European Heart Journal (2006) **27**, 1298–1304
doi:10.1093/eurheartj/ehl005

The impact of guideline compliant medical therapy on clinical outcome in patients with stable angina: findings from the Euro Heart Survey of stable angina

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Received 19 November 2005; revised 1 April 2006; accepted 6 April 2006; online publish-ahead-of-print 16 May 2006

KEYWORDS
Guideline compliance;
Prognosis;
Evidence based therapy;
Secondary prevention

Aims The European Society of Cardiology published guidelines for the management of stable angina in 1997, with the objective of promoting an evidence-based approach to the condition. This study focuses on the impact of guideline compliant medical treatment on clinical outcome in patients with stable angina.

Methods and results The Euro Heart Survey of Stable Angina is a multicentre prospective observational study conducted between 2002 and 2003. Patients with a clinical diagnosis of stable angina by a cardiologist were enrolled and follow-up was conducted at 1 year. The primary outcome of interest was death or myocardial infarction (MI). The increasing intensity of guideline compliant medical therapy was quantified by means of a simple treatment score based on the use of guideline advocated therapies: antiplatelets, statins, and beta-blockers. A total of 3779 patients were included in the initial survey. Increasing intensity of guideline compliant therapy at initial assessment was associated with a reduction in death and MI during follow-up in patients with angina and confirmed coronary disease (HR 0.68; 95% CI 0.49–0.95 per unit increase in treatment score). All cardiovascular events were also significantly reduced in this subgroup (HR 0.82; 95% CI 0.69–0.97). The benefits of guideline compliant therapy were only observed in patients with objective evidence of coronary disease.

Conclusion Guideline compliant medical therapy improves clinical outcome in patients with stable angina and objective evidence of coronary disease.

Introduction

Despite advances in prevention and treatment, coronary heart disease remains a major cause of mortality and morbidity in Europe.[1] As the most prevalent manifestation of coronary disease in the general population,[2–6] chronic stable angina contributes a considerable proportion of this burden. With the objective of standardizing the approach to diagnosis and treatment by general physicians and cardiologists, the European Society of Cardiology published guidelines for the management of stable angina in 1997,[7] guided by the evidence available at the time and consensus of expert opinion. Antiplatelet therapy was advocated for all patients with angina and lipid-lowering therapy, specifically statin drugs, for most, particularly those with total cholesterol levels >5.0 mmol/L or LDL cholesterol >2.6 mmol/L. Beta-blockers were recommended as first line therapy to reduce symptoms and ischaemia in patients with a prior MI and even in stable angina not complicated by a previous myocardial infarction (MI) on the basis of extrapolated data from post-infarction studies.[8,9] It was recommended that subsequent pharmacological management of symptoms be altered or titrated according to symptom severity and drug tolerability on an individual patient basis.

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The Euro Heart Survey of Stable Angina, a large multicentre multinational survey of the clinical presentation and management of stable angina in Europe in 2002–03, sought to evaluate adherence to these guidelines in practice,[10,11] and this report focuses on the impact of guideline compliant medical treatment on clinical outcome. The report also records the use of revascularization and the observed effects of revascularization on outcome in the contemporary population with stable angina, as included in the Euro Heart Survey.

Population

The population included in the survey has been previously described.[11,12] Briefly, consecutive patients attending cardiology services with a new presentation of stable angina were considered for enrolment. Patients in whom the cardiologist made a clinical diagnosis of stable angina caused by myocardial ischaemia due to coronary disease were enrolled. A new presentation was defined as a first ever presentation to a cardiologist or a new referral or re-referral after a period of at least 1 year of not attending (consulting) a cardiologist. Patients were not obliged to have documented evidence of ischaemia to be included, but they did have to have stable angina due to coronary disease in the opinion of the physician investigator. Exclusion criteria included unstable angina, hospitalization within 24 h of assessment (because of the likelihood of an unstable syndrome), MI within 1 year, prior revascularization, or an aetiological cause for angina other than coronary disease, such as aortic stenosis or hypertrophic cardiomyopathy. To be included in the survey, consent was obtained from each patient in the manner deemed appropriate by the local regulatory authorities.

From March 2002 to December 2002, 3779 patients with stable angina were included in the study. Follow-up information was obtained and vital status ascertained in 3259 patients (86%). A further 112 patients alive at follow-up had no information regarding occurrence of non-fatal MI, and the dates of final assessment were either missing or inconsistent in a further 116 patients. Thus, data were suitable for survival analysis for the primary outcome of interest, which included non-fatal MI, in 3031 patients. The median duration of follow-up was 13 months and interquartile range 12–15 months. The impact of guideline compliant therapy was assessed on the population with completed follow-up.

Data collection and analysis

Patients were enrolled from 197 centres in 36 countries across Europe. Follow-up was conducted by clinical review or telephone as closely as possible to 1 year from initial assessment. Details of clinical events reported by the patient were confirmed, and data regarding these events, or the results of investigations, were collected from the patient's records. Investigators were encouraged to contact the primary care physician if contact with the patient was not made. The patients medical notes were also used to capture information not reported by the patient or if it was not possible to interview the patient directly.

Definitions

The intensity of guideline compliant pharmacological intervention was quantified by a score calculated on the basis of completeness of treatment according to evidence-based guidelines for the management of stable angina published in 1997. Individual patients were accorded a score of 1 if they were prescribed each of the following groups of medications after initial assessment, antiplatelet therapy, statin therapy, or beta- blockers. Thus, the maximum score achievable was 3, if a patient was prescribed all three classes of drug, and zero, if they were not prescribed any.

Primary and secondary outcomes

The primary outcome of interest was the occurrence of death or MI, with the occurrence of all cardiovascular events as a secondary outcome. MI necessarily involved two of the following: (i) cardiac chest pain at rest lasting $>$20 min or pulmonary oedema without significant valvular heart disease or known heart failure or shock without hypovolaemia or intoxication; (ii) transient elevation of CPK to twice the upper limit of normal for the laboratory or CK MB to above the upper limit of normal for the laboratory or elevation of troponin I or T above the 99th percentile of normal in the laboratory; (iii) ECG series with the evolutionary changes of MI or development and the disappearance of localized ST segment elevation, combined with the development of T-wave inversion in at least two contiguous leads, and/or the development of pathological Q-waves. If markers of myocardial damage were present, the ECG changes could include ST depression, T-wave inversion, loss of R-wave progression, or new LBBB. All cardiovascular events refer to the occurrence of one of the following: cardiovascular death, non-fatal MI, hospitalization for unstable angina or heart failure, cerebrovascular accident, or emergency revascularization.

Statistical analysis

Descriptive statistics were used to estimate the prevalence of risk factors, baseline clinical characteristics, and pharmacological intervention index at presentation. The Student's *t*-test or ANOVA technique were used as appropriate to test for statistically significant differences in quantitative measures, and the χ^2 test was used to test for statistically significant differences in proportions. All tests were two sided and *P*-value $<$0.05 was considered statistically significant. No adjustments were made for multiple comparisons given the descriptive nature of the analyses.

Follow-up information was collected at $\sim$1 year following enrolment (median 13 months, inter-quartile range 12–15 months), and event times were recorded exactly up to 18 months after recruitment. To account for the variation in actual follow-up times, Cox's proportional hazards models[12] were employed to determine the influence of the intensity of treatment on the occurrence of death or non-fatal MI and the occurrence of all cardiovascular events in both univariate and multivariable analysis. Multivariable models included adjustment for the effects of age and gender and other relevant factors. Adjustment was made for the presence of diabetes and hypertension, as both were univariate predictors of the primary endpoint

and could also potentially affect the use of medications. The likelihood ratio test was used to test the linearity assumption for the treatment score. The effect of increasing treatment intensity was assessed in the overall population and in the subgroup with angiographically confirmed coronary disease during the follow-up period. The effect was also assessed in the wider subgroup incorporating those patients with a positive stress test who had not had angiography. Finally, the impact of treatment intensity was investigated, excluding those patients from the analysis who were not taking aspirin, beta-blockers, or statin therapy because of a contraindication in the opinion of the investigator. Analyses were performed using Stata™ statistical software.

Results

Patient profile

The initial survey population ($n = 3779$) and the population with complete data on the occurrence and timing of primary endpoints during follow-up ($n = 3031$) were similar in terms of baseline clinical characteristics (*Table 1*) and regional distribution. The majority of patients had mild-to-moderate symptoms of angina for a median of 5 (IQ range 2–11) months before presentation to a cardiologist. At the end of the follow-up period, coronary disease confirmation status was categorized according to the level of diagnostic information acquired during follow-up: the confirmed CAD group ($n = 994$) who had coronary disease confirmed angiographically; the negative investigation group ($n = 1023$) who had either a normal angiogram or, if no angiogram was performed, negative non-invasive tests; the incomplete investigation group ($n = 528$) who had either no form of functional assessment or angiography or an inconclusive non-invasive test; and the positive non-invasive group ($n = 486$) who had positive non-invasive tests without angiographic confirmation of disease. The rate of death and MI in the overall population with stable angina was 2.3 per 100 patient years and 3.9 per 100 patient years in the subgroup with confirmed coronary disease. The rate of non-fatal MI was 1.4 per 100 patient years and 3.2 per 100 patient years in the subgroup with confirmed coronary disease.

Medical therapy

After initial assessment by a cardiologist, antiplatelet therapy was prescribed in 81% of patients with angina and lipid-lowering therapy in 50%. Beta-blockers were prescribed in 67% of patients (*Table 2*). Specific patient contraindications were present in 20% of those who were not prescribed beta-blockade. At this stage, after initial assessment, the majority of patients (67%) had not even had an exercise ECG, and so treatment may have been affected by the investigator's wish to confirm the diagnosis of

Table 1 Baseline clinical characteristics of patients included in the initial survey of the Euro Heart Survey of Stable Angina and those with completed follow-up

Variable	Initial survey (total =3779)		Follow-up (total =3031)		*P*-value
	n	%	*n*	%	
Age (mean ± SD) years	3731	61 ± 11	2989	61 ± 11	0.82
% Female	3778	42	3029	42	0.85
Symptom severity (CCS class)	3472		2765		
Class I		40		39	0.15
Class II		48		49	
Class III		12		12	
Duration of angina symptoms	3520		2813		
<1 month		2		2	0.18
1–5 months		53		53	
6–11 months		21		21	
≥ 12 months		24		24	
Prior MI (>1 year before)	2901	5	2455	4	0.08
Peripheral vascular disease	3779	7	3031	7	0.76
Previous TIA or CVA	3779	6	3031	5	0.20
Respiratory disease	3779	8	3031	8	0.54
Diabetes	3666	18	2952	18	0.59
Hypertension	3676	61	2948	62	0.39
Smoking	3553		2827		
Prior		30		30	0.71
Current		23		23	
Hyperlipidaemia	3174	58	2545	57	0.02
Signs of heart failure	3769	8	3021	7	0.01
Mean systolic BP (mmHg)	3749	144 ± 22	3001	145 ± 21	0.43
Mean BMI	3406	28 ± 4	2738	28 ± 4	0.79

P-value for differences between those with and without complete follow up. Hypertension was defined as treated hypertension on antihypertensive therapy. Hyperlipidaemia was defined as treated hyperlipidaemia, on lipid lowering medication, or specific dietary modification. Diabetes was defined as treated diabetes, on insulin or oral diabetic medication, or specific dietary modification. Clinical signs of heart failure were defined as a raised jugular venous pressure (JVP), crepitations in the lung fields, a third heart sound, peripheral oedema or hepatomegaly. BMI, body mass index. CCS, Canadian Cardiovascular Society Classification.

angina due to coronary disease. The use of individual classes of medication and the mean number of antianginal drugs at 1 year post-initial assessment according to coronary disease confirmation status is also shown in *Table 2*. Patients who were incompletely investigated, or not investigated at all, received substantially less secondary preventative therapy than those with proven coronary disease, although the use of antianginal agents was at least as great.

Effect of medical therapy on clinical outcome

Increasing treatment scores, in the range 0–3, indicate progressively better guideline compliant treatment. The distribution of treatment scores at initial assessment varied significantly between patients who had negative or incomplete investigations and those who subsequently had coronary disease confirmed on coronary angiography, $P < 0.001$. In patients with confirmed CAD, 50% had a treatment score of 3, 37% a score of 2, 11% a score of 1, and 2% a score of 0 at initial assessment, when compared with 24, 23, 32, and 21% in patients with negative investigations and 9, 25, 38, and 28% in patients who were not investigated completely. The baseline characteristics of those in each treatment score category are reported in *Table 3*.

Increased treatment intensity, as measured by the treatment score, was not associated with a reduction in risk of occurrence of death and MI in the overall population, hazard ratio (HR) 1.11 [(95% CI 0.90–1.33); $P = 0.31$].

However, in the population with confirmed coronary disease, a unit increase in treatment score was associated with an HR of 0.68 [(95% CI 0.49–0.95), $P = 0.03$], which was not altered by adjustment for age and gender, (HR

Table 2 The use of secondary preventive and antianginal medications in the Euro heart Survey of Stable angina at initial assessment, and the use of these mediations at 1 year follow-up according to the level of confirmation of coronary disease

Drug	After initial cardiology assessment (%)	1 year follow-up				
		Overall ($n = 3031$) (%)	Confirmed CAD ($n = 994$) (%)	Positive non-invasive ($n = 486$) (%)	Incomplete investigation ($n = 528$) (%)	Negative investigations ($n = 1023$) (%)
Antiplatelet	81	77	93	90	76	55
Aspirin	77	73	88	88	72	52
Lipid lowering	50	57	80	59	49	38
Statin	48	56	79	58	47	37
Beta-blocker	67	64	79	74	61	46
ACE inhibitor	40	42	51	46	47	28
Nitrate	59	38	43	56	48	21
Calcium antagonist	28	25	28	27	30	18
Metabolic agent	7	6	5	9	12	4
Nicorandil	2	1	2	2	0.5	0.2
Mean number of AAs	1.6 ± 0.9	1.3 ± 0.9	1.6 ± 0.8	1.7 ± 0.9	1.5 ± 0.9	0.9 ± 0.9

AA (antianginal drugs); beta-blockers, calcium antagonists, nitrate, nicorandil, or metabolic agent.

Table 3 Baseline characteristics of patients in each treatment score (TS) category

Variable	TS 0 $n = 329$	TS 1 $n = 538$	TS 2 $n = 1097$	TS 3 $n = 1066$	*P*-value
Age (mean ± SD) years	57 ± 14	63 ± 11	62 ± 11	61 ± 10	<0.001
% Female	47	46	43	37	<0.001
Symptom severity (CCS)					
Class I	46	42	38	39	0.07
Class II	42	48	51	47	
Class III	12	10	11	14	
Prior MI (>1 year) (%)	1	3	4	7	<0.001
Peripheral vascular disease (%)	2	6	7	9	<0.001
Previous TIA/CVA (%)	2	5	5	6	0.02
Diabetes (%)	9	20	19	19	<0.001
Hypertension (%)	32	56	67	66	<0.001
Smoking (%)					
Prior (%)	19	27	30	34	<0.001
Current (%)	30	23	21	23	
Hyperlipidaemia (%)	21	36	51	80	<0.001
Signs of heart failure (%)	3	8	7	8	0.01
Mean systolic BP (mmHg)	141 ± 22	144 ± 21	146 ± 22	144 ± 21	<0.001
Mean BMI	27 ± 4	28 ± 5	28 ± 4	28 ± 4	0.79

n, number with complete data for each individual variable.

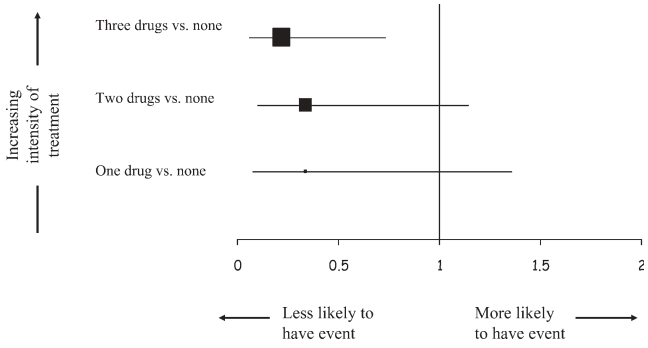

Figure 1 Hazard ratios and 95% CI for death and MI associated with increasing intensity of guideline compliant treatment in patients with stable angina and confirmed coronary disease (age and gender adjusted).

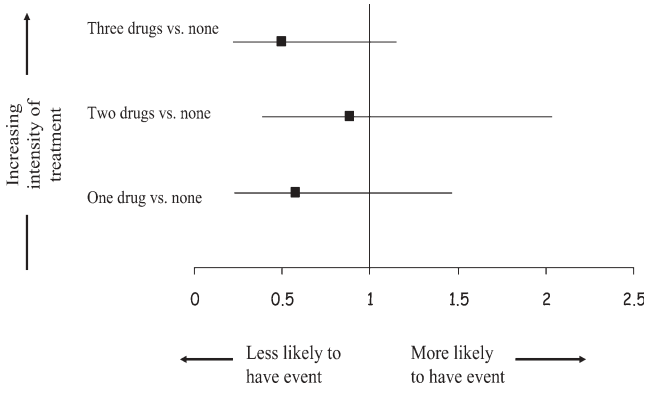

Figure 2 Hazard ratios and 95% CI for all cardiovascular events associated with increasing intensity of guideline compliant treatment in patients with stable angina and confirmed coronary disease (age and gender adjusted).

0.68; 95% CI 0.49–0.96; $P = 0.02$). Age and gender adjusted hazard ratios associated with individual treatment scores 1–3 compared with a treatment score of 0 are shown in *Figure 1*. Using the likelihood ratio test, the results did not differ significantly from linearity. Additional adjustment for the effects of hypertension or diabetes at baseline did not alter the effect or significance of increasing treatment intensity. Increasing treatment intensity remained associated with improved survival free of MI when the population was expanded to include those patients with a positive non-invasive test without angiography, (HR 0.74; 95% CI 0.54–0.99; $P = 0.05$), and when the score was applied only to those without contraindications to specific guideline-indicated treatments, (HR 0.70; 95% CI 0.49–0.99; $P = 0.05$).

The relationship between treatment intensity and all cardiovascular events in the population with confirmed coronary disease was not linear. The age and gender adjusted hazard ratios for all cardiovascular events associated with individual treatment scores 1–3 compared with a treatment score of 0 are shown in *Figure 2*.

A simplified score incorporating only antiplatelet and statin therapy did not improve the power of the treatment score to predict either death and MI or all cardiovascular events, and a four point treatment score which included the use of ACE-inhibitors was associated with a non-significant reduction in death and MI per unit increase in treatment score in the population with confirmed coronary disease, (HR 0.88; 95% CI 0.66–1.18; $P = 0.42$).

Table 4 HR associated with the use of individual drug classes in the group with confirmed CAD

Drug class	HR	95% CI	*P*-value
Aspirin	0.86	0.34–2.17	0.75
Antiplatelet therapy	0.66	0.23–1.84	0.43
Lipid lowering	0.57	0.33–0.98	0.04
Statin	0.60	0.34–1.04	0.07
Beta-blockade	0.61	0.33–1.12	0.11
ACE-inhibitor	1.57	0.88–2.81	0.12
Nitrate	1.11	0.60–2.05	0.74
Calcium antagonist	1.27	0.72–2.24	0.42

HR associated with ACE inhibitor adjusted for presence of signs of heart failure.

Although not an a priori objective of the study, the HR associated with use of individual classes of drugs in the population with coronary disease are presented in *Table 4*. Lipid-lowering therapy is the only individual therapy associated with a significant reduction in the rate of death and MI over 1 year.

Discussion

An immense volume of literature is produced on an annual basis regarding new investigations and treatments and evolving indications for existing modalities of investigation and treatment of coronary disease. The difficulties for the practicing clinician in keeping abreast of this profusion of data and in deciphering what is applicable to an individual patient are augmented by sometimes conflicting reports and compounded by the preponderance of 'single issue' randomized controlled trials. Trials of multifactorial intervention are few.[13] Professional bodies such as the ESC, ACC, and AHA have produced expert consensus guidelines[7,14] in an effort to distill the vast quantity of information to a more accessible format for clinicians and achieve a more standardized, evidence-based approach to care of individual conditions including stable angina. However, the effect of guideline compliant prescribing patterns in angina has not been assessed.

The ESC 1997 guidelines for the management of stable angina define stable angina due to coronary disease as a clinical diagnosis in the majority of patients, based on history and physical examination.[7] Supportive diagnostic tests were advised to assist in making the diagnosis when the likelihood of significant disease was low or intermediate. Hence, the population included in this survey, with a clinical diagnosis of stable angina by a cardiologist, is suitable for the application of these guidelines. The effects of treatment have been investigated both in the overall population and the population with proven coronary disease.

Although strictly the evidence base for prognostic benefit with beta-blocker therapy is limited to the post-infarction setting, the use of beta-blockers was included in the treatment score on the basis of their recommendation as first line treatment in the guidelines. Repeating the analysis using just antiplatelet therapy and statin therapy alone in the score did not improve the power of the score to predict

events. The treatment score did not include the use of ACE-inhibitor therapy because, although there have been several trials of the use of ACE-inhibitor drugs as secondary preventative therapy in patients with established cardiovascular disease since the publication of the guidelines, some,[15,16] but not all,[17] of which have suggested prognostic benefit, these drugs were not recommended for all patients with coronary disease in the European guidelines in 1997. Notwithstanding the complexities of confounding factors and the relatively small number in the confirmed coronary disease group, the trend remained towards improved outcome when the analysis was performed with ACE-inhibitors included.

Guideline compliant treatment and outcome

Observed trends towards greater use of secondary preventative drugs in practice over time are likely to reflect a variety of influences in addition to the availability of guidelines, such as the consolidation of the evidence base and the production of meta-analyses,[18–22] the confirmation of benefit in progressively wider populations,[23–27] and the lapse of time necessary for evidence to percolate to grass roots practice. Even if directly comparable data had been evaluated from a stable angina population prior to the introduction of the guidelines in 1997, it would not be possible to extricate the effects of the guidelines on practice from the influence of these and other factors. It is not possible to assert that the guidelines have improved secondary preventative practice in stable angina. But it is, nonetheless, an important finding that increased intensity of guideline compliant therapy is associated with improved survival free of MI and reduced incidence of all cardiovascular events for patients.

This conclusion must be qualified by the fact that the data are observational rather than from a controlled trial. However, a randomized controlled trial of multifactorial intervention in this context would be extremely difficult to perform, not least because of ethical difficulties in depriving patients of drugs proved to reduce mortality when studied in isolation. Although the population was not randomized, the benefits of therapy are evident despite the fact that those with higher treatment scores had a more adverse clinical profile, and the results are not altered by adjustment for factors such as age, gender, diabetes, or hypertension. The incremental benefit observed with increasing intensity of treatment, from one to all three treatments, lend support to a strategy of multiple pharmacological intervention, including the widespread use of beta-blockade as the first line antianginal therapy, early in management of stable angina, to improve prognosis. The findings are in keeping with previously documented benefits of multiple pharmacological intervention in acute coronary syndromes,[28] even though the lower event rates in this stable cohort would make it more difficult to achieve statistical significance in a relatively short time frame.

Limitations

This study is limited by the observational nature of the data, as discussed earlier. Incomplete follow-up is a limitation, as complete information regarding the timing of assessment of vital status and the occurrence of non-fatal MI was available on only 80% of the original cohort. However, the original and follow-up population were closely matched in terms of baseline characteristics, and the proportion with follow-up available is comparable to other registry data.[29] Data regarding the compliance of the patients with medication is not available, rather the concordance of the treatment with that recommended in the guidelines, and is based on the treatment initiated at initial assessment before confirmation of disease status. However, the analysis is performed on an 'intention to treat' basis, which is in line with clinical trials of individual pharmacological agents. Also, sensitivity analysis performed on the patients without contraindications to therapy showed similar results.

Conclusion

Even in this relatively short study in a non-acute setting, early intense treatment of stable angina in line with existing guidelines, in the presence of confirmed coronary disease, is associated with improved cardiovascular outcome. The findings support ongoing efforts to bridge the gap between guidelines and practice and promotion of a standardized evidence-based approach to treatment through implementation of practice guidelines in stable angina as in acute coronary syndromes.

Conflict of interest: none declared.

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