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Drug Class Literature Scan: Inhibitors of the Renin-Angiotensin-Aldosterone System (RAAS):

Focused update on angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB), and direct renin inhibitors (DRI)

Date of Review: February 2022

Date of Last Review: May 2017
Literature Search: 03/01/17 – 12/01/2021

Current Status of PDL Class:
See **Appendix 1**.

Conclusions:

- There is moderate quality evidence of no significant effect on all-cause mortality, CV mortality or heart failure hospitalizations with angiotensin converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs) in patients with heart failure with preserved ejection fraction (HFpEF).[1,2]
- There is insufficient evidence to evaluate the benefits and harms of pharmacological interventions for heart failure in patients with chronic kidney disease.[3]
- There is low quality evidence that in patients with coronary artery disease (CAD) without heart failure, treatment with a renin-angiotensin-aldosterone system (RAAS) inhibitor may reduce the risk of all-cause mortality and CV mortality when compared to placebo but not when compared to active controls. Additionally, there is no benefit seen in trials with a lower baseline risk.[4]
- There is no evidence that ACEIs or ARBs increase the risk for COVID-19 infection, severe illness due to COVID-19 or death from COVID-19. Current guidance recommends against discontinuing ACEIs or ARBs due to this concern.
- There is no new comparative evidence that one ACEI or ARB is more effective or results in more harms than another agent.
- There is no new high-quality evidence evaluating the direct renin inhibitor (DRI) on clinical outcomes in patients with hypertension.

Recommendations:

- No further review or research is needed.
- No changes recommended based on clinical evidence.
- After evaluation of costs in executive session, fosinopril, quinapril, and candesartan were made preferred on the preferred drug list (PDL).

Summary of Prior Reviews and Current Policy

- There is moderate quality evidence of no difference between ACEIs and ARBs for total mortality, cardiovascular (CV) events, or CV mortality in patients with hypertension. Incidence of adverse effects was slightly lower for ARBs compared with ACEIs primarily due to a higher incidence of dry cough with ACEIs
- In patients with hypertension, moderate quality evidence demonstrates that compared with calcium channel blockers (CCBs), renin-angiotensin system

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(RAS) inhibitors reduce death or hospitalizations for heart failure (HF) (absolute risk reduction (ARR) 1.2%), increase fatal and non-fatal stroke (absolute risk increase (ARI) 0.7%) and are similar for all-cause death, total CV events and end stage renal failure (ESRF) events

- Moderate quality evidence concluded the direct renin inhibitor (DRI), aliskiren, shows no benefit for the outcomes of major CV events, total mortality, cardiac death, myocardial infarction (MI), or stroke.
- There is moderate quality evidence that dual blockade of the RAS does not provide additional benefit in clinically relevant outcomes compared with monotherapy and increases risk of harm, specifically the risk of hyperkalemia, hypotension, renal failure and withdrawal due to adverse events.
- Rename the "ACEIs, ARBs and DRIs" PDL class to "Inhibitors of the Renin-Angiotensin-Aldosterone System (RAAS)" and include sacubitril/valsartan as a non-preferred agent in the class.
- Current prior authorization limits use of sacubitril/valsartan to patients with HFrEF with ejection fraction < 40%, on maximally tolerated ACE-I or ARB and a recommended beta-blocker.

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) comparing angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB), and direct renin inhibitors (DRI) on clinically relevant outcomes to active controls, or placebo if needed, was conducted. Sacubitril/valsartan and vericiguat were excluded from the review since they were recently evaluated. A summary of the clinical trials is available in **Appendix 2** with abstracts presented in **Appendix 3**. The Medline search strategy used for this literature scan is available in **Appendix 4**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:

After review, 11 systematic reviews were excluded due to poor quality[5-8], wrong study design of included trials (e.g., observational)[9-12], comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical)[13-15].

<u>Heart Failure</u>

A systematic review and meta-analysis evaluated the effects of treatments on mortality, hospitalizations, functional status and biomarker levels in patients with heart failure with preserved ejection fraction (HFpEF), defined as left ventricular ejection fraction (LVEF) ≥ 40%.[2] Randomized controlled trials (RCTs) comparing drug therapy with placebo, no treatment or standard medical treatment with a minimum follow-up of 12 weeks and evaluating cardiovascular (CV) outcomes were included. Trials were assessed for bias using the Cochrane Collaboration risk of bias tool and Egger test was done for publication bias. Overall, 27 articles were included in the analysis. Five were found to have high risk of bias and the remainder with low risk. Pooled analysis of ACEI's (RR 1.10; 95% CI 0.86 to 1.43) and ARBs (RR 1.02; 95% CI 0.93 to 1.12) showed no significant effect on all-cause mortality compared with control. [2] There was also no significant effect on CV mortality with ACEIs (RR 0.94; 5% CI 0.62 to 1.43) or ARBs (RR 1.02; 95% CI 0.90 to 1.14) compared to controls. [2] Pooled effects of all drugs blocking the renin-angiotensin-

aldosterone system (RAAS) showed a reduced risk for heart failure hospitalization (RR 0.90; 95% CI 0.82 to 0.98; p=0.01), with no effect seen with ACEIs or ARBs individually. [2] There were no meaningful effects when stratified by mean LVEF.

The Cochrane Collaboration evaluated the benefits and harms of pharmacological interventions for heart failure (HF) in people with HF and chronic kidney disease (CKD).[3] Randomized controlled trials of any pharmacological intervention for acute or chronic HF (with both preserved and reduced EF) and CKD were included. The primary outcomes were death and HF hospitalizations. There were 112 studies that met inclusion criteria for qualitative review with a significant number with unclear risk of bias, including selection, detection and other bias. Only 26 studies included extractable data that was included in the meta-analysis. Generally, there was insufficient evidence to make strong conclusions about the clinical effects of pharmacological interventions for HF in persons with CKD and further studies are needed to better define the clinical benefit derived with pharmacological interventions.[3] There was low quality evidence demonstrating no significant effect on all cause morality (RR 0.85; 95% CI 0.70 to 1.02; 4 studies) or CV mortality (RR 0.81; 95% CI 0.64 to 1.01; 2 studies) with ACE-Is or ARBs versus placebo and very low-quality evidence of no significant effect on HF hospitalization (RR 0.90; 95% CI 0.43 to 1.90; 2 studies).[3] There was no data on quality of life, worsening heart failure, all-cause hospitalization or worsening kidney function.

The Cochrane Collaboration assessed the effects of beta-blockers and inhibitors of the RAAS for chronic HFpEF, defined by LVEF ≥ 40%.[1] A total of 41 RCTs (n=23,492) were included. The risk of bias was often unclear with only five studies having a low risk of bias in all domains. Eight studies were identified evaluating ACEIs (n=2061). There was moderate quality evidence that ACEI likely has little or no effect on CV mortality (RR 0.93; 95% CI 0.61 to 1.42; 2 studies), all-cause mortality (RR 1.04; 95% CI 0.75 to 1.45; 5 studies) and heart failure hospitalizations (RR 0.86; 95% CI 0.64 to 1.15; 3 studies) and low-quality evidence of little or no effect on quality of life (mean difference [MD] -0.09; 95% CI -3.66 to 3.48; 2 studies). [1] There were limited data on hyperkalemia and no large clinical trials with more than 1000 participants. Pooled analysis of 8 studies (n=8755) with ARBs found high quality evidence of little or no effect on CV mortality (RR 1.02; 95% 0.90 to 1.14; 3 studies), all-cause mortality (RR 1.01; 95% CI 0.92 to 1.11; 4 studies), HF hospitalizations (RR 0.92; 95% CI 0.83 to 1.02; 3 studies), and quality of life (MD 0.41; 95% CI -0.86 to 1.67; 3 studies). [1] ARBs were associated with a higher risk of hyperkalemia (RR 1.88; 95% CI 1.07 to 3.33; 2 studies). [1] Unlike ACEIs and ARBs, there was moderate quality evidence of modest reduction in heart failure hospitalizations with angiotensin receptor neprilysin inhibitors (ARNIs) and mineralocorticoid receptor antagonists (MRAs), but no effect on all-cause or CV mortality. [1]

Hypertension

An update to the systematic review and meta-analysis evaluating pharmacotherapy for hypertension (HTN) in adults 60 years or older was recently released from the Cochrane collaboration.[16] The objective of the analysis was to quantify the benefit of antihypertensive medications compared to placebo or no treatment on all-cause mortality in people 60 years and older with mild to moderate HTN (blood pressure ≥ 140/90 mmHg). RCTs of at least one year duration were included. A total of 16 trials were included (n=26,795) in ambulatory patients with an average blood pressure of 182/95 mmHg. [16] Most trials evaluated thiazide type diuretics with a mean treatment duration of 3.8 years. At least one trial included an ACEI based treatment arm and many included subjects on background ACEI therapy. When treatments were pooled, there was a reduction in all-cause mortality with treatment versus control (10% vs. 11%; relative risk [RR] 0.91; 95% CI 0.85 to 0.97, moderate quality evidence of a reduction in CV mortality (9.8% vs. 13.6%; RR 0.72; 95% CI 0.68 to 0.77). [16] There was also moderate quality evidence of a reduction in cerebrovascular mortality and morbidity (RR 0.66; 95% CI 0.59 to 0.74) and coronary heart disease mortality and morbidity (RR 0.78; 95% CI 0.69 to 0.88). [16] Withdrawals due to adverse effects were increased with treatment (15.7%) versus control (5.4%) (RR 2.91; 95% CI 2.65 to 3.30). [16] Since the previous systematic review, only one additional trial was identified and added. Subgroup analysis demonstrates a higher magnitude of benefit in the 60- to 79-year-old patients compared to those over the age of 80. [16] This review did not evaluate differences based on the medication that was studied.

Coronary Artery Disease

Inhibitors of RAAS (ACEIs or ARBs) were evaluated in patients with coronary artery disease (CAD) without heart failure in a systematic review and meta-analysis of RCTs with at least one year of follw-up.[4] Trials were assessed for risk of bias using the Cochrane Collaboration tool. Primary outcomes were all-cause mortality, CV death, MI, stroke, angina, and heart failure. Literature search identified 24 trials (n=61,961) with an average follow up for 3.2 years. [4] Eighteen trials were placebo controlled and seven included an active control, including calcium channel blockers, thiazide diuretics and conventional treatment. RAAS inhibitors significantly reduced the risk of all-cause mortality compared to placebo (RR 0.84; 95% CI 0.72 to 0.98) but not when compared to active controls (RR 1.05; 95% CI 0.94 to 1.17).[4] Treatment with a RAAS inhibitor also reduced the risk of CV mortality (RR 0.74; 95% CI 0.59 to 0.94) and MI (RR 0.82; 95% CI 0.76 to 0.88) when compared to placebo but not when compared with active controls (RR 1.08; 95% CI 0.93 to 1.25 for CV mortality and RR 0.99; 95% CI 0.87 to 1.12 for MI). [4] Meta-regression analysis showed that the effect of RAAS inhibition on all-cause mortality, CV mortality and MI depended on control event rate with more benefit in trials with a high baseline risk but no benefit seen in trials with a lower baseline risk. Similarly, RAAS inhibitors reduced the risk of stroke, angina and heart failure when compared to placebo in patients with CAD without heart failure. [4]

New Guidelines:

Four guidelines were excluded due to poor quality rigor of development and systematic approach.[17-20] Two of these are consensus statements.[17,18]

Heart Failure:

American College of Cardiology (ACC)/American Heart Association (AHA)/Heart Failure Society of America (HFSA): Focused Update of the 2013 Guideline on the Management of Heart Failure[21]

The 2017 focused update of the 2013 guideline included revisions on biomarkers, new therapies for HFrEF, updates on HFpEF and new data on important comorbidities. Part 1 of this guideline included an update on new pharmacological therapy, including sacubitril/valsartan in HFrEF, and was reviewed in a previous class update. There were no major changes to recommendations regarding therapy with an RAAS inhibitors in this update. There remains a Class I recommendation based on level A evidence that in patients with chronic symptomatic HFrEF an ACEI or ARB should be initiated in combination with evidence-based beta blockers to reduce morbidity and mortality. There is also a Class I recommendation with level B-R evidence to consider angiotensin receptor-neprilysin inhibitor (ARNI). An ARNI should not be administered concomitantly with ACE-I or within 36 hours of the last dose due to the risk of angioedema. The update included a new Class I recommendation (level of evidence B-R) to replace ACEI or ARB with ARNI in those who tolerate therapy.

National Institute for Health and Care Excellence (NICE): Chronic heart failure in adults: diagnosis and management.[22]

The NICE updated its guidelines for chronic heart failure in adults in 2018. Recommendations were based on systematic reviews of best available evidence and consideration of cost effectiveness. The guideline recommendations were intended for primary care clinicians. The guidelines recommend first-line therapy with an ACE-I and beta blocker for those patients with HFrEF. An ARB is recommended as an alternative to ACEI for those with intolerable side effects with ACEI. The following are key guideline statements regarding therapy with sacubitril/valsartan:

- Sacubitril/valsartan is recommended as an option for treatment symptomatic chronic HFrEF, only in people:
    - With NYHA class II to IV symptoms, and
    - Left ventricular ejection fraction of 35% or less, and
    - Who are already taking a stable dose of an ACEI or ARB
- Treatment with sacubitril/valsartan should be started by a heart failure specialist with access to a multidisciplinary heart failure team

Hypertension:

Department of Veterans Affairs (VA)/Department of Defense (DoD): Clinical Practice Guideline for the Diagnosis and Management of Hypertension in the Primary Care setting[23]

The VA/DoD HTN guidelines were updated in 2020 based on a systematic review of the literature and using the GRADE framework to evaluate the body of evidence and strength of recommendations. It is intended to assist healthcare providers in the screening, diagnosis and management of HTN.[23] These guidelines include a weak recommendation to treat to a systolic BP of < 130 mmHg with a strong recommendation for < 150 mmHg for patients 60 years and over and < 140 mmHg for those 60 years and over with type 2 diabetes.[23] When drug therapy is initiated in the general population, it is strongly recommended to use one or more of the following as first line treatment: 1) Thiazide-type diuretics, 2) ACEIs or ARBs, or 3) long-acting calcium channel blockers (CCBs).[23] This recommendation was based on reviews of systematic review and meta-analysis of 50 RCTs that found no difference between ACEIs and ARBs, ACEs and thiazide-type diuretics, and ACEIs and CCBs. There are no specific recommendations made for individual medications within each class. For patients unlikely to achieve goal with monotherapy, it is recommended to consider initiating treatment with combination therapy.[23] There is also a strong recommendation against using ACEIs, ARBs, or DRIs in combination due to the increased risk for harm (kidney dysfunction and hyperkalemia). Additional recommendations are made for the following specific populations:

Population	*Recommendation*	*Strength*
• Patients aged 65 years and older	Thiazide-type diuretic as first line	Weak for
• African American patients	Avoid ACEI or ARB as monotherapy	Strong against
• Patients with CKD and albuminuria	ACEI or ARB to slow progression of CKD	Strong for
• Resistant HTN	Adding spironolactone	Weak for

National Institute for Health and Care Excellence (NICE): Hypertension in adults: diagnosis and management.[24]

The NICE updated its guidelines for chronic hypertension in adults in 2019. Recommendations were based on systematic reviews of best available evidence and consideration of cost effectiveness. The guideline recommendations were intended for primary care clinicians. The following recommendations are included for RAAS inhibitors:

- The updated guidelines recommend starting an ACEI or ARB in adults with:
  - Type 2 diabetes
  - Under 55 years old but not of black African or African-Caribbean family origin
- If an ACEI is not tolerated, offer an ARB to treat HTN
- Do not combine an ACEI or ARB to treat HTN
- If HTN is not controlled with a CCB, offer an ACEI, ARB or thiazide-like diuretic in combination
- If HTN is not controlled in adults of black African or African-Caribbean family origin who do not have type 2 diabetes, consider an ARB, in preference to an ACEI, in addition to initial step 1 treatment

COVID-19:
Since SARS-CoV-2 enters cells by binding the viral spike protein to the membrane-bound form of angiotensin-converting enzyme 2 (ACE2), there was initial concern that ACEI and ARBs could be harmful in patients with Covid-19 due to upregulation of ACE2 expression and increasing the availability of targets for SARS-CoV2.[25] Although mostly observational, current data does not provide evidence to support the theory that ACEIs or ARBs are associated with increased risks for those with COVID-19. Two randomized, open-label prospective trials (n=356) in patients hospitalized with COVID-19 have confirmed that discontinuation of ACEI or ARB did not impact severity or mortality associated with COVID-19 over 30 days.[26,27] These trials enrolled participants between March and August of 2020, prior to emergence of COVID variants, including the Delta variant.

Multiple professional scientific societies and COVID-19 guideline panels have recommended that patients should not discontinue ACEI or ARB therapy due to concern for increased risk for infection, severe illness, or death during the COVID-19 pandemic. This includes the American Heart Association/Heart Failure Society of America/American College of Cardiology[28], European Society of Cardiology[29], Canadian Cardiovascular Society[30], and the National Institutes of Health (NIH) COVID-19 Treatment Guidelines.[31]

New Formulations:
Two new formulations were approved since the last update. A new oral solution of valsartan (Prexxartan®) was FDA approved in 11/2017 and a new formulation of aliskiren (Tekturna®) oral pellets was also approved in 11/2017. However, both formulations have since been since been removed from the market.

New FDA Safety Alerts:
Contraindications, Warnings and Precautions and Drug Interactions were updated for all ACEI to include the increased risk of angioedema when an ACEI is administered within 36 hours of a neprilysin inhibitor, including sacubitril/valsartan. For patients taking an ACEI, it must be stopped and allow for a 36-hour washout period prior to starting sacubitril/valsartan.[21]

Table 1. Description of New FDA Safety Alerts

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
ACE Inhibitors Sacubitril/valsartan	NA Entresto®	07/2017	Contraindications, Warnings, Drug Interactions	Create alerts to warn against the concomitant use of Entresto and ACE inhibitors when claims are submitted for both drugs.

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Appendix 1: Current Preferred Drug List

Generic	Brand	Route	Form	PDL
benazepril HCl	BENAZEPRIL HCL	ORAL	TABLET	Y
benazepril HCl	LOTENSIN	ORAL	TABLET	Y
enalapril maleate	ENALAPRIL MALEATE	ORAL	TABLET	Y
enalapril maleate	VASOTEC	ORAL	TABLET	Y
irbesartan	AVAPRO	ORAL	TABLET	Y
irbesartan	IRBESARTAN	ORAL	TABLET	Y
lisinopril	LISINOPRIL	ORAL	TABLET	Y
lisinopril	PRINIVIL	ORAL	TABLET	Y
lisinopril	ZESTRIL	ORAL	TABLET	Y
losartan potassium	COZAAR	ORAL	TABLET	Y
losartan potassium	LOSARTAN POTASSIUM	ORAL	TABLET	Y
olmesartan medoxomil	BENICAR	ORAL	TABLET	Y
olmesartan medoxomil	OLMESARTAN MEDOXOMIL	ORAL	TABLET	Y
ramipril	ALTACE	ORAL	CAPSULE	Y
ramipril	RAMIPRIL	ORAL	CAPSULE	Y
telmisartan	MICARDIS	ORAL	TABLET	Y
telmisartan	TELMISARTAN	ORAL	TABLET	Y
valsartan	DIOVAN	ORAL	TABLET	Y
valsartan	VALSARTAN	ORAL	TABLET	Y
aliskiren hemifumarate	ALISKIREN	ORAL	TABLET	N
aliskiren hemifumarate	TEKTURNA	ORAL	TABLET	N
azilsartan medoxomil	EDARBI	ORAL	TABLET	N
candesartan cilexetil	ATACAND	ORAL	TABLET	N
candesartan cilexetil	CANDESARTAN CILEXETIL	ORAL	TABLET	N
captopril	CAPTOPRIL	ORAL	TABLET	N
enalapril maleate	ENALAPRIL MALEATE	ORAL	SOLUTION	N
enalapril maleate	EPANED	ORAL	SOLUTION	N
eprosartan mesylate	TEVETEN	ORAL	TABLET	N
fosinopril sodium	FOSINOPRIL SODIUM	ORAL	TABLET	N
lisinopril	QBRELIS	ORAL	SOLUTION	N
moexipril HCl	MOEXIPRIL HCL	ORAL	TABLET	N
perindopril erbumine	PERINDOPRIL ERBUMINE	ORAL	TABLET	N
quinapril HCl	ACCUPRIL	ORAL	TABLET	N
quinapril HCl	QUINAPRIL HCL	ORAL	TABLET	N
sacubitril/valsartan*	ENTRESTO	ORAL	TABLET	N
trandolapril	TRANDOLAPRIL	ORAL	TABLET	N
Vericiguat*	VERQUVO	ORAL	TABLET	

* These products were reviewed in June 2021 and are not the focus of this literature scan.

Appendix 2: New Comparative Clinical Trials

A total of 19 citations were manually reviewed from the initial literature search and after initial review of title and abstract (excluding trials with sacubitril/valsartan), 6 were included for more detailed evaluation. Two of these were systematic reviews and are included above. After further review, 3 citations were excluded because of wrong study design (eg, observational)[32-34], population[35], comparator (eg, no control or placebo-controlled), or outcome studied (eg, non-clinical). The remaining trial is summarized in the table below. Full abstracts are included in **Appendix 3**.

Table 1. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results		Notes/Limitations
Mehlum et al.[36] MC, DB, RCT	Valsartan (V) 80 mg versus amlodipine (A) 5 mg *doses were titrated up to goal BP of < 140/90 mm Hg	Patients with HTN and ≥1 additional CV risk factor N=14,996	Non-fatal or fatal MI, stroke, CHF, and death	<u>MI</u> V: 363 (4.8%) A: 306 (4.1%) HR 1.19; 95% CI 1.02-1.39; p=0.03 <u>Stroke:</u> V: 312 (4.1%) A: 277 (3.7%) HR 1.13; 95% CI 0.96-1.33; p=0.1	<u>CHF:</u> V:292 (3.9%) A: 340 (4.5%) HR 0.86; 95% CI 0.74-1.00; p=0.06 <u>Death:</u> V: 802 (10.7%) A: 792 (10.6%) HR 1.01; 95% CI 0.92-1.12; p=0.8	Posthoc analysis of VALUE trial

Abbreviations: BP = blood pressure; CHF = congestive heart failure; CI = confidence interval; CV = cardiovascular; DB = double blind; HR = hazard ratio; HTN = hypertension; MC = multicenter; MI = myocardial infarction; RCT = randomized clinical trial

Appendix 3: Abstracts of Comparative Clinical Trials

Mehlum M, Liestol K, Kjeldsen S, et al. Blood Pressure-Lowering Profiles and Clinical Effects of Angiotensin Receptor Blockers Versus Calcium Channel Blockers *Hypertension*. 2020 Jun;75(6):1584-1592. doi: 10.1161/HYPERTENSIONAHA.119.14443. Epub 2020 Apr 27.

Abstract

Blood pressure-lowering drugs have different blood pressure-lowering profiles. We studied if differences in blood pressure mean and variability can explain the differences in risks of cardiovascular events and death among 15 245 high-risk hypertensive patients randomized to valsartan or amlodipine and followed for 4.2 years in the VALUE trial (Valsartan Antihypertensive Long-Term Use Evaluation). We selected patients with ≥3 visits and performed Cox regression analyses, defining mean blood pressure as a time-dependent covariate and visit-to-visit and within-visit blood pressure variability as the SD. Of 14 996 eligible patients, participants in the valsartan group had higher systolic mean blood pressure by 2.2 mm Hg, higher visit-to-visit systolic variability by 1.4 mm Hg, and higher within-visit systolic variability by 0.2 mm Hg (P values <0.0001). The higher risks of myocardial infarction and stroke in the valsartan group was attenuated after adjustment for mean and variability of systolic blood pressure, from HR 1.19 (95% CI, 1.02-1.39) to 1.11 (0.96-1.30) and from HR 1.13 (0.96-1.33) to 1.00 (0.85-1.18), respectively. The lower risk of congestive heart failure in the valsartan group was accentuated after adjustment, from HR 0.86 (0.74-1.00) to 0.76 (0.65-0.89). A smaller effect was seen on risk of death, from 1.01 (0.92-1.12) to 0.94 (0.85-1.04). In conclusion, the higher risks of myocardial infarction and stroke in patients randomized to valsartan versus amlodipine were related to the drugs' different blood pressure modulating profiles. The risk of congestive heart failure with valsartan was lower, independent of the less favorable blood pressure modulating profile.

Appendix 4: Medline Search Strategy

Ovid MEDLINE(R) ALL <1946 to December 1, 2021>

1	losartan.mp. or Losartan/	10248
2	olmesartan.mp.	1718
3	telmisartan.mp.	2601
4	candesartan.mp.	3401
5	eprosartan.mp.	414
6	irbesartan.mp.	1982
7	valsartan.mp.	4837
8	azilsartan.mp.	252
9	angiotensin receptor blocker.mp. or Angiotensin Receptor Antagonists/	12158
10	benazepril.mp.	836
11	angiotensin converting enzyme inhibitors.mp. or Angiotensin-Converting Enzyme Inhibitors/	40823
12	enalapril.mp. or Enalapril/	8326
13	lisinopril.mp. or Lisinopril/	3104
14	ramipril.mp. or Ramipril/	2922
15	captopril.mp. or Captopril/	13587
16	fosinopril.mp. or Fosinopril/	626
17	moexipril.mp.	116
18	perindopril.mp. or Perindopril/	2321
19	quinapril.mp. or Quinapril/	838
20	aliskiren.mp.	1280
21	direct renin inhibitors.mp.	179
22	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21	76982
23	Cardiovascular Diseases/ or Myocardial Infarction/ or cardiovascular outcomes.mp. or Coronary Artery Disease/	394667
24	cardiovascular mortality.mp.	15148
25	23 or 24	402320
26	22 and 25	8080
27	limit 26 to (english language and full text and humans and yr="2017 -Current" and (clinical trial, all or comparative study or controlled clinical trial or guideline or meta analysis or randomized controlled trial or "systematic review"))	81
28	from 27 keep 1,6,14,18,22,24,30-31,35-36,42,45,54,56,62,66,72-73,78	19
29	from 28 keep 4,6,8,10,14,18	6

Appendix 5: Key Inclusion Criteria

Population	**Cardiovascular disease or high cardiovascular risk**
Intervention	ACE-I, ARB, DRI
Comparator	Active control or placebo
Outcomes	Major adverse cardiovascular events, cardiovascular mortality, all-cause mortality, renal outcomes
Timing	≥ 3 months
Setting	Outpatient setting for follow up