Cardiol Ther (2025) 14:117–121
https://doi.org/10.1007/s40119-025-00399-4

COMMENTARY

ACE Inhibitors and Angiotensin Receptor Blockers for the Prevention of Cardiovascular Outcomes: Recommendations from the 2024 Egyptian Cardiology Expert Consensus

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Received: December 18, 2024 / Accepted: February 5, 2025 / Published online: February 18, 2025
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Keywords: Angiotensin-converting enzyme inhibitors; Angiotensin receptor blockers; Cardiovascular outcomes; Hypertension; Randomised controlled trials; All-cause mortality; Guidelines

COMMENTARY

In 1990 a meta-analysis of 17 blood pressure (BP)-lowering trials showed the clear benefits of diuretics and beta-blockers (or both) in preventing major adverse cardiovascular (CV) events [1]. Thereafter, randomised control trial (RCT) evidence on calcium channel blockers (CCBs) began to emerge. By the end of the 1990s evidence to support the use of short-acting angiotensin-converting enzyme (ACE)-inhibitors in clinical practice emerged, initially via the somewhat flawed CAPPP [2] and ANBP2 trials [3]. Shortly thereafter, RCT evidence of the renal benefits of angiotensin receptor blockers (ARBs) drew attention via three papers in one edition of the *New England Journal of Medicine* [4–6]. The benefits of ARBs on CV events was first shown in the LIFE trial [7] in which losartan (±a thiazide) was superior to atenolol (±a thiazide) by reducing stroke but not coronary events more effectively. Although initially marketed as being very different from ACE inhibitors, the ARBs were considered by many clinicians as ACE inhibitors without a cough.

Since the beginning of this century, the superiority of ACE inhibitors or ARBs has been hotly debated. This debate included publications purporting to show that ARBs caused myocardial infarction [8] and others showing that ACE inhibitors and ARBs caused cancer [9, 10]. None of these findings now seem likely!

For the last two decades renin–angiotensin system (RAS) blockers have for many become the cornerstone of antihypertensive therapy for most patients as more RCTs involving ACE inhibitors (e.g. ALLHAT [11], HOPE [12], ASCOT [13], PROGRESS [14]) and ARBs (e.g. VALUE [15], TRANSCEND [16], ROADMAP [17]) were delivered.

Overall, the RCT data often appeared to favour ACE inhibitors over ARBs when like-for-like RCTs were compared (HOPE [12] vs TRANSCEND [16], ADVANCE [18] vs ROADMAP [17], PROGRESS [14] vs PROFESS [19]) but the only large head-to-head comparison, the ONTARGET trial [20], showed that the long-acting ARB telmisartan was overall equally effective at preventing CV events as the shorter-acting ACE inhibitor ramipril. It may be that the significantly greater 24-h BP reduction achieved by

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the ARB in this trial mitigated against the usual superiority of the ACE inhibitor in terms of CV prevention.

For many years and in keeping with these RCT data, most guidelines, particularly in relation to subgroups of hypertensive patients (post-stroke [21], chronic coronary syndromes [22], chronic kidney disease [21], diabetes [23]), recommended the preferential use of ACE inhibitors over ARBs. Furthermore, several meta-analyses comparing the impact of ACE inhibitors and ARBs on all cause-mortality in various subgroups of patients (hypertension [24], diabetes [25], coronary artery disease [26] and high-risk patients [27]) have shown no benefit with ARBs but significant beneficial effects with ACE inhibitors. Nonetheless, in more recent years and particularly in the major hypertension guidelines, the two drug classes are considered equivalent in terms of likely benefit [28–30].

Following a workshop in Egypt in 2020 focusing on which RAS blocker to use in the management of hypertension, a group of 36 Egyptian consultant cardiologists in collaboration with the CVREP Foundation decided to carry out an independent review of available data to decide for themselves what optimal practice should be concerning the choice between ACE inhibitors and ARBs.

A consensus was developed based on the three-step modified Delphi method all of which is carefully described in the accompanying article summarising their findings [31].

The authors are in agreement (>80% voting threshold) on all 11 topics addressed starting with the differential effects of ACE inhibitors and ARBs on physiological mechanisms. They report that these physiological differences are compatible with the preferential outcomes associated with the use of ACE inhibitors compared with ARBs on various primary and secondary CV events and among special populations, each of which was investigated by one of 13 working groups.

Given the strong preference for the use of ACE inhibitors identified in this consensus report, why would several major contemporary guidelines [28–30] give equal weighting to the two major classes of RAS blockers compared? Several possible reasons may be relevant. Most importantly the trial ON-TARGET trial [20] showed that telmisartan and ramipril produced equivalent CV benefits overall, although the longer-acting ARB generated significantly better 24-h BP reduction than the shorter-acting ramipril. Less persuasive arguments include the fear of cough, which is undoubtedly more common in association with ACE inhibitors. Surely, this should not hold sway if there are differential effects of the two drug classes on major CV events.

Concerns are also raised over the higher rate of angioedema associated with ACE inhibitors particularly among Black patients, but the low rates of these events [32] particularly in the context of differential benefits on all-cause mortality in favour of ACE inhibitors over ARBs suggest that these concerns are exaggerated.

Potentially worrisome is the influence of differential marketing by the pharmaceutical industry because the workforce promoting ARBs is several times greater than that promoting ACE inhibitors. Relative sales of these classes vary around the world, but ARBs predominate despite being more expensive in many parts of the world.

It is hard to believe that those responsible for producing contemporary hypertension guidelines are inappropriately biased by any of these arguments, but the 'fear' of cough seems to be the most likely culprit for what appears to be a less than objective view of the relative CV benefits of the two drug classes.

One key message arising from the exercise undertaken by the Egyptian experts is that perhaps other groups around the world might wish to evaluate in an impartial, rigorous way which RAS blocker to use in their environment and based on the best available data.

Given the huge cost of untreated and inadequately treated hypertension around the world, such a project is likely to be cost-effective.

Author Contributions. Neil Poulter wrote and revised this work as the sole author.

Funding. No funding or sponsorship was received for this study or publication of this article.

Declarations

Conflict of Interest. Neil Poulter has received financial support from several pharmaceutical companies which manufacture BP-lowering agents, for consultancy fees (Servier, Aktiia), research projects and staff (Servier, Pfizer) and for arranging and speaking at educational meetings (AstraZeneca, Lri Therapharma, Napi, Servier, Sanofi, Eva Pharma, Pfizer, Emcure India, Dr Reddy's Laboratories and Zydus). He holds no stocks and shares in any such companies.

Ethical Approval. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by the author.

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