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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.

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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[1-3]. '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'[4]. 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[5-7] and described clinical cases in which CAD was linked with a variety of upper gastrointestinal disorders[4]. 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[8,9]. The fact that this phenomenon could not be demonstrated in patients with a transplanted heart argues strongly for a neural mechanism[9]. 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[10] and that the exertional angina threshold could be lowered by acid perfusion[11]. 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[1,3].

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[7] and has been found to be

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common in some patients with both reflux and CAD[1-3]. The phenomenon is explained by 'viscero-visceral' convergence of nociceptor neural pathways onto the same second order spinothalamic tract neurons in the posterior horns of the spinal cord which has been confirmed directly in animal models[12,13] and would appear from clinical studies to be the commonest mechanism[1,3].

In clinical practice, patients with angina in whom symptoms are increasing in frequency or are occurring at rest, the primary clinical concern will be to intervene among those who on investigation have worsening coronary stenoses. From the above discussion, it would appear that among those patients who do not have critical stenoses there exists the potential for unrecognized GOR to mislead the physician, which could explain the occurrence of angina in non-exertional situations such as the angina 'linked' with meals or with recumbency and sleep[4]. Indeed, nitrates and calcium channels antagonists used in the treatment of ischaemic heart disease may provoke GOR[3,14] so that escalating treatment could in these circumstances increase chest pain, leading the physician to the erroneous conclusion that CAD was worsening. Simultaneous work up of CAD patients by a gastroenterologist is often not practical, or in the absence of an oesophageal function laboratory, simply not possible. In this clinical situation empirical acid suppression is often prescribed[15]. A small open study has provided support for the use of acid suppression by proton pump inhibitor in patients with chronic stable angina in whom both GOR and CAD have been found to co-exist[2] while a large retrospective review of patients with CAD treated with proton pump inhibitors has reported 50% reduction in patients free of chest pain, emergency room visits and hospital admissions

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compared to those not treated[15]. The utility of this approach has not been tested in a controlled clinical trial.

Our aim was therefore to test the hypothesis that among patients with stable CAD, chest pain at rest or during recumbence (at night) in whom there was a likelihood of GOR acid suppression with a proton pump inhibitor (PPI) might reduce chest pain. We investigated the efficacy of acid suppression with a PPI (Lansoprazole 30mg once a day) in patients with CAD and rest or nocturnal pain. The primary endpoint was the reduction in chest pain symptoms. Secondary endpoints were the impact of treatment on quality of life measures and on spontaneous ischaemic episodes using 24 hour Holter monitoring.

Patients and methods

An initial feasibility study was carried out by face to face interviews using a structured questionnaire survey of 106 consecutive patients with a diagnosis of CAD attending cardiology outpatients at Glenfield Hospital, Leicester, UK. The majority (95%) fulfilled the Rose criteria[16] for angina pectoris and 68% had some episodes of pain at rest and or during recumbence at night.

The trial was approved by the Leicestershire District Ethics Committee. Patients were recruited from the cardiology out patient department at Glenfield Hospital and from the waiting lists for percutaneous coronary revascularization or coronary artery bypass grafting over a 2 year period. Patients with unstable angina or acute coronary 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[1,3]. 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[1]. 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_2 receptor antagonists (H_2RA) 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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However, patients who were taking PPIs or H_2RAs, 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

For Peer Review

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[17]) 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)[18,19]. 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[18]. 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 ± standard error (SE). Analysis of covariance (ANCOVA)[20] was carried out using SAS Proc Mixed (SAS v9.1)[21]. 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.

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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 gastro-intestinal 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 form 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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patients), unwillingness to complete the trial (9 patients), bereavement (1 patient), diarrhea and abdominal pain on placebo (2 patients), increasing chest pain on Lansoprazole (1 patient). The patients' characteristics are listed in table 2.

Considering the last two weeks of each treatment period, the number of pain free days, days with pain at rest, at night, and days with exertional pain are shown in table 3 and illustrated in figures 2A and 2B. There was a significant ($p<0.02$) increase in the number of pain free days on treatment with Lansoprazole (6.7 ± 0.47) as compared to placebo (5.7 ± 0.47). Both the number of days with pain at rest (3.53 ± 0.46 vs. 4.51 ± 0.46, $p<0.005$) and pain at night (2.1 ± 0.35 vs. 2.96 ± 0.35, $p<0.009$) were significantly less on Lansoprazole than on placebo. There appeared to be no effect on exertional pain ($p=0.79$).

The effects of treatment on quality of life measures are listed in table 3. None of the measured parameters showed a significant difference between treatment with Lansoprazole and placebo. However, pain perception scores as assessed by the NHPQ (mean 23.14 [PPI] vs. 26.33 [placebo]) showed a trend ($p=0.07$) for reduction on Lansoprazole .

Two complete 24 hour tapes were available for 89 of 108 patients. Three tapes could not be analyzed due to a bundle branch block pattern. Sixteen patients refused one or both tapes citing inconvenience (15 patients) and depression (1 patient) as reasons. However, chest pain diary data were available for these subjects and are included in the

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preceding analysis. The mean number of ST shift episodes was 0.75 ± 0.21 (SE) on placebo as compared to 0.63 ± 0.22 on PPI. This difference was not significant (p= 0.64; Table 3). Only 24 patients showed any ST segment changes during the trial. No significant difference between placebo and Lansoprazole phases were found when only the 24 patients showing any ST segment changes were included in a subgroup analysis.

Discussion

This study is to our knowledge the first randomized blinded clinical trial investigating the clinical efficacy of empirical treatment with PPIs in patients with chronic stable angina due to documented CAD. The data show that standard dose Lansoprazole increases the number of pain-free days, mainly by decreasing rest and nocturnal pain symptoms. The effect is modest with on average 1 more pain free day on PPI compared to placebo. Although it is a common clinical intervention[15], the modest symptomatic benefit observed in this randomised trial could be interpreted as meaning that it is not worthwhile undertaking in unselected patients. It may be that selecting patients on the basis of abnormal testing for gastro-oesophageal reflux would identify a subgroup more likely to respond as has been found in one open study[2].

It should be noted that that none of the patients in this study had 'unstable' or worsening angina nor were patients with acute coronary syndromes studied. In all such patients, the appropriate clinical management remains urgent cardiological investigation and intervention. Our results are pertinent only to the use of PPI therapy in patients who have stable angina and are not requiring urgent cardiological intervention.

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The trial has several limitations: ideally it might have been designed as a randomized parallel group comparison between 2 separate PPI treatment and placebo arms but this would have doubled the sample size necessary. Indeed over 2800 patients were screened to find 125 who were willing to participate. Although we did not achieve our recruitment target of 130 patients, the power calculation was necessarily (since there were few data on which to base our calculations) a very crude estimate of the numbers required. Cross over designs have the problem of potential carryover effect: we sought to limit this by including a 2 week washout period between treatment periods and by only analyzing the patient diary in the last 2 weeks of each 4 week treatment period. In fact carry-over was not observed by statistical analysis by ANCOVA. An 'order effect' has also not been shown by the ANCOVA analysis: the likely impact of this would have been to reduce the size of the treatment effect, since the order 'PPI first, placebo second' is the one likely to have had a carry over effect into the second placebo treatment period. This is because acid suppression may have an effect on reducing esophageal sensitivity to acid which variably outlasts the treatment period by several weeks[22,23]. We chose Lansoprazole 30 mg administered once daily rather than higher twice daily doses often used in the investigation of non-cardiac chest pain[24]. It is known that twice daily administration of PPI produces more profound acid suppression[25] and it is therefore possible that a twice daily administration schedule would have increased the treatment effect. It is less likely that prolonging the period of acid suppression would altered the results of the study, since it is known that predictable response to treatment occurs in short periods (usually 2 weeks) of treatment with a PPI, at least in the context of patients

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with non-cardiac chest pain[24]. However, in the current study we found a modest reduction in chest pain with once daily Lansoprazole: the limitations referred to above would have been expected (if anything) to have reduced the treatment effect. The apparent lack of efficacy as far as quality of life scores are concerned is disappointing although there was a trend towards reduction of pain associated parameters.

There appeared to be no significant effect of acid suppression on spontaneous ischaemic ST segment shifts during 24 hour ambulatory electrocardiographic monitoring (although there was a slight reduction in frequency during treatment with PPI). However, only 24 patients out of 89 (patients with 2 interpretable 24 hour tapes) showed any spontaneous ST segment shifts, with no significant difference between placebo and PPI on subgroup analysis. This would suggest that, taken as a group, these patients were in the main well treated for their CAD, despite having episodes of chest pain at rest. There were a small number who continued to have ST segment shifts despite 'optimal medical therapy'. While we have not scrutinized these individuals in detail, it may be that 24 hour ST segment monitoring identifies a subgroup among which medical treatment for angina should be reviewed or coronary intervention considered more urgently.

We did not attempt to assess whether ST segment shifts were symptomatic since patients were not instructed to note the exact time of symptoms in their symptom diaries, though it is well recognized that among CAD patients undergoing 24 hour electrocardiographic monitoring the majority of ischemic ST segment shifts (>70%) are asymptomatic[26-28]. 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[26,29].

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[8,9], 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'[2,3], 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[3], 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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may reduce exertional anginal threshold[11]. It is possible that an effect on exertional angina might have been found if patients had been selected on the basis of having objective evidence of both GOR and CAD, although the patients reported by Alban Davies and colleagues had CAD only[11]. Our study was empirical, designed to test the utility of treating patients with proven CAD who also had rest or nocturnal pain, on the basis that this is a common intervention in clinical practice. The results are consistent with the conclusion that an effect of PPI therapy on exertional anginal threshold is not a likely explanation of the modest efficacy of this treatment.

In conclusion, our study supports the hypothesis that among patients with 'stable' angina, chest pain at rest or at night may be caused by acid GOR and is not necessarily a manifestation of critical CAD. Our results support the observations in earlier studies using pH monitoring that the mechanism of such pain is usually due to misinterpretation of acid-provoked oesophageal pain with anginal pain[1,3], rather than due to a cardio-oesophageal reflex[8,9]. The results also provide some justification for the use of empirical PPI therapy in patients with CAD and rest pain in addition to exertional chest pain, but only after appropriate cardiological investigation and management (either medical or interventional). There has been recent controversy about the use of PPIs (particularly omeprazole and esomeprazole) in patients using Clopidogrel since the latter is a prodrug requiring activation by CYP2C19, part of the cytochrome P450 liver microsomal enzyme system. While this enzyme is inhibited by some PPIs thus reducing the production of the active metabolite of Clopidogrel[30], the clinical effects are unclear with some case control studies suggesting a clinically relevant interaction, others not so[31,32]. The issue is

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complicated by the fact that many of these studies have not adequately excluded confounding effects, and the fact that genetically determined differences in CYP2C19 metabolism has a marked effect on Clopidogrel handling which has not been examined in these studies[32]. Since both Clopidogrel and PPIs have short serum half lives, it has been suggested that administering each at a different time (12 hours separation) might mitigate this interaction but this has not been proved. In addition to the clinical scenario explored in our study, co-prescription of PPIs and Clopidogrel is an important consideration in terms of reducing risk of upper GI bleeding. For the reasons discussed above and since the magnitude of the benefit of prescribing a PPI among patients with CAD is modest, it may be both more prudent and more cost effective (if worsening CAD has been excluded by cardiological investigation) to investigate patients with frequent rest pain with a view to proving abnormal GOR prior to initiating PPI therapy.

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Declarations of personal interests: The authors have no competing interests to declare.

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References:

1. Garcia PJ, Patel PH, Hunter WC et al. Esophageal contribution to chest pain in patients with coronary artery disease. Chest 1990 98**:** 806-810.

2. Singh S, Richter JE, Hewson EG et al. The contribution of gastroesophageal reflux to chest pain in patients with coronary artery disease. Ann Int Med 1992 117**:** 824-830.

3. Mehta A, de Caestecker JS, Camm AJ et al. Gastro-esophageal reflux in patients with coronary artery disease: how common is it and does it matter? Eur J Gastroenterol Hepatol 1996 8: 973-978

4. Smith KS, Papp C. Episodic, postural and linked angina. Br Med J 1962 2: 1425-1430.

5. Hampton AG, Beckwith JR, Wood JE. The relationship between heart disease and gallbladder disease. Ann Intern Med 1959 50: 1135 - 1148.

6. Morris JC, Shelburne PF, Orgain ES. Coronary disease and hiatal hernia : an example in support of the existence of a viscerocardiac reflex. JAMA 1963 183: 788 - 790.

For Peer Review

7. Kramer P, Hollander W. Comparison of experimental esophageal pain with clinical pain of angina pectoris and esophageal disease. Gastroenterology 1955 29**:** 719-743.

8. Chauhan A, Petch MC, Schofield PM. Esophageal stimulation can affect coronary blood flow. Lancet 1993 341**:** 1309-1310.

9. Chauhan A, Mullins PA, Taylor G et al . Cardioesophageal reflex: a mechanism for 'linked angina' in patients with angiographically proven coronary artery disease. J Am Coll Cardiol 1996 27: 1621-1628.

10. Mellow MH, Simpson AG, Watt L et al. Esophageal acid perfusion in coronary artery disease. Induction of myocardial ischemia. Gastroenterology 1983 85: 306-312.

11. Davies HA, Page Z, Rush EM et al. Esophageal stimulation lowers exertional angina threshold. Lancet 1985 (i): 1011-1014.

12. Foreman RD, Ohata CA Effects of coronary artery occlusion on thoracic spinal neurons receiving viscerosomatic inputs. Am J Physiol 1980 238: H667 - H674.

For Peer Review

13. Foreman RD, Ammon WS. Angina-like pain: spinal mechanism underlying this symptom in gallbladder disease. In : Advances in pain research and therapy. Ed. Fields HL. (Raven Press, New York) 1985 9: 177 - 184.

14. Mehta AJ, de Caestecker JS, Northfield TC. Effects of nifedipine and atenolol on gastro-esophageal reflux. Eur J Gastroenterol Hepatol 1993; 5: 627-629.

15. Liuzzo JP, Ambrose JA, Diggs P. Proton pump inhibitor use by coronary artery disease patients is associated with fewer chest pain episodes, emergency department visits and hospitalizations. Aliment Pharmacol Ther 2005 22: 95-100.

16. Rose G, McCartney P, Reid D. 'Self-administration of a questionnaire on chest pain and intermittent claudication.' British Journal Preventative Sociological Medicine 1977 31: 42-48

17. Deanfield JE, Ribiero P, Oakley K et al. Analysis of ST segment changes in normal subjects: implications for ambulatory monitoring in angina pectoris. Am J Cardiol 1984 54: 1321-1325.

For Peer Review

18. Hunt SM, McEwen J, McKenna SP. Measuring health status: a new tool for clinicians and epidemiologists. JR Coll. General Practitioners (London) 1985 35: 185-188.

19. Hunt SM, McEwen J, McKenna SP. The Nottingham Health Profile Users Manual, revised edition. Pub. Galen Research, Manchester. (1994).

20. Senn SJ. Cross-over trials in clinical research (2nd Edition). John Wiley, Chichester, England, 2002.

21. SAS 9.1.3 Language reference: Dictionary, 5th Edition, volumes 1-4, Cary, NC: SAS Institute Inc 2006.

22. Marrero JM, de Caestecker JS, Maxwell JD. Effect of famotidine on esophageal sensitivity in gastro-esophageal reflux disease. Gut 1994; 35: 447 - 450.

23. Sarkar S, Thompson DG, Woolf CJ, Hobson AR, Millane T, Aziz Q. Patients with chest pain and occult gastroesophageal reflux demonstrate visceral pain hypersensitivity which may be partially responsive to acid suppression. Am J Gastroenterol. 2004; 99:1998-2006.

For Peer Review

24. Wang WH, Huang JQ, Zheng GF et al. Is proton pump inhibitor testing an effective approach to diagnose gastroesophageal reflux disease in patients with noncardiac chest pain? A meta-analysis. Arch Intern Med. 2005; 165:1222-1228.

25. Kuo B, Castell DO. Optimal dosing of omeprazole 40 mg daily: effects on gastric and esophageal pH and serum gastrin in healthy controls. Am J Gastroenterol. 1996 91:1532-8.

26. Deanfield JE, Maseri A, Selwyn AP et al. Myocardial ischemia during daily life in patients with stable angina: its relation to symptoms and heart rate changes. Lancet 1983 ii: 753-758.

27. Selwyn AP, Fox K, Eves M et al. Myocardial ischemia in patients with frequent angina pectoris. BMJ 1978 2: 1594-1596.

28. Campbell S, Barry J, Rebecca GS et al . Active ischemia during daily life in asymptomatic patients with positive exercise tests and coronary artery disease. Am J Cardiol 1986 57: 1010-1016.

29. Nabel EG, Rocco MB, Selwyn AP. Characteristics and significance of ischemia detected by ambulatory electrocardiographic monitoring. Circulation 1987 75 (Suppl. V): V74-83.

For Peer Review

30. Gilard M , Arnaud B , Cornily JC *et al.* Influence of omeprazole on the antiplatelet action of clopidogrel associated with aspirin: the randomized, double-blind OCLA (Omeprazole CLopidogrel Aspirin) study . JACC 2008; 51: 256-60.

31. Moayyedi P, Sadowski DC. Proton pump inhibitors and Clopidogrel: hazardous interaction or hazardous interpretation of data? Can J Gastroenterol. 2009; 23: 251-2.

32. Laine L, Hennekens C. Proton Pump Inhibitor and Clopidogrel interaction: fact or fiction? Am J Gastroenterol. 2010; 105: 34-41.

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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 ≥ 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_2RA for proven acid-related conditions*

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

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Table 2: Patient characteristics

Number enrolled	125	
Number completing trial	108 (92 male)	
Age - mean ± SD, (range)	66 ± 9.3 (44-85) years	
Ethnicity	White	101
	South Asian	7
Angiographically confirmed IHD	108 *(all patients completing trial)*	
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	
Medication		
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	
*Use of 'empirical' acid secretion inhibitors**		
Proton pump inhibitor	16	
H_2 receptor antagonist	3	

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

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

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

[1]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 [×] 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 [×]. 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.

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FIGURE 1

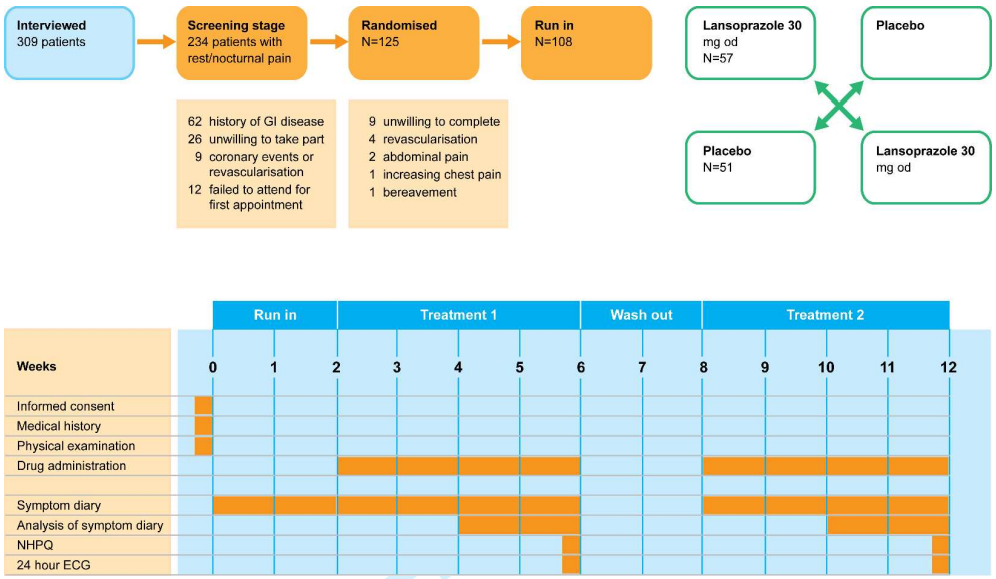

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FIGURE 2 A

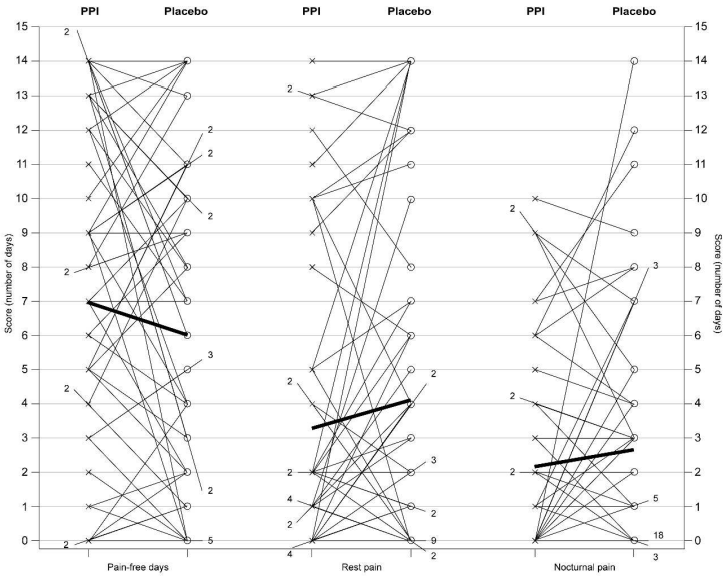
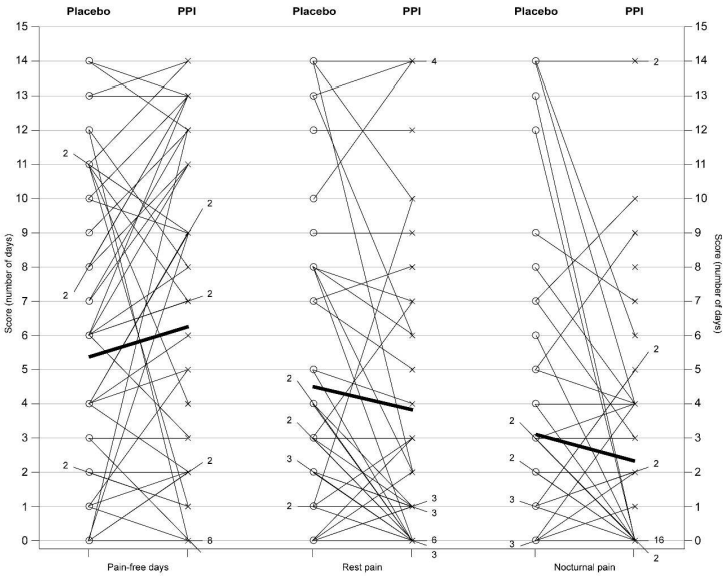

PPI
Placebo
PPI
Placebo
PPI
Placebo
Score (number of days)
Score (number of days)
Pain-free days
Rest pain
Nocturnal pain

FIGURE 2 B


Placebo
PPI
Placebo
PPI
Placebo
PPI
Score (number of days)
Score (number of days)
Pain-free days
Rest pain
Nocturnal pain

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

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	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
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	3-5
	2b	Specific objectives or hypotheses	5
Methods			
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
Randomisation:			
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

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		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	N/A
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	P 8
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	P 8
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	P 9, figure 1
	13b	For each group, losses and exclusions after randomisation, together with reasons	P 9, Figure 1
Recruitment	14a	Dates defining the periods of recruitment and follow-up	P 9
	14b	Why the trial ended or was stopped	P 9
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 2
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	P 9-11; Table 3
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	P 9-11; Table 3
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	N/A
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	N/A
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	P 9, 10
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	P 11-16
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	P 11-16
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	P 11-16
Other information			
Registration	23	Registration number and name of trial registry	N/A
Protocol	24	Where the full trial protocol can be accessed, if available	Authors
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	P 16

*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.

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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.

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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[1-3]. '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'[4]. 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[5-7] and described clinical cases in which CAD was linked with a variety of upper gastrointestinal disorders[4]. 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[8,9]. The fact that this phenomenon could not be demonstrated in patients with a transplanted heart argues strongly for a neural mechanism[9]. 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[10] and that the exertional angina threshold could be lowered by acid perfusion[11]. 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[1,3].

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[7] and has been found to be

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common in some patients with both reflux and CAD[1-3]. The phenomenon is explained by 'viscero-visceral' convergence of nociceptor neural pathways onto the same second order spinothalamic tract neurons in the posterior horns of the spinal cord which has been confirmed directly in animal models[12,13] and would appear from clinical studies to be the commonest mechanism[1,3].

In clinical practice, patients with angina in whom symptoms are increasing in frequency or are occurring at rest, the primary clinical concern will be to intervene among those who on investigation have worsening coronary stenoses. From the above discussion, it would appear that among those patients who do not have critical stenoses there exists the potential for unrecognized GOR to mislead the physician, which could explain the occurrence of angina in non-exertional situations such as the angina 'linked' with meals or with recumbency and sleep[4]. Indeed, nitrates and calcium channels antagonists used in the treatment of ischaemic heart disease may provoke GOR[3,14] so that escalating treatment could in these circumstances increase chest pain, leading the physician to the erroneous conclusion that CAD was worsening. Simultaneous work up of CAD patients by a gastroenterologist is often not practical, or in the absence of an oesophageal function laboratory, simply not possible. In this clinical situation empirical acid suppression is often prescribed[15]. A small open study has provided support for the use of acid suppression by proton pump inhibitor in patients with chronic stable angina in whom both GOR and CAD have been found to co-exist[2] while a large retrospective review of patients with CAD treated with proton pump inhibitors has reported 50% reduction in patients free of chest pain, emergency room visits and hospital admissions

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compared to those not treated[15]. The utility of this approach has not been tested in a controlled clinical trial.

Our aim was therefore to test the hypothesis that among patients with stable CAD, chest pain at rest or during recumbence (at night) in whom there was a likelihood of GOR acid suppression with a proton pump inhibitor (PPI) might reduce chest pain. We investigated the efficacy of acid suppression with a PPI (Lansoprazole 30mg once a day) in patients with CAD and rest or nocturnal pain. The primary endpoint was the reduction in chest pain symptoms. Secondary endpoints were the impact of treatment on quality of life measures and on spontaneous ischaemic episodes using 24 hour Holter monitoring.

Patients and methods

An initial feasibility study was carried out by face to face interviews using a structured questionnaire survey of 106 consecutive patients with a diagnosis of CAD attending cardiology outpatients at Glenfield Hospital, Leicester, UK. The majority (95%) fulfilled the Rose criteria[16] for angina pectoris and 68% had some episodes of pain at rest and or during recumbence at night.

The trial was approved by the Leicestershire District Ethics Committee. Patients were recruited from the cardiology out patient department at Glenfield Hospital and from the waiting lists for percutaneous coronary revascularization or coronary artery bypass grafting over a 2 year period. Patients with unstable angina or acute coronary 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[1,3]. 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[1]. 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_2 receptor antagonists (H_2RA) 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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However, patients who were taking PPIs or H_2RAs, 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[17]) 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)[18,19]. 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[18]. 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 ± standard error (SE). Analysis of covariance (ANCOVA)[20] was carried out using SAS Proc Mixed (SAS v9.1)[21]. 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.

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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 gastro-intestinal 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 form 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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patients), unwillingness to complete the trial (9 patients), bereavement (1 patient), diarrhea and abdominal pain on placebo (2 patients), increasing chest pain on Lansoprazole (1 patient). The patients' characteristics are listed in table 2.

Considering the last two weeks of each treatment period, the number of pain free days, days with pain at rest, at night, and days with exertional pain are shown in table 3 and illustrated in figures 2A and 2B. There was a significant ($p<0.02$) increase in the number of pain free days on treatment with Lansoprazole (6.7 $\pm$ 0.47) as compared to placebo (5.7 $\pm$ 0.47). Both the number of days with pain at rest (3.53 $\pm$ 0.46 vs. 4.51 $\pm$ 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 less on Lansoprazole than on placebo. There appeared to be no effect on exertional pain ($p=0.79$).

The effects of treatment on quality of life measures are listed in table 3. None of the measured parameters showed a significant difference between treatment with Lansoprazole and placebo. However, pain perception scores as assessed by the NHPQ (mean 23.14 [PPI] vs. 26.33 [placebo]) showed a trend ($p=0.07$) for reduction on Lansoprazole .

Two complete 24 hour tapes were available for 89 of 108 patients. Three tapes could not be analyzed due to a bundle branch block pattern. Sixteen patients refused one or both tapes citing inconvenience (15 patients) and depression (1 patient) as reasons. However, chest pain diary data were available for these subjects and are included in the

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preceding analysis. The mean number of ST shift episodes was 0.75 ± 0.21 (SE) on placebo as compared to 0.63 ± 0.22 on PPI. This difference was not significant (p= 0.64; Table 3). Only 24 patients showed any ST segment changes during the trial. No significant difference between placebo and Lansoprazole phases were found when only the 24 patients showing any ST segment changes were included in a subgroup analysis.

Discussion

This study is to our knowledge the first randomized blinded clinical trial investigating the clinical efficacy of empirical treatment with PPIs in patients with chronic stable angina due to documented CAD. The data show that standard dose Lansoprazole increases the number of pain-free days, mainly by decreasing rest and nocturnal pain symptoms. The effect is modest with on average 1 more pain free day on PPI compared to placebo. Although it is a common clinical intervention[15], the modest symptomatic benefit observed in this randomised trial could be interpreted as meaning that it is not worthwhile undertaking in unselected patients. It may be that selecting patients on the basis of abnormal testing for gastro-oesophageal reflux would identify a subgroup more likely to respond as has been found in one open study[2].

It should be noted that that none of the patients in this study had 'unstable' or worsening angina nor were patients with acute coronary syndromes studied. In all such patients, the appropriate clinical management remains urgent cardiological investigation and intervention. Our results are pertinent only to the use of PPI therapy in patients who have stable angina and are not requiring urgent cardiological intervention.

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The trial has several limitations: ideally it might have been designed as a randomized parallel group comparison between 2 separate PPI treatment and placebo arms but this would have doubled the sample size necessary. Indeed over 2800 patients were screened to find 125 who were willing to participate. Although we did not achieve our recruitment target of 130 patients, the power calculation was necessarily (since there were few data on which to base our calculations) a very crude estimate of the numbers required. Cross over designs have the problem of potential carryover effect: we sought to limit this by including a 2 week washout period between treatment periods and by only analyzing the patient diary in the last 2 weeks of each 4 week treatment period. In fact carry-over was not observed by statistical analysis by ANCOVA. An 'order effect' has also not been shown by the ANCOVA analysis: the likely impact of this would have been to reduce the size of the treatment effect, since the order 'PPI first, placebo second' is the one likely to have had a carry over effect into the second placebo treatment period. This is because acid suppression may have an effect on reducing esophageal sensitivity to acid which variably outlasts the treatment period by several weeks[22,23]. We chose Lansoprazole 30 mg administered once daily rather than higher twice daily doses often used in the investigation of non-cardiac chest pain[24]. It is known that twice daily administration of PPI produces more profound acid suppression[25] and it is therefore possible that a twice daily administration schedule would have increased the treatment effect. It is less likely that prolonging the period of acid suppression would altered the results of the study, since it is known that predictable response to treatment occurs in short periods (usually 2 weeks) of treatment with a PPI, at least in the context of patients

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with non-cardiac chest pain[24]. However, in the current study we found a modest reduction in chest pain with once daily Lansoprazole: the limitations referred to above would have been expected (if anything) to have reduced the treatment effect. The apparent lack of efficacy as far as quality of life scores are concerned is disappointing although there was a trend towards reduction of pain associated parameters.

There appeared to be no significant effect of acid suppression on spontaneous ischaemic ST segment shifts during 24 hour ambulatory electrocardiographic monitoring (although there was a slight reduction in frequency during treatment with PPI). However, only 24 patients out of 89 (patients with 2 interpretable 24 hour tapes) showed any spontaneous ST segment shifts, with no significant difference between placebo and PPI on subgroup analysis. This would suggest that, taken as a group, these patients were in the main well treated for their CAD, despite having episodes of chest pain at rest. There were a small number who continued to have ST segment shifts despite 'optimal medical therapy'. While we have not scrutinized these individuals in detail, it may be that 24 hour ST segment monitoring identifies a subgroup among which medical treatment for angina should be reviewed or coronary intervention considered more urgently.

We did not attempt to assess whether ST segment shifts were symptomatic since patients were not instructed to note the exact time of symptoms in their symptom diaries, though it is well recognized that among CAD patients undergoing 24 hour electrocardiographic monitoring the majority of ischemic ST segment shifts (>70%) are asymptomatic[26-28]. 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[26,29].

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[8,9], 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'[2,3], 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[3], 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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may reduce exertional anginal threshold[11]. It is possible that an effect on exertional angina might have been found if patients had been selected on the basis of having objective evidence of both GOR and CAD, although the patients reported by Alban Davies and colleagues had CAD only[11]. Our study was empirical, designed to test the utility of treating patients with proven CAD who also had rest or nocturnal pain, on the basis that this is a common intervention in clinical practice. The results are consistent with the conclusion that an effect of PPI therapy on exertional anginal threshold is not a likely explanation of the modest efficacy of this treatment.

In conclusion, our study supports the hypothesis that among patients with 'stable' angina, chest pain at rest or at night may be caused by acid GOR and is not necessarily a manifestation of critical CAD. Our results support the observations in earlier studies using pH monitoring that the mechanism of such pain is usually due to misinterpretation of acid-provoked oesophageal pain with anginal pain[1,3], rather than due to a cardio-oesophageal reflex[8,9]. The results also provide some justification for the use of empirical PPI therapy in patients with CAD and rest pain in addition to exertional chest pain, but only after appropriate cardiological investigation and management (either medical or interventional). There has been recent controversy about the use of PPIs (particularly omeprazole and esomeprazole) in patients using Clopidogrel since the latter is a prodrug requiring activation by CYP2C19, part of the cytochrome P450 liver microsomal enzyme system. While this enzyme is inhibited by some PPIs thus reducing the production of the active metabolite of Clopidogrel[30], the clinical effects are unclear with some case control studies suggesting a clinically relevant interaction, others not so[31,32]. The issue is

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complicated by the fact that many of these studies have not adequately excluded confounding effects, and the fact that genetically determined differences in CYP2C19 metabolism has a marked effect on Clopidogrel handling which has not been examined in these studies[32]. Since both Clopidogrel and PPIs have short serum half lives, it has been suggested that administering each at a different time (12 hours separation) might mitigate this interaction but this has not been proved. In addition to the clinical scenario explored in our study, co-prescription of PPIs and Clopidogrel is an important consideration in terms of reducing risk of upper GI bleeding. For the reasons discussed above and since the magnitude of the benefit of prescribing a PPI among patients with CAD is modest, it may be both more prudent and more cost effective (if worsening CAD has been excluded by cardiological investigation) to investigate patients with frequent rest pain with a view to proving abnormal GOR prior to initiating PPI therapy.

Acknowledgements

Declarations of personal interests: The authors have no competing interests to declare.

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References:

1. Garcia PJ, Patel PH, Hunter WC et al. Esophageal contribution to chest pain in patients with coronary artery disease. Chest 1990 98**:** 806-810.

2. Singh S, Richter JE, Hewson EG et al. The contribution of gastroesophageal reflux to chest pain in patients with coronary artery disease. Ann Int Med 1992 117**:** 824-830.

3. Mehta A, de Caestecker JS, Camm AJ et al. Gastro-esophageal reflux in patients with coronary artery disease: how common is it and does it matter? Eur J Gastroenterol Hepatol 1996 8: 973-978

4. Smith KS, Papp C. Episodic, postural and linked angina. Br Med J 1962 2: 1425-1430.

5. Hampton AG, Beckwith JR, Wood JE. The relationship between heart disease and gallbladder disease. Ann Intern Med 1959 50: 1135 - 1148.

6. Morris JC, Shelburne PF, Orgain ES. Coronary disease and hiatal hernia : an example in support of the existence of a viscerocardiac reflex. JAMA 1963 183: 788 - 790.

For Peer Review

7. Kramer P, Hollander W. Comparison of experimental esophageal pain with clinical pain of angina pectoris and esophageal disease. Gastroenterology 1955 29**:** 719-743.

8. Chauhan A, Petch MC, Schofield PM. Esophageal stimulation can affect coronary blood flow. Lancet 1993 341**:** 1309-1310.

9. Chauhan A, Mullins PA, Taylor G et al . Cardioesophageal reflex: a mechanism for 'linked angina' in patients with angiographically proven coronary artery disease. J Am Coll Cardiol 1996 27: 1621-1628.

10. Mellow MH, Simpson AG, Watt L et al. Esophageal acid perfusion in coronary artery disease. Induction of myocardial ischemia. Gastroenterology 1983 85: 306-312.

11. Davies HA, Page Z, Rush EM et al. Esophageal stimulation lowers exertional angina threshold. Lancet 1985 (i): 1011-1014.

12. Foreman RD, Ohata CA Effects of coronary artery occlusion on thoracic spinal neurons receiving viscerosomatic inputs. Am J Physiol 1980 238: H667 - H674.

For Peer Review

13. Foreman RD, Ammon WS. Angina-like pain: spinal mechanism underlying this symptom in gallbladder disease. In : Advances in pain research and therapy. Ed. Fields HL. (Raven Press, New York) 1985 9: 177 - 184.

14. Mehta AJ, de Caestecker JS, Northfield TC. Effects of nifedipine and atenolol on gastro-esophageal reflux. Eur J Gastroenterol Hepatol 1993; 5: 627-629.

15. Liuzzo JP, Ambrose JA, Diggs P. Proton pump inhibitor use by coronary artery disease patients is associated with fewer chest pain episodes, emergency department visits and hospitalizations. Aliment Pharmacol Ther 2005 22: 95-100.

16. Rose G, McCartney P, Reid D. 'Self-administration of a questionnaire on chest pain and intermittent claudication.' British Journal Preventative Sociological Medicine 1977 31: 42-48

17. Deanfield JE, Ribiero P, Oakley K et al. Analysis of ST segment changes in normal subjects: implications for ambulatory monitoring in angina pectoris. Am J Cardiol 1984 54: 1321-1325.

For Peer Review

18. Hunt SM, McEwen J, McKenna SP. Measuring health status: a new tool for clinicians and epidemiologists. JR Coll. General Practitioners (London) 1985 35: 185-188.

19. Hunt SM, McEwen J, McKenna SP. The Nottingham Health Profile Users Manual, revised edition. Pub. Galen Research, Manchester. (1994).

20. Senn SJ. Cross-over trials in clinical research (2nd Edition). John Wiley, Chichester, England, 2002.

21. SAS 9.1.3 Language reference: Dictionary, 5th Edition, volumes 1-4, Cary, NC: SAS Institute Inc 2006.

22. Marrero JM, de Caestecker JS, Maxwell JD. Effect of famotidine on esophageal sensitivity in gastro-esophageal reflux disease. Gut 1994; 35: 447 - 450.

23. Sarkar S, Thompson DG, Woolf CJ, Hobson AR, Millane T, Aziz Q. Patients with chest pain and occult gastroesophageal reflux demonstrate visceral pain hypersensitivity which may be partially responsive to acid suppression. Am J Gastroenterol. 2004; 99:1998-2006.

For Peer Review

24. Wang WH, Huang JQ, Zheng GF et al. Is proton pump inhibitor testing an effective approach to diagnose gastroesophageal reflux disease in patients with noncardiac chest pain? A meta-analysis. Arch Intern Med. 2005; 165:1222-1228.

25. Kuo B, Castell DO. Optimal dosing of omeprazole 40 mg daily: effects on gastric and esophageal pH and serum gastrin in healthy controls. Am J Gastroenterol. 1996 91:1532-8.

26. Deanfield JE, Maseri A, Selwyn AP et al. Myocardial ischemia during daily life in patients with stable angina: its relation to symptoms and heart rate changes. Lancet 1983 ii: 753-758.

27. Selwyn AP, Fox K, Eves M et al. Myocardial ischemia in patients with frequent angina pectoris. BMJ 1978 2: 1594-1596.

28. Campbell S, Barry J, Rebecca GS et al . Active ischemia during daily life in asymptomatic patients with positive exercise tests and coronary artery disease. Am J Cardiol 1986 57: 1010-1016.

29. Nabel EG, Rocco MB, Selwyn AP. Characteristics and significance of ischemia detected by ambulatory electrocardiographic monitoring. Circulation 1987 75 (Suppl. V): V74-83.

For Peer Review

30. Gilard M , Arnaud B , Cornily JC *et al.* Influence of omeprazole on the antiplatelet action of clopidogrel associated with aspirin: the randomized, double-blind OCLA (Omeprazole CLopidogrel Aspirin) study . JACC 2008; 51: 256-60.

31. Moayyedi P, Sadowski DC. Proton pump inhibitors and Clopidogrel: hazardous interaction or hazardous interpretation of data? Can J Gastroenterol. 2009; 23: 251-2.

32. Laine L, Hennekens C. Proton Pump Inhibitor and Clopidogrel interaction: fact or fiction? Am J Gastroenterol. 2010; 105: 34-41.

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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 ≥ 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_2RA for proven acid-related conditions*

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

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Table 2: Patient characteristics

Number enrolled	125	
Number completing trial	108 (92 male)	
Age - mean ± SD, (range)	66 ± 9.3 (44-85) years	
Ethnicity	White	101
	South Asian	7
Angiographically confirmed IHD	108 *(all patients completing trial)*	
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	
Medication		
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	
*Use of 'empirical' acid secretion inhibitors**		
Proton pump inhibitor	16	
H_2 receptor antagonist	3	

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

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

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

[1]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 [×] 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 [×]. 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.

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FIGURE 1

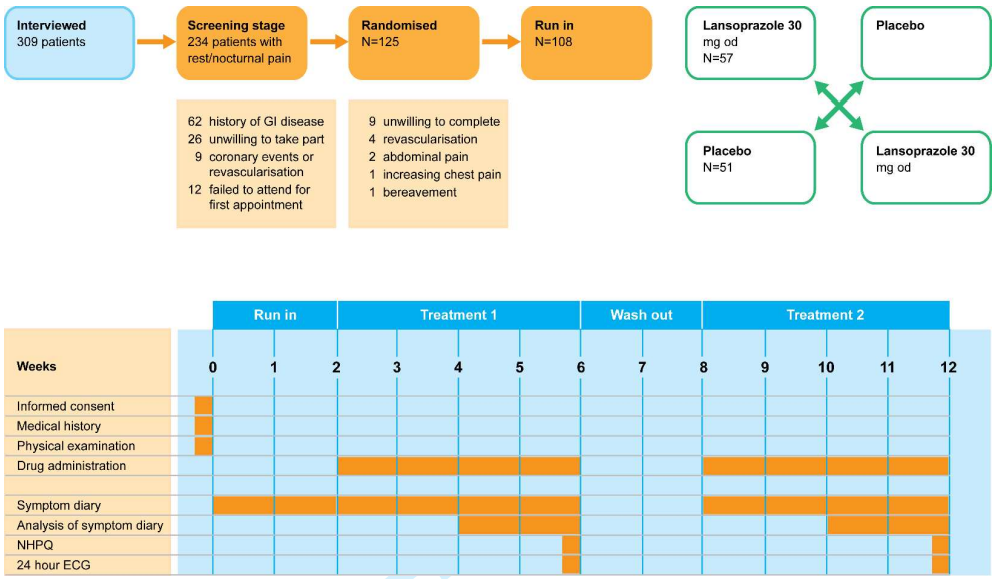

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FIGURE 2 A

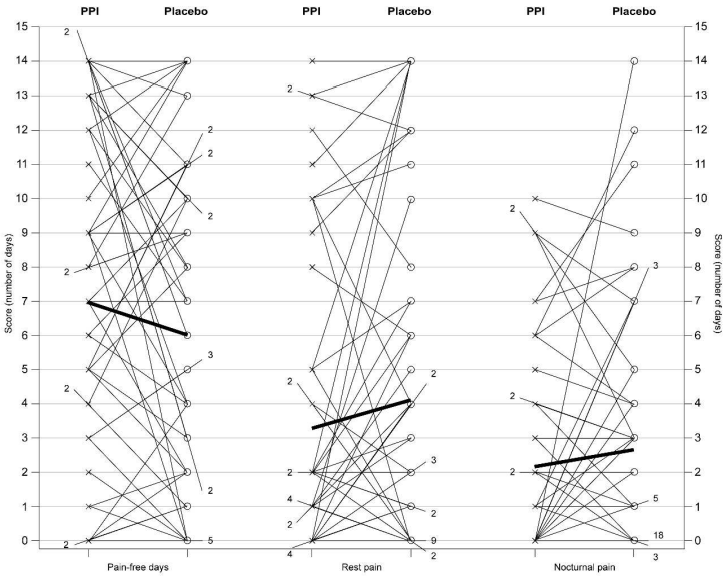
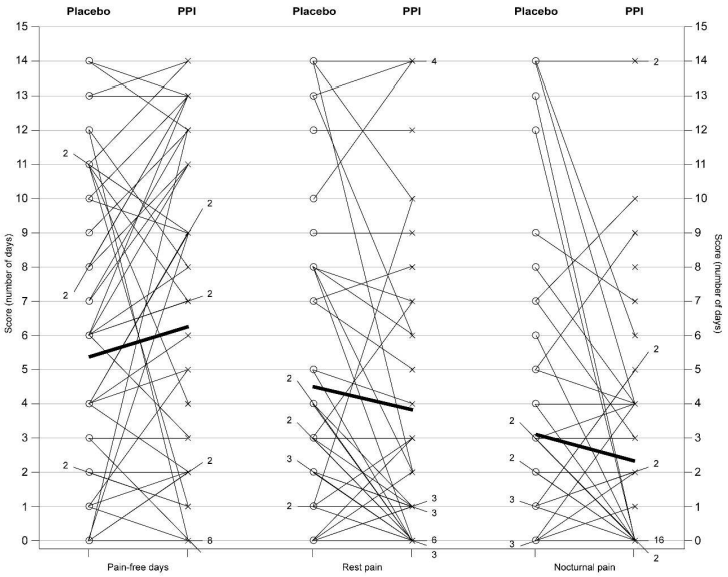

PPI
Placebo
PPI
Placebo
PPI
Placebo
Score (number of days)
Score (number of days)
Pain-free days
Rest pain
Nocturnal pain

FIGURE 2 B


Placebo
PPI
Placebo
PPI
Placebo
PPI
Score (number of days)
Score (number of days)
Pain-free days
Rest pain
Nocturnal pain