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Clinical research

Risks and benefits of optimised medical and revascularisation therapy in elderly patients with angina — on-treatment analysis of the TIME trial

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Aim To assess treatment effects of optimised medical therapy and PCI or CABG surgery on one-year outcome in patients $\geqslant$75 years old with chronic angina.
Methods and Results On-treatment analysis of the TIME data: all re-vascularised patients (REVASC $n = 174$: 112 randomised to re-vascularisation and 62 to drugs with late re-vascularisation) were compared to all patients on continued drug therapy (MED $n = 127$: 86 randomised to drugs and 41 to re-vascularisation only). Baseline characteristics of both groups were similar (age 80 ± 4 years). Risk of death at one year (adjusted hazard ratio (HR) = 1.31; 95%-CI: 0.58–2.99; $P = 0.52$) and of death/infarction (adjusted hazard ratio = 1.77; 95%-CI 0.91–3.41; $P = 0.09$) were comparable between REVASC and MED patients. Furthermore, the risk of death within 30 days was even slightly lower among REVASC patients (unadjusted hazard ratio = 0.73; 95%-CI: 0.21–2.53; $P = 0.98$). Overall, REVASC patients had greater improvements in symptoms and well-being than MED patients ($P < 0.01$). Surgical patients had similar mortality rates as angioplasty patients, but they also had greater symptomatic improvements ($P < 0.01$).
Conclusion Treated medically, elderly patients with chronic angina have a similarly high 30-day and one-year mortality as patients of the same age being re-vascularised; however, they can expect lower improvements in symptoms and well being.

Introduction

Mortality and complications of coronary artery bypass grafting (CABG) surgery and percutaneous coronary in-

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terventions (PCI) are increased in elderly patients with chronic coronary artery disease (CAD) as compared to those in younger patients.[1–6] However, little is known about risks and complications of optimised drug therapy in patients of the same advanced age which may also be increased. In general, there is a marked lack of data on the management of elderly patients with chronic CAD since they have mostly been excluded from randomised clinical trials.[7] Therefore, the risk/benefit ratio of CAD therapy may differ importantly from that of younger patients and their number asking for medical advice is increasing rapidly.

The recent Trial of Invasive vs. Medical therapy in Elderly patients with Chronic Angina (TIME) was the first prospective randomised treatment trial in elderly patients with chronic symptomatic CAD.[8] It showed that these patients had a greater benefit from an invasive strategy as compared to optimised drug therapy regarding symptom relief, improvement in quality of life (QoL) and reduction in major adverse clinical events (MACE) after 6 months. In this study, patients could be re-vascularised either by PCI or by CABG surgery. An early revascularisation hazard was observed, although the mortality difference between treatment groups was not significant (8.5% in patients assigned to the invasive, vs. 4.1% in those assigned to the optimised, medical strategy, $P = 0.15$). After one year, outcome in MACE as well as angina severity and measures of QoL were very similar based on the intention-to-treat analysis.[9] However, since patients were included and randomised based on their clinical presentation as in everyday practice and not based on angiographic findings, cross-overs occurred between both strategies. In fact, 46% of medical treatment assigned TIME patients had to be re-vascularised during the one-year follow-up due to medically uncontrolled symptoms, whereas only 73% of all invasive management assigned patients were actually re-vascularised, making an assessment of the true effects of medical and revascularisation strategies difficult. It was therefore the aim of the present prespecified "on-treatment" analysis of the TIME data to more fully describe the effects of optimised medical therapy and revascularisation on angina severity, measures of QoL and MACE in patients of the same advanced age.

Methods

Details of the TIME study have been reported previously.[8] In short, in this prospective multi-centre Swiss trial, patients aged 75 years or older with chronic angina of at least Canadian Cardiac Society (CCS) class II despite at least two anti-anginal drugs, were randomised to an optimised medical therapy or an invasive strategy with coronary angiography followed by revascularisation (PCI or CABG surgery) if feasible. The primary end-point was QoL-assessed by standardised questionnaires and the presence or absence of MACE (all death, non-fatal myocardial infarction or hospitalisation for uncontrolled symptoms/acute coronary syndrome with or without need for revascularisation) after 6 months. Myocardial infarction was a clinical diagnosis based on chest pain, typical ECG changes and enzyme elevations apart from the acute intervention. Patients were not included if they had an acute myocardial infarction within the previous 10 days, concomitant valvular or other heart disease, pre-dominant congestive heart failure or gave no consent for a possible revascularisation procedure. After collection of baseline data, QoL was assessed by self-administered questionnaires containing the Short Form 36 (SF36),[10] the Duke Activity Status Index (DASI)[11] and the Rose angina questionnaire.[12] The study was approved by the Ethics Committee of the Swiss Academy of Medical Sciences and by the local Ethics Committee of each of the 14 Swiss centres. Patients gave written informed consent. After both 6 months and one year, all surviving patients were seen again and underwent the same clinical, symptom and QoL assessments as at baseline.

For this "on-treatment" analysis, all patients with revascularisation attempted during the one-year observation period (REVASC) were compared to all patients with medical therapy alone (MED) with regard to symptoms, QoL and MACE up to one year after randomisation. Thus, for this analysis, hospitalisation for medically uncontrolled symptoms leading to revascularisation was not a major event but counted as index revascularisation and all events in REVASC patients having occurred before the index revascularisation were disregarded; accordingly, the day of revascularisation was day one for these patients. To assess the "treatment hazard" and to put it into perspective, the 30-day mortality on treatment received was determined and compared. To analyse the effect of late revascularisation in patients assigned to medical treatment on both angina severity and QoL, a special on-treatment analysis was performed in this subgroup assigned to medical treatment.

Patient details

The 174 patients in whom revascularisation was attempted (REVASC) were compared to all 123 patients who received medical therapy alone (MED) (Fig. 1). The REVASC group consisted of 112 patients assigned to PCI or CABG surgery (109 revascularised early as per protocol and three late after initial refusal) and 62 patients initially randomised to optimal medical therapy but who needed revascularisation due to refractory symptoms during follow-up. Seventy-nine percent of these revascularisations were performed in the first 6 months of the study. The MED group consisted of 86 patients who were initially randomised to medical therapy and who stayed on that therapy and also 41 patients randomised to invasive management but in whom revascularisation was not attempted because they had no significant CAD $(n = 11)$, revascularisation did not seem possible $(n = 21)$ or was refused by the patients $(n = 8)$; one patient died before revascularisation.

Statistical analysis

For this "on-treatment" analysis, quantitative and score variables were summarised in terms of mean values and standard deviations. The comparison between groups was performed by the Wilcoxon–Mann–Whitney U test. For the comparison of categorical values between groups, Fisher's exact test and the χ^2 test were used. Changes in quantitative variables within groups were assessed with the paired t-test, which was also used to assess changes in score variables within groups. Time-to-event variables with censored values were described by

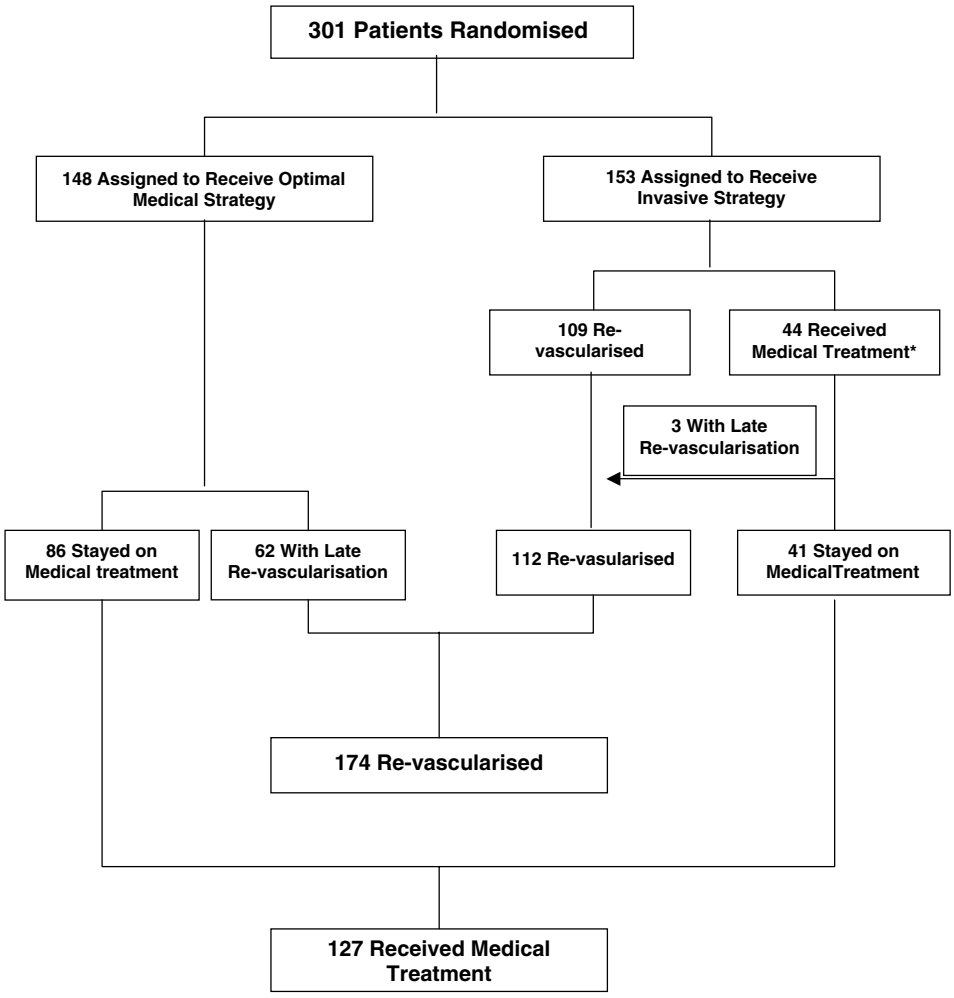

Fig. 1 Flow chart of patients for the on-treatment analysis. *Patients assigned to invasive treatment without re-vascularisation at baseline included: no catheterisation ($n = 7$); re-vascularisation not feasible ($n = 19$); re-vascularisation refused ($n = 7$); no significant CAD ($n = 11$). Note that 62/148 patients assigned to medical treatment and 3/44 patients assigned to invasive treatment without re-vascularisation at baseline were re-vascularised during follow-up for refractory symptoms.

Kaplan–Meier statistics and their inter-group differences were assessed by the log rank test or by means of proportional hazard models adjusting for baseline differences in sex, age, CCS-class and heart rate. The proportional hazard assumption was examined by including an interaction term between the group indicator variable and time. QoL questionnaires were analysed according to the specific criteria described previously.[5] A priori differences with a $P < 0.05$ were considered statistically significant. However, if statements about all six primary end-points (i.e., CCS-class, Rose-score, Duke activity score, SF36-general health, SF36-vitality and number of anti-anginal drugs) were made, individual *P*-values were multiplied by 6 (Bonferroni correction). SAS statistical software version 8.2 (SAS Institute Inc., Cary, NC, USA) was used for all analyses.

Results

Baseline characteristics and treatments performed

The baseline characteristics of MED and REVASC patients were similar (Table 1) with a mean age of 80 years and a high proportion of women in each group. There were no significant differences in risk factors, history of CAD, non-invasively determined left ventricular ejection fraction or rate of co-morbidities and the same was true for angina severity and measures of QoL. Eighty percent of MED patients received at least one additional anti-ischaemic drug and in 55% drug dosages were increased. In the REVASC group, 115 patients (66%) had PCI (86% at least one stent) and 59 patients (34%) had CABG surgery (83% at least one arterial conduit). In addition, all patients were advised regarding lipid lowering and risk factor modification.

Effect of therapy on symptoms and QoL

The effects of the two anti-anginal treatments on angina severity and measures of QoL are shown in Fig. 2. With the exception of vitality, these parameters were significantly less improved by MED therapy than by REVASC therapy, despite the fact that there was also a significant treatment effect in this group vs. baseline. In

Table 1 Baseline characteristics

	MED ($n = 127$)	REVASC ($n = 174$)	P
Age (years)	80.3 ± 3.7	79.6 ± 3.5	0.09
Women (%)	48	40	0.18
History of AMI (%)	44	49	0.41
History of PCI/CABG (%)	18	16	0.63
$\geqslant$2 risk factors (%)	54	58	0.52
$\geqslant$2 co-morbidities (%)	32	23	0.11
Angina CCS class	3.0 ± 0.9	3.1 ± 0.8	0.13
Anti-anginal drugs (n; mean $\pm$ SD)	2.5 ± 0.6	2.5 ± 0.7	0.92
LVEF (%; mean $\pm$ SD)	52.6 ± 11.8	52.6 ± 13.0	0.99
General Health (SF 36)[a]	56.4 ± 16.9	52.5 ± 18.3	0.06
Vitality (SF 36)[a]	48.5 ± 20.9	44.7 ± 21.6	0.14
Duke Activity Status Index[b]	13.6 ± 11.2	12.2 ± 11.4	0.20

AMI, acute myocardial infarction; CABG, coronary artery bypass grafting; CCS, Canadian Cardiac Society; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention.
[a]SF 36 score from 0 to 100: higher scores indicating a more favourable status.
[b]Score on a scale from 0 to 58: higher scores indicating a more favourable status.

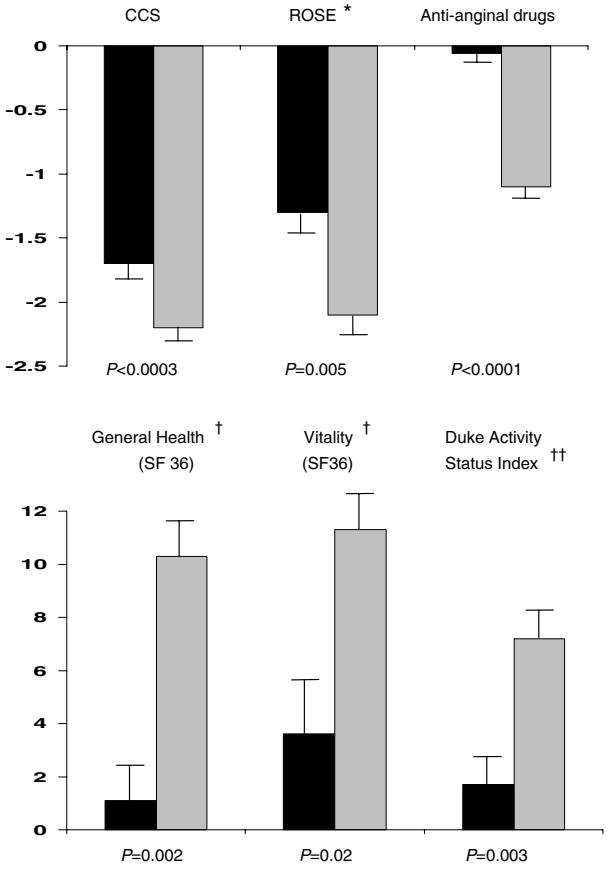

Fig. 2 Mean change ($\pm$1 SD) from baseline in angina severity, measures in QoL and anti-anginal drug use over time in both treatment groups (MEDICAL: grey bars, REVASC: black bars; P-values relate to differences in groups). *ROSE Score, Canadian Cardiac Society (CCS) class 4 indicates pain at rest and 0 indicates no pain. †SF 36 score from 0 to 100, with higher score indicating a more favourable status. ‡ Score on a scale from 0 to 58, with higher scores indicating a more favourable status. *Note*. CCS class, ROSE Score and anti-anginal drug use were not normally distributed basd on the inclusion criteria for this study; therefore P-values may be over-estimated.

accordance with these findings, MED patients needed more anti-anginal drugs after one year than REVASC patients (2.4 ± 0.11 vs. 1.4 ± 0.08; $P < 0.00001$).

Effect of therapy on MACE

Observed one-year mortality risks were comparable between REVASC and MED patients (adjusted HR = 1.31; 95%-CI: 0.58–2.99; $P = 0.52$). The observed cardiac mortality risk was the same in both groups (adjusted hazard ratio = 1.02; 95%-CI: 0.41–2.51; $P = 0.98$). In addition, the 30-day mortality index of "treatment hazard" was not significantly different between the two treatment groups (HR = 0.73; 95%-CI: 0.21–2.53; $P = 0.62$). Observed risks of MACE were very similar between the two groups (adjusted HR = 1.10; 95%-CI: 0.69–1.76; $P = 0.69$). Only the observed risk of death and/or myocardial infarction showed a larger difference between REVASC and MED patients (adjusted HR = 1.77; 95%-CI: 0.91–3.41; $P = 0.09$). The survival curves of MED and REVASC patients are illustrated in Fig. 3 and showed no relevant differences over the one-year observation period (see Table 2).

Comparison between patients re-vascularised by PCI and by CABG surgery

The choice of revascularisation mode, PCI or CABG surgery, was left to the discretion of local investigators/operators and therefore was done based on an assessment of "suitable anatomy" vs. "expected interventional risk". Accordingly, the 34% of patients treated by CABG surgery differed significantly from the 66% treated by PCI (Table 3); patients with PCI had less multi-vessel disease whereas left ventricular ejection was not significantly different from that of patients with CABG surgery. Patients selected for PCI had a similar 30-day and one-year mortality rate as patients with CABG surgery: 30 day early mortality: HR = 0.76 (95%-CI: 0.13–4.56; $P = 0.77$); mortality up to 12 month follow-up: adjusted HR = 0.97 (95%-CI: 0.31–3.05; $P = 0.96$) and there was no significant difference in the risk of death or myocardial infarction after PCI as compared to CABG surgery (adjusted HR = 1.42; 95%-CI: 0.58–3.49; $P = 0.44$). We noted a surprisingly low repeat target vessel revascularisation

rate in PCI patients of only 8%. However, angina severity showed a significantly stronger decrease, and the vitality score a significantly stronger increase, after CABG surgery than after PCI.

Comparison according to completeness of revascularisation

We analysed whether the major epicardial vessels were effectively re-vascularised (open artery without $\geqslant$75% obstruction after successful PCI or a successfully grafted artery) in order to assess whether completeness of revascularisation was responsible for the difference in symptomatic and QoL status. By this definition, complete revascularisation was achieved in 42% of patients with PCI (48/115) and in 68% of patients with CABG surgery (40/59; $P < 0.01$). Patients with incomplete revascularisation showed a similar 30-day and one-year mortality rate as patients with complete revascularisation: 30-day early mortality: HR = 0.69 (95%-CI: 0.11–4.11; $P = 0.68$); mortality up to 12-month follow-up: adjusted HR = 0.99 (95%-CI : 0.34–2.87; $P = 0.99$). In addition, the risk of deaths or myocardial infarctions after revascularisation was not significantly higher among patients with incomplete revascularisation than among those with complete revascularisation (HR = 1.74; 95%-CI : 0.78–3.86; $P = 0.18$). As expected patients with full revascularisation had a markedly higher decrease in anti-anginal drugs after one year ($P = 0.04$). However, there were no significant differences in angina severity and QoL between completely and incompletely re-vascularised patients after one year.

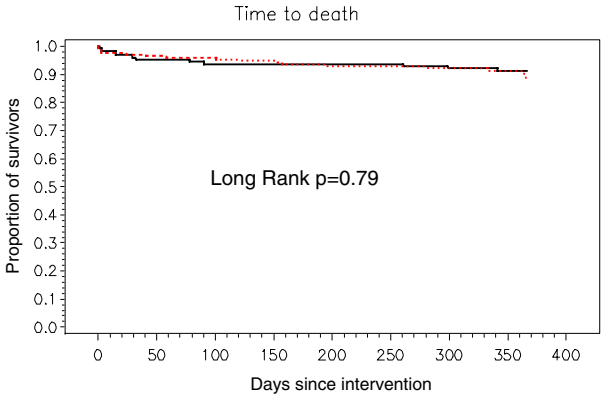

Fig. 3 Time-to-death for both treatment groups. Solid line: optimal medical treatment, dotted line: re-vascularised patients.

On-treatment findings in medical strategy-assigned TIME patients

The intention-to-treat analysis of the TIME data showed an early intervention hazard with the invasive strategy[8] and a late benefit in symptom relief/improvement in

Table 2 Effects of therapy on MACE/mortality hazard ratios (and 95%-CI) for different risks between re-vascularised patients (REVASC, $n = 174$) and medically treated patients (MED, $n = 127$)

	Hazard ratio REVASC vs. MED (unadjusted)	*P*-value[a]	Hazard ratio REVASC vs. MED (adjusted[b])	*P*-value[b]
Death	1.11 (0.51–2.43)	0.79	1.31 (0.58–2.99)	0.52
Cardiac death	0.85 (0.36–2.02)	0.72	1.02 (0.41–2.51)	0.98
Death up to 30 days	0.73 (0.21–2.53)	0.62	–[c]	
Death and/or MI	1.57 (0.84–2.95)	0.15	1.77 (0.91–3.41)	0.09
MACE	0.94 (0.6–1.47)	0.78	1.10 (0.69–1.76)	0.69

MACE, major adverse cardiac events; MI, myocardial Infarction.
[a] From log rank test.
[b] From multiple Cox regression model controlling for sex, age, CCS-class and heart rate at rest.
[c] Event numbers were too small for a multiple model.

Table 3 PCI vs. CABG: baseline characteristics

	PCI ($n = 115$)	CABG ($n = 59$)	*P*
Age (years)	79.6 ± 3.6	79.4 ± 3.4	0.72
Women (%)	38	44	0.46
History of AMI (%)	50	47	0.79
Hypertension (%)	56	76	0.008
History of PCI/CABG (%)	21	5	0.007
$\geqslant$ 2 risk factors (%)	57	59	0.81
$\geqslant$ 2 co-morbidities (%)	23	22	0.83
Multi-vessel disease (%)	81	98	0.0007
Complete re-vascularisation (%)	42	68	0.0013
Anti-anginal drugs (*n*; mean ± SD)	2.5 ± 0.7	2.5 ± 0.7	0.58
LVEF (%; mean ± SD)	51.6 ± 13.4	55.4 ± 11.4	0.24

Abbreviations as in Table 1.

QoL with the optimised medical strategy, such that after one year no significant differences in outcome between the two groups remained.[9] In this regard, the on-treatment analysis provided important insights. The relatively high 6-month mortality rate of 8.5% in patients assigned to invasive treatment (compared to 4.1% in patients assigned to medical treatment, $P = 0.15$) was actually 7.3% in 109 invasive patients receiving and 11.4% in 44 invasive patients not receiving, revascularisation as per protocol. Since all 11 invasive patients without significant CAD survived, the 6-month mortality of 33 non-re-vascularised invasive patients with CAD was 15.2% — double that of re-vascularised patients ($P = 0.18$). The late symptomatic and QoL benefit of patients assigned to medical treatment was exclusively found in patients with late revascularisation, whereas patients assigned to continual medical treatment remained more symptomatic with a lower level of well-being despite more drugs.

Discussion

In this prospective on-treatment analysis of the first randomised trial comparing an invasive, with an optimal medical, strategy in elderly patients with chronic symptomatic CAD, MED treated patients had a similarly high one-year mortality rate as REVASC patients of the same advanced age. This indicates that, compared to younger patients with CAD as usually studied, mortality is increased in these elderly CAD patients whatever treatment they received. In fact, the early intervention hazard observed previously[8] was due to the high mortality of patients assigned to invasive treatment not being re-vascularised rather than because of the intervention. REVASC therapy induced a greater relief from angina and a greater improvement in measures of QoL, a finding which also explains the late benefit observed in patients assigned to medical treatment with intention-to-treat.[9] Patients selected for PCI had a similar intervention mortality and a similar one-year death/non-fatal myocardial infarction rate to patients undergoing CABG surgery. However, CABG gave greater symptomatic relief and improvement in QoL after one year and was also associated with a higher rate of complete revascularisation. Obviously the choice of the revascularisation mode by operators led to a reasonable clinical outcome, since the overall effect of REVASC therapy regarding symptom relief and QoL assessment was significantly better than after MED therapy.

Comparison of revascularisation vs. medical therapy

In younger patients, the randomised CABG surgery, compared with medical therapy, studies have shown a survival advantage of surgery in high risk patient groups.[13–15] These studies also showed an improvement in symptomatic status and QoL, as noted in the TIME study for elderly patients. The Angioplasty Compared to Medical Therapy (ACME),[16] the Randomised Intervention Treatment of Angina 2 (RITA-2),[17] and the Atorvastatin Versus Revascularisation Treatment (AVERT)[18] studies were the only true prospective comparisons between PCI and medical therapy, related to younger patients with single or double vessel disease. They demonstrated an improvement in the severity of angina after PCI, although this was at the cost of an excess mortality and myocardial infarction rate in RITA-2.[19] The TIME study extended these findings for the first time to an elderly patient population and, importantly, demonstrated an increased risk also in elderly CAD patients on optimised drug therapy in the present on-treatment analysis. A recently published retrospective analysis of $>$6000 elderly patients indirectly supported these findings by showing that elderly patients have greater absolute risk reductions associated with surgical or percutaneous revascularisations than younger patients do.[20]

Comparison of PCI with CABG surgery

A meta-analysis of studies comparing PCI to CABG surgery[21] showed a similar long-term mortality and re-infarction rate for both procedures but more repeated interventions and a poorer outcome regarding angina relief after PCI. Our findings in elderly patients are in accordance with these results. Restenosis was the main cause for the higher rate of repeat interventions; this may soon be minimised if the first results of drug-coated stents[22] are further substantiated. As noted in the present analysis, completeness of revascularisation could not fully explain this difference in unselected elderly multivessel disease patients either, partly because surgeons achieved full revascularisation in only two-third of these patients. In younger patients it has been shown that complete revascularisation by angioplasty can improve outcome.[23]

Limitations of this study

The present pre-defined "on-treatment" analysis of a prospective randomised trial has its immanent limitations as to patient selection. Thus, the potential for bias is substantial because both treatment groups contain failures of the other treatment, i.e., failure of medical treatment among REVASC or the impossibility, or lack of necessity, to perform revascularisation among MED patients. In addition, the patient number is relatively low. This study, however, complements the primary intention-to-treat analysis and provides important clues for its interpretation and gives the first prospective trial data in elderly patients with chronic CAD. Finally, the optimised medical therapy was that which could be maximally achieved and tolerated by patients of this age group, which was less than what maximal lipid lowering and risk factor management could be; however. However, there is almost no direct evidence of their effectiveness in 80-year-old patients.

Conclusions

This prospective "on-treatment" analysis of the TIME patient population provides important insights into the effects of optimised medical and revascularisation therapy in these 80-year-old patients. The mortality of MED patients was similar to that of REVASC patients of the same advanced age, indicating that mortality is increased in these elderly CAD patients whatever treatment they receive. The early mortality hazard of invasive management was mainly due to the high mortality of CAD patients assigned to invasive management who could not be re-vascularised, rather than to the PCI or CABG surgery itself. Overall, revascularisation led to a significant improvement in angina severity and measures of QoL, compared to the optimised medical therapy. This finding could also explain the overall late benefit observed in patients assigned to medical treatment by intention-to-treat. Patients selected for PCI based on a "suitable" coronary anatomy had a similar early and one-year death/mortality rate as patients who underwent CABG surgery; however, their benefit in QoL and angina relief may be smaller. Therefore, elderly patients with chronic angina should be offered invasive evaluation and revascularisation, if feasible, because mortality is increased similarly with both treatments but improvements in symptoms and QoL are greater after successful revascularisation.

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A complete list of all investigators can be found in Ref.[8]

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