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Use of beta-blocking agents in secondary prevention after myocardial infarction: a case for evidence-based medicine?

GISSI experience, 1984–1993

F. Avanzini, G. Zuanetti, R. Latini, F. Colombo, E. Santoro, A. P. Maggioni, M. G. Franzosi, G. Tognoni, on behalf of the Gruppo Italiano di Studio sulla Sopravvivenza nell'Infarto Miocardico (GISSI) Investigators*

Department of Cardiovascular Research, Istituto di Ricerche Farmacologiche 'Mario Negri', Milano, Italy

Aims Many clinical trials conducted in the 1970s and early 1980s have shown that the long-term use of beta-blockers after an acute myocardial infarction significantly reduces mortality and reinfarction rates. This study assessed the impact of these findings in clinical practice.

Methods We retrospectively analysed the beta-blocker prescriptions for 36 817 patients with acute myocardial infarction included in three large randomized clinical trials (Gruppo Italiano di Studio sulla Sopravvivenza nell'Infarto Miocardico — GISSI, 1, 2 and 3), conducted by a highly representative sample (about 75%) of Italian coronary care units in 1984–85, 1988–89 and 1991–93.

Results The prescription of beta-blockers at discharge increased gradually from 8·5% in 1984–85 to 25·0% in 1988–89 and to 31·4% in 1991–93. A similar trend was apparent for beta-blocker prescriptions 6 months after acute myocardial infarction. The strongest predictors of beta-blocker prescription are the presence of post-infarctual angina and a history of arterial hypertension. Besides the classical contraindications, advanced age, transitory cardiac failure or arrhythmias in the acute phase of acute myocardial infarction are important predictors of non-prescription.

Conclusion The use of beta-blockers after acute myocardial infarction in Italy has increased more than three-fold in the last decade, but they are still prescribed to too few patients, especially those at higher risk, for whom the expected benefit is greater.
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Key Words: Beta-blockers, myocardial infarction, secondary prevention, pharmaco-epidemiology.

Introduction

In the decade 1975–85 many controlled clinical trials unequivocally documented that beta-blockers, besides reducing mortality in the acute phase of myocardial infarction, improve the long-term prognosis of survivors of an acute myocardial infarction. In particular, there was a significant reduction in total mortality (cardiac and sudden) of over 20%, and reinfarctions were reduced by over 25%[1–5].

These studies were conducted before the thrombolytic era, but a more recent study, the 'Thrombolysis in Myocardial Infarction (TIMI) Phase II' trial, suggests that beta-blockers are effective in the acute phase of myocardial infarction, and when used in association with aspirin and thrombolytic therapy[6]. Nevertheless, despite all the scientific evidence and clinical guidelines[7,8], beta-blockers still appear to be generally underused[9–22].

The objective of this analysis was to describe the pattern of beta-blocker prescription in the late 1980s and early 1990s in patients discharged with a diagnosis of recent acute myocardial infarction, and to identify the

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*A complete list of collaborators and participating centres appeared in *Lancet* 1986, 1:397–402 (GISSI-1), in *Lancet* 1990, 336:65–71 (GISSI-2) and in *Lancet* 1994, 343:1115–112 (GISSI-3).

Correspondence: GISSI Coordinating Center, Via Eritrea 62, 20157 Milano, Italy.

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Table 1 Main characteristics of Gruppo Italiano di Studio sulla Sopravvivenza nell'Infarto Miocardico-GISSI studies

	GISSI-1	GISSI-2	GISSI-3
Recruitment period	2/84–6/85	2/88–7/89	6/91–7/93
Study treatments	streptokinase vs control	streptokinase vs alteplase heparin vs control	lisinopril vs control nitrates vs control
Design	parallel	2 × 2 factorial	2 × 2 factorial
Inclusion criteria (interval from onset of symptoms to randomization	≤12 h	≤6 h	≤24 h
Main exclusion criteria	Contraindications to thrombolysis	Contraindications to thrombolysis	Killip class IV SBP<100
Participating CCUs (n)	176	223	200
Randomized patients (n)	11 806	12 490	19 394
Patients discharged alive with confirmed MI and complete forms (n)	9452	10 407	16 958
Patients attending the 6-month follow-up visit (n)	7277	9049	14 263

SBP=systolic blood pressure; CCU=coronary care unit; MI=myocardial infarction.

main determinants of their use. The data were assembled from a representative sample of Italian coronary care units.

Methods

The prescription of beta-blockers issued to survivors of acute myocardial infarction at discharge, and at clinical assessment 6 months after randomization, were analysed. The subjects had been recruited into three large controlled clinical trials (Gruppo Italiano di Studio sulla Sopravvivenza nell'Infarto Miocardico — GISSI 1, 2 and 3)[23–25] in which about 75% of Italian coronary care units participated.

Table 1 shows the main characteristics of the populations enrolled in the three studies. Patients discharged alive with a confirmed diagnosis of acute myocardial infarction were included in the analysis of prescriptions at discharge, namely 9452, 10 407 and 16 958, respectively, for GISSI-1, GISSI-2 and GISSI-3. Prescription analysis 6 months after acute myocardial infarction was based on treatments in use in patients examined at the 6-month follow-up visit (7277, 9049 and 14 263, respectively, in the three studies). This analysis included the beta-blocker prescription in general, but also its individual active agent in each case; no information was available on the doses used.

Variables included in the analysis

The variables included in the analysis of determinants of beta-blocker prescription represent specific indications or contraindications to their use and are the main variables characterizing populations included in studies on beta-blockers after acute myocardial infarction. The variables are: age (≥70 vs <70), gender, history of hypertension, diabetes, angina and previous myocardial infarction, signs of cardiac failure at randomization (Killip class 2 vs 1), infarct location (anterior vs other), angina post-infarction, reinfarction, bypass or coronary angioplasty during hospitalization, early and transient left ventricular failure (within 4 days after acute myocardial infarction), late left ventricular failure (appearing or persisting beyond day 4), second or third degree atrioventricular block, atrial flutter or fibrillation, sustained ventricular tachycardia, ejection fraction <40% on the pre-discharge echocardiogram, ventricular arrhythmias (≥10 ventricular ectopic beats . h^{-1}, couplets or triplets) on the 24 h ECG recording, presence of contraindications to an exercise stress test and exercise-induced ischaemia, prescription of antiarrhythmic drugs, digitalis or other inotropic drugs, calcium channel blockers, angiotensin converting enzyme inhibitors, nitrates or diuretics at discharge. All these variables were available for GISSI-2 and GISSI-3, while some were not recorded in GISSI-1 (Table 2).

To analyse beta-blocker use in secondary prevention, i.e. in the absence of specific indications, patients with a history of hypertension and those who had developed angina post-infarction or had a positive exercise stress test for ischaemia were excluded.

Statistical analysis

The chi-square test was used to assess the statistical significance of the temporal trends of beta-blocker prescription in the three studies, in the whole population and within the different subgroups.

Within each study, each variable's univariate influence in determining beta-blocker prescription was initially evaluated, followed by multivariate logistic analysis (SAS statistical package)[26], in order to define its independent contribution.

Owing to the different distribution of variables associated with the use of beta-blockers in the three studies' population, a multivariate analysis was carried out on the 36 817 patients recruited into the three studies, including all the variables homogeneously recorded, in order to evaluate the temporal trend of beta-blocker prescription controlling for those variables. A subsequent multivariate analysis was performed on

Table 2 Percentage of patients receiving beta-blockers at discharge according to their clinical characteristics in Gruppo Italiano di Studio sulla Sopravvivenza nell'Infarto Miocardico-GISSI studies

		GISSI-1 (n=9452)	GISSI-2 (n=10 407)	GISSI-3 (n=16 958)	Chi-square among the GISSI studies
Total population		8·5	25·0	31·4	
Baseline epidemiological characteristics					
Sex	female/male	7·5/8·7	21·4/25·7‡	26·2/32·8‡	**/**
Age (years)	>70/≤70	2·3/9·9	11·6/28·2‡	15·7/36·6‡	**/**
History of hypertension	Yes/No	—	27·2/23·3‡	33·7/30·2‡	**/**
History of diabetes mellitus	Yes/No	—	20·2/25·6‡	24·7/32·8‡	**/**
Previous AMI	Yes/No	6·8/8·7†	20·0/25·8‡	28·5/32·1‡	**/**
History of angina	Yes/No	—	23·6/25·3	32·0/31·3	**/**
AMI characteristics at admission					
Killip class at entry	>1/1	3·8/10·0‡	12·0/27·9‡	17·7/33·7‡	**/**
Site of AMI	anterior/other	8·4/8·5	26·5/24·1†	34·1/30·3‡	**/**
In-hospital events					
Post-AMI angina	Yes/No	9·6/8·3	25·2/24·9	32·3/31·3	**/**
Reinfarction	Yes/No	8·6/8·4	19·3/25·1†	31·6/31·4	**/**
CABG or PTCA	Yes/No	—	14·8/25·1	30·4/31·4	**/**
Early and transient LVF (within 4 days)	Yes/Never LVF	—	13·6/30·3‡	18·1/35·8‡	**/**
Late LVF (beyond day 4)	Yes/Never LVF	—	5·2/30·3‡	12·1/35·8‡	**/**
Ventricular fibrillation	Yes/No	11·2/8·3	23·1/25·1	29·3/31·6	**/**
Sustained ventricular tachycardia	Yes/No	—	18·8/25·1†	20·8/31·6‡	ns/**
Atrial fibrillation/flutter	Yes/No	—	12·1/26·0‡	15·1/32·3‡	ns/**
II or III° atrioventricular block	Yes/No	—	12·6/26·1‡	12·7/32·1‡	ns/**
Pre-discharge instrumental risk assessment					
Echocardiographic ejection fraction	<40%/≥40%	—	14·2/29·3‡	21·0/34·0‡	**/**
Exclusion from the exercise test	Yes/No	—	16·3/30·4‡	24·3/39 5‡	**/**
Positive exercise test for ischaemia	Yes/No	—	29·7/30·7	42·5/38·4‡	**/**
PVB ≥10 . h^{-1}, couplets or VT at Holter	Yes/No	—	17·7/25·7‡	26·7/32·4‡	**/**
Treatments at discharge					
ACE inhibitors	Yes/No	5·5/8·5‡	11·7/26·4‡	25·8/37·0‡	**/**
Calcium antagonists	Yes/No	6·5/10·2‡	12·9/31·5‡	21·7/33·7‡	**/**
Nitrates	Yes/No	7·2/9·2‡	21 4/30·7‡	29·4/33·6‡	**/**
Diuretics	Yes/No	5·3/9·2‡	11·6/28·1‡	14·8/34·5‡	**/**
Digitalis or other inotropic drugs	Yes/No	2·1/9·6‡	4·6/27·1‡	4·3/33·0‡	**/**
Antiarrhythmics	Yes/No	3·4/9·1‡	9·6/26·8‡	8·5/32·8‡	**/**
Aspirin	Yes/No	—	26·3/20·7‡	34·0/24·6‡	**/**

AMI=acute myocardial infarction; CABG=coronary artery bypass graft; PTCA=percutaneous transluminal coronary angioplasty; LVF=left ventricular failure; PVB=premature ventricular beats; VT=ventricular tachycardia; ACE=angiotensin converting enzyme; †$P<0·05$ and ‡$P<0·01$: chi-square within each GISSI study; ns=not significant; **$P<0·01$; —=variable not available.

the 27 365 patients from GISSI-2 and GISSI-3 including the variables collected only in these studies, to evaluate beta-blocker prescription in GISSI-3 vs GISSI2, taking into account also the additional variables.

Results

Beta-blocker prescription at discharge and 6 months

The prescription of beta-blockers at discharge has gradually increased from 8·5% in 1984–85 (GISSI-1) to 25% in 1988–89 (GISSI-2) and to 31·4% in 1991–93 (GISSI-3) (chi-square for trend: $P<0·0001$).

A similar trend is apparent for patients on beta-blockers at 6 months: 11%, 24·3% and 34·2%, respectively. The increase in the use of beta-blockers after discharge is determined both by the progressive reduction of beta-blocker discontinuation prescribed at discharge (from 35·2% in GISSI-1, to 27·2% in GISSI-2 and to 22·3% in GISSI-3) and by an increase in new prescriptions in patients discharged without beta-blockers (6·4%, 8% and 9·5% respectively).

Over the decade examined, beta-blocker prescriptions have increased in each subgroup of patients, except among patients presenting atrioventricular block (Table 2). The multivariate analysis on the 36 817 patients recruited in the three GISSI studies shows that the temporal trend is still present once all potentially confounding variables homogeneously recorded in the three studies are taken into account. Compared to 1984–85 (GISSI-1), the odds-ratio for beta-blocker prescription at discharge in 1988–89 (GISSI-2) was 3·84 (95% CI 3·51–4·21), and in 1991–93 it further increased to 5·73 (95% CI 5·23–6·26). Once the variables included only in GISSI-2 and GISSI-3 are controlled for, the odds ratio for beta-blocker prescription in GISSI-3 compared to GISSI-2 was 1·46 (95% CI 1·35–1·58).

Table 3 Determinants of beta-blocker prescription at discharge in Gruppo Italiano di Studio sulla Sopravvivenza nell'Infarto Miocardico-GISSI 1: multivariate analysis results

	Prevalence (%)	Adjusted chi-square	OR (± CI 95%)	P
Baseline epidemiological characteristics				
Female gender	17·6	1·7	1·15 (0·93–1·42)	ns
Age >70 years	19·1	67·7	0·25 (0·18–0·35)	**
History of hypertension	—			
History of diabetes mellitus	—			
Previous AMI	13·7	0·2	0·95 (0·75–1·20)	ns
History of angina	—			
AMI characteristics at admission				
Killip class at entry >1	25·1	52·8	0·42 (0·33–0·53)	**
Anterior AMI	35·6	4·9	1·19 (1·02–1·40)	*
In-hospital events				
Post-AMI angina	12·4	10·7	1·44 (1·16–1·80)	**
Reinfarction	2·5	0·2	1·13 (0·70–1·82)	ns
CABG or PTCA	—			
Early and transient LVF (within 4 days)	—			
Late LVF (beyond day 4)	—			
Ventricular fibrillation	5·8	8·9	1·56 (1·16–2·08)	**
Sustained ventricular tachycardia	—			
Atrial fibrillation/flutter	—			
II or III° AV block	—			
Pre-discharge instrumental risk assessment				
Echocardiographic ejection fraction <40%	—			
Exclusion from the exercise test	—			
Positive exercise test	—			
PVB $\geq 10 . h^{-1}$, couplets or VT at Holter	—			
Treatments at discharge				
ACE inhibitors	1·2	0·2	1·21 (0·51–2·85)	ns
Calcium antagonists	47·2	33·0	0·63 (0·54–0·74)	**
Nitrates	37·9	5·0	0·83 (0·71–0·98)	*
Diuretics	18·9	0·3	1·07 (0·84–1·36)	ns
Digitalis or other inotropic drugs	15·4	33·8	0·32 (0·22–0·47)	**
Antiarrhythmics	11·9	20·6	0·45 (0·32–0·64)	**
Aspirin	—			

AMI=acute myocardial infarction; CABG=coronary artery bypass graft; PTCA=percutaneous transluminal coronary angioplasty; LVF=left ventricular failure; PVB=premature ventricular beats; VT=ventricular tachycardia; ACE=angiotensin converting enzyme; OR=odds ratio; CI=confidence intervals; —=variable not available; ns=not significant; *P<0·05; **P<0·01.

The active principles most commonly used in the three studies are atenolol and metoprolol (18% and 51·1% of all beta-blocker prescriptions at discharge, respectively, in GISSI-1, 64% and 28% in GISSI-2, 54·1% and 36·9% in GISSI-3). The proportion of beta-blocker prescription with intrinsic sympathomimetic action gradually decreased from 10·3% in GISSI-1 to 1·5% in GISSI-2, and to 0·9% in GISSI-3.

Determinants of beta-blocker use

Table 2 summarizes beta-blocker prescriptions at discharge in GISSI-1, GISSI-2 and GISSI-3 with respect to the patients' main characteristics, while Tables 3, 4 and 5 show the results of the multivariate analyses carried out within each study. The strongest positive predictors of beta-blocker use are the presence of angina post-infarction and of a history of arterial hypertension prior to the acute myocardial infarction. However, even in the presence of these factors only one patient in four in GISSI-2 and one in three in GISSI-3 were prescribed beta-blockers (Table 2 and Fig. 1, column A). Other predictors of beta-blocker prescription are the anterior location of acute myocardial infarction and reinfarction or an episode of ventricular fibrillation during hospitalization.

On the other hand, classical contraindications — such as the presence of second or third degree atrioventricular block or of left ventricular failure — are predictors of non-prescription. Advanced age and use of calcium channel blockers are among the main predictors of non-prescription in the three studies. In GISSI-3, the prescription of angiotensin converting enzyme inhibitors at discharge (mainly represented by the study treatment lisinopril) is the strongest predictor of non-use of beta-blockers. In GISSI-2 and GISSI-3 the early appearance of transitory heart failure in the acute phase of acute myocardial infarction, and of ventricular arrhythmias on the

Table 4 Determinants of beta-blocker prescription at discharge in Gruppo Italiano di Studio sulla Sopravvivenza nell'Infarto Miocardico-GISSI 2: multivariate analysis results

	Prevalence (%)	Adjusted chi-square	OR (± CI 95%)	*P*
Baseline epidemiological characteristics				
Female gender	18·2	0·6	1·06 (0·92–1·22)	ns
Age >70 years	19·6	68·0	0·50 (0·42–0·59)	**
History of hypertension	37·3	126·3	1·89 (1·69–2·11)	**
History of diabetes mellitus	15·0	4·0	0·85 (0·73–0·99)	*
Previous AMI	13·9	0·3	1·05 (0·89–1·23)	ns
History of angina	20·3	1·0	1·07 (0·93–1·22)	ns
AMI characteristics at admission				
Killip class at entry >1	18·4	0·0	0·99 (0·78–1·26)	ns
Anterior AMI	35·2	31·6	1·36 (1·22–1·51)	**
In-hospital events				
Post-AMI angina	10·5	75·8	2·20 (1·84–2·63)	**
Reinfarction	1·8	0·4	1·14 (0·75–1·74)	ns
CABG or PTCA	1·0	9·9	0·39 (0·22–0·70)	**
Early and transient LVF (within 4 days)	18·2	34·8	0·51 (0·41–0·64)	**
Late LVF (beyond day 4)	9·1	52·9	0·28 (0·20–0·28)	**
Ventricular fibrillation	5·4	3·6	1·25 (0·99–1·57)	*
Sustained ventricular tachycardia	2·9	0·1	0·96 (0·68–1·34)	ns
Atrial fibrillation/flutter	7·6	9·7	0·67 (0·53–0·86)	**
II or III° AV block	8·3	69·3	0·38 (0·31–0·48)	**
Pre-discharge instrumental risk assessment				
Echocardiographic ejection fraction‡	14·3	5·3	0·67 (0 48–0·94)	*
Exclusion from the exercise test	38·7	28·2	0·71 (0·63–0·81)	**
Positive exercise test	26·0	1·8	1·10 (0·96–1·26)	ns
PVB $\geqslant 10 . h^{-1}$, couplets or VT at Holter†	26·7	9·5	0·79 (0·68–0·92)	**
Treatment at discharge				
ACE inhibitors	10·1	58·6	0·43 (0·35–0·53)	**
Calcium antagonists	35·1	532·6	0 23 (0 20–0·26)	**
Nitrates	61·7	78·6	0·63 (0·57–0·70)	**
Diuretics	19·3	17·9	0·69 (0·58–0·82)	**
Digitalis or other inotropic drugs	9·7	46·3	0·32 (0·23–0·45)	**
Antiarrhythmics	10·7	63·6	0·40 (0·32–0·50)	**
Aspirin	75·6	0 6	1·05 (0·93–1·19)	ns

AMI=acute myocardial infarction; CABG=coronary artery bypass graft; PTCA=percutaneous transluminal coronary angioplasty; LVF=left ventricular failure; PVB=premature ventricular beats; VT=ventricular tachycardia; ACE=angiotensin converting enzyme; OR=odds ratio; CI=confidence intervals, ns=not significant; *$P<0·05$; **$P<0·01$; ‡ejection fraction not available in 72·5% of patients; †Holter data not available in 29·6% of patients.

pre-discharge Holter recording are negative predictors of beta-blockers use with a high prevalence in both studies.

Beta-blocker use in secondary prevention

In GISSI-2 and GISSI-3, 49·5% and 47·7% of the patients, respectively, did not present at discharge specific clinical indications for beta-blocker prescription (history of arterial hypertension, angina post-infarction, or a positive exercise stress test for ischaemia); of these, 23·2% and 28·3% received beta-blockers.

As in the general population, advanced age and prescription of calcium channel blockers and angiotensin converting enzyme inhibitors at discharge were the main determinants of reduction in the use of beta-blockers (Fig. 1, column B).

Discussion

General trend of increase in the use of beta-blockers following acute myocardial infarction

Ten to 20 years ago many clinical trials evaluated the effect of beta-blocker treatment in survivors after an acute myocardial infarction (26 trials in about 25 000 patients) and showed a reduction in mortality and reinfarction rates[1–4]. These trials results have, by and large, been accepted and transferred into clinical practice. Over the last decade this has resulted in a three-fold increase in the prescription of beta-blockers at discharge after acute myocardial infarction (or a five-fold increase, if the different distribution of confounding variables in the three studies is taken into account).

Table 5 Determinants of beta-blocker prescription at discharge in Gruppo Italiano di Studio sulla Sopravvivenza nell'Infarto Miocardico-GISSI 3: multivariate analysis results

	Prevalence (%)	Adjusted chi-square	OR (± CI 95%)	P
Baseline epidemiological characteristics				
Female gender	20·7	0·3	1·03 (0·93–1·14)	ns
Age >70 years	24·8	220·1	0·45 (0·40–0·50)	**
History of hypertension	39·9	142·4	1·62 (1·49–1·75)	**
History of diabetes mellitus	15·4	19·8	0·78 (0·70–0·87)	**
Previous AMI	13·3	5·5	1·15 (1·02–1·29)	*
History of angina	17·3	11·2	1·19 (1·07–1·31)	**
AMI characteristics at admission				
Killip class at entry >1	13·4	2·3	0·88 (0·75–1·04)	ns
Anterior AMI	30·1	58·9	1·37 (1·26–1·48)	**
In-hospital events				
Post-AMI angina	12·8	72·0	1·68 (1·49–1·89)	**
Reinfarction	1·7	9·9	1·61 (1·20–2·18)	**
CABG or PTCA	1·1	2·5	0·75 (0·53–1·07)	ns
Early and transient LVF (within 4 days)	19·7	46·7	0·62 (0·54–0·71)	**
Late LVF (beyond day 4)	3·8	19·5	0·53 (0·40–0·70)	**
Ventricular fibrillation	2·0	4·6	1·35 (1·02–1·78)	*
Sustained ventricular tachycardia	1·9	3·5	0·73 (0·53–1·02)	ns
Atrial fibrillation/flutter	5·3	5·8	0·76 (0·62–0·95)	*
II or III° AV block	3·8	67·9	0·33 (0·26–0·43)	**
Pre-discharge instrumental risk assessment				
Echocardiographic ejection fraction‡	9·0	15·8	0·71 (0·60–0·84)	**
Exclusion from the exercise test	53·5	42·5	0·76 (0·70–0·82)	**
Positive exercise test	27·0	22·3	1·31 (1·17–1·46)	**
PVB $\geqslant 10 . h^{-1}$, couplets or VT at Holter†	18·2	4·1	0·90 (0·81–0·99)	*
Treatments at discharge				
ACE inhibitors	47·3	335·6	0·50 (0·46–0·54)	**
Calcium antagonists	19·0	282·2	0·40 (0·36–0·44)	**
Nitrates	51·9	44·7	0·78 (0·72–0·84)	**
Diuretics	15·9	38·6	0·65 (0·57–0·75)	**
Digitalis or other inotropic drugs	6·1	88·2	0·20 (0·14–0·28)	**
Antiarrhythmics	5·8	93·1	0·29 (0·23–0·38)	**
Aspirin	72·4	28·1	1·27 (1·16–1·38)	**

AMI=acute myocardial infarction; CABG=coronary artery bypass graft; PTCA=percutaneous transluminal coronary angioplasty; LVF=left ventricular failure; PVB=premature ventricular beats; VT=ventricular tachycardia; ACE=angiotensin converting enzyme; OR=odds ratio; CI=confidence intervals; ns=not significant; *P<0·05; **P<0·01; ‡ejection fraction not available in 28·5% of patients; †Holter data not available in 3·1% of patients.

Similar proportions of patients are also in treatment after 6 months, which indicates that the message has reached well beyond the hospital setting of care.

All the patients enrolled in the GISSI studies were admitted to coronary care units and treated by cardiologists. In Italy, the majority of patients with suspected acute myocardial infarction are treated this way, but the reported better adherence to evidence-based medicine by specialists compared to general physicians[27] prevents us extrapolating the results indiscriminately to different settings.

Moreover, it is quite likely that intensive participation in subsequent research projects in the field of acute myocardial infarction may have contributed to the attention to the treatments prescribed to these patients in the GISSI collaborating centres. More critical and rational drug use may also have been a result, as shown by the decreasing use of treatments without — or with scarce — documentation of efficacy, such as calcium channel blockers or antiarrhythmic drugs[3,28–31]. Furthermore, the GISSI-2 and GISSI-3 study protocols, on the basis of the results of the First International Study of Infarct Survival[32], recommended the use of intravenous beta-blockers (atenolol specifically) in the acute phase of myocardial infarction, and this may also have contributed to an increased use in the subsequent phase.

A similar trend over the last few years of a gradual increase in the use of beta-blockers has also been observed in other countries[9,10,13–15] and probably indicates a generalized acceptance of the results of controlled clinical trials in clinical practice, as well as lessening in the fears often associated with the use of this class of drugs.

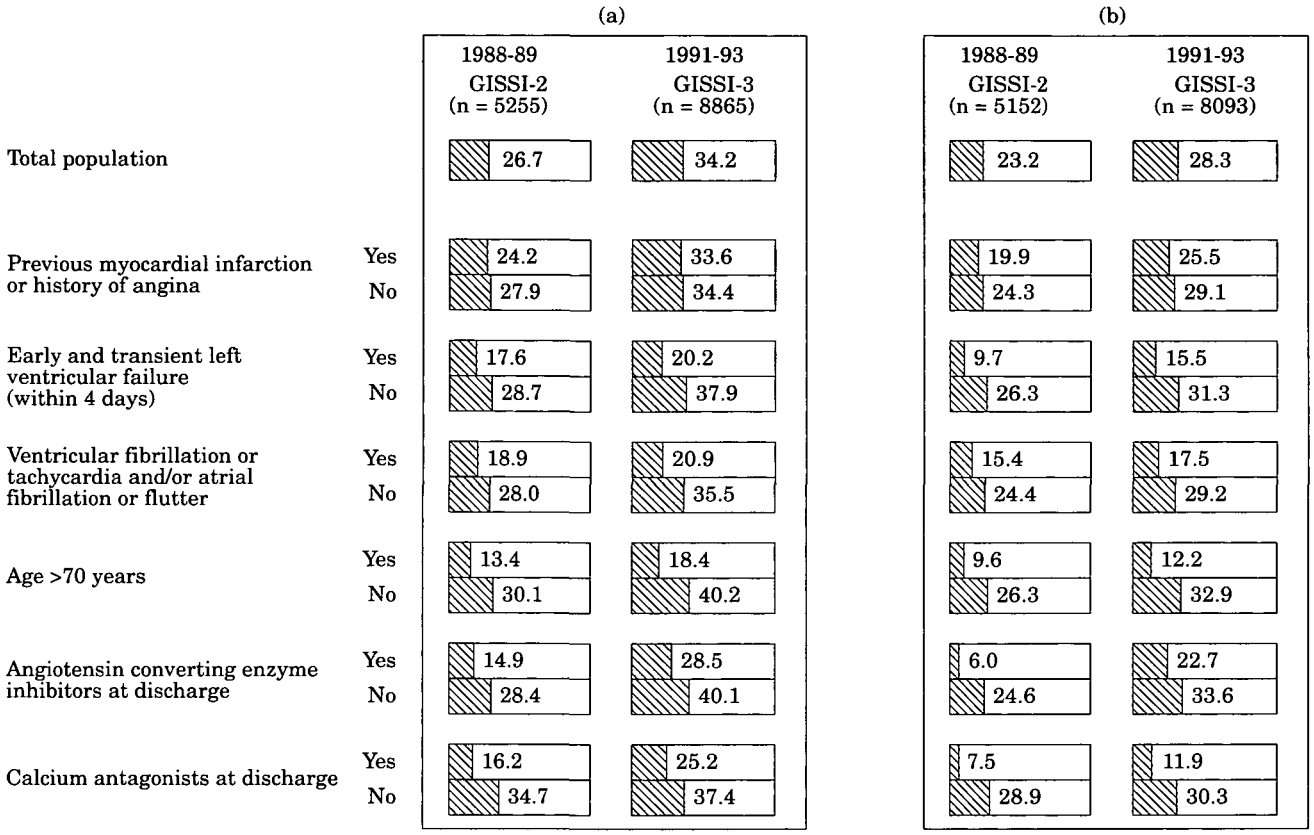

Figure 1 **Prescription of beta-blockers at discharge in patients with (a) and without (b) clinical indications (history of hypertension, post-myocardial infarction angina or positive exercise test) in Gruppo Italiano di Studio sulla Sopravvivenza nell'Infarto Miocardico-GISSI 2 and 3 studies according to their clinical characteristics (▨ percentage of patients receiving β-blockers in presence (yes) or absence (no) of each condition).**

Persistent under-use of beta-blockers

Alongside these positive results, there are also negative aspects. Notwithstanding the significant increase in the use of beta-blockers after acute myocardial infarction, too many patients are still denied the advantages of such treatment, even among subjects presenting specific clinical indications for its use, such as hypertension or angina (Fig. 1). Since the proportion of subjects not included in the large beta-blocker trials owing to the presence of a contraindication to beta-blockade was generally below 20%[16,33,34], clearly to date less than half of the patients who could benefit from this treatment actually receive it.

The Italian data indicating regular under-use of beta-blockers are also documented in other countries[9–22]. Recent studies report that only 28–33% of infarct survivors receive beta-blockers[11,17]. Disagreement on the applicability of the beta-blocker trial results is borne out by the broad range of rates of use, which are higher than 80% in Scandinavia and in some areas of the United States, countries involved in the major trials on beta-blockers after acute myocardial infarction[17,18].

It is very likely that factors other than the results of clinical trials have played, and still play, an important role, such as the fear of side effects, often quite unjustified, and market pressures for the prescription of other drugs[9,16,36–45]. It should be stressed in this respect that in the multivariate analysis conducted on the three GISSI studies, the most important predictor for non-prescription of beta-blockers was the use of calcium channel blockers, a class of drugs with clinical indications overlapping those of beta-blockers, albeit with insufficient evidence of benefit in terms of survival or reinfarction and much greater costs[28,29].

Choice of the active principle

The prevailing use of beta-blockers without intrinsic sympathomimetic activity may indicate that particular attention has been given to the results of studies showing less benefit with beta-blockers with this ancillary property[1]. The widespread use of atenolol and more limited use of metoprolol, in spite of the well-documented efficacy of timolol and propranolol, seems to contradict the evidence-based prescription[46]. This attitude is probably related to the perceived better safety of β-1 selective agents[47] and to the results of trials of intravenous beta-blockers in the acute phase of myocardial infarction. The First International Study of Infarct Survival results[32] led to a sharp increase in the use of

beta-blockers in general, and atenolol in particular, in the acute phase of myocardial infarction, from less than 10% in GISSI-1 to 45% in GISSI-2, with a parallel increase in the subsequent phase[23,24].

Determinants of prescription of beta-blockers after acute myocardial infarction

Analysis of the determinants of beta-blocker use in the GISSI studies has shown that those patients classified according to the Beta-Blocker Pooling Project[4] as belonging to the subgroups at higher risk of death and reinfarction and more likely to benefit from a beta-blocker prophylaxis (i.e. patients with a history of prior acute myocardial infarction or angina, and/or developing electrical or mechanical complications during hospitalization) are less likely to receive the treatment (Fig. 1). This is probably due to the fear of using beta-blockers in patients who have presented, if only temporarily, signs of heart failure: a fear quite unjustified on the basis of the results both of clinical trials in the post-acute myocardial infarction phase[4,33,34,36,37] and of the more recent trials which have evaluated the promising role of beta-blockers in patients with heart failure[48–51]. In patients with arrhythmias, the under-utilization of beta-blockers is probably due to the preferential prescription of other antiarrhythmic compounds, for which no evidence of benefit is available, or there is evidence of an increased mortality risk after acute myocardial infarction[3,5].

In all GISSI studies elderly subjects constitute a subgroup of high risk subjects with a low rate of beta-blocker prescription, confirming the results of other studies[9,12,16,22,38–40]. Although under-use of beta-blockers in the elderly denies a potential benefit to a considerable fraction of high-risk patients, the evidence on beta-blockade efficacy for secondary prevention in this age group is scanty, since patients over 70 or 75 have generally been excluded from clinical trials[1,4]. It may be worth stressing, however, that over the years, a relative increment above average has been observed among elderly subjects and among these developing electrical or mechanical complications during hospitalization.

In the GISSI studies, the prescription of calcium antagonists is one of the main determinants of non-use of beta-blockers. This is particularly disappointing in the light of clear-cut benefits of beta-blockers in secondary prevention, compared with the marginal benefits observed in trials which used verapamil and diltiazem, and the risks in trials using short-acting dihydropyridines[28,29]. These trial results strongly influenced the use of calcium antagonists in the GISSI studies: the prescription of calcium antagonists decreased from 47·2% in GISSI-1 to 35·1% in GISSI-2, to 19% in GISSI-3. Calcium antagonists are now prescribed almost exclusively in patients with specific clinical indications such as angina or hypertension[31].

GISSI-3 provided evidence of a relevant negative interaction between beta-blockers and angiotensin converting enzyme inhibitors at discharge. This indicates that in practice two policies of secondary prevention of documented efficacy[25,52,53] may influence each other to the extent of determining a lesser advantage than that theoretically expected in the population of survivors after acute myocardial infarction.

The increased prescription of beta-blockers in patients treated with aspirin in GISSI-3 may indicate that cardiologists are paying particular attention to secondary prevention drugs post-acute myocardial infarction.

In summary, although the use of beta-blockers following an acute myocardial infarction in Italy has increased over five-fold, it still involves less than half of the patients who could benefit from the treatment. The potential advantage of beta-blockers is further reduced by their being less commonly prescribed to high risk patients, who could derive greater benefits. Of these, in particular, the elderly and subjects with left ventricular dysfunction should formally be evaluated in clinical trials, in order to define the advantage of beta-blockers and of their association with other pharmacological treatments, especially angiotensin converting enzyme inhibitors.

Merely issuing clinical practical guidelines does not necessarily change physicians' behaviour. The central role of continuing medical education in bridging the gap between research and practice is unquestionable, but the methods, based on traditional or more innovative approaches, are open to debate[54–56]. Our data suggest that physicians' participation in large-scale clinical trials can per se contribute to more evidence-based care of patients.

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