

# openheart Angiotensin receptor blockers for prevention of cardiovascular disease: where does the evidence stand?

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## ABSTRACT

Angiotensin receptor blockers (ARBs) are the most commonly used among blood pressure-lowering drugs worldwide, despite the absence of sound evidence of effectiveness in large and unbiased clinical trials. Meta-analyses published in recent years and reviewed here have not given support to this preference, suggesting that ARBs may be ineffective in the prevention of all cause mortality and major cardiovascular events (particularly myocardial infarction). There is evidence that ARB can be harmful for the kidney, particularly in patients with diabetes and in the elderly. It may be time to call for a moratorium on the preference for ARB in the management of hypertension and in patients with high cardiovascular risk.

Angiotensin receptor blockers (ARBs) are the most commonly used blood pressure-lowering drugs in the world. Nonetheless, the results of large trials and meta-analyses published in recent years and reviewed here have not given support to this preference, suggesting that they may be ineffective in the prevention of all cause mortality and major cardiovascular (CV) events (particularly myocardial infarction). Moreover, there is evidence that ARBs can increase the incidence of acute kidney damage, particularly in patients with diabetes and in the elderly. It may be time to call for a moratorium on the preference for ARB in the management of hypertension and in patients with high cardiovascular risk.

In a descriptive review, we identified that ARBs were ineffective in preventing CV outcomes in seven large placebo-controlled trials in patients with high CV risk.<sup>1</sup> In five of these studies, the treatment with an ARB was not superior to placebo in the prevention of major CV events,<sup>2–6</sup> and in two there was higher CV mortality in patients treated with an ARB instead of placebo.<sup>7 8</sup> Moreover, treatment with ARBs was associated with worse renal outcomes in some trials, such as increased incidence of microalbuminuria,

renal impairment and decreased glomerular filtration rate.<sup>6 7 9–11</sup> The presumptive efficacy of ARB in the prevention of atrial fibrillation was not confirmed by four large studies specifically designed to investigate this effect.<sup>6 12–14</sup>

Four meta-analyses of these and other trials converged in the identification of lack of effectiveness of ARBs in the prevention of major cardiovascular outcomes. The first explored the efficacy of ARBs in the prevention of myocardial infarction and other CV outcomes.<sup>15</sup> Patients had various criteria for enrolment in the trials included in this meta-analysis, such as hypertension, heart failure, diabetes, stroke, atrial fibrillation and others. In total, 37 randomised clinical trials (RCTs), with 147 020 participants, were evaluated. When compared with placebo or active treatment, ARBs were ineffective in the prevention of myocardial infarction (relative risk (RR) 0.99, 95% CI 0.92 to 1.07), death, cardiovascular death or angina pectoris. Compared with controls, ARBs were associated with a reduction in the risk of stroke, heart failure and new onset diabetes.

The second meta-analysis investigated the efficacy of renin–angiotensin–aldosterone system (RAAS) inhibitors over CV morbidity–mortality trials.<sup>16</sup> The trials should have at least two-thirds of patients with hypertension. The meta-analysis included 158 998 patients. RAAS inhibition either with ACE inhibitors (ACEi) or ARB was associated with a 5% reduction in all-cause mortality (RR 0.95, 95% CI 0.91 to 1.00) and a 7% reduction in CV mortality (RR 0.93, 95% CI 0.88 to 0.99). When the trials were divided by the class of RAAS inhibitor, the effect was identified to be entirely due to ACEi (RR 0.90, 95% CI 0.84 to 0.97). Treatment with an ARB had no effect in the prevention of all-cause mortality (RR 0.99, 95% CI 0.94 to 1.04).

Another meta-analysis explored the efficacy of ACEi and ARB in the prevention of



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cardiovascular disease (CVD) in patients with diabetes and hypertension.<sup>17</sup> Compared to placebo or other active treatment, in 23 studies with 32 827 patients with diabetes, ACEi significantly reduced the risk of all-cause mortality by 13% (RR 0.87; 95% CI 0.78 to 0.98), the incidence of CV deaths by 17% (0.83; 0.70 to 0.99), major CV events by 14% (0.86; 0.77 to 0.95), including myocardial infarction by 21% (0.79; 0.65 to 0.95) and heart failure by 19% (0.81; 0.71 to 0.93). In contrast with the effectiveness of ACEi, ARBs were ineffective in reducing the risk for all-cause mortality (RR 0.94; 95% CI, 0.82 to 1.08) in 13 studies controlled by placebo or other active treatment, with a total of 23 867 patients with diabetes. With the exception of a reduction in the risk of heart failure (0.70; 0.59 to 0.82), ARBs were ineffective in the prevention of CV death (1.21; 0.81 to 1.80) and major CV events (0.94; 0.85 to 1.01).

A fourth meta-analysis addressed the efficacy and safety of ARB in elderly patients, in comparison with active and placebo comparators.<sup>18</sup> A total of 113 386 participants were included. The incidence of all-cause mortality and myocardial infarction were higher and marginally significant in participants treated with ARB (RR 1.03, 95% CI 1.00 to 1.06 and 1.04, 95% CI 0.96 to 1.12, respectively). Stroke and heart failure were less frequent in patients treated with an ARB. Hypotension and hyperkalemia were more common with ARB. A more striking result, however, was the 48% increase in the risk of acute kidney injury (95% CI from 24% to 97%). This risk was similar to the risk described in individual studies.<sup>1</sup>

The only study where an ARB was superior to the comparator was the LIFE trial.<sup>19</sup> This study compared losartan with atenolol, a  $\beta$ -blocker known to be ineffective in the prevention of cardiovascular events in elderly patients.<sup>20</sup> Additionally, despite the fact that losartan significantly reduced stroke compared to atenolol, there were fewer patients with atrial fibrillation, tobacco use and isolated systolic hypertension at baseline in the losartan arm, giving an unfair advantage—specifically to the stroke end point—that achieved significance.<sup>21</sup> The possibility that the LIFE trial is an outlier was demonstrated in the meta-analysis of patients with diabetes.<sup>17</sup> In the analysis with an active control group, the large heterogeneity ( $I^2=49\%$ ) was mainly derived from the LIFE study. After excluding the LIFE study, heterogeneity and a trend for efficacy of ARB disappeared ( $I^2=0\%$ ; RR 0.96; 95% CI 0.77 to 1.20).

It is hard to explain how ARBs have reached such a high level of preference in the treatment of hypertension worldwide, in the face of this overwhelming volume of evidence demonstrating that they are probably ineffective in the prevention of all-cause mortality and many manifestations of CV disease. The excessive valorisation of the first studies performed with these drugs, which investigated surrogate outcomes and were underpowered to evaluate the effects over hard outcomes, may have originated the misconception about their efficacy. The

basic research was oriented to the investigation of mechanisms of action and effects of these drugs, and the number of manuscripts describing favourable effects of ARBs on experimental models is uncountable. The massive commercial promotion of ARBs also had a key role in the establishment of this preference. Many scientists and opinion leaders worked towards helping pharmaceutical companies to proclaim the superiority of ARBs over traditional blood pressure-lowering drugs, despite the absence of head-to-head comparisons with diuretics in large RCTs. In addition, three RCTs published in influential journals, which had showed very favourable effects of ARB, were recently retracted because of scientific fraud.<sup>22–24</sup>

The guidelines for the management of hypertension, led mostly by the same opinion leaders, share the recommendation that ARBs should be the first options to treat hypertension, particularly in patients with diabetes and renal disease.<sup>25–27</sup> These almost homogeneous recommendations surely had a major role in the generation of the common belief about the superiority of ARBs. And finally, doctors contributed to this preference, since in the daily clinical practice they perceived that these drugs were well tolerated (ie, ‘ACEi without the cough’) and could not obviously perceive their inefficacy to prevent CV outcomes. In the face of frequent unsatisfactory blood pressure control with an ARB alone, diuretics used to be added to the ARB to get better blood pressure response.

The preference for ARBs is not supported by evidence in the literature and may be denying patients the benefits of being treated with proven blood pressure-lowering agents. It may be time to call for a moratorium on the preference for ARBs in the prevention of CVD in patients with hypertension or diabetes.

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