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Clinical presentation of acute coronary syndrome in patients previously treated with nitrates

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Aims **Several reports have suggested that nitrates limit acute ischaemic damage by a mechanism similar to preconditioning. This study aims to evaluate the effect of chronic oral nitrates on the clinical presentation and short-term outcomes of patients admitted with acute coronary syndrome (ACS).**

Methods **A retrospective cohort study was conducted in patients with ACS admitted to 62 acute care units from 2010 to 2011. A propensity score-matched samples analysis was performed.**

Results **We analysed 3171 consecutive patients, of whom 298 (9.4%) were chronically treated with nitrates. Patients previously treated with nitrates had higher comorbidity and disease severity at admission, lower prevalence of ACS with ST elevation, lower troponin elevation, higher prevalence of initial Killip class 2–4 and higher hospital mortality. The propensity score-matched analysis confirmed that previous use of nitrates is independently associated with a lower prevalence of ST-elevation ACS [odds ratio (OR) 0.53, 95% confidence interval (CI) 0.36–0.78; $P = 0.0014$] and a lower troponin elevation (OR 0.61, 95% CI 0.41–0.92) but not with Killip class on admission (OR 1.18, 95% CI 0.83–1.67, $P = 0.3697$) or mortality (OR 0.71, 95% CI 0.37–1.38, $P = 0.3196$).**

Conclusion **The results support the hypothesis that nitrates have a protective effect on acute ischaemic injury.**

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Introduction

Several studies have shown that repeated brief episodes of ischaemia protect the heart from subsequent prolonged ischaemia.[1,2] This phenomenon, known as ischaemic preconditioning, is a powerful mechanism that limits the amount of necrosis after coronary occlusion and may explain the limited infarct size in patients with preinfarction angina.[3–6]

Nitrates produce an effect akin to ischaemic preconditioning through a similar mechanism of action.[7–9] Recent observational studies in humans showed that chronic nitrate use was associated with a shift away from ST elevation myocardial infarction in favour of non-ST elevation acute coronary syndrome (ACS) and with lower release of markers of cardiac necrosis.[10,11]

The main limitation of these studies lies in the huge baseline differences between patients chronically treated with nitrates and untreated patients, making it difficult to separate, using traditional statistical methods, the effects due to nitrate consumption from the effects due to its covariates. Although it is not a substitute for a randomized controlled trial, a matched analysis using a propensity score can significantly reduce this bias.[12]

This study aimed to evaluate, through a propensity-matched analysis, the effect of chronic oral nitrates on the presentation and the short-term outcomes of patients hospitalized for ACS.

Materials and methods

Setting and study population

The study is based on data from the ARIAM-SEMICYUC Registry, a voluntary registry of patients with suspected ACS admitted to coronary care units or ICUs in 62 public and private hospitals in Spain and Andorra. Each year, over a period of 3 months, the participating centres anonymously submit patient data. The study population analysed in this study corresponds to the patients included in the surveys of 2010 (from 16 April to 15 July) and 2011 (15 April to 14 July).

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All consecutive patients admitted during the two study periods with a diagnosis of suspected ACS within 48 h of evolution were considered for inclusion in the study. The patients under 18 years of age and patients with a final diagnosis other than ACS were excluded. The cases referred to other hospitals not participating in the study who were later lost to follow-up were excluded from the analysis of hospital mortality but were not excluded from the study.

Analysis of variables and clinical outcomes

The previous use of oral nitrates was examined according to the medical record.

The evaluated clinical outcomes were the relative prevalence of ST elevation myocardial infarction and non-ST elevation ACS; the level of plasma troponin (normal, elevation less than or equal to five times the upper limit of normal, elevation greater than five times the upper limit of normal); the Killip class on admission; and the hospital mortality. These outcomes are consistent with those reported in two previous studies on this topic.[10,11] In addition, other covariates (coronary risk factors, medical history and previous treatments) were measured and are presented in Table 1.

Statistical analysis

Initially, we conducted a descriptive statistical and graphical analysis of the study population by calculating proportions for categorical variables or medians and interquartile ranks for quantitative variables. Hypothesis tests were performed using chi-square tests for comparing proportions or the Mann–Whitney test for quantitative variables. The strength of the association between nitrate consumption and clinical outcomes was estimated by calculating the standardized differences, odds ratios (ORs) and the corresponding 95% confidence limits.

To control the confounding effect of the covariates of nitrate consumption, a propensity score for nitrate therapy was developed using a logistic regression model that included 19 variables. This score included all of the determinants that were considered a priori that could be related to the use of nitrates, such as history of coronary

Table 1 Baseline characteristics and short-term evolution (raw population)

	Nitrates ($n=297$)	No nitrates ($n=2873$)	Standardized differences
Baseline characteristics			
Age (median, interquartile range)	76 (68–81)	65 (54–76)	6.0
Female sex (%)	26.9	23.2	8.5
Smoker (%)	43.1	56.2	26.4
Arterial hypertension (%)	80.5	57.7	50.9
Dyslipidaemia (%)	63.8	45.7	37.0
Diabetes (%)	52.4	26.7	54.5
Previous angina (%)	40.6	11.3	70.9
Previous infarction (%)	56.7	13.0	103.2
Known coronary lesions (%)	55.7	10.3	110.3
Test of myocardial ischaemia (%)	17.6	5.5	38.6
Previous coronary angiography (%)	55.2	11.3	105.3
Previous percutaneous coronary intervention (%)	24.8	6.7	51.3
Previous coronary surgery (%)	11.2	2.0	37.7
Peripheral arterial disease (%)	16.1	04.1	40.6
Previous stroke (%)	9.7	4.2	21.8
Chronic renal failure (%)	16.1	2.8	46.7
CHF (%)	15.1	2.1	47.7
Bleeding (%)	7.4	1.2	30.9
Previous aspirin use (%)	75.8	22.0	127.7
Aspirin within the last 7 days (%)	58.4	14.7	101.8
Previous clopidogrel use (%)	36.2	7.0	75.9
Previous beta-blockers use (%)	53.7	14.3	91.5
Previous ACE/ARB use (%)	54.4	30.5	49.8
Previous antiarrhythmics (%)	4.4	1.5	17.2
Clinical presentation and short-term prognosis			
GRACE score (median, interquartile range)	146 (125–170)	127 (104–155)	1.2
Main diagnosis			
STEMI (%)	22.1	53.0	67.3
NSTEMI (%)	52.9	35.8	34.9
Unstable angina (%)	25.0	11.2	36.4
Troponin			
Normal (%)	18.9	7.3	34.9
<5 UL (%)	23.3	13.1	26.7
>5 UL (%)	57.8	79.6	48.4
Initial Killip class ≥ 2 (%)	39.2	23.7	33.9
Maximum Killip class ≥ 2 (%)	44.6	30.9	28.5
ICU/CCU mortality (%)	6.6	3.8	12.6
Hospital mortality (%)	10.8	6.7	14.6

Results are expressed as the percentage or median (interquartile rank), except standardized differences that are expressed as absolute values. ACE/ARA, angiotensin-converting enzyme inhibitor/angiotensin receptor antagonist; CHF, congestive heart failure; D_{st}, standardized differences; CCU, coronary care unit; NSTEMI, non-ST elevation acute myocardial infarction; STEMI, ST elevation acute myocardial infarction; UL, upper limit of normality.

artery disease, hypertension and heart failure (Table 2). The discriminative ability of the propensity score was analysed by calculating the area under the receiver operating characteristic (ROC) curve. Then, each one of the exposed patients was matched with the unexposed patient with the closest propensity score, whereas those pairs whose propensity scores differed by more than 0.05 points were excluded. The identical distribution of covariates between the samples exposed to nitrates and the control group was examined by calculating the standardized differences. To account for the matched nature of the data, the strength of the association between the prior use of nitrates and clinical outcomes in paired samples was estimated using a conditional logistic regression.

All analyses were two-tailed with alpha significance level of 5% and were performed using StatsDirect version 2.7.8 statistical software.[13]

Ethical and legal aspects

The ARIAM-SEMICYUC registry complies with Spanish legislation on postauthorization observational studies for drugs for human use (SAS/3470/2009 Order of 16 December), and has been recognized by the Spanish Ministry of Health as a Registry of interest for the National Health System.

Results

Study population

For inclusion, we considered 3259 patients with suspected ACS, of which we excluded 59 patients who received a final diagnosis other than ACS [myocarditis/pericarditis ($n=32$), transient apical dysfunction syndrome ($n=13$) or other causes of nonischaemic pain ($n=14$)]. Twenty-nine additional patients were excluded due to the lack of information about the prior use of nitrates. Of the 3171 eligible patients, 298 (9.4%) were treated chronically with nitrates.

Table 2 Propensity score for nitrate therapy (logistic regression model)

Variable	Coefficient	*P*
$Beta_0$	−7.917487	<0.0001
Age (years)	0.052074	<0.0001
Female sex	−0.024959	0.8965
Smoker	−0.04786	0.7833
Diabetes	0.516546	0.0008
Hypertension	−0.028902	0.8804
Dyslipidaemia	0.141665	0.3665
Previous angina	1.358229	<0.0001
Previous infarction	0.962965	<0.0001
Peripheral arterial ischaemia	0.247915	0.302
History of stroke	0.137843	0.6034
Chronic renal failure	0.498179	0.0462
Congestive heart failure	0.623999	0.0214
Known coronary lesions	0.733101	<0.0001
History of bleeding	0.985229	0.0066
Use of aspirin	1.009001	<0.0001
Use of clopidogrel	0.541271	0.0029
Use of beta-blockers	0.569919	0.0006
Use of ACE/ARA	0.238453	0.1335
Previous antiarrhythmics use	0.364499	0.344

ACE/ARA, angiotensin-converting enzyme inhibitor/angiotensin receptor antagonist.

Univariate analysis

Compared with the controls, patients pretreated with nitrates (exposed group) showed a higher prevalence of risk factors and coronary antecedents (myocardial infarction or angina, previous coronary angiography or existence of known coronary lesions), higher comorbidity (diabetes, hypertension, congestive heart failure, chronic renal failure) and more frequent treatment with aspirin, clopidogrel and beta blockers (Table 1, Fig. 1).

Regarding the clinical presentation, patients pretreated with nitrates showed a low prevalence of ST segment elevation acute myocardial infarction and a lower prevalence of troponin peak values greater than five times the upper limit of normal. A lower prevalence of troponin elevation was detected both in patients with ACS with ST elevation [OR 0.37, 95% confidence interval (CI) 0.20–0.71] and non-ST elevation ACS (OR 0.48, 95% CI 0.35–0.65).

With respect to the initial severity, patients pretreated with nitrates had a higher GRACE score[14] at admission, a higher prevalence of Killip class 2–4 and an increased mortality in the acute care unit and hospital.

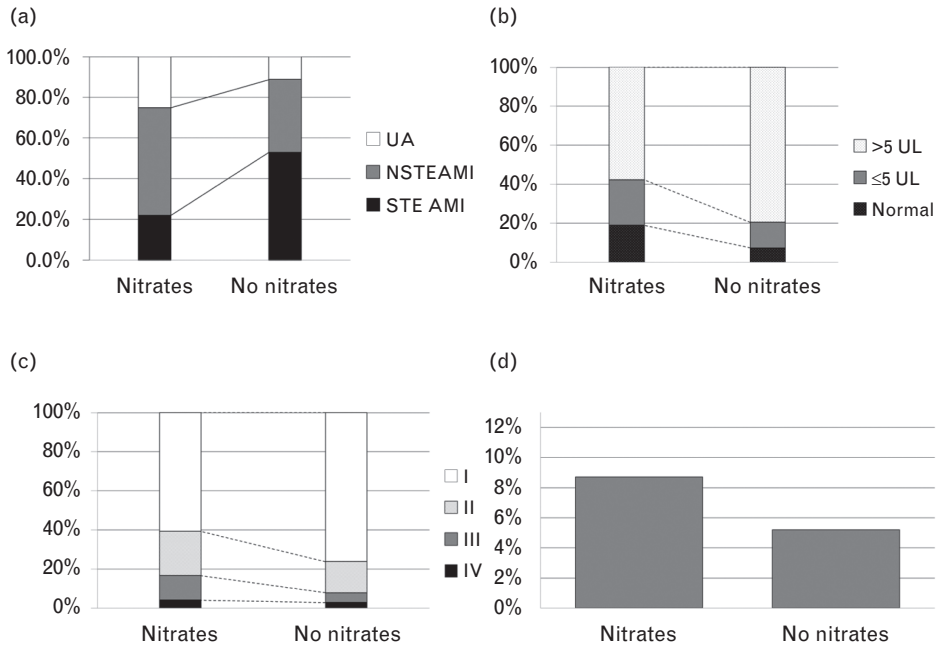
The delay between symptom onset and arrival at the emergency room was similar in patients pretreated and not treated with nitrates [160 min (88, 221) vs. 151 min (81.5, 303.5), $P=0.7882$]. No difference in delay between those pretreated and not treated with nitrates was found after stratifying by the type of ACS [ACS with ST elevation: 121.5 min (60, 260) vs. 141 min (77, 271), $P=0.3911$; ACS without ST elevation: 164 min (90, 325) vs. 163 min (90, 346), $P=0.6415$].

Propensity score matched cohort study

The propensity score showed a high degree of discrimination with an area under the ROC curve of 0.912 (0.899–0.925). Finally, 278 matched pairs of exposed/unexposed patients could be obtained. The two samples showed a homogeneous distribution of the covariates (Table 3).

The matched analysis corroborated the finding of a lower prevalence of ST elevation myocardial infarction in the group pretreated with nitrates, with a similar prevalence of patients with unstable angina in the two groups (Table 4, Fig. 2). Parallel to this unequal distribution of the various forms of ACS, patients pretreated with nitrates showed a lower prevalence of substantial (more than five times normal) elevations of troponin [OR 0.61, 95% CI 0.41–0.92, $P=0.0175$) with no significant statistical differences in the prevalence of normal levels. The trend towards a lower troponin elevation in patients treated with nitrates was slightly modified after controlling the effect of the type of ACS using conditional

Fig. 1



Clinical outcomes in patients exposed and unexposed to nitrate treatment. (a) Type of ACS. (b) Troponin elevation. (c) Initial Killip class. (d) Hospital mortality. ACS, acute coronary syndrome.

logistic regression [OR 0.68, 95% CI 0.44–1.03, $P = 0.0746$).

In contrast, after controlling for the effect of covariates, the differences in the Killip class disappeared, and mortality in the group pretreated with nitrates was lower than in the control group (OR 0.71, no significant differences) (Table 4, Fig. 2).

Discussion

In summary, the raw results of the study showed that ACS patients pretreated with nitrates had a high comorbidity and initial severity, high short-term mortality, a strikingly low prevalence of myocardial infarction with ST elevation and a low elevation of troponin. A more refined analysis, using samples matched by propensity score, suggests that the Killip class and increased mortality in patients pretreated with nitrates was attributable to confounding. In contrast, the latter analysis reaffirmed the lower prevalence of ST elevation myocardial infarction in patients pretreated with nitrates. Similarly, the adjusted analysis showed a negative association between consumption of nitrate and prevalence of a significant elevation of troponin (greater than five times the upper limit of normal), with no significant differences in the prevalence of patients with normal troponin (i.e. with unstable angina). The nonsignificant trend towards lower troponin elevation in patients treated with nitrates persisted after adjusting for the effect of the type of ACS, suggesting that lower troponin elevation is not entirely due to the higher prevalence of non-ST elevation ACS in these patients. Altogether, these findings suggested that nitrates protect the myocardium during severe acute ischaemia.

The validity of these results must be examined in detail. First, the possibility of type I error seems unlikely because the variables examined were prespecified, and the results are consistent with previous studies.[10,11] Because our study is not powered to detect a mortality reduction of about 30%, as observed in the matched cohort analysis, the effect of the use of nitrates on mortality cannot be determined.

One could argue that patients pretreated with nitrates have had more previous episodes of myocardial infarction and are therefore less susceptible to necrosis and have a more developed collateral circulation, which would explain the lower prevalence of myocardial infarctions with ST elevation and the lower troponin elevation in this group. However, differences were observed both in patients with ST elevation ACS and patients without ST elevation and persisted in the matched analysis (Table 3), in which the history of coronary heart disease was balanced in the two groups.

It would be reasonable to assume that patients treated with nitrates have a closer contact with healthcare resources and a better understanding of their disease

Table 3 Baseline characteristics and short-term evolution (matched samples)

	Nitrates ($n = 278$)	No nitrates ($n = 278$)	Standardized differences
Baseline characteristics			
Age (median, interquartile range)	75 (67–81)	75 (67–80)	0.4
Female sex (%)	26.4	25.3	2.5
Smoker (%)	44.5	46.3	3.6
Arterial hypertension (%)	79.9	79.5	1.0
Dyslipidemia (%)	63.7	65.2	3.1
Diabetes (%)	50.2	49.1	2.2
Previous angina (%)	37.4	39.9	5.1
Previous infarction (%)	54.2	55.3	2.2
Known coronary lesions (%)	52.4	51.7	1.4
Test of myocardial ischaemia (%)	17.7	16.8	2.4
Previous coronary angiography (%)	50.4	45.6	9.6
Previous percutaneous coronary intervention (%)	25.7	32.0	13.9
Previous coronary surgery (%)	11.5	7.2	14.8
Peripheral arterial disease (%)	15.0	12.5	7.3
Previous stroke (%)	9.9	10.3	1.3
Chronic renal failure (%)	13.6	11.0	7.9
CHF (%)	13.6	10.3	10.2
Bleeding (%)	7.0	6.2	3.2
Previous aspirin use (%)	74.4	72.8	3.6
Aspirin within the last 7 days (%)	56.4	57.9	3.0
Previous clopidogrel use (%)	34.4	33.3	2.3
Previous beta-blockers use (%)	51.3	52.8	3.0
Previous ACE/ARB use (%)	53.5	56.4	5.8
Previous antiarrhythmics (%)	4.4	4.4	0.0
Clinical presentation and short-term prognosis			
GRACE score (median, interquartile range)	145 (123–169)	145 (122–170)	0.0
Main diagnosis			
STEMI (%)	22.5	36.5	31.1
NSTEMI (%)	53.8	38.0	32.1
Unstable angina (%)	23.8	25.6	4.2
Troponin			
Normal (%)	18.7	14.5	11.3
<5 UL (%)	21.9	17.1	12.1
>5 UL (%)	59.4	68.4	18.8
Initial Killip class $\geq 2\%$	39.3	35.2	8.5
Maximum Killip class $\geq 2\%$	45.5	42.8	5.4
ICU/CCU mortality (%)	6.0	7.6	6.3
Hospital mortality (%)	9.0	12.4	11.2

Results are expressed as the percentage or median (interquartile rank), except standardized differences that are expressed as absolute values. ACE/ARA, angiotensin-converting enzyme inhibitor/angiotensin receptor antagonist; CHF, congestive heart failure; D_{st}, standardized differences; CCU, coronary care unit; NSTEMI, non-ST elevation acute myocardial infarction; STEMI, ST elevation acute myocardial infarction; UL, upper limit of normality.

than patients without prior treatment, so that they could go to the hospital with relatively mild symptoms (minor myocardial injury) or at an earlier time, allowing for earlier therapeutic intervention and a limitation of infarct size. However, this hypothesis fits poorly with the disease severity and the initial Killip class observed in patients pretreated with nitrates. Moreover, no differences were found between the onset of symptoms and arrival at the emergency department in patients in whom this information was available.

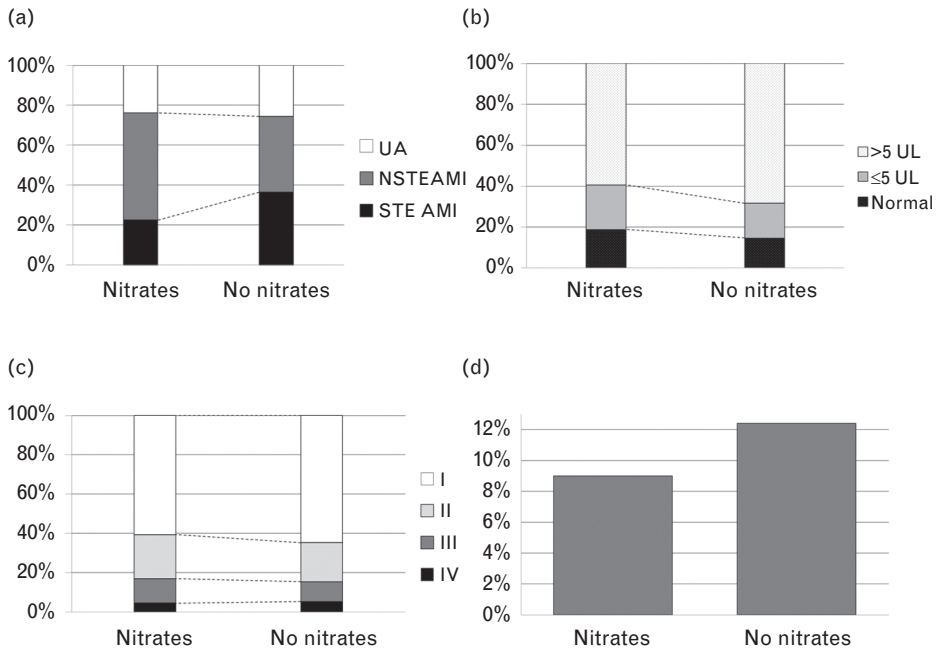
The main limitation of the study is its observational nature and the large differences in case mix between the exposed and control groups. This study has tried to minimize these differences by matching the propensity score for treatment, which is one of the better statistical tools for controlling case mix.[12] This score included all of the determinants that were considered a priori that could be related to the use of nitrates, the match was almost complete and the covariates were properly balanced in the two matched samples. However, we cannot ensure

Table 4 Association between prior use of nitrates and clinical outcomes

	Crude analysis		Matched analysis	
	Observed OR (95% CI)	*P*	Adjusted OR (95% CI)	*P*
Non-ST elevated ACS	3.78 (2.85–5.07)	<0.0001	1.89 (1.28–2.81)	0.0014
High vs. normal troponin	0.33 (0.24–0.48)	<0.0001	0.84 (0.51–1.40)	0.5225
Troponin $>5 \times$ UL vs. ≤ 5	0.35 (0.27–0.46)	<0.0001	0.61 (0.41–0.92)	0.0175
Initial Killip class >1	2.07 (1.62–2.66)	<0.0001	1.18 (0.83–1.67)	0.3697
Hospital mortality	1.74 (1.08–2.70)	0.0119	0.71 (0.37–1.39)	0.3196

ACS, acute coronary syndrome; CI, confidence interval; OR, odds ratio; UL, upper normal limit.

Fig. 2



Clinical outcomes in matched cohort samples. (a) Type of ACS. (b) Troponin elevation. (c) Initial Killip class. (d) Hospital mortality. ACS, acute coronary syndrome.

that the analysis has controlled all important prognostic variables or the existence of residual confounding;[15] therefore, this study does not replace a randomized trial.

In conclusion, our results are consistent with the previously described findings[10,11] that suggest a possible protective effect of nitrates on acute ischaemic damage.

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References

1 Murry CE, Jennings RB, Reimer KA. Preconditioning with ischemia: a delay of lethal cell injury in ischemic myocardium. *Circulation* 1986; **74**:1124–1136.
2 Yellon DM, Downey JM. Preconditioning the myocardium: from cellular physiology to clinical cardiology. *Physiol Rev* 2003; **83**:1113–1151.
3 Napoli C, Liguori A, Chiariello M, *et al.* New-onset angina preceding acute myocardial infarction is associated with improved contractile recovery after thrombolysis. *Eur Heart J* 1998; **19**:411–419.
4 Palacios Ortega F, Latour Perez J, Mahave Del Rio MA, *et al.* Preinfarction angina. Clinical prevalence and significance [in Spanish]. *Med Intensiva* 1991; **15**:415–418.
5 Rezkalla S, Kloner R. Ischemic preconditioning and preinfarction angina in the clinical arena. *Nat Clin Pract Cardiovasc Med* 2004; **1**:96.
6 Siracusano L, Girasole V, Alvaro S, Chiavarino ND. Myocardial preconditioning and cardioprotection by volatile anaesthetics. *J Cardiovasc Med (Hagerstown)* 2006; **7**:86–95.
7 Banerjee S, Tang XL, Qiu Y, *et al.* Nitroglycerin induces late preconditioning against myocardial stunning via a PKC-dependent pathway. *Am J Physiol Heart Circ Physiol* 1999; **277**:H2488–H2494.
8 Hill M, Takano H, Tang XL, *et al.* Nitroglycerin induces late preconditioning against myocardial infarction in conscious rabbits despite development of nitrate tolerance. *Circulation* 2001; **104**:694–699.
9 Jneid H, Chandra M, Alshaher M, *et al.* Delayed preconditioning-mimetic actions of nitroglycerin in patients undergoing exercise tolerance tests. *Circulation* 2005; **111**:2565–2571.
10 Ambrosio G, Del Pinto M, Tritto I, *et al.* Chronic nitrate therapy is associated with different presentation and evolution of acute coronary syndromes: insights from 52,693 patients in the Global Registry of Acute Coronary Events. *Eur Heart J* 2010; **31**:430–438.

11 Timoteo AT, Mamede A, de Lurdes Ferreira M, *et al.* Is chronic nitrate therapy associated with a different clinical presentation of acute coronary syndrome? *Rev Port Cardiol* 2007; **26**:135–143.
12 Austin PC. A critical appraisal of propensity-score matching in the medical literature between 1996 and 2003. *Stat Med* 2008; **27**:2037–2049.
13 StatsDirect statistical software. Altrincham, Cheshire, UK: StatsDirect Ltd.; 2008.
14 Granger CB, Goldberg RJ, Dabbous O, *et al.* Predictors of hospital mortality in the global registry of acute coronary events. *Arch Intern Med* 2003; **163**:2345.
15 Deeks J, Dinnes J, D'Amico R, *et al.* Evaluating nonrandomised intervention studies. *Health Technol Assess* 2003; **7**:1–173.