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EDITORIAL

Angiotensin-converting enzyme inhibitors: first-line agents in cardiovascular protection?

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This editorial refers to 'Angiotensin-converting enzyme inhibitors reduce mortality in hypertension: a meta-analysis of randomized clinical trials of renin–angiotensin–aldosterone system inhibitors involving 158 998 patients'†, by L.C. van Vark *et al.*, on page 2088

The renin-angiotensin-aldosterone system (RAAS) is essential for the regulation of blood pressure, cardiovascular and renal function. Drugs inhibiting the RAAS, particularly angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs), represent the cornerstone of blood pressure control and considered key components of the modern comprehensive management of cardiovascular disease.[1]

In essential hypertension, utilization of ACE inhibitors and ARBs is based on their effectiveness of lowering blood presssure, high tolerability, and the possibility to prevent or reverse target organ damage. Importantly, controlled clinical trials have demonstrated that these drugs can reduce cardiovascular morbidity and mortality.[1] ACE inhibitors and ARBs, however, differ in their mechanisms of action and also their effectiveness in reducing clinical, particularly cardiovascular outcomes, and can therefore not be viewed as interchangeable.

The study by van Vark *et al.*[2] demonstrates the following important findings: (i) in hypertensive patients, RAAS blockade is associated with a significant reduction of all-cause mortality; (ii) but this benefit is limited to ACE inhibitors and not shared by ARBs.

The present results are not surprising, as they confirm and extend previous reports indicating that ACE, but not ARBs, reduce cardiovascular morbidity and mortality.

In a recent meta-analysis of 11 trials (55 050 patients) by Strauss and Hall that compared ARBs with either placebo or active treatments, only stroke was less likely in patients treated with ARBs than in those receiving a comparator.[3] Their benefit in reducing stroke notwithstanding, ARBs did not reduce total mortality, but increased the risk of myocardial infarction (MI) by 8% [95% confidence interval (CI) 1–16%; $P = 0.03$]. The same authors also conducted parallel analyses for ACE inhibitors,[3] demonstrating that ACE inhibitors decreased overall mortality, cardiovascular death, and MI by 9, 12, and 14%, respectively. In all cases, and in contrast to the ARB analyses, the differences were strongly statistically significant.[3]

The BPLTTC (Blood Pressure Lowering Treatment Trialists' Collaboration)[4] assessed the blood pressure-dependent and -independent effects of ACE inhibitors and ARBs on major cardiovascular events in patients with hypertension, diabetes, a history of coronary heart disease, or cerebrovascular disease in a meta-regression analysis of data from 26 trials involving either drug class.[4] The authors reported similar blood pressure-dependent effects of ACE inhibitors and ARBs for the risk of stroke, coronary heart disease, and heart failure. In terms of blood pressure-independent effects, however, only ACE inhibitors were associated with a significant additional relative risk reduction for major coronary disease events of 9% ($P = 0.004$).

A 2009 meta-analysis of studies included in the BPLTTC analysis as well as more recent ARB trials provided a database of ~100 000 patients from 26 randomized non-heart failure trials of ARBs.[5] The authors observed a 13% reduction in the risk of stroke ($P = 0.022$), but a trend toward increased risk of MI, especially when compared with active treatment ($P = 0.06$).

A 2011 meta-analysis included all randomized clinical trials comparing ARBs with controls (placebo or active treatment)[6], with a total of 37 randomized trials and >147 000 patients. When compared with controls, ARBs were not found to be associated with a reduction in risk of MI [relative risk (RR) 0.99; 95% CI 0.92–1.07]. There was also no detectable beneficial effect for the outcome of MI in trials comparing ARBs vs. placebo (RR 0.93; 95% CI 0.81–1.07), as well as for the outcome of all-cause or cardiovascular death, despite lower blood pressure with ARBs. When compared with active treatment, the relative risk of MI with ARBs was 1.04 (95% CI 0.98–1.11), while all-cause and cardiovascular death were also not reduced.[6]

The ESH/ESC hypertension guidelines published back in 2007 stated that all classes of antihypertensive drugs should be potentially

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considered as first choice.[1] However, guidelines also indicate that ACE inhibitors have more compelling indications as compared with ARBs, indirectly supporting a greater beneficial effect of one drug class as compared with the other. It is worth noting that the only indication specific for ARBs is the cough caused by the ACE inhibitors.

Importantly, ACE inhibitors and ARBs have a different mechanism of action. The inhibition of bradykinin degradation exerted by ACE inhibitors is often considered an 'adjunctive' mechanism with a limited clinical significance. This view should be partially corrected, since for most ACE inhibitors the ability to block the ACE site responsible for bradykinin degradation is almost the same as the activity on the site responsible for the conversion of angiotensin I into angiotensin II.[7] If we consider the potential effect of bradykinin on the cardiovascular system, it is conceivable that this pathway might be at least partially responsible for many effects of ACE inhibitors usually attributed to RAAS blockade. In hypertensive patients, bradykinin can act on the endothelium by a nitric oxide (NO)-independent pathway, possibly by the activation of endothelium-derived hyperpolarizing factors.[8] Through this compensatory mechanism, bradykinin can evoke endothelium-dependent relaxation or tissue plaminogen activator release, even in the presence of impaired NO availability, an effect not shared by other endothelial agonists, including acetylcholine.[8] It is not surprising that in comparative studies in patients with hypertension or coronary artery disease, ACE inhibitors, but not ARBs, can improve endothelial function in large arteries.[9,10]

In contrast, ARBs act biologically via a selective blockade of the angiotensin II type 1 receptor (AT1), leaving the other angiotensin receptors relatively unopposed. When ARBs were introduced into clinical practice in 1995, they were expected to lead to similar, if not greater, blood pressure-lowering effects than ACE inhibitors, which do not interfere at the receptor level, but rather reduce the formation of angiotensin II (and the breakdown of bradykinin).

Importantly, as a consequence of the AT1 receptor blockade by ARBs, angiotensin II levels increase several fold through uncoupling of the negative feedback mechanism. The increased levels of angiotensin II lead in turn to unopposed stimulation of unopposed AT2 receptors. Although it has been proposed that the stimulation of AT2 receptors mediates vasodilatation and NO release,[11] which would be potentially beneficial, more recent data suggest that AT2 stimulation may also be involved in promoting vascular growth, inflammation, and fibrosis.[11] Indeed, overexpression of the AT2 receptor in human cardiac myocytes leads to cardiac hypertrophy,[12] whereas AT2 receptor-deficient mice appear to be protected against cardiac hypertrophy.[13] Interestingly, unopposed stimulation of the AT2 receptor by ARBs has been put forward by Strauss and Hall as a potential explanation for the so-called sartans paradox, i.e. the increase of MI associated with the use of ARBs.[3]

Finally, van Vark *et al.* correctly comment that ONTARGET and DETAIL, the only two large-scale clinical trials comparing an ACE inhibitor vs. an ARB, performed in patients with high cardiovascular risk and diabetic nephropathy, respectively, showed no difference between these drug classes. It should however be emphasized that in both studies telmisartan showed a greater blood pressure reduction as compared with ramipril in ONTARGET[14] and enalapril in DETAIL.[15] Of note, in the recently published Randomized Olmesartan and Diabetes Microalbuminuria Prevention (ROADMAP) trial,[16] the ARB was associated with a delayed onset of microalbuminuria, but this benefit came at the cost of an excess of fatal cardiovascular events among patients with pre-existing coronary heart disease (15 cardiovascular deaths in patients randomized to olmesartan, compared with a total of three cardiovascular deaths in the control group).

Since the goal of hypertension management must be the reduction of cardiovascular morbidity and total mortality and not only of surrogates of evidence, such as blood pressure and proteinuria, particular attention should be paid to the choice of agent in high-risk hypertensive patients. As such, the results of recent clinical trials and meta-analyses indicating that treatment with ACE inhibition, but not with ARBs, leads to a statistically significant further reduction in mortality in hypertensive patients, provide further evidence that ACE inhibitors should be considered the drugs of first choice and ARBs should be restricted to patients intolerant of ACE inhibitors. Given the high prevalence of hypertension in populations worldwide, this may result in a considerable number of lives saved.

Conflict of interest: F.R. has disclosed industry relationships with Aventis, Bayer, Biotronik, Cardiorentis, Merck & Company, Novartis, Pfizer, Roche, Servier, and St Jude Medical. S.T. has disclosed industry relationships with Boheringer, Novartis, Pfizer, Recordati, Roche, Servier, and Takeda.

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CARDIOVASCULAR FLASHLIGHT

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Huge left atrial thrombus after left atrial appendage occlusion with a Watchman device

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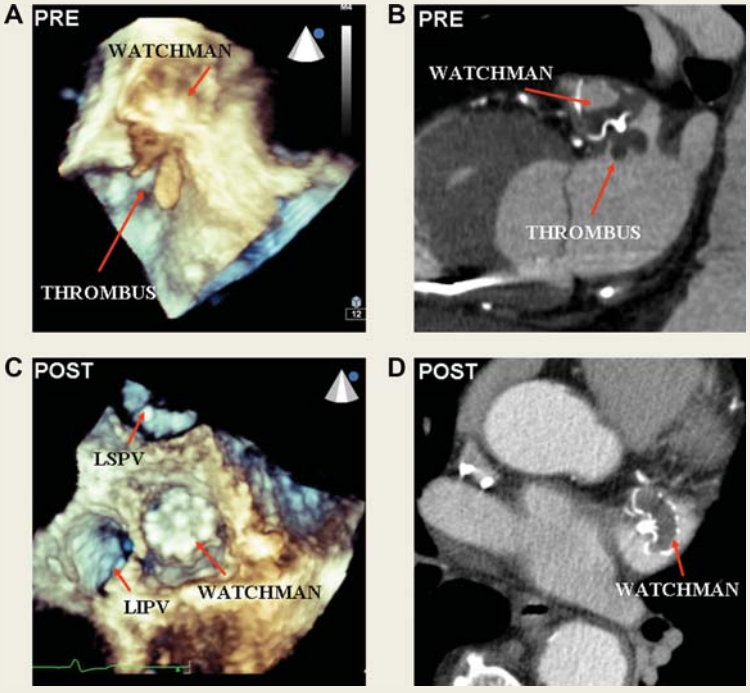
The feasibility and safety of transcatheter left atrial appendage occlusion with the Watchman™ Device (Atritech Inc., Plymouth, MN, USA) for stroke prevention in atrial fibrillation (AF) has recently been described. To our knowledge, a case of huge thrombus formation on the external surface of this device has not been described so far.

A 78-year-old man with permanent AF suffered from cerebral haemorrhage while on oral anticoagulation therapy; after 2 months, he was undertaken to an uneventful left atrial appendage occlusion using a 33 mm-sized Watchman™ device. The patient was discharged on oral anticoagulant, but the therapeutic target was difficult to be kept. After 2 months, a transoesophageal echocardiogram showed the presence of a big, floating, stalked thrombus on the atrial side of the Watchman device, apparently originating from the screw's lodging (*Panel A*). The finding was confirmed by computed tomographic (CT) imaging (*Panel B*). Oral anticoagulation therapy was associated with low-molecular-weight heparin for 2 more months with an INR target of 3–3.5. The patient remained completely asymptomatic, without any neurological event. A transoesophageal echocardiogram and CT scan were then repeated and demonstrated the complete resolution of the left atrial thrombus (*Panels C* and *D*). Thus, anti-platelet therapy was initiated.



It is interesting to point out how the stalked thrombus seems to arise from the screw's threads, the only part of the device uncovered by nitinol, which could represent a potential pro-thrombotic source.

Panels A and *B*. Transoesophageal echo and computed tomographic scan of the huge left atrial thrombus on the Watchman™ device, respectively. *Panels C* and *D*. Transoesophageal echo and computed tomographic scan of thrombus resolution, respectively.