

Long-Term Outcome in Elderly Patients With Chronic Angina Managed Invasively Versus by Optimized Medical Therapy Four-Year Follow-Up of the Randomized Trial of Invasive Versus Medical Therapy in Elderly Patients (TIME)

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Background—There are no prospective trial data on long-term outcomes in 80-year-old patients with chronic angina with regard to antiischemic therapy.

Methods and Results—To assess long-term survival and quality of life (QoL) in patients from the Trial of Invasive versus Medical Therapy in the Elderly (TIME), all 276 1-year survivors (of a total 301 patients) were contacted after a median of 3.1 years (range, 1.1 to 5.9 years). At baseline, patients were 80 ± 4 years old, 42% were women, and they were designated as being in angina class 3.2 ± 0.7 , despite their taking 2.5 ± 0.7 antiischemic drugs. Patients were randomized to an invasive (n=153) or an optimized medical (n=148) strategy. Survival of invasive-strategy versus medical-strategy patients was 91.5% versus 95.9% after 6 months, 89.5% versus 93.9% after 1 year, and 70.6% versus 73.0% after 4.1 years ($P=NS$). Mortality was independently increased in patients ≥ 80 years of age, with prior heart failure, ejection fraction ≤ 0.45 , and ≥ 2 comorbidities, and without revascularization within the first year. Revascularization within the first year improved survival in invasive-strategy ($P=0.07$) and medical-strategy ($P<0.001$) patients. The early benefit of both treatments in angina relief and QoL was maintained long term, but freedom from major events remained higher in invasive-strategy versus medical-strategy patients (39% versus 20%, $P<0.0001$).

Conclusions—Long-term survival was similar for patients assigned to invasive and medical treatment. The benefits of both treatments in angina relief and improvement in QoL were maintained, but nonfatal events occurred more frequently in patients assigned to medical treatment. Irrespective of whether patients were catheterized initially or only after drug therapy failure, their survival rates were better if they were revascularized within the first year. (*Circulation*. 2004;110:1213-1218.)

Key Words: aging ■ angina ■ survival ■ drugs ■ revascularization

No prospective trial data are available on long-term outcomes in 80-year-old patients with chronic angina with regard to antiischemic therapy. In younger patients (mean age, 58 years), 7-year data have recently been reported from the Randomized Intervention Treatment of Angina (RITA)-2 Trial.¹ It showed that in relatively low-risk patients with an overall 7-year mortality rate of 8.2%, percutaneous coronary intervention (PCI) did not change the risk of death or infarction compared with continued medical therapy but that it improved angina and exercise tolerance. Long-term results of randomized studies comparing PCI with coronary artery bypass graft (CABG) surgery performed in 50- to 70-year-old patients suggested that PCI was less effective in angina relief than CABG surgery but that there were no differences in long-term survival between the 2 revascularization methods.²⁻⁴ However, in the large Alberta Provincial Project for Outcomes Assessment in Coronary Heart Disease

(APPROACH) cohort, adjusted 4-year mortality rates for CABG, PCI, and medical therapy in patients 70 to 79 years of age ranged between 13% and 21% and in patients ≥ 80 years of age, from 23% for CABG surgery, to 28% for PCI, and to 40% for medical therapy.⁵

The Trial of Invasive versus Medical therapy in Elderly patients with chronic angina (TIME) was the first prospective, randomized study to compare an optimized medical strategy with an invasive strategy in patients ≥ 75 years of age.⁶ It showed early benefits in angina relief and improvements in quality of life (QoL) at the price of a small, early intervention hazard. After 1 year there was, however, no longer any significant difference in death, myocardial infarction (MI), or symptomatic status between the 2 treatment strategies,⁷ mainly because of the fact that a large percentage (43%) of medical treatment-assigned patients needed late revascularization for refractory angina.

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*A list of main investigators for the TIME Study appears in the Appendix.

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na.⁸ This raised questions about long-term outcome in these elderly patients.

Therefore, the present follow-up study was conducted in all 276 TIME patients who survived the first 365 days to assess a possible prognostic advantage of either treatment strategy in these elderly symptomatic patients, to define predictors of long-term survival, and to evaluate the long-term effect of both treatment strategies on symptoms, QoL, and late nonfatal events.

Methods

Trial Design

The design of the TIME study has been reported previously.⁶ In short, 301 patients aged 75 years or older from 14 Swiss hospitals were included after written, informed consent was obtained and if they presented with Canadian Cardiac Society (CCS) class II or greater angina, despite being medicated with at least 2 antianginal drugs. The patients were randomized to an invasive (INV; n=153) or an optimized medical (MED; n=148) strategy. INV included coronary angiography in all patients, followed by revascularization if feasible; in fact, 79 patients (52%) received PCI, 30 patients (20%) underwent CABG surgery, and 43 (28%) did not undergo revascularization, and therefore, had medical treatment only; 1 patient died before the start of study treatment. Drug treatment of MED patients was optimized by at least 1 additional antiischemic drug in 80% and by dosage increases in 55%, for an average of 3.1 ± 0.6 antiischemic drugs per patient.

The predefined primary end point of the study was QoL after 6 months, ie, relief of angina, improvement in standardized measures of QoL, and freedom from major adverse clinical events (death, nonfatal MI, or hospitalization for refractory angina/acute coronary syndrome with or without the need for revascularization). MI was a clinical diagnosis based on typical symptoms, ECG changes, and cardiac enzyme elevations. The main secondary end point was assessment of the same end points after 12 months. The ethics committees of all participating hospitals approved the study.

Data Collection and Long-Term Follow-Up

Demographic and clinical data were obtained at baseline and after 6 and 12 months. For late follow-up, all survivors of the first 365 days were contacted again after a median of 3.1 years (range, 1.1 to 5.9 years) by questionnaire, followed by queries to patients, relatives, or treating physicians, if necessary. Thus, total median follow-up was about 4 years after randomization. Survival status is known for all patients, and causes of death were verified by hospital or autopsy records and death certificates. Deaths were classified by an independent committee as noncardiac only if unequivocal evidence of cancer (n=13), stroke (n=4), sepsis (n=1), or suicide (n=1) was present. Nonfatal cardiac events included nonfatal MIs and hospitalizations for any cardiac reason (including need for revascularization). QoL questionnaires returned by 91% of all survivors contained questions of the short-form SF12,⁹ the Duke Activity Status Index (DASI¹⁰), the Rose questionnaire,¹¹ and questions about CCS angina class and medications. Relevant comorbidities recorded were prior stroke, peripheral vascular disease, severe chronic pulmonary obstructive disease, ulcer or liver disease, chronic renal insufficiency, and history of tumor. Primary end-point events for the present analysis were all deaths, cardiac deaths, hospitalizations for cardiac causes (including nonfatal infarction and late revascularization), angina severity, measures of QoL, and antianginal drug use.

Statistics

All data were analyzed according to the intention-to-treat principle by standard methods as previously described.^{6,7} Quantitative and score variables were summarized in terms of mean values and standard deviations, and comparison between groups was done with the Wilcoxon Mann-Whitney test. For the comparison of categorical variables between groups, Fisher's exact test and the χ^2 test were

TABLE 1. Baseline Characteristics of 276 Survivors of the First 365 Days

Patient Groups	MED (n=139)	INV (n=137)	P
Age, mean \pm SD, y	80 \pm 4	80 \pm 4	0.99
Female, %	42	42	0.99
Hypertension, %	58	64	0.37
Diabetes mellitus, %	22	20	0.70
Cigarette smoking, %	32	37	0.33
Hypercholesterolemia, %	44	50	0.34
Family history, %	44	31	0.03
≥ 2 Risk factors, %	56	55	0.82
Prior MI, %	49	42	0.27
Prior CABG/PCI, %	20	18	0.80
Prior CHF, %	10	12	0.67
Prior TIA/stroke, %	7	10	0.38
Peripheral vascular disease, %	13	21	0.07
COPD, %	7	10	0.51
Ulcer/liver disease, %	6	7	0.56
Chronic renal insufficiency, %	11	11	0.95
≥ 2 Comorbidities, %	21	27	0.23

CHF indicates congestive heart failure; COPD, chronic obstructive pulmonary disease; and TIA, transient ischemic attack. All other abbreviations are as defined in text.

used. Average changes in quantitative variables within individuals were assessed with the paired *t* test, which was also used to assess average individual changes in score variables. Time-to-event variables with censored values were described by Kaplan-Meier statistics, and their differences between groups were assessed with the log-rank test or by proportional-hazards models adjusted for sex, age, family history of coronary artery disease, use of specific drugs, and the presence of peripheral vascular disease. We identified potential predictors of death by univariate analysis; to assess their relative importance, they were then jointly included in a multiple Cox regression model. Apart from the occurrence of critical events, we were interested in the QoL of our patients at the end of follow-up. We therefore did not conduct a repeated-measures analysis and did not adjust probability values of differences between treatment groups for repeated comparisons. However, we corrected the probability values associated with average individual changes in QoL variables during follow-up by multiplying them by the number of QoL end points (ie, SF12-physical, SF12-mental, ROSE score, and DASI) considered.

Results

Baseline Findings

Of the initial 301 TIME patients, 276 (91.7%) survived the first year: 137 of 153 (89.5%) INV and 139 of 148 (93.9%) MED patients. Detailed information on baseline comparability of the 2 treatment groups has been published previously.⁶ Baseline data of the 276 1-year survivors are summarized in Table 1. In brief, at study inclusion they were, on average, 80 years old; 42% were women; 55% had ≥ 2 risk factors; there was a history of infarction in 46%, of heart failure in 11%, and of PCI or CABG surgery in 17%; at least 2 comorbidities were present in 24%; and CCS class II angina was present in 18%, class III in 47%, and class IV in 35%. During the first 365 days of the study, 9 INV and 17 MED patients had

TABLE 2. Major Events During Long-Term Follow-Up (Between Day 365 and Late Follow-Up)

	INV (n=137)	MED (n=139)	P	HR	P
All death, %	21.2	22.3	0.88	0.68	0.18
Cardiac death, %	13.9	17.3	0.51	0.56	0.10
Patients with nonfatal MI, %	4.4	0.7	0.07	5.24	0.13
Patients with late PCI/CABG, %	2.9	2.9	0.98	1.41	0.67
Patients with cardiac hospitalization, %	20.4	13.0	0.11	2.37	0.01
Patients with major clinical events, %	45.3	37.4	0.22	1.43	0.08

HR indicates hazard ratios adjusted for sex, age, family history of coronary artery disease, peripheral vascular disease, and baseline treatment differences. All other abbreviations are as defined in text.

suffered a nonfatal MI ($P=0.11$), and 12 INV versus 61 MED patients had undergone nonprotocol revascularization ($P<0.001$), which was a repeated intervention in 11 INV patients. CCS angina class at the start of this long-term follow-up study was 1.3 ± 1.7 (INV) and 1.4 ± 1.6 (MED; $P=0.82$), significantly lower than at the start of the study 1 year earlier ($P<0.001$). Similarly, measures of QoL had significantly improved during the first year of the study. At the beginning of the long-term follow-up, MED patients were still taking 2.0 ± 1.2 antianginal drugs compared with 1.5 ± 1.1 drugs in INV patients ($P<0.001$).

End-Point Events

During long-term follow-up, 60 of 276 patients (21.7%) died, 21.2% of the INV group and 22.3% of the MED group ($P=0.88$). Forty-three of these deaths were classified as cardiac, for cardiac death rates of 13.9% (INV) and 17.3% (MED; $P=0.51$). The crude event rates are shown in Table 2. There were no significant differences between any of these single events; however, after adjustment for baseline differences, the proportion of patients with any of these major events tended to be larger for INV-assigned versus MED-assigned strategies: 45.3% versus 37.4% ($P=0.08$), mainly because of more cardiac (re)hospitalizations.

For the entire TIME study period, ie, a total of median 4.1 years of follow-up after randomization, mortality in these initially (on average) 80-year-old patients was 85 of 301 (28.2%), or 6.9%/y, 29.4% for the INV group and 27.0% for the MED group ($P=0.70$). There were also no significant differences in cardiac death (21% versus 22%, or 5.3%/y) or nonfatal infarction (12% versus 12%), but cardiac (re)hospitalizations, particularly nonprotocol-assigned late revascularizations, were more frequent in MED-assigned patients (45% versus 12%, $P<0.0001$, even after baseline adjustment), resulting in overall nonfatal cardiac event rates of 68% versus 37% for MED versus INV patients, respectively ($P<0.0001$), or in rates of freedom from major events over the 4-year study period of 39% for INV- versus only 20% for MED-assigned patients ($P<0.0001$). Kaplan-Meier survival curves of patients without cardiac death and without major events are shown in Figure 1, comparing the 276 1-year survivors (right) with all 301 TIME patients (left).

Predictors of Death

Significant univariate predictors of death were age >80 years, angina CCS class IV at initial presentation, diabetes, 2

or more comorbidities, prior heart failure, reduced left ventricular ejection fraction ≤ 0.45 , no revascularization within the first year, female sex, and no β -blocker but diuretic or angiotensin-converting enzyme inhibitor therapy. The same parameters were predictive of cardiac death except for female sex. Among comorbidities, the presence of peripheral vascular disease and previous ulcer disease carried a particular mortality risk ($P<0.03$ for each). After adjustment for baseline differences in a stepwise logistic regression model, age >80 years, prior heart failure, left ventricular ejection fraction ≤ 0.45 , 2 or more comorbidities, and no revascularization within the first year of the TIME study remained independent predictors of cardiac mortality, as shown in Figure 2. In other words, younger patients with preserved left ventricular function, no history of heart failure, with a maximum of 1 comorbidity, and particularly those who were revascularized within the first year had a better survival rate than their counterparts. The effect of revascularization on long-term survival is shown in Figure 3A. Importantly, this beneficial effect of revascularization was noted similarly in INV-assigned as well as in MED-assigned patient subgroups (Figure 3B).

Long-Term Effect on Angina and QoL

The effects of both treatment strategies on angina severity and QoL as measured by the Rose score, the SF12 physical summary score, and the DASI score over the entire study period are shown in Figure 4, as well as the average number of antianginal drugs per patient used. The early beneficial effect of both treatment strategies noted previously⁷ was maintained long term, although the small early advantage in favor of INV management disappeared. In addition, MED patients were taking significantly more antianginal drugs during most of the study period than INV patients. In contrast, the SF12 mental-component summary scores did not change significantly in either treatment group ($P=0.29$) and remained fairly constant throughout the entire study period.

Discussion

The present findings of the TIME study provide the first randomized evidence of 2 present-day antiischemic treatment strategies: optimized drug therapy or revascularization by PCI or CABG surgery (when judged feasible) in elderly patients presenting with chronic angina. It is important to note

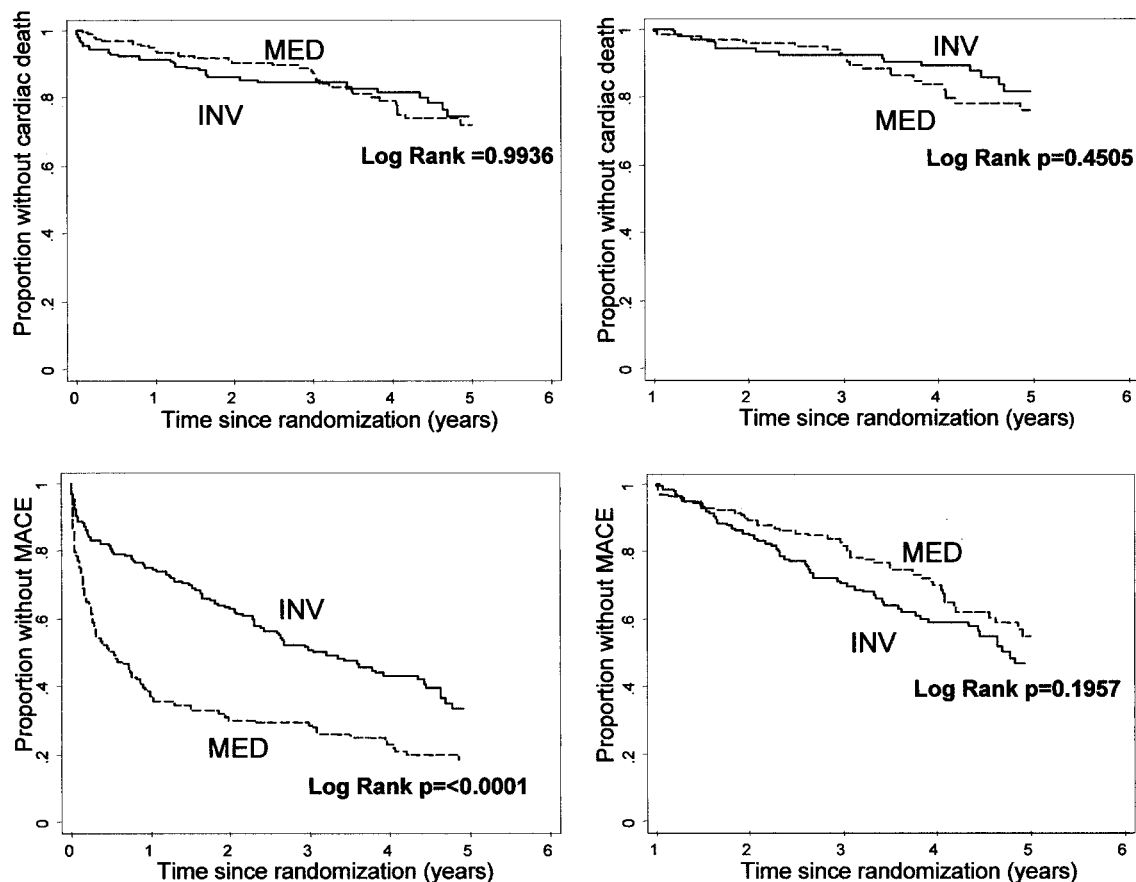


Figure 1. Survival without cardiac death (top) and freedom from major clinical events (MACE; bottom) of all 301 TIME patients (left) and of 276 1-year survivors (right). Note similar survival for both patient groups but greater freedom from major clinical events for INV- vs MED-treatment-assigned patients, with main separation of curves during first year. All other abbreviations are as defined in text.

that TIME patients were selected solely on the basis of their clinical presentation as observed in everyday practice and not on angiographic findings; therefore, there were “crossovers” in both directions within the first year: 28% of INV-assigned patients who did not need or could not be revascularized and 46% of MED-assigned patients who needed PCI or CABG surgery because of refractory symptoms. Overall, 4-year mortality was 28% and was very similar for both treatment strategies. Independent predictors of better cardiac survival were age <80 years, preserved left ventricular function, no prior heart failure, no or only 1 comorbid disease, and revascularization within the first year. Revascularization reduced mortality in both treatment strategies; however, despite the randomized study design, patients were selected for revascularization: in INV strategy-assigned patients, it was only performed if revascularizable disease was present (7% had no relevant stenoses, 13% were not suitable for revascularization, and 5% refused); in MED strategy-assigned patients, PCI or CABG surgery was only allowed if drug-refractory angina developed and if their coronary anatomy was suitable for revascularization.

A similarly high long-term mortality for a PCI-based compared with a drug therapy-based strategy was also found in the RITA-2 trial¹; however, overall 7-year mortality was only 8.4%, or 1.2%/y, compared with the 4-year mortality of

28.2%, or 6.9%/y, in the elderly TIME population. This difference may be explained by the generally older (>20 years older) TIME population and the more severe symptoms/disease in TIME versus RITA-2 subjects. Note that mortality was similarly increased for MED and INV strategies in TIME. The present data compare favorably with the 4-year mortality rates observed in the APPROACH cohort⁵ for CABG, PCI, and medical therapy, respectively: for age 70 to 79 years, 13%, 16%, and 21%, and for age ≥ 80 years, 23%, 28%, and 40%. In that cohort study, patients were obviously much more selected for revascularization compared with medical therapy than in the randomized TIME trial, and therefore, these results have to be compared with the present findings with regard to the impact of revascularization within the first year (Figure 3A): In this case, mortality was 20% with versus 39% without revascularization. Thus, the composite message of these studies, and particularly of the TIME findings, seems to be that with regard to long-term prognosis, patients with chronic angina may be managed with optimized drug therapy or according to an invasive strategy; however, catheterization is advised if symptoms become refractory, and revascularization should be performed if feasible, even in elderly patients, without fear of a higher mortality than with drug therapy.

With regard to late nonfatal events, the present follow-up investigation showed a trend toward more of such events in

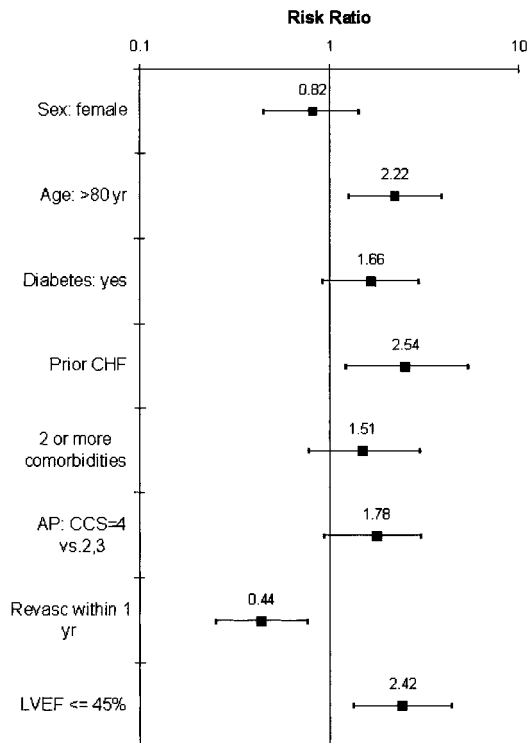


Figure 2. Predictors of cardiac death. Hazard ratios, indicating higher (to right side) or lower (to left side of centerline) risk; each estimated hazard ratio was adjusted for all other factors shown. AP indicates angina pectoris; CHF, congestive heart failure; LVEF, left ventricular ejection fraction; and Revasc, Revascularization. All other abbreviations are as defined in text.

the INV strategy–assigned patients after the first year of the study. Overall, however, nonfatal events were noted in almost twice as many MED- as INV-therapy–assigned patients (68% versus 37%, $P<0.0001$), obviously occurring mainly early. In addition, the present long-term findings of symptoms and well-being show that the early beneficial effect of both treatment strategies on angina severity and measures of QoL could be maintained more or less up to the end of long-term follow-up. Similarly to the findings of RITA-2,¹ however, the early advantage of the INV strategy in symptom relief disappeared over time, most likely because of the increasing number of MED strategy–assigned patients being revascularized.^{8,12} Still, MED patients were taking significantly more antianginal drugs throughout the study. Thus, the main advantage of the INV strategy seems to be an earlier symptomatic benefit, a lower rate of nonfatal follow-up events, and a lower need for antiischemic drugs, factors that may be particularly relevant for elderly patients.

Optimized medical therapy in TIME meant an increase of and a dosage adjustment of antiischemic therapy to what these elderly patients were willing and able to take. Obviously, optimal therapy may theoretically be more, including a statin^{13,14} besides aspirin and even an angiotensin-converting enzyme inhibitor^{15,16} in all patients. Although we encouraged patients to take aspirin and statins, statins particularly were not taken or even discontinued for many reasons. Thus, there may be room for further improvement in drug therapy. Patients treated with PCI received stents in 86% of cases, but

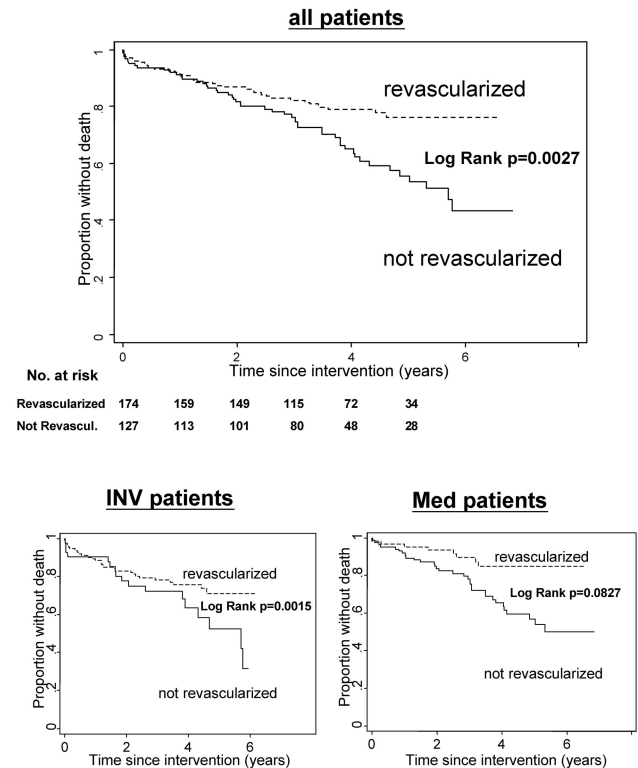


Figure 3. Effect of revascularization during first year on long-term survival: all patients subdivided by revascularization status after 1 year (top) and subgroups of INV- and MED-treatment–assigned patients subdivided by revascularization status after 1 year (bottom). Note better survival in revascularized patients overall and irrespective of initial treatment assignment. Abbreviations are as defined in text.

no drug-eluting stents were available at the time of the study.¹⁷ Both aspects may lead to reduced event rates in future similar investigations. No study-prompted patient contacts were done between the 1-year secondary end-point visit and the late follow-up questionnaire. Still, follow-up was complete with regard to survival and remarkably good with regard to completed questionnaires (91%), thus ensuring valid results. In view of the difficulty and therefore, lack of randomized trial data in such elderly patients,¹⁸ the present long-term findings should be relevant to this rapidly increasing patient population.

Conclusions

Long-term outcome findings of the TIME study suggest that, by intention-to-treat, an INV strategy and a MED strategy for elderly patients with chronic angina despite standard drug therapy have similar outcomes. Mortality rate is increased particularly in patients >80 years of age and in those with prior heart failure, reduced left ventricular function, 2 or more relevant comorbidities, and no revascularization within the first year. The benefit in symptom relief and improvement in well-being is maintained with either strategy, but the early advantage of the INV strategy in this regard disappears over time. The MED strategy involves, however, overall a larger number of late nonfatal events, mostly hospitalizations and late revascularizations. Thus, on the basis of evidence from

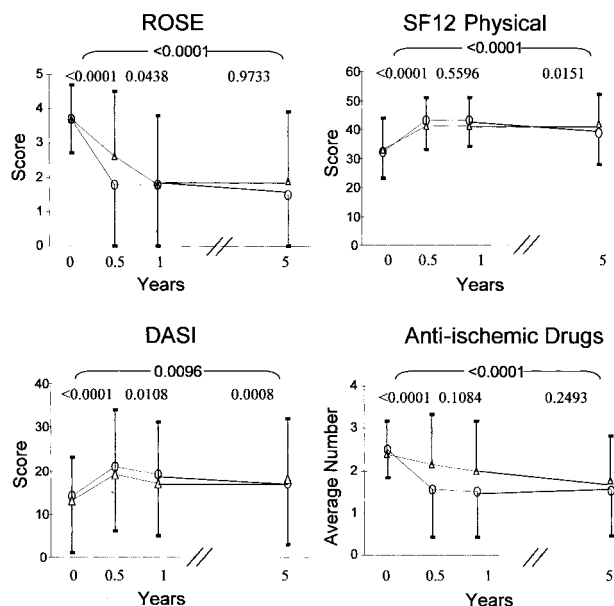


Figure 4. Effect of both antiischemic treatments on parameters of angina severity (Rose score), QoL (SF12 physical-component summary score), DASI, and number of antiischemic drugs used in 276 1-year survivors. Probability values relate to differences in both groups over time. Rose score of 4 indicates pain at rest and 0 indicates no pain. DASI scores range from 0 to 58, with higher scores indicating more favorable status. SF12 scores range from 0 to 100 with, higher scores indicating more favorable status. Triangles indicate MED assignment; circles, INV assignment.

the TIME study, elderly patients and their physicians may choose either an INV strategy with early symptom relief and improvement in well-being, at the “cost” of an early investigation and revascularization, or a MED strategy with a similar long-term outcome but more drugs and a >50% chance of late nonfatal events, mainly hospitalizations for refractory symptoms with the need for late revascularization.

Appendix

We acknowledge the work of all investigators, and we thank all participating patients.

The TIME Investigators

Matthias Pfisterer (principal investigator); main investigators (TIME study centers): Peter Buser, Stefan Osswald (University Hospital Basel); André Vuillomenet (Kantonsspital Aarau); Franz Eberli (University Hospital Bern); Heinz Schlaepfer (Regionalspital Biel); Peter Rickenbacher (Kantonsspital Bruderholz); Paul Dubach (Kantonsspital Chur); Urs Allemann (Clara Hospital, Basel); Eric Eeckhout (University Hospital, Lausanne); W. Estlinbaum (Kantonsspital Liestal); Tiziano Moccetti (Cardiocentro Lugano); Paul Erne (Kantonsspital Luzern); Walter Angehrn (Kantonsspital St. Gallen); Osmund Bertel (Triemli Hospital, Zürich); and Wolfgang Amann (University Hospital, Zürich).

Long-term follow-up and data collection: Barbara Ankli and Raban Jeger.

Statistics: Christian Schindler and Letizia Grize (Medical Statistics, Institute for Social and Preventive Medicine, University Hospital, Basel, Switzerland).

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