Clinical trials update from the European Society of Cardiology: CHARM, BASEL, EUROPA and ESTEEM

Alison P Coletta*, John G.F. Cleland†, Nick Freemantle‡, Huan Loh*, Anwar Memon*, Andrew L Clark*

*Department of Cardiology, University of Hull, Castle Hill Hospital, Cottingham, Kingston-upon-Hull HU15 5JQ, UK
†Department of Primary Care and General Practice, University of Birmingham, Edgbaston, Birmingham B15 2TT, UK
‡Bridlington and District Hospital, Bessingby Road, Bridlington YO16 4QP, UK

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Abstract

This article contains a series of reports on recent research developments in the field of heart failure. Reports of key presentations made at the European Society of Cardiology meeting, held in Vienna, Austria, between 30 August and 3 September 2003 are reported. In the CHARM study, candesartan reduced cardiovascular deaths and hospital admissions for heart failure, both in patients who were already taking an ACE-inhibitor and in those who were ACE intolerant. However, results in patients with preserved left ventricular function were less conclusive. The BASEL study supports the use of B-type natriuretic peptide testing to confirm the diagnosis of heart failure in patients presenting with acute dyspnoea. In EUROPA, the largest ever study of secondary prevention of coronary artery disease, long-term treatment with perindopril reduced the incidence of cardiovascular death, myocardial infarction (MI) and cardiac arrest. The ESTEEM study showed that the oral thrombin inhibitor ximelagatran plus aspirin was more effective than aspirin alone in the prophylaxis of major cardiovascular events following MI.

Keywords: CHARM; BASEL; EUROPA; ESTEEM

1. CHARM: Candesartan in Heart failure – Assessment of Reduction in Mortality and morbidity

Angiotensin II type 1 receptor blockers (ARBs) such as candesartan, by virtue of their pharmacologically distinct mechanism of action, may show additional benefit in patients who are already receiving an ACE-inhibitor and may be effective in patients who are unable to tolerate an ACE-inhibitor. A large proportion of heart failure patients are reported to have preserved systolic function; however, there are currently very few data available on the optimal treatment for these patients. The CHARM study was designed to address these issues.

CHARM was a double blind, randomised, placebo controlled, parallel group study of the ARB candesartan.

cilexatil in patients with chronic heart failure (CHF).

The CHARM programme consisted of three separate studies, each looking at a different CHF patient population. CHARM-Alternative recruited patients with a low left ventricular ejection fraction (LVEF) ≤40% who were intolerant to ACE-inhibitor treatment. CHARM-Added recruited patients with LVEF ≤40% who were already taking an ACE-inhibitor. CHARM-Preserved recruited patients with preserved left ventricular systolic function (LVEF >40%), who either were (19%) or were not taking an ACE-inhibitor. The primary objective in all three studies was to evaluate the effect of candesartan on the combined endpoint of cardiovascular death or heart failure hospitalisation. In the combined analysis of data from all three studies the effect on all-cause mortality was assessed. The rationale and design [1], baseline characteristics [2] and main results of CHARM have been reported [3–6].

The CHARM study recruited 7601 patients in 26 countries and 618 centres. Recruitment commenced in
March 1999 and patients were followed-up for a minimum of 2 years. Patients were randomised to treatment with either candesartan or placebo, titrated to a target dose of 32 mg per day.

In the overall CHARM programme, the mean age of patients was 66 years, 32% were female and 3% were in NYHA class IV. The mean LVEF was 29% in those with LVSD and 54% in those without. Concomitant medication included beta-blockers (55%), spironolactone (17%), diuretics (83%), statins (42%) and aspirin (55%).

Candesartan reduced cardiovascular deaths and hospital admissions for heart failure in patients with LVSD, whether or not they were already taking an ACE-inhibitor. However, in patients with preserved systolic function there was only a trend towards a difference in effect between candesartan and placebo (Table 1). In patients with LVSD, candesartan reduced all-cause mortality significantly (12% relative reduction; \( P = 0.018 \)), although the effect was of borderline significance (9% relative reduction; \( P = 0.055 \) (\( P = 0.032 \) adjusted for baseline co-variates)) in the overall programme and not significant in any of the individual component trials (13% in Alternative, 11% in Added and no effect on total mortality in Preserved).

The results of CHARM-Alternative provide firm evidence to support data from previous studies that patients with heart failure who are unable to tolerate an ACE-inhibitor should be treated with an ARB. An overview of published trial data comparing an ARB with placebo in patients with heart failure and LVSD not taking an ACE-inhibitor suggests a reduction in mortality of approximately 21% (Odds ratio 0.79; 95% CI 0.66–0.94) (Table 1 and Fig. 1a), compared to an overall 17% reduction in mortality with ACE-inhibitors reported in a recent meta-analysis (Odds Ratio 0.83; 95% CI 0.76–0.90) [7].

In patients who can tolerate ACE-inhibitors, CHARM-Added suggests additional benefit from candesartan. The trend to a reduction in mortality in CHARM-Added was not observed in Val-HeFT [8] but the reduction in all-cause mortality or hospitalisation for heart failure was very similar when adjusted for patient-years follow-up. The results of CHARM-Added overturn the negative results observed with candesartan (at doses of only 4 or 8 mg/day) in RESOLVD [9]. Overall, addition of an ARB to an ACE-inhibitor does not appear to have an effect on mortality (Fig. 1b), one way or the other, but does reduce the overall and heart failure specific risk of hospitalisation substantially. The scientific debate about whether or not there is benefit from adding an ACE-inhibitor to an ARB may be over, but the debate on the clinical importance of the size of the effect now needs to take place. Whether these should be based on the results of meta-analysis with all its uncertainties or on the results of large individual clinical trials will also be a matter for debate.

An overview of placebo-controlled trials of ARBs in the treatment of heart failure is given in Table 1 [3–5,8–13].

The issue of polytherapy [14] and its rationalisation are becoming ever more important. The overall CHARM programme suggested that candesartan exerted similar effects in the presence or absence of spironolactone, an agent that was used predominantly in patients with LVSD. If there is a convincing effect of candesartan in this population, then quadruple therapy with an ACE-inhibitor, beta-blocker, aldosterone antagonist and angiotensin receptor blocker may become standard therapy for heart failure with LVSD. Many doctors will be uncomfortable with this suggestion, but if their patients can be shown to benefit then attitudes must change. The research community will no doubt invent ‘polypills’ with multiple medications. Such a concept has already been suggested albeit with mostly non-evidence-based medications [15]. From a patient’s perspective, they tend to count the number, the size, the ease of swallowing, the taste and the side effects of medication. Patients are probably not concerned about how many compounds they contain, if they are safe, effective and do not entail taking extra pills.

For patients with preserved systolic function, the CHARM-Preserved results provided no convincing evidence of a reduction in mortality, but a modest effect on heart failure admissions was observed (~10 less heart failure admissions for every 100 treated for 3 years), although not all-cause admissions. Heart failure constituted the reason for hospitalisation in only one of every eight admissions, compared to one in every three in patients with LVSD. The SWEDIC study does not yet provide powerful evidence for a benefit from beta-blockade in heart failure [16]. Accordingly, we do not yet have convincing evidence for effective treatments in patients with heart failure with preserved global left ventricular systolic dysfunction. One reason for the lack of success of clinical trials in this area is the probable marked heterogeneity of this ‘syndrome’, which will comprise long-axis systolic dysfunction, impaired cardiac myocyte relaxation, increased myocardial stiffness, pericardial restraint and misdiagnosis [17]. A substantial number of these patients may actually not be suffering from a cardiac problem [18]. Natriuretic peptides may have an important role in defining this syndrome as patients with heart failure symptoms and preserved left ventricular systolic dysfunction have a much poorer prognosis if they have raised plasma concentrations of natriuretic peptides [19]. The PEP-CHF study [20], which investigates the effect of perindopril, should report in 2004. We will have to wait for some more time for the results of the I-PRESERVE study of irbesartan [17].
Table 1
Summary of placebo controlled trials of ARBs in the treatment of heart failure

<table>
<thead>
<tr>
<th>Study (Ref)</th>
<th>Patients</th>
<th>Follow-up (months)</th>
<th>Number of deaths</th>
<th>% Mortality</th>
<th>Total number of hospitalisations</th>
<th>Death or HF hospitalisation</th>
<th>% Death or HF hospitalisations</th>
<th>Total HF hospitalisations</th>
<th>Hospitalisations per patient</th>
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<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>ARB</td>
<td>Placebo</td>
<td>ARB</td>
<td>Placebo</td>
<td>Placebo</td>
<td>ARB</td>
<td>Placebo</td>
<td>Placebo</td>
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<tr>
<td>LVSD and no background ACE-inhibitor</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Losartan meta-analysis [10]</td>
<td>274</td>
<td>616</td>
<td>3</td>
<td>11</td>
<td>4.7</td>
<td>1.8</td>
<td>1.8</td>
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<td>na</td>
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<td>Candesartan meta-analysis [11]</td>
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<td>1287</td>
<td>3</td>
<td>11</td>
<td>1.8</td>
<td>1.6</td>
<td>1.6</td>
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<td>na</td>
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<tr>
<td>Val-HeFT subset [12]</td>
<td>181</td>
<td>185</td>
<td>23</td>
<td>32</td>
<td>27.1</td>
<td>17.3</td>
<td>17.3</td>
<td>262</td>
<td>199</td>
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<tr>
<td>Japanese Candesartan Study [13]</td>
<td>144</td>
<td>148</td>
<td>5</td>
<td>2</td>
<td>2.1</td>
<td>1.4</td>
<td>1.4</td>
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<td>na</td>
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<tr>
<td>Total</td>
<td>2220</td>
<td>3249</td>
<td>372</td>
<td>330</td>
<td>16.8</td>
<td>10.2</td>
<td>10.2</td>
<td>2097</td>
<td>1917</td>
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<td>Hospitalisations per patient</td>
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<td>1.60*</td>
<td>1.60*</td>
<td>553</td>
<td>473</td>
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<tr>
<td>LVSD and background ACE-inhibitor</td>
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<td>RESOLVD [9]</td>
<td>109</td>
<td>332</td>
<td>1</td>
<td>4</td>
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<td>8.7</td>
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<td>na</td>
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<tr>
<td>Val-HeFT-main [8]</td>
<td>2318</td>
<td>2326</td>
<td>23</td>
<td>435</td>
<td>18.8</td>
<td>19.9</td>
<td>19.9</td>
<td>2844</td>
<td>2657</td>
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<tr>
<td>CHARM-Added [3]</td>
<td>1272</td>
<td>1276</td>
<td>41</td>
<td>412</td>
<td>32.4</td>
<td>29.5</td>
<td>29.5</td>
<td>2798</td>
<td>2462</td>
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<tr>
<td>Total</td>
<td>3699</td>
<td>3934</td>
<td>28</td>
<td>851</td>
<td>23.0</td>
<td>22.1</td>
<td>22.1</td>
<td>5642</td>
<td>5119</td>
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<td></td>
<td></td>
<td>1.57*</td>
<td>1.42*</td>
<td>1.42*</td>
<td>1321</td>
<td>1274</td>
</tr>
<tr>
<td>All LVSD</td>
<td>5919</td>
<td>7183</td>
<td>1223</td>
<td>1199</td>
<td>20.7</td>
<td>16.7</td>
<td>16.7</td>
<td>7739</td>
<td>7036</td>
</tr>
<tr>
<td>Hospitalisations per patient</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.62*</td>
<td>1.47*</td>
<td>1.47*</td>
<td>1874</td>
<td>1747</td>
</tr>
<tr>
<td>Preserved left ventricular systolic function</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.69*</td>
<td>1.66*</td>
<td>1.66*</td>
<td>366</td>
<td>333</td>
</tr>
<tr>
<td>CHARM-Preserved [5]</td>
<td>1509</td>
<td>1514</td>
<td>36</td>
<td>237</td>
<td>15.7</td>
<td>16.1</td>
<td>16.1</td>
<td>2545</td>
<td>2510</td>
</tr>
<tr>
<td>Hospitalisations per patient</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.69*</td>
<td>1.66*</td>
<td>1.66*</td>
<td>366</td>
<td>333</td>
</tr>
</tbody>
</table>

na, not available.

*Not adjusted for duration of follow-up.
Fig. 1. (a) Meta-analysis of mortality data from randomised controlled trials comparing an angiotensin receptor blocker to placebo in patients with left ventricular systolic dysfunction and NOT receiving an ACE-inhibitor \([4,10–13]\). Only patients who were NOT taking an ACE-inhibitor in the Val-HeFT study are included in this analysis. Exact pooled odds ratios shown. Test for heterogeneity \(P = 0.2\). Random effects odds ratio 0.70 (95% CI 0.43 to 1.00). Random effects NNT = 45, (95% CI 14 to \(\infty\)). Analysis of data for the composite of death and HF hospitalisation showed a benefit of the ARB over placebo, odds ratio 0.70 (95% CI 0.60 to 0.82).

Fig. 1. (b) Meta-analysis of mortality data from randomised controlled trials comparing an angiotensin receptor blocker to placebo in patients with left ventricular systolic dysfunction receiving an ACE-inhibitor \([3,8,9]\). Only patients who WERE taking an ACE-inhibitor in the Val-HeFT study are included in this analysis. Full random effects odds ratio is 1.08 (95% CI 0.62 to 2.60). Some evidence of heterogeneity \(P\) for heterogeneity \(= 0.04\). Analysis of data for the composite of death and HF hospitalisation showed a benefit of the ARB over placebo, odds ratio 0.90 (95% CI 0.82 to 0.99).
The differential diagnosis of acute dyspnoea can be complex, since the shortness of breath may be due to heart failure, COPD or other causes. Diagnostic uncertainty can lead to misdiagnosis and consequently a delay in initiating appropriate therapy in these patients. B-type natriuretic peptide (BNP) has been shown to be a sensitive and specific marker of heart failure in the urgent-care setting [21,22].

The aim of the BASEL study was to evaluate rapid BNP testing in patients presenting with acute dyspnoea. The primary endpoint was time to discharge and total treatment costs. Four hundred and fifty two patients admitted to the emergency department with acute shortness of breath underwent clinical evaluation (history, physical examination, ECG, chest X-ray and routine blood tests). In addition, 225 of the patients were randomised to undergo rapid BNP testing. BNP levels of <100 pg/ml were considered to indicate that the patient did not have CHF. Levels >500 pg/ml confirmed the presence of CHF and therapy was initiated as appropriate. Levels between 100 and 500 pg/ml were regarded as inconclusive and the diagnosis was made on the basis of clinical judgement.

The mean age of patients included in the study was 70 years, 43% were female, 50% had coronary artery disease and 55% were hypertensive. BNP testing reduced the mean time to hospital discharge by 23% and reduced treatment costs by 26% (Table 2). Hospital readmission rates were reduced from 85% in the control group to 75% in the BNP tested patients and intensive care admissions from 24 to 15%, respectively. In hospital mortality was 9% in the control group and 6% in the BNP group. Thirty-day mortality and readmission rates were similar in both groups.

A final discharge diagnosis of heart failure was made in 50% of patients in the control group compared with 40% in the BNP group. COPD was the diagnosis in 11% of patients in the control group and 22% of patients in the BNP group; this may suggest that some patients in the control group were incorrectly diagnosed as having heart failure.

This was an open study, therefore it is possible that patients who were randomised to the BNP test group may have undergone faster treatment than those in the control group due to an investigator bias. In addition, the lack of a defined threshold level for BNP, with levels between 100 and 500 pg/ml giving an uncertain diagnosis, is problematic. However, it was concluded that BNP is a useful test for the diagnosis of heart failure in patients presenting with acute dyspnoea.

3. EUROPA: European trial on Reduction Of cardiac events with Perindopril in patients with stable coronary Artery disease

ACE-inhibitors have been shown to reduce the incidence of cardiovascular events in high risk patients in a number of large-scale studies [23,24]. The EUROPA study was designed to evaluate the effect of adding perindopril treatment to standard therapy, on the incidence of cardiovascular events in lower risk patients with documented coronary artery disease. The results have been published [25].

The study was conducted in 424 centres in 24 countries. Patients were pre-treated with perindopril for 4 weeks (titrated from 2 up to 8 mg/day) to assess their tolerance to the target dose of the drug, prior to randomisation. Ninety percent of patients tolerated 8 mg/day and were randomised to treatment with either perindopril or placebo. 6110 received perindopril and 6108 received placebo. The mean age of patients was 60 years, 86% were male, 65% of patients had a previous MI, only 2% had moderate or severe angina, 55% had undergone revascularisation and 12% of patients were diabetic. Concomitant medication included platelet inhibitors (92%), beta-blockers (62%) and lipid lowering agents (58%). Patients with known heart failure or blood pressure >180/100 mmHg were excluded as ACE-inhibitors are known to be effective in these patients. The mean follow-up was 4.2 years during which >80% of patients remained on blinded perindopril (similar to placebo) and only 7% required a dose reduction. Perindopril reduced blood pressure by an average of 5/2 mmHg.

The primary endpoint was a composite of cardiovascular mortality, non-fatal myocardial infarction (MI) and cardiac arrest, which was reduced from 9.9 to 8.0% (1.8 absolute and 20% relative risk reduction) by perindopril compared with placebo (P=0.0003). Individual endpoint data showed a relative risk reduction of 14% for cardiovascular mortality (4.1% reduced to 3.5%), 22% for non-fatal MI (6.8% reduced to 5.2%) and 46% (0.2% reduced to 0.1%) for cardiac arrest. Hospital admission for heart failure was reduced from 1.7% on placebo to 1.0% on perindopril (absolute 0.7% and relative 39% risk reduction; P=0.002). There was a trend for a reduction in all-cause mortality (6.9 to 6.1%; ns) but no effect on stroke (1.7 to 1.6%). Both treatments were well tolerated and patient compliance was good.

These results confirm those of the HOPE study in a lower risk population. The results of the PEACE study
Table 3

Studies of secondary prevention following MI comparing anti-platelet (AP) and high or moderate dose anti-coagulant (AC) agents alone and in combination (Comb)

<table>
<thead>
<tr>
<th>Study (Ref)</th>
<th>Agents used</th>
<th>Duration (months)</th>
<th>Numbers randomised</th>
<th>Total mortality, No. of deaths (%)</th>
<th>Re-infarction, No. of events (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>AP</td>
<td>AC</td>
</tr>
<tr>
<td>Meta-analysis 1999 [28]</td>
<td>High or moderate intensity anti-coagulant vs. Aspirin</td>
<td>Variable</td>
<td>1731 (#1431) 1726 (#1440) na</td>
<td>124 (7.2) 120 (7.0) na</td>
<td>76 (5.3)# 71(4.9)# na</td>
</tr>
<tr>
<td>Meta-analysis 1999 [28]</td>
<td>High or moderate intensity anti-coagulant and aspirin vs. aspirin</td>
<td>Variable</td>
<td>240 na 240</td>
<td>7 (2.9) na 4 (1.7)</td>
<td>18 (7.5) na 10 (4.2)</td>
</tr>
<tr>
<td>CHAMP [29]</td>
<td>Aspirin, Warfarin</td>
<td>32</td>
<td>2537 na 2522</td>
<td>438(17.3) na 444 (17.6)</td>
<td>333 (13.1) na 336 (13.3)</td>
</tr>
<tr>
<td>WARIS II [30]</td>
<td>Aspirin, Warfarin</td>
<td>48</td>
<td>1206 1216 1208</td>
<td>92 (7.6) 96 (7.9) 95 (7.9)</td>
<td>117 (9.7) 90 (7.4) 69 (5.7)</td>
</tr>
<tr>
<td>ASPECT-2 [31]</td>
<td>Aspirin, Warfarin</td>
<td>26</td>
<td>336 325 332</td>
<td>15 (4.5) 4 (1.2) 9 (2.7)</td>
<td>14 (4.2) 13 (4.0) 10 (3.0)</td>
</tr>
<tr>
<td>ESTEEM [26]</td>
<td>Aspirin, Ximelagatrana</td>
<td>6</td>
<td>638 na 1245</td>
<td>21 (3.3) na 39 (3.1)</td>
<td>34 (5.3) na 43 (3.5)</td>
</tr>
<tr>
<td>Comparisons</td>
<td>AP vs. Comb</td>
<td></td>
<td></td>
<td>11.6</td>
<td>10.7</td>
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<tr>
<td>(% of patients)</td>
<td>AP vs. AC</td>
<td></td>
<td></td>
<td>7.1</td>
<td>6.7</td>
</tr>
</tbody>
</table>

na, data not available.
# Patient numbers were different for re-infarction.

All dosage groups combined.
[26], comparing placebo and trandolapril in a similar population, are awaited. PEP-CHF addresses the use of ACE-inhibitors in elderly patients with diastolic heart failure [20] and should report in 2004. Whilst there is clear statistical evidence of a benefit with ACE-inhibitors in patients with or at high risk of coronary vascular disease, the clinical relevance and magnitude of effect should be examined with care. The absolute benefits of treatment are directly related to the absolute risk of developing an event. Application of these results to an annual risk of an event of 5% (higher than HOPE [approximately 4% per annum for the composite] or EUROPA [approximately 2% per annum for the composite]) will reduce absolute risk by 1% (i.e. one patient in every hundred will benefit). Further debate on what magnitude of benefit is required to justify treatment is necessary.

4. ESTEEM: Efficacy and Safety of The oral thrombin inhibitor ximelagatran in combination with aspirin, in patients with recent Myocardial damage

Ximelagatran is the first of a new class of direct thrombin inhibitors, which offer the benefit of oral administration and may not require regular monitoring of coagulation. The ESTEEM study is the first evaluation of the long-term use of ximelagatran in high-risk patients following MI.

ESTEEM was a phase II, randomised, double-blind study, which was conducted in 191 centres in 18 countries. A maximum of 14 days following MI, 1883 patients were randomised to treatment with either ximelagatran (24, 36, 48 or 60 mg bd) or placebo. All patients also received 160 mg aspirin daily. Treatments were administered for 6 months. The primary endpoint was a composite of death, MI and severe recurrent ischemia. The results of the ESTEEM study have been published [27].

The mean age of patients included in the study was 69 years and 69% were male. Patients were randomised to treatment a mean of 6.6 days after the index event.

For all four dose groups combined, ximelagatran significantly reduced the risk of the primary endpoint (12.7%) compared to placebo (16.3%). (HR 0.76 (0.59–0.98) \( P = 0.0357 \)). There was no evidence of any difference in efficacy between the four different doses of ximelagatran.

There was a slight increase in bleeding events in the ximelagatran groups compared with placebo, but this was not significant. There was no difference in the incidence of major bleeds; however, there was a dose-related increase in total bleeds. There was also a transient elevation of liver enzymes observed on ximelagatran, which also appeared to be dose-related as reported in previous studies [28].

It was concluded that phase III trials are now required to confirm these findings, and that comparative studies with clopidogrel and warfarin are required.

A summary of the results of previously reported studies investigating the effects of anti-platelet agents compared to or in addition to anti-platelet agents following MI are shown in Table 3 [27,29–32].

References


