Selection of Medication in Hospitalised Elderly Patients with Angina Pectoris

Marise Gauci, Joseph M Cacciottolo, James C McElnay

Abstract

Objective: To evaluate medication changes in hospitalised elderly patients diagnosed with angina pectoris and to compare the selection of medication with evidence-based treatment guidelines.

Design: Review of medical notes and patient interview.

Setting: St. Luke's Hospital, Malta; January - May 2001.

Subjects: 226 patients, aged 60 years or over, with a history of chronic stable angina and a discharge diagnosis of angina.

Main outcome measures: Prevalence of use of antiplatelet agents, lipid lowering agents, beta-blockers, calcium channel blockers, nitrates, potassium channel openers and cellular anti-ischaemic agents; presence of co-morbidities, concurrent medication and adverse effects.

Results: Prior to discharge, 77% of patients were receiving antiplatelet agents and 27% were receiving lipid lowering agents. The most frequent anti-ischaemic agents used were nitrates (97%) and second-generation dihydropyridine calcium channel blockers (59%). Beta-blockers were used in 31% of patients and non-dihydropyridine calcium channel blockers were used in 4% of patients. Potassium channel openers (nicorandil) and cellular anti-ischaemic agents (trimetazidine) were used in 5% and 19% of patients respectively.

Of patients discharged on a single anti-ischaemic agent, 96% were prescribed nitrates, while 64% of those on two agents were prescribed nitrates and dihydropyridine calcium channel blockers. Beta-blockers, nicorandil and trimetazidine were generally used in conjunction with at least two other anti-ischaemic agents. The major medication changes involved the addition, or increase in dose, of amlodipine and isosorbide dinitrate. The major determinants affecting choice of medication were age and co-morbidities.

Conclusion: Medication selection for chronic stable angina was not in accordance with treatment guidelines.

Keywords

angina pectoris, antiplatelet agents, beta-blockers, calcium channel blockers, nicorandil, nitrates, statins, trimetazidine

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Introduction

Various pharmacological agents are used in the medical management of chronic stable angina pectoris either to alleviate symptoms or to decrease the complications of the disease. There is strong evidence that the use of aspirin reduces the risk of death and recurrent events in patients with coronary artery disease (CAD)[1] and is therefore recommended for all patients in the absence of contraindications.[2-4] Significant reductions in mortality rate and major coronary events have been demonstrated with the use of statins.[5] Treatment guidelines indicate that the use of statins is warranted when the LDL-cholesterol level is greater than 3.0 mmol/L.[2,3] Beta-blockers have been shown to be effective in the prevention of long-term angina symptoms and in the reduction of cardiovascular morbidity and mortality.[6,7] Beta-blockers are thus considered as first-line agents in the management of chronic stable angina[2-4]. Non-dihydropyridine calcium channel blockers such as diltiazem and verapamil are the preferred alternatives when the use of beta-blockers is contraindicated.[3,4] Although such agents are effective in relieving symptoms, evidence of their effectiveness in reducing morbidity and mortality is limited. Long-acting dihydropyridine calcium channel blockers such as amlodipine are suitable for providing long-term symptomatic relief. Although there is clinical trial evidence for efficacy in symptom control, nitrates have not been shown to reduce mortality in patients with CAD. For this reason, nitrates are no longer considered as the first choice for long-term treatment of chronic stable angina.[2-4] Potassium channel openers have so far been considered as appropriate for symptomatic relief, however, results from a recent large-scale study show significant reductions in morbidity and mortality with the use of nicorandil.[8] Recent guidelines are now recommending angiotensin converting enzyme (ACE) inhibitors in patients with significant CAD (by angiography or previous myocardial infarction (MI)) who also have diabetes and/or left ventricular systolic dysfunction.[9] Cellular anti-ischaemic agents, such as trimetazidine, increase cell tolerance to ischaemia. The place

of these agents in established guidelines for the management of chronic stable angina is, however, unclear.

Treatment selection requires a comparison of clinical trial evidence and the consideration of those factors that may make one drug preferable to another in a particular patient. The main objectives of the study were to examine the medication changes following hospitalisation of elderly patients diagnosed with angina; to assess the influence of factors such as age, gender, co-morbidities, concurrent medication, adverse effects and compliance on drug selection; and to compare the selection of medication with evidence-based treatment guidelines.

Methods
Study design
Patients admitted to St. Luke's Hospital (Malta) with anginal symptoms were screened according to the inclusion and exclusion criteria of the study. Information was obtained by document review and patient interview following patient consent. Patients' medical notes provided patient details, past medical history, laboratory investigations, drug treatment on admission, and other relevant information such as adverse effects and compliance. The medication prescribed on discharge was noted from the medication sheet and the discharge letter. A structured closed-question format was adopted for the interview schedule. Questions were asked with respect to adverse effects, compliance to the administration and storage of angina medication, and supply of medication.

Patient selection
The Admissions Register of the Emergency and Admissions Department was screened three times weekly for patients admitted with a presenting complaint of chest pain. The respective wards were visited and medical notes were consulted in order to select patients.

Inclusion criteria
Patients of both sexes who were admitted during the period January to May 2001, who (a) were 60 years or over; (b) had a history of chronic stable angina; and (c) were diagnosed as suffering from angina during the admission under review.

Exclusion criteria
(a) patients with an impression of angina in whom the diagnosis was still unconfirmed at the time of discharge; (b) patients initially diagnosed as having angina but later confirmed to have suffered an MI during the admission reviewed; and (c) patients who did not reside locally.

Time schedule
A pilot study was conducted during January 2001 with 15 patients (5% of the predicted study population). The remainder of the study population was recruited between February to May 2001.

Study population
A total of 226 patients, representing all the patients admitted during the time period indicated and who met the selection criteria, were included in the study.

Statistical analysis
The data obtained from the study was sorted using Microsoft® Excel 97 SR-1 and analysed using Bio-Medical Data Package (BMDP).

The primary analysis included an assessment of the changes in drug and drug formulation as well as changes in dose and dosage regimen, when comparing the medication schedule on discharge with that on admission. The results were statistically evaluated using the McNemar test for symmetry, with P values of 0.05 or less considered statistically significant. The chi-square (χ^2) test for linear trend was used to assess the use of a drug/drug group in relation to the number of agents used with P values of 0.05 or less considered statistically significant. Analysis of potential predictors (including age, gender, co-morbidities, concurrent drug treatment) for the use of the drug/drug group was performed. The results were statistically evaluated using the χ^2 test of association, with P values of 0.05 or less considered statistically significant.

Results
Male patients (n=133) represented 59% of admissions while 41% were female patients (n=93). The age of the patients ranged between 60 and 91 years, with a mean age of 72.3 years (SD 7.6). The most common co-morbidities were hypertension, heart failure and diabetes (Table 1). There were 42 patients (19%) admitted under the care of a consultant cardiologist, while 184 patients (81%) were admitted under the care of other consultant physicians.

Figure 1 illustrates the extent of use of each agent on admission and on discharge. Statistically significant

Table 1: *Patients with co-morbid conditions*

| Co-morbid condition	Number (%) of patients
Hypertension	147 (65)
Heart failure	108 (48)
Previous MI	56 (25)
Heart block	26 * (12)
Aortic stenosis	2 (1)
Diabetes mellitus	98 (43)
Asthma	11 (5)
Chronic obstructive pulmonary disease	13 (6)
Peripheral vascular disease	13 (6)
Peptic ulcer disease	7 (3)
Depression	17 (8)

first degree atrioventricular block (1); right bundle branch block (9); left bundle branch block (16)

Figure 1: *Percentage of patients using specific agents on admission and on discharge*
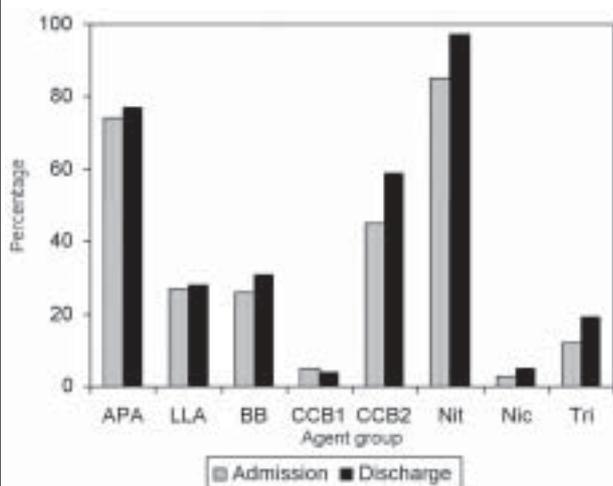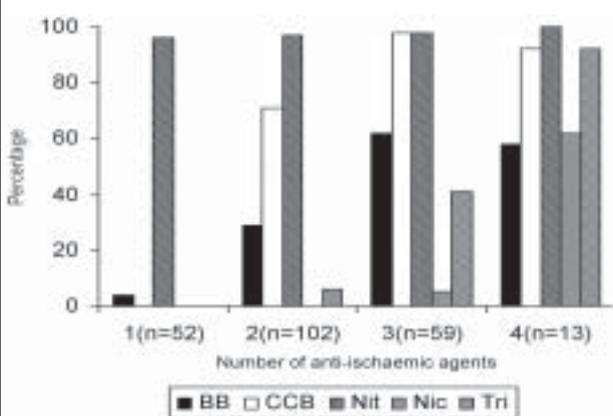

APA: antiplatelet agent; LLA: lipid lowering agent; BB: beta-blocker; CCB1: non-dihydropyridine calcium channel blocker; CCB2: long-acting dihydropyridine calcium channel blocker; Nit: nitrate; Nic: nicorandil; Tri: trimetazidine

Figure 2: *Percentage of patients using beta-blockers and total number of concurrent anti-ischaemic agents on discharge*
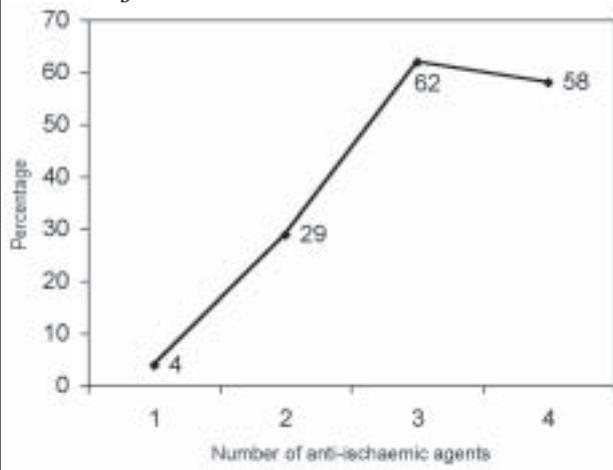
Figure 3: *Percentage of patients using each anti-ischaemic agent and total number of concurrent anti-ischaemic agents on discharge*

BB : beta-blocker; CCB : calcium channel blocker; Nit : nitrate; Nic : nicorandil;Tri : trimetazidine

characteristics at the time of discharge were identified for antiplatelet agents (mainly aspirin), lipid lowering agents (mainly statins) and beta-blockers. When patients with peptic ulcer disease, epigastric pain associated with aspirin, or those on concurrent warfarin or ticlopidine therapy were excluded, the proportion of patients on aspirin was 93% on discharge. A significant negative association was evident for aspirin use and age (>75years). The association between aspirin use and gender, physician specialty, history of MI, hypertension, hyperlipidaemia and diabetes was not of statistical significance. Age (≤75years), cardiology specialty, previous angioplasty and history of MI were positively associated with the use of lipid lowering agents. No significant association was noted with gender, previous coronary bypass or diabetes. When patients with chronic obstructive pulmonary disease or asthma were excluded, the proportion of patients on beta-blockers was 35% on discharge. A significant negative association was evident with beta-blocker use and age, heart block, heart failure, peripheral vascular disease and digoxin use. Although no significant association between beta-blocker use and history of MI was noted, when categorised according to the time period (≤3years, >3years), a positive association was present in favour of the shorter time period since the MI (Table 2).

The major medication changes involved the addition, or increase in dose, of amlodipine and isosorbide dinitrate. Figure 2 illustrates the extent of beta-blocker use on discharge in relation to the number of anti-ischaemic agents prescribed (P=0.000, χ^2 for linear trend). Similar trends were also evident with the use of calcium channel blockers, potassium channel openers and cellular anti-ischaemic agents. Figure 3 illustrates the components of treatment combinations on discharge. The most frequent combination of anti-ischaemic agents was that of two agents in 102 (45%) patients, and in 65 (64%) of these cases the combination involved nitrates and long acting dihydropyridine calcium channel blockers.

Discussion

Factors which have been significantly associated with aspirin use include male gender, patient age, history of MI, hyperlipidaemia and care by cardiologist, all being positive predictors.[10-14] These and other potential predictors were tested for in the study population. Only with patient age was there a significant association in that aspirin was used less frequently in patients greater than 75 years of age. Although aspirin therapy in the most elderly patients may carry an increased risk of complications, it is in this population that aspirin is likely to have the greatest absolute benefit[13].

Various trials have demonstrated the benefit of statins post-MI.[5,15,16] In the study population, a statistically significant association was in fact present in the patient group having a history of MI. Lipid lowering agents were less commonly used in patients older than 75 years of age, an expected finding when considering that the local treatment protocol in use at the time of the study did not suggest treatment with lipid lowering agents

in this age group. The recent large trials that have demonstrated mortality benefit of cholesterol lowering with statins in CAD, involved patients younger than 75 years of age. It is likely, however, that older patients would show similar benefits.[18] An increased likelihood of use of lipid lowering agents in males (compared to females) with dyslipidaemia and CAD has been reported.[14,17] Such gender inequalities were not observed in the study undertaken.

Despite strong evidence that beta-blockers improve survival, the results of the study undertaken indicate that only a minority of patients were taking this medication on admission and on discharge. Moreover, beta-blockers were not being used as single agents but were more commonly used as adjunctive treatment with two or more other anti-ischaemic agents, suggesting that beta-blockers were not being used as first-line agents. The use of beta-blockers was significantly lower in patients older than 75 years of age, a finding that has also been observed in other studies.[19] The decreased use of beta-blockers in patients with heart failure was statistically significant. Guidelines for the management of heart failure in fact recommend the use of beta-blockers for stable, mild to moderate heart failure caused by left ventricular systolic dysfunction. In this situation, the precaution to be taken is the use of low doses in the initial period with slow titration. Since no indication of the grade of severity of heart failure was present in the medical notes, any extent of underutilisation of beta-blockers could not be evaluated. The association between beta-blocker use and history of MI was not statistically significant. Several studies have reported the underutilisation of beta-blockers for secondary prevention after MI.[12,20] However, when the time period since the MI was considered (≤3years, and >3years), the relationship was significant in that beta-blockers were more commonly used in the former group, a finding reported by other investigators.[19] In spite of the fact that beta-blockers are considered to be of particular value in patients with hypertension and CAD, use of beta-blockers in this patient group did not achieve the statistical significance reported in similar studies.[19]

Although the non-dihydropyridine calcium channel blockers are considered preferable to dihydropyridine calcium channel blockers for the management of chronic stable angina in patients intolerant to beta-blockers, these agents were used in only a small proportion of patients. Conversely, long-acting dihydropyridine calcium channel blockers were the second most commonly used anti-ischaemic agents after nitrates. The results suggest that these agents, particularly amlodipine, were considered as second line agents in combination with nitrates.

Long-acting nitrates were prescribed in the majority of patients on admission as well as on discharge. When considering patients on monotherapy with anti-ischaemic agents, there is a clear implication that nitrates were still the preferred choice.

A number of limitations of the study were identified. These included incomplete documentation of information, inadequate

Table 2: *Characteristics associated with patients receiving beta-blockers on discharge*

Characteristic	% of patients on beta-blockers	P χ² test for association
Sex		
Male	36	0.73
Female	33	
Age		
≤75 years	43	0.001
>75 years	20	
Physician specialty		
Cardiology	45	0.10
Non-cardiology	32	
Co-morbidities		
Hypertension		
No	26	0.06
Yes	39	
Diabetes mellitus		
No	35	0.81
Yes	33	
Hyperlipidaemia		
No	31	0.06
Yes	45	
History of MI		
No	35	0.90
Yes	34	
≤3 years	52	0.05
>3 years	25	
Heart block		
No	37	0.05
Yes	15	
Heart failure		
No	46	0.0001
Yes	20	
Peripheral vasc. dis.		
No	37	0.006
Yes	0	
Depression		
No	34	0.76
Yes	38	
Concurrent treatment		
Digoxin		
No	37	0.01
Yes	6	
Amiodarone		
No	36	0.06
Yes	9	
CCBs		
No	41	0.18
Yes	31	

CCBs: Calcium channel blockers. Patients with chronic obstructive pulmonary disease or asthma were excluded.

patient knowledge, ungraded disease severity, readmission bias and the effect of covariates. Furthermore, the clinicians' choice of medication at the time of discharge might have been affected by investigations or interventions then pending.

Conclusion

The results of the study indicate that nitrates were still considered as the most appropriate first-line agents in the management of chronic stable angina. Second generation dihydropyridine calcium channel blockers were considered as the most appropriate second line agents. Despite the evidence and recommendations in treatment guidelines favouring the use of beta-blockers as first-line agents, the results suggest that these agents were underutilised. Furthermore, non-dihydropyridine calcium channel blockers, which are recommended as the alternative to beta-blockers, were hardly used at all. The high frequency of aspirin use, on the other hand reflected appropriate management. The appropriateness of use of lipid lowering agents could not be fully assessed because of the relative unavailability of lipid levels, although the latter fact in itself suggests a possible underutilisation of these agents.

A number of predictors indicating inappropriate under-use of specific medications were identified. Of particular importance was age in the case of aspirin, lipid lowering agents and beta-blockers, and heart failure in the case of beta-blockers.

In general, the findings of the study suggest that the management of chronic stable angina was not always in accordance with evidence-based treatment guidelines, and indicates a substantial need for optimising the medical management of this disease.

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