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

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Context The risk-benefit ratio of invasive vs medical management of elderly patients with symptomatic chronic coronary artery disease (CAD) is unclear. The Trial of Invasive versus Medical therapy in Elderly patients (TIME) recently showed early benefits in quality of life from invasive therapy in patients aged 75 years or older, although with a certain excess in mortality.

Objective To assess the long-term value of invasive vs medical management of chronic CAD in elderly adults in terms of quality of life and prevention of major adverse cardiac events.

Design One-year follow-up analysis of TIME, a prospective randomized trial with enrollment between February 1996 and November 2000.

Setting and Participants A total of 282 patients with Canadian Cardiac Society class 2 or higher angina despite treatment with 2 or more anti-anginal drugs who survived for the first 6 months after enrollment in TIME (mean age, 80 years [range, 75-91 years]; 42% women), enrolled at 14 centers in Switzerland.

Interventions Participants were randomly assigned to undergo coronary angiography followed by revascularization (if feasible) (n=140 surviving 6 months) or to receive optimized medical therapy (n=142 surviving 6 months).

Main Outcome Measures Quality of life, assessed by standardized questionnaire; major adverse cardiac events (death, nonfatal myocardial infarction, or hospitalization for acute coronary syndrome) after 1 year.

Results After 1 year, improvements in angina and quality of life persisted for both therapies compared with baseline, but the early difference favoring invasive therapy disappeared. Among invasive therapy patients, later hospitalization with revascularization was much less likely (10% vs 46%; hazard ratio [HR], 0.19; 95% confidence interval [CI], 0.11-0.32; $P<.001$). However, 1-year mortality (11.1% for invasive; 8.1% for medical; HR, 1.51; 95% CI, 0.72-3.16; $P=.28$) and death or nonfatal myocardial infarction rates (17.0% for invasive; 19.6% for medical; HR, 0.90; 95% CI, 0.53-1.53; $P=.71$) were not significantly different. Overall major adverse cardiac event rates were higher for medical patients after 6 months (49.3% vs 19.0% for invasive; $P<.001$), a difference which increased to 64.2% vs 25.5% after 12 months ($P<.001$).

Conclusions In contrast with differences in early results, 1-year outcomes 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.

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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) surgery[6] and after percutaneous coronary intervention (PCI).[7] The recent Trial of Invasive versus Medical therapy in Elderly patients (TIME) with chronic symptom-

See also p 1157.

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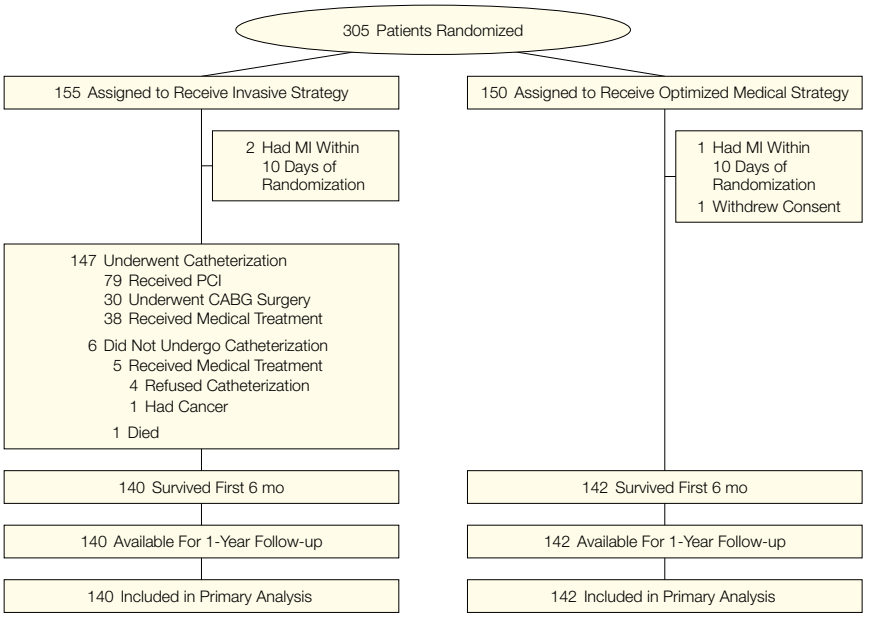
Figure 1. Flow of Patients in the Study



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 antianginal 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 Rose[11] 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 presented 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 χ^2 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

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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 parametrizations 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;

Table 1. Baseline Characteristics*

Characteristic	No. (%) of Patients	
	Invasive (n = 140)	Optimized Medical (n = 142)
Age, mean (SD), y	80 (3.6)	80 (3.5)
Women	59 (42.1)	59 (41.5)
Risk factors		
Hypertension	89 (63.6)	82 (57.7)
Diabetes	29 (20.9)	32 (22.5)
Current smoking	52 (37.1)	45 (31.7)
Hypercholesterolemia	69 (50.4)	63 (44.7)
History		
Prior infarction	59 (42.1)	71 (50.0)
Prior PCI	11 (7.9)	12 (8.5)
Prior CABG	15 (10.7)	17 (12.0)
Comorbidity		
Prior CHF	17 (12.3)	16 (11.4)
CVA	14 (10.0)	11 (7.8)
COPD	12 (8.6)	9 (6.4)
Peripheral artery disease	30 (21.6)	19 (13.5)
Ulcer/liver disease	9 (6.5)	8 (5.6)
Renal insufficiency	16 (11.6)	15 (10.6)
Other diseases	38 (27.5)	34 (24.6)
Mini-Mental State Examination, mean (SD)†	26.4 (2.0)	26.6 (1.7)
Symptoms		
Angina CCS 2	28 (20)	37 (26)
Angina CCS 3	66 (47)	67 (47)
Angina CCS 4	46 (33)	38 (27)
Dyspnea	78 (55.7)	82 (57.7)
Vital signs, mean (SD)		
Pulse rate (minute – 1)	69 (14)	69 (13)
Systolic blood pressure, mm Hg	138 (23)	137 (22)
Diastolic blood pressure, mm Hg	76 (13)	77 (12)
Drug therapy		
Anti-anginal drugs		
β-Blocker	116 (83.5)	102 (72.3)
Calcium antagonist	70 (51.1)	71 (50.0)
Long-acting nitrates	103 (74.6)	106 (74.6)
Molsidomine	54 (39.4)	51 (35.9)
Potassium blockers	1 (0.7)	8 (5.6)
Diuretics	51 (37.2)	50 (35.2)
ACE inhibitors	29 (21.0)	47 (33.1)
Lipid-lowering drugs	32 (23.4)	31 (22.0)
Aspirin	117 (84.8)	116 (81.7)
Warfarin	17 (12.4)	17 (12.0)
Heparin	25 (18.2)	25 (17.6)
LVEF, mean (SD), %	53.8 (11.9)	52.9 (12.7)
Angiographic findings of vessels diseased, %		
0	11 (8)	
1	19 (14)	
2	26 (19)	
3	79 (59)	
LM	17 (13)	

Abbreviations: ACE, angiotensin-converting enzyme; CABG, coronary artery bypass grafting; CCS, Canadian Cardiac Society classification; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; LM, left main disease (counted in 2 or 3 vessel disease groups); LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention.

*There were no significant differences between the 2 groups (invasive vs optimized medical), except for ACE inhibitor use ($P = .03$), β-blockers ($P = .03$), and potassium blockers ($P = .04$).

†Mini-Mental State Examination (score range, 0-30) with lower scores indicating more cognitive impairment.

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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*

Events by Month	No. (%) Invasive (n = 153)	No. (%) Optimized Medical (n = 148)	*P* Value†	Hazard Ratio, Invasive vs Optimized Medical (95% Confidence Interval)‡	*P* Value
No. of deaths					
0-6	13 (8.5)	6 (4.1)	.15	2.20 (0.84-5.80)	.11
7-12	4 (2.9)	6 (4.2)	.75	0.69 (0.19-2.43)	.56
0-12	17 (11.1)	12 (8.1)	.44	1.51 (0.72-3.16)	.28
No. of cardiac deaths					
0-6	11 (7.1)	5 (3.4)	.20	2.25 (0.78-6.47)	.13
7-12	2 (1.4)	5 (3.5)	.45	0.41 (0.08-2.12)	.29
0-12	13 (8.5)	10 (6.7)	.67	1.36 (0.59-3.10)	.47
No. of myocardial infarctions§					
0-6	12	17	.46	0.79 (0.36-1.74)‖	.56
7-12	2	3	.66	0.67 (0.11-4.01)‖	.66
0-12	14	20	.37	0.75 (0.36-1.55)‖	.44
Patients with death or myocardial infarction					
0-6	20 (13.1)	20 (13.5)	>.99	1.0 (0.54-1.87)	.99
7-12	6 (4.3)	9 (6.3)	.60	0.69 (0.24-1.93)	.48
0-12	26 (17.0)	29 (19.6)	.65	0.90 (0.53-1.53)	.71
No. of hospitalizations with revascularization§					
0-6	11	56	<.001	0.18 (0.09-0.35)‖	<.001
7-12	5	15	.02	0.35 (0.13-0.99)‖	.047
0-12	16	71	<.001	0.19 (0.11-0.32)‖	<.001
Total No. of hospitalizations§					
0-6	16	74	<.001	0.18 (0.10-0.32)‖	<.001
7-12	12	32	.004	0.40 (0.20-0.80)‖	.01
0-12	28	106	<.001	0.19 (0.12-0.30)‖	<.001
No. of MACE§					
0-6	41	97	<.001	0.33 (0.22-0.51)	<.001
7-12	18	41	.003	0.44 (0.23-0.83)	.01
0-12	59	138	<.001	0.31 (0.21-0.45)	<.001
Patients with MACE					
0-6	29 (19.0)	73 (49.3)	<.001		
7-12	14 (10.0)	32 (22.5)	.004		
0-12	39 (25.5)	95 (64.2)	<.001		

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 0 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[8] 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 uncontrolled 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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toms and improvement in quality of life in both treatment groups until 12 months, but the difference of these findings between the 2 treatment groups in favor of invasive therapy noted after 6 months disappeared after 12 months based on the intention-to-treat analysis. This was associated with a further improvement in these parameters in optimized medical–assigned patients who underwent late revascularization; whereas, there were no relevant additional changes in invasive therapy patients during late follow-up.

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

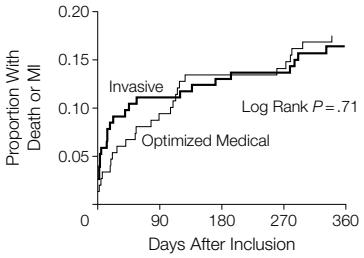
The intervention hazard in higher risk populations such as elderly patients is well known to be increased.[6,7] Previous studies in younger patients have pointed to a longer-term benefit of revascularization.[4] Whether these benefits can be extrapolated to elderly patients is not clear. For example, 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 group[12]; however, in that study, patients 75 years or older did no longer benefit from invasive therapy.[13] In the present study, mortality rates from intervention were lower than previously reported[6,7,14,15] 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 trials[1,4,15] 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 osteoarthritis[16] or whether they reflect a true treatment effect. The fact that sub-

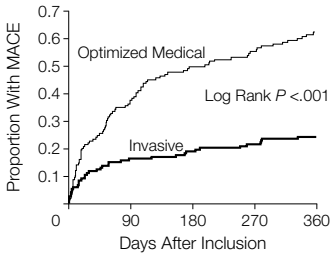
Figure 2. Time to Death or Nonfatal Myocardial Infarction (MI) in Both Treatment Groups



No. at Risk					
Optimized Medical	148	135	128	127	122
Invasive	153	136	133	132	99

Note the small early hazard in invasive patients (thick line), which is balanced during later follow-up (optimized medical therapy, thin line).

Figure 3. Rates of Major Adverse Clinical Events (MACE) Over Time



No. at Risk					
Optimized Medical	148	92	74	66	55
Invasive	153	128	124	120	90

MACE curves continue to diverge throughout 12 months due to an increasing number of late revascularizations in optimized medical therapy patients.

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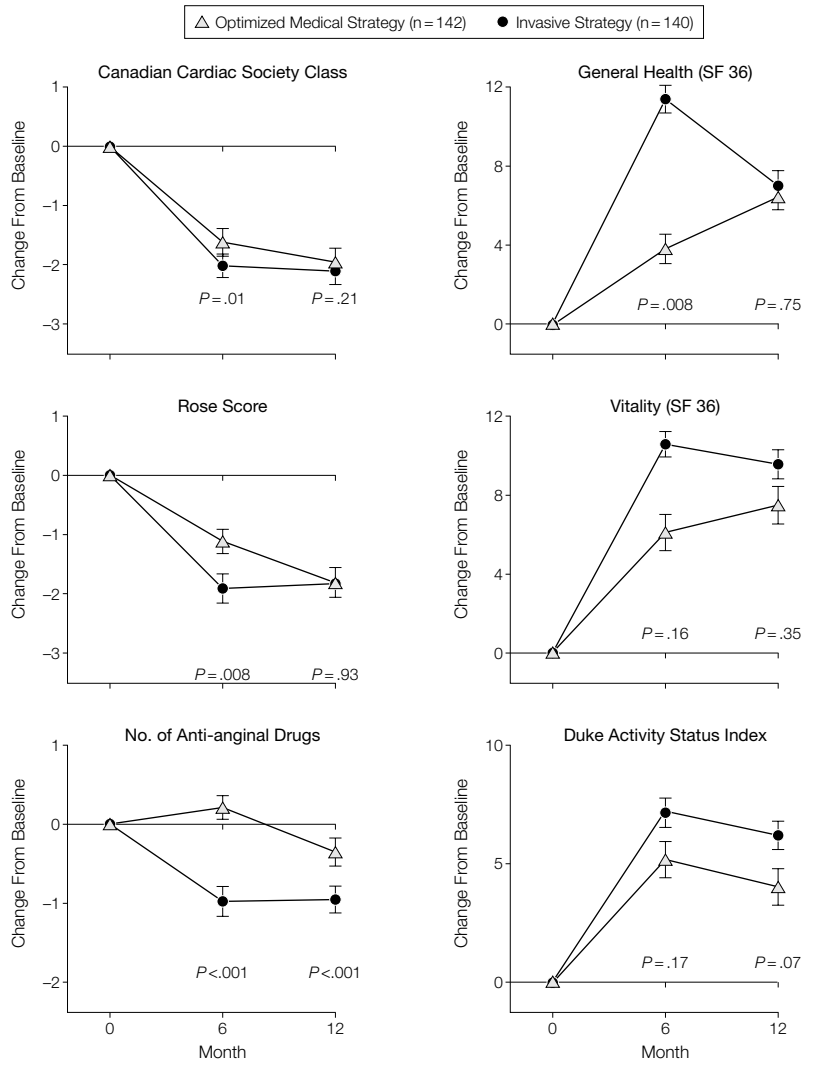
jective improvement persisted in invasive therapy patients throughout the 12-month follow-up, an observation that is in accordance with findings of previous randomized controlled trials on persistent symptomatic improvements after CABG surgery[17] or PCI[18,19] vs medical management in younger patients, 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 ontreatment analysis of these effects over time may help to further differentiate placebo-like from true treatment effects.

Figure 4. Mean Change From Baseline in Angina Severity, Measures in Quality of Life, and Anti-anginal Drug Use Over Time in Both Treatment Groups



Angina Canadian Cardiac Society class and Rose score: 4 indicates pain at rest and 0 indicates no pain. Duke Activity Status Index scored on a scale from 0 to 58 with higher scores indicating a more favorable status. Short Form 36 (SF 36) items (general health and vitality) scored on a scale from 0 to 100 with higher scores indicating a more favorable status. After 6 months, angina relief and improvement in quality of life was significant for both treatment groups vs baseline (all $P<.05$) but greater after invasive therapy management. After 1 year, anginal and quality of life status of optimized medical patients approached that of invasive patients, but anti-anginal drugs remained fewer. *P* values are for between-group comparisons at 6 and 12 months. Error bars indicate SE.

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

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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.

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