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Value of First Day Angiography/Angioplasty In Evolving Non-ST Segment Elevation Myocardial Infarction: An Open Multicenter Randomized Trial

The VINO Study

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Aims Direct angioplasty is an effective treatment for ST-elevation myocardial infarction. The role of very early angioplasty in non-ST-elevation infarction is not known. Thus, a randomized study of first day angiography/angioplasty vs early conservative therapy of evolving myocardial infarction without persistent ST-elevation was conducted.

Methods One hundred and thirty-one patients with confirmed acute myocardial infarction without ST-segment elevations were randomized within 24 h of last rest chest pain: 64 in the first day angiography/angioplasty group and 67 in the early conservative group (coronary angiography only after recurrent or stress induced myocardial ischaemia).

Results All patients in the invasive group underwent coronary angiography on the day of admission (mean randomization–angiography time 6·2 h). First day angioplasty of the infarct related artery was performed in 47% of the patients and bypass surgery in 35%. In the conservative group, 55% underwent coronary angiography, 10% angioplasty and 30% bypass surgery within 6 months. The primary end-point (death/reinfarction) at 6 months occurred in 6·2% vs 22·3% ($P<0·001$). Six month mortality in the first day angiography/angioplasty group was 3·1% vs 13·4% in the conservative group ($P<0·03$). Non-fatal reinfarction occurred in 3·1% vs 14·9% ($P<0·02$).

Conclusions First day coronary angiography followed by angioplasty whenever possible reduces mortality and reinfarction in evolving myocardial infarction without persistent ST-elevation, in comparison with an early conservative treatment strategy.
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Key Words: Non-ST-segment elevation myocardial infarction, early invasive treatment strategy, acute coronary syndromes, coronary angioplasty, coronary artery bypass grafting.

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Introduction

Reperfusion therapy (thrombolysis or primary angioplasty) has a major role in the treatment of acute myocardial infarction with ST-segment elevations[1–5]. However, the distinction between ST-segment elevation and non-ST-segment elevation myocardial infarction is not clear: Q wave and non-Q wave myocardial infarction are just two variants of the same entity with considerable overlap. There is clear evidence that in non-ST-segment elevation myocardial infarction the application of thrombolytics is not beneficial and may be harmful[6–9]. The role of first day coronary angioplasty in evolving non-ST-elevation myocardial infarction has never been tested in a prospective randomized trial. The only randomized trial on non-Q wave myocardial infarction (not including patients with unstable angina pectoris) was the VANQWISH trial[10]. Influenced by

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Table 1 Inclusion and exclusion criteria in the VINO study

Inclusion criteria (All must be positive for enrolment)	Rest ischaemic chest pain, lasting more than 20 min, within the last 24 h before randomization
	ECG evidence of acute myocardial ischaemia without ST-segment elevations (ST-segment depressions minimally 0·1 mm in at least two contiguous leads and/or negative T waves or documented old LBBB/RBBB,
	CK-MB higher than 1·5 × upper limit of normal and/or positive troponin I assay
Exclusion criteria (Presence of any of these criteria excludes patient)	Unstable post-infarction angina pectoris resistant to maximal pharmacotherapy
	Cardiogenic shock
	Acute LBBB or RBBB or ST segment elevations $\leq$2 mm in two leads
	Q-wave myocardial infarction or intravenous thrombolysis less than 1 month
	Coronary angioplasty or bypass surgery less than 6 months
	Any concomitant disease which may have possible influence on 1 year prognosis
	Lack of patient cooperation

LBBB/RBBB=left or right bundle branch block; CK-MB=creatine kinase myocardial bands.

the VANQWISH results (and having positive experience with direct angioplasty in more than 1000 patients with ST-elevation myocardial infarction) we designed the hypothesis of this study according to three main principles:

(1) Coronary angiography as soon as possible after admission and confirmation of the diagnosis of infarction by biochemical markers of myocardial necrosis.
(2) Immediate angioplasty of the infarct related artery whenever possible.
(3) Bypass surgery urgently (within 1 week) only in patients with recurrent rest chest pain and later (between weeks 3–6) in pharmacologically stabilized patients.

Thus, the aim was to establish the efficacy of first day coronary angiography with immediate angioplasty of the infarct-related vessel whenever possible (or carefully timed coronary bypass surgery in patients not suitable for angioplasty) in comparison with a 'classical' early conservative strategy (coronary angiography performed only after recurrent or stress-induced myocardial ischaemia).

We chose the acronym 'VINO' (Value of First Day Coronary Angiography/Angioplasty In Evolving Non ST-Segment Elevation Myocardial Infarction. An Open Multicenter Randomized Trial) for this study.

Methods

Enrolment for the VINO trial started 4 May 1998. Eligible patients were enrolled either directly at the Cardiocenter Vinohrady or at the 10 participating community hospitals in the Czech Republic. An ECG was performed before randomization and then every day during the time in hospital. Blood was sampled for creatine kinase, creatine kinase myocardial bands and troponin I before randomization and for creatine kinase myocardial bands at 24, 48 and 72 h after randomization.

Inclusion and exclusion criteria are summarized in Table 1. When patients met inclusion criteria and had signed a written consent, they were randomly assigned (using sealed, sequentially numbered envelopes) to first day angiography/angioplasty, or conservative treatment. A total of 380 patients with evolving acute myocardial infarction without persistent non-ST-segment elevation confirmed by the measurement of creatine kinase myocardial bands isoenzymes or troponin I tests were screened over 22 months.

Study patients characteristics

One hundred and thirty-one patients met the inclusion criteria and were randomly assigned to the first day angiography/angioplasty treatment strategy (64 patients) or the conservative treatment strategy (67 patients). There were no significant differences between the two groups in terms of age, sex and baseline clinical characteristics, which reflects the initial clinical risk stratification. Also, pharmacotherapy during the initial hospitalization and after discharge (day 30) did not differ except in the use of nitrates which was significantly higher in the conservative group (Table 2).

First day angiography/angioplasty treatment strategy guidelines were characterized by a coronary angiogram as soon as possible after randomization followed by immediate coronary angioplasty of the culprit coronary lesion+stent implantation whenever suitable (single-vessel disease or multivessel disease with TIMI 0–2 flow in the infarct-related artery).

Later, carefully timed (3–4 weeks after index myocardial infarction) coronary bypass surgery was performed in patients with left main coronary artery disease or multivessel disease with TIMI-3 flow in all arteries. Urgent (within 1 week) coronary bypass surgery was performed in severe (>70%) left main stenosis or in multivessel disease with recurrent rest chest pain.

Conservative treatment strategy guidelines were characterized by initial medical treatment with coronary

Table 2 Comparison of baseline clinical characteristics of the patients randomized to the early invasive and conservative treatment strategies. ± values means ± SD

Characteristics	Invasive strategy n=64	Conservative strategy n=67	*P*<
Age (years)	65·7 ± 10·8	66·2 ± 10·6	ns
Female (n=)	23	28	ns
Hypertension (%)	59·4	43·3	ns
Diabetes mellitus (%)	29·7	20·9	ns
Prior AMI (%)	21·9	29·9	ns
Killip class II+III (%)	32	35	ns
Anterior AMI (%)	50	56	ns
ST depression AMI (%)	47	46	ns
Baseline ejection fraction (%)	52·7 ± 10·7	53·8 ± 11·7	ns
Beta-blockers* (%)	78	73	ns
ACEI (%)	48	46	ns
CaA (%)	8	10	ns
Lipid-lowering drug (%)	45	42	ns
Nitrates (%)	25	43	0·02

AMI=acute myocardial infarction.
*Medication recommended after discharge. (Ticlopidine was added for 1 month in patients with stent.) ACEI=angiotensin converting enzyme inhibitors; ASA=acetylosalicylic acid; UFH/LMWH=unfractionated or low molecular weight heparin; CaA=calcium antagonists.

angiography and subsequent revascularization only in the presence of recurrent myocardial ischaemia (rest angina and/or ECG demonstrating ≥ 2 mm ST-segment depressions or elevations in at least two leads lasting >5 min or persistent at least 1 mm ST-segment depressions during initial hospitalization) or symptom-limited exercise test positivity (chest pain and ST-segment depressions of at least 2 mm recorded during peak exercise or a redistribution defect in at least one main vascular region on thallium scintigraphy).

A symptom limited bicycle exercise test on day 30 after randomization for risk stratification was performed in both groups. Patients who were unable to exercise underwent thallium^{201} dipyridamole myocardial scintigraphy. The patients in the conservative group remained in the hospital where they were randomized.

Both groups of patients received an initial 250 mg bolus of aspirin i.v.+a bolus of 5000 units of unfractionated heparin, according to the protocol of the study. Subsequently, all patients were treated for at least 3 days with a continuous infusion of unfractionated heparin to maintain an activated partial prothrombin time in the range of 50–75 s, or with a full therapeutic dose of low molecular weight heparin. All patients continued with oral aspirin 200 mg daily for the duration of the study. After stent implantation, 250 mg of ticlopidine twice daily was added for 1 month. Concomitant use of antiischaemic and other drugs in the coronary care unit and during follow-up was at the discretion of the attending physician.

Follow-up

All patients were examined in the Cardiocenter, Vinohrady, 1 month after discharge, for risk restratification. A symptom-limited exercise test was performed and pharmacotherapy controlled. At the end of each month for up to 6 months, communication with the patient and treating general practitioner was made by phone to evaluate the end-points.

End-points

The primary end-point of the trial pre-specified in the protocol was a composite of death or non-fatal recurrent myocardial infarction 6 months after the randomization. Recurrent non-fatal myocardial infarction was defined as recurrent ischaemic chest pain, lasting >20 min+evidence of presumably new ischaemic ECG changes+creatine kinase myocardial bands higher than 1·5 × the upper limit of normal (all criteria had to be present >72 h after randomization). Fourteen days after the index myocardial infarction, a positive troponin I assay was also used as a biomarker to identify recurrent myocardial infarction. Where possible, patients performed a symptom-limited exercise test, and a 2D echocardiographic left ventricular ejection fraction was measured before discharge from the initial hospitalization. They were then followed-up at day 30, and 6 months. We also analysed the length of the initial hospitalization and the number of subsequent hospitalzations for unstable angina pectoris.

Statistical analysis

All data were sent to and analysed by the independent statistician from the Department of Biophysiology at the 1st Medical Faculty of Charles University of Prague, who was blinded to the treatment strategy. Continuous

Table 3 Comparison of the number of coronary angiographies and revascularization procedures at 6 months after randomization groups of the early invasive and conservative treatment strategies

	Invasive strategy n=64	Conservative strategy n=67	*P*<
CAG at 6 months (%)	100	55	0·0001
Revascularizations at 6 months (%)	73	39	0·0001
Direct PTCA ± stent (%)	47	3	0·0001
Elective PTCA ± stent (%)	5	10	ns
CABG (%)	35	30	ns

CAG=coronary angiography; PTCA=percutaneous transluminal coronary angioplasty; CABG=coronary artery bypass grafting.

data are presented as means ± SD. Odds ratios and 95% confidence intervals were used to compare the strategies with respect to the end-points. An analysis of dispersion ANOVA test for repeated measurements and a t-test for two independent groups were used. Survival curves were used to characterize the timing of end-points during follow-up according to the method of Kaplan and Meier. The Mantel–Cox test for comparison of two functions of survival and the Fisher test for qualitative variables were used.

Results

Interventions

The number of coronary angiographies and revascularization procedures in both groups of patients are summarized in Table 3. There was a significant difference between the first day angiography/angioplasty group and the conservative group, in the use of coronary angiographies: 100% vs 55%; and revascularizations: 73% vs 39% at 6 months ($P<0·0001$). Nearly half of the patients in the first day angiography/angioplasty group, 47% vs 3% ($P<0·0001$) in the conservative group, underwent coronary angioplasty on the admission day. There was no significant difference between groups in the use of the elective angioplasty (5% vs 10%), coronary artery bypass surgery (35% vs 30%) or the number of complete revascularizations (51% vs 58%). Stents were used in 44% vs 50% (ns) of patients who underwent angioplasty. Also, no statistically significant difference was found between either group in terms of anatomical angiographic findings (Table 4). A substantial number of patients in both groups (50% vs 46%, ns) had three-vessel disease or extremely diffuse coronary atherosclerotic lesions. In some of these patients, revascularization was not technically feasible. The prevalence of multivessel coronary disease was 75% vs 77% (ns).

The average time from randomization to coronary angiography in the first day angiography/angioplasty group was 6·2 h (0·5–22) vs 61 days (17 h–96 days) in the conservative group ($P<0·0001$). Time to coronary angioplasty was 8·6 h (0·75–28), vs 55 days (27 h–85 days),

Table 4 Comparison of coronary angiography findings in percentage of patients, who actually underwent coronary angiography

Early treatment strategy	1VD	2VD	3VD	LMD	Diffuse
Invasive (%)	20	25	45	5	5
Conservative (%)	11	31	43	12	3
P value=	ns	ns	ns	ns	ns

1VD=one vessel disease; 2VD=two vessel disease; 3VD=three vessel disease; LMD=left main coronary artery disease; Diffuse=diffuse coronary artery disease with a stenosis no more than 50% of the luminal diameter.

($P<0·0001$) and time to coronary artery bypass surgery, 34 days (2–42) vs 86 days (20–227) ($P<0·0001$). Coronary angioplasty was successful (residual stenosis less than 50% and TIMI 3 flow at the end of procedure) in 93% of patients in the first day angiography/angioplasty group and in 95% of patients in the conservative group who underwent the procedure (ns).

No patient during the first day or during elective coronary angioplasty in either group of patients died in hospital, and there were no major procedure complications leading to prolonged hospital stay or specific treatment. Coronary artery bypass surgery in-hospital mortality was 4·2% in the first day angiography/angioplasty group and 5·4% in the conservative group (ns).

End-point analysis

At the 30-day visit there was a trend towards lower mortality in the first day angiography/angioplasty group, as compared to the conservative group, of 1·6% vs 7·5% (ns) which became statistically significant at 6 months, 3·1% (two events) vs 13·4% (nine events) ($P<0·03$). There were similar findings in the incidence of recurrent non-fatal myocardial infarction, 1·6% vs 7·5% at 30 days (ns) and 3·1% (two events) vs 14·9% (10 events) ($P<0·02$) at 6 months. The primary composite end-point of mortality or non-fatal recurrent myocardial infarction was non-significantly lower in the first day

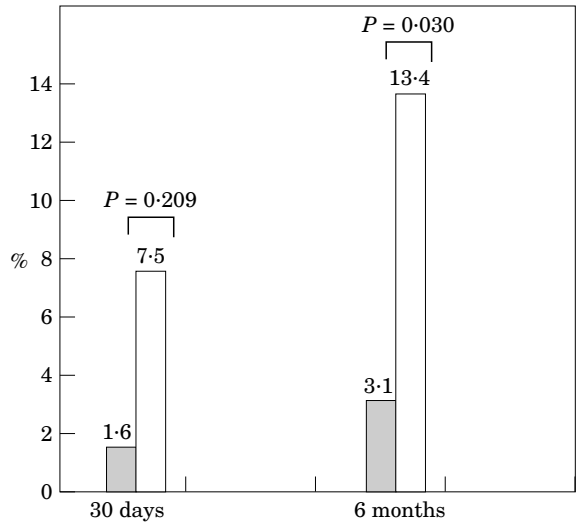

Figure 1 **Comparison of the mortality in groups of patients randomly assigned to the early invasive (▨) and conservative (□) treatment strategy.**

angiography/angioplasty group, compared to the conservative group, at 30 days, 3·1% vs 10·4% ($P<0·165$), but was statistically significant at 6 months, 6·3% (four events) vs 22·4% (15 events) ($P<0·001$). This means the higher probability of death or non-fatal myocardial infarction in the conservative strategy group: RR = 3·34, CI 95%, $P<0·001$ (Figs 1 and 2).

Symptom-limited exercise tests at day 30 were performed in 48 patients (75%) from the first day angiography/angioplasty group and in 55 patients (82%) from the conservative group (ns). The positivity of the exercise test was significantly lower in the first day angiography/angioplasty strategy group, 17·2% vs 37·3% ($P<0·001$).

The length of hospitalization for an index myocardial infarction was significantly shorter in the first day angiography/angioplasty group, compared to the conservative group, 8·2 ± 2·9 vs 10·4 ± 3·1 days ($P<0·0001$), and there were non-significantly fewer subsequent hospitalizations for unstable angina up to 30 days and 6 months, 6·3% vs 8·9% and 3·1% vs 8·6%.

Discussion

The question, what is the best very early treatment strategy in non-Q wave myocardial infarction and what is its influence on short- and long-term prognosis still remains open. Risk stratification in clinical practice and individual risk profiles help to select patients for urgent

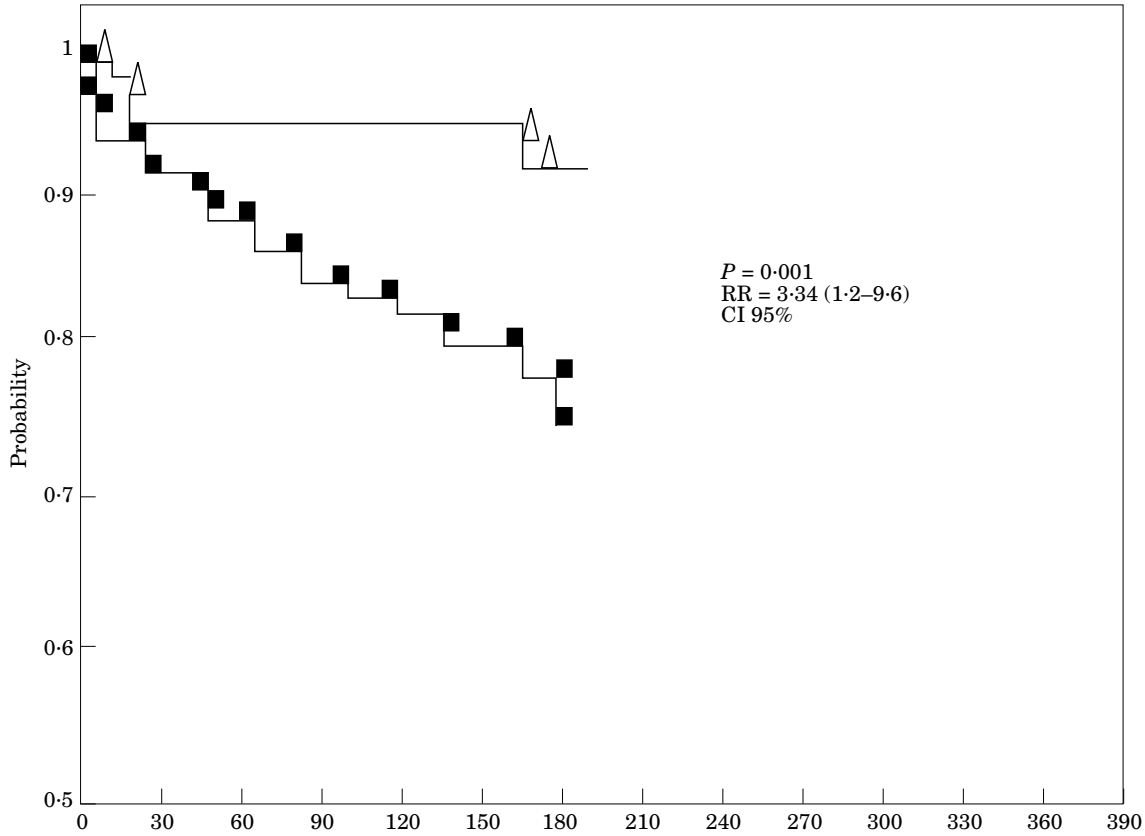

Figure 2 **Kaplan–Meier survival analysis of the probability of event-free survival (mortality or non-fatal myocardial infarction) according to the treatment strategy during the 6 months of follow-up. △ = invasive; ■ = conservative.**

coronary angiography[11–31]. According to the recently published ENACT study (a pan-European survey of acute coronary syndromes) there are major differences between countries in the use of angiography and percutaneous coronary intervention in myocardial infarction patients. Overall, only 33% of the patients underwent angiography and 23% percutaneous coronary intervention[32]. The in-hospital mortality of patients with acute non-ST-elevation myocardial infarction is lower than those with Q wave myocardial infarction, but its long-term prognosis is similar or worse[33–41]. These patients are usually older, have important co-morbidity and more risk factors. They may sustain a small amount of myocardial loss but may also have a significant amount of viable, yet ischaemic myocardium, placing them at high risk for future cardiac events[42]. The infarct-related artery in non-ST-elevation myocardial infarction is patent in approximately 50% of angiograms[43].

There is no doubt about the importance of knowing the coronary anatomy of these patients, but little is known about how important it is to have this information very early after the diagnosis is confirmed to enable an immediate decision to be made about the possibility/necessity, timing and type of the revascularization procedure, thus allowing patient therapy to be tailored more appropriately. Nevertheless, new European Society of Cardiology Guidelines on the management of patients with acute coronary syndromes without persistent ST-segment elevations declared that an early invasive strategy be reserved only for high risk patients. In the absence of high risk features, either an early conservative or an early invasive strategy in hospitalized patients without contraindications for revascularization is recommended[44].

Also contemporary ACC/AHA Guidelines for the treatment of acute myocardial infarction do not recommend early coronary angiography in stabilized patients with non-Q wave myocardial infarction[45].

State of the art

To date, there are no published prospective randomized studies comparing very early (within hours after admission) angiography and revascularization with conservative treatment. Furthermore, the role of very early coronary angioplasty and carefully timed early bypass surgery in the treatment of acute non-ST-segment elevation myocardial infarction is not known. Three major prospective randomized studies evaluated the impact of an invasive treatment strategy on the prognosis of the patients with non-Q wave myocardial infarction. Chronologically the first one was the TIMI IIIB study which randomized, after initial pharmacological stabilization, 1473 acute coronary syndrome patients into a group appointed for early coronary angiography (18 to 48 h after randomization) and a group appointed for conservative treatment. In the invasive group 61% of the patients were revascularized; however, in the conservative group 49% were also revascularized. The primary composite end-point of death, myocardial infarction or a positive symptom-limited exercise stress test at 6 weeks occurred in 18·1% of patients assigned to the early conservative strategy and in 16·2% of patients assigned to the early invasive strategy (P=ns)[46].

The VANQWISH trial randomized 920 patients with acute non-Q wave myocardial infarction for coronary angiography and revascularization if possible, or for early conservative strategy. Randomization was performed up to 72 h after the last chest pain. The average time from randomization to angiography was 2 days. Only 44% of the patients assigned to the invasive strategy were finally revascularized, but 33% of the patients in conservative strategy were finally also revascularized.

The primary composite end-point of mortality or non-fatal myocardial infarction was more frequent in the invasive strategy group (7·8% vs 3·2% P<0·004). The 30-day mortality of the patients in the invasive group treated with coronary angioplasty was 0%, but of those treated with bypass surgery was unusually high (11·6%) and this had a major influence on the poor results of the invasive strategy group[10].

Different results have recently been published by the FRISC II Investigators who used a more aggressive design for the 1219 patients assigned for early invasive treatment. Patients were randomized up to 48 h after the last ischaemic chest pain and coronary angiography was performed between 2–7 days. Revascularization within the first 10 days was performed in 71% of the invasive group and in 9% of the non-invasive group. The end-point of death or myocardial infarction after 1 year occurred less frequently in the invasive group, 10·4% vs 14·1% (RR=0·74 [0·60–0·92], P<0·005). The authors concluded that an invasive approach should be the preferred strategy in patients with unstable coronary artery disease and signs of ischaemia on electrocardiography or raised levels of biochemical markers of myocardial damage[47].

Contribution of the VINO study

The VINO study extends these data by using an even more aggressive very early invasive approach with angiography as soon as possible after confirmation of the diagnosis of non-ST-segment elevation myocardial infarction. Revascularization is also used, with immediate coronary angioplasty whenever suitable, or carefully timed coronary bypass surgery when angioplasty is not possible. The patients were randomized no later than 24 h after the last ischaemic chest pain at rest. In the invasive group the average time from randomization to coronary angiography was 6·2 h, to angioplasty 8·6 h and to bypass surgery 34 days.

Only patients with confirmed myocardial infarction were allowed to be randomized and 'lower risk' patients with only unstable angina pectoris were excluded. Although there is evidence that coronary bypass can be performed safely in these patients anytime after 48 h, we

tried to reduce the peri-operative risk by postponing surgery up to approximately 1 month after the index myocardial infarction[48]. Only patients with recurrent chest pain and with multivessel disease or patients with severe left main coronary artery disease underwent coronary bypass surgery during the first week.

When the VINO study was planned in 1997, it was presumed that only a difference in the primary composite end-point, of mortality or non-fatal myocardial infarction between the two strategies in a period of 6 months could be achieved. However, after the 6 months follow-up had been completed, analysis revealed that except for the difference in the primary composite end-point, 6·3% vs 22·4% ($P<0·001$), there was also a statistically significant difference in mortality alone, 3·1% vs 13·4% ($P<0·03$), favouring a very early invasive approach. This relatively poor 6 months outcome of the patients initially managed conservatively, in comparison with some previously published data, was explained by higher age and multiple co-morbidities. The average age of the VINO patient population was 66 years. Furthermore, half of the VINO patients had ST-segment depressions on the admission ECG and anterior location of non-Q wave myocardial infarction; one-third had clinical signs of left ventricular dysfunction. Only a few patients were found consequently to have a normal or nearly normal coronary anatomy (3% in the conservative group). Patients with unstable angina pectoris, who are known to have significantly lower mortality than patients with non-Q wave myocardial infarction, were not enrolled. Our data are also consistent with those recently published by the MITI Investigators.

The MITI group retrospectively compared the outcome of stable patients with non-ST-segment elevation acute myocardial infarction who received early coronary angiography and eventually percutaneous intervention, with those who were treated only conservatively. Patients treated with the early invasive strategy had a lower 30-day (5·5% vs 9·5%, $P<0·03$) and 4-year mortality (20% vs 37%, $P<0·001$). In-hospital mortality of patients who received coronary angiography within 6 h of admission was significantly lower than those who entered the catheterization laboratory later (1·1% vs 7·1%, $P<0·005$)[49].

Although we found that the length of the hospital stay for the index myocardial infarction was significantly reduced and there were non-significantly fewer subsequent hospitalizations in the early invasive group, it was not the aim of the VINO study to establish the cost effectiveness of the treatment strategies used. Moreover, bias was introduced because the invasive group patients were sent to the higher level hospital while the conservative group patients were not. A larger study, TIMI-18 TACTICS, is designed to answer an important cost/effect question. The second part of this study, presented at the AHA Congress 2000[51], also confirmed the better outcome of patients with unstable angina pectoris/non-Q wave myocardial infarction who were treated using an invasive approach. The primary end-point of death/myocardial infarction/rehospitalization at 6 months was less frequent in the invasive treatment group (15·9% vs 19·4%, $P<0·025$) and a considerable effect of the invasive treatment strategy was seen first in the subgroup of troponin T positive patients (14·3% vs 24·2%, $P<0·001$ for primary end-point)[50,51].

There are some limitations to our study. First, the number of patients is small. A definitive and conclusive decision about the effectiveness of a very early invasive treatment strategy must be confirmed in a larger prospective randomized trial. Second, the interventions were done in only one 'high volume tertiary centre' so the results may not be easily duplicated in smaller hospitals.

Further, no glycoprotein IIb/IIIa inhibitors were used in the study. However, the routine use of glycoprotein IIb/IIIa inhibitors is at present not recommended by new European Society of Cardiology Guidelines for the management of patients with acute coronary syndromes without persistent ST-segment elevations[43]. Moreover, there is good evidence that the intravenous application of glycoprotein IIb/IIIa inhibitors is particularly effective in conjunction with early percutaneous revascularization procedures. The recently presented GUSTO IV–ACS study showed no benefit from abciximab in patients with unstable angina pectoris and non-Q wave myocardial infarction who did not undergo early coronary intervention[51]. Therefore, one can assume that the use of glycoprotein IIb/IIIa inhibitors would have no impact on the VINO study results[53–56].

We conclude that the immediate invasive treatment strategy (first day angiography/angioplasty) in patients with acute myocardial infarction without persistent ST-segment elevations, using urgent coronary angiography as soon as possible and immediate coronary angioplasty whenever suitable (or carefully timed coronary artery bypass grafting) is safe and reduces the mortality and reinfarction rate. It also reduces the length of a hospital stay for an index event in comparison with a conservative, ischaemia-guided treatment strategy. First day PTCA is feasible in nearly half of the patients with evolving myocardial infarction without persistent ST-segment elevations. The majority of the remainder of these patients benefited from carefully timed coronary artery bypass surgery. We hope that these promising data, which are based on a small number of patients and events, are validated in a large randomized trial.

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Appendix 1

The following persons contributed intellectually to the paper by organizing randomization procedures and transport from community hospitals:
David Vencour, MD, Department of Internal Medicine, Community Hospital Nymburk; Pavel Kordas, MD, Katarina Strachová, MD, Department of Internal Medicine, Community Hospital Hořovice; Petr Tyl, MD, Department of Internal Medicine, Community Hospital Louny; Vladimír Soukup, MD, Department of Internal Medicine, Community Hospital Říčany; Antonín Loutocký, MD, Department of Internal Medicine, Community Hospital Prague 2; Jindřich Charouzek, MD, PhD, Department of Internal Medicine, Community Hospital Tábor; Eva Kosová, MD, Department of Internal Medicine, Community Hospital Prague 9; Ilona Kašíková, MD, Department of Internal Medicine, Community Hospital Roudnice; Gabriel Marcínek, MD, Department of Internal Medicine, Community Hospital Slaný; Tomáš Kubíček, MD, Department of Internal Medicine, Community Hospital Mladá Boleslav.

Apendix 2

Approval

The study complies with the Declaration of Helsinki. Study design and patients' written consent was approved by Independent Ethics Committee of 3rd Medical School and University Hospital Královské Vinohrady, Ruská 87, Prague 10, 100 00, Czech Republic.