

# Management of chronic heart disease in the elderly

## TIME studies in perspective

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### Summary

Two problems predominate in elderly patients with heart disease: chronic coronary artery disease (CAD) and chronic congestive heart failure (CHF). We addressed both of these problems in two separate prospective randomised multicentre management trials. The findings of these studies are discussed in the light of other randomised controlled trials on the treatment of chronic CAD and intensified hormone-based CHF therapy. The implications are that elderly patients should be offered invasive evaluation and revascularisation if their symptom/ischaemic risk is high and coronary anatomy suitable for revascularisation. They will benefit from rapid symptom relief and improvement in quality of life. Alternatively, they could be managed with optimal drug therapy only and undergo invasive evaluation and revascularisation if medical management fails, as will be the case in a third to half of patients. In contrast, elderly patients with CHF will not benefit from intensified treatment as younger patients do. Thus, the findings suggest that specific CHF trials in elderly patients are warranted to obtain a better definition of their treatment options, which seem more limited than in younger patients.

According to Swiss federal statistics, life expectancy has increased tremendously in Switzerland during the last 35 years: for women from about 76 years in 1970 to 84 years in 2006, and for men from 70 to 79.1 years during the same time period [1]. Thus, the number of elderly Swiss inhabitants, particularly those aged  $\geq 75$  years, has risen sharply. The leading cause of death in Switzerland in 2006 was still "cardiovascular" for women (39.5%) and men (34.6%) [1] and again this was even more so in patients aged  $\geq 75$  years. Among these cardiovascular deaths, those due to coronary artery disease (CAD) are by far the most prominent. In addition, CHF or end-stage heart failure was a main

reason for morbidity associated with frequent hospitalisations and dependence on medical treatment [2]. Thus, CAD and CHF represent the most important challenges in the aging population, for which

there is a lack of randomised controlled trial data [3].

The TIME studies were therefore initiated as prospective multicentre trials to assess whether an intensified invasive or hormone-guided treatment strategy would yield an outcome benefit in elderly patients with CAD or CHF: the Trial of Invasive versus Medical Therapy in Elderly Patients with Chronic CAD (TIME; 4) and the Trial of Intensified BNP-guided versus standard symptom-guided Medical Therapy in Elderly Patients with Congestive Heart Failure (TIME-CHF, 5).

The aim of the present report is to summarise the most important results of these two trials and to compare findings with other similar studies in patients with chronic CAD and CHF respectively. This should have reasonable management implications for elderly patients with chronic angina or dyspnoea due to heart failure.

*Key words: chronic heart disease; elderly; TIME study; Swiss II study; BARI-2D*

### Elderly patients with chronic angina

#### The TIME study

The TIME study initially published in 2001 [4] reported on 301 patients aged 75 years or over with chronic stable angina CCS class II or greater, despite at least 2 antianginal drugs. Based on this clinical presentation, patients were randomised to two treatment strategies: optimal medical therapy consisting of the addition of at least one more antiischaemic drug in 80% of patients, and/or an increase in antiischaemic drug dose in 55%, or an invasive strategy consisting of coronary angiography with a view of revascularisation

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(percutaneous coronary intervention [PCI] or coronary bypass graft surgery [CABG]), which was performed in 71%. The first endpoint was symptom relief and quality of life (QoL) together with freedom from major adverse cardiac events (MACE: death, myocardial infarction [MI], secondary revascularisation) after 6 months, with additional follow-ups after 1 year and 4 years.

### Results of TIME

After 6 months [4], both treatment strategies reduced angina severity and improved QoL significantly compared to baseline ( $p < 0.01$ ), but these improvements were more pronounced in invasively managed patients (significant for angina severity and overall health status). MACE rate was lower while antiischaemic drug therapy could be reduced in invasively managed patients and remained so for up to one year ( $p < 0.001$ ; [6]), mainly due to the need for follow-up revascularisations in medically managed patients: more than 40% of these were revascularised during the first year of study for medically refractory symptoms or acute coronary syndromes [6]. This led to an improvement in symptomatic status and measures of QoL in patients randomised to a medical strategy such that, overall, differences in angina severity and QoL between treatment groups were no longer present after one year.

A cost substudy [7] showed that despite increased costs initially (due to the higher angiography and intervention costs) in the invasive group, this cost difference disappeared to a great extent by one year due to more practitioner's visits, more follow-up investigations and revascularisations in patients randomised to medical management. The average cost of preventing one MACE was CHF 10 100 (−800/+28 300), indicating that invasive management was cost-effective. The authors concluded that an invasive approach may not be denied to elderly patients with chronic CAD on grounds of cost.

After an average follow-up of 4.1 years, patients who were revascularised during the initial year of study had significantly better survival than medically managed patients [8]. This was also true if patients were analysed by intention-to-treat in their randomised treatment groups. However, this survival benefit was observed only late, after 4 years of observation. In fact, revascularisation during the initial year of the study and female gender were the only independent predictors of better survival, whereas age  $\geq 80$  years, diabetes, prior CHF and  $\geq 2$  comorbidities were predictors of a higher mortality.

### TIME implications

Overall implications of these TIME findings may be summarised as follows: elderly patients with chronic angina refractory to at least 2 antianginal drugs should be offered coronary angiography despite their higher rate of comorbidities and periinterventional risks com-

pared with younger patients. If revascularisation is feasible and is performed, these patients benefit twice: in early symptom relief and improvement in QoL, as well as in long-term survival. An early invasive strategy of this kind is cost-effective. However, patients may also choose to be treated medically first and undergo coronary angiography with a view to possible revascularisation only when symptoms become refractory. This will be the case in almost half of patients managed medically, while the others will not need invasive evaluation and treatment; they will continue to have symptoms but at a lower level and with continued drug therapy.

### Other major randomised controlled trials in patients with chronic CAD

#### The COURAGE study

The Clinical Outcomes Utilising Revascularisation and Aggressive Drug Evaluation (COURAGE) trial [9] studied as the main question, in 2287 patients with stable angina/ischaemia and a coronary anatomy suitable for PCI, whether PCI combined with medical therapy would be superior to optimal medical therapy alone. Thus patients had to be catheterised first and randomisation was done on the basis of angiographic findings only. Patients with severe angina CCS  $\geq$ III, a markedly positive stress test or severe CHF, and patients with extensive CAD not suitable for PCI or in urgent need of PCI, were therefore excluded.

The primary endpoint of all death or non-fatal MI did not differ between the two treatment groups over a mean follow-up of 4.6 years (HR 1.05, 95% CI: 0.87–1.27;  $p = 0.62$ ). However, in invasively-treated individuals the rate of angina-free patients was significantly higher in a study period of up to 3 years. In addition, follow-up revascularisations were less often needed (21% versus 33%,  $p < 0.001$ ) during the initial year and a significant reduction in antiischaemic drug therapy was possible throughout the study. The conclusions could be summarised as follows: as an initial management strategy in patients with stable CAD, PCI did not improve outcome when compared to optimal medical therapy, but did reduce the prevalence of angina and the need for subsequent revascularisations and antianginal drug therapy.

#### Open Artery Trial

The Open Artery Trial (OAT) studied the question whether PCI to open an occluded infarct-related artery after acute myocardial infarction would be superior to medical therapy alone for a 3-year outcome [10]. The study included 2166 stable patients with an occluded infarct-related artery 3–28 days after acute MI. Patients with left main or three vessel disease or with severe symptoms (angina CCS  $\geq 3$ ; dyspnoea NYHA  $\geq 3$ ) were excluded.

The primary endpoint of death, MI and/or stroke combined after 3 years did not significantly differ between the two treatment groups (HR 1.16, 95%CI: 0.92–1.45;  $p = 0.20$ ). However, in PCI patients the rate of angina was significantly reduced during up to 2 years of follow-up, and the rate of non-protocol follow-up revascularisation was significantly lower (18.3% versus 22.0%,  $p = 0.03$ ). We concluded from OAT (Basel was an OAT centre) that, compared to medical therapy, invasive treatment did not change the rate of death/MI or stroke; but it did reduce the frequency of angina and the need for non-protocol revascularisations during follow-up.

### SWISSI II study

The Swiss Study of Silent Ischaemia II (SWISSI II) trial studied the question whether PCI is superior to medical therapy, both combined with risk factor control in patients with only silent myocardial ischaemia after MI [11]. The study included 201 patients with silent myocardial ischaemia documented by stress imaging within 3 months of MI and a coronary anatomy suitable for PCI. Patients with any angina, no ischaemia, 3-vessel disease or no CAD were excluded.

The primary endpoint, survival free of cardiac death, non-fatal MI and/or revascularisation during a 10-year follow-up, was significantly higher in the PCI compared to the medical group (HR 0.33, 95% CI: 0.20–0.55;  $p < 0.001$ ). In addition, in PCI treated patients the rate of objective signs of ischaemia during repeated stress tests and antiischaemic drug therapy was significantly lower throughout the study period. We concluded from SWISSI II that in patients with recent MI, silent ischaemia verified by stress imaging and 1-2-vessel CAD, PCI, compared to medical therapy, reduced signs of exercise ischaemia, the need for antiischaemic drug therapy and follow-up revascularisations, and lowered the long-term MACE rate and mortality.

### BARI-2D

The most recent study, **Bypass Angioplasty Revascularisation Investigation – Type 2 Diabetes (BARI-2D)** addressed the question whether PCI or CABG surgery combined with optimal medical therapy is superior to optimal medical therapy alone in stable CAD patients with diabetes mellitus [12]. 2368 patients with type II diabetes mellitus and stable CAD documented by angina CCS 0–2 in 82%, a positive stress test and a coronary anatomy suitable for PCI or CABG were included. Patients in need of immediate revascularisation, with left main CAD, dyspnoea NYHA  $\geq 3$  or prior PCI/CABG within the last year were excluded.

The primary endpoint of all-cause mortality after 5 years did not significantly differ between the two treatment strategies (HR 0.5, 95% CI: –2.0–3.1;  $p = 0.97$ ) nor did survival free from MI or stroke. However, medically managed patients needed follow-up revasculari-

sation in 42%; unfortunately, no data on follow-up revascularisations in the invasive group and no ischaemic outcomes were described in the initial publication. The authors concluded that in BARI-2D there was no significant difference in rates of death and MACE between patients with PCI/CABG and those with optimal medical therapy, but that the rate of follow-up revascularisations was high in the medical treatment group. BARI-2D also tested 2 diabetes treatment strategies, insulin sensitisation versus insulin provision, which also yielded no difference in clinical outcomes.

### Comparison of TIME with other RCT findings

Table 1 summarises key points of these 5 major RCTs in patients with chronic CAD. Comparison of these trials affords important insights into outcomes in relation to patient selection and management strategies. Four studies were basically mortality studies (COURAGE, BARI-2D, OAT, SWISSI II) with three of them including non-fatal MI in their primary endpoint, with, in addition, CHF (OAT) or revascularisation (SWISSI II). In contrast, TIME had symptom severity/QoL as the primary endpoint, whereas it was a secondary endpoint in COURAGE, OAT and SWISSI II (although in SWISSI II it was objective signs of ischaemia). Accordingly, 2 studies (TIME and SWISSI II) had angina/ischaemia as the main inclusion criterion, whereas in the other 3 inclusion was defined as “stable CAD” usually with mild or no angina/ischaemia but a pre-randomisation defined CAD “suitable for revascularisation”; in fact this was also true of SWISSI II and thus only TIME randomised patients before cath were based solely on clinical presentation.

Thus, *ischaemic risk* defined as angina CCS class  $\geq 2$  and/or documented ischaemia in all patients was highest in TIME and SWISSI II. In contrast, ischaemic risk was lowest in OAT and low to medium in COURAGE and BARI-2D. This is paralleled to some extent by the rates of cross-over to revascularisation for medically-managed patients: this was highest in TIME, followed by BARI-2D, COURAGE and SWISSI II, and lowest in OAT.

In contrast, *mortality risk* as defined by the overall annual mortality was highest in TIME, moderate in OAT and BARI-2D, lower in COURAGE and lowest in SWISSI II. This is paralleled by the other most relevant prognostic factors age and left ventricular ejection fraction (LVEF) at baseline: age being highest in TIME (by definition) and lowest in SWISSI II, whereas LVEF was worst in OAT followed by TIME, and chiefly normal in the other three studies (table 2).

The mode of revascularisation was only PCI in COURAGE, OAT and SWISSI II but either PCI or CABG in TIME and BARI-2D. In both of these latter studies, subgroup analyses suggested a somewhat better symptomatic/combined endpoint outcome for the

**Table 1**  
Comparison of the major randomized controlled trials discussed.

	<b>TIME</b>	<b>OAT</b>	<b>SWISSI II</b>	<b>COURAGE</b>	<b>BARI-2D</b>
Year of 1st publication	2001	2007	2007	2008	2009
Journal 1st publication	Lancet	NEJM	JAMA	NEJM	NEJM
n	301	2166	201	2287	2368
Age	80 ± 4	59 ± 11	55 ± 9	62 ± 11	62 ± 9
Target of therapy a)	symptoms/QoL	death/MI/CHF	death/MI/revascularisation	death/MI	death
b)	survival	symptoms	ischemia	symptoms	death/MI/stroke
Patient selection	clin. presentation	occluded IRA	silent ischaemia/coronary anatomy	coronary anatomy	ischaemia/coronary anatomy
Angina CCS	II-IV	0-II	0	0-III	78% 0-II
Time after MI	–	3–28 days	<3 months	–	–
Exclusions	<75 years ACS <10 days	LM/3VD CCS ≥III NYHA ≥III	LM/3VD any angina	CCS IV ischaemia II NYHA ≥IV LVEF <30%	immediate revasc. needed LM NYHA ≥III
CAD 1-2VD	40%	82% (1VD)	100%	70%	?
LVEF	52 ± 13%	48% (<50%)	57%	62 ± 10%	“82% normal”
Revasc.	PCI/CABG	PCI	PCI	PCI	PCI/CABG
Medical therapy	“optimal”	open	“optimal”	“optimal”	“optimal”
Follow-up (yrs)	4.1	3	10	4.6	5
Mortality/year	4.4%	2.5%	1.2%	1.6%	2.1%

ACS = acute coronary syndrome; CABG = coronary artery bypass graft surgery; CAD = coronary artery disease; CCS = Canadian Cardiac Society class; CHF = congestive heart failure; clin = clinical; IRA = infarct related artery; LM = left main coronary disease; LVEF = left ventricular ejection fraction; MI = myocardial infarct; NYHA = New York Heart Association class; “optimal” = as defined in each study; PCI = percutaneous coronary intervention; QoL = quality of life; revasc = revascularisation; VD = vessel disease.

**Table 2**  
Comparison of ischaemic and mortality risks in the different trials.

	<b>TIME</b>	<b>OAT</b>	<b>SWISSI II</b>	<b>COURAGE</b>	<b>BARI-2D</b>
Inclusion	stable CAD angina	stable post MI occluded IRA	stable post MI silent ischaemia suitable anatomy	stable CAD suitable anatomy	stable CAD suitable anatomy
Age group	elderly	average	younger	average	average
LV function	slightly reduced	reduced	normal	normal	normal
1° endpoint	symptoms/QoL	death/MI/CHF	cardiac death/MI/PCI	death/MI	death
2° endpoint	survival	symptoms	ischaemia	symptoms	death/MI/stroke
Ischaemic risk	+++	(+)	+++	+	++
Mortality risk	+++	++	(+)	(+)	+

CAD = coronary artery disease; CHF = congestive heart failure; IRA = infarct related artery; MI = myocardial infarct; PCI = percutaneous coronary intervention; QoL = quality of life; LV = left ventricle.

somewhat sicker patients selected for CABG surgery (TIME on treatment CK, BARI).

Taken together, the findings of these 5 studies seem to suggest that if the ischaemic burden is high and the coronary anatomy suitable for revascularisation, and if comorbidities are not limiting as they sometimes are in elderly patients, then patients with chronic CAD benefit from invasive management, with more rapid symptom relief and improvement in QoL,

than from optimal medical therapy alone. Optimal medical therapy fails in a sizable percentage of patients, resulting in a need for revascularisation in a third to almost half of patients, but in up to 40% and more within the first year (TIME; BARI-2D). Thus, in fact, these studies compare *two treatment strategies*: one with immediate revascularisation combined with medical therapy and risk factor control, and the other with initial optimisation of medical therapy and risk

factor control followed by revascularisation if rendered necessary by refractory symptoms. In view of these complex strategies incorporating both invasive and medical therapies it is not surprising that short-term mortality was not different between the randomisation groups, even irrespective of baseline mortality risk (tables 1 + 2). There is, however, a certain suggestion that patients who are revascularised, be it by treatment assignment or by early need due to refractory symptoms, also benefit in long-term survival, i.e. after  $\geq 4$  years (TIME, SWISSI II).

Thus, *patients and their doctors may choose* between an early revascularisation strategy combined with reduced drug therapy long-term, or an optimised drug therapy with the need to be revascularised for refractory symptoms within one year in a third to half of patients. These patients will be more symptomatic early on, but will have a 50–66% chance of not having to undergo invasive procedures. Thus, the choice is between symptoms and revascularisation risk, i.e. it will be largely determined by *baseline symptom severity* and *suitability for revascularisation*.

### Elderly patients with chronic congestive heart failure

#### TIME-CHF

The prime reason for cardiac morbidity, particularly in elderly patients, is heart failure. Unfortunately, most CHF treatment trials excluded elderly patients [5], with the result that it is unknown whether findings of patients averaging 60–74 years also apply to patients  $\geq 75$ , as increasingly seen in daily practice. Since these elderly patients with CHF are less able and willing to be physically active, it is also questionable whether standard symptom-guided therapy is optimal in them or whether an intensified BNP-guided treatment strategy would not be more appropriate.

To address these questions we performed the TIME-CHF study as a multicentre German-Swiss trial randomising 622 patients with dyspnoea  $\geq$ II, a pro-brain natriuretic peptide (pro-BNP) level of  $\geq$ twice the upper limit of normal and a history of hospitalisation for CHF within one year, to an intensified BNP-guided versus a standard symptom-guided strategy [5]. Patients were stratified into two age groups:  $\geq 75$  years versus 60–74 years (control). The primary focus was on patients with a baseline LVEF  $\leq 45\%$  ( $n = 499$ ), whereas a separate analysis was done in 123 patients with a preserved LVEF.

Patients received increasing doses and medications to treat CHF according to current guidelines, in order to reduce BNP-levels to at least twice the upper limit of normal and NYHA class to at least II (intensified group) or to the same level of symptoms only (standard group). Treatment was uptitrated up to 6 months with

a final follow-up after 18 months. The primary endpoint was survival free of any hospitalisation, with survival and survival free of CHF hospitalisations as main secondary endpoints.

#### TIME-CHF results

Overall, intensified BNP-guided therapy did not improve the primary endpoint of survival free of any hospitalisation (HR 0.92, 95% CI: 0.73–1.15;  $p = 0.46$ ); however, there was a trend in survival in favour of BNP-guided therapy (HR 0.68, 95% CI: 0.46–1.01;  $p = 0.06$ ) and a significant benefit in the disease-specific endpoint “survival free of heart failure hospitalisations” (HR 0.66, 95% CI: 0.49–0.90;  $p = 0.008$ ). These beneficial effects of the intensified BNP-guided approach were more pronounced and significant for both secondary endpoints in younger patients ( $n = 210$ , average age  $69 \pm 4$  years), but not at all different in the elderly ( $n = 289$ , average age  $82 \pm 4$  years). Symptoms and BNP levels were significantly reduced by both treatment strategies without relevant differences between them.

#### Conclusions and implications of TIME-CHF

We concluded from this study that an intensified BNP-guided treatment approach did not improve the overall survival without any hospitalisation, and that this was particularly true in elderly patients. However, the disease-specific endpoint survival without heart failure hospitalisations was significantly improved overall and this was almost exclusively the case in younger patients. This finding is in agreement with earlier smaller-scale studies on this topic [13–16] which, together with TIME-CHF, suggest that a BNP-guided strategy reduces mortality by 26% in patients below age 75 years. In addition, TIME-CHF indicated that treatment recommendations based on trials of patients below age 75 years may not be directly applied to older patients. In fact, these patients may respond differently, partly due to their higher rate of comorbidities and partly due to their more severe underlying disease. Also, disease-specific endpoints may not reveal “the whole story” as demonstrated in TIME-CHF: the beneficial treatment effect noted in disease-specific endpoints was no longer present in the overall endpoint more relevant to the patients: to stay alive and out of hospital for whatever reason. Thus, CHF studies in elderly patients with CHF are certainly warranted.

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