

## REVIEW

# Clopidogrel in non-ST segment elevation acute coronary syndromes: an overview of the submission by the British Cardiac Society and the Royal College of Physicians of London to the National Institute for Clinical Excellence, and beyond

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A comprehensive appraisal was undertaken on behalf of the British Cardiac Society and the Royal College of Physicians of London to assess the use of clopidogrel in acute coronary syndromes. The appraisal was submitted to the National Institute for Clinical Excellence (NICE) in August 2003 and contributed to the development of the recently published guidelines for the use of clopidogrel in acute coronary syndromes. The submission to NICE and more recent publications evaluating the use of clopidogrel are reviewed.

with an average of eight days of oral administration.<sup>6</sup>

After activation, clopidogrel is a selective and irreversible inhibitor of ADP induced platelet aggregation.<sup>4</sup> The inhibitory effect occurs selectively through the platelet P2Y<sub>12</sub> receptor inhibiting binding of ADP.<sup>2</sup> Physiologically, ADP binds to the P2Y<sub>12</sub> receptor inhibiting adenylyl cyclase and decreasing platelet cAMP. This results in ADP induced activation of the glycoprotein IIb/IIIa receptor.<sup>6</sup>

A loading dose (300 mg) has been shown to reduce the time taken to reach maximum inhibition of platelet aggregation in healthy volunteers.<sup>4</sup> In patients undergoing elective percutaneous coronary intervention (PCI), 300 mg, 3–24 hours before stenting resulted in greater platelet inhibition at the time of stenting and postprocedurally than a 75 mg dose given at the procedure.<sup>7</sup> The CREDO (clopidogrel for the reduction of events during observation) study suggests that the 300 mg loading dose before stenting needs to be given more than six hours before the procedure for maximum benefit.<sup>8</sup>

A 600 mg loading dose may lead to more rapid platelet inhibition.<sup>9,10</sup> The antiplatelet action of clopidogrel may also be enhanced by a 600 mg loading dose, even though patients are taking clopidogrel in the long term.<sup>11</sup> The higher loading dose of clopidogrel has now been evaluated in a clinical trial of non-ST segment elevation ACS.<sup>12</sup> In addition, it has been assessed before elective coronary stenting, where its use may obviate the need for intravenous administration of IIb/IIIa inhibitor.<sup>13</sup>

Importantly, clopidogrel administration is associated with highly variable individual responses leading to some patients being

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## CLOPIDOGREL: THE DRUG

Clopidogrel is a thienopyridine derivative that inhibits the platelet ADP receptor. Metabolism of clopidogrel by the hepatic cytochrome P450 system produces an active metabolite (thiol derivative that is undetected in plasma) and an inactive circulating metabolite (carboxylic acid derivative).<sup>2</sup> Plasma concentrations of the inactive circulating metabolite peak one hour after oral administration.<sup>3</sup> Clopidogrel's half life is eight hours after single or repeat dosing, with excretion in the urine and faeces.<sup>4</sup>

About 50% of an oral dose of clopidogrel is absorbed from the gut,<sup>4</sup> and the bioavailability of clopidogrel is unaffected by food.<sup>3</sup> Bleeding times are unaffected by age, renal dysfunction, and Child-Pugh class A or B cirrhosis.<sup>4</sup> Nevertheless, the manufacturer still advises that the drug be used with caution by patients with moderate hepatic disease and bleeding diatheses.<sup>3</sup> Dose adjustment is unnecessary in renal disease.<sup>4</sup> Steady state pharmacokinetics can be achieved

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**Abbreviations:** ACS, acute coronary syndromes; CABG, coronary artery bypass graft; CAPRIE, clopidogrel versus aspirin in patients at risk of ischaemic events; CI, confidence interval; CREDO, clopidogrel for the reduction of events during observation; CURE, clopidogrel in unstable angina recurrent events; MI, myocardial infarction; NICE, National Institute for Clinical Excellence; PCI, percutaneous coronary intervention; PCI-CURE, percutaneous coronary intervention-clopidogrel in unstable angina to prevent recurrent events; PRAIS-UK, prospective registry of acute ischaemic syndromes in the UK; STEMI, ST elevation myocardial infarction; TIMI, thrombolysis in myocardial infarction

described as “clopidogrel resistant”.<sup>14</sup> More recently the interindividual variability in platelet inhibition that occurs with clopidogrel administration has been shown to correlate with cytochrome P450 3A4 metabolic activity.<sup>15</sup>

### THE CLINICAL PROBLEM

Coronary artery disease is the most common cause of death in the UK, with one in four men and one in six women dying of the disease (resulting in > 120 000 deaths in the UK in 2001).<sup>16</sup> “Acute coronary syndrome” refers to a clinical syndrome arising from myocardial ischaemia with or without infarction. There are three main groups of clinical diagnoses: ST elevation myocardial infarction (STEMI), non-STEMI, and unstable angina. The focus of this submission was non-ST segment elevation ACS (that is, including non-STEMI and unstable angina).

In the Euro Heart Survey of ACS, non-ST segment elevation ACS was more common than ST segment elevation ACS (51% v 42%).<sup>17</sup> For patients with non-ST segment elevation ACS, the in-hospital and 30 day mortality rates were 2.4% and 3.5%, respectively.<sup>17</sup> The rate of death or myocardial infarction (MI) in the PRAIS-UK (prospective registry of acute ischaemic syndromes in the UK) registry of non-ST segment elevation ACS was 12.2% at six months.<sup>18</sup>

Thus, non-ST segment elevation ACS are both common and an important cause of morbidity and mortality. These patients can be risk stratified (by evidence based methods such as the TIMI (thrombolysis in myocardial infarction) risk score)<sup>19–20</sup> and should be aggressively treated to improve outcomes.

### THE CAPRIE STUDY

The CAPRIE (clopidogrel versus aspirin in patients at risk of ischaemic events) study,<sup>21</sup> published in 1996, was the first large, randomised, controlled trial investigating the use of clopidogrel (table 1<sup>21–23</sup>). This established the efficacy and safety of clopidogrel as a secondary preventative agent compared with aspirin in patients with a history of ischaemic stroke (onset  $\geq$  1 week and  $\leq$  6 months before randomisation), MI (onset  $\leq$  35 days before randomisation), or symptomatic peripheral arterial disease.<sup>21</sup> The CAPRIE study did not evaluate the use of clopidogrel and aspirin in combination and did not apply directly to patients with ACS. However, these results (table 1), showing a small advantage of clopidogrel over aspirin, have paved the way for the subsequent trials investigating the use of clopidogrel.

### THE CURE STUDY

The CURE (clopidogrel in unstable angina recurrent events) study recruited 12 562 patients hospitalised within 24 hours of the onset of chest pain with a diagnosis of ACS.<sup>22</sup> Initial inclusion criteria allowed for patients > 60 years of age who had a history of coronary artery disease but no acute ECG changes. After the first 3000 patients were enrolled, only patients with myocardial necrosis or ECG changes (higher risk patients) were included in the study. All patients received aspirin (75–325 mg/day) and were subsequently randomly assigned to clopidogrel (loading dose of 300 mg followed by 75 mg/day) or placebo. The mean duration of treatment was nine months. The rate of the first primary outcome (composite of death from cardiovascular cause, non-fatal MI, and stroke) was significantly reduced from 11.4% to 9.3% (relative risk 0.80, 95% confidence interval (CI) 0.72 to 0.90,  $p < 0.001$ ) by the addition of clopidogrel. The second primary outcome, which additionally included refractory ischaemia (recurrent chest pain in hospital lasting > 5 minutes with new ischaemic ECG changes while the patient was receiving optimal medical treatment and leading to additional interventions by midnight of the next calendar

day) was also significantly reduced by the addition of clopidogrel ( $p < 0.001$ ). The rate of each component of the primary outcomes also tended to be lower with clopidogrel treatment, whereas the reductions in MI (relative risk 0.77, 95% CI 0.67 to 0.89) and refractory ischaemia in hospital (relative risk 0.68, 95% CI 0.52 to 0.90) were significant. The benefit of clopidogrel was evident by 24 hours of randomisation and was maintained up to the end of the study protocol. The apparently beneficial effects were seen across a variety of groups with no difference between patients < 65 and those > 65 years of age, with and without ST segment shift, with and without enzyme shift, with and without diabetes, or treated and not treated by revascularisation. The authors concluded that clopidogrel is beneficial in patients with ACS without ST segment elevation.

The treatment effect of clopidogrel was also analysed according to the TIMI risk score.<sup>23</sup> The first primary outcome increased proportionally with increasing risk according to the TIMI risk score. The relative risk reduction was similar for each subgroup but a greater absolute reduction was seen in patients with a higher TIMI risk score. This is the only recent intervention that has been shown to be of significant incremental benefit over aspirin in patients with low risk ACS.<sup>24</sup>

A time dependent analysis was also performed and a consistent benefit was seen within the first seven days and between day 8 and day 30.<sup>25</sup> In the first 24 hours after randomisation there was a 20% relative risk reduction in the primary outcome for the clopidogrel group.

### PCI-CURE STUDY

The PCI-CURE (percutaneous coronary intervention-clopidogrel in unstable angina to prevent recurrent events) substudy was a prospectively designed observational study that examined the effects of clopidogrel on patients who had invasive management (PCI) of non-ST elevation ACS within the main CURE study.<sup>26</sup> A total of 2658 patients undergoing PCI in the CURE study had been randomly assigned double blind treatment with clopidogrel ( $n = 1313$ ) or placebo ( $n = 1345$ ). PCI was performed at the discretion of the attending physician with no randomisation to this intervention. Patients were pretreated with aspirin and study drug for a median of six days before PCI during the initial hospital admission. After PCI, the majority of patients in both groups (placebo and clopidogrel) received open label thienopyridine for four weeks, after which the original study drug was started again for a mean of eight months. The primary end point was a composite of cardiovascular death, MI, or urgent target vessel revascularisation within 30 days of PCI. The main analysis was by intention to treat.

Significantly fewer patients in the clopidogrel group than in the placebo group had a primary outcome of cardiovascular death, MI, or urgent revascularisation by 30 days after PCI (relative risk 0.70, 95% CI 0.5 to 0.97,  $p = 0.03$ ). In addition, significantly fewer patients in the clopidogrel group than in the placebo group reached the composite of cardiovascular death or MI by 30 days (relative risk 0.66, 95% CI 0.44 to 0.99,  $p = 0.04$ ). Individually, patients given clopidogrel had significantly fewer MIs (relative risk 0.56, 95% CI 0.35 to 0.89) and Q wave MIs by 30 days (relative risk 0.35, 95% CI 0.18 to 0.70) than patients given placebo. The results for the primary end point remained significant when patients who had received open label thienopyridine before PCI were excluded from the analysis. Most patients received open label thienopyridine for 2–4 weeks after PCI (> 80% in both groups), indicating that this early postprocedural benefit was mainly due to the effects of clopidogrel pretreatment. Beyond 30 days the event-free survival curves continue to separate. The event rates between 30 days and

**Table 1** Summary of major randomised controlled trials investigating the use of clopidogrel

Trial	No of patients	Criteria	Protocol	Outcome	p Value
CAPRIE <sup>21</sup>	19185	Symptomatic atherosclerotic disease (peripheral or cerebral disease or IHD)	Aspirin 325 mg v clopidogrel 75 mg	Composite event*: 5.32% clopidogrel v 5.83% aspirin In patients with PVD: 3.71% clopidogrel v 4.86% aspirin	0.043 0.0028
CURE <sup>22</sup>	12562	ACS without ST segment elevation	Clopidogrel (300 mg bolus followed by 75 mg daily for up to 1 year) and aspirin v placebo and aspirin	First primary outcome†: 9.3% clopidogrel v 11.4% placebo Second primary outcome‡: 16.5% clopidogrel v 18.8% placebo	<0.001 <0.001
PCI-CURE <sup>26</sup>	2658	PCI (at physician's discretion) in CURE patients	Clopidogrel and aspirin v placebo and aspirin. Patients requiring stents received open labelled thienopyridine for 2–4 weeks after the procedure	Primary outcome§: 4.5% clopidogrel v 6.4% placebo	0.03
CREDO <sup>8</sup>	2116	Patients undergoing elective PCI (including 1117 with unstable angina)	Clopidogrel 300 mg loading dose or placebo before PCI. All patients received aspirin and clopidogrel for 1 month after PCI. Aspirin + clopidogrel v aspirin + placebo after 1 month until 1 year	28 day primary outcome**: 6.8% clopidogrel v 8.3% placebo 1 year primary outcome††: 8.5% clopidogrel v placebo 11.5%	0.23 0.02

\*Ischaemic stroke, myocardial infarction (MI), or vascular death; †composite of death from cardiovascular causes, non-fatal MI, or stroke; ‡the first primary outcome or refractory ischaemia; §observational study based on patients enrolled in the CURE (clopidogrel in unstable angina recurrent events) study; \*composite of cardiovascular death, MI, or urgent target vessel revascularisation within 30 days of percutaneous intervention; \*\*composite of death, MI, or urgent target vessel revascularisation in the per-protocol population; ††composite of death, MI, or stroke in the intent to treat population.  
ACS, acute coronary syndromes; CAPRIE, clopidogrel versus aspirin in patients at risk of ischaemic events; CREDO, clopidogrel for the reduction of events during observation; IHD, ischaemic heart disease; PCI, percutaneous coronary intervention; PCI-CURE, percutaneous coronary intervention-clopidogrel in unstable angina to prevent recurrent events; PVD, peripheral vascular disease.

the end of follow up are consistently lower in the clopidogrel treated patients (cardiovascular death or MI: clopidogrel 3.1%, placebo 3.9%, relative risk 0.79, 95% CI 0.53 to 1.20; cardiovascular death, MI, or rehospitalisation: clopidogrel 25.3%, placebo 28.9%, relative risk 0.86, 95% CI 0.74 to 1.00). When interpreting these results it must be remembered that this was an observational study of a randomised treatment in a selected treatment group.

### CREDO STUDY

The CREDO study aimed at evaluating the effects of long term treatment (12 months) with clopidogrel (75 mg once daily) in patients undergoing elective PCI.<sup>8</sup> In addition, the effects of a preprocedural loading dose of clopidogrel (300 mg) were examined. Both treatments were given in addition to aspirin (325 mg daily from day 1 to day 28, and 81–325 mg daily from day 29 to 12 months). Patients were considered eligible for enrolment if they had symptomatic coronary disease referred for, or thought to be at high likelihood for, PCI. A total of 2116 patients were randomly assigned to receive a 300 mg loading dose of clopidogrel (n = 1053) or placebo (n = 1063) 3–24 hours before PCI. All patients subsequently took clopidogrel 75 mg for 28 days and the loading dose group then received clopidogrel 75 mg daily and the control group received placebo from day 29 to 12 months. A large number of patients in the CREDO study had a diagnosis of unstable angina or recent MI before enrolment (1117 of 2116, 53%; 290 of 2116, 14%, respectively). Unfortunately, the authors did not capture data on which patients with MI had STEMI and non-STEMI, or how many patients with unstable angina had a positive biochemical marker for myocardial necrosis (S Steinhilber, personal communication, 2003). None the less, while precise numbers cannot be defined, a significant proportion of the CREDO study patients had a non-ST segment elevation ACS.

The main outcome measures were the composite of death, MI, or urgent target vessel revascularisation at 28 days (per-protocol group) and the composite of death, MI, or stroke at one year (by intention to treat analysis). Pretreatment with clopidogrel was associated with a non-significant reduction in the primary end point at 28 days. An important interaction

was noted between the duration of pretreatment and the degree of protection from adverse cardiac events. Those given clopidogrel 3–6 hours before PCI gained no benefit from pretreatment, whereas those receiving the loading dose > 6 hours before PCI experienced a 38.6% relative risk reduction in the 28 day primary end point (95% CI –1.6% to 62.9%, p = 0.051). Random assignment to long term clopidogrel treatment was associated with a significant reduction in the primary end point at one year (26.9% reduction in relative risk, 95% CI 3.9% to 44.4%, p = 0.02). The subgroup analysis of ACS patients showed a similar reduction in relative risk (27.6%), although this did not reach significance. Interestingly only 63% of patients in the clopidogrel group and 61% of patients in the control group completed the one year course of treatment.

The CREDO results are consistent with the CURE and PCI-CURE data, reflecting an early effect with clopidogrel that is maintained by prolonged treatment of up to 12 months. Although the primary end points are different for each study, relative risk reductions are similar for the composite of death and MI up to one year in the CREDO and PCI-CURE populations (24% and 25%, respectively).

### SAFETY DATA INCLUDING BLEEDING RISK

Clopidogrel already has a well established safety profile compared with aspirin. In the CAPRIE study the overall incidence of adverse events among the clopidogrel recipients was similar to that among the aspirin group, although the frequency of individual events varied.<sup>21</sup> The overall frequency of bleeding disorders was similar between the two groups (9.27% clopidogrel v 9.28% for aspirin, not significant).<sup>21</sup> The incidence of all gastrointestinal haemorrhages was significantly lower in the clopidogrel group (1.99%) than in the aspirin group (2.66%).<sup>21</sup>

The definition of major bleeding varies considerably in the studies of antiplatelet treatment in non-ST segment elevation ACS.

In the CURE study major bleeding episodes were defined as substantially disabling bleeding, intraocular bleeding leading to the loss of vision, or bleeding necessitating the transfusion of at least two units of blood.<sup>22</sup> Major bleeding

was classified as life threatening if the bleeding episode was fatal or led to a reduction in the haemoglobin concentration of at least 5 g/dl or to substantial hypotension requiring the use of intravenous inotropic agents; if it necessitated a surgical intervention; if it was a symptomatic intracranial haemorrhage; or if it necessitated the transfusion of four or more units of blood.<sup>22</sup>

The original criteria for a "major bleed" (from the TIMI trial) are bleeding leading to a haemoglobin drop of  $\geq 5$  g/dl or an intracranial haemorrhage.<sup>27</sup> This definition was used in several large trials of glycoprotein IIb/IIIa inhibitors in unstable angina or non-STEMI.<sup>28</sup> In some trials, a modified TIMI definition has been used, in which each unit of blood transfused is counted as a 1 g/dl drop in haemoglobin.<sup>29</sup> The CURE definition of major bleeding is therefore considerably broader than that used in other large randomised trials of ACS, an important consideration when comparing the results between trials.

The rate of major bleeding was significantly more common in the clopidogrel group than in the placebo group in the CURE study (3.7% v 2.7%, relative risk 1.38, 95% CI 1.13 to 1.67,  $p = 0.001$ ) and the excess of major bleeding was due to gastrointestinal haemorrhage and bleeding at the sites of arterial punctures.<sup>22</sup> Table 2 shows how, depending on the definition used, the relative risk of bleeding can vary.<sup>29</sup> Owing to its large sample size, CURE had more power than other ACS trials to assess bleeding incidence.

The CURE trial is one of the largest randomised investigations of antiplatelet treatment in ACS patients undergoing coronary artery bypass graft (CABG) surgery (over 2000 patients). Patients requiring CABG surgery were given clopidogrel in the same manner as aspirin (that is, if aspirin was discontinued for several days before CABG surgery, then it was also recommended that the study drug be discontinued for this period).<sup>29</sup> Most patients undergoing CABG surgery in CURE had the study drug stopped for a short period of time before surgery (median five days).<sup>22</sup> If surgery was urgent, however, CABG surgery proceeded while the patient was still receiving the study drug, as would be the case with aspirin.<sup>29</sup> In the 910 patients in whom the study drug was withheld more than five days before CABG surgery, no increase in major bleeding within seven days of surgery was noted.<sup>22</sup> The study drug was discontinued within five days before CABG surgery (including up to the time of surgery) in 912 resulting in a trend towards an increase in major bleeding of 9.6% in the clopidogrel group versus 6.3% in the placebo group (relative risk 1.53,  $p = 0.06$ ).<sup>22</sup> The need for surgical revascularisation in patients with ACS is considerable with about 20% of patients having surgical disease.<sup>30</sup> In the UK where the median time to surgery after ACS is likely to be more than five days, perioperative complications due to discontinuing clopidogrel less than five days before surgery is unlikely to be of clinical significance. However, this has caused concern among physicians from the USA where the

median time to surgery is less than four days.<sup>30 31</sup> Furthermore, the use of clopidogrel and aspirin in combination given preoperatively within seven days of CABG surgery is associated with an increased risk of postoperative bleeding, repeat operation, and greater postoperative morbidity.<sup>32</sup> Nevertheless, after a further subgroup analysis the CURE investigators have concluded that: "the benefits of starting clopidogrel on admission appear to outweigh the risks, even among those who proceed to CABG surgery during the initial hospitalisation".<sup>33</sup>

It should also be noted that an incremental increase in bleeding risk in the CURE study population was observed as the dose of aspirin increased.<sup>34 35</sup> The rates of major bleeding were higher as the dose of aspirin rose from  $\leq 100$  mg to 100–300 mg and  $> 300$  mg in both placebo treated (2.0%, 2.2%, and 4.0%, respectively) and clopidogrel treated patients (2.5%, 3.5%, and 4.9%, respectively).<sup>34 35</sup> Given the lack of data indicating improved outcome with higher doses of aspirin, the European Society of Cardiology recommend that when clopidogrel and aspirin are given together, the aspirin dose should be  $\leq 100$  mg.<sup>35</sup>

Further analysis of the CURE data showed that major bleeding occurred more often with increasing TIMI risk score.<sup>23</sup> The excess of bleeding with clopidogrel compared with placebo was similar in each category of risk. The risk of bleeding in the entire clopidogrel treated group was proportional to the benefit of this treatment across all categories of risk. The authors concluded that the ratio of benefit to risk of clopidogrel treatment is maintained across all categories of risk stratification.<sup>23</sup>

In CURE, when the primary composite of cardiovascular death, MI, or strokes and life threatening bleeding are combined into an efficacy–safety end point, there remains a highly significant benefit of clopidogrel over placebo (relative risk 0.84, 95% CI 0.76 to 0.93,  $p = 0.001$ ).<sup>29</sup> Expanding this outcome to include refractory ischaemia requiring intervention or major bleeding raises the relative risk to 0.87 (95% CI 0.79 to 0.96,  $p = 0.005$ ).<sup>29</sup>

Clopidogrel has a low propensity for drug interaction. Safety has been confirmed during coadministration of other commonly prescribed cardiovascular drugs.<sup>4</sup> Coadministration of atorvastatin was shown to alter the efficacy of clopidogrel in one poorly designed retrospective study that used an unvalidated method to test platelet aggregation.<sup>36 37</sup> In the prospective INTERACTION study (S Steinhubl, personal communication, 2003), no interaction has been reported between clopidogrel and the statin class of drugs. In addition, no interaction was observed in a post hoc analysis of the CREDO population.<sup>38</sup>

Clopidogrel has a low potential for inducing peptic ulcers<sup>4</sup> and has a gastrointestinal safety profile superior to that of aspirin alone.<sup>21 39 40</sup> Hypersensitivity reactions to clopidogrel are rare.<sup>4</sup> Thrombotic thrombocytopenic purpura has been reported with clopidogrel (occurring within the first two weeks of administration),<sup>41</sup> although the incidence is low at about four cases per million patients receiving the drug.<sup>4</sup> Non-cardiac side effects are seen less often with clopidogrel than with ticlopidine in patients undergoing elective PCI.<sup>42</sup> Neutropenia (neutrophil count  $< 1.2 \times 10^9/l$ ) was seen in 0.1% of the CAPRIE patients taking clopidogrel with an equivalent incidence observed in patients taking aspirin.<sup>21</sup>

## COST EFFECTIVENESS

Only limited data were available on the cost effectiveness of clopidogrel in addition to aspirin in the management of non-ST segment elevation ACS at the time of the submission.<sup>43–47</sup> In general, these data show that the use of clopidogrel is comparable with other cost effective treatments in cardiovascular medicine. A cost appraisal by the University

**Table 2** Bleeding in CURE according to TIMI major, GUSTO severe, and CURE life threatening definitions<sup>29</sup>

	Placebo (n = 6303)	Clopidogrel (n = 6259)	RR	p Value
CURE life threatening	112 (1.8%)	135 (2.2%)	1.21	0.13
GUSTO severe	70 (1.1%)	78 (1.2%)	1.12	0.48
TIMI major	73 (1.15%)	68 (1.1%)	0.94	0.70

GUSTO, global use of strategies to open occluded arteries in acute coronary syndromes; RR, relative risk; TIMI, thrombolysis in myocardial infarction.

of York has found that the cost per additional quality adjusted life-year (based on an incremental cost effectiveness ratio) associated with clopidogrel combination treatment for one year compared with aspirin alone was £6078.<sup>1</sup>

## SUMMARY POINTS

- The addition of clopidogrel (300 mg bolus then 75 mg daily for 3–12 months, mean nine months) to aspirin in the treatment of patients with non-ST segment elevation ACS who meet CURE study entry criteria (low to high risk) reduced the composite of death from cardiovascular cause, non-fatal MI, and stroke by 18% (relative risk reduction) or by 2.1% (absolute risk reduction).
- The benefit of clopidogrel (relative risk reduction) for these patients is consistent for all TIMI risk scores as well as early and late time periods. However, the absolute risk reduction is greatest in patients with higher TIMI risk scores.
- Benefits of clopidogrel in these patients is seen with or without revascularisation (PCI or CABG surgery).
- For patients with non-ST segment elevation ACS undergoing PCI, the addition of clopidogrel to aspirin reduced the risk of cardiovascular death, MI, or urgent revascularisation at 30 days after the PCI by 30%. These benefits were maintained up to one year.
- The one year results of the CREDO study are consistent with the CURE and PCI-CURE data, reflecting a lower risk of atherothrombotic events when clopidogrel is added to aspirin in the treatment of patients who have had a PCI.
- Assessment of bleeding risk was rigorous in the CURE study. The addition of clopidogrel to aspirin led to an increase in major and minor bleeding (in accordance with CURE criteria) in these patients.
- Clopidogrel would best be discontinued at least five days before CABG surgery (if this is possible) to prevent perioperative complications.
- Clopidogrel monotherapy has a superior gastrointestinal safety profile to aspirin monotherapy.

## RECOMMENDATIONS

- For patients presenting to hospital with non-ST segment elevation ACS (low to high risk), clopidogrel (300 mg bolus followed by 75 mg daily) should be given in addition to aspirin ( $\leq 100$  mg). The greatest absolute benefit is achieved among those with the highest cardiovascular risk.
- Combination treatment with clopidogrel and aspirin in patients with non-ST segment elevation ACS should be continued for 12 months.<sup>1</sup> Aspirin maintenance dose should be  $\leq 100$  mg.
- If CABG surgery is planned, clopidogrel should be discontinued at least five days before surgery if possible.
- NICE have recommended discontinuation of clopidogrel 12 months after the most recent episode of non-ST segment elevation ACS.<sup>1</sup>

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## IMAGES IN CARDIOLOGY

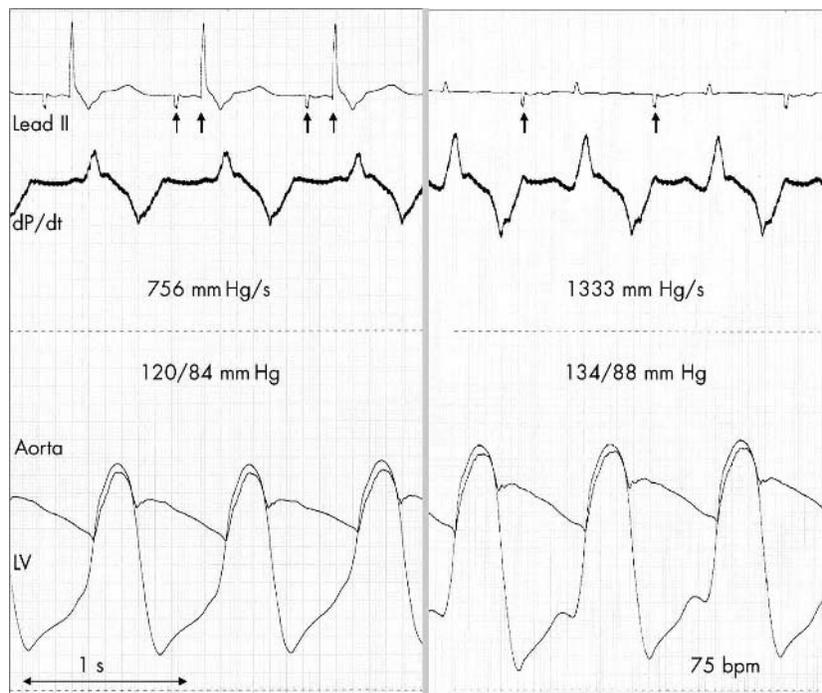
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### Inappropriate pacemaker therapy in congestive heart failure

A 67 year old patient with advanced congestive heart failure (CHF) caused by coronary artery disease (CAD) was referred for evaluation of cardiac resynchronisation therapy (CRT). After implantation of a dual chamber pacemaker six months earlier, the clinical status of the patient had worsened from New York Heart Association (NYHA) functional class III to IV with recurrent pulmonary oedema. Pacemaker implantation had been performed after the patient, already showing first degree atrio-ventricular (AV) block, exhibited a complete AV block during a coronary intervention. During cardiac catheterisation left ventricular (LV) haemodynamic response to different pacemaker settings was evaluated.

This figure shows recordings of the ECG and LV and aortic pressure, together with the rate of LV pressure development (dP/dt). The left panel exhibits the haemodynamic response with the original pacemaker settings—dual chamber pacing using the default AV delay of 170 ms—while the right panel illustrates right atrial pacing at the same rate. In conjunction with a first degree AV block (PQ time of 260 ms) the narrow QRS complex indicated undisturbed intra-ventricular conduction. Changing modes was accompanied by a remarkable increase in LV and aortic systolic pressure and an augmentation in LV maximal positive dP/dt by ~76%.

Instead of CRT the patient received reprogramming of the current system. By setting the AV delay to 300 ms, unfavourable right ventricular stimulation could be minimised. Despite unchanged medication the patient's clinical status improved to NYHA class III and remained stable during the following two years.



Obviously, the negative impact of artificial left bundle branch block outweighed the benefits of corrected first degree AV block in this patient with CHF.

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