Diabetes mellitus type 2 and angina pectoris: novel insights in diagnosis, prognosis and treatment
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Citation for published version (APA):
Cardiac complications in type 2 diabetic patients with mild anginal complaints and documented reversible myocardial perfusion defects, results of the MERIDIAN trial

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For the Multicenter trial of Early Revascularization In patients with Diabetes mellitus type 2 and mild ANginal symptoms (MERIDIAN trial) investigators

Netherlands Heart Journal, 2006 Dec;12:409
Abstract

Objective
To compare early invasive treatment with continued pharmacological treatment in patients with diabetes mellitus type 2, mild anginal symptoms and documented myocardial ischemia.

Methods
Patients with type 2 diabetes mellitus and mild anginal symptoms underwent myocardial perfusion scintigraphy (MPS). Patients with myocardial ischemia were randomly assigned to early invasive or continued pharmacological treatment. All patients were followed for the occurrence of MACE (death, non-fatal myocardial infarction or hospitalization for unstable angina pectoris).

Results
A total of 156 patients were randomized when the sponsor (ZonMW) prematurely terminated the study because of a slow recruitment rate. With a mean follow-up of 2.1±0.6 years, 9 of 79 patients assigned to early invasive treatment developed MACE compared to 10 of 77 patients randomized to continued pharmacological treatment, annual event rate 5.4 % vs. 6.3%, hazard ratio 0.89, 95% CI 0.36-2.20, p=0.34. Due to the limited number of included patients and the low event rate, the study did not have sufficient power for the study objective.

Conclusions
Patients with diabetes mellitus type 2, mild anginal complaints and documented myocardial ischemia, under appropriate medical treatment, have a lower than anticipated annual event rate of MACE of ± 5-6% which questions the beneficial effect of early revascularization.
Introduction

To date, approximately 150 million people worldwide are diagnosed with diabetes mellitus and this number is expected to double before 2025. Type 2 diabetes mellitus accounts for 90%-95% of all cases. Patients with diabetes mellitus type 2 are at 2-4 fold higher risk of coronary artery disease (CAD) compared to their non-diabetic counterparts and manifest CAD earlier in life. Moreover, patients with diabetes mellitus are more likely to have an atypical or less distinct expression of their anginal symptoms. Myocardial ischemia is already present in ± 20% of asymptomatic patients with type 2 diabetes mellitus. When CAD does become overt; these patients have a worse cardiovascular prognosis. Early detection and subsequent adequate treatment might help to improve their cardiovascular prognosis.

Developments in both medical and invasive treatment of angina pectoris have shown to be effective in reducing symptoms and the risk of complications in patients with anginal complaints. According to the current American and European guidelines for percutaneous coronary interventions, the majority of patients with only mild anginal symptoms (Canadian Cardiovascular Society (CCS) class I-II/IV) can be treated medically for their complaints. However, whether these recommendations apply to patients with diabetes mellitus is unclear. Because of their higher risk for cardiac complications, one could speculate that this specific patient population might benefit from a more aggressive approach of their mild anginal complaints. The BARI-trial suggested that patients with diabetes mellitus might benefit from bypass-surgery, although this could not be confirmed in the BARI-registry. Since then, there has been an impressive reduction in cardiac complications, particularly in-stent restenosis and repeat revascularizations, after the introduction of GPIIb/IIIa receptor inhibitors, ADP-antagonists and drug-eluting stents.

We therefore conducted this prospective randomized multicenter MERIDIAN trial, to determine whether patients with diabetes mellitus type 2, mild anginal symptoms and documented myocardial ischemia would benefit from an optimized early invasive treatment (with drug-eluting stents and GPIIb/IIIa receptor inhibitors, when indicated) compared to an optimized continued pharmacological treatment.
Patients and Methods

The MERIDIAN trial was conducted in 20 hospitals in the Netherlands (see appendix A for the list of participating centers). Patients with mild, stable (≥ 2 months) complaints of angina pectoris (CCS I-II/IV) and type 2 diabetes mellitus, without a short-term indication for coronary revascularization, were eligible for randomization in the MERIDIAN trial. Patients underwent myocardial perfusion scintigraphy (MPS) in order to document myocardial ischemia. Patients with myocardial ischemia were randomly assigned to an early invasive treatment or to a continued pharmacological treatment. Patients without myocardial ischemia on MPS were treated according to routine clinical practice. The trial complied with the Declaration of Helsinki. The medical ethical committees of the participating centers approved the protocol and all patients gave written informed consent before the MPS.

Type 2 diabetes mellitus was defined as either one of the following: fasting glucose > 7.0 mmol/L or non-fasting > 11.0 mmol/L; treatment with oral anti-diabetic medication; treatment with oral anti-diabetic medication and insulin; onset of insulin treatment at age ≥ 50 years. Exclusion criteria were 1) percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) in the preceding six months; 2) unstable angina pectoris (UAP) or myocardial infarction (MI) in the preceding two months; 3) known coronary anatomy unsuitable for coronary intervention; 4) clinical symptoms of heart failure or known ejection fraction < 35%; 5) known valvular disease; 6) known congenital heart disease; 7) apparent cardiomyopathy; 8) history of bleeding diathesis; 9) severe hypertension (systolic blood pressure ≥ 180 mmHg or diastolic blood pressure ≥ 100 mmHg, after treatment); 10) familial hypercholesterolemia; 11) serious bronchial asthma; 12) plasma creatinin level > 250 μmol/L; 13) body-weight > 120 kg; 14) co-existent condition associated with limited life expectancy or other circumstances that prevent follow-up; 15) pregnant women or women of child bearing potential who do not use adequate contraception; 16) age under 30 years.

All eligible patients underwent initial clinical and laboratory evaluation prior to MPS or X-ECG. ECG-abnormalities were defined as the presence of ST-T changes, Q-waves, T-wave inversion or left bundle branch block on the rest-ECG.

Ischemia detection

Stress and rest scintigraphy (with single-photon emission computed tomography (SPECT)) was performed with $^{99m}$Tc labeled perfusion tracers (Tetrofosmin or sesta-MIBI) or Thallium-201, according to the guidelines of the American Society of
Nuclear Cardiology. Symptom limited exercise was the preferred stress modality. Experienced nuclear physicians analyzed the images in 17 myocardial segments using a (semi)-quantitative 5-point scorings-system ranging from 0 (normal distribution) to 4 (absent distribution of radiofarmacon). The summed difference score (SDS) was calculated by subtracting the summed score of rest images (summed rest score, SRS) from the summed score of stress images (summed stress score, SSS). Reversible myocardial perfusion defects, indicative for myocardial ischemia, were defined as SDS ≥3, located in one or more adjacent segments.

Exercise stress testing (X-ECG) was permitted for detection of ischemia if MPS was unavailable. X-ECG was performed according to the guidelines of the American Heart Association of the Exercise Standards for Testing and Training. Significant ischemia was defined as ST-segment depression of at least 1 mm, horizontal or down sloping, 80ms from the J point in at least two adjacent leads.

**Treatment strategy**

Patients assigned to early invasive treatment underwent coronary angiography. The choice of revascularization procedures was performed by a ‘heart team’ consisting of an interventional cardiologist and cardio-thoracic surgeon. Revascularization procedures were performed within 2 months after randomization. Routine protocols of the participating hospitals were used for all invasive procedures. For all PCI-procedures, the aim was to treat all culprit lesions, preferably with paclitaxel-coated stents and GP IIb/IIIa receptor inhibitors. Clopidogrel was given at a starting dose of 300 mg before PCI and continued until at least 1 month after stenting and at least 6 months after placement of drug-eluting stents.

In patients assigned to continued pharmacological treatment, coronary angiography was only performed when anginal complaints progressed to a level which could not sufficiently be controlled by medical therapy alone.

All patients received, if not contra-indicated, aspirin, high-dosed lipid-lowering therapy and ACE-inhibition.

**Follow-up**

Randomized patients visited the out-patient clinic 2 months after randomization and at 6-month intervals until termination of follow-up at January 1st, 2006. All patients were followed for the occurrence of major adverse coronary events (MACE), defined as a composite of all-cause mortality, non-fatal MI, or hospitalization for UAP. MI was...
Early termination of the study

At July 8th, 2004, one of the financial sponsors, the Netherlands Organization for Health Research and Development (ZonMw) decided to prematurely terminate the MERIDIAN trial because of a disappointing recruitment rate.

Statistical analysis

Data are presented as number of patients (proportion) or as mean ± standard deviation (SD). Continuous variables were compared by Student’s unpaired t test or Mann-Whitney test where appropriate. Categorical variables were compared by χ² or Fisher’s exact test where appropriate. The annual event rates of MACE were calculated by dividing the actual number of events by the total exposure years. The main clinical analysis consisted of a single comparison between the two treatment groups of the (combined) primary clinical end point, involving all randomized patients. Kaplan-Meier cumulative
survival rates were compared using the log-rank test. The Cox proportional hazards model was used to determine the independent predictors of the occurrence of MACE. Treatment effect was expressed as a hazard ratio with corresponding 95% confidence interval. The intention-to-treat principle was adopted for the main analyses. Analyses were performed using SPSS for Windows version 12.0 (SPSS Inc, Chicago, IL, USA). Values of p <0.05 were considered statistically significant.

The original study size calculation was made under the assumption that the expected event rate in the pharmacologically treated group was at least 40% within two years. With 400 patients in each treatment arm, the study would have had 85% power (2-sided) to detect a relative reduction in event rate with 25% (i.e., from 40 to 30%; RR = 0.75). Furthermore, it was assumed that 1200 patients needed to undergo MPS screening to randomize 800 patients with a positive MPS.

**Results**

Between October 1\textsuperscript{st} 2002 and July 8\textsuperscript{th} 2004, a total of 339 patients were screened in 20 participating centers. Ischemia-detection was performed in 335 patients: 327 underwent MPS, 2 patients underwent MPS + X-ECG and 6 underwent only X-ECG. In total 156 (47%) patients were randomized; 79 patients to an early invasive treatment and 77 patients to a continued pharmacological strategy (figure 1). Baseline characteristics are shown in table 1. The distribution of characteristics was typical for a diabetic population. The population was predominantly male, with a median age of 65 years and approximately 50% had a known history of CAD. The majority of patients (87%) were overweight (BMI>24.9 kg/m²), the mean duration of diabetes mellitus was 8 years, and approximately 35% needed insulin therapy. The use of lipid-lowering therapy, aspirin and beta-blockade at baseline was high in both groups.

**Treatment and follow-up (table 2)**

All patients assigned to early invasive treatment underwent CAG. No, or only non-significant coronary abnormalities were detected in 18 (23%) patients. In 3 patients (2 patients with single-vessel disease and 1 patient with multi-vessel disease) no intervention was possible and 1 patient refused further treatment. Of the remaining 57 patients, 38 were referred for PCI and 19 for CABG. In one PCI-procedure, the guide wire could not cross the stenosis and the procedure was terminated prematurely. All other PCIs were procedurally successful.
Complications of the PCI-procedure occurred in 4 patients; one procedure-related MI (CK-MB ≈ 2x the upper limit of normal), one case of transient vision-problems and 2 prolonged hospitalizations because of haematomas at the puncture site. Of patients randomized to CABG, one patient developed an ischemic cerebrovascular accident and 2 patients atrial fibrillation.

Table 1. Baseline characteristics.

<table>
<thead>
<tr>
<th>Clinical characteristics</th>
<th>Early invasive n=79</th>
<th>Continued pharmacological n=77</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender</td>
<td>59 (75)</td>
<td>57 (74)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>65 (8)</td>
<td>65 (9)</td>
</tr>
<tr>
<td>CCS II/IV</td>
<td>37 (47)</td>
<td>38 (49)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>28.9 (3.9)</td>
<td>29.6 (4.8)</td>
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**Drug therapy**

<table>
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<tr>
<td>Aspirin</td>
<td>72 (91)</td>
<td>63 (82)</td>
</tr>
<tr>
<td>Statin</td>
<td>53 (67)</td>
<td>57 (74)</td>
</tr>
<tr>
<td>ACE-inhibition</td>
<td>29 (37)</td>
<td>31 (40)</td>
</tr>
<tr>
<td>Beta blockade</td>
<td>62 (78)</td>
<td>49 (64)</td>
</tr>
<tr>
<td>Long-acting nitrates</td>
<td>30 (38)</td>
<td>41 (53)</td>
</tr>
<tr>
<td>Calcium-antagonists</td>
<td>38 (48)</td>
<td>39 (51)</td>
</tr>
<tr>
<td>Insulin</td>
<td>32 (41)</td>
<td>24 (31)</td>
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**Risk factors**

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<tbody>
<tr>
<td>Hypertension</td>
<td>45 (57)</td>
<td>35 (45)</td>
</tr>
<tr>
<td>Smoking</td>
<td>17 (22)</td>
<td>13 (17)</td>
</tr>
<tr>
<td>Previous smoker</td>
<td>41 (52)</td>
<td>42 (55)</td>
</tr>
<tr>
<td>Family history</td>
<td>25 (32)</td>
<td>25 (32)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>52 (66)</td>
<td>48 (62)</td>
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**Medical history**

<table>
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<th>Continued pharmacological n=77</th>
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</thead>
<tbody>
<tr>
<td>Previous MI</td>
<td>27 (34)</td>
<td>25 (32)</td>
</tr>
<tr>
<td>Previous PCI</td>
<td>22 (28)</td>
<td>12 (16)</td>
</tr>
<tr>
<td>Previous CABG</td>
<td>10 (13)</td>
<td>16 (21)</td>
</tr>
<tr>
<td>Duration of DM (years)</td>
<td>8.6 (7)</td>
<td>7.2 (6)</td>
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**Diagnostic tests**

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<tbody>
<tr>
<td>ECG-abnormalities</td>
<td>45 (57)</td>
<td>45 (58)</td>
</tr>
<tr>
<td>MPS SDS&lt;3</td>
<td>1 (1)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>MPS SDS 3-8</td>
<td>43 (56)</td>
<td>42 (58)</td>
</tr>
<tr>
<td>MPS SDS ≥ 8</td>
<td>33 (43)</td>
<td>30 (41)</td>
</tr>
<tr>
<td>Positive exercise ECG</td>
<td>3 (4)</td>
<td>5 (7)</td>
</tr>
</tbody>
</table>

Table 1. Values are presented as n (%) or as mean (SD) unless otherwise indicated. No significant differences were found between the two randomization groups. CCS= Canadian Cardiovascular Society; BMI= body mass index; ACE= angiotensin-converting enzyme; MI= myocardial infarction; PCI= percutaneous coronary intervention; CABG= coronary artery bypass grafting; SDS=summed difference score.
In 22 (29%) of patients randomized to continued pharmacological treatment, the treating cardiologist proceeded to an invasive diagnostic test. Elective coronary angiography without further revascularization was performed in 7 patients, with subsequent PCI in 8 patients and with CABG in 6 patients. Furthermore, one patient underwent a CABG in the setting of an acute myocardial infarction.

### Occurrence of MACE

The mean follow-up was 2.1 ± 0.6 years and for both treatment groups. During this period, a total of 19 patients (9 patients randomized to early invasive treatment and 10 patients randomized to continued pharmacological treatment) developed MACE. The estimated cumulative event rate was 11.4 percent (annual event rate 5.4%) for the patients randomized to early invasive treatment and 13.0 percent (annual event rate 6.3%) in the group assigned to continued pharmacological treatment (hazard ratio

<table>
<thead>
<tr>
<th>Invasive procedure</th>
<th>Early invasive n=79</th>
<th>Continued pharmacological n=77</th>
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</thead>
<tbody>
<tr>
<td>CAG, no revascularization</td>
<td>22 (28)</td>
<td>7 (9)</td>
</tr>
<tr>
<td>No abnormalities</td>
<td>13 (16)</td>
<td>5 (4)</td>
</tr>
<tr>
<td>Single-vessel disease</td>
<td>5 (9)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Multi-vessel disease</td>
<td>4# (4)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Repeat CAG, no revascularization</td>
<td>1 (1)</td>
<td>0 0</td>
</tr>
<tr>
<td>PCI</td>
<td>38 (47)</td>
<td>8 (10)</td>
</tr>
<tr>
<td>Single-vessel disease</td>
<td>20 (24)</td>
<td>6* (8)</td>
</tr>
<tr>
<td>Multi-vessel disease</td>
<td>18 (23)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Repeat PCI</td>
<td>1 (1)</td>
<td>0 0</td>
</tr>
<tr>
<td>CABG</td>
<td>19 (24)</td>
<td>7 (9)</td>
</tr>
<tr>
<td>Single-vessel disease</td>
<td>0 0</td>
<td>1* (1)</td>
</tr>
<tr>
<td>Multi-vessel disease</td>
<td>19** (24)</td>
<td>6 (8)</td>
</tr>
<tr>
<td>Repeat CABG</td>
<td>1 (1)</td>
<td>0 0</td>
</tr>
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Table 2. Data are presented as number (percentage). CAG = coronary angiography; PCI = percutaneous coronary intervention; CABG = coronary artery bypass grafting. # = one patient refused further revascularization. * = one patient presented with a significant left main stenosis. ** 4 patients presented with significant left main stenoses. All patients who underwent randomization driven PCI received acetylsalicylic-acid and low-molecular weight heparin according local protocol. Clopidogrel was given to all but one patient and was continued for a mean period of 7 months (1-12 months). Intra-venous GP IIb/IIIa receptor inhibitors were administered in 19 patients. In 3 patients balloon angioplasty was performed, 15 patients received one or more bare-metal stents and 18 received one or more drug-eluting stents.
0.89; 95 percent confidence interval 0.36-2.20; p=0.34) (table 3, figure 2). No significant differences were found for the separate components of MACE.

### Actual power of the study

The early termination led to a study size of 156 patients with a mean follow-up of 2.1 years. If this observed event rate would have persisted with 2 x 400 patients, the study would have been underpowered to detect the pre-specified relative reduction in event rate of 25% and more than 2000 patients per group would have been needed for sufficient power.
Discussion

This study was conducted to determine whether patients with diabetes mellitus type 2, mild anginal symptoms and documented myocardial ischemia would benefit from early invasive treatment compared to continued pharmacological treatment. No differences between the treatment strategies were observed, although the study was underpowered for this objective. Moreover, the MACE rate in both treatment groups was much lower than beforehand anticipated.

Actual event rate

The MERIDIAN trial was designed in the late nineties and the power calculation was based on two landmark trials published in that period. First of all, the study of Haffner et al. reported that patients with diabetes mellitus type 2 with and without a previous history of MI were at an averaged 2.2-3 fold higher risk of cardiovascular events compared with their non-diabetic counterparts. Secondly, the LIPID-trial, in which an observed 2-year risk for all-cause mortality, non-fatal MI and hospitalization for UAP of approximately 16% was reported in conservatively treated non-diabetic patients.

To our knowledge, the LIPID trial was the only study to define hospitalization for UAP as a study endpoint, with an average event rate of 8% in 2 years. These results led to the assumption that patients assigned to continued pharmacological treatment would have an estimated 2-year MACE rate of 2.5 x 16% = 40%. The observed MACE rate in the MERIDIAN trial was much lower than anticipated, ranging between 11-13% in 2.1 years (annual event rate of MACE of 5.4 and 6.3 for respectively patients assigned to early invasive treatment and continued pharmacological treatment).

The more recent published trials report similar numbers of approximately 4-9% annual event rate. These studies however did not include hospitalization for UAP in the combined endpoint. Therefore, even in comparison with these studies, the MACE rate found in our study of diabetic patients with only mild anginal symptoms with documented myocardial ischemia is rather low.

The different time periods in which the studies were conducted, can account in part for the decrease in observed event rate. The patient inclusion of the study of Haffner et al. and the LIPID trial was completed in respectively 1984 and 1992. Thus, these patients did not receive the today’s optimized medical treatment (i.e. lipid-lowering therapy and ACE-inhibition) and were less aware of the need of life style adjustment and risk. It has been stated that more than half of the decrease in cardiac mortality from 1981-2000 is related to reductions in major risk factors. Secondly, the decrease in event rate can be...
explained by differences in the populations studied. For instance, mortality-rates may vary substantially with ethnicity; Finnish patients are known to have a higher risk of CAD. Therefore, the high event rates found in the study of Haffner et al. might not be applicable to the general population. Furthermore, the LIPID trial was a secondary prevention trial; only patients with an MI or hospitalization for UAP in the past 3 years were eligible for inclusion.

Revascularization vs. Pharmacological therapy

Five randomized studies compared invasive therapy with medical therapy in patients with stable angina pectoris. Just recently, one of these studies, the MASS-II, presented a retrospective sub analysis of 190 type 2 diabetic patients with stable angina pectoris and documented myocardial ischemia. They described a significant benefit of coronary revascularization compared with medical treatment after the first year. However, they found an averaged hazard rate of 9.3 after 2 years; this rate lies much higher than the cumulative hazard rate of all-cause mortality as estimated with the Kaplan-Meier method in our medically treated diabetics (hazard rate of 2.6 at 2 years). Because the use of aspirin, lipid-lowering agents and anti-anginal medication was similar between the MASS-II and our study, this higher event rate is most likely related to the differences in the patient population. For instance in the MASS-II, patients were excluded from participation if they had a history of coronary revascularization. Furthermore patients were more symptomatic (CCS II-III/IV) in the presence of angiographically documented multivessel disease including a proximal lesion of >70%. Based on these randomized studies, the ACC/AHA stated in their guidelines that it seemed prudent to consider medical therapy for the initial management of most patients with anginal complaints (CCS I-II/IV). In the MERIDIAN trial, we speculated that this conclusion might not hold true for diabetic patients because of their higher risk of cardiac complications and their less pronounced presentation of anginal complaints. During a mean follow-up of 2.1 years, no differences between the treatment strategies were observed. Whether this observation will remain true in a larger, sufficiently powered population of diabetics will be answered by ongoing trials on treatment strategy in diabetic patients with stable angina pectoris. However, the annual MACE rate in these patients, under appropriate medical treatment, as found in our study of approximately 5-6% is much lower than anticipated. With an annual complication rate (including repeat revascularization) after coronary revascularization of at least 10%, one may question the potential benefit of early revascularization.
Conclusions
Approximately half of all type 2 diabetic patients with only mild anginal complaints have reversible myocardial perfusion defects on MPS. Those patients exhibit an annual event rate of MACE of ± 5-6%. Therefore it can be argued that these patients may not benefit from an invasive approach and subsequent revascularization. It is more reasonable to install life-style advices, continued pharmacological therapy and close surveillance of their symptoms.

Acknowledgments
We thank all the investigators and coordinators of the MERIDIAN trial, all nuclear physicians, and the medical and nursing staff in the recruitment and intervention centers who made the trial possible. The MERIDIAN trial was funded by The Dutch Heart Foundation and The Netherlands Organization for Health Research and Development.
Appendix A.

The following investigators and research coordinators, all in the Netherlands, enrolled patients in the MERIDIAN trial:
Amsterdam, Academic Medical Center - J. J. Piek;
Amsterdam, OLVG - G. J. Laarman;
Amsterdam VU Medical Center - G. Veen, J.G.F Bronzwaer;
Amsterdam, Slotervaart Hospital - C.A. de Groot, C.E. Schotborgh;
Amsterdam, St. Lucas-Andreas Hospital - A.R.Willems;
Amsterdam, Boven-IJ Hospital - A.L.M. Bakx;
Amstelveen, Amstelland Hospital - W.L. ten Holt;
Almere, Flevo Hospital - A.S.J.M. Sadee;
Apeldoorn, Gelre Hospitals - W.T.J. Jap Tjoen San;
Blaricum, Gooi-Noord Hospital - G. Hoedemaker;
Breda, Amphia Hospital - P.H.J.M. Dunselman;
Eindhoven, Catharina Hospital - R.H. Michels;
Groningen, Academic Medical Center - F.Zijlstra;
Haarlem, Kennemer Hospital, location EG - B. de Vlies, G. Kan;
Hengelo, Midden Twente Hospital - A. Derks;
Hoorn, Westfries Gasthuis Hospital - C.L. Janus, D.C.G. Basart;
Maastricht, Academic Medical Center - C. de Zwaan, F.W.H.M Bär;
The Hague, Medical Center Haaglanden - L.H. Savalle;
Reference List


(38) Soares PR, Hueb WA, Lemos PA et al. Coronary revascularization (surgical or percutaneous) decreases mortality after the first year in diabetic subjects but not in nondiabetic subjects with multivessel disease: an analysis from the Medicine, Angioplasty, or Surgery Study (MASS II). *Circulation* 2006 July 4;114(1 Suppl):I420-I424.
