Irbesartan (Aprovel) for prevention of cardiovascular complications in patients with persistent atrial fibrillation

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The National Horizon Scanning Centre Research Programme is part of the National Institute for Health Research
Irbesartan (Aprovel) for prevention of cardiovascular complications in patients with persistent atrial fibrillation

Target group
 Persistent atrial fibrillation (AF) – adjunct therapy to anticoagulation treatment for the prevention of cardiovascular complications.

Technology description
 Irbesartan (Aprovel) is an oral angiotensin II receptor blocker (ARB) mainly used for treatment of hypertension. Its mode of action is to block the activation of angiotensin II AT₁ receptors which directly causes vasodilation, a reduction in the secretion of vasopressin and a reduction in the production and secretion of aldosterone, the combined effect of which is a reduction in blood pressure.

Irbesartan is postulated to reduce cardiovascular events in patients with AF by lowering blood pressure, reducing AF by promoting regression of left ventricular hypertrophy, preventing atrial remodelling, and preventing atherosclerotic vascular lesions by blocking the rennin-angiotensin system.

Irbesartan 300mg is an oral formulation given once daily. Irbesartan is currently licensed for the treatment of hypertension and renal disease in hypertensive type 2 diabetes mellitus.

Irbesartan is currently in phase III clinical trials for heart failure with preserved systolic function (HF-PSF).

Innovation and/or advantages
 If results from ongoing trials are positive, irbesartan would be the first antihypertensive treatment to demonstrate a reduction in cardiovascular events in patients in AF irrespective of patients’ hypertensive status.

Developer
 Bristol-Myers Squibb and sanofi-aventis.

Availability, launch or marketing dates, and licensing plans:
 In phase III clinical trials.

NHS or Government priority area:
 This topic is relevant to:
 • The National Stroke Strategy (2007).
 • The National Service Framework for Older People (2001).
 • The National Service Framework for Coronary Heart Disease (2000).

Relevant guidance
 • NICE clinical guideline. Stroke: The diagnosis and acute management of stroke and transient ischaemic attacks. 2008¹.
 • NICE clinical guideline. The management of atrial fibrillation. 2006².
 • SIGN. Cardiac arrhythmias in coronary heart disease. 2007³.
 • NLH guidance. Atrial fibrillation. 2007⁴.
Clinical need and burden of disease

AF is the most common sustained cardiac arrhythmia. In Scotland the prevalence of AF has been estimated at 8.4 cases per 1,000 population, and is higher amongst men (men 9.4 per 1,000 vs. women 7.9 per 1,000). Applying this prevalence to England and Wales equates to 451,322 people with the condition. There were 109,646 finished consultant in-patient episodes for AF (ICD I48) in 2006/07. AF is predominantly a disease of the elderly and its prevalence increases with age from 0.5% at age 50-59 to almost 9% at age 80-89. The population prevalence of AF has risen over time and is likely to increase in the future.

AF remains a potent risk factor for thromboembolism, accounting for approximately 15% of all thromboembolic strokes. Comorbid factors such as hypertension, diabetes mellitus, congestive heart failure and prior stroke, all serve to increase the risk of stroke in AF, and the risks are cumulative.

Existing comparators and treatments

Rate control options include:
- beta-blockers or rate-limiting calcium-channel blockers (diltiazem or verapamil) are the preferred initial monotherapy
- digoxin (a cardiac glycoside) monotherapy especially if there is also heart failure
- electrophysiological or surgical interventions for rate and rhythm control

If monotherapy is inadequate a beta-blocker or a rate-limiting calcium-channel blocker is given with digoxin.

Rhythm control options include:
- amiodarone (class III antiarrhythmic agent) - requires specialist initiation and it has a high incidence of adverse effects.

Antithrombotic therapy:
- Guidelines recommend the use of adjusted-dose warfarin for patients with AF at high risk and aspirin for those deemed at low risk or for those who cannot safely receive adjusted-dose warfarin.

Efficacy and safety

<table>
<thead>
<tr>
<th>Trial code</th>
<th>NCT00249795, ACTIVE-I: irbesartan vs placebo; phase III</th>
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<tbody>
<tr>
<td>Sponsor</td>
<td>sanofi-aventis</td>
</tr>
<tr>
<td>Status</td>
<td>Ongoing</td>
</tr>
<tr>
<td>Location</td>
<td>America, Europe (inc. UK), China, Southeast Asia</td>
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<tr>
<td>Design</td>
<td>Randomised, double-blind, placebo controlled, factorial assignment.</td>
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<tr>
<td>Participants in trial</td>
<td>n=9,000; systolic bp ≤ 110mmHg; evidence of AF (eligible patients from ACTIVE-A or ACTIVE-W); not already receiving an ARB; no proven</td>
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indication for ARBs unless an ACE (angiotensin converting enzyme) inhibitor can be substituted. Randomised to irbesartan 300mg per day or placebo.

<table>
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<tr>
<th>Follow-up</th>
<th>5 years.</th>
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<tr>
<td>Primary outcome</td>
<td>Composite outcome of stroke, MI or vascular death. Composite outcome of stroke, MI, vascular death or hospitalisation for heart failure.</td>
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<tr>
<td>Secondary outcomes</td>
<td>Total mortality, stroke, hospitalization for heart failure and other heart failure episodes.</td>
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<tr>
<td>Expected reporting date</td>
<td>-</td>
</tr>
</tbody>
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**Estimated cost and cost impact**

The annual cost of irbesartan 300mg once daily is £220.

**Potential or intended impact – speculative**

**Patients**

☑ Reduced morbidity  ☑ Reduced mortality or increased survival  ☑ Improved quality of life for patients and/or carers

☐ Quicker, earlier or more accurate diagnosis or identification of disease  ☐ Other:  ☐ None identified

**Services**

☐ Increased use  ☐ Service reorganisation required  ☐ Staff or training required

☑ Decreased use. If vascular events and hospitalisation reduced.  ☐ Other:  ☑ None identified

**Costs**

☐ Increased unit cost compared to alternative  ☐ Increased costs: more patients coming for treatment  ☐ Increased costs: capital investment needed

☑ New costs: additional therapy  ☑ Savings: If vascular events and hospitalisation prevented  ☐ Other:

**References**

5 American College of Cardiology/American Heart Association/European Society of Cardiology. Guidelines for the management of patients with atrial fibrillation. 2006.

4 British National Formulary No. 55, March 2008
30/06/2008).


