Uncomplicated non-Q wave myocardial infarction: long-term prognosis with a conservative echo-stress guided management strategy

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Key words:
Coronary angiography; Myocardial revascularization; Non-Q wave infarction; Prognosis; Stress echocardiography.

Background. **Whether an invasive or a conservative strategy should form the basis of an optimal management strategy for non-Q wave myocardial infarction is at present still subject of debate. We reported our observational experience with the long-term follow-up of patients with a first uncomplicated non-Q wave myocardial infarction and submitted to a conservative treatment strategy based on the in-hospital stress echocardiography and treadmill exercise.**

Methods. **We studied 134 consecutive patients admitted for a first uncomplicated non-Q wave myocardial infarction between 1991 and 1994. All patients were submitted to a dipyridamole echocardiography test (DET) between 5-7 days after admission and to a treadmill test before discharge. Coronary angiography and myocardial revascularization (coronary angioplasty or coronary artery bypass grafting) were performed according to the outcomes of the stress echo and treadmill test.**

Results. **The early and delayed follow-up results were quite good: 2.9% early hard events, 15% delayed hard events. DET negativity identified patients with a lower risk of both spontaneous and hard events. Multivariate analysis indicated the DET as the only predictive variable of spontaneous events within 1 year (p = 0.0001), of delayed spontaneous events (p = 0.0001) and of delayed hard events (p = 0.05).**

Conclusions. **In this study, revascularization procedures performed on the basis of stress echo result in good short- and long-term outcomes in stabilized uncomplicated non-Q wave myocardial infarction. The patients with a negative DET had a very low rate of events. DET positivity identifies a higher risk group of patients, whatever treatment they subsequently undergo.**

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Introduction

Optimal diagnostic and treatment strategies for non-Q wave myocardial infarction patients is an undergoing process in clinical cardiology, as rapid progress is being made in the understanding and treatment of this syndrome. At present there is debate[1-10] as to whether an invasive or a conservative strategy should be the basis of an optimal non-Q wave myocardial infarction management strategy.

Prospective studies are the cornerstone of modern evidence-based decision making, but observational studies are important complementary tools that offer useful information for the improvement of care and outcomes[11].

This paper deals with our observational experience with the long-term follow-up of patients with a first uncomplicated non-Q wave myocardial infarction, submitted to a conservative therapeutic strategy on the basis of the in-hospital stress echocardiography and treadmill exercise. A secondary aim was to evaluate the prognostic stratification by non-invasive diagnostic techniques, when the natural history of the disease is modified by myocardial revascularization procedures (coronary angioplasty-PTCA and/or coronary artery bypass grafting-CABG).

Methods

The initial study population consisted of 134 consecutive patients admitted to our Cardiology Department for a first episode of uncomplicated non-Q wave myocardial infarction between 1991 and 1994. All eligible patients had a clinical presentation consistent with an evolving acute myocardial infarction, creatine kinase-MB isoenzyme levels > 1.5 times the hospital upper limit of normal, and the absence of new pathologic Q waves or of a significant loss

of the R force on serial electrocardiograms. Patients were excluded if they exhibited, in the coronary care unit, signs of heart failure, major arrhythmias, recurrent rest ischemia and angina; patients with extensive persistent anterolateral ischemia were excluded too. Patient selection was independent of ST sloping at the time of presentation. The non-Q wave myocardial infarction was anterior in 38%, inferior in 32%, and other in 30% of patients. Forty-six percent of patients were submitted to systemic thrombolysis; at ECG performed at the time of admission, 48% had ST-segment elevation and 40% had ST-segment downsloping (Table I).

All 134 (104 males, 30 females, age 37-75 years, average 58.6 years) had a technically acceptable acoustic window and underwent a dipyridamole echocardiography test (DET) between 5-7 days after admission; 126 out of 134 patients were also submitted to a treadmill test before discharge. The decision to submit the patients to coronary angiography and, if necessary to a myocardial revascularization procedure (PTCA or CABG) was based on the outcomes of the stress echo and of the treadmill test.

Dipyridamole echocardiography. All patients underwent a complete two-dimensional echocardiographic study before DET. Dipyridamole infusion was administered as follows: 0.56 mg/kg over 4 min followed by a 2-min pause, and then 0.28 mg/kg over 2 min. Hence, the cumulative dose of 0.84 mg/kg was administered in 8 min. This infusion modality is intermediate between the standard[12] and the accelerated protocols[13]. Two-dimensional echocardiography and 12-lead ECG monitoring was performed during DET and for 10 min thereafter. On the basis of ECG criteria, a test was considered positive if a horizontal or downsloping ST-segment depression ≥ 0.1 mV with a duration of ≥ 0.08 s was detected. On the basis of echocardiographic criteria, a test was considered positive when we observed:

Table I. Baseline characteristics of the enrolled patients.

Age (years)	56 ± 10
Sex (M/F)	104/30 (78%/22%)
Hypertension	55 (39%)
Smoke	85 (61%)
Diabetes	31 (22%)
Hypercholesterolemia	94 (67%)
Thrombolysis	62 (46%)
Anterior MI	51 (38%)
Inferior MI	43 (32%)
Other MI	40 (30%)
ST-segment elevation	65 (48%)
ST-segment downsloping	54 (40%)
Positive ET	44 (33%)
Positive DET	81 (60%)

DET = dipyridamole echocardiography test; ET = exercise test; MI = myocardial infarction.

- marked worsening of segmental wall motion asynergy (e.g. hypokinesia to akinesia or dyskinesia);
- extension of asynergy to adjacent segments perfused by the same coronary artery;
- development of new asynergy, adjacent or remote, in segments without asynergy at rest.

Ventricular function was also evaluated at baseline and at peak stress by means of semiquantitative assessment of a wall motion score index, calculated according to a segmental score ranging from 1 = normal to 2 = hypokinetic, to 3 = akinetic, to 4 = dyskinetic; the segments evaluated were 16. All echocardiographic studies were performed by expert echocardiographers who used an HP Sonos 1500 or 2500 machine (Andover, MA, USA) with a 2.5 MHz probe and recorded images on videotape. Endovenous aminophylline was administered over 5 min after dipyridamole infusion.

Exercise electrocardiographic test. The patients underwent the Bruce protocol treadmill exercise test which was suspended in case of symptoms or when the heart exceeded 140 b/min. One hundred and twenty-six out of 134 patients underwent the exercise electrocardiographic test (ET). The remaining 8 patients, all with a very positive DET, did not consent to the test. Owing to either very early fatigue or basal ECG abnormalities, the ET was not diagnostic in 18 patients. The test was performed without antianginal therapy. The development of angina or the appearance of a horizontal or downsloping ST segment with a depression of ≥ 0.1 mV and with a duration of ≥ 0.08 s were taken as evidence of a positive ET.

Coronary angiography. Ninety-two patients underwent coronary angiography on the basis of a positive echo stress or ET. The procedure was performed in multiple projections. The diagnosis of critical coronary artery disease was defined by an obstruction of at least 70% of the normal diameter in an epicardial coronary artery or 50% in the left main trunk. In the presence of critical coronary artery disease and related echo stress ischemia, patients were submitted to PTCA or to CABG; in the absence of critical coronary artery disease or echo stress ischemia medical therapy was prescribed.

Follow-up. Follow-up data were obtained by staff physicians visiting the patients in the outpatient clinic and by telephone interview. The length of follow-up ranged from 4 to 8 years (mean 6.5 years). The clinical data of those who died outside our hospital were collected from the family doctors and/or relatives. One-year follow-up data were obtained for all patients; complete follow-up data were obtained for 128 patients. We considered cardiac death, non-fatal myocardial reinfarction, angina pectoris and cardiac heart failure as "spontaneous cardiac events". Cardiac death and non-fatal myocardial infarction were defined as "hard

events". PTCA and CABG should be considered as therapeutic events with a possible influence on the outcome.

Statistical analysis. Kaplan-Meier life table estimates of survival, of infarction-free survival, and of all spontaneous event-free survival were used to summarize the follow-up. The statistical significance was determined using the log-rank test.

The sensitivity, specificity, negative (NPV) and positive predictive values (PPV) were obtained using standard definitions; statistical significance was calculated using the comparing ratios test.

Knowing the sensitivity and specificity of a test (e.g. DET or ET), the Bayes simplified theorem[14] was applied. When the pre-test probability of events (hard or spontaneous) is known, it is possible to obtain the post-test probability of subsequent events. This value represents the PPV when the test is positive and the reciprocal of the NPV when it is negative[15].

Multivariate discriminant analysis[16] was used to determine whether non-invasive tests were predictors of spontaneous events. The variables selected for evaluation were: age, sex, admission ST-segment elevation, and the ET and DET results.

Results

Basal echocardiography. The left ventricular ejection fraction was normal or only slightly reduced. In fact, in 81 patients (60.5%) it was ≥ 50%, in 38 (28.3%) it was 45-50%, and in 15 (11.2%) it was 40-45%. The baseline wall motion score index was 1.26 ± 0.28.

Dipyridamole echocardiography. The test was safe and no major complications were observed. It was positive in 81 patients (60.5%). The wall motion score index during DET was 1.41 ± 0.28. As shown by Kaplan-Meier life table estimates, in patients with a negative and positive DET the final survivals without hard events were respectively 95 and 70% ($p < 0.01$). The survivals without spontaneous events were respectively 90 and 45% ($p < 0.001$). DET positivity selected patients with a higher risk of both spontaneous and hard events regardless of revascularization (Figs. 1 and 2).

The DET sensitivity, specificity, PPV, and NPV for spontaneous or hard events at 1 year of follow-up are reported in table II; 6.6-year follow-up data are reported in table III. The DET sensitivity, specificity and NPV were significantly better than those of the ET (Tables II and III) while there was no difference for the PPV.

At multivariate analysis by discriminant function with respect to age, sex, admission ST-segment elevation and ET, DET was found to be the only predictive variable of 1-year spontaneous events ($p = 0.0001$), delayed spontaneous events ($p = 0.0001$), and delayed hard events ($p = 0.05$). Age was also predictive of delayed hard events ($p < 0.05$), but not for 1-year hard events.

As shown in table IV[12,17], the incremental value of negative DET was very satisfactory with regard to the absence of both spontaneous and hard events; on the contrary, the incremental value of positive DET was poor.

Treadmill exercise test. The ET was often submaximal and 8 patients with a very positive DET refused it. The ET was a predictor of spontaneous events ($p < 0.03$), but not of hard events. The survivals without hard events were 86 and 94% respectively in patients with a positive and negative ET; the survivals without spontaneous events were respectively 49 and 69% ($p < 0.03$).

The ET sensitivity, specificity, PPV and NPV in identifying patients with spontaneous events or with hard events at 1 year of follow-up are reported in table II, while the 6.6-year follow-up data are reported in table III. At discriminant analysis the ET was not predictive of spontaneous or hard events at the early or delayed follow-up.

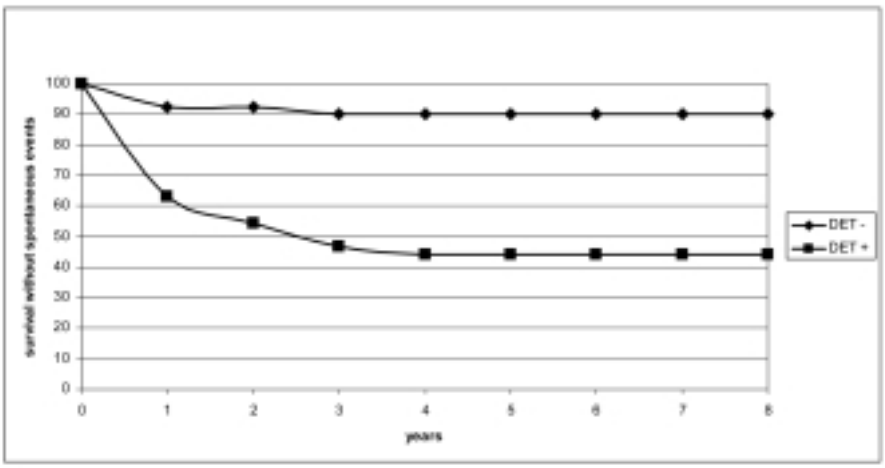

Figure 1. *Spontaneous events in patients with a positive and with a negative dipyridamole echocardiography test (DET).*

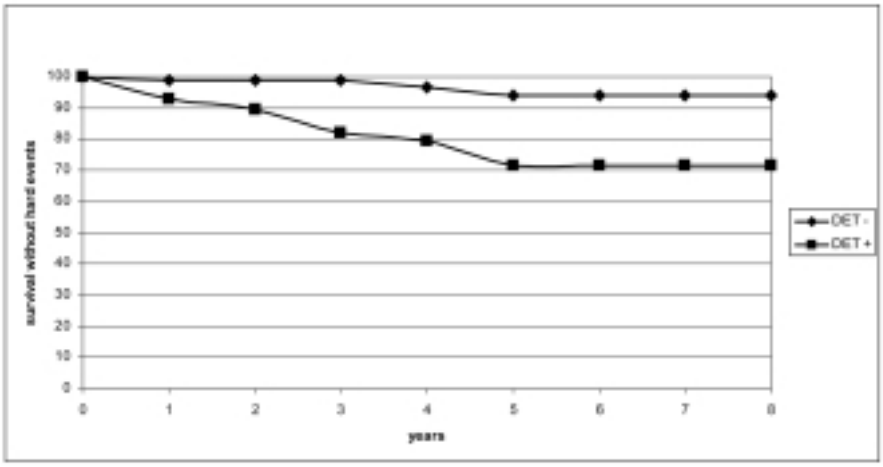

Figure 2. *Hard events in patients with a positive and with a negative dipyridamole echocardiography test (DET).*

Table II. Prognostic value of the dipyridamole echocardiography test (DET) and exercise test (ET) after 1 year of follow-up.

	Sensitivity	Specificity	PPV	NPV
Spontaneous events				
ET	0.55	0.67	0.47	0.73
DET	0.90	0.48	0.49	0.89
p	< 0.001	< 0.005	NS	0.005
Hard events				
ET	0.25	0.59	0.02	0.95
DET	1	0.34	0.06	0.95
p	< 0.001	< 0.001	NS	NS

NPV = negative predictive value; PPV = positive predictive value.

Table III. Prognostic value of the dipyridamole echocardiography test (DET) and exercise test (ET) after 6.6 years of follow-up.

	Sensitivity	Specificity	PPV	NPV
Spontaneous events				
ET	0.51	0.67	0.63	0.55
DET	0.88	0.57	0.71	0.79
p	< 0.001	NS	NS	< 0.001
Hard events				
ET	0.28	0.58	0.09	0.84
DET	0.93	0.37	0.18	0.97
p	< 0.001	< 0.005	NS	< 0.05

Abbreviations as in table II.

In the 15 patients with an ET duration < 4 min we observed a high specificity: respectively 93% for delayed spontaneous events and 88% for delayed hard events. The sensitivity was low both for delayed spontaneous (22%) and delayed hard events (25%). On the other hand, the predictive power was satisfactory both for early and delayed spontaneous events (respectively $p < 0.03$ and $p < 0.05$).

The 18 patients with a non-inconclusive ET had no hard events; 6 spontaneous events occurred within 1 year of follow-up. At delayed follow-up there were 4 hard events (1 cardiac death) and 9 spontaneous events. An inconclusive ET was not a predictor of hard and spontaneous events; however, due to the small sample size, it was not possible to reach definite statistical conclusions.

Follow-up. In the whole population consisting of 134 patients with a follow-up lasting 1 year we registered: 1 cardiac death (0.7%), 4 hard cardiac events (2.9%), 36 patients who complained of angina (27%) and 39 spontaneous cardiac events (29%); PTCA or CABG was performed in 44 patients (33%). There were few hard events, despite the high frequency of angina and of the need for revascularization procedures.

Table IV. Incremental value of dipyridamole echocardiography test (DET).

Author	DET	P1	P2	Follow-up
Cecchi et al.	DET+	0.03	0.04	1-year hard events
	DET-	0.03	0.0008	1-year hard events
	DET+	0.47	0.63	1-year spontaneous events
	DET-	0.47	0.17	1-year spontaneous events
	DET+	0.16	0.19	6.6-year hard events
	DET-	0.16	0.22	6.6-year hard events
	DET+	1.04	0.66	6.6-year spontaneous events
	DET-	1.04	0.23	6.6-year spontaneous events
Neskovic et al.[17]	DET+	0.01	0.03	16-month hard events
	DET-	0.01	0.0001	16-month hard events
	DET+	0.2	0.37	16-month spontaneous events
	DET-	0.2	0.06	16-month spontaneous events
Picano et al.[12]	DET+	0.098	0.11	30-month hard events
	DET-	0.098	0.07	30-month hard events
	DET+	0.43	0.46	30-month spontaneous events
	DET-	0.43	0.18	30-month spontaneous events

P1 = pre-test probability of events; P2 = post-test probability of events.

The Kaplan-Meier life table estimates of survival (Fig. 3) and of hard event-free survival (Fig. 4) confirmed this trend even for the delayed follow-up. The spontaneous events were prevalent during the 4-year period after the acute infarction.

Follow-up was completed in 128 patients; we observed: 9 deaths (7%), 5 cardiac deaths (3.9%), 20 hard events (15.6%), 47 patients with angina (36.7%); in 58 patients (45%) a revascularization procedure (PTCA or CABG) was necessary.

Discussion

As recently indicated[11] cohort studies may be a valuable tool to fill the gap between the randomized studies and clinical practice. A long follow-up, such as in our series, lends further support to this concept.

Usually, in spite of a smaller infarct size[18-21] and of a better left ventricular function[22-24] and intra-hospital prognosis, patients with a non-Q wave myocardial infarction have an unexpectedly high long-term mortality, as compared to patients with a Q wave myocardial infarction[24-30]. On the basis of this prognostic paradox non-Q wave myocardial infarction is now considered as a specific entity in the spectrum of acute coronary syndromes. The best therapeutic strategy for this condition is still subject of debate[1-10].

Our study shows that these patients, as seen at the bedside, do have on the whole a good long-term prognosis. This holds true both for cases with ST-segment elevation and depression. In the latter however spontaneous events did occur more frequently. It must be stressed that our series cannot be compared with others because of our case selection and risk stratification strategy. Non-Q wave myocardial infarction is a broad subgroup of acute

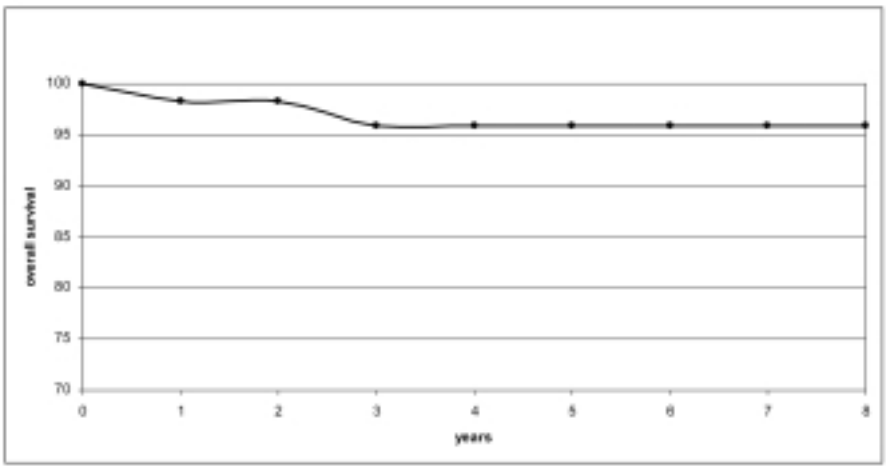

Figure 3. *Overall survival.*

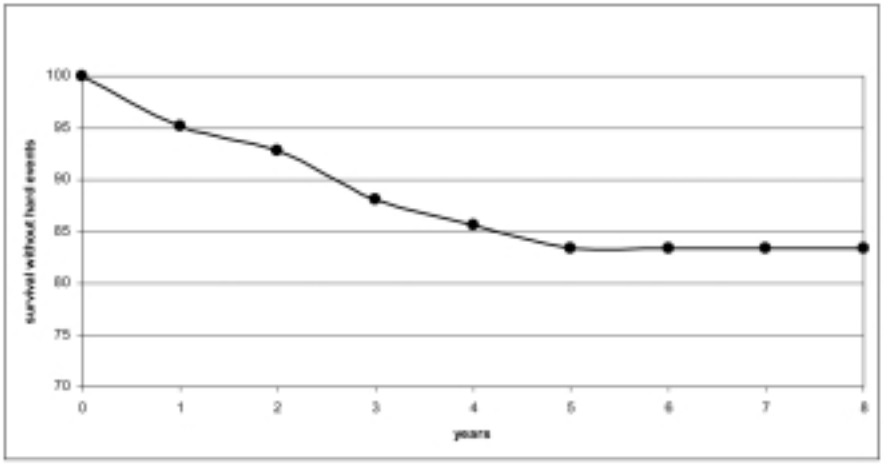

Figure 4. *Survival without hard events.*

coronary syndromes and the prognosis is quite variable, depending on patient selection, age, gender, non-ST-segment elevation, associated risk factors and therapy: the death rate at 1 year varies from 1 to 18% in many series; a 2-2.5% yearly death rate is reported in various series with a follow-up ranging from 3 to 10 years[24-30].

Our results indicate that early DET may be a useful and safe tool in uncomplicated non-Q wave myocardial infarction with non-extensive anterolateral ischemia. In fact, we found a death rate at 1 year < 1% and < 1%/year cardiac death rate at delayed follow-up. The rate of revascularization (33%) was lower than in the invasive strategy arm of FRISC II (78%), TIMI IIIB (55%) and VANQWISH (44%) at earlier follow-up. Our strategy is similar to the conservative one of the VANQWISH study, which utilized perfusional scintigraphy. DET is a more friendly stress technique, it can be safely performed very early after the acute event and is less time- and resource-consuming. The early and delayed outcomes are good. Though DET has less diagnostic sensitivity than dobutamine and perfusional scintigraphy for the detection of coronary stenosis, it is better for prognostic purposes.

Our observational follow-up indicates a higher rate of events in DET-positive patients as compared to those who were DET-negative. Furthermore, the latter had a very low rate of events, and coronary angiography and revascularization could be safely avoided. Hence, important conclusions may be drawn: in our as well as in other series[31,32], patients with negative DET have a good long-term prognosis after an uncomplicated non-Q wave myocardial infarction. Finally, a positive DET outcome identifies a group of patients at higher risk, regardless of the treatment; this may be attributable to more extensive coronary artery disease unrecognizable at the time of the index coronary angiography[33-35].

It is well known that after an acute myocardial infarction the ET prognostic factors are inability to exercise and ischemia at a low work load[36,37]. In our series, with a submaximal protocol, the group of patients with an inconclusive ET or who were unable to exercise is too small to conclude anything about its prognostic significance. In the 15 patients with ET positivity at first stage of Bruce, we found a very high specificity for spontaneous and hard events at delayed follow-up. The exclusion of 8 patients who refused the ET, after a very positive DET, probably contributed to weaken the prognostic information of the ET in our series.

Due to the low incidence of events during follow-up, the incremental value of a positive DET is low and on the contrary is good if DET is negative. A similar result has been reported in a previous series including patients with an uncomplicated Q wave myocardial infarction[38]. One could be led to the conclusion that, in selected patients with a low probability of cardiac events, the non-invasive ischemic test is useful for prognostic stratification. However, this test must be performed[39]. In fact, in spite of the fact that it adds little to the information derivable from a positive DET, it can really be useful in guiding the cardiologist when deciding on the best revascularization procedure thus favoring a satisfactory outcome; a negative DET almost certainly excludes early and late spontaneous hard events. Some events cannot be predicted by any test (e.g. ET, DET, scintigraphy, coronary angiography), because these tests cannot predict plaque inflammation and related phenomena[40-42] which are not related to the severity of the patient's hemodynamic picture at the time they are performed[35]. With regard to revascularization procedures, DET is better than ET in revealing the presence of responsible lesions and better clarifying the extent and severity of ischemia. The superiority of DET has also been confirmed by other authors[17,39,41,43]. Our observational study helps to confirm that non-invasive tests hold a prominent place in the management of the stable patient recovering from a first uncomplicated non-Q wave myocardial infarction and that now we need prospective randomized studies with cost-effectiveness analysis.

Study limitations and conclusions. This is not a randomized trial but rather an observational study. We cannot infer any conclusions about a better prognostic strategy, whether invasive or non-invasive, in non-Q wave myocardial infarction. However, this kind of study is useful because it presents the results as they are obtainable in the field of general cardiology practice in our country. Often randomized trials are performed in excellent centers, sometimes rather different to the actual clinical reality. This observational study shows the feasibility and good results of a DET-guided strategy in the prognostic stratification of uncomplicated non-Q wave myocardial infarction. In our opinion, the use of early DET after an uncomplicated non-Q wave myocardial infarction should be more often taken into consideration.

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