Outcome of Elderly Patients With Chronic Symptomatic Coronary Artery Disease With an Invasive vs Optimized Medical Treatment Strategy
One-Year Results of the Randomized TIME Trial

Matthias Pfisterer, MD, FESC, FAHA
Peter Buser, MD
Stefan Osswald, MD
Urs Allemann, MD
Wolfgang Amann, MD
Walter Angehrn, MD
Eric Eeckhout, MD
Paul Erne, MD
Werner Estlinbaum, MD
Gabriela Kuster, MD
Tiziano Moccetti, MD
Barbara Naegeli, MD
Peter Rickenbacher, MD
for the Trial of Invasive versus Medical therapy in Elderly patients (TIME) Investigators

Whereas randomized clinical trials have shown that younger patients with chronic symptomatic coronary artery disease (CAD) benefit from revascularization regarding symptom relief and quality of life,1–4 no such data exist for patients older than 75 years.5 However, procedure-related mortality increases with age both after coronary artery bypass graft (CABG) surgery6 and after percutaneous coronary intervention (PCI).7 The recent Trial of Invasive versus Medical therapy in Elderly patients (TIME) with chronic angina6,7 with chronic angina in elderly patients with chronic angina are similar with regard to symptoms, quality of life, and death or nonfatal infarction with invasive vs optimized medical strategies based on this intention-to-treat analysis. The invasive approach carries an early intervention risk, while medical management poses an almost 50% chance of later hospitalization and revascularization. JAMA. 2003;289:1117-1123

See also p 1157.

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Figure 1. Flow of Patients in the Study

305 Patients Randomized

155 Assigned to Receive Invasive Strategy

2 Had MI Within 10 Days of Randomization

147 Underwent Catheterization

79 Received PCI

30 Underwent CABG Surgery

38 Received Medical Treatment

6 Did Not Undergo Catheterization

5 Received Medical Treatment

4Refused Catheterization

1 Had Cancer

1 Died

140 Survived First 6 mo

140 Available For 1-Year Follow-up

140 Included in Primary Analysis

150 Assigned to Receive Optimized Medical Strategy

1 Had MI Within 10 Days of Randomization

1 Withdrew Consent

142 Survived First 6 mo

142 Available For 1-Year Follow-up

142 Included in Primary Analysis

MI indicates myocardial infarction; PCI, percutaneous coronary intervention; and CABG, coronary artery bypass graft surgery.

atic CAD was the first to show that patients older than 75 years with chronic angina despite standard medical therapy benefit from anti-ischemic therapy.8 This benefit was greater with invasive than with optimized medical management regarding symptom relief and improvement in quality of life, however, at a certain excess in early mortality. Whether these short-term effects translate into long-term benefits for either treatment strategy in these elderly patients is unknown as well as whether the observed early intervention hazard may be balanced during longer-term follow-up.

We therefore planned and prospectively performed a follow-up evaluation of all TIME patients after 1 year regarding symptoms, quality of life, and major adverse clinical events (MACE). The specific aims of this follow-up study were to assess whether the early effects of both treatment strategies on anginal status and quality of life noted after 6 months would persist in these elderly patients, whether observed differences in outcome between revascularization and optimized medical therapy would still be present after 12 months, and whether the expected mortality risk of invasive therapy in this elderly patient group would decrease over time compared with medically managed patients.

METHODS

Details of the TIME study protocol have been described previously.8 In short, in this prospective randomized multicenter Swiss trial, 301 of 305 patients (4 protocol violations) aged 75 years or older with chronic angina with Canadian Cardiac Society class 2 or higher despite treatment with at least 2 anti-anginal drugs were randomized to an optimized medical therapy (n = 148) or an invasive strategy (n = 153) with coronary angiography followed by revascularization (PCI or CABG surgery), if feasible (FIGURE 1). Patients were excluded for acute myocardial infarction (MI) within the previous 10 days, concomitant valvular or other heart disease, predominant congestive heart failure, or no consent for a possible revascularization procedure. Randomization by center was performed by telephone to the coordinating center. The study was approved by the ethics committee of the Swiss Academy of Medical Sciences and by the local ethics committees of each of the 14 Swiss centers. Patients gave written informed consent.

The primary end point was defined as quality of life assessed by standardized questionnaires and freedom from MACE (death, nonfatal MI, or hospitalization for uncontrolled symptoms or acute coronary syndrome with or without need for revascularization) after 6 months. Late revascularization in either treatment group was considered an event only if patients needed hospitalization for angina at rest or with minimal exertion despite optimized medical therapy and were transferred by their treating physicians not involved in the study organization.

After collection of baseline data (TABLE 1), quality of life was assessed by a self-administered questionnaire containing the Short Form 36,9 the Duke Activity Status Index (DASI),10 the Rose11 angina questionnaire, and questions about education and social status. For this prospective 1-year follow-up study, all surviving patients were observed again in the outpatient clinics of each center. The same case report form and quality of life questionnaires as at baseline and after 6 months were completed. Information regarding survival and MACE could be obtained in all patients and quality of life questionnaires (filled out by patients themselves in 73% of cases) were analyzable in 86% of surviving patients.

All analyses were performed on an intention-to-treat basis and statistical methods were the same as in the main trial.8 In short, quantitative and score variables were summarized in terms of means and SDs and the comparison between groups was performed by using a Wilcoxon Mann-Whitney test. For the comparison of categorical values between groups, Fisher exact test and the χ² test were used. Changes in quantitative variables within groups were assessed with the paired t test and the signed rank test, which was also used to assess changes...
in score variables within groups. To avoid bias due to competing risks, deaths were considered as censored events in all survival analyses involving nonlethal end points. Time variables with censored values were described by Kaplan-Meier method statistics.

Quality of life questionnaires were analyzed according to the specific tests used. Group differences in average changes of quality of life scores within 6 and 12 months, respectively, were first assessed separately using the Wilcoxon Mann-Whitney test. In a second step, we used mixed linear models to simultaneously estimate average changes during the first 6 and 12 months, respectively, in either study group. Thereby, no constraints were imposed on the covariance structure of the 2 residuals per patient. Alternative parameterizations of these models were used to assess the statistical significance of group differences in these estimates and in estimated average changes between the 2 follow-up assessments.

The primary end point was analyzed by intention-to-treat as a composite end point and all components separately as secondary end points. \( P < .05 \) was considered a significant difference. SAS statistical software version 8.2 (SAS Institute Inc, Cary, NC) was used for all analyses.

Sample size was estimated based on the findings of the Angioplasty Compared to MEdicine (ACME) trial\(^2\) in which 100 patients 2 times led to significant differences in exercise time and symptoms. In the elderly TIME population, we assumed we needed 150 patients who were assigned to invasive management to reach 100 revascularized patients. A sample size of 154 patients 2 times would allow to detect a significant difference in primary end point events at a level of 5% with a power of 80%, if they occurred at rates of 40% for optimized medical and 25% for invasive therapy, respectively.

**RESULTS**

Between February 1996 and November 2000, 305 patients were enrolled;
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however, 4 were excluded by the critical event committee for protocol violation. Of the 301 patients initially included in the TIME study, 282 patients (94%) survived the first 6 months and were available for prospective follow-up after 12 months (Figure 1). The mean age (range) of the 282 patients available for analysis was 80 years (75-91 years) with a high prevalence of risk factors, a high prevalence of previous CAD events, and relevant comorbidities in more than 60% of patients (Table 1). Forty-two percent of patients were women.

At baseline, 235 of 301 patients (78%) had angina Canadian Cardiac Society class 3 to 4 despite a mean (SD) of 2.5 (0.7) anti-anginal drugs. In 118 optimized medical patients (80%), at least 1 anti-anginal drug was added and in 81 patients (55%), anti-anginal drug dosages were increased; whereas, 79 invasive therapy patients (52%) were treated by PCI, 30 (20%) by CABG surgery, and 43 (28%) by medical therapy (11 [7%] no significant CAD, 19 [12%] revascularization not possible, and 13 [8%] no consent).

### Table 2. Major Adverse Clinical Events During Follow-up of 0 to 6 Months, 7 to 12 Months, and 0 to 12 Months*

<table>
<thead>
<tr>
<th>Events by Month</th>
<th>Invasive (n = 153)</th>
<th>Optimized Medical (n = 148)</th>
<th>P Value</th>
</tr>
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<tr>
<td>No. of deaths</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-6</td>
<td>13 (8.5)</td>
<td>6 (4.1)</td>
<td>.15</td>
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<td>7-12</td>
<td>4 (2.9)</td>
<td>6 (4.2)</td>
<td>.75</td>
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<td>0-12</td>
<td>17 (11.1)</td>
<td>12 (8.1)</td>
<td>.44</td>
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<tr>
<td>No. of cardiac deaths</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-6</td>
<td>11 (7.1)</td>
<td>5 (3.4)</td>
<td>.20</td>
</tr>
<tr>
<td>7-12</td>
<td>2 (1.4)</td>
<td>5 (3.5)</td>
<td>.45</td>
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<tr>
<td>0-12</td>
<td>13 (8.5)</td>
<td>10 (6.7)</td>
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<td>No. of myocardial infarctions§</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>0-6</td>
<td>12</td>
<td>17</td>
<td>.46</td>
</tr>
<tr>
<td>7-12</td>
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<td>3</td>
<td>.66</td>
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<td>0-12</td>
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<td>.37</td>
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<tr>
<td>No. of hospitalizations with revascularization§</td>
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<td>0-6</td>
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<td>20 (13.5)</td>
<td>&gt;.99</td>
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<td>9 (6.3)</td>
<td>.60</td>
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<td>No. of MACE§</td>
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<tr>
<td>Total No. of hospitalizations§</td>
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<td>No. of hospitalizations§</td>
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<td>59</td>
<td>138</td>
<td>&lt;.001</td>
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</table>

**Abbreviation:** MACE, major adverse clinical events.

*Data for 0 to 6 months and 0 to 12 months include all patients in study (n = 301), and data for 7 to 12 months only include patients who survived to 6 months.
†Fisher exact test and Wilcoxon rank sum test, respectively. Patients having died before the respective observation period were excluded.
‡Univariate Cox proportional hazard model for time to first event.
§There were several patients who had more than 1 event; therefore, percentages are not included.
¶Deaths were considered as censored events.

Major Adverse Clinical Events

Detailed data on MACE are summarized in Table 2 for each 6-month period (0-6 months and 7-12 months) as well as for the total follow-up (0-12 months). Mortality rate for each 6-month period decreased in invasive therapy patients from 8.5% to 2.9%, whereas it stayed unchanged in optimized medical patients (4.1% and 4.2%, respectively). The small early hazard of the invasive strategy reported earlier is also reflected in the time to death or nonfatal MI as shown in Figure 2. Note that after 6 to 9 months, the curves crossed. Seven of the 10 late deaths were cardiac: 2 of 140 (1.4%) invasive and 5 of 142 (3.5%) optimized medical patients. During the 1-year follow-up, 106 hospitalizations for medically uncontrollable symptoms were noted in optimized medical vs 28 in invasive therapy (P<.001) and 68 patients (46%) randomized to optimized medical management needed 71 revascularizations (PCI, 42 [27% patients]; CABG surgery, 29 [19% patients]) vs only 16 (10%) late revascularizations (PCI, 13 [8%]; CABG, 3 [2%]) in patients initially randomized to the invasive therapy strategy (P<.001). Overall MACE rates were significantly higher for optimized medical patients after 6 months (73 [49.3%] vs 29 [19.0%] invasive therapy; P<.001), a difference that increased to 95 (64.2%) of optimized medical vs 39 (25.5%) of invasive therapy after 12 months (P<.001). Figure 3 illustrates these time trends in overall MACE rates.

Symptoms and Quality of Life

Angina severity, number of anti-anginal drugs used, and selected measures of quality of life at baseline as well as after 6 and 12 months are shown for both treatment groups as changes from baseline over time in Figure 4. There was a persistent marked relief of symp-
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COMMENT

This follow-up study of the first prospective randomized trial comparing an invasive with an optimized medical strategy in elderly patients with chronic angina demonstrates that the beneficial effect of both anti-ischemic therapies on quality of life and MACE rates noted early persisted and that the early unfavorable mortality trend observed with invasive therapy disappeared during late follow-up. The advantage of invasive vs optimized medical therapy regarding symptom relief and improvement in quality of life noted after 6 months disappeared in the intention-to-treat analysis during late follow-up. Significantly more optimized medical patients needed hospitalization for medically uncontrollable symptoms and significantly more received late revascularization for that reason.

Risk of Revascularization in Elderly Patients

The intervention hazard in higher risk populations such as elderly patients is well known to be increased.6,7 Previous studies in younger patients have pointed to a longer-term benefit of revascularization.8 Whether these benefits can be extrapolated to elderly patients is not clear. For example, the Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock (SHOCK) trial could show a survival benefit only after late follow-up in a very high-risk patient group9; however, in that study, patients 75 years or older did no longer benefit from invasive therapy.10 In the present study, mortality rates from intervention were lower than previously reported6,7,14,15 despite the fact that patients were selected on clinical presentation only and not on a suitable coronary angiographic anatomy for revascularization and that their risk factor, CAD history, and comorbidity rates were relatively high. The observed mortality rate with current interventional techniques may serve as further argument not to withhold revascularization to elderly patients for fear of a high-intervention risk. A recent large cohort study supports this interpretation suggesting that, in addition, elderly patients paradoxically have greater absolute risk reductions associated with revascularization than do younger patients.14

Early vs Late Revascularization

This study may be analyzed as a comparison between early and late revascularization: PCI or CABG surgery was performed in 65% of invasive therapy patients early (per protocol) and in 46% of optimized medical patients late (due to refractory symptoms). A similarly high rate of crossovers from medical to revascularization therapy has been noted in previous trials4,14,15 and may not be surprising in view of the symptomatic status of TIME patients at inclusion. In the present follow-up study, rates of death and death or nonfatal MI were similar after 1 year and there was no longer a significant difference in angina relief or improvement in quality of life between treatment groups. So why not wait on medical therapy until revascularization becomes urgently necessary? The present intention-to-treat analysis suggests that this is a reasonable option for such patients if their symptoms are acceptably controlled by medical therapy and they do not have to take the risk of revascularization; however, if medical treatment fails, revascularization may be performed later. However, if, at presentation, they cannot accept their angina and reduced quality of life with a 50% chance of hospitalization with late revascularization, they can choose early revascularization. After 1 year, outcome will be very similar for both options, although death may well occur earlier with early revascularization.

The early improvements in symptoms and quality of life noted in invasive therapy patients were also observed with optimized medical patients during late follow-up, in parallel with a large proportion of these patients being revascularized. One may speculate whether these benefits of revascularization on subjective well-being were merely a placebo-like effect of the intervention similarly to the one recently observed after arthroscopic treatment of osteoarthritis16 or whether they reflect a true treatment effect. The fact that sub-

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Objective improvement persisted in invasive therapy patients throughout the 12-month follow-up, an observation that is in accordance with findings of previous randomized controlled trials on persistent symptomatic improvements after CABG surgery,17 or PCI18,19 vs medical management in younger patients, favors the interpretation of a true symptomatic treatment benefit of revascularization even in an elderly patient population. In view of the limited number of invasive therapy–assigned patients effectively being revascularized and the relatively large crossover rate of optimized medical–assigned patients in the clinical settings of the present study, only an on-treatment analysis of these effects over time may help to further differentiate placebo-like from true treatment effects.

Quality of Life and Major Events

For this study, quality of life was defined as a primary end point consisting of standardized self-administered questionnaires and freedom from MACE. Questionnaires were given at baseline, after 6 and 12 months but not at the time of major events. How, then, may events have influenced measures of quality of life? If we would assume an arbitrary scale of quality of life and set well-being at 10, then death (no quality of life) would be 0. This would be in disfavor of the invasive therapy strategy (17 invasive vs 12 optimized medical deaths after 1 year). Nonfatal MI would get a value of 1 to 2, an event that was somewhat more frequent in optimized medical patients (20 vs 14 invasive therapy) turning the quality of life balance more or less back to even level. Hospitalization for acute coronary syndrome, also a predefined event incompatible with well-being, might get a value of 3 to 4 on the quality of life scale. This was observed significantly more often in optimized medical vs invasive therapy patients (106 vs 28) and would reduce their quality of life outcome markedly. Hence, incorporating events into quality of life may suggest an overall quality of life benefit of invasive therapy; however, such a hypothetical analysis would mainly be driven by hospitalization for symptoms at rest, the softest end point. Because of this and because formal utilities were not obtained prospectively, we presented measures of quality of life and results of MACE separately and strictly according to the intention-to-treat principle.

Limitations

The primary end point of this study was quality of life and not mortality. To assess the effect of therapy on mortality, either a much larger sample size or at least a much longer-term follow-up would be necessary. Despite the relatively small number of patients included in TIME, the results of this study...
are relevant for elderly patients in general because patients were included based on clinical presentation and not on specific angiographic findings. Major issues not fully addressed are the mode of revascularization (PCI vs CABG surgery) and costs of the different management strategies, because costs may be particularly relevant in the fast growing elderly population with CAD. Finally, because results of studies in younger patients may not simply be extrapolated to elderly populations, the same caution should be applied to transfer the present findings in elderly patients to younger patients.

Conclusions

This follow-up study in elderly patients with symptomatic CAD demonstrates that after 1 year there was no difference in quality of life between an early invasive vs an optimized medical strategy. This takes into account that almost half of the optimized medical therapy-assigned patients needed hospitalization for acute coronary syndrome followed by revascularization during follow-up. Thus, overall MACE rate was significantly higher in optimized medical vs invasive therapy patients; however, death or nonfatal MI occurred at similar rates after 1 year. This implies that elderly patients with angina pectoris refractory to standard drug therapy have a choice between an early invasive strategy that carries a certain early intervention risk and an optimized medical strategy that carries a chance of late hospitalizations and revascularizations. After 1 year, quality of life outcome and survival will be similar.

Author Affiliations: Departments of Cardiology, University Hospitals, Basel (Drs Pfisterer, Buser, Osswald, and Kuster), Zurich (Dr Ammann), Lausanne (Dr Eckhout), State Hospitals, St Gallen (Dr Angermann), Triemli Zurich (Dr Naegeli), Lucerne (Dr Erne), Liestal (Dr Estlinbaum), Lugano (Dr Moccetti), Bruderholz (Dr Rickenbacher), and Glarus Hospital Basel (Dr Allemann), Switzerland.

REFERENCES

5. Estlinbaum, Kuster, Moccetti, Naegeli, Rickenbacher. TIME Investigators: Steering Committee: Matthias Pfisterer, MD, principal investigator (Basel); Urs Allemann, MD, Basel (Basel), Wolfgang Ammann, MD (Zurich), Walter Angermann, MD (St Gallen), O. Bertel (Zurich), Paul Erne, MD (Luzern), Werner Estlinbaum, MD (Liestal), Eric Eckhout, MD (Lausanne), Tiziano Moccetti, MD (Lugano), Peter Rickenbacher, MD (Bruderholz), Francois Ricoux (Genf), Ronald Schonenberger (Solothurn); Critical Events Committee/Data and Safety Monitoring Board: Dieter Burkhardt, MD, Basel (Basel), Ferenc Pollath, MD (Zurich), Willy Rutschhauser, MD (Geneva); Statistics: Christian Schindler, PhD, Institute of Social and Preventive Medicine, University Hospital Basel, Switzerland.

Drafting of the manuscript: Pfisterer.
Critical revision of the manuscript for important intellectual content: Pfisterer, Buser, Osswald, Allemann, Amann, Angehrn, Eckhout, Erne, Estlinbaum, Kuster, Moccetti, Naegeli, Rickenbacher.
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Study supervision: Pfisterer, Buser, Osswald, Allemann, Amann, Angehrn, Eckhout, Erne, Estlinbaum, Kuster, Moccetti, Naegeli, Rickenbacher.

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