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Supplementary information

Aldosterone synthase inhibitors for the treatment of cardiovascular disease

In the format provided by the authors and unedited

Supplementary Box 1 | Available clinical evidence supporting use of aldosterone synthase inhibitors

Several aldosterone synthase inhibitors are currently being evaluated in clinical trials for cardiovascular and renal diseases.

Baxdrostat
In phase II and phase III trials in patients with resistant or uncontrolled hypertension, baxdrostat significantly reduced systolic blood pressure and suppressed aldosterone production without evidence of clinically relevant cortisol suppression.

Lorundrostat
Lorundrostat has demonstrated significant blood pressure reductions in randomized trials of patients with uncontrolled or treatment-resistant hypertension. Hyperkalaemia and mild reductions in renal function have been observed in a small proportion of some participants.

Dexfadrostat
In a randomized study of patients with primary aldosteronism, dexfadrostat reduced the aldosterone-to-renin ratio and lowered ambulatory blood pressure, suggesting effective suppression of excess autonomous aldosterone production.

Vicadrostat (BI-690517)
In patients with chronic kidney disease receiving renin–angiotensin system blockade, vicadrostat reduced albuminuria in a dose-dependent manner, although hyperkalaemia occurred more frequently at higher doses.

Ongoing studies
Large randomized trials are currently evaluating the long-term safety and cardiovascular effects of aldosterone synthase inhibition in both sexes and across multiple patient populations.

Supplementary Box 2 | Clinical development of aldosterone synthase inhibitors

Several important questions remain regarding the clinical role of aldosterone synthase inhibitors (ASIs).

Comparative efficacy
Direct comparisons between ASIs and mineralocorticoid receptor antagonists (MRAs) are currently lacking. Hence, although there are some theoretical advantages, it remains unclear whether suppression of aldosterone synthesis provides benefits over receptor blockade in terms of blood pressure control or cardiovascular protection.

Cardiovascular outcomes
Although ASIs reduce aldosterone concentrations and lower blood pressure in early trials, their effects on major cardiovascular outcomes, including myocardial infarction, stroke and heart failure events, remain to be proven.

Long-term safety
Sustained inhibition of aldosterone biosynthesis could potentially affect adrenal steroidogenesis or electrolyte balance. Although available data showed no major concerns, long-term safety data are required, particularly in subgroups of patients at high risk.

Hyperkalaemia risk
Both MRAs and ASIs increase serum potassium levels. The relative incidence and clinical implications of hyperkalaemia with MRAs are known but that with ASIs remain to be established particularly in elderly patients with decreased eGFR and/or diabetes, who are at risk of developing hyperkalaemia.

Patient selection
Identification of the patient populations most likely to benefit from aldosterone synthase inhibition — such as individuals with primary aldosteronism or chronic kidney disease or Black patients with hypertension— requires further investigation.

Combination therapy
The optimal integration of ASIs with established therapies targeting the renin–angiotensin–aldosterone system, including MRAs, ACE inhibitors, ARBs and SGLT2 inhibitors, remains to be determined.

Supplementary Box 3 | Remaining uncertainties regarding aldosterone synthase inhibition

Although early clinical studies suggest that aldosterone synthase inhibitors (ASIs) effectively suppress aldosterone production and reduce blood pressure, several important questions remain regarding their clinical role.

Prevention of clinical outcomes

Do ASIs improve cardiovascular and renal outcomes in patients with inappropriate aldosterone secretion, including those with resistant hypertension, primary aldosteronism or heart failure?

Degree of aldosterone suppression required

Do different clinical conditions characterized by absolute or relative aldosterone excess require different degrees of aldosterone inhibition to achieve optimal therapeutic benefit?

Comparative effectiveness versus MR antagonists

Are ASIs more effective, safer or better tolerated than mineralocorticoid receptor antagonists (MRAs) in patients with inappropriate aldosterone secretion?

Adverse effects

Do ASIs differ from MRAs in their propensity to cause adverse effects such as hyperkalaemia or endocrine effects related to steroid receptor cross-reactivity?

Sex differences

Is there sexual dimorphism in the clinical response or safety profile of ASIs?

Use during pregnancy

Are ASIs safe for use during pregnancy?

Combination therapy

Can ASIs be safely combined with MRAs, angiotensin II receptor blockers or sodium–glucose cotransporter-2 inhibitors?

Special clinical settings

Are ASIs safe in patients receiving non-steroidal anti-inflammatory drugs that may induce hyporeninaemic hypoaldosteronism?

Chronic kidney disease

Can ASIs be used safely in patients with advanced chronic kidney disease (stage >3)?

Correction of potassium depletion

Are ASIs superior to MRAs in correcting tissue potassium depletion in patients with primary aldosteronism?

Ethnic differences

Do the efficacy and safety of ASIs and MRAs differ across populations with different genetic or ethnic backgrounds?