A systematic review assessing the long-term effects of maintaining RAASi treatment in patients with chronic kidney disease

Mitchell, CR[a], Chen, G[b], Squirrell, D[b], Fleming, C[a], Batson, S[a]
[a]Mtech Access, Bicester, United Kingdom
[b]AstraZeneca, United Kingdom

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Introduction

Hyperkalaemia is a potentially life-threatening condition, with the risk of developing hyperkalaemia significantly increasing in patients with renal impairment, such as chronic kidney disease (CKD). The risk is further exacerbated in patients with CKD who take medications such as renin-angiotensin-aldosterone system inhibitors (RAASi) which can also increase potassium levels in the blood [1, 2].

RAASi therapies are the cornerstone treatment for patients with CKD, however due to the association with hyperkalaemia, RAASi therapies are often down-titrated or discontinued in response to a hyperkalaemic episode [3].

RAASi therapies offer cardio-renal protective benefits in patients with CKD and whilst the down-titration or discontinuation of RAASi is effective in resolving the hyperkalaemic episode, patients may lose the important cardio-renal benefits of RAASi therapy. There is therefore an unmet need for new treatment approaches for hyperkalaemia, to allow effective management of elevated potassium levels whilst allowing patients with CKD to continue RAASi therapy.

The purpose of this systematic review (SR) was to answer the following questions:

What are the long-term clinical effects (cardiovascular [CV] events, mortality, hospitalisation) when patients with CKD with concomitant hyperkalaemia discontinue or down titrate RAASi?

What are the long-term clinical benefits (CV events, mortality, or hospitalisation) of taking RAASi therapies in patients with CKD?

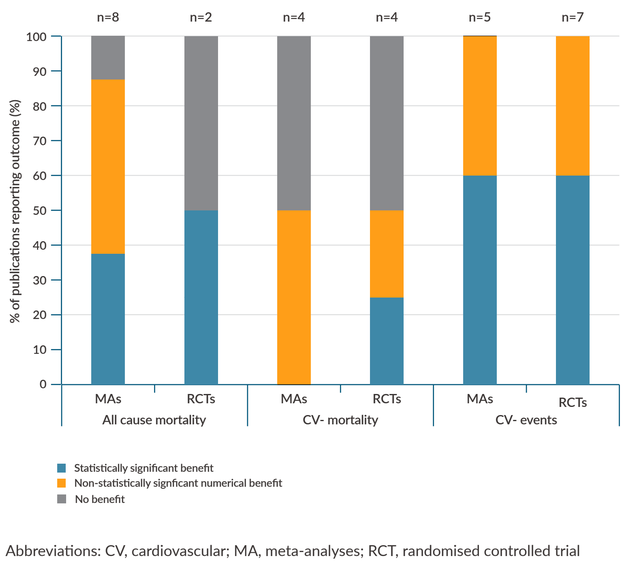
What are the long-term disease progression benefits of taking RAASi in patients with CKD?

Methods

- MEDLINE®, MEDLINE® In-Process, Embase and The Cochrane Library were interrogated on 14th January 2019
- Results from the searches were downloaded into an Excel database and citations were screened for eligibility by two analysts at title/abstract and full publication review stages
- References were deemed relevant if they investigated the outcomes of RAASi treatment assessed in randomised controlled trials (RCTs) or SR/meta-analyses conducted in adult patients with CKD or diabetic nephropathy and were published in English from 1998 onwards. Non-RCT publications reporting the effects of RAASi down titration, withdrawal, or dose response were also eligible
- Outcomes assessed were CV events, mortality, hospitalisation and measures of disease progression (e.g. change in glomerular filtration rate [GFR] and progression to end stage renal disease [ESRD])

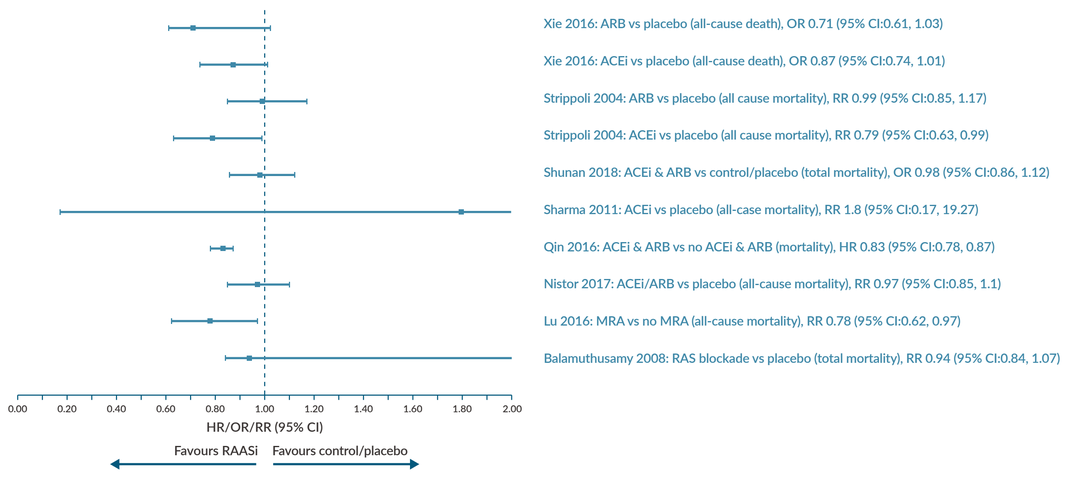
Results

Figure 1: Publications reporting the effects of RAASi treatment compared with placebo on long term outcomes in patients with CKD (n=total number of publications reporting outcome)



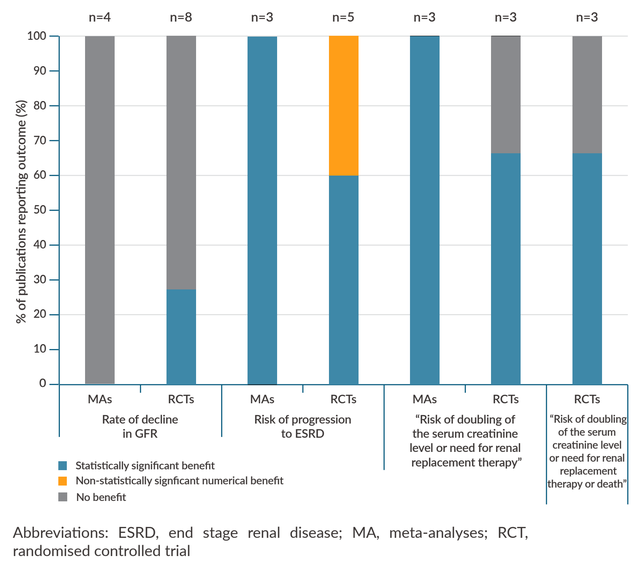
Abbreviations: CV, cardiovascular; MA, meta-analyses; RCT, randomised controlled trial

Figure 2: Forest plot of the risks reported across the meta-analyses for all-cause mortality in CKD for the comparison of RAASi versus placebo/control. Note that the forest plot includes mixed measures of relative treatment effect due to inconsistent reporting of measures of treatment effect across the meta-analyses identified



Abbreviations: ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; HR, hazard ratio; MRA, mineralocorticoid receptor antagonist; OR, odds ratio; RAS, renin-angiotensin system; RR, risk ratio

Figure 3: Publications reporting the effects of RAASi treatment compared with placebo on disease progression in patients with CKD (n=total number of publications reporting outcome)



Abbreviations: ESRD, end stage renal disease; MA, meta-analyses; RCT, randomised controlled trial

- In total, 57 references met the inclusion criteria [4-60].

What are the long-term clinical effects when patients with CKD with concomitant hyperkalaemia discontinue or down titrate RAASi?

One study was identified that addressed this research question [7]

Mortality risk (n=1)

RAASi discontinuation was associated with increased mortality risk among CKD patients compared with CKD patients who continued treatment [7]

What are the long-term clinical effects when patients with CKD discontinue or down titrate RAASi?

One study was identified that addressed this research question [17]

Composite endpoint "doubling of serum creatinine, ESRD, or death" (n=1)

Treatment with a low versus high dose of RAASi significantly increased the risk of this composite endpoint [17]

What are the long-term clinical benefits of taking RAASi in patients with CKD? (Figure 1)

Seven RCTs [8, 21, 38, 42, 47, 48, 52] and ten meta-analyses [5, 25, 34, 35, 41, 46, 53, 55, 56, 59] addressed this research question

All-cause mortality (n=10) (Figure 2)

RAASi therapy statistically significantly reduced the risk of all-cause mortality in 3/8 (38%) meta-analyses [34, 46, 56] and a further 4/8 (50%) reported a non-statistically significant numerical benefit of RAASi [5, 41, 55, 59] compared with placebo. One of two (50%) RCTs examining this endpoint reported that the risk was significantly reduced with RAASi compared with placebo [21] (Figure 2). Two publications reported no benefit of RAASi therapy on all-cause mortality compared with placebo [38, 53]

CV mortality (n=8)

There was a numerical reduction in risk of CV mortality in patients treated with RAASi therapies compared with placebo in 2/4 (50%) meta-analyses [5, 59]. For RCTs 1/4 (25%) showed a statistically significant reduction in risk of this endpoint [21] and 1/4 (25%) showed a numerical reduction [42] compared with placebo. No beneficial effects of RAASi therapy on CV mortality was observed in four studies compared with placebo [8, 38, 41, 55]

CV events (n=12)

RAASi therapy reduced the risk of CV events compared with placebo either statistically significantly in 3/5 (60%) meta-analyses [5, 55, 59] or numerically in 3/5 (40%) meta-analyses [41, 53]. For RCTs, this result was statically significant in 3/7 (43%) studies [8, 47, 52] and numerically positive in two studies [21, 38]. Two RCTs reported no beneficial effects of RAASi therapy on CV events compared with placebo [42, 48]

What are the long-term disease progression benefits of taking RAASi in patients with CKD? (Figure 3)

Twenty seven RCTs [4, 6, 9, 11, 13, 16, 18-20, 22, 23, 26, 28, 30-32, 36, 39, 43, 45, 49-51, 54, 57, 58, 60] and 12 meta-analyses [10, 12, 14, 15, 24, 27, 29, 33, 37, 40, 41, 44] addressed this research question

Risk of progression to ESRD (n=8)

RAASi statistically significantly reduced the risk of patients progressing to compared with placebo in 3/3 (100%) of meta-analyses [27, 33, 44] and in 3/5 (60%) RCTs [11, 13, 50]. A numerical reduction in risk was observed in 2/5 (40%) RCTs [32, 60]

Composite endpoint "risk of doubling of the serum creatinine level or need for renal replacement therapy" (n=6)

RAASi statistically significantly reduced the risk of this composite measure of disease progression compared with placebo in 3/3 (100%) of meta-analyses [27, 29, 41] and 2/3 (33%) of RCTs [39, 60]. One RCT publication reported no beneficial effect of RAASi on this outcome compared with placebo [57]

Composite endpoint "doubling of the serum creatinine level or need for renal replacement therapy or death" (n=3)

RAASi statistically significantly reduced the risk of this composite measure of disease progression compared with placebo in 2/3 (67%) of RCTs [23, 32]. One RCT publication reported no beneficial effect of RAASi on this outcome compared with placebo [18]

Rate of decline in GFR (n=12)

RAASi therapy statistically significantly reduced the rate of decline in GFR compared with placebo in 3/8 (38%) of identified RCTs [9, 13, 23]. No beneficial effects were observed compared with placebo in the other five RCTs [31, 50, 57, 60, 61] or in any of the four identified meta-analysis publications that reported on this endpoint [24, 33, 41, 62]

Summary and conclusions

- The current study provides a comprehensive review of the published evidence on the effects of RAASi therapy on clinically meaningful outcomes in patients with CKD.
- There was a paucity of data:
  - for the long-term clinical effects when patients with CKD with concomitant hyperkalaemia discontinue or down titrate RAASi, however one study reported that RAASi discontinuation was associated with increased mortality risk [7].
  - regarding down titration/dose response of RAASi in patients with CKD, however one RCT publication reported that low versus high dose of RAASi significantly increased the risk of the composite endpoint "doubling of the serum creatinine, ESRD, or death" [17].
- The majority of the evidence identified supported the use of RAASi in CKD to improve long-term clinical outcomes. There is evidence that RAASi therapy reduces the risk of all-cause mortality and CV events as the majority of studies identified reported either a statistically significant or a numerical benefit with RAASi treatment compared with placebo, although the effects of RAASi treatment on the risk of CV mortality were not conclusive.
- Data from the literature overwhelmingly reported that RAASi therapy significantly delayed disease progression onset of ESRD in patients with CKD and reduced the risk of CV-related outcomes and composite endpoints versus placebo. However, only a small number of the identified studies showed RAASi therapy to significantly reduce the rate of eGFR decline.
- The outcomes of this systematic review provide evidence to support the value of new therapies for the long-term management of hyperkalaemia in CKD patients to treat RAASi-induced hyperkalaemia and to enable patients to continue guideline-recommended RAASi therapies.

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