Early invasive versus ischaemia-guided strategies in the management of non-Q wave myocardial infarction patients with and without prior myocardial infarction

Results of Veterans Affairs Non-Q Wave Infarction Strategies In Hospital (VANQWISH) trial

P. S. Heggunje¹, M. J. Wade¹, R. A. O’Rourke², R. E. Kleiger³, P. C. Deedwania⁴, P. W. Lavori⁵ and W. E. Boden¹ for the Veterans Affairs Non-Q-Wave Infarction Strategies in Hospital (VANQWISH) trial investigators*

¹Veterans Affairs Medical Center and the State University of New York Health Science Center, Syracuse, New York; ²University of Texas Health Science Center at San Antonio, Texas, ³Washington University School of Medicine, St. Louis, Missouri, ⁴Veterans Affairs Medical Center, Fresno California and the ⁵Palo Alto VA Medical Center, Palo Alto, California, U.S.A.

Aims To compare the role of early invasive vs conservative management strategies in treating patients with non-Q wave myocardial infarction with or without a prior myocardial infarction.

Background In patients recovering from non-Q wave myocardial infarction, the prognosis among patients with a first non-Q wave myocardial infarction is significantly better than in patients with a prior myocardial infarction, yet physicians often adopt an early invasive strategy to treat patients with a first non-Q wave myocardial infarction.

Methods Non-Q wave myocardial infarction patients enrolled in the VANQWISH trial with a history of prior myocardial infarction were compared to those with a first non-Q wave myocardial infarction, for the trial primary end-point of death or myocardial infarction at 1 and 12 months, as well as for the initial randomized treatment strategy.

Results Of the 920 non-Q wave myocardial infarction patients, 396 had a history of prior myocardial infarction and 524 did not. Patients with a history of prior myocardial infarction were older and had a higher incidence of multiple high-risk baseline characteristics than those with a first non-Q wave myocardial infarction. Compared to the group with a first myocardial infarction, the prior myocardial infarction group suffered more events at both 1 month (11% vs 6%, P=0.007) and at 12 months (29% vs 16%, P<0.001). This difference in outcome remained significant even after adjusting for confounding variables (P<0.001 at 12 months). Among the non-Q wave myocardial infarction patients with a prior myocardial infarction, the frequency of death or recurrent myocardial infarction was similar in both invasive and conservative groups during the first year of follow-up. Among the first non-Q wave myocardial infarction group, those assigned to the conservative strategy had significantly fewer events (3% vs 9%, P=0.009 at 1 month; 12% vs 20%, P=0.016 at 12 months) and mortality (1% vs 5%, P=0.012 at one month; 5% vs 11%, P=0.009 at 12 months) than those assigned to early invasive strategy.

Conclusion A history of prior myocardial infarction identifies a moderately high-risk subset of non-Q wave myocardial infarction patients who display similar long-term outcomes regardless of the strategy assignment; however, patients with a first non-Q wave myocardial infarction may fare better with a conservative or ischaemia-guided approach during the first post infarction year.


© 2000 The European Society of Cardiology

Key Words: Non-Q wave myocardial infarction, invasive, ischaemia-guided.

See page 1989 for the Editorial comment on this article
**Introduction**

As a group, patients with non-Q wave myocardial infarction suffer more ischaemic complications (reinfarction and post infarction angina) after they are discharged from hospital than patients with Q wave infarction\(^\text{1-3}\). Accordingly, an aggressive early revascularization strategy is favoured by many physicians, but the best approach to managing these patients remains controversial\(^\text{4,5}\). Several recent studies of patients with acute coronary syndromes have shown either no effect or an adverse effect when routine coronary angiography is followed by early myocardial revascularization\(^\text{6-10}\).

While the entire cohort of non-Q wave myocardial infarction patients may not benefit from an early invasive strategy, the beneficial effects of such a strategy may be more appropriate in high-risk subsets. A history of prior myocardial infarction has been noted to be an important risk factor for morbidity and mortality after an acute myocardial infarction\(^\text{11,12}\). Long-term follow-up data from both Thrombolysis In Myocardial Infarction (TIMI) phase II trial and the Multicenter Diltiazem Post-Infarction Trial showed a strong and independent association between non-fatal reinfarction and death among subsets of patients with prior myocardial infarction\(^\text{13,14}\).

Contrary to these observations, physicians often adopt an aggressive approach in the treatment of patients with a first non-Q wave myocardial infarction. Although the importance of separating a first from subsequent non-Q wave myocardial infarction has been recently highlighted\(^\text{15}\), a number of clinical trials of non-Q wave myocardial infarction have included patients with a first as well as subsequent infarctions, making the distinction between these two infarct subgroups less clear\(^\text{16-18}\). There are few data from prospective, randomized clinical trials evaluating the relative merits of early invasive vs conservative management strategies in non-Q wave myocardial infarction patients with or without a history of prior myocardial infarction.

We hypothesized that high-risk non-Q wave myocardial infarction patients, such as those with a history of prior myocardial infarction, might actually benefit from an early invasive strategy whereas those with a first non-Q wave myocardial infarction would not. To test this hypothesis, we performed a post-hoc analysis of the Veterans Affairs Non-Q Wave Infarction Strategies in-Hospital trial database, comparing the clinical characteristics and outcomes of treatment strategies of non-Q wave myocardial infarction patients without a history of prior myocardial infarction to those with a history of prior myocardial infarction.

**Methods**

**Study organization and Patient selection**

Details of the VANQWISH trial design and main study findings have been published previously\(^\text{10,19}\). Patient enrolment began in 1993, after the protocol had been approved by the institutional review boards of 17 participating centres. Briefly, eligible patients had a clinical presentation consistent with evolving acute myocardial infarction, creatine kinase-isoenzymes >1.5 times the hospital upper limit of normal, absence of new abnormal Q waves (or R waves for posterior infarction) and left bundle branch block on serial electrocardiograms. Eligible patients were randomly assigned to either an early invasive strategy or an ischaemia-guided management strategy within 24–72 h of the onset of symptoms. All study patients gave informed, written consent to participate in the study.

The electrocardiographic analysis was modelled after the Atlanta code\(^\text{20}\) with serial tracings obtained at multiple time points after non-Q wave infarction symptom onset during the initial 24–72 h of hospitalization in the coronary care unit. At least one electrocardiogram was obtained 48 h after admission to exclude late development of Q waves. Electrocardiographically, study patients were defined by the absence of new, abnormal Q waves (i.e. 0.04 s in duration in two or more contiguous leads within a lead group) or R waves (>0.04 s in lead V\(_1\) and an R: S ratio >1 in lead V\(_2\)).

Prior myocardial infarction was prespecified to be one of the five covariates. Only patients with a history of enzymatically or electrocardiographically documented previous myocardial infarction were included in the prior myocardial infarction group. All other patients were considered to have a first non-Q wave myocardial infarction.

**Testing and treatment**

The details of testing and treatment used in both strategies have been published previously\(^\text{10}\). Briefly, patients assigned to the invasive strategy underwent coronary angiography as the initial diagnostic test soon after randomization. Subsequent management (specifically, the decision to proceed to myocardial revascularization) was not mandated by protocol. Patients assigned to the ischaemia-guided approach underwent some form of stress testing\(^\text{10}\) (exercise thallium scintigraphy was preferred) as the initial non-invasive diagnostic test, and underwent invasive testing and revascularization procedures only after demonstration of objective evidence of ischaemia. Both groups received similar medical treatment.

**Follow up**

Patient enrollment ended on 31 December 1995. Patients were seen 1 month after discharge and at 3-monthly intervals thereafter, until the trial ended on 31 December 1996. All patients were followed-up for a minimum of 12 months or until they met the primary end-point of the study.
End points

The primary end-point of the trial was death or recurrent non-fatal myocardial infarction. All-cause mortality was a secondary end-point. An independent, three member End-Point Committee, who were blinded to all clinical information relating to strategy assignment, reviewed and adjudicated all suspected trial primary end-points.

Statistical analysis

Categorical baseline characteristics between groups were analysed using Fisher’s Exact Test, whereas continuous outcomes were tested with the Student’s t-test. Independence between clinical outcomes and prior myocardial infarction status and between clinical outcomes and strategy assignment was also assessed by Fisher’s Exact Test. Kaplan-Meier curves were used to graphically describe the event and mortality distributions between the myocardial infarction and strategy assignment groups. Hazard ratios (HR) were adjusted using Cox proportional-hazards regression models.

Results

Characteristics of the study population

The baseline characteristics of the non-Q wave infarction patients with a history of prior myocardial infarction (n=396) vs those with no history of prior myocardial infarction (n=524) are presented in Table 1. Strategy assignment was evenly distributed between the two groups. Patients with a history of prior myocardial infarction were older and had a higher incidence of multiple high-risk baseline characteristics such as hypertension, hypercholesterolaemia, peripheral vascular disease, and a history of prior CABG and PTCA. Compared to the first myocardial infarction group, a higher percentage of non-Q wave infarction patients with prior myocardial infarction had other cardiac abnormalities such as valvular heart disease. Peak creatine kinase release was higher in patients with a first myocardial infarction.

Medications taken during the week prior to randomization were found to be significantly more prevalent in the prior myocardial infarction group compared to the first myocardial infarction group, including a higher usage rate of nitrates, beta-blockers, calcium antagonists, aspirin, warfarin, lipid-lowering drugs, and ACE inhibitors (P<0.001). All of these medications were more likely to be taken by the prior myocardial infarction group.

Table 2 shows the distribution of baseline characteristics according to treatment strategy assignment. Left ventricular ejection fraction was significantly different with respect to treatment strategy in both first myocardial infarction and prior myocardial infarction groups, although the data on left ventricular ejection fraction was limited due to missing values (see the footnote under Table 2). Neurological disorder and a history of CABG were the only other variables that predicted strategy assignment in prior myocardial infarction and first myocardial infarction groups, respectively.

Clinical outcome according to prior myocardial infarction status

Figure 1 shows the event and mortality rate comparisons between the prior myocardial infarction and first myocardial infarction groups. At 1 month, the prior myocardial infarction group had significantly higher composite (death or myocardial infarction) events (11% vs 6%, P=0.007) than the first myocardial infarction group, but there was no significant difference in mortality (5% vs 3%, P=0.147)). At 12 months, both composite cardiac events (29% vs 16%, P<0.001) and mortality (13% vs 8%, P=0.008) were significantly higher in the prior myocardial infarction group than the first myocardial infarction group.

Adjusted analysis

Since numerous baseline variables predicted myocardial infarction status, the Cox proportional-hazards regression model was utilized to adjust the hazard ratio for those factors that were prognostic indicators of recurrent cardiac events and mortality. At 1 month, there was a more than 80% higher cardiac event rate in the prior myocardial infarction group [hazard ratio (HR) and 95% confidence interval (CI)=1.83 (1.15, 2.92)] compared to the first myocardial infarction group, but the difference in mortality alone was not significant [HR=1.65 (0.80, 3.39)]. At 12 months, the prior myocardial infarction group experienced significantly higher combined events [HR=1.75 (1.32, 2.34)] and a 50% higher mortality [HR (95% CI)=1.51 (0.99, 2.28)] than the first myocardial infarction group (Figs 2 and 3), although the latter comparison was of borderline statistical significance.

Extent of coronary artery disease and use of invasive cardiac procedures according to prior myocardial infarction status

Among the prior myocardial infarction and first myocardial infarction groups, a similar number of patients (71% vs 67%, P=0.223) underwent cardiac catheterization during the first year. Patients with a history of prior myocardial infarction had a higher incidence of three-vessel coronary artery disease (58% vs 35%,
Clinical outcomes in prior myocardial infarction group according to treatment strategy

Figures 4 and 5 show the cardiac event and mortality rate comparisons between strategy assignment for patients who did and did not have a prior myocardial infarction. Among the 396 patients who had a prior myocardial infarction, 199 were assigned to the routine invasive strategy and 197 to the ischaemia-guided strategy. At 1 month, among patients randomized to the routine invasive strategy, compared to the ischaemia-guided strategy, the cardiac event rate was 13% vs 9% (P=0.333), and the mortality rate 6% vs 4% (P=0.470).

At 12 months, the number of recurrent cardiac events (30% vs 27%, P=0.657) and deaths (15% vs 12%, P=0.556) were also similar among the patients assigned to invasive and ischaemia guided strategies, respectively.

Among patients with a history of prior myocardial infarction who underwent CABG during the first post-infarction year (n=86), a similar number of cardiac events (33% vs 30%, P=0.820) and deaths (15% vs 8%, P=0.327) occurred in those assigned to invasive (n=46) vs ischaemia-guided (n=40) treatment strategies. By contrast, among the patients who underwent PTCA (n=60), those assigned to an ischaemia-guided strategy...
Among the non-Q wave myocardial infarction patients without a history of prior myocardial infarction, the probability of 12 months event-free survival was significantly higher in the group assigned to the ischaemia-guided strategy than those assigned to the routine invasive strategy (Fig. 6). Figure 7 shows Kaplan–Meier analysis of the probability of survival according to the strategy assignment in patients with no history of prior myocardial infarction during follow-up. The Cox proportional hazard ratio comparing the routine invasive strategy to the ischaemia-guided strategy was 2.49 (95% confidence interval, 1.27 to 4.89). Since the baseline characteristics of the non-Q wave myocardial infarction patients (n=23) showed a trend towards more events (52% vs 27%, P=0.060) and deaths (22% vs 5%, P=0.095) than those assigned to early invasive strategy (n=37) at 1 year.

Clinical outcomes in first myocardial infarction group according to treatment strategy

Among the first myocardial infarction group, the ischaemia-guided arm (n=261) fared better than the routine invasive arm (n=263) at 1 month (3% vs 9%, P=0.012 for death) and at 12 months (12% vs 20%, P=0.016 for events; 5% vs. 11%, P=0.009 for death). Among the non-Q wave myocardial infarction patients without a history of prior myocardial infarction, the probability of 12 months event-free survival was significantly higher in the group assigned to the ischaemia-guided strategy than those assigned to the routine invasive strategy (Fig. 6). Figure 7 shows Kaplan–Meier analysis of the probability of survival according to the strategy assignment in patients with no history of prior myocardial infarction during follow-up. The Cox proportional hazard ratio comparing the routine invasive strategy to the ischaemia-guided strategy was 2.49 (95% confidence interval, 1.27 to 4.89). Since the baseline characteristics of the non-Q wave myocardial infarction patients (n=23) showed a trend towards more events (52% vs 27%, P=0.060) and deaths (22% vs 5%, P=0.095) than those assigned to early invasive strategy (n=37) at 1 year.

Clinical outcomes in first myocardial infarction group according to treatment strategy

Among the first myocardial infarction group, the ischaemia-guided arm (n=261) fared better than the routine invasive arm (n=263) at 1 month (3% vs 9%, P=0.012 for death) and at 12 months (12% vs 20%, P=0.016 for events; 5% vs. 11%, P=0.009 for death). Among the non-Q wave myocardial infarction patients without a history of prior myocardial infarction, the probability of 12 months event-free survival was significantly higher in the group assigned to the ischaemia-guided strategy than those assigned to the routine invasive strategy (Fig. 6). Figure 7 shows Kaplan–Meier analysis of the probability of survival according to the strategy assignment in patients with no history of prior myocardial infarction during follow-up. The Cox proportional hazard ratio comparing the routine invasive strategy to the ischaemia-guided strategy was 2.49 (95% confidence interval, 1.27 to 4.89). Since the baseline characteristics of the non-Q wave myocardial infarction patients (n=23) showed a trend towards more events (52% vs 27%, P=0.060) and deaths (22% vs 5%, P=0.095) than those assigned to early invasive strategy (n=37) at 1 year.

Clinical outcomes in first myocardial infarction group according to treatment strategy

Among the first myocardial infarction group, the ischaemia-guided arm (n=261) fared better than the routine invasive arm (n=263) at 1 month (3% vs 9%, P=0.012 for death) and at 12 months (12% vs 20%, P=0.016 for events; 5% vs. 11%, P=0.009 for death). Among the non-Q wave myocardial infarction patients without a history of prior myocardial infarction, the probability of 12 months event-free survival was significantly higher in the group assigned to the ischaemia-guided strategy than those assigned to the routine invasive strategy (Fig. 6). Figure 7 shows Kaplan–Meier analysis of the probability of survival according to the strategy assignment in patients with no history of prior myocardial infarction during follow-up. The Cox proportional hazard ratio comparing the routine invasive strategy to the ischaemia-guided strategy was 2.49 (95% confidence interval, 1.27 to 4.89). Since the baseline characteristics of the non-Q wave myocardial infarction patients (n=23) showed a trend towards more events (52% vs 27%, P=0.060) and deaths (22% vs 5%, P=0.095) than those assigned to early invasive strategy (n=37) at 1 year.

Clinical outcomes in first myocardial infarction group according to treatment strategy

Among the first myocardial infarction group, the ischaemia-guided arm (n=261) fared better than the routine invasive arm (n=263) at 1 month (3% vs 9%, P=0.012 for death) and at 12 months (12% vs 20%, P=0.016 for events; 5% vs. 11%, P=0.009 for death). Among the non-Q wave myocardial infarction patients without a history of prior myocardial infarction, the probability of 12 months event-free survival was significantly higher in the group assigned to the ischaemia-guided strategy than those assigned to the routine invasive strategy (Fig. 6). Figure 7 shows Kaplan–Meier analysis of the probability of survival according to the strategy assignment in patients with no history of prior myocardial infarction during follow-up. The Cox proportional hazard ratio comparing the routine invasive strategy to the ischaemia-guided strategy was 2.49 (95% confidence interval, 1.27 to 4.89). Since the baseline characteristics of the non-Q wave myocardial infarction patients (n=23) showed a trend towards more events (52% vs 27%, P=0.060) and deaths (22% vs 5%, P=0.095) than those assigned to early invasive strategy (n=37) at 1 year.

Clinical outcomes in first myocardial infarction group according to treatment strategy

Among the first myocardial infarction group, the ischaemia-guided arm (n=261) fared better than the routine invasive arm (n=263) at 1 month (3% vs 9%, P=0.012 for death) and at 12 months (12% vs 20%, P=0.016 for events; 5% vs. 11%, P=0.009 for death). Among the non-Q wave myocardial infarction patients without a history of prior myocardial infarction, the probability of 12 months event-free survival was significantly higher in the group assigned to the ischaemia-guided strategy than those assigned to the routine invasive strategy (Fig. 6). Figure 7 shows Kaplan–Meier analysis of the probability of survival according to the strategy assignment in patients with no history of prior myocardial infarction during follow-up. The Cox proportional hazard ratio comparing the routine invasive strategy to the ischaemia-guided strategy was 2.49 (95% confidence interval, 1.27 to 4.89). Since the baseline characteristics of the non-Q wave myocardial infarction patients (n=23) showed a trend towards more events (52% vs 27%, P=0.060) and deaths (22% vs 5%, P=0.095) than those assigned to early invasive strategy (n=37) at 1 year.

Clinical outcomes in first myocardial infarction group according to treatment strategy

Among the first myocardial infarction group, the ischaemia-guided arm (n=261) fared better than the routine invasive arm (n=263) at 1 month (3% vs 9%, P=0.012 for death) and at 12 months (12% vs 20%, P=0.016 for events; 5% vs. 11%, P=0.009 for death). Among the non-Q wave myocardial infarction patients without a history of prior myocardial infarction, the probability of 12 months event-free survival was significantly higher in the group assigned to the ischaemia-guided strategy than those assigned to the routine invasive strategy (Fig. 6). Figure 7 shows Kaplan–Meier analysis of the probability of survival according to the strategy assignment in patients with no history of prior myocardial infarction during follow-up. The Cox proportional hazard ratio comparing the routine invasive strategy to the ischaemia-guided strategy was 2.49 (95% confidence interval, 1.27 to 4.89). Since the baseline characteristics of the non-Q wave myocardial infarction patients (n=23) showed a trend towards more events (52% vs 27%, P=0.060) and deaths (22% vs 5%, P=0.095) than those assigned to early invasive strategy (n=37) at 1 year.

Clinical outcomes in first myocardial infarction group according to treatment strategy

Among the first myocardial infarction group, the ischaemia-guided arm (n=261) fared better than the routine invasive arm (n=263) at 1 month (3% vs 9%, P=0.012 for death) and at 12 months (12% vs 20%, P=0.016 for events; 5% vs. 11%, P=0.009 for death). Among the non-Q wave myocardial infarction patients without a history of prior myocardial infarction, the probability of 12 months event-free survival was significantly higher in the group assigned to the ischaemia-guided strategy than those assigned to the routine invasive strategy (Fig. 6). Figure 7 shows Kaplan–Meier analysis of the probability of survival according to the strategy assignment in patients with no history of prior myocardial infarction during follow-up. The Cox proportional hazard ratio comparing the routine invasive strategy to the ischaemia-guided strategy was 2.49 (95% confidence interval, 1.27 to 4.89). Since the baseline characteristics of the non-Q wave myocardial infarction patients (n=23) showed a trend towards more events (52% vs 27%, P=0.060) and deaths (22% vs 5%, P=0.095) than those assigned to early invasive strategy (n=37) at 1 year.

Clinical outcomes in first myocardial infarction group according to treatment strategy

Among the first myocardial infarction group, the ischaemia-guided arm (n=261) fared better than the routine invasive arm (n=263) at 1 month (3% vs 9%, P=0.012 for death) and at 12 months (12% vs 20%, P=0.016 for events; 5% vs. 11%, P=0.009 for death). Among the non-Q wave myocardial infarction patients without a history of prior myocardial infarction, the probability of 12 months event-free survival was significantly higher in the group assigned to the ischaemia-guided strategy than those assigned to the routine invasive strategy (Fig. 6). Figure 7 shows Kaplan–Meier analysis of the probability of survival according to the strategy assignment in patients with no history of prior myocardial infarction during follow-up. The Cox proportional hazard ratio comparing the routine invasive strategy to the ischaemia-guided strategy was 2.49 (95% confidence interval, 1.27 to 4.89). Since the baseline characteristics of the non-Q wave myocardial infarction patients (n=23) showed a trend towards more events (52% vs 27%, P=0.060) and deaths (22% vs 5%, P=0.095) than those assigned to early invasive strategy (n=37) at 1 year. 
patients assigned to the two treatment strategies were similar, and the only dissimilar variable (prior CABG) did not predict clinical outcomes, it was not necessary to adjust for any of the baseline variables.

Of the 524 patients with a first myocardial infarction, 87 patients underwent CABG and 93 PTCA, while 10 patients underwent both procedures during the first follow-up year. At 12 months, patients undergoing CABG experienced more events than those undergoing PTCA (26% vs 14%, \( P=0.042 \)). Among the patients with a first myocardial infarction who underwent CABG during the first post-infarction year (n=97), those assigned to the invasive (n=56) and ischaemia-guided (n=41) strategies experienced a similar number of events.

**Figure 1** Comparison of events and death according to myocardial infarction status at 1 month and 12 months of follow-up. The statistical significance between proportions is represented by a number of asterisks (*). *\( P=0.05 \), **\( P=0.01 \), ***\( P=0.001 \), ****\( P=0.0001 \). ■=prior myocardial infarction; □=no prior myocardial infarction.

**Figure 2** Kaplan–Meier analysis of the probability of event-free survival according to myocardial infarction status during 12 months of follow-up. The events included in this analysis were death and recurrent non-fatal myocardial infarction (primary end-point of VANQWISH). The Cox proportional-hazard ratio comparing the prior to the no prior myocardial infarction group was 1.75 (95% confidence interval, 1.32 to 2.34).
Figure 3  Kaplan–Meier analysis of the probability of survival according to myocardial infarction status during 12 months of follow-up. Death from any cause was included in this analysis. The Cox proportional-hazard ratio comparing the prior to the no prior myocardial infarction group was 1.51 (95% confidence interval, 0.99 to 2.28).

Figure 4  Comparison of events and death according to strategy assignment in patients with no history of prior myocardial infarction at 1 month and 12 months of follow-up. The statistical significance between proportions is represented by a number of asterisks (*). *P=0.05, **P=0.01, ***P=0.001, ****P=0.0001. ■=ischaemia-guided; □=routine invasive.

Discussion

The results of this post-hoc analysis indicate that among patients with non-Q wave myocardial infarction, those with a history of prior myocardial infarction have a worse clinical outcome in the first post-infarction year than those presenting with a first myocardial infarction. In addition, for the first time, we have shown that
even in this high-risk group, a routine early invasive strategy does not result in a greater benefit than a more conservative ischaemia-guided approach.

It is well recognized that subsequent infarcts pose a much higher risk than first infarcts. Analysis of 3 years’ follow-up data from the Thrombolysis In Myocardial Infarction (TIMI) trial showed that non-fatal reinfarction was a strong and independent predictor of subsequent death, with a nearly two- to six-fold increase in the risk of death in patients with reinfarction compared to a matched control group\[13\]. Similarly, late mortality after reinfarction was found to be three times higher than those without reinfarction in the Multicenter Diltiazem Postinfarction trial research group\[14\].

Figure 5  Comparison of events and death according to strategy assignment in prior myocardial infarction patients at 1 month and 12 months of follow-up. The statistical significance between proportions is represented by a number of asterisks (*). *P=0·05, **P=0·01, ***P=0·001, ****P=0·0001. ■=ischaemia-guided; □=routine invasive.

Figure 6  Kaplan–Meier analysis of the probability of event-free survival according to strategy assignment in patients with no history of prior myocardial infarction during 12 months of follow-up. The events included in this analysis were death and recurrent non-fatal myocardial infarction (primary end-point of VANQWISH). The Cox proportional-hazard ratio comparing the routine invasive to the ischaemia guided strategy was 1·75 (95% confidence interval, 1·12 to 2·73).
history of prior infarction correlated significantly with in-hospital mortality in both thrombolytic-eligible and ineligible patients presenting with acute myocardial infarction[11,12]. The results of this study confirm and extend the findings from prior studies that have identified reinfarction as a major risk factor for subsequent cardiac events. At 12 months, patients with a history of prior myocardial infarction had a 63% higher relative mortality rate than those who presented with a first myocardial infarction. Patients with a history of prior myocardial infarction were older and had a much higher incidence of multiple high-risk baseline characteristics than those who presented with a first myocardial infarction, which could have accounted for the worse outcome in this group. However, even after adjustment for the confounding baseline variables, patients with a history of prior myocardial infarction showed a significantly higher incidence of events and a strong trend towards increased mortality than those with a first myocardial infarction. A lower ejection fraction, and a higher prevalence of three-vessel coronary artery disease and high grade stenosis of the proximal left anterior descending artery are other potential reasons that could have accounted for the worse outcome in these patients. The information on ejection fraction as well as coronary artery anatomy was missing in many of our patients, which did not permit further analysis.

Choice of treatment strategy for non-Q wave myocardial infarction patients with a history of prior myocardial infarction

Although patients with a history of prior infarction proved to be a high risk subgroup of non-Q wave myocardial infarction, the results of this study do not support a routine invasive management strategy in these patients. The results are consistent with the main results. 
of the VANQWISH trial\textsuperscript{10} and the subgroup analysis of 476 patients with non-Q wave myocardial infarction in TIMI IIIB\textsuperscript{6}. A slight, non-significant excess in death/myocardial infarction during the first month in the routine invasive strategy group was not counterbalanced by any decrease in the rate of cardiac events during the subsequent 11 months of follow-up. No prospective study has addressed this issue in an exclusive population of non-Q wave myocardial infarction patients with a history of prior myocardial infarction. However, the possibility of a better outcome with an invasive strategy if patients undergo PTCA as the sole revascularization procedure cannot be excluded from this study.

Although it is difficult to elucidate the reasons for this rather counterintuitive finding, one or many of the following potential factors may play a role. Firstly, even in these high-risk patients with prior myocardial infarction, an ischaemia-guided approach might have been effective in promoting adequate risk stratification but succeeded in avoiding unnecessary invasive procedures. Secondly, very high-risk non-Q wave myocardial infarction patients with ongoing ischaemic complications in the coronary care unit, who were otherwise eligible to participate in the study, were excluded because of the likelihood of requiring coronary intervention. Only 9\% of patients fell into this category in this study. This 'need for revascularization' was expected to filter out the highest risk group who would probably benefit from early revascularization procedures. Thirdly, invasive cardiac procedures, in particular CABG surgery, are known to be associated with a higher risk of cardiac events in the immediate post-infarction period compared to more elective procedures performed at a later period. However, in this study we were unable to demonstrate a clear cause-and-effect relationship between invasive procedures and worse clinical outcome, although this could have been due to the relatively small sample size. Fourthly, it is possible that the patients assigned to invasive strategy received less aggressive medical treatment than those assigned to ischaemia-guided approach, since the intensity of medical treatment was left to the discretion of the treating physicians rather than being protocol guided.

### Table 4 Strategy comparison of patients who did and did not have a prior myocardial infarction

<table>
<thead>
<tr>
<th>Event by time period</th>
<th>Prior MI</th>
<th></th>
<th>First MI</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Inv. (n=199)</td>
<td>Con. (n=197)</td>
<td>P-value**</td>
<td>Inv. (n=263)</td>
</tr>
<tr>
<td>Death/MI 1 month, no. (%)</td>
<td>25 (13)</td>
<td>18 (9)</td>
<td>0.3329</td>
<td>23 (9)</td>
</tr>
<tr>
<td>Death 1 year, no. (%)</td>
<td>11 (6)</td>
<td>7 (4)</td>
<td>0.4704</td>
<td>12 (5)</td>
</tr>
<tr>
<td>Death/MI 1 year, no. (%)</td>
<td>59 (30)</td>
<td>54 (27)</td>
<td>0.6570</td>
<td>52 (20)</td>
</tr>
<tr>
<td>Death 1 year, no. (%)</td>
<td>29 (15)</td>
<td>24 (12)</td>
<td>0.5556</td>
<td>29 (11)</td>
</tr>
</tbody>
</table>

Inv. = routine invasive strategy; Con. = ischaemia-guided strategy.

**Fisher’s Exact Test for independence

### Choice of treatment strategy in patients presenting with first non-Q wave myocardial infarction

Contrary to widely held clinical beliefs, the results of this study support the use of a more conservative or ischaemia-guided approach to managing patients who present with a first non-Q wave myocardial infarction. Among the patients who presented with first non-Q wave myocardial infarction, patients treated with a routine invasive strategy had significantly more events than those managed more conservatively at both 1 and 12 months. Compared to the ischaemia-guided group, 1-year mortality was 2.5 times higher in the routine invasive group. Considering the low rate of cardiac events in the ischaemia-guided group, it seems unlikely that more aggressive management would have resulted in a different outcome. Once again, no prospective study has addressed this issue in patients who presented with non-Q wave myocardial infarction and no history of prior myocardial infarction. Unless new evidence is provided, a more conservative, ischaemia-guided approach should be the strategy of choice in the management of patients with an uncomplicated non-Q wave myocardial infarction who do not have a history of prior myocardial infarction.

It is notable that among the first non-Q wave myocardial infarction patients who underwent PTCA, those assigned to an early invasive arm showed a trend towards better outcome than those assigned to an ischaemia-guided strategy. This difference was statistically non-significant and is probably related to selection bias, since the two groups were not randomized. Further studies are necessary to establish the superiority of an early invasive strategy with PTCA as the dominant revascularization strategy in selected patients with non-Q wave myocardial infarction without a history of prior myocardial infarction.

The above findings highlight the importance of knowing whether or not a patient with non-Q wave myocardial infarction has had a prior myocardial infarction before deciding upon a management strategy. However,
it should be emphasized that clinical decision making is quite often a complex process, and due consideration should be given to several other variables such as patient age, severity of angina or heart failure, co-morbid diseases, extent of inducible ischaemia, coronary anatomy and left ventricular function before choosing a particular management strategy.

**Limitations of the study**

This was a post-hoc analysis and is thus exposed to all of the inherent risks of retrospective subgroup analyses. However, it should be emphasized that a history of prior myocardial infarction was a pre-specified, stratifying variable in the main VANQWISH trial and accordingly, a nearly equal number of patients were randomized to an early invasive or ischaemia-guided strategies. Prior myocardial infarction was diagnosed by clinical history and Q waves on the admission ECG, which could have resulted in misclassifying a small number of these patients. The number of events in some of the comparisons was small, and thus findings based on these comparisons may not be definitive. In fact, the first myocardial infarction patients who underwent PTCA as a part of an initial invasive strategy had a slightly better outcome than those who underwent PTCA as a part of ischaemia-guided strategy. However, the numbers were too small to draw any conclusions. A larger sample size might have yielded a more definitive conclusion. These results should be considered exploratory since correlated end-points at various time points were analysed. As a result, the type I error is not well defined. It should also be noted that the number of events could not be adjusted for baseline left ventricular function as this information was either not obtained at baseline or was missing in many study patients. Since this was a stratified randomization, it is possible that groups were reasonably matched for left ventricular ejection fraction at baseline but this cannot be assumed. Finally, the study was conducted mainly in men and the results may not be applicable to women.

**Conclusions**

In summary, this post-hoc analysis confirms and extends the prior observation that among the patients with non-Q wave myocardial infarction, those with a history of prior myocardial infarction have worse clinical outcomes in the first post-infarction year than those who present with a first myocardial infarction. These patients have multiple, higher risk baseline characteristics than those with first myocardial infarction, but a history of prior myocardial infarction seems to confer an independent risk for an adverse outcome during the first post-infarction year. Even in this high-risk subset of non-Q wave myocardial infarction patients, a routine invasive strategy does not improve the long-term clinical outcome and above those achieved by a more selective-invasive or ischaemia-guided approach. However, in non-Q wave myocardial infarction patients without a history of prior myocardial infarction, an ischaemia-guided approach appears to result in superior outcome during the first post-infarction year than those managed by an early invasive strategy.

We would like to acknowledge the expert secretarial and word processing assistance by Ms Gail A. Bonham in the preparation of this manuscript.

**References**


