Cardiac complications in type 2 diabetic patients with mild anginal symptoms and documented reversible myocardial perfusion defects

Results of the MERIDIAN trial

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Background/Objective. To compare early invasive treatment with continued pharmacological treatment in patients with diabetes mellitus type 2, mild anginal symptoms and documented myocardial ischaemia.
Methods. Patients with type 2 diabetes mellitus and mild anginal symptoms underwent myocardial perfusion scintigraphy (MPS). Patients with myocardial ischaemia were randomly assigned to early invasive or continued pharmacological treatment. All patients were followed for the occurrence of MACE (death, nonfatal myocardial infarction or hospitalisation for unstable angina pectoris).
Results. A total of 156 patients were randomised 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 with 10 of 77 patients randomised to continued pharmacological treatment, annual event rate 5.4 vs. 6.3%, hazard ratio 0.89, 95% CI 0.36 to 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.
Conclusion. Patients with diabetes mellitus type 2, mild anginal symptoms and documented myocardial ischaemia, under appropriate medical treatment, have a lower than anticipated annual event rate of MACE of ±5 to 6% which questions the beneficial effect of early revascularisation. (*Neth Heart J* 2006;14:409-16.)

Keywords: diabetes mellitus type 2, angina pectoris, randomised controlled trials, myocardial revascularisation, drug therapy

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To date, approximately 150 million people worldwide have documented diabetes mellitus and this number is expected to double before 2025.[1] Type 2 diabetes mellitus accounts for 90 to 95% of all cases. Patients with diabetes mellitus type 2 are at two- to fourfold higher risk of coronary artery disease (CAD) compared with their nondiabetic counterparts and manifest CAD earlier in life.[2] Moreover, patients with diabetes mellitus are more likely to have an atypical or less distinct expression of their anginal symptoms. Myocardial ischaemia is already present in ±20% of asymptomatic patients with type 2 diabetes mellitus.[3] When CAD does become overt, these patients have a

worse cardiovascular prognosis.[4-8] 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 symptoms.[9-15] 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.[16-18] 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 to their mild angina. The BARI trial suggested that patients with diabetes mellitus might benefit from bypass surgery, although this could not be confirmed in the BARI registry.[19,20] Since then, there has been an impressive reduction in cardiac complications, particularly in-stent restenosis and repeat revascularisations, after the introduction of GP IIb/IIIa receptor inhibitors, ADP antagonists and drug-eluting stents.[9,10,15,21,22]

We therefore conducted this prospective randomised multicentre MERIDIAN (**M**ulticentre Trial of Early **R**evascularisation **I**n Patients with **Di**abetes Mellitus Type 2 and Mild **An**ginal Symptoms) trial to determine whether patients with diabetes mellitus type 2, mild anginal symptoms and documented myocardial ischaemia would benefit from an optimised early invasive treatment (with drug-eluting stents and GP IIb/IIIa receptor inhibitors, when indicated) compared with an optimised continued pharmacological treatment.

Patients and Methods

The MERIDIAN trial was conducted in 20 hospitals in the Netherlands (see appendix 1 for the list of participating centres). Patients with mild, stable (≥2 months) symptoms of angina pectoris (CCS I-II/IV) and type 2 diabetes mellitus, without a short-term indication for coronary revascularisation, were eligible for randomisation in the MERIDIAN trial. Patients underwent myocardial perfusion scintigraphy (MPS) in order to document myocardial ischaemia. Patients with myocardial ischaemia were randomly assigned to an early invasive treatment or to a continued pharmacological treatment. Patients without myocardial ischaemia on MPS were treated according to routine clinical practice. The trial complied with the Declaration of Helsinki. The medical ethical committees of the participating centres 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 nonfasting >11.0 mmol/l; treatment with oral antidiabetic medication; treatment with oral antidiabetic 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 hypercholesterolaemia; 11) serious bronchial asthma; 12) plasma creatinine level >250 µmol/l; 13) body weight >120 kg; 14) coexistent 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 exercise stress testing (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.

Ischaemia detection

Stress and rest scintigraphy (with single-photon emission computed tomography (SPECT)) was performed with ^{99m}Tc labelled perfusion tracers (Tetrofosmin or sesta-MIBI) or Thallium-201, according to the guidelines of the American Society of Nuclear Cardiology.[23,24] Symptom limited exercise was the preferred stress modality. Experienced nuclear physicians analysed the images in 17 myocardial segments using a (semi)-quantitative five-point scoring system ranging from 0 (normal distribution) to four (absent distribution of radiopharmacon).[23] 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 ischaemia, were defined as SDS ≥3, located in one or more adjacent segments.

X-ECG was permitted for detection of ischaemia 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.[25] Significant ischaemia was defined as ST-segment depression of at least 1 mm, horizontal or down sloping, 80 ms from the J point in at least two adjacent leads.

Treatment strategy

Patients assigned to early invasive treatment underwent coronary angiography. The choice of revascularisation procedures was performed by a 'heart team' consisting of an interventional cardiologist and cardiothoracic surgeon. Revascularisation procedures were performed

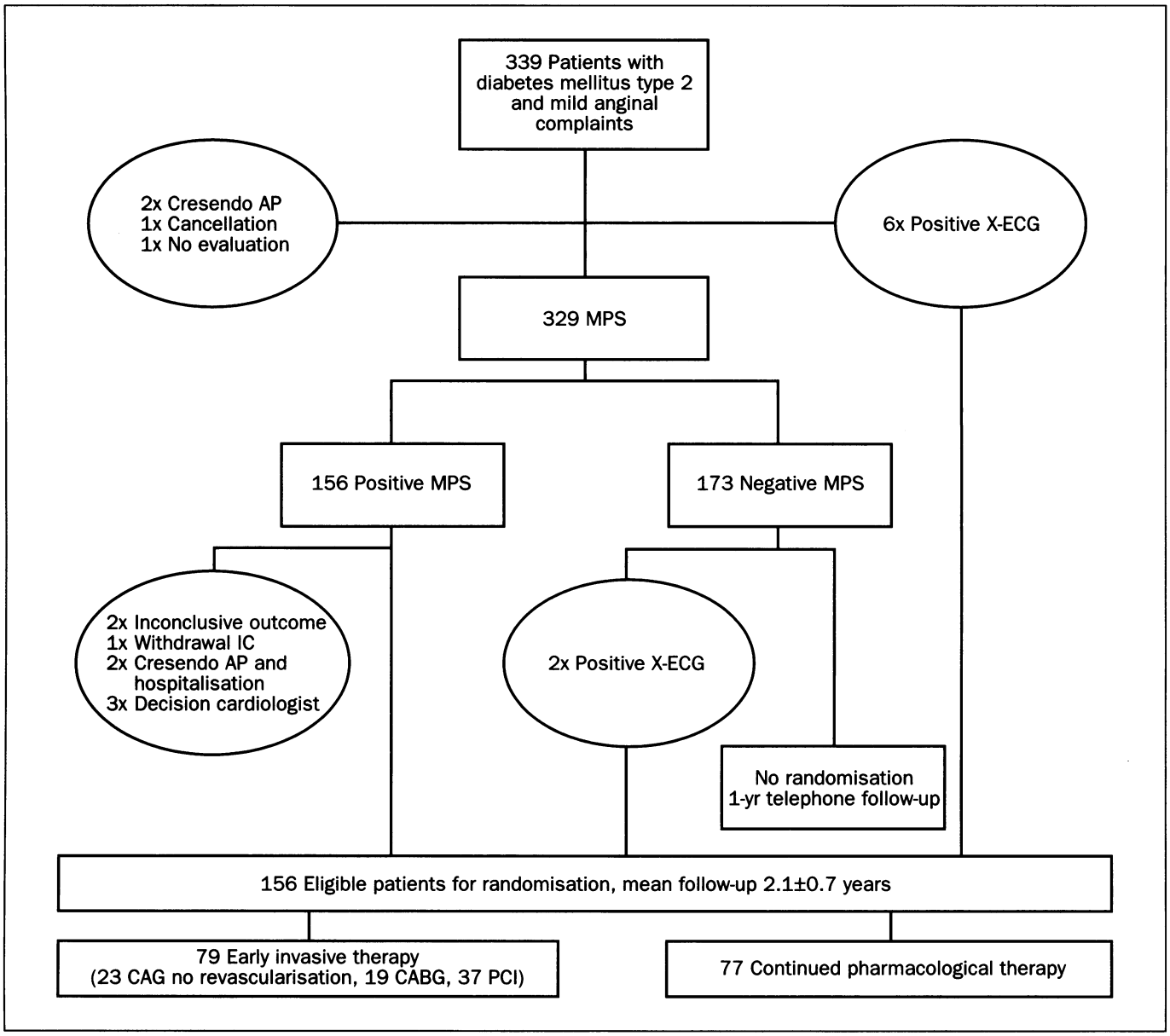

Figure 1. Study design MERIDIAN trial. AP=angina pectoris, MPS=myocardial perfusion scintigraphy, X-ECG=exercise stress testing, IC=informed consent, CAG=coronary angiography; PCI=percutaneous coronary intervention, CABG=coronary artery bypass grafting.

within two months after randomisation. 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 one month after stenting and at least six months after placement of drug-eluting stents.

In patients assigned to continued pharmacological treatment, coronary angiography was only performed when anginal symptoms progressed to a level which could not sufficiently be controlled by medical therapy alone. If not contraindicated, all patients received aspirin, high-dose lipid-lowering therapy and ACE inhibition.

Follow-up

Randomised patients visited the outpatient clinic two months after randomisation and at six-month intervals until termination of follow-up on 1 January 2006. All patients were followed for the occurrence of major adverse coronary events (MACE), defined as a composite of all-cause mortality, nonfatal MI, or hospitalisation for UAP. MI was defined as an elevation in the CK-MB level above twice the upper limit of normal. MI in the setting of CABG required the documentation of new Q waves on the ECG.

Early termination of the study

On 8 July 2004, one of the financial sponsors, the Netherlands Organisation 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 χ^2 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 endpoint, involving all randomised 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 on the assumption that the expected event rate in the pharmacologically treated group would be at least 40% within two years. With 400 patients in each treatment arm, the study would have had 85% power (two-sided) to detect a relative reduction in event rate of 25% (i.e., from 40 to 30%; RR = 0.75). Furthermore, it was assumed that 1200 patients needed to undergo MPS screening to randomise 800 patients with a positive MPS.

Results

Between 1 October 2002 and 8 July 2004, a total of 339 patients were screened in 20 participating centres. Ischaemia detection was performed in 335 patients: 327 underwent MPS, two patients underwent MPS + X-ECG and six underwent only X-ECG. In total 156 (47%) patients were randomised; 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/m^2), the mean duration of diabetes mellitus was eight years, and approximately 35% needed insulin therapy. The use of lipid-lowering therapy, aspirin and β-blockade at baseline was high in both groups.

Table 1. Baseline characteristics.

	Early invasive (n=79)	Continued pharmacological (n=77)
Clinical characteristics		
Male gender	59 (75)	57 (74)
Age (years)	65 (8)	65 (9)
CCS II/IV	37 (47)	38 (49)
BMI (kg/m^2)	28.9 (3.9)	29.6 (4.8)
Drug therapy		
Aspirin	72 (91)	63 (82)
Statin	53 (67)	57 (74)
ACE inhibition	29 (37)	31 (40)
Beta blockade	62 (78)	49 (64)
Long-acting nitrates	30 (38)	41 (53)
Calcium antagonists	38 (48)	39 (51)
Insulin	32 (41)	24 (31)
Risk factors		
Hypertension	45 (57)	35 (45)
Smoking	17 (22)	13 (17)
Previous smoker	41 (52)	42 (55)
Family history	25 (32)	25 (32)
Hypercholesterolaemia	52 (66)	48 (62)
Medical history		
Previous MI	27 (34)	25 (32)
Previous PCI	22 (28)	12 (16)
Previous CABG	10 (13)	16 (21)
Duration of DM (years)	8.6 (7)	7.2 (6)
Diagnostic tests		
ECG abnormalities	45 (57)	45 (58)
MPS SDS<3	1 (1)	1 (1)
MPS SDS 3-8	43 (56)	42 (58)
MPS SDS≥8	33 (43)	30 (41)
Positive exercise ECG	3 (4)	5 (7)

CCS=Canadian Cardiovascular Society, BMI=body mass index, MI=myocardial infarction, PCI=percutaneous coronary intervention, CABG=coronary artery bypass grafting, DM=diabetes mellitus, MPS=myocardial perfusion scintigraphy, SDS=summed difference score.

Treatment and follow-up

Table 2 shows the treatment and extent of CAD. All patients assigned to early invasive treatment underwent CAG. No, or only non-significant coronary abnormalities were detected in 18 (23%) patients. In three patients (two patients with single-vessel disease and one patient with multi-vessel disease) no intervention was possible and one patient refused further treatment. Of the remaining 57 patients, 38 were referred for PCI and 19 for CABG. In one PCI procedure, the guide

Table 2. Invasive procedures and extent of coronary artery disease

	Early invasive (n=79)	Continued pharmacological (n=77)
Invasive procedure		
CAG, no revascularisation	22 (28)	7 (9)
- No abnormalities	13 (16)	5 (4)
- Single-vessel disease	5 (9)	1 (1)
- Multi-vessel disease	4# (4)	1 (1)
Repeat CAG, no revascularisation	1 (1)	0 (0)
PCI	38 (47)	8 (10)
- Single-vessel disease	20 (24)	6* (8)
- Multi-vessel disease	18 (23)	2 (3)
Repeat PCI	1 (1)	0 (0)
CABG	19 (24)	7 (9)
- Single-vessel disease	0 (0)	1* (1)
- Multi-vessel disease	19** (24)	6 (8)
Repeat CABG	1 (1)	0 (0)

Data are presented as number (percentage). CAG=coronary angiography, PCI= percutaneous coronary intervention, CABG=coronary artery bypass grafting. #=one patient refused further revascularisation. *=one patient presented with a significant left main stenosis. **4 patients presented with significant left main stenoses. All patients who underwent randomisation driven PCI received acetylsalicylic acid and low-molecular-weight heparin according to the local protocol. Clopidogrel was given to all but one patient and was continued for a mean period of 7 months (1-12 months). Intravenous 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.

wire could not cross the stenosis and the procedure was terminated prematurely. All the other PCIs were procedurally successful.

Complications of the PCI procedure occurred in four patients; one procedure-related MI (CK-MB ≈ 2x the upper limit of normal), one case of transient vision problems and two prolonged hospitalisations because of haematomas at the puncture site. Of patients randomised to CABG, one patient developed an ischaemic cerebrovascular accident and two patients atrial fibrillation.

In 22 (29%) of the patients randomised to continued pharmacological treatment, the treating cardiologist proceeded to an invasive diagnostic test. Elective coronary angiography without further revascularisation was performed in seven patients, with subsequent PCI in eight patients and with CABG in six 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 for both treatment groups. During this period, a total of 19 patients (nine patients randomised to early invasive treatment and ten patients randomised to continued pharmacological treatment) developed MACE. The estimated cumulative event rate was 11.4% (annual event rate 5.4%) for the patients randomised to early invasive treatment and 13.0% (annual event rate 6.3%) in the group assigned to continued pharmacological treatment (hazard ratio 0.89; 95% confidence interval 0.36 to 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 population of 156 patients with a mean follow-up of 2.1 years. If this observed event rate had persisted with 2 x 400 patients, the study would have been underpowered to detect the prespecified relative reduction in event rate of 25% and more than 2000 patients per group would have be needed for sufficient power.

Discussion

This study was conducted to determine whether patients with diabetes mellitus type 2, mild anginal symptoms and documented myocardial ischaemia would benefit from early invasive treatment compared

Table 3. Cumulative rates of the composite endpoint and its components during follow-up and by presenting features.

	Early invasive (n=79)	Continued pharmacological (n=77)	Hazard ratio (95% CI)	p value
Outcome (n, %)				
MACE	9 (5.4)	10 (6.3)	0.89 (0.36-2.20)	0.34
- All-cause mortality	8 (4.7)	3 (1.8)	2.83 (0.75-10.71)	0.8
- Cardiac mortality	5 (2.2)	2 (1.2)	2.52 (0.49-12.98)	0.13
- Nonfatal MI	3 (1.8)	4 (2.5)	0.73 (0.16-3.26)	0.27
- Hospitalisation for UAP	1 (0.6)	3 (1.8)	0.33 (0.03-3.17)	0.68

Data presented as number of patients (annual event rate). CI=confidence interval. Estimated event rates and hazard ratios of the composite endpoint (MACE) include the first event (all-cause mortality, nonfatal myocardial infarction (MI), or hospitalisation for unstable angina pectoris (UAP)) for each patient during follow-up. The composite events include all such events.

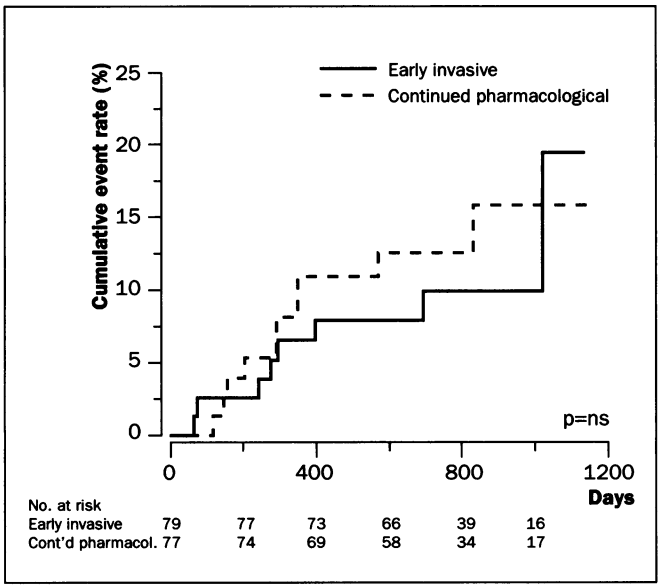

Figure 2. Kaplan-Meier estimates of the cumulative rate of MACE as a function of treatment strategy. Kaplan-Meier cumulative event rate estimates the occurrence of MACE (all-cause mortality, nonfatal myocardial infarction or hospitalisation for unstable angina pectoris) as a function of treatment strategy. Annual event rate of patients randomised to early invasive treatment 5.4 vs. 6.3 annual event rate in patients randomised to continued pharmacological treatment, p=0.34.

with 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 anticipated beforehand.

Actual event rate

The MERIDIAN trial was designed in the late 1990s and the power calculation was based on two landmark trials published in that period. First of all, the study by Haffner et al. reported that patients with diabetes mellitus type 2 with and without a previous history of MI were at a mean 2.2 to 3 fold higher risk of cardiovascular events compared with their nondiabetic counterparts.[26] Secondly, the LIPID trial, in which an observed two-year risk for all-cause mortality, nonfatal MI and hospitalisation for UAP of approximately 16% was reported in conservatively treated nondiabetic patients.[27] To our knowledge, the LIPID trial was the only study to define hospitalisation for UAP as a study endpoint, with an average event rate of 8% in two years. These results led to the assumption that patients assigned to continued pharmacological treatment would have an estimated two-year MACE rate of 2.5 × 16% = 40%. The observed MACE rate in the MERIDIAN trial was much lower than anticipated, ranging from 11 to 13% in 2.1 years (annual event rate of MACE of 5.4 and 6.3 for patients assigned to early invasive treatment and continued pharmacological treatment, respectively).

The more recent published trials report similar numbers of approximately 4 to 9% annual event rate.[13,28-31] These studies, however, did not include hospitalisation 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 ischaemia 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 by Haffner et al. and the LIPID trial was completed in 1984 and 1992, respectively. Thus, these patients did not receive today's optimised medical treatment (i.e. lipid-lowering therapy and ACE inhibition) and were less aware of the need for lifestyle adjustment and risk. It has been stated that more than half of the decrease in cardiac mortality from 1981 to 2000 is related to reductions in major risk factors.[32] 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.[33] Therefore, the high event rates found in the study by 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 hospitalisation for UAP in the past three years were eligible for inclusion.

Revascularisation vs. pharmacological therapy

Five randomised studies compared invasive therapy with medical therapy in patients with stable angina pectoris.[17,34-36,37] Just recently, one of these studies, the MASS-II, presented a retrospective subanalysis of 190 type 2 diabetic patients with stable angina pectoris and documented myocardial ischaemia.[38] They described a significant benefit for coronary revascularisation compared with medical treatment after the first year. However, they found an average hazard rate of 9.3 after two years; this rate is 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 two years). Because the use of aspirin, lipid-lowering agents and antianginal 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 revascularisation. 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 randomised 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 symptoms (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 com-

plications 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.[39,40]

However, the annual MACE rate in these patients, under appropriate medical treatment, as found in our study of approximately 5 to 6%, is much lower than anticipated. With an annual complication rate (including repeat revascularisation) after coronary revascularisation of at least 10%, one may question the potential benefit of early revascularisation.

Conclusion

Approximately half of all type 2 diabetic patients with only mild anginal symptoms have reversible myocardial perfusion defects on MPS. Those patients exhibit an annual event rate of MACE of ± 5 to 6%. Therefore it can be argued that these patients may not benefit from an invasive approach and subsequent revascularisation. It is more reasonable to introduce lifestyle advice, continued pharmacological therapy and close surveillance of their symptoms.

Acknowledgments

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Appendix 1.

The following investigators and research coordinators, all in the Netherlands, enrolled patients in the MERIDIAN trial:
Amsterdam, Academic Medical Centre - J.J. Piek
Amsterdam, Onze Lieve Vrouwe Gasthuis - G.J. Laarman
Amsterdam, VU University Medical Centre - 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 Centre Groningen - F. Zijlstra
Haarlem, Kennemer Hospital - B. de Vlies, G. Kan
Hengelo, Midden Twente Hospital - A. Derks
Hoorn, Westfries Gasthuis Hospital - C.L. Janus, D.C.G. Basart
Maastricht, University Hospital - C. de Zwaan, F.W.H.M.Bär
The Hague, Medical Centre Haaglanden - L.H. Savalle
Zwolle, Isala Clinics, Weezenlanden and Sophia Hospital - H. Suryapranata, A.H.E.M. Maas