Beta-blockers and antithrombotic treatment for secondary prevention after acute myocardial infarction

Towards an understanding of factors influencing clinical practice


The European Secondary Prevention Study Group

Aims Long-term beta-blockade reduced mortality after acute myocardial infarction by about a quarter in a series of published trials. Representative data on beta-blocker use for secondary prevention are scanty but indicate wide variations. We have analysed European practice, and sources of variation, by regional sampling of acute myocardial infarction patients admitted to hospital in 11 countries during the period January 1993–June 1994.

Methods and results Treatment data for 4035 representative patients were collected for the hospital phase and 6 months after discharge. A logistic regression model was developed to describe the predictors of beta-blocker use. In the 11 regional samples, 6–38% (20% overall) of patients had no recorded contraindications but were discharged without a beta-blocker. In the absence of perceived contraindications, there was a strong, independent negative association between age and odds of treatment (P < 0.001), and women were less likely to be treated than men (adjusted odds ratio 0.76, 95% CI 0.58–0.99). Discontinuation of beta-blocker treatment by 6 months was significantly less likely in regions where the proportion given such treatment at discharge was high. In contrast, use of antithrombotic agents in the samples was consistently high.

Conclusions There is persisting low use of beta-blocker secondary prophylaxis, particularly in the elderly and in women, not attributable to perceived contraindications or intolerance. Considerable regional variations persist despite shared trials evidence. Discharge treatment strongly influences long-term medication.

Key Words: Myocardial infarction, drug therapy, drug utilization, secondary prevention, β-adrenoceptor antagonists.

Introduction

The evidence base supporting the long-term use of beta-blockers after acute myocardial infarction is extensive. By 1985 the potential health gain had been identified following enrollment of over 20 000 patients in 24 randomized, controlled trials testing the long-term use of beta-blockers[1]. The benefit of treatment estimated by meta-analysis was substantial; total mortality and non-fatal reinfarctions were decreased by about a quarter, and the incidence of sudden death by about a third[1,2]. However, there appears to be great variation in the translation of these data, derived from selected trial samples, to clinical practice. Large differences in use at hospital discharge are seen between regions, with proportions ranging from 19% to 70%[3–5]. Reasons for such variation despite a shared knowledge base are unknown but warrant investigation, in a large representative sample, because under-utilization may have serious public health consequences.

Although information may be available for selected samples[6], data describing typical practice are sparse and determinants of prescribing are largely unknown. The decision to prescribe a beta-blocker for secondary prevention in an individual patient is likely to be a strategic decision made at a senior level following confirmation of the diagnosis. This contrasts with thrombolysis, where established under-use might...
be attributable to the narrow time opportunity for administration and difficulty in early diagnosis[31].

The European Secondary Prevention Study was designed to describe typical practice in representative samples taken from 11 European regions. We report here international variations in beta-blocker use and predictors of use in individual patients.

Method

Study sample

Typical prescribing practice in 11 geographically defined European regions was identified at three time points following acute myocardial infarction; on admission, at discharge and at 6 months post-acute myocardial infarction. The study regions (median population 1-6 million) contained a mix of urban and rural settings, and of teaching and non-teaching hospitals providing representative study samples. The combined source population was 19.8 million. All acute myocardial infarction patients (or in one region a 50% random sample of all) discharged from, or who died in, hospital with the main discharge diagnosis of acute myocardial infarction were studied during a defined interval of January 1993-June 1994. The samples represent typical practice within the region from which they are taken and have been described previously[7]. To limit the within-region standard errors to ≤3%, sample sizes of >250 patients per region were sought. Cohorts of patients were followed retrospectively from hospital admission to follow-up 6 months later. Necessary approval for the study was obtained locally by each national collaborator.

Data retrieval

Sampling and data collection on acute treatment were performed retrospectively to avoid influencing practice. Medical history at presentation and treatment given in hospital and at discharge were abstracted directly from the hospital medical notes. Data were not collected on drug and dose details due to lack of evidence of differential efficacy by either drug or by dose.

Details of treatment at 6 months post acute myocardial infarction were collected mainly by direct communication with the patient in order to determine the exact therapy the patient was taking rather than what the doctor believed or the medical records stated. In all but one region the patient was contacted directly, usually by telephone or alternatively by letter or at a clinic visit. Information from the patient was supplemented if necessary by data from physicians obtained by telephone or letter. In Switzerland patients could not be approached directly because of privacy laws; here data were collected by letter to the treating physician. In one region details of beta-blocker and antithrombotic use were collected from patients and from GP records and consistency between these two sources was confirmed (concordance 93%). A standard data collection form, translated as necessary, was used for all time points. Anonymised forms were checked for completeness before entry into the study. For the study as a whole, covering all patients and all time points, data fields were 98% complete.

Statistical analysis

The actual proportion of drug use observed is reported as the observed proportion. The shortfall is calculated for use at discharge and defined as the percentage of all patients who (a) had no documented perceived contraindication to therapy and (b) did not receive treatment (Fig. 1). The contraindications were agreed by consensus as: previous adverse reaction to beta-blockers, asthma, chronic obstructive airways disease, diabetes, peripheral vascular disease and left ventricular failure on admission. A broad definition of contraindication was used so as to identify patients in whom there was an unequivocal absence of documented explanation for non-treatment. Contraindications for antithrombotic treatment (aspirin/anticoagulants) were: previous adverse reaction to aspirin, history of known or suspected peptic ulcer and bleeding disorder.

The unadjusted associations between beta-blocker use and patient characteristics were estimated using univariate logistic regression. The strength of the association was expressed as the odds ratio (OR) and 95% confidence interval (95% CI). The reference group is stated for each analysis. Unconfounded estimates of odds ratios for beta-blocker utilization in different patient groups were obtained using multiple logistic regression using sex, age and centre as explanatory variables. Since the dependence of beta-blocker prescribing on age was strongly non-linear, age was modelled throughout as a six-level categorical variable (<45, 45–54, 55–64, 65–74, 75–84, ≥85 years). Separate models were developed for beta-blocker use at discharge and at six months after acute myocardial infarction. Patients admitted on a beta-blocker were excluded from all logistic regression analyses to focus on the initiation of beta-blocker therapy.
Results

Patient characteristics

A total of 4035 representative patients with a discharge diagnosis of acute myocardial infarction were studied from the 11 regional samples (Table 1). Details of these patients have previously been reported[7]. The mean age was 68 years, but female patients (33%) were on average 8 years older than males (mean 73 vs 65 years). Over three-quarters (77%) of the study sample were admitted to a coronary care unit. Of the 3453 patients discharged alive, 271 (8%) died in the 6 months following acute myocardial infarction and another 375 (11%) were lost to the study. Follow-up data were therefore available for 88% of known or possible survivors at 6 months. Loss to follow-up in different regions ranged from 2–31% (median 7%) of the original sample discharged alive. Greatest loss was experienced in three countries (Austria, Switzerland, Lithuania). Reasons for these losses were patient relocation for two countries and reliance on data from physicians in Switzerland where privacy laws restrict direct access to patients.

Beta blocker use at discharge

The observed prescription of beta-blockers at discharge showed a 2.5-fold difference (Fig. 2). The estimated shortfall in all patients at discharge ranged from 6–38% across the regional samples (20% for the whole study). For this proportion, beta-blocker therapy was not prescribed despite lack of documented perceived contraindications.

After excluding 659 patients admitted on a beta-blocker and 50 patients for whom data on contraindications were unknown, 48% (1611) of patients had at least one contraindication to beta-blocker therapy on admission. Of the remaining 1715 patients, all of whom by the criteria adopted in this study were suitable for treatment with beta-blockers, 1589 were discharged alive. Beta-blocker use was unknown for one patient, leaving 1588 patients to form the group for further detailed analysis. The proportion of patients receiving a beta-blocker in this group was only 58% although the proportion varied widely from centre to centre (from 35% to 85%). In the initial exploration of this group, univariate analyses revealed that females were much less likely to receive beta-blockers than males (OR in females =0.57, P<0.001). There was also a strong negative association between older age and odds of treatment (P<0.001).

In order to estimate the independent effects of age and sex, multiple logistic regression was undertaken.

Table 1 Discharge and long-term use of beta blockers and antithrombotic agents in 11 European samples

<table>
<thead>
<tr>
<th>Country of regional sample</th>
<th>No of patients discharged alive</th>
<th>No of patients available for follow-up at 6 months</th>
<th>Observed beta-blocker use (%)</th>
<th>Observed beta-blocker use at discharge (%)</th>
<th>Observed beta-blocker use at 6 months post AMI* (%)</th>
<th>Anti-thrombotic use at discharge (%)</th>
<th>Anti-thrombotic use at 6 months post AMI (%)</th>
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</thead>
<tbody>
<tr>
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<td>302</td>
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<td>8</td>
<td>32</td>
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<td>24</td>
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<td>71</td>
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<td>88</td>
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<td>Greece</td>
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<td>49</td>
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<td>87</td>
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<tr>
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<td>3</td>
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<td>27</td>
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<td>53</td>
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<tr>
<td>All</td>
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<td>2807</td>
<td>13</td>
<td>46</td>
<td>46</td>
<td>87</td>
<td>84</td>
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</tbody>
</table>

*Patients not admitted on beta-blocker.

Figure 2 Observed beta-blocker use (■) and calculated shortfall (○) at discharge in all patients in 11 European samples. (Observed use includes some patients with study-defined contraindications).
on this group of patients \((n=1588)\). In a model including both age and sex, the odds ratio for female sex, and that for each of the older age groups in comparison with the baseline \((0-44\text{ years})\) group, were closer to unity than the corresponding univariate \(ORs\). These falls in the \(ORs\) reflect the fact that females were older than males. However, after controlling for confounding the independent effects of age and sex remained significant. In order to control for any further confounding due to centre, centre was added to the model as an 11-level categorical variable. This resulted in a very substantial improvement in fit \((\text{likelihood ratio test: } \chi^2_{10} = 200, \, P < 0.001)\) reflecting the wide centre-to-centre differences in beta-blocker use. In this model the effect of sex was just statistically significant \((OR\,\text{for female sex was } 0.76, \, 95\% \, CI\, 0.58 \, to \, 0.99, \, P = 0.049)\), the odds ratio fell rapidly with increasing age (Fig. 3), and the overall effect of age was highly significant \((\text{likelihood ratio test for deletion of age variables: } \chi^2_{5} = 91, \, P < 0.001)\). Older age was strongly and independently associated with a decreasing probability of receiving beta-blocker treatment. In addition, there is a just significant independent tendency for women not to receive treatment.

Use of intravenous beta-blockers showed a 100-fold difference \((0.5\%-54\%)\) in the regional samples (Table 1) and showed a significant positive association between use of oral beta-blockers at discharge and inpatient iv beta-blocker use \((\text{Spearman's } P = 0.658, \, P < 0.05)\).

**Beta-blocker use 6 months after acute myocardial infarction**

The proportion discontinuing treatment by 6 months after acute myocardial infarction might be expected to be higher in the regions where the proportion of patients treated at discharge was high. In fact the reverse was true (Fig. 4). The OR for continued use at 6 months for a 10\% increase in beta-blocker use at discharge was 1.33 \((95\% \, CI \, 1.22-1.47)\) after controlling for potential confounding by age and sex. Neither age nor sex had a significant effect on continuation of therapy in this multivariate model. Restricting this subgroup further to those patients without a perceived contraindication to therapy, a very similar result is seen \((OR\,\text{ for continued use at 6 months for an increase in beta-blocker use at discharge of } 10\%\, \text{was } 1.41 \,(95\% \, CI \, 1.26-1.58))\).

It was considered possible that patients lost to follow up at 6 months may be more likely to have stopped treatment, if so the reported proportion remaining on treatment would be over-estimated. The analysis was repeated using the worst case assumption that all patients discharged on a beta-blocker but lost to follow-up had stopped treatment by 6 months. The result was qualitatively unchanged.

**Antithrombotic agent use**

The observed proportion of antithrombotic agent use in all patients at discharge and at 6 months after acute myocardial infarction is shown in Table 1. At discharge, aspirin was used in 73\%, anticoagulant in 10\% and both agents in 4\% of patients. Shortfall at discharge was estimated at only 8\% for the total sample. High levels of use were maintained at 6 months post acute myocardial infarction, with aspirin used in 72\%, anticoagulant in 9\% and both agents in 3\% of patients.

**Discussion**

This study has examined beta-blocker use in a truly representative sample of patients taken from a large
study population and therefore provides a unique insight into current prescribing patterns. A potential 20% under-utilization of beta-blockers at hospital discharge following acute myocardial infarction has been identified, 7 years after the beneficial effects of long-term beta-blocker use had been reported. This estimated shortfall was calculated utilizing very broad contraindications to beta-blocker therapy so is unlikely to be an over-estimate. If the range of perceived contraindications was narrowed, as might be strongly argued, the shortfall would increase even further. For example, an area of debate is the treatment of diabetic patients. In those patients not admitted on a beta-blocker, diabetes was clearly associated with a decreased likelihood of receiving a beta-blocker at discharge (OR = 0.70, P < 0.001). In the patient group not admitted on a beta-blocker and without perceived contraindications, only 58% of patients actually received beta-blocker therapy at discharge. This result is consistent with the reported low use in all acute myocardial infarction patients without contraindications at discharge from four university hospitals. Therefore, medical contraindications alone do not explain the low use of beta-blockers.

There is a large regional variation in beta-blocker use for secondary prevention in both the observed proportion and estimated shortfall. Why does such variation occur in light of the shared trials literature? Perhaps it is indicative of wide disagreement on the interpretation and generalizability of the trial results or due to differing perceptions of the hazard of therapy. Certainly, opinion is divided as to whether long-term beta-blocker treatment should be given to all who do not have a contraindication or whether beta-blockers should only be prescribed for those at moderate and high risk.

Use in all patients in the absence of a contraindication as has been advocated but challenged by others. In the patient group not admitted on a beta-blocker and without perceived contraindications, only 58% of patients actually received beta-blocker therapy at discharge. This result is consistent with the reported low use in all acute myocardial infarction patients without contraindications at discharge from four university hospitals. Therefore, medical contraindications alone do not explain the low use of beta-blockers.

Older age and female sex were identified as independent predictors of lower oral beta-blocker use among patients without perceived contraindications. Decreased use in older patients may reflect a less aggressive general approach to the long-term management of older patients or greater concerns about possible side-effects. Alternatively, lower use may result from less trials’ evidence in this patient sub-group.

A high upper age limit for recruitment, beta-blocker efficacy for secondary prevention does not appear to decrease in older patients. This negative effect of older age on prescribing has been reported previously for beta-blockers and persisted after controlling for confounding by multiple factors. The size and power of the present study allows identification of a statistically significant negative association of female sex and beta-blocker use. As there is no evidence that women obtain less benefit from long-term beta-blocker therapy than men, the lower use in women can not be justified. Decreased access to treatment associated with female sex has previously been reported for beta-blockers.

All patients had a discharge diagnosis of acute myocardial infarction and the ‘time window’ to initiate long-term beta-blocker therapy is broad, difficulty in diagnosis and time restrictive therapeutic opportunity should not have been influencing factors in the treatment decision process. This contrasts with the use of thrombolytics, where these issues were identified as significant contributory factors. In addition, initiation of long-term beta-blocker therapy in an individual patient is likely to be a strategic decision made at a senior level. The significant association between the level of beta-blocker prescribing at discharge and use of the intravenous formulation during admission may reflect a general approach to the use of beta-blockers. Perhaps some regions are enthusiastic about the benefits of beta-blockers resulting in a ‘beta-blocker friendly’ culture and extensive prescribing while other regions are less enthusiastic, generating lower levels of use.

Long-term continuation of secondary preventive therapy after acute myocardial infarction appears to be significant and positively associated with hospital discharge prescribing practice. The level of antithrombotic and of beta-blocker prescribing at hospital discharge was highly predictive of the long-term use of these therapies. For beta-blockers, high levels of use were sustained by several regions and the overall proportion who had ceased treatment at 6 months was similar to previous reports of 13% and 23%. There is no evidence to suggest that high use of beta-blockers at discharge is associated with a high drop-out at 6 months. Indeed, it appears that regions with a high use at discharge have a low cessation rate at 6 months, suggesting high tolerability and a continued effort to ensure long-term administration. Neither age nor sex were significant factors associated with the discontinuation of long-term beta-blocker therapy. Relatively few patients were initiated on a beta-blocker after hospital discharge, which reinforces previous reports that beta-blockers for secondary prevention are rarely initiated in the community.

The knowledge base to support the long-term use of antithrombotic agents, and particularly aspirin post acute myocardial infarction, is also strong. The estimated shortfall for antithrombotic agents is substantially less than that for beta-blockers although there was great variation in the choice of prescribed regimen.

Uniformly high use of antithrombotic agents in the samples shows that translation of trial data into practice does occur in this group of prescribers. Why this should happen extensively with antithrombotic agents and not with beta-blockers is unknown. Perhaps there is a greater willingness to extrapolate the trial results to the wider clinical population alongside a perception of low...
risk of aspirin administration\[21\]. It is apparent that international variation in beta-blocker use is not a general phenomenon affecting other forms of secondary prevention. As hospital discharge practice strongly directs long-term treatment, efforts to optimize the use of beta-blockers for secondary prevention should be focused primarily on the hospital sector.

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References

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Appendix

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