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Clinical research

Cost-effectiveness of invasive versus medical management of elderly patients with chronic symptomatic coronary artery disease☆

Findings of the randomized trial of invasive versus medical therapy in elderly patients with chronic angina (TIME)

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Aim To compare benefits and costs of invasive versus medical management in elderly patients with chronic angina.

Methods and results In a predefined subgroup of 188 patients of the Trial of Invasive versus Medical therapy in Elderly patients with chronic angina (TIME), one-year benefits were assessed as freedom from major events and improvements in symptoms and quality of live. Costs were determined as one-year costs of resource utilisation. Invasive patients had higher 30-day, but lower months 2–12 hospital and intervention costs than medical patients, resulting in somewhat higher one-year costs for invasive management ($p = 0.08$). However, billing data available for a subgroup of patients showed higher practitioner's charges in the medical patients (adjusted $p = 0.0015$).

Incremental costs to prevent one major event by invasive management averaged CHF 10100 (95% CI: −800 to 28300) or € 6965, ranging from average CHF 5100 (€ 3515) to CHF 11600 (€ 8000) in a best, compared to a worst, case scenario.

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Conclusions Early increased costs of revascularization in invasive patients were balanced after one year by increased practitioners' charges and symptom-driven late revascularizations in medical patients. Therefore, the invasive strategy with improved clinical effectiveness at only marginally higher costs as medical management was cost-effective. Costs should not be an argument against invasive management of elderly patients with chronic angina.

Introduction

In times of health-economic constraints, analyses of new treatment costs or new indications relative to observed healthcare benefits become important, particularly if such therapies are evaluated in the fastest growing population segment of elderly patients. This is certainly true for the management of chronic symptomatic coronary artery disease (CAD) which is most prevalent in men and women above the age of 75 years. Yet, even in younger patients, no trial-based cost-effectiveness analyses of percutaneous coronary interventions (PCI) relative to medical therapy are available[1] and only a few comparing coronary artery bypass graft (CABG) surgery to medicine.[2–5] The latter studies suggested that CABG surgery is most economically attractive when applied to high-risk patients and those with severe symptoms.[4]

The Trial of Invasive versus Medical therapy in Elderly patients (TIME) was the first randomized trial which compared two treatment strategies in patients $\geqslant$75 years of age with chronic symptomatic CAD.[6] It showed that an invasive strategy using coronary angiography followed by PCI or CABG surgery, if feasible, was superior to optimised drug therapy in reducing symptoms and improving measures of quality of life (QoL) at the cost of a non-significant early intervention hazard. After one year, treatment benefit persisted but patients assigned to medical management showed late improvements in symptom relief and well-being in association with late revascularizations in almost half of them.[7] It was therefore concluded that patients above the age of 75 years with chronic angina may choose between an early invasive strategy with early symptomatic benefit at a certain small intervention risk and an optimised medical strategy with a 50% chance of late hospitalisation and revascularization. Note that patients were selected for the TIME study based on their clinical presentation and not based on angiographic findings; thus, only 72% of invasive treatment-assigned patients were in fact revascularized whereas 46% of medical treatment-assigned patients needed revascularization during follow-up.

In view of the magnitude of the concerned patient population, the implementation of such study results into treatment guidelines may induce a relevant health-economic burden. This prospect may make responsible doctors reluctant today to apply such a strategy to 80-year-old patients. However, the TIME study offered the opportunity not only to assess the relative clinical benefits of both treatment strategies but also the relative costs and, on that basis, to perform a formal cost-effectiveness analysis. The aim of the present substudy, therefore, was to compare relative benefits and costs of both treatment strategies in a pre-specified representative subgroup of TIME patients over a one year period. The hypothesis was that the increased clinical effectiveness of the invasive strategy would be paralleled by increased costs.

Methods

In the prospective Swiss multi-centre TIME study, patients aged 75 years or older with chronic angina pectoris of Canadian Cardiac Society class $\geqslant$ II, despite at least 2 anti-anginal drugs, were randomized to a strategy of optimised medical therapy (MED) or an invasive strategy (INV) with coronary angiography followed by PCI or CABG surgery if feasible. The primary endpoint was QoL assessed by standardised questionnaires and freedom from major adverse clinical events (MACE): death, non-fatal myocardial infarction or hospitalisation for uncontrolled symptoms/acute coronary syndrome with or without need for revascularization. Patients were excluded mainly for acute myocardial infarction within the previous 10 days, concomitant valvular or other heart disease, predominant congestive heart failure and no consent for a possible revascularization procedure. Details of the TIME study have been reported previously.[6] After collection of baseline data, QoL was assessed by self-administered questionnaires including the Short Form 36 (SF36),[8] the Duke Activity Status Index (DASI[9]), the Rose angina questionnaire[10] and questions about education and socioeconomic status. In all surviving patients, the same evaluations of clinical and QoL status were performed after 6 and 12 months. 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 centres. Patients gave written informed consent.

Patients

For the present cost-effectiveness analysis, all 188 patients of 4 hospitals of Northern Switzerland were included (62% of the total TIME population), i.e. patients from only two Swiss cantons with a similar health care system and common insurance companies. Note that in Switzerland, all patients have statutory health care insurance, but type of insurance and health plans vary considerably between cantons and insurance companies. Baseline characteristics and outcome parameters were compared to the total TIME population (n = 301) to document the representativity of the subgroup.

Assessment of costs

Reliable healthcare related cost estimates are difficult to obtain in Switzerland. There are few real cost data and no large administrative databases allowing for an easy access to claims data. In

Table 1 Parameters of cost calculation

Unit	Cost/unit (CHF)	(€)
Hospital stay (1 day)	650	345
Intensive care (1 day)	3000	1380
Coronary angiography	2800	1931
PCI	4800	3310
CABG	11000	7586
Stress echocardiography	750	517
Stress scintigraphy	750	517

this situation, a double approach to cost assessment was adopted. First, inpatient resource use was prospectively recorded over the one year observation period of the TIME trial. It was valued by unit cost estimates derived from the official Swiss medical tariff system (TARMED), taking into account local particularities (Table 1).[11] These cost estimates are available for all 188 patients of both treatment groups included in this substudy. Resources taken into account include hospital days (intensive care separated from general ward) as well as invasive and major non-invasive procedures relating to CAD.

Secondly, all involved third party payers were asked to provide information on their insured total health care charges over the one-year study period. Four insurance companies collaborated and a total of 56 patients gave their special written informed consent thus forming the basis for an analysis of patient-level medical claims data. To calculate in- and outpatient charges, all claims from hospital stays, private physician visits as well as visits to cardiologists, angiologists and neurologists, pharmacy claims and claims of rehabilitation services were collected over the one-year study period.

We refer to the results of the first-mentioned approach as costs and used them for the base case calculation of cost-effectiveness. The results of the second-mentioned approach are referred to as charges and were used in the sensitivity analysis as described below.

Assessment of cost-effectiveness

Detailed clinical effectiveness results have been published previously for the total TIME population[6,7]; the results presented here relate to the subgroup of 188 TIME patients with available cost data. Incremental clinical effectiveness, the denominator in the cost-effectiveness equation, was expressed as the difference between the INV compared to MED treatment groups in terms of event-free survival and in terms of global QoL over time. The study was not powered to detect a mortality difference and such a difference was not found; therefore, measures of QoL assessed by standardized questionnaires and as freedom from major non-fatal events were main determinants of effectiveness despite the fact that hospitalisations also appear on the cost side of the cost-effectiveness equation. To estimate a summary measure of global QoL over the entire study period, utilities were computed from SF36-scores[12] collected at inclusion, and after six and twelve months. Utilities at critical events were assumed to be the minimum of the two utilities assessed at the beginning and the end of the respective six-month period. For all other time points, utilities were estimated by linear interpolation. The utility value of the third assessment was carried forward until the end of the one-year period whenever this assessment occurred earlier. The average utility over the one year study period was then computed as the area under the polygonal line resulting from this procedure, '0' representing death and '1' optimal health.

Incremental cost-effectiveness was calculated as the incremental cost required to prevent one major adverse event and as the incremental cost to improve the average utility during the first year among survivors.

Statistics

All data were analysed based on the intention-to-treat principle. Data on costs and charges are presented in Swiss currency CHF; (1 Euro ≅ 1.45 CHF). Data on costs and charges are summarized by mean values and their standard errors and by the three quartiles. With count variables, the maximum is given in addition. Differences in means of cost-related variables (including the number of hospital days per patient and the individual frequencies of different types of interventions) and of event rates between the two treatment arms were assessed using bootstrap *t*-tests. On the other hand, differences in QoL scores, numbers of anti-anginal drugs and in quantitative baseline variables between the two groups were assessed using the Wilcoxon—Mann—Whitney test as previously described.[6] Differences in survival curves between groups were assessed using the log-rank test and hazard ratios were estimated by Cox-regression. All *p*-values reported in tables and figures are two-sided. For additive components of a major variable, Bonferroni-adjusted values are given (Tables 3—5, Fig. 2). In order to differentiate between early (intervention-related for invasive patients) and follow-up costs, we separated costs accumulated during the first 30 days from those accumulated between days 31 and the end of the one year follow-up. Bootstrap techniques were used to estimate 95% confidence intervals (95% CI) for differences in average costs and effect measures (i.e. number of MACE, number of days without MACE, utility score) and for the incremental cost-effectiveness ratios presented (each of these simulations using 50 000 replicate[13]), and also to assess the shape of the joint sampling distribution of the differences in average individual costs and effects between the two treatment groups (with 5000 replicate per simulation). Presenting cost-effectiveness results as ratios with 95% confidence intervals is insufficient, as their interpretation depends on the quadrants of the cost-effectiveness plane (CE plane) into which they fall.[14] For example, in the assessment of a less efficient, but cheaper new treatment strategy (represented in the lower left quadrant of the CE plane), a numerically high cost-effectiveness ratio would be favorable, whereas in the familiar situation of a more expensive, but more efficient strategy (upper right quadrant), the opposite is true.[14] The remaining quadrants represent situations where the evaluated strategy is more expensive and less effective (dominated; upper left quadrant) or less expensive and more effective (dominant; lower right quadrant). This is taken into account by an additional graphical representation of the bootstrapping results in the CE plane, with 95%- and 50%-confidence ellipses describing their degree of uncertainty.

Sensitivity analysis

Uncertainty is present in the effectiveness and resource use results as well as in the unit cost estimates used for cost-effectiveness calculation. Uncertainty in the two first-mentioned entities is of a stochastic nature and covered by the probabilistic methods described in the statistics section. But uncertainty in unit cost estimates required additional sensitivity analyses. To this effect, bootstrapping procedures were repeated with unit costs varied according to a best case and a

worst case scenario based on the observed variation of patient-specific charges available for 56 patients. The boundaries of the non-parametric 99% confidence interval of individual charge-to-cost-ratios were multiplied by the base case unit cost estimates to determine the range of unit cost variation.

Results

Baseline characteristics

Baseline characteristics of the study group ($n = 188$) subdivided into the two treatment strategies, INV and MED, are shown in Table 2. There were no significant differences between these groups at baseline. Neither were there significant differences between the total study group of 188 patients and the complementary TIME population not included in this cost analysis ($n = 113$), nor did the subgroup with data concerning charges ($n = 56$) differ from the complementary subgroup of 132 patients considered in the present analysis (data not shown). This was true for clinical data as well as measures of QoL.

Effectiveness

One year outcome of the study group (Table 3) was similar to that of the total TIME population. MACE occurred significantly less frequently in INV as compared to MED patients (0.38 per INV patient versus 1.0 per MED patient, $p < 0.0001$, corresponding to 23% INV patients with MACE versus 65% MED patients with MACE, $p < 0.0001$), although the rate of death or non-fatal myocardial infarction was similar for both groups after one year (0.20 per INV patient, 0.26 per MED patient, $p = 0.29$). The same trend towards an early intervention hazard regarding mortality noted in the overall trial[5] was observed in the cost substudy population with a hazard ratio of 2.18 (95% CI: 0.74—6.38; $p = 0.16$). The benefit in MACE over time used for the present cost-effectiveness analysis is shown graphically in Fig. 1 as shaded area between the two event-free survival curves. There was a significant reduction in angina severity and improvement in measures of QoL for both treatment groups versus baseline after 6 and 12 months but the difference between the two treatment groups observed after 6 months was reduced after 12 months due to 52% of MED patients needing revascularization during follow-up. The benefit of INV versus MED man-

Table 2 Baseline characteristics

	Medical	Invasive	Complementary TIME patients
n	94	94	113
Age (years)	79.5 ± 3.3	79.4 ± 3.4	80.6 ± 3.9
Women (%)	44	44	43
Prior infarction (%)	59	49	35
Prior revascularization (%)	22	18	11
⩾2 risk factors (%)	53	63	54
⩾2 co-morbid illnesses (%)	21	29	28
Angina class 3—4 (%)	75	78	81
Anti-anginal drugs (number)	2.5 ± 0.7	2.5 ± 0.7	2.5 ± 0.6
Non-invasive LVEF (%)	51.4 ± 13.0	51.5 ± 13.4	54.3 ± 11.0
Multi-vessel disease (%)	—	79	78

Table 3 One year outcome (events per patient and number of death)

	MED[a]	INV[a]	*p*-value unadjusted
n	94	94	
Deaths	5 (5.3%)	10 (10.6%)	0.28[b]
Non-fatal infarctions/patient	0.20 ± 0.049 (0/0/0/2)	0.10 ± 0.034 (0/0/0/2)	0.08[c]
Deaths/infarctions/patient	0.26 ± 0.052 (0/0/0/2)	0.20 ± 0.054 (0/0/0/3)	0.48[c]
Hospitalisations without revascularization/patient	0.22 ± 0.053 (0/0/0/2)	0.09 ± 0.033 (0/0/0/2)	0.03[c,d]
Hospitalisations with revascularization/patient	0.52 ± 0.064 (0/0/1/3)	0.10 ± 0.034 (0/0/0/2)	<0.0001[c,e]
MACE/patient	1.0 ± 0.104 (0/1/1/5)	0.38 ± 0.091 (0/0/0/5)	<0.0001[c]

[a] Mean value ± SEM, in parentheses: 25th, 50th, 75th percentile and maximum.
[b] Assessed using Fisher's exact test.
[c] Assessed using the bootstrap *t*-test.
[d] *p*-value = 0.09.
[e] *p*-value <0.0003 with Bonferroni adjustment accounting for the fact that the number of MACE is the sum of the 3 components: deaths/infarctions, hosptalisations without revascularization and hospitalisations with revascularization.

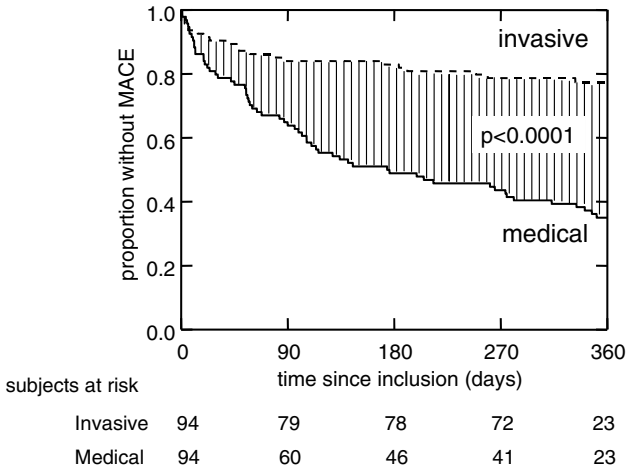

Fig. 1 Survival without MACE for INV (dotted line) versus MED patients (solid line). The shaded area in between represents the benefit of INV management over time, i.e. the average gain in event-free time after inclusion. The relatively low number of patients at risk at day 360 are due to many one year controls before that day censored in this figure.

agement on the different measures of QoL over time was again similar to the main trial: greater improvement in INV patients during early months but no longer significant differences after one year (data not shown). In addition, angina severity as measured by the Rose score improved significantly earlier and more persistently in INV as compared to MED patients ($p < 0.02$) and therefore, the number of anti-anginal drugs per patient was significantly lower after one year on INV therapy (1.3 ± 1.0 (quartiles 0.5/1/2) versus 2.1 ± 1.3 (quartiles 1/2/3) drugs in MED patients, $p < 0.0001$).

Costs and charges

Resource use results are shown in Table 4. The mean number of hospital days per patient at baseline was larger in the INV as compared to the MED group ($p = 0.04$, Bonferroni-adjusted) because many MED patients remained ambulatory throughout. During follow-up, INV patients had less hospital days on average ($p = 0.05$) resulting in a similar total hospital stay per patient of 19.4 days for INV and 21.6 days for MED patients, respectively ($p = 0.53$). Coronary angiography and PCI were used more frequently in INV than in MED patients ($p < 0.0006$, Bonferroni-adjusted) but CABG surgery was used similarly in both groups although at much lower rates than PCI. Overall, total costs per patient, i.e. including costs for non-invasive tests, were only marginally higher in INV as compared to MED patients: CHF 27 580 (mean) ± 2088 (SEM) versus 22 176 (mean) ± 2264 (SEM) per patient ($p = 0.08$), the quartiles being 13 850/21 550/34 500 and 3900/19 675/31 350, respectively. Thus, INV patients had higher 30 day costs (CHF 21 065 ± 1299 versus

Table 4 Study related resource use over one year (units per patient)

	Medical[a]	Invasive[a]	p-value[b] unadjusted
n	94	94	
Hospital days/patient			
Baseline	7.0 ± 1.22 (0/1/10/76)	10.6 ± 0.95 (4/8/15/66)	0.02
Follow-up	14.6 ± 2.16 (0/8/20/118)	8.7 ± 2.08 (0/0/7/100)	0.05
Total	21.6 ± 2.67 (3/15/28/146)	19.42.34 (7/11/22/113)	0.53
Coronary angiographies/patient	0.63 ± 0.071 (0/1/1/3)	1.12 ± 0.037 (1/1/1/3)	<0.0001[c]
PCI/patient	0.29 ± 0.062 (0/0/0/3)	0.72 ± 0.067 (0/1/1/3)	<0.0001[c]
CABG/patient	0.26 ± 0.045 (0/0/1/1)	0.30 ± 0.047 (0/0/1/1)	0.52
Noninvasive tests/patient	0.35 ± 0.056 (0/0/1/2)	0.46 ± 0.065 (0/0/1/2)	0.22

[a] Mean value ± SEM, in parentheses: 25th, 50th, 75th percentile and maximum.
[b] Assessed using bootstrap *t*-test.
[c] p-value <0.0006 each with Bonferroni adjustment accounting for the fact that the average total cost per subject was computed as a weighted sum of the average individual numbers of six 6 units: hospital days, ICU-days, coronary angiographies, CABG, PCI and non-invasive tests.

8479 ± 1481; $p < 0.0002$, Bonferroni-adjusted) but lower months 2—12 follow-up costs than MED patients (CHF 6515 ± 1580 versus 13697 ± 1722; $p = 0.004$ Bonferroni-adjusted) as shown in Fig. 2.

Detailed results of patient-specific charges in the subgroup of 56 patients with these data are given in Table 5. Besides more hospitalisations during follow-up as noted above, MED patients had also significantly more practitioners' charges: MED patients consulted their private physicians on average ten times more frequently than INV patients during the first month of the study and three times more often during the following 11 months. Thus, and in contrast to total cost results, mean total charges per patient were marginally lower for INV patients: CHF 26220 versus 32070 for MED patients, the medians being CHF 19986 versus CHF 20530 ($p = 0.47$). These results were not significantly altered if patients who died during follow-up were excluded from the analyses of costs and charges.

Cost-effectiveness

Over the one year study period, 0.61 (95% CI: 0.35—0.87; $p < 0.0001$) major events per patient were prevented at

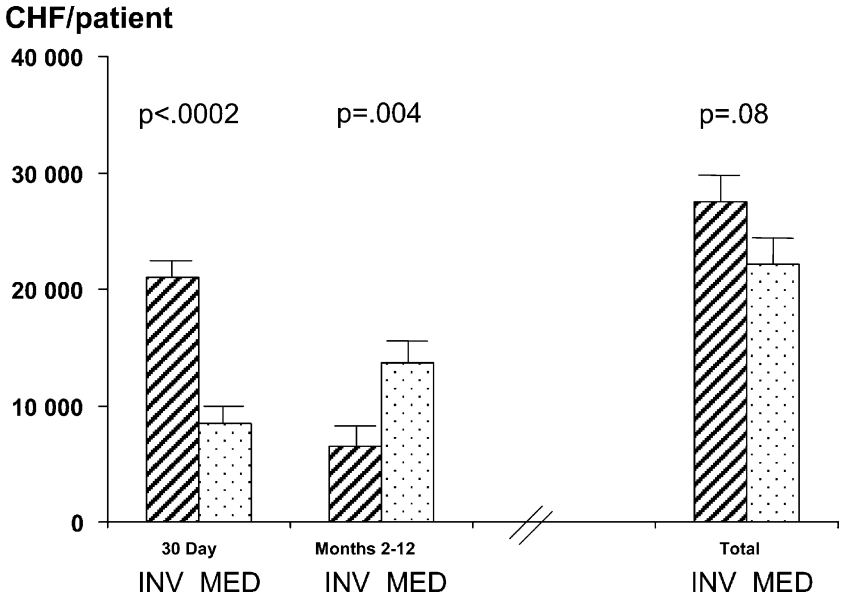

Fig. 2 Average costs (bars) with standard errors (whiskers) for both treatment strategies (INV = grey, MED = white) during the first 30 days, during months 2—12 and for the entire one year period. Note the early increased costs of the INV strategy compared to the late increased costs of the MED strategy.

Table 5 Mean patient-specific charges over one year

	Medical[a]	Invasive[a]	*p*-value[b] unadjusted
n	28	27	
General practitioner	1404 ± 299 (0/949/2451)	208 ± 111 (0/0/0)	0.0003[c]
Specialist	967 ± 277 (0/297/1059)	1299 ± 230 (129/1210/2031)	0.37
Pharmacy	2208 ± 479 (664/1454/2889)	2176 ± 400 (481/1692/3833)	0.96
Hospitalisation	24720 ± 6165 (4609/13388/25056)	20678 ± 3228 (9454/13168/31658)	0.57
Rehabilitation	2772 ± 752 (0/0/5610)	1859 ± 645 (0/0/4590)	0.36
Total charges	32070 ± 6791 (9517/20530/37130)	26220 ± 3520 (13543/19986/40173)	0.47

[a] Charges in CHF: mean value ± SEM, 25th, 50th and 75th percentile (in parentheses).
[b] Assessed using bootstrap *t*-test.
[c] *p*-value 0.0015 with Bonferroni adjustment accounting for the fact that the total charges are the sum of the total charges of the five given subcategories.

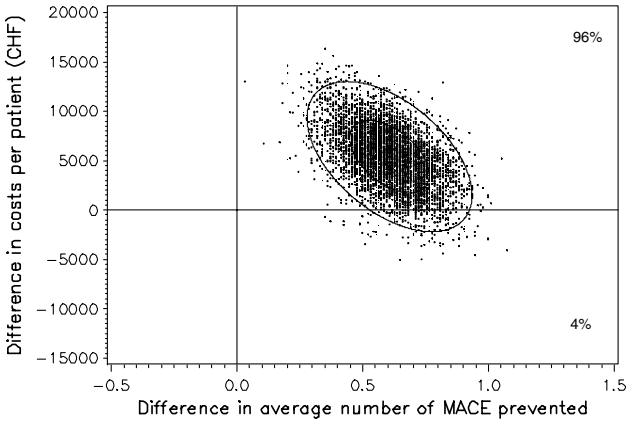

Fig. 3 Bootstrap results (5000 replicates) for incremental cost-effectiveness, i.e. costs associated with the average number of MACE prevented, of INV versus MED treatment. The outer ellipse represents the 95%-confidence region for the true incremental cost-effectiveness of INV as compared to MED treatment. The inner ellipse defines the 50%-confidence region. The center of the ellipse represents the point estimate of incremental effects and costs, i.e. −0.61 MACE prevented with CHF 5404 per patient.

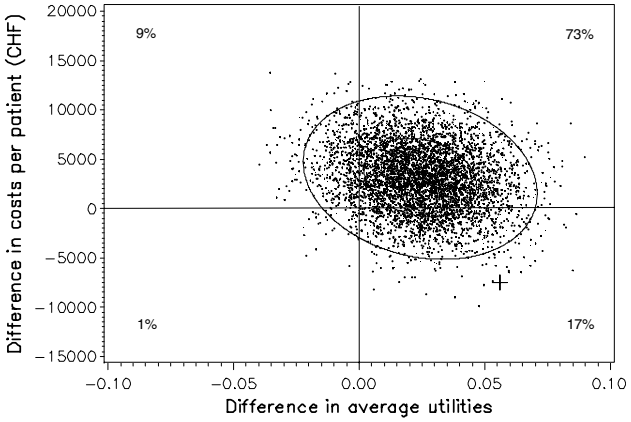

Fig. 4 Bootstrap results (5000 replicates) for incremental cost-effectiveness, i.e. costs associated with the average individual gain in utility, in the first year among survivors with complete information on QoL according to SF36 ($n = 66$ and 58 for MED and INV patients, respectively). The outer ellipse represents the 95%-confidence region for the true incremental cost-effectiveness of INV as compared to MED treatment. The inner ellipse defines the 50%-confidence region. The center of the ellipse represents the point estimate of incremental effects and costs, i.e., 0.024 utility units gained with CHF 3120 per patient.

an average cost of CHF 5404 (95% CI: −640 to +11 450; $p = 0.08$) per patient managed invasively compared to one on medical strategy (Fig. 3). This is equivalent to an average incremental cost to prevent one major clinical event of CHF 10 100 (95% CI: −800 to +28 300; $p = 0.08$) or € 6965. The incremental cost per day without MACE averaged CHF 68, corresponding to € 47; the average incremental cost to postpone the first major event by an average of 91 days (95% CI: 53—129; $p < 0.0001$) was CHF 5404 or € 3730. In Fig. 3, the datapoints representing bootstrapping results are contained in the upper right (96%) and lower right (4%) quadrants of the CE plane, indicating a higher effectiveness of the INV strategy at higher costs, with a small possibility of a higher effectiveness at lower costs.

Despite the significant benefit in angina severity and reduction in anti-anginal therapy, the difference in utilities between the two treatment groups based on the SF36 assessment was small: 0.024 (95% CI: −0.013 to 0.061; $p = 0.2$) at an average cost of CHF 3120 or € 2152 per patient and year (Fig. 4). The majority of data points is again situated in the upper right quadrant of the cost-effectiveness plane, but there are points in all four quadrants, indicating a more indifferent situation.

Results of sensitivity analyses showed that for the worst case scenario, an increased incremental cost-effectiveness ratio of CHF 11 600 (95% CI: −900 to 32 500) or of € 8000. In the best case scenario, this value decreased to CHF 5100 (95% CI: −400 to 14 200) or to € 3515.

Discussion

This pre-defined cost-effectiveness analysis of the TIME study shows that an invasive strategy in elderly patients with angina pectoris refractory to standard drug therapy

is cost-effective over a one-year observation period. Costs and charges were not significantly higher for the INV as compared to the MED strategy over this time period and there was a significant benefit of INV over MED therapy regarding freedom from MACE as well as regarding angina reduction. In the base case analysis, incremental costs to prevent one additional major event were in the range of CHF 10000 (€ 6900) which is small compared to the incremental costs of other treatments preventing life-threatening events.[1] The accompanying confidence interval, taking into account random variation in effectiveness and resource use results was even crossing the zero line towards a situation of higher effectiveness at lower costs.

Early costs of revascularization in the severely symptomatic patients studied in TIME were offset by late costs in medical therapy-assigned patients: increased rate of late symptom-driven revascularization and increased costs of private physician visits pointing towards a relevant shift of costs based on the type of care delivered to INV and MED patients. Thus, costs of revascularization should not be a reason to withhold an invasive strategy to elderly patients with chronic angina despite standard medical therapy.

Previous cost-effectiveness analyses comparing CABG surgery with medical therapy concluded that CABG surgery has a highest cost-effectiveness ratio in high risk patients in whom surgery improves survival.[2–4] In patient subsets where mortality is not reduced, CABG surgery is cost-effective only if symptoms are severe.[4] These findings are confirmed by the present analysis in patients with symptoms refractory to usual drug therapy, although only a minority of them were revascularized by CABG surgery. Most patients (72%) were revascularized by PCI as in the Angioplasty Compared to MEdicine (ACME),[15] the Second Randomized Intervention Treatment of Angina (RITA-2)[16] or the Atorvastatin VErsus Revascularization Treatments (AVERT)[17] trials. In none of these trials were formal cost-effectiveness analyses performed.[1] They all included relatively low risk patients with mild to moderate symptoms and a suitable anatomy for PCI. Whereas the increased early costs of PCI diminished progressively during the longer-term follow-up in the ACME trial,[18] this was not the case in the RITA-2 trial.[19] These differing results of RITA-2 which contrast also to the present findings of the TIME study may be explained by a low stent use in RITA-2 inducing increased rates of peri-procedural infarctions and repeat interventions, a very low revascularization rate during follow-up in medically treated patients (20%/3 years versus 46%/1 year in TIME) reflecting the mild symptoms of patients in RITA-2 and the restricted intervention use in the United Kingdom. Outpatient visits and costs in medical patients of RITA-2 were similar in both treatment groups but markedly increased in TIME patients, again most likely due to the more severe symptoms of TIME patients. Therefore, the differences in costs, and cost-effectiveness, between these studies may be explained by patient selection (severity of symptoms) and procedural differences (the mode of revascularization). Thus, the finding of the present analysis indicates that revascularization is cost-effective if patients are severely symptomatic, just as has been described for CABG surgery.[4]

In elderly patients, the rate of complications and the length of hospital stay increases after CABG surgery[20] as well as after PCI.[21] Retrospective comparative analyses[22,23] in relatively small groups of patients suggested that the benefit of revascularization in elderly symptomatic patients tends to be greater and, therefore, cost-effectiveness is increased. The present analysis of the first prospective revascularization versus medical management trial in elderly patients confirms these observations in a formal cost-effectiveness analysis. We used freedom of MACE and improvement in QoL as measures of effectiveness as we defined QoL — and not survival — as the primary endpoint of this trial with 80-year-old patients. This has limitations however because hospitalisations formally appear on both sides of the cost-effectiveness equation. We have hypothesized on the relative benefit of death, infarction and hospitalizations on outcome in the TIME study before.[7] The same limitations are relevant and have been discussed for such analyses after angioplasty and stenting[23–25] and recently for the economic evaluation of drug-eluting stents.[26] They should help to provide policymakers with a meaningful and comparative ratio of different treatments despite the fact that they do not primarily affect survival.

QoL was expressed in terms of an estimated mean utility summarising assessments after 6 and 12 months compared to baseline and the development over time. However, QoL was not assessed at the point in time of major events where utilities would have been lowest. Therefore, estimated average utilities over one year likely did not fully capture the actual difference in QoL benefit (as suggested by the significant difference in MACE in favor of INV management). In addition, anti-ischaemic therapy aimed at reduction in angina is reflected in only one of the eight domains of the SF36 from which utility values were derived. In addition, the differences in angina severity and number of anti-anginal drugs needed could not be incorporated in the present cost-effectiveness calculation. If these factors could have been included in the formal incremental cost-effectiveness analysis regarding QoL, the results would have favored the INV strategy even more.

Conclusions

The findings of this pre-defined cost-effectiveness analysis of elderly patients with chronic angina refractory to standard drug therapy show that an invasive strategy with coronary angiography followed by revascularization if feasible is cost-effective over a one-year observation period relative to optimised medical therapy. The early increased costs of revascularization are balanced by increased private practitioner's charges and symptom-driven late revascularizations. This suggests that an invasive strategy with improved clinical effectiveness at only marginally increased costs over one year, compared to optimised medical management, may even be

considered a 'preferred' strategy. Thus, increased intervention costs should not be an argument to withhold an invasive strategy to an elderly patient with symptomatic chronic CAD. These conclusions are relevant to elderly patients presenting to their private physicians for angina refractory to standard anti-anginal therapy as was the case with participants of the TIME study.

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