New analysis of LIFE trial shows reduction of new-onset atrial fibrillation with losartan

A new analysis of the LIFE study has shown that losartan can reduce new-onset atrial fibrillation in hypertensive patients with left ventricular hypertrophy. General practitioner Brian Crichton summarises this new analysis and explains how losartan might achieve these effects.

Introduction

Drug intervention in hypertension has been shown to have well-proven benefits, particularly in high-risk individuals.[1] But patients who have been treated for hypertension still have significantly higher rates of hypertension-related cardiovascular complications than people without hypertension.[1]

Researchers believe that this might be the result of failure to achieve normal blood pressure and/or residual target organ damage such as left ventricular hypertrophy (LVH).[1]

The Losartan Intervention for Endpoint reduction (LIFE) trial showed that a losartan-based regimen reduced the risk of combined cardiovascular morbidity and death better than an atenolol-based regimen for similar reductions in blood pressure. In addition, losartan produced a greater reduction (25%) in the rate of fatal and non-fatal stroke.[1]

Latest analyses

In a new analysis of the LIFE study, published earlier this year in two papers in the *Journal of the American College of Cardiology*, researchers published the results of a study comparing the effects of losartan and atenolol on new-onset atrial fibrillation (AF).[2,3]

The aim of the study was to evaluate whether different antihypertensive treatment regimens with similar blood pressure reduction have different effects on new-onset AF.[2]

In the LIFE study, 9,193 hypertensive patients with LVH were randomised to once-daily losartan- or atenolol-based antihypertensive therapy. For the new-onset AF study, 8,851 patients without AF by electrocardiogram or history, with documented sinus rhythm, and thus at risk of developing AF, were followed for 4.8 +/- 1.0 years.[2]

The analysis was based on a primary composite end point which was the first occurrence of cardiovascular death, fatal or non-fatal stroke, and fatal or non-fatal myocardial infarction (MI). Additional end points included all-cause mortality and the first occurrence of each component of the composite end point, whether or not preceded by another component of the primary end point, including 380 cardiovascular deaths, 485 strokes and 367 MIs.[2]

In a second analysis,[3] the investigators assessed the impact of antihypertensive treatment in hypertensive patients with electrocardiographic LVH and a history of AF. As part of the LIFE study, 342 hypertensive patients were assigned to losartan- or atenolol-based therapy for 1,471 patient years of follow-up.[3]

> ***'Losartan could have parallel effects on atrial and ventricular hypertrophy'***
>
> Brian Crichton

The primary composite end points were the first occurrence of cardiovascular death, fatal or non-fatal stroke, and fatal or non-fatal MI. Patients with multiple end points were counted as having had an event in all relevant end point analyses, but only the first event in a specific category counted in any individual analysis.[3]

Results

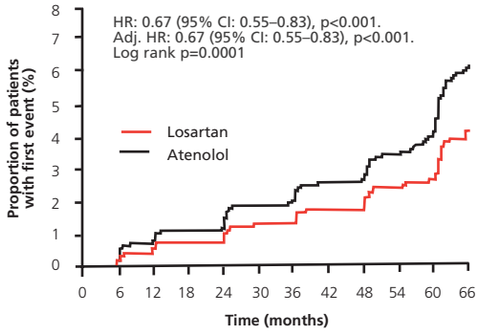
Losartan reduced the rate of new-onset AF by 33% (figure 1), which surprised investigators as many clinicians regard beta blockade as the first-line therapy to prevent AF as well as preferred treatment for rate-control in established AF. In addition, patients receiving losartan-based therapy tended to stay in sinus rhythm longer.[2]

The analysis showed that 150 patients on losartan developed new-onset AF, compared with 221 patients taking atenolol. Patients with new-onset AF had an approximately three times higher risk of fatal or non-fatal stroke, and double the risk of cardiovascular morbidity and mortality, which highlights the importance of preventing AF.[2]

The investigators said that, as far as they were aware, the results were the first to show that one antihypertensive regimen is more effective than another with equal blood pressure reduction in reducing new-onset AF.[2]

In patients with pre-existing AF, losartan-based antihypertensive therapy was more effective than an atenolol-based regimen in reducing the risk of the primary composite end point of cardiovascular morbidity and

Figure 1. Angiotensin II receptor blockade with losartan reduces new-onset atrial fibrillation and subsequent stroke compared to atenolol[2]



Key: CI = confidence interval; HR = hazard ratio

Adapted from Watchell *et al*.[2]

cardiovascular mortality as well as the secondary end points of stroke and cardiovascular death in hypertensive patients with electrocardiographic LVH and a history of AF.[3]

It also found that hypertensive patients with AF who do not need beta blockade for heart rate control seem to benefit more from losartan-based treatment than from conventional antihypertensive and anti-arrhythmic treatment.[3]

Among hypertensive patients with LVH and a history of AF, treatment with losartan was associated with a 42% risk reduction in the composite end point of stroke, MI and cardiovascular death, a 45% reduction in the risk of stroke and a 42% reduction in the risk of cardiovascular death when compared with atenolol.[3]

Treatment with losartan and atenolol had statistically similar effects on MI and hospitalisation for angina and heart failure.[3]

Discussion

One explanation for the added benefit of losartan in preventing new-onset AF and associated events in hypertensive patients with LVH could be the parallel effects of losartan on regression of atrial and ventricular hypertrophy.[2] The recent LIFE echocardiography substudy[4] shows that patients with LVH also exhibit increased left atrial size, which has been associated with increased stroke risk in normotensive and hypertensive adults.[5] The greater regression of electrocardiographic and echocardiographic LVH with losartan- versus atenolol-based therapy[6,7] may have been paralleled by a greater reduction of left atrial overload and dilatation, thereby reducing stimuli to new-onset AF.

Further analyses from the LIFE echocardiography study will investigate whether left atrial diameter decreases with reduction in LV mass during treatment and whether this is related to a reduction in subsequent events.[3]

AF is the most common sustained cardiac arrhythmia and is a major cause of morbidity and mortality.[8] Once developed, AF can be difficult to manage, with recent estimates suggesting that patients receiving warfarin, the current treatment of choice for AF, continue to remain at risk of stroke or haemorrhage due to suboptimal treatment control.[9]

It is estimated that more than half a million people in the UK have AF, which puts them at a five-times greater risk of stroke than the general population.[10] Treatment of the condition costs the NHS around £459 million a year and represents a significant burden on patients and healthcare professionals.[11]

People with high blood pressure are at greater risk of developing AF and the combination of AF and hypertension further increases cardiovascular risk.[3]

Managing AF is currently a big challenge for general practitioners because of the difficulties of effective anticoagulation and the amount of work that this involves in terms of monitoring.[11] We must not forget that patients too are affected by AF and its physical and psychosocial sequelae. These can have a considerable effect on their quality of life and that of their families.

The broader consequences for society are that there is a large number of people with a long-term condition, which puts further pressure on the NHS and, potentially, on occupancy of hospital beds.[11]

Thus a treatment option which reduces the risk of patients developing AF while also lowering blood pressure effectively, such as with losartan, would be extremely valuable to general practitioners and cardiologists. I believe that these findings have the potential for a significant and positive impact on current practice.

Conflict of interest

BC has attended advisory boards for Altana, Astra Zeneca, GlaxoSmithKline, Roche, Sanofi-Aventis and Yamanouchi.

Brian Crichton
General Practitioner and Honorary Teaching Fellow, Warwick University Medical School, Hobs Moat Medical Centre, Solihull

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