Clinical Investigations

Importance of a History of Hypertension for the Prognosis after Acute Myocardial Infarction—for the Bucindolol Evaluation in Acute Myocardial Infarction Trial (BEAT) Study Group

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Summary

Background: Arterial hypertension is a major risk factor for cardiovascular events. The prognosis for hypertensive patients after acute myocardial infarction (MI) is uncertain because of the sparse and somewhat contradictory data.

Hypothesis: Our study aimed to investigate the importance of hypertension to prognosis after an MI in patients receiving contemporary medical therapy.

Methods: We performed a retrospective study using a large register from the Bucindolol Evaluation in Acute myocardial infarction Trial (BEAT). The register comprised 3,326 patients admitted between June 1998 and August 1999 with an enzyme-verified MI to 33 Danish coronary care units. Hypertension was considered present when a previous diagnosis of hypertension was accompanied by relevant medical therapy. Survival information for all patients was obtained in January 2002.

Results: Of the 3,326 patients studied, 825 were hypertensive. Overall, 28.4% had died by January 2002. The unadjusted hazard ratio associated with hypertension was 1.2 (95% confidence limit [CI] 1.1–1.4, $p = 0.004$). Hypertensive patients were older, and after adjustment for age the hazard ratio

associated with hypertension was 1.04 (CI 0.9–1.2, $p = 0.6$). Adjustment for further covariates did not change the result.

Conclusion: Our study showed that after an acute MI the survival rate of patients with and without a history of hypertension was identical when they received contemporary medical therapy.

Key words: hypertension, myocardial infarction, angiotensin-converting enzyme inhibitor, beta blocker, survival

Introduction

Arterial hypertension and myocardial infarction (MI) are both well-known risk factors for future cardiovascular events, but only a few studies have addressed the question of whether a history of hypertension adds to future risk after an acute MI when revascularization strategies are employed. Such analyses are important for prioritizing medical therapy, and, in particular, in the choice between angiotensin-converting enzyme (ACE) inhibitors and angiotensin-2 receptor blockers. In an array of studies that address therapy after MI and therapy for hypertension, angiotensin-2 receptor blockers have shown better results in hypertension^{1,2} than after MI. After MI, there is currently only indirect evidence from heart failure studies,³ in which the evidence for the benefits of ACE inhibitors is overwhelming.^{4–6} In two analyses from the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI-2),^{7,8} a history of hypertension was found to be an important risk factor in patients with MI who were receiving thrombolysis. In the Secondary Prevention Reinfarction Israeli Nifedipine Trial (SPRINT), previous hypertension was associated with a 30% increased risk for reinfarction in the first year after an initial MI in men, but not in women.⁹ Herlitz *et al.*¹⁰ found a history of hypertension to lack independent prognostic information, while Gustafsson *et al.*¹¹ found antecedent hypertension to be a risk factor in patients < 65 years

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of age, but not in older patients. Thus, the importance of a history of hypertension for the future risk of patients with MI is uncertain. Furthermore, all these studies were performed before ACE inhibitors were widely used, and it has been demonstrated that ACE inhibitors are particularly beneficial in patients with hypertension in whom left ventricular (LV) function is reduced.^{5, 12} Therefore, it is important to study the prognostic implication of a history of hypertension in patients with MI in groups of patients undergoing contemporary medical treatment strategy. We have addressed the question in a large database of consecutive patients with MI recruited in 1998–1999.

Patients and Methods

Patients in this study were from the Danish arm of the Bucindolol Evaluation in Acute myocardial infarction Trial (BEAT) register and comprised 3,326 consecutive patients with MI admitted to 33 Danish coronary care units between June 1998 and August 1999, with a follow-up period until January 2002. The BEAT study randomized 343 patients with reduced LV function to receive the beta blocker bucindolol or placebo. The study was closed prematurely when bucindolol development was discontinued; the study power was consequently low. There was no detectable benefit in mortality, but significantly fewer reinfarctions occurred during bucindolol treatment.¹³

The definition of MI included typical symptoms and/or electrocardiographic changes suggestive of MI or ischemia, accompanied by raised blood levels (twice the upper normal limit) of a marker of myocardial damage. Almost exclusively, creatine kinase-MB was the marker used locally. Any significant elevation of troponin-T/I was also considered to meet the definition of MI.

A history of arterial hypertension was assumed present when diagnosed by a physician and when patients received medical treatment for hypertension. Congestive heart failure was considered present when the patient received treatment for heart failure or pulmonary congestion and when these conditions were observed in the hospital.

A complete medical history was recorded in all patients in the BEAT register. Videotaped two-dimensional echocardiography was sent to a core laboratory and evaluated for LV function. Wall motion was examined using the 16-segment model,¹⁴ but with a reverse scoring system¹⁵ where -1 is dyskinesia, 0 akinesia, 1 hypokinesia, 2 normokinesia, and 3 hyperkinesia. Wall motion index was calculated as the sum of scores divided by 16. An approximate ejection fraction can be derived from this wall motion index by multiplying it by 30 .¹⁶

Survival status of all patients was ascertained in March 2002 by interrogation of the Danish Central Person Register, where all deaths in the country are registered within 2 weeks. Eight patients were lost to follow-up and considered censored at the time they were last known to be alive.

The BEAT study was carried out according to the Declaration of Helsinki.

Statistical Analyses

Group comparisons of discrete and continuous variables were performed with chi-square and rank sum tests. Survival curves were constructed with the Kaplan Meier method. Statistical analyses of survival data were performed with proportional hazard models after testing of assumptions (linearity of continuous variables, interaction analysis, proportional hazard assumption). All analyses were performed with the Statistical Analysis Software, version 8.0 (SAS Institute, Cary, N.C., USA).

Results

Between June 1998 and August 1999, 3,326 consecutive patients were included in the BEAT register: 825 patients (25%) with and 2,501 patients (75%) without hypertension. Demographic characteristics are shown in Table I. Hypertensive patients are slightly older, more often women, and less often smokers; they more often have previous cardiovascular disease and diabetes, and they are more often treated with cardiovascular drugs.

Univariate Survival Analysis

In March 2002, 960 patients (29%) had died. Mortality among hypertensive patients was 33% ($n = 271$) and was 28% ($n = 689$) among normotensive subjects. Univariate proportional hazard analysis showed a significantly increased risk of mortality in hypertensive patients compared with normotensive patients (Table II, Model A). Figure 1 shows the survival curves of hypertensive and normotensive patients subdivided by age ≥ 70 and < 70 years, respectively. As expected, a high-risk group was distinct from a low-risk group, but survival of normotensives and hypertensives was not significantly different between the groups.

Multivariate Survival Analysis

To adjust for differences in demographic data, several multivariate models were examined using the variables shown in Table I. Because age is of paramount influence on risk, a model including only hypertension and age was constructed initially (Table II, Model B). There was no prognostic information associated with hypertension after adjusting for age. Inclusion of further variables did not change the result (Table II, Model C). In addition to those shown in Table II, further models were constructed using medication at admission as well as at discharge; these models produced identical results with respect to the risk associated with hypertension. Interaction between hypertension and age was studied in multivariate analyses, and the result was of borderline significance with a p value of 0.06 . Because of this borderline significance and for comparison with older trials, we performed multivariate analyses of patients below and above 65 years of age. In younger patients, a history of hypertension conferred a risk of 1.2 (0.7 – 1.9) com-

TABLE I Baseline characteristics

Variable	Hypertensive patients n = 825 (25%)	Normotensive patients n = 2,501 (75%)	p Value
Male sex	481 (58)	1752 (70)	<0.001
Age (years, mean 5–95 percentiles)	71 (51–87)	67 (44–87)	<0.001
< 70 years	366 (44)	1,343 (54)	
≥ 70 years	459 (56)	1,156 (46)	
Current smokers	277 (34)	1,185 (47)	<0.001
Left ventricular function, WMI, mean, 5–95 percentiles	1.5 (0.8–2.0)	1.5 (0.8–2.0)	NS
History of AMI	254 (31)	676 (27)	0.04
History of angina pectoris	310 (38)	703 (28)	<0.001
History of CHF or CHF during hospitalization	439 (53)	1,121 (45)	<0.001
History of stroke	146 (18)	199 (8)	<0.001
History of diabetes	188 (23)	281 (11)	<0.001
Thrombolysis/primary PTCA %	37/3	31/2	<0.01/0.06
In hospital PTCA/CABG %	4/1	4/2	0.8/0.08
Drug therapy at the time of hospital admission			
Beta blocker	268 (32)	382 (15)	<0.001
ACE inhibitor	240 (29)	215 (9)	<0.001
AT2 antagonist	75 (9)	21 (1)	<0.001
Calcium antagonist	336 (41)	334 (13)	<0.001
Diuretics	436 (53)	526 (21)	<0.001
At least one of the above	773 (94)	937 (37)	<0.001
Died during hospitalization	54 (7)	160 (6)	0.9
Drug therapy for patients discharged alive			
Beta blocker	481 (63)	1,380 (59)	0.08
ACE inhibitor	337 (44)	780 (33)	<0.001
AT2 antagonist	79 (10)	56 (2)	<0.001
Calcium antagonist	219 (28)	346 (15)	<0.001
Diuretics	473 (61)	897 (38)	<0.001
At least one of the above	752 (98)	2,123 (91)	<0.001

Numbers in parentheses are percentages.

Abbreviations: ACE = angiotensin-converting enzyme, AMI = acute myocardial infarction, AT2 = angiotensin-2 receptor antagonist, CHF = congestive heart failure, CI = confidence interval, WMI = wall motion index, NS = not significant.

pared with 1.0 (0.8–1.2) in older patients. In this analysis, interaction was very weak with a p value of 0.14.

Discussion

This study demonstrated that in patients with MI, a history of hypertension did not confer additional risk for mortality during the subsequent years. In univariate analyses, there was a moderate excess mortality risk associated with hypertension, that disappeared after adjusting for age. The study accurately reflected European treatment standards in 1999 as demonstrated in the EUROASPIRE II survey of coronary patients, in which a total of 38% received an ACE inhibitor and 63% a beta blocker at the time of the interview.¹⁷ The current study is readily comparable with Gustafsson *et al.*'s study of patients from 1990 to 1992. The two studies were performed in the same hospitals using a nearly identical procedure.¹¹ In

Gustafsson's study, there was an increased risk (RR = 1.4) for patients aged ≤ 65 with a history of hypertension; there was also a significant interaction between age and history of hypertension, whereas in the current study this is a trend (p value = 0.06 and 0.13, respectively) when the cut-off at age 65 is used, as in Gustafsson's study. This trend is also clear from Figure 1, which shows that the difference between mortality curves for patients with and without hypertension is more prominent in younger patients. There are slightly fewer patients in the present study, and it is possible that a larger population would have resulted in a significant correlation between age and a history of hypertension. However, the most prominent difference between the two studies appears to be the use of ACE inhibitors. In the present study, 38% of the patients with hypertension received an ACE inhibitor or an angiotensin-2 receptor antagonist compared with 13% in the study by Gustafsson. Patients in Gustafsson's study were enrolled while screening for the Trandolapril Cardiac Evaluation

TABLE II Proportional hazard models of the risk associated with hypertension

Variable	Relative risk ratio	p Value	95% confidence limit
Model A: Univariate analysis with hypertension as the only variable			
Hypertension	1.2	0.004	1.1–1.4
Model B: Multivariate analysis with age and sex as confounding variables			
Hypertension	1.04	0.6	0.9–1.2
Age - per year	1.08	<0.0001	1.069–1.083
Model C: Multivariate analysis with all available covariates			
Hypertension	0.99	0.8	0.8–1.2

Other variables in model: Wall motion index, age, sex, history of myocardial infarction, angina, stroke and diabetes, heart failure, smoker, discharge medical treatment with beta blocker, diuretic, digitalis, angiotensin-converting enzyme inhibitor, angiotensin-2 antagonist calcium blocker, thrombolysis, primary revascularization, later revascularization percutaneously or by surgery.

(TRACE) study, which demonstrated a particularly beneficial effect of ACE inhibitors in patients with a history of hypertension.^{5,12} Therefore, our results may reflect that the excess risk of hypertension is removed by ACE inhibitor therapy. In accordance with this interpretation, retrospectively collected data from the Acute Infarction Ramipril Efficacy (AIRE) study have demonstrated that a history of hypertension was an independent indicator of poor prognosis in placebo-treated but not in ramipril-treated patients.¹⁸ Post hoc analysis of the Survival of Myocardial Infarction Long-term Evaluation (SMILE) study also demonstrated a highly beneficial effect of ACE inhibitor treatment on patients with a positive history of hypertension.¹⁹ Another possibility is that, in general, hypertensive populations or treatment of these populations is changing. The use of calcium antagonists was surprisingly high (41%) among hypertensive patients, compared with the 1990–1992 study by Gustafsson (31%). Similarly, in the present study, the use of beta blockers had increased from 25 to 32% at admission. Nevertheless, the current study is one of a

few larger studies available that have included consecutive patients without any selection criteria and in which medical therapy is contemporary.

Several studies have demonstrated that the risk of cardiovascular morbidity and mortality is increased in hypertensive patients.^{20–23} This observation is also reflected in the current study by demonstrating that hypertensive patients have a high prevalence of prior angina and MI. Against this background it may seem surprising that LV function did not depend on the presence of hypertension. A possibility could be that well-regulated hypertension offers protection against LV failure.^{24,25} We found that 24.8% of patients with MI had a history of hypertension, which is in accordance with previous postmyocardial infarction studies.^{8,18}

The results of the current study are relevant to the choice between ACE inhibitors and angiotensin-receptor blockers in hypertensive patients surviving an infarction. Since hypertension did not confer independent risk, and since no post MI angiotensin-receptor blocker study is available, it appears reasonable to continue prioritizing ACE inhibitors in patients post MI whether or not they have a history of hypertension.

In our present study, beta blockers were less frequently used in normotensive patients at admission, but at discharge the use was markedly increased to a level similar to that in hypertensive patients. Most post acute MI beta-blocker studies were performed years ago, before the era of revascularization and the widespread use of ACE inhibitors. However, in one recent large clinical trial, carvedilol significantly decreased the frequency of all-cause and cardiovascular mortality and recurrent, nonfatal MI in a population post acute MI.²⁶ Beta blockers are not known to be superior as secondary prevention of cardiovascular mortality in post acute MI patients with previous hypertension compared with previously normotensive patients. In general hypertension, data indicate that beta-blocker treatment actually is less beneficial in patients >60 years of age compared with other antihypertensive treatment—that is, diuretics, in the prevention of cardiovascular morbidity and mortality.²⁷ Therefore, it is not likely that the increased use of beta blockers can explain why the outcome was similar in normotensive and hypertensive patients in this study.

FIG. 1 Mortality in hypertensive and normotensive patients after a myocardial infarction.

Limitations

The diagnosis of hypertension was based on a medical history and the need for medical therapy, and the vast majority of patients were on therapy at the time of hospital admission. We do not have blood pressure recordings during hospitalization, but feel that they would not have been of further help, since blood pressure falls in many patients with hypertension at the time of an infarction.

Conclusion

Our analysis shows that after an acute MI, survival rates for patients with and without a history of hypertension are identical when contemporary medical therapy is employed. Nevertheless, there was a trend toward an increased risk for younger hypertensive patients, as demonstrated in a previous study.

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