

Direct Renin Inhibitors, Angiotensin Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers

Key Questions and Inclusion Criteria

Key Questions

1. For adults with diagnosed coronary heart disease, hypertension, left ventricular dysfunction, heart failure, nondiabetic chronic kidney disease, or diabetic nephropathy, what is the effectiveness and efficacy and what are the harms of aliskiren compared with placebo?
 - 1a. When used as monotherapy?
 - 1b. When used in combination with angiotensin converting enzyme inhibitor (ACE-I) and angiotensin II receptor blocker (AIIRA) drugs?
2. For adults with diagnosed coronary heart disease, hypertension, left ventricular dysfunction, heart failure, nondiabetic chronic kidney disease, or diabetic nephropathy, what are the inter-class differences in effectiveness and efficacy between direct renin inhibitor (DRI), ACE-I and AIIRA drugs?
 - 2a. When used as monotherapy?
 - 2b. When used in combination with one another?
3. For adults with diagnosed coronary heart disease, hypertension, left ventricular dysfunction, heart failure, nondiabetic chronic kidney disease, or diabetic nephropathy, what are the inter-class differences in harms between DRI, ACE-I and AIIRA drugs?
4. Are there subgroups based on demographics (age, racial groups, gender), other medications, or co-morbidities for which there are inter-class differences between DRI, ACE-I and AIIRA drugs?

Inclusion Criteria

Populations

Adults with any of the following indications:

- Diagnosed coronary heart disease (including post-myocardial infarction)
- Hypertension
- Left ventricular dysfunction
- Heart failure
- Nondiabetic chronic kidney disease, with or without proteinuria
- Diabetic nephropathy, defined as documented diabetes, with either microalbuminuria or macroalbuminuria, and any level of renal function. Trials of diabetics with normoalbuminuria will be excluded.

Excluded:

- Renal transplanation

Interventions

Drug Type	Active Ingredients	Drug Name
Direct Renin Inhibitor (DRI)	Aliskiren	Tekturna, Rasilez ^a
Angiotensin Converting Enzyme Inhibitor (ACE-I)	Benazepril	Lotensin
	Captopril	Capoten
	Cilazapril ^a	Inhibace
	Enalapril	Vasotec
	Fosinopril	Monopril
	Lisinopril	Prinivil, Zestril
	Moexipril ^b	Univasc
	Quinapril	Accupril
	Ramipril	Altace
	Perindopril	Aceon, Coversyl ^a
	Trandolapril	Mavik
Angiotensin II Receptor Blocker (ARB, A2RA)	Losartan	Cozaar
	Telmisartan	Micardis
	Candesartan	Atacand
	Eprosartan	Teveten
	Irbesartan	Avapro
	Olmesartan ^b	Benicar
	Valsartan	Diovan

^aOnly available in Canada, ^bNot available in Canada

Effectiveness/efficacy outcomes (all outcomes included for all populations)

1. All-cause mortality, cardiovascular mortality, sudden death
2. Cardiovascular events (e.g., stroke, myocardial infarction, or death or hospitalization due to heart failure)
3. Chronic kidney disease, end-stage renal function, dialysis, transplantation
4. Changes in renal function, including serum creatinine, estimated glomerular filtration rate, proteinuria and albuminuria (total amount over a 24-hour period, but not solely short-term excretion rates per minute or per hour), creatinine clearance
5. Quality-of-life
6. Symptomatic improvement in heart failure symptoms (e.g., heart failure class, functional status, visual analogue scores, exercise tolerance tests with symptom outcomes)
7. Cardiovascular hospitalizations
8. Overall withdrawals

Harms

- Numbers of adults who experienced the following:
 - ≥ 1 adverse event
 - ≥ 1 serious adverse event (i.e., life-threatening or requiring medical intervention, including hospitalization)
- Total withdrawals due to any adverse event
- Specific harms (Including, but not limited to hypotension, hyperkalemia, acute kidney injury, cough, angioedema, gastrointestinal effects) or withdrawals due to specific harms
- Harms considered to be major are those that require unanticipated and/or urgent medical treatment (including, but not limited to hypotension, hyperkalemia, acute kidney injury, angioedema)

Study designs

Effectiveness/efficacy

1. Randomized controlled trials, controlled clinical trials, and good-quality systematic reviews that:
 - a. Compared aliskiren to placebo
 - b. Made direct inter-class comparisons between individual DRI, ACE-I and AIIRA drugs. Trials that assume a class effect and only provide a comparison to a treatment group consisting of multiple AIIRA's or multiple ACEI's (e.g., don't stratify by individual AIIRA's or ACEI's) will be excluded.

Harms

1. Randomized controlled trials, controlled clinical trials, and good-quality systematic reviews included for effectiveness/efficacy outcomes that:
 - a. Compared aliskiren to placebo
 - b. Made direct inter-class comparisons between DRI, ACE-I and AIIRA drugs.
2. Large single-group or multi-group population-based cohort ($N \geq 1,000$) or case-control ($N \geq 500$ cases) studies that evaluated major harms. If none found, studies of $N \geq 200$ will be considered.