National Horizon Scanning Centre

Clopidogrel (Plavix) in combination with aspirin for prevention of vascular events in patients with atrial fibrillation

August 2008

This technology summary is based on information available at the time of research and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes.
Clopidogrel (Plavix) in combination with aspirin for prevention of vascular events in patients with atrial fibrillation

**Target group**
- Paroxysmal, persistent or permanent atrial fibrillation (AF), with a high risk of vascular events - unable or unwilling to tolerate oral anticoagulation (OAC) therapy.

People with AF who are at high risk of vascular events include those who:
- have had previous ischaemic stroke, transient ischaemic attack (TIA) or thromboembolic event
- are aged ≥75 with hypertension, diabetes or vascular disease
- have clinical evidence of valve disease, heart failure, or impaired left ventricular (LV) function on echocardiography

**Technology description**
Clopidogrel (Plavix) is an oral antiplatelet agent which causes irreversible blockade of the adenosine diphosphate (ADP) receptor (P2Y12) on platelet cell membranes. The blockade of this receptor inhibits platelet aggregation by blocking activation of the glycoprotein IIb/IIIa pathway.

Aspirin (acetylsalicylic acid) is a non-steroidal anti-inflammatory agent (NSAID) which also acts as an antiplatelet agent by inhibiting thromboxane A2 formation in platelets thus inhibiting platelet aggregation.

Thrombi that form in low pressure systems such as the venous system and the cardiac atria (such as those associated with AF), are rich in fibrin and trapped erythrocytes (red thrombi), and are better treated by anticoagulation with agents such as heparin and warfarin. Antiplatelet therapy offers only modest protection against stroke in patients with nonvalvular AF: about a 20% reduction, which is much less than that afforded by anticoagulants (about 65%)².

Clopidogrel 75mg and aspirin 75-100mg are both oral formulations given once daily.

Clopidogrel monotherapy is currently licensed for prevention of atherosclerotic events in peripheral arterial disease (PAD), myocardial infarction (MI) and stroke. Clopidogrel, in combination with low-dose aspirin, is licensed for both acute coronary syndrome (ACS) without ST-segment elevation and for acute MI with ST-segment elevation. The use of clopidogrel in addition to aspirin for ACS is associated with an increased risk of bleeding³.

**Innovation and/or advantages**
The benefits and risks associated with this combination in patients with AF who cannot take OAC therapy, remains unclear.

**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:

Relevant guidance

- SIGN. Cardiac arrhythmias in coronary heart disease. 2007^8.
- American College of Cardiology (ACC), American Heart Association (AHA) and European Society of Cardiology (ESC) guidelines. Guidelines for the management of patients with atrial fibrillation. 2006^10.

Clinical need and burden of disease

AF is the most common sustained cardiac arrhythmia^8. 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)^14. 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 2006/07^15. 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 80-89^8. The population prevalence of AF has risen over time and is likely to increase in the future^16.

AF remains a potent risk factor for thromboembolism, accounting for approximately 15% of all thromboembolic strokes^17. 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^18.

Expert opinion suggests that approximately 75% of patients with AF are eligible for OAC (e.g. warfarin) but only an estimated 25% of eligible patients receive it. The dose-response of warfarin is complex and its activity is easily altered by concurrent medications, food interactions, alcohol and illness. Many patients decline treatment with warfarin for a wide variety of reasons including the inconvenience of dosing adjustments and regular blood tests to monitor INR values, dietary restrictions, the risks of minor and major bleeding, and under-appreciation or lack of knowledge regarding the risk of stroke, or poor adherence to the treatment regimen^19.
Existing comparators and treatments

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.20

Efficacy and safety

<table>
<thead>
<tr>
<th>Trial code</th>
<th>NCT00050817, CHARISMA – subgroup analysis3,21 Clopidogrel and aspirin versus aspirin alone, phase III</th>
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<tbody>
<tr>
<td>Sponsor</td>
<td>sanofi-aventis</td>
</tr>
<tr>
<td>Status</td>
<td>Completed</td>
</tr>
<tr>
<td>Location</td>
<td>America, Europe, Asia, Australia, South Africa.</td>
</tr>
<tr>
<td>Design</td>
<td>Post-hoc subgroup analysis of a randomised, double-blind, placebo controlled trial</td>
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<tr>
<td>Participants in trial</td>
<td>n=15603; ≥ 45 years, a history of AF and at least one of: (1) a combination of atherothrombotic risk factors (2) documented cerebrovascular disease (transient ischaemic attack (TIA) or ischaemic stroke (IS) within 5 years), (3) documented coronary artery disease (CAD), (4) documented PAD. Randomised to clopidogrel 75mg plus aspirin 75-162mg or placebo plus aspirin.</td>
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<tr>
<td>Follow-up</td>
<td>28 months</td>
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<tr>
<td>Primary outcomes</td>
<td>Occurrence of stroke, myocardial infarction, or cardiovascular mortality.</td>
</tr>
<tr>
<td>Secondary outcomes</td>
<td>Hospitalisations for ischaemic events, severe bleeding.</td>
</tr>
<tr>
<td>Key results</td>
<td>Rate of stroke (ischaemic and haemorrhagic) 2.2% per year with clopidogrel plus aspirin and 2.1% per year with placebo plus aspirin (hazard ratio 1.03, 95% CI 0.49-2.13); rate of all-cause mortality 9.7% with clopidogrel plus aspirin and 8.8% with placebo plus aspirin (hazard ratio 1.12, CI 0.65-1.90); rate of composite of stroke, MI or vascular death 11.7% with clopidogrel plus aspirin and 9.5% with aspirin alone (hazard ratio 1.24, CI 0.75-2.05); rate of severe or fatal extracranial haemorrhage 2.0% with clopidogrel plus aspirin and 1.0% with aspirin alone (P&lt;0.51).</td>
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<tr>
<td>Adverse effects</td>
<td>Increased number of excess bleeds.</td>
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<thead>
<tr>
<th>Trial code</th>
<th>NCT0024317822 (ACTIVE-W): clopidogrel plus aspirin vs OAC, phase III.</th>
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<tr>
<td>Sponsor</td>
<td>sanofi-aventis</td>
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<tr>
<td>Status</td>
<td>Terminated</td>
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<tr>
<td>Location</td>
<td>America, Europe (inc. UK), Australia, Southeast Asia, South Africa.</td>
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<tr>
<td>Design</td>
<td>Randomised, open-label, active control</td>
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<tr>
<td>Participants in trial</td>
<td>n=6,706; evidence of AF, eligible to take OAC; at least one of: ≥ 75 years, on treatment for hypertension, prior stroke, TIA or non-central nervous system (CNS) systemic embolus, left ventricular dysfunction with left ventricular ejection fraction (LVEF) estimated by ECG or angiogram to be &lt; 45%, PAD, age 55 to 74 years with either: diabetes requiring drug therapy, or documented previous MI or CAD. Randomised to clopidogrel 75mg plus aspirin 75-100mg or OAC.</td>
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<thead>
<tr>
<th>Trial code</th>
<th>NCT0024987323 (ACTIVE-A): clopidogrel plus aspirin vs aspirin alone phase III.</th>
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<tr>
<td>Sponsor</td>
<td>sanofi-aventis</td>
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<tr>
<td>Status</td>
<td>Ongoing, in follow-up</td>
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<td>Location</td>
<td>America, Europe (inc. UK), China, Southeast Asia, South Africa.</td>
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<tr>
<td>Design</td>
<td>Randomised, double-blind, active control</td>
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<tr>
<td>Participants in trial</td>
<td>n=7,500; evidence of AF, contraindication to or unwilling to take OAC; at least one of: ≥ 75 years, on treatment for hypertension, prior stroke, TIA or non-CNS systemic embolus, left ventricular dysfunction with LVEF estimated by ECG or angiogram to be &lt; 45%, PAD, age 55 to 74 years with either: diabetes requiring drug therapy, or documented previous MI or CAD. Randomised to clopidogrel 75mg plus aspirin 75-100mg or aspirin 75-100mg.</td>
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### Follow-up

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<th>Primary outcome</th>
<th>Time to stroke, non-CNS systemic embolism, MI or vascular death.</th>
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<tr>
<td>Secondary outcomes</td>
<td>Major haemorrhage, total mortality and stroke, individual components of the primary outcome.</td>
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<tr>
<td>Key results</td>
<td>Cumulative risk of a primary event in the clopidogrel plus aspirin group was 5.64% per year vs 3.93% in the OAC group. The study was terminated early because of clear evidence of superiority of OAC therapy.</td>
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<td>Expected reporting date</td>
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### Estimated cost and cost impact

The annual cost of clopidogrel 75mg once daily and aspirin 75mg once daily are £460 and £5.60 respectively.

### Potential or intended impact – speculative

Unless the ongoing trials show a positive risk benefit for the combination of clopidogrel and aspirin in AF, the combination is unlikely to enter standard practice.

### 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: adverse effects of treatment
- ☑ Service reorganisation required
- ☑ Staff or training required
- ☑ Decreased use: if vascular events prevented
- ☑ Other:
- ☑ None identified

### Costs

- ☑ Increased unit cost compared to alternative
- ☑ Increased costs: more patients coming for treatment
- ☑ Increased costs: capital investment needed
- ☑ New costs:
- ☑ Savings: If vascular events prevented
- ☑ Other:

### References


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a British National Formulary No. 55, March 2008
10 American College of Cardiology, American Heart Association and European Society of Cardiology guidelines. Guidelines for the management of patients with atrial fibrillation. 2006.