended. JNC8 does not make any recommendations regarding preference of ACEIs versus ARBs. As such, a review of the literature was conducted to determine whether ARBs offer better cardioprotection compared to ACEIs (see Appendix 1).

To summarize, most of the studies found no evidence that ARBs offer greater protection than ACEIs. In a meta-analysis by Li et al, ARBs did not differ from ACEIs in terms of total mortality and CV outcomes in patients with primary hypertension.[3] Another meta-analysis by Al Khalaf et al found a lack of cardioprotection by ARBs in high risk patients (hypertension, type 2 diabetes, or renal disease) without heart failure.[4] In fact, this study found that ARBs increase the risk of myocardial infarction. Several retrospective cohort studies were reviewed; only Pai et al found that ARBs were more effective for stroke prevention in patients with hypertension and diabetes.[5] Hasvold et al found no difference in cardiovascular disease risk between candesartan and enalapril in patients with hypertension.[6] Lastly, Hsieh et al found that both ARBs and ACEIs decrease the risk for new onset atrial fibrillation.[7] In terms of guidelines, the JNC8 (2014) does not make any recommendations regarding preference of ACEIs versus ARBs for treatment of hypertension.[1] Based on this review of the medical literature, there is conflicting evidence regarding whether ARBs offer better cardioprotection compared to ACEIs. As such, additional trials need to be conducted to determine whether ARBs improve cardiovascular outcomes relative to ACEIs.

Appendix 1: Studies evaluating the cardioprotective effects of ARBs for treatment of hypertension.

Study	Objective	Methods	Results	Author conclusions
Meta-analyses				
Li et al (2014)[3]	Compare effects of ACEIs vs. ARBs on mortality, CVEs in pts with primary HTN	-Meta-analysis of RCTs (1946-July 2014) comparing ACEIs to ARBs for at least 1 year -Note: included pts with both controlled and uncontrolled HTN; did not exclude pts due to co-morbid conditions	-Included 9 RCTs (N=11,007 pts) -Total mortality: no significant difference between ACEIs and ARBs (RR 0.98; 95% CI 0.88 – 1.10) -Total CVE: no significant difference (RR 1.07; 95% CI 0.96 – 1.19) -CV mortality: no significant difference (RR 0.98; 95% CI 0.85 – 1.13) -WDAEs: lower incidence of dry cough for ARBs vs ACEIs (RR 0.83; 95% CI 0.74 – 0.93; ARR 1.8%, NNTB: 55 over 4.1y)	-ARBs do not differ from ACEIs in terms of total mortality and CV outcomes -ARBs caused fewer WDAEs -Limitations: potential for publication bias
Al Khalaf et al (2009)[4]	Determine the effect of ARBs on CV outcomes in high-risk pts without HF	-Meta-analysis of RCTs (1990-April 2008) involving ARBs ranging from 2w–5y -Included trials comparing ARBs to placebo, ACEI, BB, or CCB -Note: included pts with HTN, diabetes, renal dysfunction, and HF (reported results in HF pts, but focus of study was on non-HF pts)	-Included 37 RCTs (N=89,901) -Incidence of MI was higher in ARB-treated pts vs. controls (OR 1.09; 95% CI 1.00 – 1.18; p=0.05) -Incidence of stroke did not differ significantly (results not reported) -Incidence of CV death did not differ significantly (OR 1.00; 95% CI 0.95 – 1.07; p-value not reported) -Incidence of all-cause deaths did not differ significantly (OR 0.99; 95% CI 0.96 – 1.05; p-value not reported)	-ARBs do not provide CV protection in high-risk pts without HF -ARBs had an increased risk of MI -Limitations: heterogeneity of the included studies

Study	Objective	Methods	Results	Author conclusions
Retrospective cohort studies				
Hsieh et al (2016)[7]	Determine whether ARBs are more effective than ACEIs in prevention of AF in pts with HTN	-Retrospective cohort study; followed pts for up to 8y -Note: pts received other antihypertensive agents in combination with ACEI or ARB -Utilized health insurance database in Taiwan (2000-2011) -Included pts ≥55y with hypertension and had used at least 1 antihypertensive agent -Excluded pts with history of cardiac arrhythmias	-Compared 3 groups of pts: those on ACEI (n=8,034), ARB (n=6,205), or non-users (n=10,836) -1,619 pts developed new-onset AF -Use of ACEIs (adjusted HR 0.53; 95% CI 0.47 – 0.59; p<0.001) and ARBs (adjusted HR 0.51; 95% CI 0.44 – 0.58; p<0.001) reduced risk of AF versus non-users -ARBs were better at preventing AF in pts with history of stroke or TIA compared to ACEIs (p=0.012)	-ARBs and ACEIs decrease new-onset AF in pts with HTN as part of combination treatment with other agents -Pts with a history of stroke or TIA had fewer instances of new-onset AF with ARBs versus ACEIs -Limitations: study design, inability to measure adherence, no access to BP measurements, included mainly East Asian pts

Study	Objective	Methods	Results	Author conclusions
Pai et al (2016)[5]	Determine whether ARBs or ACEIs are more effective in preventing ischemic stroke in pts with HTN and T2DM	-Retrospective cohort study -Utilized health insurance database in Taiwan (1997-2010); followed pts until occurrence of stroke or up to end of 2010 -Included pts ≥18y with an initial diagnosis of HTN and diagnosed with T2DM later -Excluded pts with history of stroke, AMI, ACS, AF, HF, or CKD	-Compared 4 groups of pts: those on ACEI (n=2,161), ARB (n=1,703), both ACEI & ARB (n=165) or neither agent (n=1,416) -Incidence rates of stroke for ARB, neither agent, ACEI, and both ACEI & ARB were 23.02, 24.06, 30.23, and 37.86 per 1000 person-years, respectively -Compared to those on neither agent, the adjusted HRs were 1.27 (95% CI 1.02 – 1.58), 0.95 (95% CI 0.74 – 1.22), and 1.56 (95% CI 0.99 – 2.47) for ACEI, ARB, and ACEI/ARB, respectively -Use of high doses of ARBs resulted in a significant reduction in risk of stroke (adjusted HR 0.42; 95% CI 0.24 – 0.75)	-ARBs more effective than ACEIs for stroke prevention in pts with HTN and T2DM -Limitations: study design, exclusion of pts with baseline CV comorbidities and CKD, inability to measure adherence, included mainly East Asian pts
Hasvold et al (2014)[6]	Evaluate differences in risk of new-onset T2DM and CVD between candesartan and enalapril in pts with HTN	-Retrospective cohort study of medical records from Swedish primary care centers (1999-2007) -Excluded pts with CVD, DM, CKD, malignancy	-Compared 2 groups of pts: those on candesartan (4,265) or enalapril (n=11,725) -Pts treated with candesartan had a lower risk of developing new-onset T2DM than those on enalapril (HR 0.81; 95% CI 0.69 – 0.96; p=0.01) -For CVD: no difference was observed between groups (HR 0.99; 95% CI 0.87 – 1.13; p=0.86)	-Pts treated with candesartan had a lower risk of new-onset T2DM compared to enalapril -No difference in CVD risk between candesartan and enalapril

ACE=angiotensin-converting enzyme inhibitor; ACS=acute coronary syndrome; AF=atrial fibrillation; AMI=acute myocardial infarction; ARB=angiotensin receptor blocker; ARR=absolute risk reduction; BB=beta blocker; CCB=calcium channel blocker; CI=confidence interval; CKD=chronic kidney disease; CV=cardiovascular; CVE=cardiovascular events; T2DM=diabetes mellitus; HF=heart failure; HR=hazard ratio; HTN=hypertension; MI=myocardial infarction; NNTB=number needed to treat for an additional beneficial outcome; pts=patients; RCTs=randomized controlled trials; RR=risk ratio; w=weeks; TIA=transient ischemic attack; tx=treatment; WDAEs=withdrawals due to adverse effects; y=years

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