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**Clinical trial: chest pain due to presumed gastro-oesophageal reflux in coronary artery disease - controlled study of lansoprazole versus placebo**

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**Clinical trial: chest pain due to presumed gastro-oesophageal reflux in coronary artery disease - controlled study of lansoprazole versus placebo**

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**ABSTRACT.**

*Introduction:* Gastro-oesophageal reflux (GOR) and coronary artery disease (CAD) commonly co-exist. CAD patients may mistake GOR-induced pain for cardiac pain or GOR might provoke angina. *Hypothesis:* GOR might contribute to nocturnal/rest chest pain among CAD patients. *Methods:* Double-blind placebo-controlled crossover study investigating effect of Lansoprazole on chest pain; 125 patients with angiographically proven CAD enrolled with at least one weekly episode of nocturnal/rest pain, randomized to Lansoprazole 30mg daily or placebo with crossover after 4 weeks. Symptoms recorded and QOL assessed by Nottingham Health Profile Questionnaire; ST segment depression episodes counted from 24hour electrocardiographic monitoring in final week of both periods. *Statistical analysis:* ANCOVA with period and carryover analysis. *Results:* 108 patients completed. There was a modest increase in pain-free days on Lansoprazole vs placebo ( $p<0.02$ ), with fewer days with pain at rest ( $p<0.05$ ) and at night ( $p<0.009$ ) on Lansoprazole vs placebo, but no significant differences in ST segment depression episodes ( $p=0.64$ ). There was a trend for reduction of the 'physical pain' QOL domain. *Conclusion:* Among CAD patients, Lansoprazole modestly increases pain-free days and reduces rest/nocturnal pain. Since Lansoprazole did not affect ST segments, this may be by suppression of GOR-provoked pain misinterpreted as angina rather than acid-provoked ischaemia.

## Introduction

Gastro-oesophageal reflux (GOR) and coronary artery disease (CAD) are both common conditions: it is therefore not surprising that both can co-exist in some patients<sup>1-3</sup>. 'Linked angina' was a term introduced many years ago by Smith and Papp to describe patients with '...an anginal syndrome ... blending with pain or discomfort arising from non-cardiac sources'<sup>4</sup>. They pointed out the neural link between viscera (such as gallbladder and oesophagus) and heart demonstrated in clinical observations of cardiac ischaemia in response to distension of biliary tree or oesophagus<sup>5-7</sup> and described clinical cases in which CAD was linked with a variety of upper gastrointestinal disorders<sup>4</sup>. These observations have since been elegantly revisited and confirmed in a series of studies in patients with CAD and 'Syndrome X', finding reduced coronary perfusion in response to acid infusion of the esophagus<sup>8,9</sup>. The fact that this phenomenon could not be demonstrated in patients with a transplanted heart argues strongly for a neural mechanism<sup>9</sup>. The possible clinical relevance of acid induced cardiac ischaemia is shown by studies demonstrating that anginal pain together with electrocardiographic evidence of cardiac ischemia could be provoked by acid perfusion<sup>10</sup> and that the exertional angina threshold could be lowered by acid perfusion<sup>11</sup>. More recent studies of CAD patients monitored with both ambulatory pH and electrocardiography have shown the association of some episodes of cardiac ischaemia with spontaneous acid reflux<sup>1,3</sup>.

Another mechanism for interaction between oesophageal pain and angina is the potential for the 2 symptoms to be confused by patients. This was first recognized by Kramer and Hollander using oesophageal balloon distension<sup>7</sup> and has been found to be

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2 common in some patients with both reflux and CAD<sup>1-3</sup>. The phenomenon is explained by  
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4 'viscero-visceral' convergence of nociceptor neural pathways onto the same second order  
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6 spinothalamic tract neurons in the posterior horns of the spinal cord which has been  
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8 confirmed directly in animal models<sup>12,13</sup> and would appear from clinical studies to be the  
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10 commonest mechanism<sup>1,3</sup>.  
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14 In clinical practice, patients with angina in whom symptoms are increasing in  
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16 frequency or are occurring at rest, the primary clinical concern will be to intervene  
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18 among those who on investigation have worsening coronary stenoses. From the above  
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20 discussion, it would appear that among those patients who do not have critical stenoses  
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22 there exists the potential for unrecognized GOR to mislead the physician, which could  
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24 explain the occurrence of angina in non-exertional situations such as the angina 'linked'  
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26 with meals or with recumbency and sleep<sup>4</sup>. Indeed, nitrates and calcium channels  
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28 antagonists used in the treatment of ischaemic heart disease may provoke GOR<sup>3,14</sup> so that  
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30 escalating treatment could in these circumstances increase chest pain, leading the  
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32 physician to the erroneous conclusion that CAD was worsening. Simultaneous work up  
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34 of CAD patients by a gastroenterologist is often not practical, or in the absence of an  
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36 oesophageal function laboratory, simply not possible. In this clinical situation empirical  
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38 acid suppression is often prescribed<sup>15</sup>. A small open study has provided support for the  
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40 use of acid suppression by proton pump inhibitor in patients with chronic stable angina in  
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42 whom both GOR and CAD have been found to co-exist<sup>2</sup> while a large retrospective  
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44 review of patients with CAD treated with proton pump inhibitors has reported 50%  
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46 reduction in patients free of chest pain, emergency room visits and hospital admissions  
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2 compared to those not treated<sup>15</sup>. The utility of this approach has not been tested in a  
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4 controlled clinical trial.  
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9 Our aim was therefore to test the hypothesis that among patients with stable CAD,  
10 chest pain at rest or during recumbence (at night) in whom there was a likelihood of GOR  
11 acid suppression with a proton pump inhibitor (PPI) might reduce chest pain. We  
12 investigated the efficacy of acid suppression with a PPI (Lansoprazole 30mg once a day)  
13 in patients with CAD and rest or nocturnal pain. The primary endpoint was the reduction  
14 in chest pain symptoms. Secondary endpoints were the impact of treatment on quality of  
15 life measures and on spontaneous ischaemic episodes using 24 hour Holter monitoring.  
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#### 24 **Patients and methods**

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26 An initial feasibility study was carried out by face to face interviews using a  
27 structured questionnaire survey of 106 consecutive patients with a diagnosis of CAD  
28 attending cardiology outpatients at Glenfield Hospital, Leicester, UK. The majority  
29 (95%) fulfilled the Rose criteria<sup>16</sup> for angina pectoris and 68% had some episodes of pain  
30 at rest and or during recumbence at night.  
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39 The trial was approved by the Leicestershire District Ethics Committee.  
40 Patients were recruited from the cardiology out patient department at Glenfield Hospital  
41 and from the waiting lists for percutaneous coronary revascularization or coronary artery  
42 bypass grafting over a 2 year period. Patients with unstable angina or acute coronary  
43 syndromes were not recruited: patients were only recruited from waiting lists for  
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coronary revascularization, if they were classed as 'routine' which at the time of the study meant at least 3 months' procedural wait. To calculate the numbers needed for the study, we used figures derived from previous studies for expected numbers of chest pain episodes per day in patients with CAD during combined ambulatory pH and electrocardiographic monitoring, together with their estimates of the proportion associated with reflux episodes<sup>1,3</sup>. Garcia et al reported  $1.71 \pm 1.75$  chest pain episodes per day in patients with IHD in whom an oesophageal contribution to chest pain was suspected<sup>1</sup>. Based on these figures and an expected 33% reduction in chest pain episodes on treatment with proton pump inhibitors, we calculated that 130 patients would have to be enrolled in this trial to lend it 80% power at a 5% level of statistical significance.

All patients had angiographically documented coronary artery disease with at least 50% stenosis in one main epicardial coronary vessel. Subjects were invited to participate in the study if, in addition to exertional angina, they had at least one episode of chest pain at rest or during the night per week. This was assessed by monitoring symptoms with the help of diaries during a run in period of observation (continuing their usual anti-anginal medication) for two weeks prior to enrolment.

Eligibility and exclusion criteria are listed in table 1. Current medication was recorded. Patients on PPIs or H<sub>2</sub> receptor antagonists (H<sub>2</sub>RA) for overt dyspeptic and GOR associated symptoms were excluded; we specifically excluded any patients with endoscopically diagnosed peptic ulceration and oesophagitis, as well as any patients complaining of ulcer-type dyspepsia (meal related or nocturnal epigastric pain).



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2 However, patients who were taking PPIs or H<sub>2</sub>RAs, which were empirically prescribed  
3 for chest pain, were allowed to participate after discontinuing the relevant drug for four  
4 weeks.  
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10 The trial carried a double blind cross over design and is illustrated by the flow  
11 chart in Figure 1. All patients continued their usual cardiac medication. After obtaining  
12 written consent, patients were randomly assigned either to receive Lansoprazole 30 mg  
13 once daily or placebo once daily for a period of four weeks following a run in period of  
14 two weeks. Both Lansoprazole and matching placebo were supplied by Wyeth  
15 Pharmaceutical, Taplow, Maidenhead, UK. After a two week wash out phase the patients  
16 were crossed over.  
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27 Patients were given a symptom diary and asked to indicate for each day whether  
28 they had experienced any of the following: exertional chest pain, chest pain at rest or  
29 during recumbence (at night). Our intention had been to analyze the total number of chest  
30 pain events (on exertion, at rest, at night). However, since we found that only 56 of the  
31 108 patients completing the trial had entered the actual number of chest pain episodes as  
32 instructed in their symptom diaries, and the remainder had simply recorded whether chest  
33 pain occurred or not in each 24 hour period, we made a decision to analyze the number of  
34 days with (or without) symptoms. To minimize carry over effects only the last two weeks  
35 of each study treatment period were analyzed. In addition 24hour ambulatory ECG  
36 monitoring (Reynolds Lifecard, Reynolds Medical Ltd, Harforde Court, Hertford, United  
37 Kingdom) was performed during the last week of each 4 week trial period to detect  
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spontaneous ST segment shifts. The number of ST segment shifts (more than 1mm down-sloping ST depression or ST-elevation for at least 80 milliseconds from the J point compared with the isoelectric segment and lasting at least 60 seconds in 1 or more channels<sup>17</sup>) was counted and compared between placebo and active treatment (Reynolds Lifecard, Reynolds Medical Ltd, Harforde Court, Hertford, United Kingdom).

Quality of life was assessed using the Nottingham Health Profile questionnaire (NHPQ)<sup>18,19</sup>. This includes six domains of quality of life (energy, pain, emotional reactions, sleep, social isolation and physical mobility). The questionnaire has been validated in a large number of studies of chronic ill health including cardiovascular illness<sup>18</sup>. The questionnaire was administered at the start of the run in period and at the end of each of the two treatment periods.

Results are expressed as mean  $\pm$  standard error (SE). **Analysis of covariance (ANCOVA)<sup>20</sup> was carried out using SAS Proc Mixed (SAS v9.1)<sup>21</sup>. Statistical significance required  $p < 0.05$ . The treatment effect involved comparing the number of pain free days, days with rest and nocturnal pain and days with exertional pain on treatment versus placebo. Terms for period and carry-over effects were entered into the statistical models, and patient was declared as a random effect.** The Nottingham Health Profile scores (each of six quality of life domains) were also compared for the two treatment periods. ST-segment shift frequency was compared **in the same way.**

## Results

Patients for the study were recruited from cardiology out patients (2450 case notes reviewed) and, in the early phase of the trial, from the waiting list for coronary artery bypass surgery (379 patients). Out patients were initially screened through review of their medical case notes and patients on the waiting list for bypass grafting were invited via letter. Only 23 subjects on the waiting list responded to the letter of which 4 were willing to take part, all of whom eventually completed the trial. All other patients were not willing to participate in a clinical trial prior to their planned surgery.

In the out-patient cohort only one fifth of patients (524) had complained about ongoing chest pain (any chest pain including exertional pain, pain at rest or nocturnal pain) at their most recent out-patient visit. Of these, 309 patients were willing to attend for a screening visit (see Figure 1); 234 patients in this cohort appeared to have either rest or nocturnal chest pain or both. However, 62 patients had a history of documented gastrointestinal disease (chiefly peptic ulcer disease or gastro-oesophageal reflux disease demonstrated by prior endoscopy), 26 patients were unwilling to take part – mainly citing inconvenience- after further information was provided, 9 patients underwent revascularisation or suffered a cardiac event. The remaining patients cited various other reasons or simply failed to attend for their first trial visit. Eventually 125 patients entered the run in phase of the trial (including the four patients from the CABG waiting list).

Of the 125 patients enrolled, 108 completed the trial (Figure 1). Seventeen patients dropped out for the following reasons: emergency bypass grafting or percutaneous revascularization due to development of acute coronary syndromes (4

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2 patients), unwillingness to complete the trial (9 patients), bereavement (1 patient),  
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4 diarrhea and abdominal pain on placebo (2 patients), increasing chest pain on  
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6 Lansoprazole (1 patient). The patients' characteristics are listed in table 2.  
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11 Considering the last two weeks of each treatment period, the number of pain free  
12 days, days with pain at rest, at night, and days with exertional pain are shown in [table 3](#)  
13 [and illustrated in figures 2A and 2B](#). There was a significant ( $p<0.02$ ) increase in the  
14 number of pain free days on treatment with Lansoprazole ( $6.7 \pm 0.47$ ) as compared to  
15 placebo ( $5.7 \pm 0.47$ ). Both the number of days with pain at rest ( $3.53 \pm 0.46$  vs.  $4.51 \pm$   
16  $0.46$ ,  $p<0.005$ ) and pain at night ( $2.1 \pm 0.35$  vs.  $2.96 \pm 0.35$ ,  $p<0.009$ ) were significantly  
17 less on Lansoprazole than on placebo. There appeared to be no effect on exertional pain  
18 ( $p=0.79$ ).  
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29 The effects of treatment on quality of life measures are listed in [table 3](#). None of  
30 the measured parameters showed a significant difference between treatment with  
31 Lansoprazole and placebo. However, pain perception scores as assessed by the NHPQ  
32 (mean 23.14 [PPI] vs. 26.33 [placebo]) showed a trend ( $p=0.07$ ) for reduction on  
33 Lansoprazole .  
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41 Two complete 24 hour tapes were available for 89 of 108 patients. Three tapes  
42 could not be analyzed due to a bundle branch block pattern. Sixteen patients refused one  
43 or both tapes citing inconvenience (15 patients) and depression (1 patient) as reasons.  
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45 However, chest pain diary data were available for these subjects and are included in the  
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2 preceding analysis. The mean number of ST shift episodes was  $0.75 \pm 0.21$  (SE) on  
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4 placebo as compared to  $0.63 \pm 0.22$  on PPI. This difference was not significant ( $p= 0.64$ ;  
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6 **Table 3**). Only 24 patients showed any ST segment changes during the trial. No  
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8 significant difference between placebo and Lansoprazole phases were found when only  
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10 the 24 patients showing any ST segment changes were included in a subgroup analysis.  
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### 13 14 **Discussion**

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16 This study is to our knowledge the first randomized blinded clinical trial  
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18 investigating the clinical efficacy of empirical treatment with PPIs in patients with  
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20 chronic stable angina due to documented CAD. The data show that standard dose  
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22 Lansoprazole increases the number of pain-free days, mainly by decreasing rest and  
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24 nocturnal pain symptoms. The effect is modest with on average 1 more pain free day on  
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26 PPI compared to placebo. Although it is a common clinical intervention<sup>15</sup>, the modest  
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28 symptomatic benefit observed in this randomised trial could be interpreted as meaning  
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30 that it is not worthwhile undertaking in unselected patients. It may be that selecting  
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32 patients on the basis of abnormal testing for gastro-oesophageal reflux would identify a  
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34 subgroup more likely to respond as has been found in one open study<sup>2</sup>.  
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40 It should be noted that that none of the patients in this study had 'unstable' or  
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42 worsening angina nor were patients with acute coronary syndromes studied. In all such  
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44 patients, the appropriate clinical management remains urgent cardiological investigation  
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46 and intervention. Our results are pertinent only to the use of PPI therapy in patients who  
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48 have stable angina and are not requiring urgent cardiological intervention.  
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5 The trial has several limitations: ideally it might have been designed as a  
6 randomized parallel group comparison between 2 separate PPI treatment and placebo  
7 arms but this would have doubled the sample size necessary. Indeed over 2800 patients  
8 were screened to find 125 who were willing to participate. Although we did not achieve  
9 our recruitment target of 130 patients, the power calculation was necessarily (since there  
10 were few data on which to base our calculations) a very crude estimate of the numbers  
11 required. Cross over designs have the problem of potential carryover effect: we sought to  
12 limit this by including a 2 week washout period between treatment periods and by only  
13 analyzing the patient diary in the last 2 weeks of each 4 week treatment period. In fact  
14 carry-over was not observed by statistical analysis by ANCOVA. An 'order effect' has  
15 also not been shown by the ANCOVA analysis: the likely impact of this would have been  
16 to reduce the size of the treatment effect, since the order 'PPI first, placebo second' is the  
17 one likely to have had a carry over effect into the second placebo treatment period. This  
18 is because acid suppression may have an effect on reducing esophageal sensitivity to acid  
19 which variably outlasts the treatment period by several weeks<sup>22,23</sup>. We chose  
20 Lansoprazole 30 mg administered once daily rather than higher twice daily doses often  
21 used in the investigation of non-cardiac chest pain<sup>24</sup>. It is known that twice daily  
22 administration of PPI produces more profound acid suppression<sup>25</sup> and it is therefore  
23 possible that a twice daily administration schedule would have increased the treatment  
24 effect. It is less likely that prolonging the period of acid suppression would altered the  
25 results of the study, since it is known that predictable response to treatment occurs in  
26 short periods (usually 2 weeks) of treatment with a PPI, at least in the context of patients  
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2 with non-cardiac chest pain<sup>24</sup>. However, in the current study we found a modest reduction  
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4 in chest pain with once daily Lansoprazole: the limitations referred to above would have  
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6 been expected (if anything) to have reduced the treatment effect. The apparent lack of  
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8 efficacy as far as quality of life scores are concerned is disappointing although there was  
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10 a trend towards reduction of pain associated parameters.  
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15 There appeared to be no significant effect of acid suppression on spontaneous  
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17 ischaemic ST segment shifts during 24 hour ambulatory electrocardiographic monitoring  
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19 (although there was a slight reduction in frequency during treatment with PPI). However,  
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21 only 24 patients out of 89 (patients with 2 interpretable 24 hour tapes) showed any  
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23 spontaneous ST segment shifts, with no significant difference between placebo and PPI  
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25 on subgroup analysis. This would suggest that, taken as a group, these patients were in  
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27 the main well treated for their CAD, despite having episodes of chest pain at rest. There  
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29 were a small number who continued to have ST segment shifts despite 'optimal medical  
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31 therapy'. While we have not scrutinized these individuals in detail, it may be that 24 hour  
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33 ST segment monitoring identifies a subgroup among which medical treatment for angina  
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35 should be reviewed or coronary intervention considered more urgently.  
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40 We did not attempt to assess whether ST segment shifts were symptomatic since  
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42 patients were not instructed to note the exact time of symptoms in their symptom diaries,  
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44 though it is well recognized that among CAD patients undergoing 24 hour  
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46 electrocardiographic monitoring the majority of ischemic ST segment shifts (>70%) are  
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48 asymptomatic<sup>26-28</sup>. Other modalities such as exercise tolerance testing might be more  
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suitable to detect the effect of acid suppressants on the cardiac ischaemia but were deemed inappropriate because of the potential risk of exercise-induced arrhythmia among patients with known IHD. However, ambulatory electrocardiographic monitoring has good accuracy compared to both exercise ECG testing and positron emission tomography to detect reversible defects in myocardial perfusion<sup>26,29</sup>.

It would seem likely from our observations that the mechanism of the beneficial effect we observed on chest pain reduction, particularly at night and at rest, was not generally due to an effect on the 'cardio-oesophageal reflex' described by Chauhan and colleagues<sup>8,9</sup>, as we would have expected to see a reduction in ST segment shifts during PPI treatment. However, since ST segment shift were only seen in about 30% of our patients such an effect could have been 'swamped' by the majority of normal ambulatory studies. We did not find a significant effect of PPI when we confined our analysis to the subgroup of 24 patients with ST segment changes on ambulatory recording. Thus, these findings are consistent with previous observations that most episodes of chest pain in CAD subjects associated with reflux occur when acid-induced pain is misinterpreted by patients as 'angina'<sup>2,3</sup>, but we cannot exclude the possibility that cardiac ischaemia may occur in some patients as a result of a cardio-oesophageal reflux as observed in a minority of patients in one study<sup>3</sup>, particularly as we did not carry out pH monitoring in our subjects.

It is also pertinent that we failed to find a reduction in exertional chest pain episodes during PPI treatment, since one study has suggested that intra-oesophageal acid



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2 may reduce exertional anginal threshold<sup>11</sup>. It is possible that an effect on exertional  
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4 angina might have been found if patients had been selected on the basis of having  
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6 objective evidence of both GOR and CAD, although the patients reported by Alban  
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8 Davies and colleagues had CAD only<sup>11</sup>. Our study was empirical, designed to test the  
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10 utility of treating patients with proven CAD who also had rest or nocturnal pain, on the  
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12 basis that this is a common intervention in clinical practice. The results are consistent  
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14 with the conclusion that an effect of PPI therapy on exertional anginal threshold is not a  
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16 likely explanation of the modest efficacy of this treatment.  
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21 In conclusion, our study supports the hypothesis that among patients with 'stable'  
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23 angina, chest pain at rest or at night may be caused by acid GOR and is not necessarily a  
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25 manifestation of critical CAD. Our results support the observations in earlier studies  
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27 using pH monitoring that the mechanism of such pain is usually due to misinterpretation  
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29 of acid-provoked oesophageal pain with anginal pain<sup>1,3</sup>, rather than due to a cardio-  
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31 oesophageal reflex<sup>8,9</sup>. The results also provide some justification for the use of empirical  
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33 PPI therapy in patients with CAD and rest pain in addition to exertional chest pain, but  
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35 only after appropriate cardiological investigation and management (either medical or  
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37 interventional). There has been recent controversy about the use of PPIs (particularly  
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39 omeprazole and esomeprazole) in patients using Clopidogrel since the latter is a prodrug  
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41 requiring activation by CYP2C19, part of the cytochrome P450 liver microsomal enzyme  
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43 system. While this enzyme is inhibited by some PPIs thus reducing the production of the  
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45 active metabolite of Clopidogrel<sup>30</sup>, the clinical effects are unclear with some case control  
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47 studies suggesting a clinically relevant interaction, others not so<sup>31,32</sup>. The issue is  
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2 complicated by the fact that many of these studies have not adequately excluded  
3 confounding effects, and the fact that genetically determined differences in CYP2C19  
4 metabolism has a marked effect on Clopidogrel handling which has not been examined in  
5 these studies<sup>32</sup>. Since both Clopidogrel and PPIs have short serum half lives, it has been  
6 suggested that administering each at a different time (12 hours separation) might mitigate  
7 this interaction but this has not been proved. In addition to the clinical scenario explored  
8 in our study, co-prescription of PPIs and Clopidogrel is an important consideration in  
9 terms of reducing risk of upper GI bleeding. For the reasons discussed above and since  
10 the magnitude of the benefit of prescribing a PPI among patients with CAD is modest, it  
11 may be both more prudent and more cost effective (if worsening CAD has been excluded  
12 by cardiological investigation) to investigate patients with frequent rest pain with a view  
13 to proving abnormal GOR prior to initiating PPI therapy.  
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### 27 **Acknowledgements**

28  
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31  
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33 an unrestricted educational grant from Wyeth Pharmaceutical Laboratories. Wyeth  
34 Laboratories kindly supplied Lansoprazole and matching placebo tablets for the trial.  
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**Table 1. Eligibility criteria**

*Inclusion criteria*

Age > 18yr

Angiographically documented coronary artery disease with a stenosis of at least 50% in one main coronary vessel

At least one episode of rest or nocturnal chest pain per week in addition to exertional angina

*Exclusion criteria*

Pregnancy

Upper gastrointestinal disorder clearly identified by prior investigation (peptic ulcer, endoscopic oesophagitis) or typical symptoms (heartburn  $\geq$  once a week)

Severe comorbidity (malignancy, previous disabling stroke and advanced chronic airflow limitation)

Coronary artery bypass surgery in the past 12 months

Patients on PPIs or H<sub>2</sub>RA for proven acid-related conditions\*

*\*Patients on 'empirical' acid suppression allowed provided treatment stopped for 4 weeks*

**Table 2: Patient characteristics**

Number enrolled	125
Number completing trial	108 (92 male)
Age - mean $\pm$ SD, (range)	66 $\pm$ 9.3 (44-85) years
Ethnicity	White 101 South Asian 7
Angiographically confirmed IHD	108 ( <i>all patients completing trial</i> )
Single vessel disease	3
Two or more vessel disease	105
History of myocardial infarction	41
History of coronary bypass grafting	19
History of percutaneous revascularization	60
Diabetes mellitus	24
Arterial hypertension	48
<i>Medication</i>	
Calcium channel antagonists	68
Potassium channel activators	37
Beta blockers	70
Oral nitrates	64
Aspirin and other antiplatelet drugs	96
Cholesterol lowering drugs	92
ACE inhibitors or angiotensin 2 RA	74
<i>Use of 'empirical' acid secretion inhibitors*</i>	
Proton pump inhibitor	16
H <sub>2</sub> receptor antagonist	3

\* Patients with proven gastro-oesophageal reflux or peptic ulcers were excluded from the study

Table 3: Results of ANCOVA analysis of variables, including treatment effect, period effect and carry-over. NHPQ = Nottingham Health Profile Questionnaire, with specific domains listed. Plac = placebo treatment, PPI = Lansoprazole treatment. \* indicates significant difference ( $p < 0.05$ ).

Variable	Treatment effect (p)	Period effect (p)	Sequence effect [carry-over] (p)
	Mean values for placebo and PPI		
<b>Pain free days</b>	0.02 *	0.49	0.43
Adjusted mean no. of days	Plac=5.7, PPI=6.7		
<b>Night Pain</b>	0.009 *	0.59	0.59
Adjusted mean no. of days	Plac =2.96, PPI =2.1		
<b>Rest Pain</b>	0.005 *	0.96	0.57
Adjusted mean no. of days	Plac =4.5, PPI =3.5		
<b>Exertional Pain</b>	0.79	0.35	0.31
Adjusted means	Plac =4.4, PPI =4.3		
<b>NHPQ Energy Levels</b>	0.98	0.26	0.19
Adjusted mean score	Plac =38.4, PPI =38.3		
<b>NHPQ Emotional Reaction</b>	0.95	0.44	0.74
Adjusted mean score	Plac =19.0, PPI =19.1		
<b>NHPQ Pain</b>	0.07	0.21	0.19
Adjusted mean score	Plac =26.3, PPI =23.1		
<b>NHPQ Physical Activity</b>	0.95	0.04 *	0.11
Adjusted mean score	Plac =19.7, PPI =19.8		
<b>NHPQ Sleep</b>	0.24	0.95	0.55
Adjusted mean score	Plac =25.6, PPI =27.9		
<b>NHPQ Social Isolation</b>	0.61	0.28	0.73
Adjusted mean score	Plac =10.2, PPI =10.9		
<b>ST Segment Shifts<sup>1</sup></b>	0.64	0.08	0.55
Geometric means	Plac =2.1, PPI =1.9		

<sup>1</sup>Skewed data so log values used

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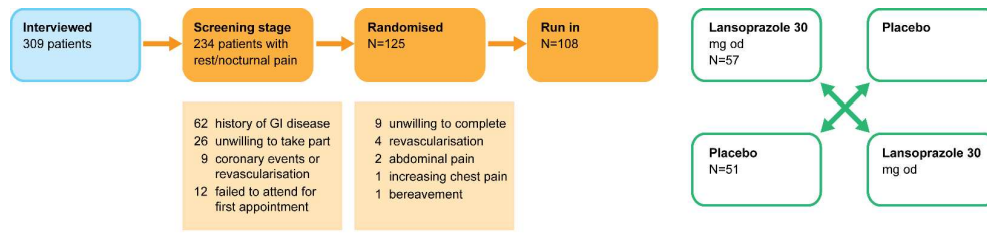
LEGENDS TO FIGURES:

Figure 1: Flow chart of the cross over design. 24 hour ECGs were carried out during the last week of each treatment phase. Patients were asked to fill out the Nottingham Health Profile Questionnaires [NHPQ] during the last day of each of the two treatment phases.

Figure 2a: Individual scores [pain free days, days with rest pain and days with nocturnal pain] for patients who took PPI [x] first followed by placebo [o]. Identical scores for several patients are denoted by extended lines with the number of patients with identical scores given next to the line. The bold lines indicate mean scores.

Figure 2b: Individual scores [pain free days, days with rest pain and days with nocturnal pain] for patients who took placebo [o] first followed by PPI [x]. Identical scores for several patients are denoted by extended lines with the number of patients with identical scores given next to the line. The bold lines indicate mean scores.

FIGURE 1

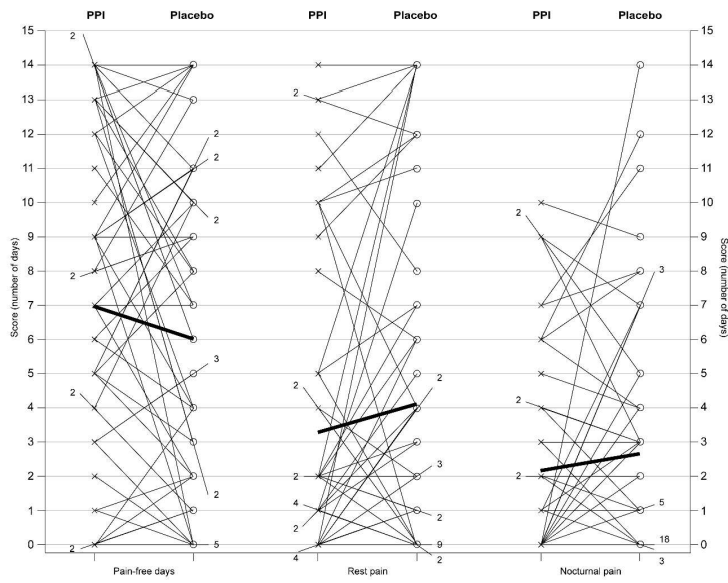


	Run in		Treatment 1				Wash out		Treatment 2				
Weeks	0	1	2	3	4	5	6	7	8	9	10	11	12
Informed consent	█												
Medical history	█												
Physical examination													
Drug administration			█	█	█	█	█			█	█	█	█
Symptom diary		█	█	█	█	█	█			█	█	█	█
Analysis of symptom diary											█	█	█
NHPQ													█
24 hour ECG							█						█

Peer Review

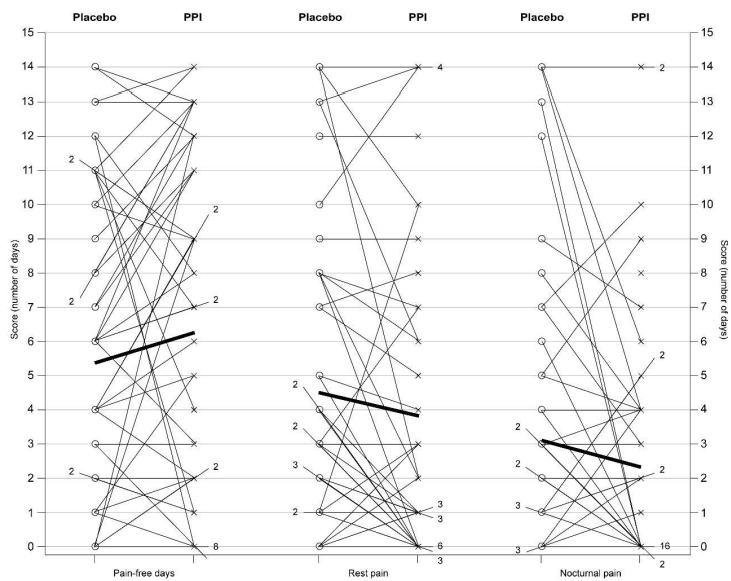
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FIGURE 2 A



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FIGURE 2 B



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## CONSORT 2010 checklist of information to include when reporting a randomised trial\*

Section/Topic	Item No	Checklist item	Reported on page No
<b>Title and abstract</b>			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
<b>Introduction</b>			
Background and objectives	2a	Scientific background and explanation of rationale	3-5
	2b	Specific objectives or hypotheses	5
<b>Methods</b>			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	5-8
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	7
Participants	4a	Eligibility criteria for participants	Table 1; p6-7
	4b	Settings and locations where the data were collected	P5, 6
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	Figure 1, p7
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	P 7-8
	6b	Any changes to trial outcomes after the trial commenced, with reasons	P 7
Sample size	7a	How sample size was determined	P 6
	7b	When applicable, explanation of any interim analyses and stopping guidelines	N/A
<b>Randomisation:</b>			
Sequence generation	8a	Method used to generate the random allocation sequence	P 7
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	P 7
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	P 7
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	P 7
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	P 7



1		assessing outcomes) and how	
2		11b If relevant, description of the similarity of interventions	N/A
3	Statistical methods	12a Statistical methods used to compare groups for primary and secondary outcomes	P 8
4		12b Methods for additional analyses, such as subgroup analyses and adjusted analyses	P 8
5			
6	<b>Results</b>		
7	Participant flow (a	13a For each group, the numbers of participants who were randomly assigned, received intended treatment, and	P 9, figure 1
8	diagram is strongly	were analysed for the primary outcome	
9	recommended)	13b For each group, losses and exclusions after randomisation, together with reasons	P 9, Figure 1
10	Recruitment	14a Dates defining the periods of recruitment and follow-up	P 9
11		14b Why the trial ended or was stopped	P 9
12			
13	Baseline data	15 A table showing baseline demographic and clinical characteristics for each group	Table 2
14	Numbers analysed	16 For each group, number of participants (denominator) included in each analysis and whether the analysis was	P 9-11; Table
15		by original assigned groups	3
16			
17	Outcomes and	17a For each primary and secondary outcome, results for each group, and the estimated effect size and its	P 9-11; Table
18	estimation	precision (such as 95% confidence interval)	3
19		17b For binary outcomes, presentation of both absolute and relative effect sizes is recommended	N/A
20	Ancillary analyses	18 Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing	N/A
21		pre-specified from exploratory	
22	Harms	19 All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	P 9, 10
23			
24	<b>Discussion</b>		
25	Limitations	20 Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	P 11-16
26	Generalisability	21 Generalisability (external validity, applicability) of the trial findings	P 11-16
27	Interpretation	22 Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	P 11-16
28			
29	<b>Other information</b>		
30	Registration	23 Registration number and name of trial registry	N/A
31	Protocol	24 Where the full trial protocol can be accessed, if available	Authors
32	Funding	25 Sources of funding and other support (such as supply of drugs), role of funders	P 16
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\*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see [www.consort-statement.org](http://www.consort-statement.org).

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**Clinical trial: chest pain due to presumed gastro-oesophageal reflux in coronary artery disease - controlled study of lansoprazole versus placebo**

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**Keywords:** Coronary artery disease ischaemic heart disease, gastro-oesophageal reflux, chest pain, proton pump inhibitor

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**ABSTRACT.**

*Background:* Gastro-oesophageal reflux (GOR) and coronary artery disease (CAD) commonly co-exist. CAD patients may mistake GOR-induced pain for cardiac pain or GOR might provoke angina. *Aim:* GOR might contribute to nocturnal/rest chest pain among CAD patients. *Methods:* Double-blind placebo-controlled crossover study investigating effect of Lansoprazole on chest pain; 125 patients with angiographically proven CAD enrolled with at least one weekly episode of nocturnal/rest pain, randomized to Lansoprazole 30mg daily or placebo with crossover after 4 weeks. Symptoms recorded and QOL assessed by Nottingham Health Profile Questionnaire; ST segment depression episodes counted from 24hour electrocardiographic monitoring in final week of both periods. *Statistical analysis:* ANCOVA with period and carryover analysis. *Results:* 108 patients completed. There was a modest increase in pain-free days on Lansoprazole vs placebo ( $p<0.02$ ), with fewer days with pain at rest ( $p<0.05$ ) and at night ( $p<0.009$ ) on Lansoprazole vs placebo, but no significant differences in ST segment depression episodes ( $p=0.64$ ). There was a trend for reduction of the 'physical pain' QOL domain. *Conclusion:* Among CAD patients, Lansoprazole modestly increases pain-free days and reduces rest/nocturnal pain. Since Lansoprazole did not affect ST segments, this may be by suppression of GOR-provoked pain misinterpreted as angina rather than acid-provoked ischaemia.

## Introduction

Gastro-oesophageal reflux (GOR) and coronary artery disease (CAD) are both common conditions: it is therefore not surprising that both can co-exist in some patients<sup>1-3</sup>. 'Linked angina' was a term introduced many years ago by Smith and Papp to describe patients with '...an anginal syndrome ... blending with pain or discomfort arising from non-cardiac sources'<sup>4</sup>. They pointed out the neural link between viscera (such as gallbladder and oesophagus) and heart demonstrated in clinical observations of cardiac ischaemia in response to distension of biliary tree or oesophagus<sup>5-7</sup> and described clinical cases in which CAD was linked with a variety of upper gastrointestinal disorders<sup>4</sup>. These observations have since been elegantly revisited and confirmed in a series of studies in patients with CAD and 'Syndrome X', finding reduced coronary perfusion in response to acid infusion of the esophagus<sup>8,9</sup>. The fact that this phenomenon could not be demonstrated in patients with a transplanted heart argues strongly for a neural mechanism<sup>9</sup>. The possible clinical relevance of acid induced cardiac ischaemia is shown by studies demonstrating that anginal pain together with electrocardiographic evidence of cardiac ischemia could be provoked by acid perfusion<sup>10</sup> and that the exertional angina threshold could be lowered by acid perfusion<sup>11</sup>. More recent studies of CAD patients monitored with both ambulatory pH and electrocardiography have shown the association of some episodes of cardiac ischaemia with spontaneous acid reflux<sup>1,3</sup>.

Another mechanism for interaction between oesophageal pain and angina is the potential for the 2 symptoms to be confused by patients. This was first recognized by Kramer and Hollander using oesophageal balloon distension<sup>7</sup> and has been found to be

1  
2 common in some patients with both reflux and CAD<sup>1-3</sup>. The phenomenon is explained by  
3  
4 'viscero-visceral' convergence of nociceptor neural pathways onto the same second order  
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6 spinothalamic tract neurons in the posterior horns of the spinal cord which has been  
7  
8 confirmed directly in animal models<sup>12,13</sup> and would appear from clinical studies to be the  
9  
10 commonest mechanism<sup>1,3</sup>.  
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14 In clinical practice, patients with angina in whom symptoms are increasing in  
15  
16 frequency or are occurring at rest, the primary clinical concern will be to intervene  
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18 among those who on investigation have worsening coronary stenoses. From the above  
19  
20 discussion, it would appear that among those patients who do not have critical stenoses  
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22 there exists the potential for unrecognized GOR to mislead the physician, which could  
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24 explain the occurrence of angina in non-exertional situations such as the angina 'linked'  
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26 with meals or with recumbency and sleep<sup>4</sup>. Indeed, nitrates and calcium channels  
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28 antagonists used in the treatment of ischaemic heart disease may provoke GOR<sup>3,14</sup> so that  
29  
30 escalating treatment could in these circumstances increase chest pain, leading the  
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32 physician to the erroneous conclusion that CAD was worsening. Simultaneous work up  
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34 of CAD patients by a gastroenterologist is often not practical, or in the absence of an  
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36 oesophageal function laboratory, simply not possible. In this clinical situation empirical  
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38 acid suppression is often prescribed<sup>15</sup>. A small open study has provided support for the  
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40 use of acid suppression by proton pump inhibitor in patients with chronic stable angina in  
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42 whom both GOR and CAD have been found to co-exist<sup>2</sup> while a large retrospective  
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44 review of patients with CAD treated with proton pump inhibitors has reported 50%  
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46 reduction in patients free of chest pain, emergency room visits and hospital admissions  
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2 compared to those not treated<sup>15</sup>. The utility of this approach has not been tested in a  
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4 controlled clinical trial.  
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9 Our aim was therefore to test the hypothesis that among patients with stable CAD,  
10 chest pain at rest or during recumbence (at night) in whom there was a likelihood of GOR  
11 acid suppression with a proton pump inhibitor (PPI) might reduce chest pain. We  
12 investigated the efficacy of acid suppression with a PPI (Lansoprazole 30mg once a day)  
13 in patients with CAD and rest or nocturnal pain. The primary endpoint was the reduction  
14 in chest pain symptoms. Secondary endpoints were the impact of treatment on quality of  
15 life measures and on spontaneous ischaemic episodes using 24 hour Holter monitoring.  
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#### 24 **Patients and methods**

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26 An initial feasibility study was carried out by face to face interviews using a  
27 structured questionnaire survey of 106 consecutive patients with a diagnosis of CAD  
28 attending cardiology outpatients at Glenfield Hospital, Leicester, UK. The majority  
29 (95%) fulfilled the Rose criteria<sup>16</sup> for angina pectoris and 68% had some episodes of pain  
30 at rest and or during recumbence at night.  
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39 The trial was approved by the Leicestershire District Ethics Committee.  
40 Patients were recruited from the cardiology out patient department at Glenfield Hospital  
41 and from the waiting lists for percutaneous coronary revascularization or coronary artery  
42 bypass grafting over a 2 year period. Patients with unstable angina or acute coronary  
43 syndromes were not recruited: patients were only recruited from waiting lists for  
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3 coronary revascularization, if they were classed as 'routine' which at the time of the  
4 study meant at least 3 months' procedural wait. To calculate the numbers needed for the  
5 study, we used figures derived from previous studies for expected numbers of chest pain  
6 episodes per day in patients with CAD during combined ambulatory pH and  
7 electrocardiographic monitoring, together with their estimates of the proportion  
8 associated with reflux episodes<sup>1,3</sup>. Garcia et al reported  $1.71 \pm 1.75$  chest pain episodes  
9 per day in patients with IHD in whom an oesophageal contribution to chest pain was  
10 suspected<sup>1</sup>. Based on these figures and an expected 33% reduction in chest pain episodes  
11 on treatment with proton pump inhibitors, we calculated that 130 patients would have to  
12 be enrolled in this trial to lend it 80% power at a 5% level of statistical significance.  
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25 All patients had angiographically documented coronary artery disease with at  
26 least 50% stenosis in one main epicardial coronary vessel. Subjects were invited to  
27 participate in the study if, in addition to exertional angina, they had at least one episode  
28 of chest pain at rest or during the night per week. This was assessed by monitoring  
29 symptoms with the help of diaries during a run in period of observation (continuing their  
30 usual anti-anginal medication) for two weeks prior to enrolment.  
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39 Eligibility and exclusion criteria are listed in table 1. Current medication was  
40 recorded. Patients on PPIs or H<sub>2</sub> receptor antagonists (H<sub>2</sub>RA) for overt dyspeptic and  
41 GOR associated symptoms were excluded; we specifically excluded any patients with  
42 endoscopically diagnosed peptic ulceration and oesophagitis, as well as any patients  
43 complaining of ulcer-type dyspepsia (meal related or nocturnal epigastric pain).  
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However, patients who were taking PPIs or H<sub>2</sub>RAs, which were empirically prescribed for chest pain, were allowed to participate after discontinuing the relevant drug for four weeks.

The trial carried a double blind cross over design and is illustrated by the flow chart in Figure 1. All patients continued their usual cardiac medication. After obtaining written consent, patients were randomly assigned either to receive Lansoprazole 30 mg once daily or placebo once daily for a period of four weeks following a run in period of two weeks. Both Lansoprazole and matching placebo were supplied by Wyeth Pharmaceutical, Taplow, Maidenhead, UK. After a two week wash out phase the patients were crossed over.

Patients were given a symptom diary and asked to indicate for each day whether they had experienced any of the following: exertional chest pain, chest pain at rest or during recumbence (at night). Our intention had been to analyze the total number of chest pain events (on exertion, at rest, at night). However, since we found that only 56 of the 108 patients completing the trial had entered the actual number of chest pain episodes as instructed in their symptom diaries, and the remainder had simply recorded whether chest pain occurred or not in each 24 hour period, we made a decision to analyze the number of days with (or without) symptoms. To minimize carry over effects only the last two weeks of each study treatment period were analyzed. In addition 24hour ambulatory ECG monitoring (Reynolds Lifecard, Reynolds Medical Ltd, Harforde Court, Hertford, United Kingdom) was performed during the last week of each 4 week trial period to detect



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spontaneous ST segment shifts. The number of ST segment shifts (more than 1mm down-sloping ST depression or ST-elevation for at least 80 milliseconds from the J point compared with the isoelectric segment and lasting at least 60 seconds in 1 or more channels<sup>17</sup>) was counted and compared between placebo and active treatment (Reynolds Lifecard, Reynolds Medical Ltd, Harforde Court, Hertford, United Kingdom).

Quality of life was assessed using the Nottingham Health Profile questionnaire (NHPQ)<sup>18,19</sup>. This includes six domains of quality of life (energy, pain, emotional reactions, sleep, social isolation and physical mobility). The questionnaire has been validated in a large number of studies of chronic ill health including cardiovascular illness<sup>18</sup>. The questionnaire was administered at the start of the run in period and at the end of each of the two treatment periods.

Results are expressed as mean  $\pm$  standard error (SE). Analysis of covariance (ANCOVA)<sup>20</sup> was carried out using SAS Proc Mixed (SAS v9.1)<sup>21</sup>. Statistical significance required  $p < 0.05$ . The treatment effect involved comparing the number of pain free days, days with rest and nocturnal pain and days with exertional pain on treatment versus placebo. Terms for period and carry-over effects were entered into the statistical models, and patient was declared as a random effect. The Nottingham Health Profile scores (each of six quality of life domains) were also compared for the two treatment periods. ST-segment shift frequency was compared in the same way.

## Results

Patients for the study were recruited from cardiology out patients (2450 case notes reviewed) and, in the early phase of the trial, from the waiting list for coronary artery bypass surgery (379 patients). Out patients were initially screened through review of their medical case notes and patients on the waiting list for bypass grafting were invited via letter. Only 23 subjects on the waiting list responded to the letter of which 4 were willing to take part, all of whom eventually completed the trial. All other patients were not willing to participate in a clinical trial prior to their planned surgery.

In the out-patient cohort only one fifth of patients (524) had complained about ongoing chest pain (any chest pain including exertional pain, pain at rest or nocturnal pain) at their most recent out-patient visit. Of these, 309 patients were willing to attend for a screening visit (see Figure 1); 234 patients in this cohort appeared to have either rest or nocturnal chest pain or both. However, 62 patients had a history of documented gastrointestinal disease (chiefly peptic ulcer disease or gastro-oesophageal reflux disease demonstrated by prior endoscopy), 26 patients were unwilling to take part – mainly citing inconvenience- after further information was provided, 9 patients underwent revascularisation or suffered a cardiac event. The remaining patients cited various other reasons or simply failed to attend for their first trial visit. Eventually 125 patients entered the run in phase of the trial (including the four patients from the CABG waiting list).

Of the 125 patients enrolled, 108 completed the trial (Figure 1). Seventeen patients dropped out for the following reasons: emergency bypass grafting or percutaneous revascularization due to development of acute coronary syndromes (4

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2 patients), unwillingness to complete the trial (9 patients), bereavement (1 patient),  
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4 diarrhea and abdominal pain on placebo (2 patients), increasing chest pain on  
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6 Lansoprazole (1 patient). The patients' characteristics are listed in table 2.  
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11 Considering the last two weeks of each treatment period, the number of pain free  
12 days, days with pain at rest, at night, and days with exertional pain are shown in [table 3](#)  
13 [and illustrated in figures 2A and 2B](#). There was a significant ( $p<0.02$ ) increase in the  
14 number of pain free days on treatment with Lansoprazole ( $6.7 \pm 0.47$ ) as compared to  
15 placebo ( $5.7 \pm 0.47$ ). Both the number of days with pain at rest ( $3.53 \pm 0.46$  vs.  $4.51 \pm$   
16  $0.46$ ,  $p<0.005$ ) and pain at night ( $2.1 \pm 0.35$  vs.  $2.96 \pm 0.35$ ,  $p<0.009$ ) were significantly  
17 less on Lansoprazole than on placebo. There appeared to be no effect on exertional pain  
18 ( $p=0.79$ ).  
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29 The effects of treatment on quality of life measures are listed in [table 3](#). None of  
30 the measured parameters showed a significant difference between treatment with  
31 Lansoprazole and placebo. However, pain perception scores as assessed by the NHPQ  
32 (mean 23.14 [PPI] vs. 26.33 [placebo]) showed a trend ( $p=0.07$ ) for reduction on  
33 Lansoprazole .  
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41 Two complete 24 hour tapes were available for 89 of 108 patients. Three tapes  
42 could not be analyzed due to a bundle branch block pattern. Sixteen patients refused one  
43 or both tapes citing inconvenience (15 patients) and depression (1 patient) as reasons.  
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45 However, chest pain diary data were available for these subjects and are included in the  
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2 preceding analysis. The mean number of ST shift episodes was  $0.75 \pm 0.21$  (SE) on  
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4 placebo as compared to  $0.63 \pm 0.22$  on PPI. This difference was not significant ( $p= 0.64$ ;  
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6 **Table 3**). Only 24 patients showed any ST segment changes during the trial. No  
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8 significant difference between placebo and Lansoprazole phases were found when only  
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10 the 24 patients showing any ST segment changes were included in a subgroup analysis.  
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### 13 14 **Discussion**

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16 This study is to our knowledge the first randomized blinded clinical trial  
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18 investigating the clinical efficacy of empirical treatment with PPIs in patients with  
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20 chronic stable angina due to documented CAD. The data show that standard dose  
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22 Lansoprazole increases the number of pain-free days, mainly by decreasing rest and  
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24 nocturnal pain symptoms. The effect is modest with on average 1 more pain free day on  
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26 PPI compared to placebo. Although it is a common clinical intervention<sup>15</sup>, the modest  
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28 symptomatic benefit observed in this randomised trial could be interpreted as meaning  
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30 that it is not worthwhile undertaking in unselected patients. It may be that selecting  
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32 patients on the basis of abnormal testing for gastro-oesophageal reflux would identify a  
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34 subgroup more likely to respond as has been found in one open study<sup>2</sup>.  
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40 It should be noted that that none of the patients in this study had 'unstable' or  
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42 worsening angina nor were patients with acute coronary syndromes studied. In all such  
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44 patients, the appropriate clinical management remains urgent cardiological investigation  
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46 and intervention. Our results are pertinent only to the use of PPI therapy in patients who  
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48 have stable angina and are not requiring urgent cardiological intervention.  
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5 The trial has several limitations: ideally it might have been designed as a  
6 randomized parallel group comparison between 2 separate PPI treatment and placebo  
7 arms but this would have doubled the sample size necessary. Indeed over 2800 patients  
8 were screened to find 125 who were willing to participate. Although we did not achieve  
9 our recruitment target of 130 patients, the power calculation was necessarily (since there  
10 were few data on which to base our calculations) a very crude estimate of the numbers  
11 required. Cross over designs have the problem of potential carryover effect: we sought to  
12 limit this by including a 2 week washout period between treatment periods and by only  
13 analyzing the patient diary in the last 2 weeks of each 4 week treatment period. In fact  
14 carry-over was not observed by statistical analysis by ANCOVA. An 'order effect' has  
15 also not been shown by the ANCOVA analysis: the likely impact of this would have been  
16 to reduce the size of the treatment effect, since the order 'PPI first, placebo second' is the  
17 one likely to have had a carry over effect into the second placebo treatment period. This  
18 is because acid suppression may have an effect on reducing esophageal sensitivity to acid  
19 which variably outlasts the treatment period by several weeks<sup>22,23</sup>. We chose  
20 Lansoprazole 30 mg administered once daily rather than higher twice daily doses often  
21 used in the investigation of non-cardiac chest pain<sup>24</sup>. It is known that twice daily  
22 administration of PPI produces more profound acid suppression<sup>25</sup> and it is therefore  
23 possible that a twice daily administration schedule would have increased the treatment  
24 effect. It is less likely that prolonging the period of acid suppression would altered the  
25 results of the study, since it is known that predictable response to treatment occurs in  
26 short periods (usually 2 weeks) of treatment with a PPI, at least in the context of patients  
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2 with non-cardiac chest pain<sup>24</sup>. However, in the current study we found a modest reduction  
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4 in chest pain with once daily Lansoprazole: the limitations referred to above would have  
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6 been expected (if anything) to have reduced the treatment effect. The apparent lack of  
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8 efficacy as far as quality of life scores are concerned is disappointing although there was  
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10 a trend towards reduction of pain associated parameters.  
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15 There appeared to be no significant effect of acid suppression on spontaneous  
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17 ischaemic ST segment shifts during 24 hour ambulatory electrocardiographic monitoring  
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19 (although there was a slight reduction in frequency during treatment with PPI). However,  
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21 only 24 patients out of 89 (patients with 2 interpretable 24 hour tapes) showed any  
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23 spontaneous ST segment shifts, with no significant difference between placebo and PPI  
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25 on subgroup analysis. This would suggest that, taken as a group, these patients were in  
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27 the main well treated for their CAD, despite having episodes of chest pain at rest. There  
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29 were a small number who continued to have ST segment shifts despite 'optimal medical  
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31 therapy'. While we have not scrutinized these individuals in detail, it may be that 24 hour  
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33 ST segment monitoring identifies a subgroup among which medical treatment for angina  
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35 should be reviewed or coronary intervention considered more urgently.  
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40 We did not attempt to assess whether ST segment shifts were symptomatic since  
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42 patients were not instructed to note the exact time of symptoms in their symptom diaries,  
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44 though it is well recognized that among CAD patients undergoing 24 hour  
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46 electrocardiographic monitoring the majority of ischemic ST segment shifts (>70%) are  
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48 asymptomatic<sup>26-28</sup>. Other modalities such as exercise tolerance testing might be more  
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2 suitable to detect the effect of acid suppressants on the cardiac ischaemia but were  
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4 deemed inappropriate because of the potential risk of exercise-induced arrhythmia among  
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6 patients with known IHD. However, ambulatory electrocardiographic monitoring has  
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8 good accuracy compared to both exercise ECG testing and positron emission tomography  
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10 to detect reversible defects in myocardial perfusion<sup>26,29</sup>.  
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14 It would seem likely from our observations that the mechanism of the beneficial  
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16 effect we observed on chest pain reduction, particularly at night and at rest, was not  
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18 generally due to an effect on the 'cardio-oesophageal reflex' described by Chauhan and  
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20 colleagues<sup>8,9</sup>, as we would have expected to see a reduction in ST segment shifts during  
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22 PPI treatment. However, since ST segment shift were only seen in about 30% of our  
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24 patients such an effect could have been 'swamped' by the majority of normal ambulatory  
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26 studies. We did not find a significant effect of PPI when we confined our analysis to the  
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28 subgroup of 24 patients with ST segment changes on ambulatory recording. Thus, these  
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30 findings are consistent with previous observations that most episodes of chest pain in  
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32 CAD subjects associated with reflux occur when acid-induced pain is misinterpreted by  
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34 patients as 'angina'<sup>2,3</sup>, but we cannot exclude the possibility that cardiac ischaemia may  
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36 occur in some patients as a result of a cardio-oesophageal reflux as observed in a  
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38 minority of patients in one study<sup>3</sup>, particularly as we did not carry out pH monitoring in  
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40 our subjects.  
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45 It is also pertinent that we failed to find a reduction in exertional chest pain  
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47 episodes during PPI treatment, since one study has suggested that intra-oesophageal acid  
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2 may reduce exertional anginal threshold<sup>11</sup>. It is possible that an effect on exertional  
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4 angina might have been found if patients had been selected on the basis of having  
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6 objective evidence of both GOR and CAD, although the patients reported by Alban  
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8 Davies and colleagues had CAD only<sup>11</sup>. Our study was empirical, designed to test the  
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10 utility of treating patients with proven CAD who also had rest or nocturnal pain, on the  
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12 basis that this is a common intervention in clinical practice. The results are consistent  
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14 with the conclusion that an effect of PPI therapy on exertional anginal threshold is not a  
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16 likely explanation of the modest efficacy of this treatment.  
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21 In conclusion, our study supports the hypothesis that among patients with 'stable'  
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23 angina, chest pain at rest or at night may be caused by acid GOR and is not necessarily a  
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25 manifestation of critical CAD. Our results support the observations in earlier studies  
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27 using pH monitoring that the mechanism of such pain is usually due to misinterpretation  
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29 of acid-provoked oesophageal pain with anginal pain<sup>1,3</sup>, rather than due to a cardio-  
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31 oesophageal reflex<sup>8,9</sup>. The results also provide some justification for the use of empirical  
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33 PPI therapy in patients with CAD and rest pain in addition to exertional chest pain, but  
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35 only after appropriate cardiological investigation and management (either medical or  
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37 interventional). There has been recent controversy about the use of PPIs (particularly  
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39 omeprazole and esomeprazole) in patients using Clopidogrel since the latter is a prodrug  
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41 requiring activation by CYP2C19, part of the cytochrome P450 liver microsomal enzyme  
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43 system. While this enzyme is inhibited by some PPIs thus reducing the production of the  
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45 active metabolite of Clopidogrel<sup>30</sup>, the clinical effects are unclear with some case control  
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47 studies suggesting a clinically relevant interaction, others not so<sup>31,32</sup>. The issue is  
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2 complicated by the fact that many of these studies have not adequately excluded  
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4 confounding effects, and the fact that genetically determined differences in CYP2C19  
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6 metabolism has a marked effect on Clopidogrel handling which has not been examined in  
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8 these studies<sup>32</sup>. Since both Clopidogrel and PPIs have short serum half lives, it has been  
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10 suggested that administering each at a different time (12 hours separation) might mitigate  
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12 this interaction but this has not been proved. In addition to the clinical scenario explored  
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14 in our study, co-prescription of PPIs and Clopidogrel is an important consideration in  
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16 terms of reducing risk of upper GI bleeding. For the reasons discussed above and since  
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18 the magnitude of the benefit of prescribing a PPI among patients with CAD is modest, it  
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20 may be both more prudent and more cost effective (if worsening CAD has been excluded  
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22 by cardiological investigation) to investigate patients with frequent rest pain with a view  
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24 to proving abnormal GOR prior to initiating PPI therapy.  
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36 Laboratories kindly supplied Lansoprazole and matching placebo tablets for the trial.  
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**Table 1. Eligibility criteria**

*Inclusion criteria*

Age > 18yr

Angiographically documented coronary artery disease with a stenosis of at least 50% in one main coronary vessel

At least one episode of rest or nocturnal chest pain per week in addition to exertional angina

*Exclusion criteria*

Pregnancy

Upper gastrointestinal disorder clearly identified by prior investigation (peptic ulcer, endoscopic oesophagitis) or typical symptoms (heartburn  $\geq$  once a week)

Severe comorbidity (malignancy, previous disabling stroke and advanced chronic airflow limitation)

Coronary artery bypass surgery in the past 12 months

Patients on PPIs or H<sub>2</sub>RA for proven acid-related conditions\*

*\*Patients on 'empirical' acid suppression allowed provided treatment stopped for 4 weeks*



**Table 2: Patient characteristics**

Number enrolled	125
Number completing trial	108 (92 male)
Age - mean $\pm$ SD, (range)	66 $\pm$ 9.3 (44-85) years
Ethnicity	White 101 South Asian 7
Angiographically confirmed IHD	108 ( <i>all patients completing trial</i> )
Single vessel disease	3
Two or more vessel disease	105
History of myocardial infarction	41
History of coronary bypass grafting	19
History of percutaneous revascularization	60
Diabetes mellitus	24
Arterial hypertension	48
<i>Medication</i>	
Calcium channel antagonists	68
Potassium channel activators	37
Beta blockers	70
Oral nitrates	64
Aspirin and other antiplatelet drugs	96
Cholesterol lowering drugs	92
ACE inhibitors or angiotensin 2 RA	74
<i>Use of 'empirical' acid secretion inhibitors*</i>	
Proton pump inhibitor	16
H <sub>2</sub> receptor antagonist	3

\* Patients with proven gastro-oesophageal reflux or peptic ulcers were excluded from the study

Table 3: Results of ANCOVA analysis of variables, including treatment effect, period effect and carry-over. NHPQ = Nottingham Health Profile Questionnaire, with specific domains listed. Plac = placebo treatment, PPI = Lansoprazole treatment. \* indicates significant difference ( $p < 0.05$ ).

Variable	Treatment effect (p)	Period effect (p)	Sequence effect [carry-over] (p)
	Mean values for placebo and PPI		
<b>Pain free days</b>	0.02 *	0.49	0.43
Adjusted mean no. of days	Plac=5.7, PPI=6.7		
<b>Night Pain</b>	0.009 *	0.59	0.59
Adjusted mean no. of days	Plac =2.96, PPI =2.1		
<b>Rest Pain</b>	0.005 *	0.96	0.57
Adjusted mean no. of days	Plac =4.5, PPI =3.5		
<b>Exertional Pain</b>	0.79	0.35	0.31
Adjusted means	Plac =4.4, PPI =4.3		
<b>NHPQ Energy Levels</b>	0.98	0.26	0.19
Adjusted mean score	Plac =38.4, PPI =38.3		
<b>NHPQ Emotional Reaction</b>	0.95	0.44	0.74
Adjusted mean score	Plac =19.0, PPI =19.1		
<b>NHPQ Pain</b>	0.07	0.21	0.19
Adjusted mean score	Plac =26.3, PPI =23.1		
<b>NHPQ Physical Activity</b>	0.95	0.04 *	0.11
Adjusted mean score	Plac =19.7, PPI =19.8		
<b>NHPQ Sleep</b>	0.24	0.95	0.55
Adjusted mean score	Plac =25.6, PPI =27.9		
<b>NHPQ Social Isolation</b>	0.61	0.28	0.73
Adjusted mean score	Plac =10.2, PPI =10.9		
<b>ST Segment Shifts<sup>1</sup></b>	0.64	0.08	0.55
Geometric means	Plac =2.1, PPI =1.9		

<sup>1</sup>Skewed data so log values used

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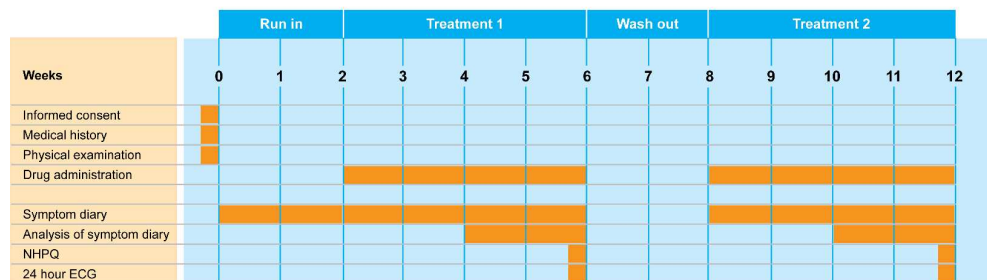
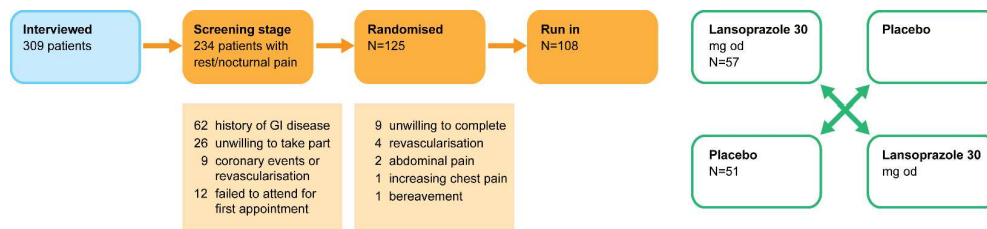
LEGENDS TO FIGURES:

Figure 1: Flow chart of the cross over design. 24 hour ECGs were carried out during the last week of each treatment phase. Patients were asked to fill out the Nottingham Health Profile Questionnaires [NHPQ] during the last day of each of the two treatment phases.

Figure 2a: Individual scores [pain free days, days with rest pain and days with nocturnal pain] for patients who took PPI [x] first followed by placebo [o]. Identical scores for several patients are denoted by extended lines with the number of patients with identical scores given next to the line. The bold lines indicate mean scores.

Figure 2b: Individual scores [pain free days, days with rest pain and days with nocturnal pain] for patients who took placebo [o] first followed by PPI [x]. Identical scores for several patients are denoted by extended lines with the number of patients with identical scores given next to the line. The bold lines indicate mean scores.

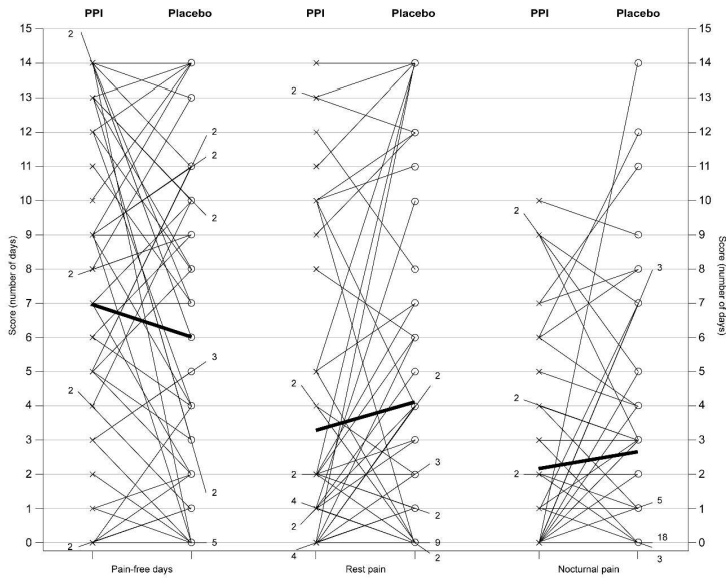
FIGURE 1



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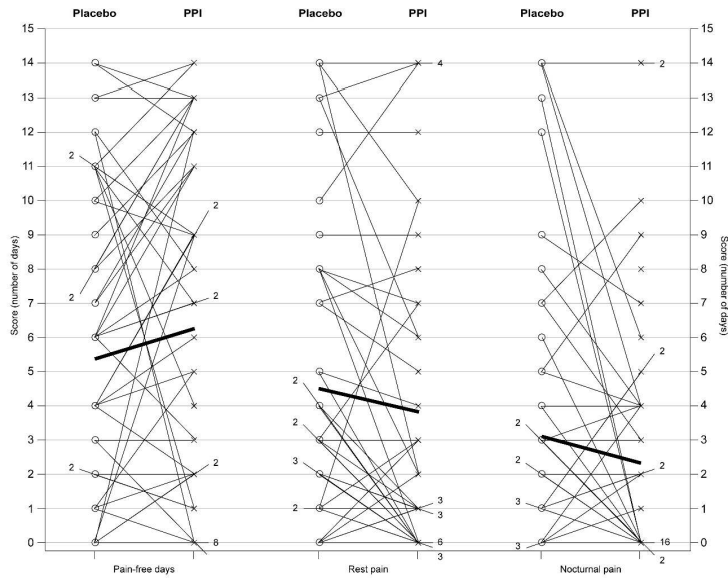
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FIGURE 2 A



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FIGURE 2 B



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