Drug Use Research & Management Program
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PDL Classes: ACEIs/ARBs/DRIs

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Current Status of PDL Class:

Current Preferred Agents	Current Non-Preferred Agents
ACEIs	
Benazepril	Perindopril (Aceon®)
Captopril	
Enalapril	
Fosinopril	
Lisinopril	
Moexipril	
Quinapril	
Ramipril	
Trandolapril	
ARBs	
Olmesartan (Benicar®)	Candesartan (Atacand®)
Losartan	Eprosartan (Teveten®)
Telmisartan (Micardis®)	Irbesartan (Avapro®)
	Valsartan (Diovan®)
	Azilsartan medoxomil (Edarbi®)
DRIs	
	Aliskiren (Tekturna®)
Combination Products	
Benazepril-HCTZ	Amlodipine/olmesartan (Azor®)
Olmesartan-hydrochlorothiazide (Benicar HCT®)	Amlodipine/valsartan (Exforge®)
Captopril/HCTZ	Telmisartan/amlodipine (Twynsta®)
Enalapril/HCTZ	Aliskiren/valsartan (Valturna®)
Fosinopril/HCTZ	Aliskiren/amlodipine/HCTZ (Amturnide®)
Lisinopril/HCTZ	Aliskiren/amlodipine (Tekamlo®)
Losartan/HCTZ	Amlodipine/benzepril (Lotrel®)
Telmisartan/HCTZ (Micardis HCT®)	Trandolapril/verapamil (Tarka®)
Quinapril/HCTZ	Tekturna/HCTZ
moexiprilHCTZ	Valsartan/HCTZ (Diovan HCT®)

Abbreviations: ACEI – Ace Inhibitor, ARBs – Angiotensin Receptor Blockers, DRIs-direct renin inhibitor.

Previous Conclusions and Recommendation:

- There are no clinically significant differences among angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs).
- Rates of cough were lower with ARBs than ACEIs. However, overall rates of withdrawal were the same.
- DUE to a lack of comparative effectiveness research for any clinical outcomes, recommend maintaining all DRIs and products containing a DRI as non-preferred on the PDL.
- Due to lack of long term studies demonstrating a reduction of cardiovascular (CV) events and mortality or long-term safety compared to multiple alternatives, recommend making azilsartan a nonpreferred ARB.

Research Questions:

- Is there any new comparative evidence on ACE-Is, ARBs, or DRIs on mortality, cardiovascular events, end-stage renal disease, or quality of life?
- Is there any new comparative safety evidence of Beta Blockers??
- Are there subpopulations of patients for which one medication or preparation is more effective or associated with fewer adverse effects?

Conclusions and Recommendations:

- There is moderate quality evidence that dual blockade of the renin-angiotensin system does not provide any benefit in all-cause mortality and CV mortality compared with monotherapy. There is also an increase in the risk of hyperkalemia, hypotension, renal failure, and withdrawal due to adverse events with dual therapy compared to monotherapy.[1]
- There is moderate quality of evidence of no difference between ACEIs and ARBs in mortality, CV mortality, hospitalizations, and stroke.
- New JNC8 guidelines recommend ACEIs and ARBs (in addition to thiazide diuretics and calcium channel blockers) as initial treatment options in the general nonblack population for the treatment of hypertension (HTN) based on comparable efficacy on overall mortality, CV, and cerebrovascular outcomes. [2]
- There is insufficient evidence evaluating azilsartan/chlorthalidone combination therapy on long term clinical outcomes. Maintain as non-preferred and evaluate comparative costs in executive session.
- There is no new comparative efficacy or safety evidence for preference of one agent over another within each class. Evaluate comparative costs in executive session; Make captopril, fosinopril, moexipril, quinapril, and trandolapril and the HCTZ combination products non-preferred due to low use and high relative price and grandfather patients for 12 months.

Methods:

The DERP scan was used to identify any new comparative research on the ACEI's that has emerged since the last P&T review. [3] An additional MEDLINE search was conducted using ARBs and DRIs as search terms with limits for human studies and English language, randomized controlled trials (RCTs) and meta-analyses. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were searched for high quality systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts, and the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines. Forty three citations resulted initially for the DRI search. After exclusion due to wrong comparator, poor study design, or wrong outcomes, 3 systematic reviews and 7 RCTs were identified. An initial 322 citations resulted from the ARB literature search, resulting in 4 potentially relevant systematic reviews and 3 RCTs. Poor quality systematic reviews were not included in this review, as well as reviews that only measured surrogate endpoints.[4,5]

Systematic Reviews:

A systematic review evaluated aliskiren/amlodipine vs. aliskiren/HCTZ in hypertension.[6] A MEDLINE search through December 2012 reported on 19 studies (n=13,614). The primary endpoint was reduction from baseline to the end of treatment in mean clinical systolic blood pressure (SBP) and diastolic blood pressure (DMP). The quality of the RCTs was assessed by the Jada scale. All but one study were given a quality score of 4 or 5. An indirect comparison showed that aliskiren/amlodipine was more effective than aliskiren/HCTZ in both mean SBP (weighted mean difference [WMD] -3.36 mm Hg; p=0.97) and mean DBP (WMD -3.39 mm Hg; p=0.78). There was no difference in adverse events or withdrawals due to adverse events.

The effect of combination treatment with aliskiren and blockers of the renin-angiotensin system on hyperkalemia and acute kidney injury was assessed in a systematic review and meta-analysis.[7] Two reviewers used the Cochrane checklist to assess the risk of bias in included studies. Ten RCTs were identified and included in the review. The risk of bias was

low. The risk of hyperkalemia was significantly higher among those given aliskiren in combination with an ACEI or ARB than among those given ACEI or ARB monotherapy (RR 1.58; 95% CI 1.24-2.02; NNH 43) as well as compared to aliskiren monotherapy (RR 1.67, 95% CI 1.01-2.79; NNH50). The risk of acute kidney injury was not significantly increased with aliskiren in combination with an ACEI or ARB compared to ACEI or ARB monotherapy (RR 1.14; 95% CI 0.68-1.89) or aliskiren monotherapy (RR 0.80; 95% CI 0.31-2.04). Many of these studies were small and not designed to measure safety outcomes.

A systematic review was done to compare the long term efficacy and adverse events of dual blockade of the renin-angiotensin system with monotherapy.[1] A total of 33 trials met the inclusion criteria. A combination of an ACEI and ARB was used in 22 trials. Eighteen trials were deemed to be at low risk of bias and the remainder to be at high risk. Seven trials reported on all-cause mortality. When compared with monotherapy alone, dual therapy had no benefit on all-cause mortality (RR 0.97; 95% CI 0.89-1.06, p=0.50). In a subgroup analysis, mortality was increased in the cohort of patients without heart failure (15.3% vs. 15.0%; RR 1.07, 95% CI 1.00-1.14; p=0.04) but not in the group with heart failure. Dual therapy also had no significant benefit on CV mortality (14.7% vs. 15.7%; RR 0.96; 95% CI 0.88-1.05; p=0.38. Based on 5 trials, dual therapy was associated with a reduction in admissions to hospital for heart failure compared with monotherapy (10.3% vs. 18%; RR 0.82; 95% CI 0.74-0.92; p=0.0003). For observed safety outcomes, dual therapy was associated with a significant increase in the risk of hyperkalemia (RR 1.55; 95% CI 1.32-1.82, p<0.001) compared with monotherapy, as well as an increased risk of renal failure (RR 1.41; 95% CI 1.09-1.85; p=0.01). There was also an increase seen in withdrawals due to adverse events in the dual group compared to monotherapy (17.1% vs. 14.5%; RR 1.27; 95% CI 1.21-1.32; p<0.001).

A Cochrane Systematic Review assessed the benefits and harms of ARBs compared with ACEIs or placebo in their use for chronic heart failure.[8] A total of 24 studies met the inclusion criteria for review. Results demonstrated that, in patients with left ventricular ejection fraction (LVEF) of 40% or lower, the reduction in total mortality with ARB therapy was of borderline statistical significance compared to placebo (RR 0.87; 95% CI 0.76-1.00). However, when including only the trials with full reporting, there was no statistically significant difference (RR 0.91; 95% CI 0.79-1.04) between ARBs and placebo. There was no difference between ARBs and placebo for CV and non-CV mortality. Eight studies compared ARBs to ACEIs and showed no difference between them in total mortality, CV mortality, or non-CV mortality. There was also no difference between ACEIs and ARBs in total hospitalizations (RR 1.00; 95% CI 0.92-1.08), MI (RR 1.00; 95% CI 0.62-1.63), and stoke (RR 1.63; 95% CI 0.77-3.44) but withdrawals due to adverse effects were lower with ARBs (RR 0.63; 95% CI 0.52-0.76). Combinations of ARBs and ACEIs increased the risk of withdrawals due to adverse effects, but did not reduce total mortality or hospitalizations versus ACEI's alone.

A review by Savarese et al., assessed the effects of ACEIs and ARBs on the composite outcome of CV death, MI, and stroke, and on all-cause death, new-onset HF, and new-onset diabetes mellitus.[9] Using the PRISMA methods, RCTs comparing either an ARB or an ACEI with placebo were considered for the analysis and were assessed for quality using the Detsky method. ACEIs significantly reduced the risk of the composite outcome by 14.9% compared with placebo (OR 0.830; 95% CI 0.74-0.93/ p=0.001). They significantly reduced the risk of MI (OR 0.81; 95% CI 0.75-0.88; p<0.001) and stroke (OR 0.8; 95% CI 0.7-0.9/ p-0.004), but did not show a difference in reduction in CV death (OR 0.9; 95% CI 0.8-1.03; p=0.112). ACEIs significantly reduced the risk of all-cause death, new-onset HF and new-onset diabetes mellitus. ARBs also reduced the risk of the composite outcome (OR 0.92; 95% CI 0.9-0.98/ p=0.005). ARBs did not reduce the risk of CV death (OR 1.033; 95% CI 0.9-1.3, p=0.75), but did significantly reduce the risk of stroke (OR 0.9; 95% CI 0.8-0.98; p=0.011). There was no difference seen in risk of MI, all-cause death, or new-onset HF.

A meta-analysis evaluated the effect of ARBs on the development of new-onset type 2 diabetes. RCTs were included and assessed for quality using the Cochrane handbook.[10] Eleven RCTs with 79,773 patients were included. Overall, new onset diabetes was significantly lowered in the ARB group compared to the control group (9.9% vs. 11.9%; OR 0.79; 95% CI 0.74-084; p<0.000001). ARBs were associated with a reduction in the risk of new-onset diabetes compared with

placebo, beta-blockers, calcium channel blockers, and non-ARBs. However, diabetes was defined differently among the trials and the incidence of diabetes was not the primary outcome of the trials.

New Guidelines:

JNC8:

Evidence-based guidelines for the treatment of hypertension were recently released from the Eighth Joint National Committee (JNC8)[2] The following recommendations were made regarding the drug selection for the treatment of hypertension:

- In the general nonblack population, initial antihypertensive treatments should include a thiazide-type diuretic, calcium channel blocker, ACEI, or ARB (Moderate recommendation – Grade B).
    - Each of these classes had comparable effects on overall mortality and CV, cerebrovascular, and kidney outcomes.
    - No preference of a specific agent in each class was given.

Canadian Hypertension Education Program

The Canadian guidelines for the management of Hypertension were updated in 2012 with the following main recommendations regarding drug selection:[11]

- An ACEI or ARB is recommended for most patients with HTN and coronary artery disease (Grade A).
- For patients with stable angina, Beta blockers are preferred as initial therapy (Grade B).
- For patients with coronary artery disease, but without coexisting systolic heart failure, the combination of an ACEI and ARB is not recommended (Grade B).
- For patients who have had a recent myocardial infarction (MI), initial therapy should include both a Beta blocker and an ACE inhibitor (Grade A).
- An ARB can be used if the patient is intolerant of an ACEI (Grade A).
- After acute stroke, treatment with an ACEI and diuretic combination is preferred (Grade B).

Safety Alerts:

In April 2012, the FDA released a safety announcement warning of possible risks when using medicines containing aliskiren with ACEIs and ARBs in patients with diabetes or kidney impairment.[12] These drug combinations should not be used in patients with diabetes. This is a result of preliminary data from a clinical trial (ALLTITUDE).[13] In ALLTITUDE, the risks of kidney impairment, low blood pressure, and hyperkalemia in a group of patients taking aliskiren plus an ARB or ACEI increased relative to a group of patients taking placebo plus an ARB or ACEI. There was also a slight excess of CV events in the aliskiren group.

New Drugs:

The combination of azilsartan medoximil and cholrthalidone (Edarbyclor®) was recently FDA approved as a fixed-dose combination medication for patients with an inadequate response to monotherapy or those in whom multiple drugs are required to achieve blood pressure control.[14] This is the only ARB found in combination with the diuretic, chlorthalidone. There are no head to head trials comparing hydrochlorothiazide to chlorthalidone in CV events.

A double-blind RCT compared the antihypertensive efficacy of azilsartan/chlorthalidone versus azilsartan or chlorthalidone monotherapy in 1714 patient with stage 2 HTN over 8 weeks.[15] Azilsartan/chlorthalidone 40mg/25mg and 40mg/12.5mg significantly lowered SBP compared to monotherapy.

A second RCT evaluated the efficacy of azilsartan/chlorthalidone with olmesartan/hydrochlorothiazide in 1071 patients with stage 2 HTN.[16] Twenty four SBP was reduced by 5.3 mm Hg more in the azilsartan group compared to the olmesartan group (95% CI -7.6 to -3.1 mmHg; $p<0.001$) at the end of 12 weeks. Reductions in 24-hour mean DBP with

azilsartan/chlorthalidone were also superior to olmesartan/hydrochlorothiazide (p<0.001). Lastly, a larger percentage of patients receiving azilsartan/chlorthalidone 40/25 mg than olmesartan/hydrochlorothiazide 40/25 mg reached target BP of less than 140/90 mm Hg (81.4% vs. 74.6%; p<0.05). However, these were not therapeutically equivalent doses of chlorthalidone and hydrochlorothiazide which limits the ability to effectively compare the two.

Lastly, a study compared different thiazide diuretics in combination with azilsartan.[17] Patients (n=609) with a mean SBP of 160-190 mm Hg started azilsartan 40 mg with addition of chlorthalidone 12.5 mg or hydrochlorothiazide 12.5 mg at week 2. Fewer patients required titration to higher doses of azilsartan/chlorthalidone than did those on azilsartan/hydrochlorothiazide (30.8% vs. 345.9%; p<0.001). Also, trough SBP after 10 weeks responded significantly better to chlorthalidone combination than with hydrochlorothiazide (-37.8 vs. -32.8; p<0.001).

There are no clinical trials assessing clinical outcomes for azilsartan/chlorthalidone.

Study	Comparison	Population	Primary Outcome	Results
DRI's				
Littlejohn et al.[18] RCT, DB	Aliskiren/amlodipine combination vs. aliskiren vs. amlodipine vs. placebo	Adults with primary hypertension (n=1688)	Change in mean sitting DBP from baseline to week 8	All four aliskiren/amlodipine combination doses provided significantly greater reductions in mean DBP than the monotherapies (p>0.05).
Nicholls et al.[19] RCT, DB	Aliskiren vs. placebo	Adults with CAD, SBP 125-139 mm Hg, and 2 additional CV risk factors (n=613)	Percent atheroma volume (PAV) (progression of coronary atherosclerosis)	PAV did not differ between participants treated with aliskiren (−0.33%; 95%CI, 0.68%to 0.02%) and placebo (0.11%; 95%CI, −0.24%to 0.45%) (between-group difference, −0.43%[95%CI, −0.92%to 0.05%]; P = .08).
Vakris et al.[20] DB	Aliskiren/valsartan vs. valsartan	Adults with hypertension, type 2 diabetes, and stage 1 or 2 chronic kidney disease (n=1143)	Ambulatory blood pressure	the addition of aliskiren to valsartan was associated with an incremental benefit of 4.0 mm Hg of lowering in 24-hour SBP and 2.4 mm Hg of lowering in 24-hour DBP (both P<.001).
Lizakowski et al.[21] RCT, DB	Aliskiren vs. perindopril vs. placebo	Patients with non-diabetic chronic kidney disease (n=14)	24 hour proteinuria	<u>24-h proteinuria decrease compared to placebo:</u> Alis 150mg: 23% Alis: 300mg 36%

				P=0.001 Perin 5mg: 7.1% Perin 10 mg: 25.1% P=0.04
Gheorghiade et al.[22] RCT, DB, PC	Aliskiren vs. placebo in addition to standard therapy	Hemodynamically stable hospitalized heart failure patients (n=1639)	CV death or HF rehospitalization	<u>DV death + HF rehospitalization at 6 mo:</u> Alisk: 24.9% Plac: 26.5% HR 0.92; 95% CI 0.76-1.12; p=0.41
ALTITUDE[13] RCT, DB	Aliskiren vs.placebo as an adjunct to ACEI or ARB		Composite of the time to CV death or first occurrence of cardiac arrest; nonfatal MI; nonfatal stroke; HF hospitalization; ESRD, death due to kidney disease, or doubling of the baseline serum creatinine level	Interim analysis Composite outcome: Alis: 18.3% Plac: 17.1% HR 1.08; 95% CI 0.98-1.20; p=0.12 Trial was stopped prematurely
ASSERTIVE[23] RCT, DB, DD	Aliskiren 150 mg vs. telmisartan 40mg (n=822)	Adults with hypertension and a 7-day treatment withdrawal	24 h mean ambulatory SBP after a 7-day treatment withdrawal	<u>Change in SBP:</u> Alisk: +2.7 ± 0.466 mm HG Telm: + 6.5 ± 0.461 mmHg Difference : -3.8 mmg Hg; p<0.0001 in favor of aliskiren
ARBs				
Bonner et al.[24] RCT, DB	Azilsartan vs. Ramipril	Patients with stage 1 or 2 HTN (n=884)	Change from baseline to week 24 in trough, seated, clinic SBP	<u>SBP Change from Baseline:</u> AZL 40mg: -20.6 mmHg AZL 80 mg: -21.2 mmHg RAM 10mg: -12.2 mmHg P<0.001 for both AZL doses vs. RAM 10mg
Lee et al.[25] RCT, DB, noninferiority	Amlodipine/benazepril vs. valsartan/HCTZ	Patients with DM and HTN and Microalbuminuria (n=169)	Mean change in DBP at 16 weeks	<u>Mean change in DBP:</u> Amlodipine/benazepril is noninferior to valsartan/HCTZ in blood pressure lowing (difference, -0.9 mm HG; 95% CI -3.5 to 1.6)
Rakugi et al.[26] RCT, DB	Azilsartan vs. candesartan	Japanese patients with essential HTN	Change from baseline in the sitting DBP at week 16	<u>Mean change in DBP:</u> Azil: -12.4 mmHg Cand: -9.8 mm Hg Least squares means -2.6 mm HG (95% CI -4.08 to -1.22), p=0.0003

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