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MINIREVIEWS

Conservative strategy for treatment of stable coronary artery disease

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Abstract

Patients with coronary artery disease vary widely in terms of prognosis, which is mainly dependent on ventricular function. In relation to the major outcomes of death and myocardial infarction, it is not clear in the literature if an invasive strategy of myocardial revascularization is superior to a conservative strategy of optimized medical therapy. Moreover, with the exception of patients with left main coronary disease, this similarity in prognosis also occurs in different subgroups of patients.

Key words: Coronary artery disease; Angina pectoris; Myocardial revascularization; Coronary angioplasty; Myocardial infarction; Prognosis; Disease-free survival

Core tip: Despite the evolution of myocardial revascularization techniques, the mainstay of treatment of stable coronary artery disease is optimal medical therapy. With the better understanding of the mechanisms underlying atherosclerosis, medical therapy develops and shows similar results in terms of survival and freedom from myocardial infarction compared to coronary interventions. Moreover, clinical trials have also demonstrated similar results between conservative and invasive strategies in various subgroups of patients, previously found to benefit from coronary interventions. In this review article, the authors discuss the results from main trials on specific groups of coronary artery disease patients which compared conservative and invasive strategies.

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INTRODUCTION

The first studies on the evolution of patients with stable coronary artery disease (CAD) and preserved left systolic ventricular function demonstrated a low incidence of major cardiac events, death or myocardial infarction, in non-revascularized patients, despite their anatomical complexity. Moreover, retrospective studies that compared optimized medical therapy (OMT) alone with coronary artery

bypass surgery (CABG) demonstrated similar rates of death or myocardial infarction in patients both with single-vessel or multivessel disease, in the presence of preserved systolic ventricular function.

In clinical conditions like diabetes mellitus or in elderly patients, the literature demonstrates that the conservative strategy of OMT is as safe as invasive strategies are, for the majority of CAD patients.

Although sub analyses from important studies have suggested surgery would be a safer strategy in patients with CAD and impaired ventricular function, this information has been questioned by a recent important prospective randomized clinical trial, which demonstrated similar results of medical therapy compared to bypass surgery.

Despite the evolution of CABG and percutaneous coronary intervention (PCI) in the last 20 years, with the widespread use of arterial grafts and surgery without the use of extra-corporeal circulation, and the emergence of pharmacological stents, the improvement in medical therapy also occurred substantially with the use of antiplatelets, beta-blockers, angiotensin-converting enzyme inhibitors and statins. Currently, these are the basis of pharmacological CAD treatment, but other options with specific mechanisms of action as ranolazine and ivabradine have also emerged as potential adjunct therapy. In addition, technical problems of invasive strategies, such as graft failure and restenosis of stents, deserve attention in this matter. Moreover, clinical complications of interventions also carry risks, especially related to cerebrovascular accidents after surgery and the possible need for future interventions with PCI. On the other hand, some specific subgroups of CAD patients do benefit by invasive strategies.

Thus, a conservative OMT strategy with multi-factorial control is a safe option for the treatment of the majority of CAD patients, especially those with well-preserved ventricular function. Invasive strategies are important tools for the management of CAD patients, and should be reserved particularly for patients with refractory symptoms, for those who develop acute coronary syndromes, and possibly for select patients with ischemic heart failure.

In this review article, the authors discuss the major findings of studies, especially clinical trials, comparing medical therapy with invasive coronary interventions, in terms of major outcomes, death and MI, in different clinical settings.

EVOLUTION OF CORONARY ARTERY DISEASE PATIENTS

The natural history of patients with CAD is impossible to observe in epidemiological studies for ethical reasons. Even if patients refuse coronary interventions, they still receive medical therapy and instruction on lifestyle modifications, which result in changes in their clinical evolution. Consequently, the evolution of CAD patients may be observed in prospective studies, and especially in randomized groups that include patients receiving medical therapy alone.

The evolution of patients with chronic, stable CAD was demonstrated in an important study published in 1989[1]. In this study, from 1977 to 1983, 150 stable CAD patients, including 92% with multivessel disease and also patients with left main coronary disease or equivalent (39.3%) with a formal indication for coronary surgical revascularization refused the procedure. They were followed for two to eight years until 1985, and medically treated with beta-blockers, nitrates, calcium-channel blockers, aspirin, and dipyridamole. Differently from modern treatment, at that time, they were not treated with angiotensin-converting enzyme inhibitors or with statins, important medications of current therapy. Despite anatomic complexity, the estimated overall survival in eight years was 89%, which represents an average annual mortality rate of 1.37%. Of note, only 10% of patients had myocardial infarction and 4% requested surgical revascularization during follow-up.

One of the first randomized studies that compared medical therapy alone with coronary bypass surgery in stable CAD patients was the Coronary Artery Surgery Study (CASS) trial[2], published in 1983. In this study, 780 CAD patients were randomized to one of the two strategies and followed for 5 years. Interestingly, in this study, the average annual mortality rate for patients assigned to medical therapy was 1.6% and to surgery 1.1% (P = 0.34). Analyzing only the patients with an ejection fraction ≥ 0.50 (75% of the entire population of the trial), those assigned to medical therapy had annual mortality rates of 1.1%, 0.6%, and 1.2%, respectively, for single-, double-, and triple-vessel disease. Patients with an ejection fraction $\geqslant$ 0.50 assigned to surgery had similar mortality rates 0.8%, 0.8%, and 1.2%, respectively, for single-, double-, and triple-vessel disease. There were no statistical differences between the two treatment strategies.

Analysis of ten-year follow-up of patients from the CASS trial[3] demonstrated an overall survival of 79% and 82% in medical and surgery groups, respectively, or an average annual mortality rate of 2.1% and 1.8% (P = 0.25).

The results of these studies demonstrate that annual mortality rates for stable CAD patients with normal ejection fraction is low and range from 0.8% to 2.1%, even in those with multivessel disease. In addition, these studies were performed during a time when patients did not receive statins or angiotensin-converting enzyme inhibitors, which are medications with the potential to lower this risk. Although great numbers of patients in these studies had a low-risk profile (preserved systolic ventricular function, stable non-limiting symptoms, and young patients), their

prognostic information is essential for understanding the results of studies on invasive strategies.

SINGLE-VESSEL CAD PATIENTS

As mentioned previously, the CASS trial as well as other trials have demonstrated that single-vessel CAD patients have low annual mortality rates, especially in the presence of preserved ventricular function (1.1% and 0.8%, respectively, for medical therapy and bypass surgery). Moreover, this good prognosis is similar among different treatment strategies.

One of the studies that addressed the comparative results of different strategies in this scenario of single-vessel CAD patients was the Medical, Angioplasty or Surgery Study Ⅰ trial[4]. This study evaluated 214 CAD patients with an isolated severe lesion > 80% at the proximal portion of the left anterior descending coronary artery. Patients with stable symptoms and well-preserved ventricular function were selected and randomized to medical therapy alone (n = 72), balloon angioplasty (n = 72), or CABG (n = 70) with an internal thoracic artery. After an average of 3-year follow-up, the primary end-point of cardiac death, myocardial infarction, or refractory angina requiring revascularization was 12%, 17%, and 3%, for medical therapy, angioplasty, and CABG. This difference was mainly dependent on new revascularizations, because mortality and myocardial infarction were similar in the 3 treatment strategies.

Another important study on single-vessel CAD patients was published in 1992[5] and compared medical therapy alone with angioplasty with the use of stents. Patients with severe stenosis in one coronary artery were randomized and followed for 6 mo. In that period, myocardial infarction occurred in 5 patients who underwent angioplasty and in 3 patients in the medical therapy group. However at the end of the follow-up, a higher number of patients assigned to angioplasty were free of angina (64% × 46% in angioplasty and medical therapy, respectively, P < 0.01), and performed better on exercise treadmill tests, despite higher costs and complications in the angioplasty group.

Thus, in the subset of single-vessel CAD patients, unless limited by refractory symptoms, the strategy of optimal medical therapy poses a similar prognosis in terms of survival and myocardial infarction compared to invasive strategies. However, patients with severe symptoms, especially if refractory to medical interventions may benefit in terms of alleviation of symptoms with angioplasty.

MULTIVESSEL CAD PATIENTS

The three most important studies conducted in the 1970's and 1980's that compared the strategy of medical therapy alone with bypass surgery were the Veterans Affairs (VA) Cooperative Study[6], the European Coronary Surgery Study (ECSS)[7], and CASS[2].

Most of the patients enrolled in these trials had multivessel CAD, and the European Study only enrolled such patients.

The VA Cooperative Study included 686 CAD patients with stable angina, electrocardiographic signs of previous infarction or ischemic changes in exercise, and at least one major coronary artery with ⩾ 50% stenosis. Patients were randomized to medical therapy alone or bypass surgery and were followed for 18 years. This study demonstrated similar rates of overall survival (33% and 30% for MT and CABG, respectively, P = 0.60), and similar rates of myocardial infarction (41% and 49% for MT and CABG, respectively). Importantly, in patients with preserved ventricular function, irrespective of the number of diseased coronary arteries, patients assigned to medical therapy had similar rates of death and myocardial infarction as those assigned to bypass surgery. On the other hand, the group with left main disease or with a high angiographic risk, characterized as triple-vessel disease associated with impaired left ventricular function, had better survival associated with bypass surgery. Of note, 41% of medical therapy patients underwent surgery during the entire 18-year follow-up.

Consistent with the findings of the VA Study, the CASS trial also showed that patients with single-, double-, or triple-vessel coronary disease had similar rates of overall survival and myocardial infarction in medical therapy and bypass surgery, if they had preserved systolic ventricular function (defined as an ejection fraction ⩾ 0.50). CASS also showed that in patients with impaired ventricular function and triple-vessel disease, surgery was a better survival option. Of note, these 5-year results were confirmed by a 10-year follow-up study[8].

Another important study, the ECSS demonstrated some differences compared to the two previous studies. This trial included 767 men with normal left ventricular function and multivessel disease and randomized them to bypass surgery or medical therapy. Differently from VA and CASS, ECSS showed higher survival rates after 5- and 12-year follow-up for surgically treated patients, but the difference between treatments in the 5-year follow-up decreased in the 12-year results (70.6% ± 5.8% *vs* 66.7% ± 5.3%, P = 0.04). However, this better survival with bypass surgery only occurred in triple-vessel disease patients. Survival of double-vessel disease patients was similar in the two strategies.

After these 3 studies, the only study that compared an invasive with a conservative strategy of OMT and included three groups of treatments was the Medical, Angioplasty or Surgery Study (MASS-Ⅱ)[8]. In this study, 611 patients with multivessel proximal CAD, preserved systolic ventricular function and stable

symptoms were randomized to receive OMT alone (n = 203), CABG surgery (n = 203), or PCI (n = 205) with the use of conventional stents. After 5-year follow-up[8], the combined primary end-points of death, myocardial infarction, and additional revascularization favored the patients assigned to bypass surgery (21.2%, 32,7% and 36.0%, respectively, for CABG, PCI and MT, P = 0.0026), especially due to a significant reduction in the rates of new revascularizations (3.9%, 11.2%, and 9.4%, respectively for CABG, PCI, and MT). However, mortality and myocardial infarction rates were statistically similar between the 3 groups. After 10-year follow-up[9], overall survival was similar between the 3 treatment groups (74.9%, 75.1%, and 69%, respectively, for CABG, PCI, and MT, P = 0.089). However, the incidences of myocardial infarction and cardiac deaths favored the surgical group. Importantly, after 10 years about 40% of MASS Ⅱ trial patients assigned to medical therapy did not develop any complications. In addition, combined and isolated end-points were similar between medical therapy and angioplasty groups.

Compared to the first studies (VA, ECSS, and CASS), the MASS trial was a more contemporary study, in which medical therapy included the use of statins, angiotensin-converting enzyme inhibitors, and dual antiplatelet therapy after PCI. However, the higher annual mortality in this trial compared to the previous ones may be due to a higher-risk profile, as patients were older at study entry, had a higher proportion of diabetics, and more complex and diseased coronary arteries (higher frequency of triple-vessel disease and lesions at the proximal portion of the left anterior descending artery). Thus, this higher-risk profile of patients from the MASS trial seemed to benefit from surgery, information similar to that of the VA and ECSS trials. The high-risk profile patients from the CASS trial also demonstrated the benefits of bypass surgery, but in this study this profile included patients with impaired ventricular function.

The MASS trial showed that medical therapy had similar outcomes when medical therapy was compared to angioplasty. However, this was not the primary objective of this study.

However, this was the major finding of another important study published in 2007, the COURAGE trial[10]. This study aimed at evaluating the clinical significance of PCI in stable CAD patients. With this purpose, 2287 patients with objective evidence of myocardial ischemia and significant CAD were randomized between 1999 and 2004 to OMT alone (n = 1138) or PCI with OMT (n = 1149). After a median 4.6-year follow-up, the primary end-point of overall death and myocardial infarction occurred in 19.0% in the PCI group and 18.5% in the medical therapy group (P = 0.62). Other isolated end-points such as myocardial infarction or hospitalization for acute coronary syndromes had similar rates in both groups. On the other hand, symptoms were better controlled by PCI, but still with a modest reduction in these rates compared to OMT.

Some meta-analysis of studies comparing PCI with medical therapy alone[11,12] demonstrated similar results, even when only patients with objective myocardial ischemia were included in the analysis[13].

Thus, the information from these trials shows that even for multivessel patients, with preserved ejection fraction, stable non-limiting symptoms, medical therapy is a safe alternative. The groups of patients who benefit from bypass surgery are those with a higher anatomical or clinical risk profile, such as patients with left main disease or limiting symptoms. The option for bypass surgery should also consider peri-procedural risks and the possibility of recent graft failure, which is mainly dependent on the surgeon's technical ability but also by anatomic characteristics, especially the coronary bench that will receive the graft. The option for PCI in stable CAD patients should also be carefully evaluated because it does not protect patients from myocardial infarction, hospitalizations, and or from the risk of death. PCI could be indicated for those patients with limiting symptoms despite optimized medical therapy and with an anatomy favorable to the procedure.

IMPAIRED VENTRICULAR FUNCTION AND CAD

As already mentioned, the CASS trial[2] was one of the first randomized trials to demonstrate that bypass surgery is superior in terms of overall survival compared to medical therapy alone in patients with triple-vessel CAD and impaired ventricular function. Interestingly, in this context, only patients with a great percentage of jeopardized ischemic myocardium had the benefits of revascularization, because single- and double-vessel disease patients with impaired ventricular function had similar survival rates with bypass surgery compared to medical therapy. However, one should consider that the CASS trial enrolled only 160 patients with left ventricular dysfunction, so that it could not have power enough to demonstrate potential differences between treatment groups. On the other hand, medical therapy at that time was quite different from current medical therapy for heart failure. For the entire population of the CASS trial, 64% of the medical group received beta-blockers at 60 mo after randomization, while only 34% of the surgical group received beta-blockers at the same follow-up period. Besides, angiotensin-converting enzyme inhibitors were not disposable at that time, nor were aldosterone blockers, which are also current essential medications for the treatment of heart

failure patients. Similarly, anesthesia, cardioplegia methods, and surgical technique have also improved since CASS trial.

Interestingly, an analysis from the CASS registry[14] with patients with severe left ventricular dysfunction, manifested by an ejection fraction below 0.36, demonstrated that the group of patients assigned to surgery had an improvement in survival compared to medical therapy patients, despite a high operative mortality of 6.9%. Moreover, a higher benefit of surgery over medical therapy was observed in patients with ejection fraction below 0.26 (5-year survival of 63% *vs* 43%, respectively, for surgery and medical therapy, $P = 0.005$) and in patients with predominantly anginal symptoms. The patients in whom heart failure symptoms predominated did not receive benefits from surgery over medical therapy. Thus, surgery probably benefited heart failure patients who had some extent of viable and ischemic myocardium, and probably did not benefit those with non-viable, fibrotic myocardium.

The findings from the CASS trial and registry were the basis for cardiology guidelines recommendations and cardiology practice supporting CABG in this scenario in the following decades.

Recently, the STICH (Surgical Treatment for Ischemic Heart Failure) trial[15], published in 2011, questioned the superiority of CABG for CAD patients with impaired ventricular function. This was a multicenter, randomized, clinical trial, in which CAD patients amenable to surgery who had an ejection fraction of 0.35 or less were randomized to OMT or CABG plus OMT. During the 56-mo follow-up, the primary end-point of overall death occurred in 41% of the medical therapy group and in 36% of the CABG group ($P = 0.12$). Of note, 17% of medical therapy group patients underwent CABG during follow-up.

In this contemporary trial, the hypothesis tested in previous studies, including CASS, that bypass surgery would be superior to medical therapy in terms of survival was contradicted by the results of such a well-designed study. Some reasons might be pointed out for this interesting finding. First, medical therapy for heart failure has improved continuously during the last 20 years. The better knowledge of the physiopathology of heart failure lead to the development and use of classes of medications directed to neurohormonal cascades[16,17] related to the progression of ventricular dysfunction. In many clinical trials[18-20], these medications were proven to positively influence survival, and currently beta-blockers, angiotensin-converting enzyme inhibitors, and aldosterone blockers are the main stain of modern treatment. On the other hand, despite its higher initial risk of complications, bypass surgical treatment of ischemic heart failure may benefit patients with jeopardized ischemic myocardium, amenable to revascularization. Of note, 52% of the population of the STICH trial had Canadian Cardiac Society (CCS) angina class 0 or 1, and 37% had dyspnea New York Heart Association (NYH) class Ⅲ or Ⅳ. However, subgroup analysis did not show differences when angina or dyspnea groups were compared. Thus, a great percentage of patients might have fibrotic ischemic scars not amenable to improving its function by bypass surgery. Thus, on the one hand, medical therapy improved substantially over time and changed the outcomes of heart failure patients. On the other hand, surgery was performed in patients with a great variability of ischemic heart disease. The patients with the highest likelihood of benefitting from CABG would be those with a higher percentage of hibernating myocardium (potential to improve function with revascularization), and especially if suitable to be revascularized (good distal benches to receive an arterial or venous grafts).

DIABETES AND CAD

In stable CAD patients, diabetes mellitus confers higher rates of complications and a worse prognosis[21]. Considering that some previous trials have demonstrated that CABG was superior to medical therapy alone in high-risk groups of patients, the BARI 2D trial[22] proposed studying the comparative results of a strategy of OMT *vs* a strategy of coronary revascularization (PCI or CABG) for type-2 diabetic CAD patients. After 5 years, the primary end-point of overall survival was similar between the 2 groups (survival rates of 88.3% and 87.9%, respectively, for revascularization and medical therapy alone, $P = 0.97$). Moreover, the rates of freedom from cardiovascular events (death, myocardial infarction, or stroke) were also similar between groups (77.2% and 75.9%, respectively, for revascularization and medical therapy groups, $P = 0.70$). When patients were stratified by the choice of PCI or CABG as the appropriate intervention, in the PCI stratum, survival and composite end-points were similar between medical therapy and PCI. In CABG stratum, survival was similar between medical therapy and CABG, although the rates of cardiovascular events were higher in medical therapy than in CABG.

Contrary to results of the BARI 2D trial, a substudy of 10-year results of the MASS Ⅱ trial[23] analyzed diabetic CAD patients in terms of comparative outcomes among medical therapy, PCI, and CABG in a long-term follow-up. Among diabetic patients ($n = 232$), mortality rates were 37.5%, 31.3%, and 27.5%, respectively, for medical therapy, PCI, and CABG ($P = 0.015$ for CABG *vs* medical therapy). Cardiac mortality also favored CABG-assigned patients, as the rates were 26.1%, 18.8%, and 12.5%, respectively ($P = 0.005$ for CABG *vs* medical therapy).

The strong evidence from BARI 2D is not con-

Table 1 Main randomized clinical trials comparing medical therapy alone with coronary interventions in stable coronary artery disease patients

Clinical scenario	Clinical trial	Randomization period	*n*	Study groups	Annual mortality	Main findings
Single-vessel CAD	MASS I (3.5 yr)	1988-1991	214	MT 72 PCI 72 CABG 70	MT 0 PCI 0.4% CABG 0.4%	Similar mortality and MI among the 3 groups
Multivessel CAD (majority of trials' patients)	VA (18 yr)	1972-1974	686	MT 354 CABG 332	MT 3.7% CABG 3.9%	Similar mortality and MI rates in the 2 groups
	ECSS (12 yr)	1973-1976	767	MT 373 CABG 394	MT 2.7% CABG 2.4%	Mortality higher in MT group in 3-vessel disease patients
	CASS (10 yr)	1975-1979	780	MT 390 CABG 390	MT 2.1% CABG 1.9%	Similar mortality in 1, 2 or 3-vessel with EF ⩾ 0.50. CABG was superior in 3-vessel with EF < 0.50
	MASS II (5 yr)	1995-2000	611	MT 203 PCI 205 CABG 203	MT 2.4% PCI 2.3% CABG 1.6%	Similar mortality in the 3 groups. Similar events in MT and PCI. CABG superior in terms of reinterventions
	COURAGE (4.6 yr)	1999-2004	2287	MT 1138 PCI 1149	MT 1.8% PCI 1.65%	Similar mortality and events in the 2 groups
Impaired ventricular function	STICH (4.6 yr)	2002-2007	1212	MT 602 CABG 610	MT 8.8% CABG 7.7%	Similar mortality rates. CABG superior in terms of hospitalization for cardiac causes
Diabetes mellitus	BARI 2D (5.3 yr)	2001-2005	2368	MT 1192 CABG/ PCI 1176	MT 2.3% CABG/PCI 2.2%	Similar mortality and MI rates in the 2 strategies
Elderly	TIME (3.1 yr)	1996-2000	282	MT 142 CABG/PCI 140	MT 7.2% CABG/PCI 6.8%	Similar mortality and MI rates between the 2 strategies

CAD: Coronary artery disease; MASS: Medical, Angioplasty or Surgery Study; VA: Veterans Affairs; ECSS: European Coronary Surgery Study; STICH: Surgical Treatment for Ischemic Heart Failure; TIME: Medical Therapy in Elderly patients; MT: Medical therapy; PCI: Percutaneous coronary intervention; CABG: Coronary artery bypass surgery.

firmed by other substudies like the MASS trial. A higher risk profile in the MASS trial, as well as the intensity of treatment in BARI 2D may explain in part such differences.

ELDERLY PATIENTS AND CAD

With the aging of the world population in recent decades, CAD has become more frequent. In addition, in the elderly, the likelihood of severe and diffuse CAD is higher than in younger populations[24]. Moreover, due to higher rates of procedure-related complications[25,26] and a lack of clinical trials comparing treatments in patients older than 65 years, the treatment of this specific population becomes even more challenging.

A sub analysis from the CASS registry[27] showed that in 1985 older CAD patients surgically treated had better survival rates compared to medically treated patients, during a 6-year follow-up (adjusted 6-year survival 79% and 64%, respectively, for surgical and medical therapy groups, $P < 0.0001$). However, this study should be carefully analyzed as this was a non-randomized study, and there were important baseline differences between the two treatment groups.

Another prospective, observational study published in 2002 analyzed clinical data and outcomes of all patients who underwent catheterization and revascularization in the province of Alberta, Canada[28]. This study showed that in 3 age cohorts (< 70 years, 70-79 years, and ⩾ 80 years), CABG was superior to PCI and medical therapy alone in terms of overall survival during 4-year follow-up. However, this study has also to be analyzed carefully because its design was observational, non-randomized, and included a great range of risk profiles, such as acute coronary syndrome patients as well as patients with impaired ventricular function, which may have favored surgical results.

One of the few studies designed to compare a conservative *vs* an invasive strategy for the treatment of elderly CAD patients was the Trial of Invasive *vs* Medical therapy in Elderly patients (TIME), published in 2004[29]. In this study, patients age 75 years or older, with Canadian Cardiac Society (CCS) class Ⅱ or greater angina, despite taking at least 2 classes of anti-anginal drugs, were randomized to medical therapy alone or to angiography and appropriate coronary revascularization (PCI or CABG). Despite their high-risk profile (mean age at entry 80-year-old, 82% with CCS class Ⅲ or Ⅳ angina), survival was similar between patients in the two strategies (91.5% *vs* 95.9% after 6 mo, 89.5% *vs* 93.9% after 1 year, and 70.6% *vs* 73.0% after 4.1 years, respectively, for medical therapy and revascularization strategies, P = NS). However, late revascularizations were more frequent in the medical therapy than in the revascularization group (45% *vs* 12%, $P < 0.0001$).

Post-hoc analysis of elderly CAD patients from the COURAGE trial[30] also demonstrated similar survival rates between conservative and invasive

strategies.

A recent post-hoc analysis of patients 65 years or older from the 10-year follow-up of the MASS Ⅱ trial[31] also showed similar overall survival rates comparing the three treatment strategies, medical therapy, PCI with conventional stents or CABG (63%, 69% and 66%, P = 0.93). The rates of myocardial infarction were also similar among the three groups. However, as demonstrated in the TIME trial, the rates of additional revascularizations were lower in the CABG group (Table 1).

EXTENSION OF MYOCARDIAL ISCHEMIA

Although ESC guidelines[32] and some retrospective studies[33,34] have suggested that patients with myocardial ischemia extension greater than 10% benefit from myocardial revascularization, no prospective study have confirmed this finding. Currently, the on-going International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) trial, which aims at randomizing 8000 coronary artery disease patients with moderate or severe ischemia to an invasive or a conservative strategy, should help to bring some reliable information in this matter.

CLINICAL IMPLICATIONS AND CONCLUSION

Despite the strength of several study findings, significant developments in aggressive MT and lifestyle prescriptions with comprehensive risk factor modification have continued to occur since trials were conducted, and this may impact the outcomes of an MT-based strategy, even in the long-term follow-up. Further evidence in this long-running debate will be provided by the results of current trials of the initial MT strategy in patients with stable multivessel disease and preserved ventricular function. Moreover, results of studies on drug-eluting stents demonstrating the superiority of CABG over PCI have been questionable, and some might argue that this procedural refinement makes the present results obsolete. However, data from randomized and nonrandomized trials show that this new type of stent has no advantageous effect on death and nonfatal MI relative to bare-metal stents despite yielding striking reductions in rates of restenosis and repeat revascularization procedures. Thus, we believe that the observations reported herein with respect to death and MI remain applicable to contemporary practice.

In summary, several trials strongly show the benefits of PCI and CABG over MT in regard to some end points at long-term follow-up, although with similar rates of overall mortality. Additionally, CABG surgery is associated with higher rates of event-free survival.

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