Long-term follow-up after early intervention with intravenous diltiazem or intravenous nitroglycerin for unstable angina pectoris


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Aims In a double-blind randomized trial in unstable angina it was shown that intravenous diltiazem reduced ischaemic events in the first 48 h after inclusion better than intravenous nitroglycerin. The present study was performed to establish the long-term prognosis of the randomized patients, with respect to their initial treatment assignment.

Methods and Results One year follow-up data on ischaemic end-points and anti-ischaemic medication were recorded. Results were available for all of the 121 randomized patients. One hundred and sixty-seven primary end-point events were recorded, of which 54 occurred in the first 48 h and 113 during the follow-up. Survival analysis showed that event-free survival was significantly better in the diltiazem group (45·0%) than in the nitroglycerin group (34·4%), P =0·04. The incidence rate after 48 h and one year for cardiac death are, respectively, 0% and 4·1%. The trend in anti-ischaemic medication was higher in the nitroglycerin group. For beta-blockers, this trend became significant after 12 months (P =0·03).

Conclusion These results show that the initial benefit obtained by early treatment with intravenous diltiazem was preserved during the first year after the initial hospitalization, and that, despite the high risk of cardiac events in our population, the overall mortality 12 months after inclusion was low.

Key Words: Unstable angina, intravenous diltiazem, prognosis.

Introduction

Patients with unstable angina are generally considered to be at risk of recurrent and possibly irreversible ischaemia, resulting in progression to myocardial infarction or sudden cardiac death. Therefore, the objectives of treatment are not only pain relief but also prevention of recurrent ischaemia or myocardial infarction. Since patients with the clinical syndrome of unstable angina pectoris form a heterogeneous group\(^1\), the short- and long-term clinical outcome varies in the patient group studied\(^2\)–\(^9\). Recently, we published a report on a randomized, double-blind trial of intravenous diltiazem vs nitroglycerin for unstable angina pectoris\(^{10}\). This showed that intravenous diltiazem is better than intravenous nitroglycerin at significantly reducing ischaemic events in the first 48 h. The present study was performed to establish the long-term prognosis of the total randomized study population, as well as to investigate whether the initial beneficial treatment effects in the diltiazem group also altered the long-term prognosis of this group compared with the patients initially randomized to treatment with intravenous nitroglycerin. To establish the long-term prognosis of the patients enrolled in the previous study, the diagnostic and therapeutic procedures as well as the incidence of events, i.e. unstable angina, myocardial infarction, death from cardiac ischaemia and the need for revascularization procedures, were recorded both in hospital and during one year of follow-up. Furthermore, follow-up data on anti-ischaemic medication, i.e. long-acting nitrates, beta-blockers and calcium channel blockers, were collected.
Patients and methods

Patient selection

Patients were screened for eligibility to the trial in the emergency room. Unstable angina was defined as (a) crescendo angina superimposed on a pre-existing pattern of relatively stable, exertion-related angina, or (b) angina of new onset (within one month) brought on by slight exertion, or (c) angina at rest or during light activity occurring within 12 h of admission and lasting more than 15 min. Furthermore, as described earlier, ECG characteristics of ischaemia had to be present. The exclusion criteria are described in detail elsewhere. In summary, patients were excluded if they had a myocardial infarction on admission, a heart rate <50 beats·min⁻¹, systolic blood pressure <90 mmHg, second- or third-degree atrioventricular conduction disturbances, severe heart failure (New York Heart Association class III-IV), sick sinus syndrome, atrial fibrillation or atrial flutter, intraventricular conduction disturbances (QRS>100 ms) or any other permanent inability to judge the ST segment for ischaemic deviations, use of drugs affecting the ST segment, and known intolerance for calcium channel blockers or nitrates.

Treatment

After informed consent was obtained from patients eligible for the study, they were randomized to treatment with intravenous diltiazem or intravenous nitroglycerin, which is described in detail elsewhere. In summary, diltiazem was started as a loading dose of 25 mg, followed by a continuous infusion to a maximum dose of 25 mg·h⁻¹. A nitroglycerin infusion was started as a saline bolus (visually identical to the diltiazem bolus), followed by a continuous infusion to a maximum dose of 5 mg·h⁻¹. Anginal complaints persisting after 1 h on the maximum dose of the study drug were taken to be an end-point. The study drug was then stopped and additional therapy, either with anti-ischaemic drugs or with invasive procedures, could be initiated as thought necessary by the treating physician.

Calcium channel blockers and long-acting nitrates used previously were stopped at admission. The dosage of other previously used drugs was kept constant. According to the treatment strategy for unstable angina in our clinic at the start of the study, all patients were also given intravenous heparin (5000 U bolus followed by a continuous infusion) to raise the activated partial thromboplastin time (APTT) of 2–3 times the control level for 48 h, after which aspirin was initiated.

Data collection and follow-up

Data collection in the first 48 h is described elsewhere. In summary, demographic data and history were recorded at admission. Ischaemic end-points for survival analysis were refractory angina, defined as persistent, or recurrent and persistent angina despite a maximum dose of study medication necessitating additional therapy. Myocardial infarction was defined as typical anginal pain lasting for more than 30 min with enzymatic evidence of infarction (i.e., CK/CK-MB exceeding twice the local upper limit for normal), and death due to cardiac ischaemia was defined as death following typical anginal pain with ST-segment changes and/or enzymatic evidence of infarction.

Follow-up data after discharge were acquired by review of the clinical records or through a simple questionnaire sent to the general practitioner. The occurrence of death due to cardiac ischaemia, myocardial infarction, scheduled and unscheduled revascularization procedures (i.e., percutaneous transluminal coronary angioplasty and coronary artery bypass grafting), recurrent angina (divided into angina with and without the necessity of treatment within a coronary care unit), were recorded until one year after admission.

Outcome definitions

The primary end-point events during follow-up were defined in line with the end-points of the double-blind phase, i.e., cardiac death, myocardial infarction, recurrent angina necessitating treatment within a coronary care unit and non-scheduled CABG or PTCA, each individually and as a composite end-point. In the composite end-point, each patient with one or more end-point events was included. Other cardiac events, i.e., scheduled CABG or PTCA and recurrent angina without the necessity of treatment within a coronary care unit, were analysed separately.

Statistical analysis

The rates of event and survival were estimated according to the Kaplan-Meier method and compared to the distribution of time before the occurrence of the first ischaemic event by means of a log-Rank test.

For comparison of the clinical characteristics a chi-square, two-tailed Fisher’s exact test, Wilcoxon-Mann-Whitney test, or Student’s t-test were used as appropriate. A two-sided probability level of 0.05 or less was considered to indicate statistical significance.

All analyses presented here were performed using the Statistical Analysis System package version 6.08 (SAS Institute, Cary, N.C.).

Results

As described elsewhere, between October 1991, and December 1993, 129 patients were randomised. Eight patients were excluded from analysis. The remaining 121
Follow-up data (48 h–1 year) of the total study population

During follow-up after the blinding period (48 h) five (4.1%) patients died, one as a complication of a high risk PTCA during the initial hospitalization, the other four patients died after discharge. Twelve (9.9%) patients had a myocardial infarction, four (3.3%) during initial hospitalization (of which one occurred during a CABG and one as a complication of a PTCA) and eight (6.6%) after discharge. Forty (33.9%) patients were treated on the coronary care unit because of recurrent angina pectoris; 33 (64.7%) episodes of recurrent angina occurred during the initial hospitalization, and 18 (36.2%) after discharge. Forty-one (33.9%) patients had a non-scheduled revascularization procedure; 31 (68.8%) of these procedures were performed during the initial hospitalization and 14 (31.1%) during follow-up.

Table 2 shows the number of patients with non-fatal myocardial infarctions and the mortality during the first 48 h and the first year. The incidence rate of non-fatal myocardial infarction was 19.0% during the first 48 h and a further 9.9% during the first year. For cardiac death the incidence rates are, respectively, 0% and 4.1%

Figure 1 shows the ischaemic end-point free survival in the first month after inclusion, according to an
intention-to-treat analysis and based on the primary end-points. The diltiazem group (53.3%) showed a significantly better event-free survival compared to the nitroglycerin group (39.3%), $P = 0.02$. Figure 2, the ischaemic end-point free survival during one year follow-up, shows that the initial benefit in the diltiazem group is maintained during follow-up. The event-free survival for the diltiazem group is 45.0% compared to 34.4% in the nitroglycerin group, $P = 0.04$.

Table 3 shows the primary end-point events as they were recorded during the one year follow-up. A total number of 167 primary end-point events were recorded, of which 54 occurred in the first 48 h: 18 in the diltiazem group vs 36 in the nitroglycerin group, and 113 during the follow-up: 53 events in the diltiazem group and 60 events in the nitroglycerin group. In the first 48 h after hospitalization, refractory angina as well as the composite end-point of death, myocardial infarction, non-scheduled revascularization and refractory angina occurred significantly less in the diltiazem group: refractory angina eight (13.3%) vs 18 (39.5%), $P < 0.05$; composite 25 (41.0%) vs 13 (21.7%), $P = 0.03$. There were no significant differences between the two treatment groups for each end-point individually or as a composite end-point during follow-up after the blinded period. Recurrent angina not necessitating treatment in a coronary care unit, and the number of scheduled revascularization procedures, did not differ significantly: 14 and 13, respectively, in the diltiazem group vs 16 and 9, respectively, in the nitroglycerin group.

The anti-ischaemic medication, i.e. long acting nitrates, calcium channel blockers, and beta-blockers is summarized in Table 4. There are no significant differences between the diltiazem and nitroglycerin groups as regards long acting nitrates and calcium channel blockers. In contrast, at 3 and 6 months after admission the trend in the number of patients using beta-blockers is higher in the nitroglycerin group than the diltiazem group, 38 (65.5%) vs 29 (48.3%), $P = 0.07$ and 34 (58.6%) vs 24 (40.0%), $P = 0.07$. This trend becomes significant after 12 months: nitroglycerin group 35 (55.2%) vs 20 (33.3%) for the diltiazem group, $P = 0.03$. Overall, there were no significant differences in the use of aspirin, except 3 months after admission, when there were 38 (65.5%) patients using aspirin in the nitroglycerin group vs 25 (41.7%) in the diltiazem group ($P = 0.01$). There were no differences in the number of patients treated with ACE inhibitors, diuretics and digoxin during follow-up.

**Discussion**

Recently, we showed in a randomized double-blind study\[10\] that intravenous diltiazem was more effective...
The incidence of myocardial infarction was 3% vs 8% in the group initially randomized to nifedipine (not significant). In our study, another 63 to conventional treatment, i.e. propranolol if calcium channel blockers are not contraindicated and isosorbide dinitrate. Randomization. Mortality in the group receiving conventional treatment was 3% vs 8% in the group initially randomized to nifedipine (not significant). In our study, we observed a major difference in ischaemic end-point-free survival in the first days after admission. This early beneficial effect of intravenous diltiazem could be preserved during follow-up. This result underscores the importance of early treatment. On a par with the findings in the survival analysis is the lower use of beta-blockers in the diltiazem group.

The number of large randomized trials with calcium channel blockers and beta-blockers in patients with unstable angina is limited [13–15]. Almost no studies reported the long-term result of early intervention with calcium channel blockers [14,15], making it difficult to compare our results with others. Muller et al. [16] randomized 63 patients to short-acting nifedipine and another 63 to conventional treatment, i.e. propranolol if not contraindicated and isosorbide dinitrate. Randomized medication was administered until day 14. Vital status was determined by a telephone call 6 months after randomization. Mortality in the group receiving conventional treatment was 3% vs 8% in the group initially randomized to nifedipine (not significant). In our study, we observed a major difference in ischaemic end-point-free survival in the first days after admission. This early beneficial effect of intravenous diltiazem could be preserved during follow-up. This result underscores the importance of early treatment. On a par with the findings in the survival analysis is the lower use of beta-blockers in the diltiazem group.

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Table 4 Anti-ischaemic medication taken during one year follow-up

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<th>Nitroglycerin</th>
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<td><strong>Nitroglycerin</strong></td>
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<td>after 48 h</td>
<td>25 (43·1%)</td>
<td>21 (35·0%)</td>
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<td>3 month</td>
<td>25 (43·1%)</td>
<td>17 (28·3%)</td>
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<td>6 month</td>
<td>17 (29·3%)</td>
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<td>12 month</td>
<td>15 (25·9%)</td>
<td>17 (28·3%)</td>
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<td><strong>Calcium channel blockers</strong></td>
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<tr>
<td>after 48 h</td>
<td>16 (27·6%)</td>
<td>11 (18·3%)</td>
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<tr>
<td>3 month</td>
<td>28 (48·3%)</td>
<td>26 (43·3%)</td>
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Nitrates = long acting nitrates.

than intravenous nitroglycerin in reducing cardiac events. Patients randomized to treatment with diltiazem were more likely to survive without ischaemic endpoints. The data from this study reminds us that calcium channel blockers are a very heterogenous group and that conclusive data in regard to dihydropyridines [11] may not be true for other classes of calcium channel blockers [12].

The present study was performed to establish the long-term prognosis of the randomized patients in general as well as with respect to their initial treatment assignment. This study showed that the initial benefit obtained by early treatment with intravenous diltiazem was preserved during the first year after the initial hospitalization. Furthermore, the study population in general showed a high incidence of cardiac events, with a low incidence of mortality.

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Before implications on the management of unstable angina can be derived from this study, it should be taken into account that the results of the present study are based on a post-hoc analysis. However, it should be stated that the investigators who registered the cardiac events, as well as the members of the endpoint committee, were blinded for the initial treatment assignment.
In conclusion, the initial benefit obtained by early treatment with intravenous diltiazem was preserved during the first year after the initial hospitalization. Furthermore, although our study population had a relatively high risk of cardiac events, the overall mortality 12 months after inclusion was low.

References