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A Meta-Analysis of 20 Randomized Trials of a PCI-Based Strategy in Patients With Stable Coronary Artery Disease

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Abbreviations

BMS	-	Bare metal stent
CABG	-	Aorto-coronary bypass surgery
CAD	-	Coronary artery disease
CHD	-	Coronary heart disease
CI	-	Confidence interval
DES	-	Drug eluting stent
LDL	-	Low-density lipoprotein
MI	-	Myocardial infarction
OR	-	Odds ratio
OMT	-	Optimal medical treatment
PCI	-	Percutaneous coronary intervention
RR	-	Relative risk
SES	-	Sirolimus eluting stent
WHO	-	World Health Organisation

Abstract

Objectives As the role of percutaneous coronary intervention in the management of stable coronary artery disease compared to optimal medical treatment is still controversial, the aim of the present analysis was the evaluation of the impact on long-term mortality of these two treatment options in patients with symptoms or signs of myocardial ischemia but no acute coronary syndrome.

Methods We identified 20 randomized trials comparing an invasive treatment strategy with medical treatment in 9679 patients with symptoms or signs of myocardial ischemia but no acute coronary syndrome. Of these patients, 4751 were randomized to receive percutaneous coronary intervention and 4928 to receive optimal medical treatment. The primary end point was all-cause death. The length of follow-up was in the range between 12 and 122 months, 53 months on average.

Results In the percutaneous coronary intervention group, 365 patients died as compared to 415 patients in the medical treatment group, which corresponds to a non-significant 10% reduction in the odds ratio of all-cause death (Odds ratio, 0.90; 95% Confidence interval, 0.77 to 1.04; *P*=0.73 for heterogeneity across the trials). Of these deaths, 159 patients in the intervention-group died from cardiac causes compared to 191 patients in the medical treatment group (Odds ratio, 0.81; 95% Confidence interval, 0.61 to 1.09). Regarding non-fatal myocardial infarction, percutaneous coronary intervention was associated with no significant improvement compared to optimal medical treatment (Odds ratio, 0.92; 95% Confidence interval, 0.70 to 1.20).

Conclusions This meta-analysis, comparing percutaneous coronary intervention with optimal medical treatment in patients with stable coronary artery disease, showed no statistically significant differences regarding overall mortality, cardiac death or non-fatal myocardial infarction. However, all endpoint-analyses showed a trend toward a benefit of percutaneous coronary intervention. Therefore, sufficiently powered larger trials are required to prove this conclusively.

1 Coronary heart disease (CHD)

1.1 Pathogenesis of atherosclerosis and formation of thrombi

A number of vascular diseases cause hardening of the arterial walls with consecutive loss of elasticity as well as narrowing of the lumen because of wall thickening (Böcker et al., 2008). Atherosclerosis is the most significant form of these types of vascular diseases (Böcker et al., 2008). The term atherosclerosis was coined by the WHO and refers to the calcification of arteries. According to the WHO, atherosclerosis is defined as “a variable combination of alterations initially of the intima, consisting of a focal accumulation of fatty substances, complex carbohydrates, blood components, connective tissue and calcium deposits, combined with alterations of the media“ (Riede et al., 2009).

Atherosclerosis describes a condition involving the large and medium-sized elastic and muscular arteries transgressing from the intima into the media. It is associated with progressive lipid deposits (“athero-” part of the term) and diffuse propagation of collagen fibers (”-sclerosis“ part of the term) and is characterized by a chronic inflammatory reaction (Riede et al., 2004).

The resulting alterations of the arterial wall proceed according to the following pathogenic reaction (Figure 1): the first step is damage of the endothelium (type 1 lesion). Risk factors including for example hypercholesterinemia or smoking and vertebration of vessel junctions are discussed as possible causes. The endothelium then forms chemokines and adhesion molecules for monocytes and lymphocytes. They excrete pro-inflammatory cytokines, thus contributing to the monocyte-to-macrophage differentiation. The nitrogen dioxide production is reduced, causing vasoconstriction. Because of the initial endothelial lesion, combined with an oversupply of “low density”

lipoprotein (LDL) circulating in the blood, LDL reaches the subintimal space. There, it is oxidized into oxLDL by free radicals of the endothelial cell and by macrophages. The oxLDL is taken up into the macrophages via scavenger receptor and the cholesterol esters in lysosomes are divided. However, re-esterification takes place if there is an oversupply of cholesterol esters.

Because of vascular deposits, the macrophages are then transformed into so-called foam cells which accumulate in the intima and morphologically appear as yellowish, raised, streaky foci (”fatty streaks“, type 2 lesion) on the inside of the artery. The produced foam cells do not possess the enzymes required for digesting the cholesterol which therefore crystallizes. Because cytotoxic T-lymphocytes additionally excrete perforins, this leads to the apoptotic death of the foam cells.

The multiple “deaths” of the foam cells generate an instable lipid plaque in the subintima (“atheroma“, type 3-4 lesion), a liquid pulp of fat containing cholesterol crystals. The proliferation of local mediamyocytes is stimulated by pro-inflammatory endothelin 1 and interleukin 1 as well as by growth factors released from still functional macrophages.

The endothelial cells, which are also stimulated, are attracting thrombocytes with their platelet activation factor, which equally promote the fibrotization (“fibroatheroma”, type 5 lesion) via platelet-derived growth factor PDGF. This ultimately leads to calcification. The cells of the fibroatheroma form matrix metalloproteases which soften the cover plate of the plaque. The plaque can subsequently rupture and cause an embolism. In addition, these cells generate increasing quantities of the procoagulatory “tissue factor“. A “non-occlusive thrombus” (type 6 lesion) develops if blood seeps into the plaque and coagulation factors meet the thrombogenic material.

An “occlusive thrombus“ can develop if the balance between prothrombotic stimuli and fibrinolysis is unfavorable, resulting in the occlusion of the vessel and inducing for example a myocardial infarction (MI) (Riede et al., 2004).

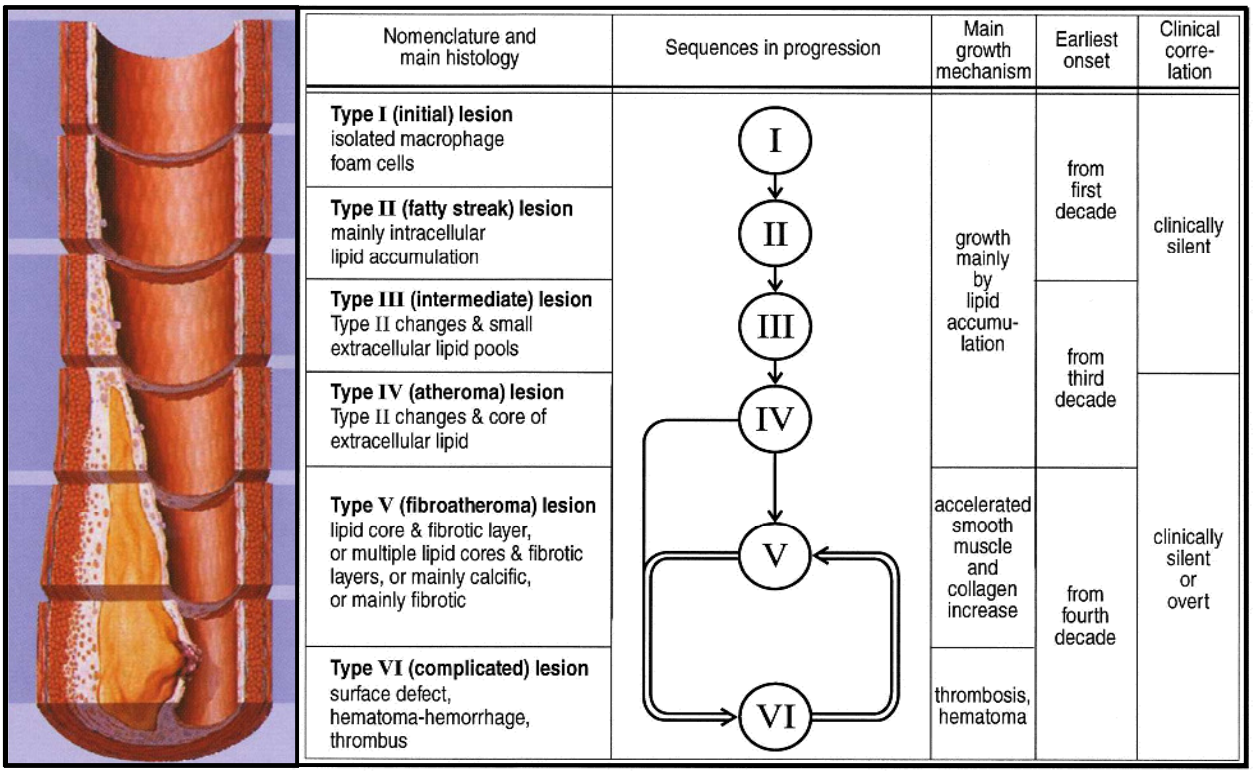

Figure 1 Flow diagram in center column indicates pathways in evolution and progression of human atherosclerotic lesions. Roman numerals indicate histologically characteristic types of lesions defined at left of flow diagram. The arrows indicate sequence in which characteristic morphologies may change.

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1.2 Angina pectoris and myocardial infarction

CHD is the manifestation of atherosclerosis in the coronary arteries (Herold et al., 2010). High-grade stenoses in these arteries impair the blood flow and hence cause coronary insufficiency, an imbalance between oxygen requirement and oxygen supply in the myocardium (Herold et al., 2010). Coronary stenoses are classified into different degrees of severity, depending on the reduction of the vessel diameter in percent (Herold et al., 2010):

Grade I: 25-49%	hemodynamically insignificant stenosis
Grade II: 50-74%	hemodynamically significant stenosis
Grade III: 75-99%	critical stenosis
Grade IV: 100%	complete occlusion

Regional perfusion impairments of the myocardium are only expected if the vascular lumen is narrowed by more than 50% (hemodynamically significant stenosis). If more than 75% of the lumen of a coronary artery are occluded by atherosclerotic lesions (critical stenosis), the coronary reserve (difference between maximum possible coronary perfusion and coronary perfusion at rest) is depleted. In this case, the blood supply in connection with an increased need for oxygen of the working myocardium, such as for instance with physical exercise, is expected to be inadequate. The same is true at rest in the presence of a 90% stenosis (Herold et al., 2010, Böcker et al., 2008).

Angina pectoris is the main symptom of coronary insufficiency and is accompanied by pain in the retrosternal region. Patients typically perceive the pain as constricting, oppressive, stinging or burning and it can radiate into the neck, the lower jaw, the shoulders, the upper abdominal region or into the left (or right) arm and all the way to the ulnar finger tips. These symptoms usually have a crescendo-decrescendo character (Dietel et al., 2009).

We distinguish between two types of angina pectoris: with stable angina pectoris, patients experience the same, stable symptoms for a prolonged period of time. They occur in a reproducible fashion in connection with physical or psychological stress, last for five to ten minutes and respond with regression within one or two minutes of the sublingual administration of nitroglycerin (Herold et al., 2010).

Instable angina pectoris can develop from the stable form both in connection with an increased intensity and frequency or occur for the first time at rest. Any first incidence of angina or angina pectoris developing with increasing pain, increasing duration or

increasing frequency is referred to as instable angina pectoris. It is not associated with an acute risk of infarction (Herold et al., 2010; Gerok et al., 2007).

An MI is an ischemic myocardial necrosis usually occurring due to CHD (Herold et al., 2010). It generally develops if a vulnerable plaque ruptures, a coronary artery with atherosclerotic alterations is subsequently occluded by a thrombus and the coronary perfusion is therefore abruptly reduced. The associated pain resembles the one associated with angina pectoris, but usually occurs at rest, is more severe and lasts longer (Dietel et al., 2009).

The diagnosis of an MI is established if the pain at rest lasts more than 20 minutes, is associated with ST-segment elevations in the electrocardiogram or if the serological markers for necrotic cardiomyocytes (Troponin T or Troponin I, creatine kinase isoenzyme) are elevated (Siegenthaler et al., 2006).

1.3 Epidemiology of CHD

According to the WHO, CHD is currently the leading cause of death worldwide. At 8.3% of all causes of death, CHD was the number one of all causes of death in the causes of death statistics in Germany in 2011 (Federal Office of Statistics Germany, 2011). Overall, more than 50.000 people develop an acute MI and nearly 400 of 100'000 patients are treated for clinical symptoms of angina pectoris each year in Germany. Due to its variety of clinical manifestations (angina pectoris, MI, sudden cardiac death, cardiac insufficiency), CHD is the leading cause for inability to work, premature disability and death in western industrialized nations (Gerok et al., 2007).

The result of a global study conducted by the WHO with the short name MONICA project shows that almost 50% of all infarction patients die within the first four weeks of suffering a MI (Herold et al., 2010). An additional 5-10% of all infarction patients experience sudden cardiac death within two years of a MI (Herold et al., 2010).

The incidence of a coronary event rises sharply with age, where statistics indicate that men are diagnosed with sclerotic coronary arteries ten to 20 years earlier than women. However, the incidence of CHD in women approximates the one of men with increasing age. The incidence of CHD in the age group of 65 to 94 years is twice as high in men and three times as high in women compared to the age group of 35 to 64 years. In addition, the CHD mortality in men at a younger age of 25 to 34 years is three times as high (at age 74 to 84 1.6 times as high) as in women (Wilson et al., 2010).

A reduction in the CHD mortality rates by more than 24% has been documented in most European countries and the USA since 1975. This trend is particularly apparent in regions with an advanced healthcare system. Improvements in the therapy of CHD are responsible for this in 50% of cases. The remaining 50% are ascribed to the reduction of risk factors, predominantly the reduction of smoking and the treatment of hypercholesterinemia (Wilson et al., 2010).

In view of the ageing population and the concurrent increase in the incidence of CHD in older age, it is expected that the disease will continue to be prevalent (Herold et al., 2010).

1.4 Risk factors

The risk factors for coronary sclerosis coincide with those for general atherosclerosis. Risk factors are factors which can statistically promote the pathogenesis of a disease. On the one hand, this can be a genetic predisposition and on the other hand environmental influences and risk-promoting behaviors such as smoking (Böcker et al., 2008). Depending on their relevance for the progression of atherosclerosis, they are classified into first order (e.g. hypercholesterinemia, hypertension, nicotine abuse, diabetes mellitus, age and gender) and second order risk factors (e.g. adiposity, lack of exercise, stress, hyperuricemia and hormonal factors) (Böcker et al., 2008).

The genetically determined family predisposition poses a particularly high risk (Walter et al., 2000). Especially in connection with the incidence of an acute MI in very young patients, the genetic predisposition is being discussed as one of the leading causal risk factor (Walter et al., 2000). The main risk factors for atherosclerosis are illustrated in Table 1.

Table 1: Main risk factors for atherosclerosis

Age and gender:	The risk of death due to CHD is similar in men and women. However, manifestations of atherosclerosis develop at a younger age in men than in women (Kreuzer et al., 2003). The risk of developing atherosclerosis in women is only significantly elevated after menopause, likely due to the decrease in protective estrogens in the blood (Steffel et al., 2011). In the elderly, the incidence rates are equal for both genders (Kreuzer et al., 2003).
Lipid profile:	A permanently elevated LDL value combined with a low "high density" lipoprotein (HDL) blood level promotes the development of atherosclerosis. Oxidized LDL stimulates an inflammatory reaction in the vessel wall. In contrast, HDL counteracts atherogenesis by transporting cholesterol out of the peripheral tissue for further processing in the liver (Kreuzer et al., 2003).
Nicotine:	Cigarette smoking considerably increases the risk of CHD, by approximately 70 to 80% when smoking one package of cigarettes daily compared to the CHD risk of non-smokers. Among other things, it facilitates the LDL oxidation as well as the lipid storage in the vessel wall (Kreuzer et al., 2003).
Hypertension:	Permanent hypertension alters the regulation of the proliferation and migration of vascular smooth muscle cells. An imbalance of the formation of vasodilators and vasoconstrictors by the endothelium results in an elevated systemic blood pressure and atheromatous lesions. The endothelial dysfunction represents the link between hypertension and atherosclerosis (Rosenthal et al., 2004).

Diabetes mellitus: Hyperglycemia associated with diabetes mellitus causes an increased glycosylation of proteins. This facilitates the LDL oxidation and storage in the vessel wall as well as the monocyte chemotaxis. In addition, it promotes the inflammation of vessel wall cells as well as the endothelial dysfunction (Kreuzer et al., 2003).

Adiposity: Adiposity predominantly causes hypertension, diabetes mellitus or hypercholesterinemia and therefore has an atherogenic effect due to different risk factors (Kreuzer et al., 2003).

Genetic factors: The genetic predisposition can be gathered mainly from the family history. An elevated genetic risk of atherosclerosis may be present if a first-degree relative experienced a vascular event before age 60 (Kreuzer et al., 2003).

1.5 Treatment of CAD

Percutaneous coronary interventions are increasingly being used in patients with various manifestations of coronary artery disease. They represent an established treatment strategy which improves survival and survival free of recurrent myocardial infarction in patients with ST-segment elevation myocardial infarction (Keeley et al., 2003, Boersma et al., 2006).

Early invasive therapy also improves long-term survival and reduces late myocardial infarction in patients with non–ST-segment elevation acute coronary syndromes (Bavry et al., 2006). Although PCI reduces symptoms in patients without

acute coronary syndromes (Hochmann et al., 2007), its effects on the prognosis of these patients are still not defined.

Current guidelines for the management of patients with stabile angina pectoris emphasize risk factor modification; especially smoking cessation, diabetes management, lipid lowering, anti-hypertensive and as anti-anginal medication as well as exercise (Farker et al., 2007). In the last decades, important advances in the field of pharmacology have been made, which have provided patients with stable coronary artery disease with effective drugs able to improve significantly their prognosis such as antiplatelet agents, statins, beta-blockers and angiotensin-converting–enzyme inhibitors (Abrams et al., 2005, Peters et al., 2007, Opie et al., 2006).

Regarding the improvement of the optimal medical therapy as well as in the field of interventional cardiology, the prognostic advantages of PCI over OMT in this large subset of patients is unclear. The assessment of this issue has been difficult for at least 2 reasons. First, patients with stable coronary artery disease have a very good prognosis and large sample size studies are required to assess potential differences in treatments regarding rare events (Timmis et al., 2007, Rihal et al., 2003). All studies performed to date were far from having sufficient power to assess mortality. Second, there is a certain risk associated with PCI, which leads to aggregation of events in a relatively short period after the procedure. Any potential beneficial effect if PCI compared to medical treatment alone may require time to offset this early excess risk, so that an extended follow-up may enable a more unbiased evaluation of the relative merits of these treatment strategies.

In an attempt to overcome these difficulties, several meta-analysis have been performed to determine the role of PCI in patients with stable CAD, some suggesting a relief of angina symptoms (Bucher et al., 2000, Wijeysundra et al., 2010, Pursnani et al., 2012), others showing no effect on mortality, myocardial infarction or need for revascularization in the PCI-based strategy (Kastritis et al., 2005 and 2007). One analysis, published in 2008 by Schömig et al., even showed a reduction of overall-mortality (OR 0.8, 95% CI 0.65, 0.99).

These conflicting results underscore the need of a new, comprehensive and updated meta-analysis including all existing trials, to evaluate whether PCI, when added to an optimal medical treatment, improves the clinical long-term prognosis of patients with stable coronary artery disease when compared to medical therapy alone.

2 Methods

2.1 Background

In most medical areas exist numerous trials relating to one topic attempting to answer similar questions. Some of these individual clinical trials show uncertainty because of their small size or conflict regarding their results. Aggregating these studies in a systematic and unbiased way may allow a clearer result to appear.

Meta-analysis is a statistical procedure which allows synthesizing research results by using various statistical methods to retrieve, select, and combine results from previous separate but related studies and data and is used to assess the clinical effectiveness of healthcare interventions. It integrates the results of several independent trials which are considered as comparable and transforms them from numerous small into one large study with many participants.

The usual way of displaying data from a meta-analysis is by pictorial representation. Results from each trial are displayed graphically as a black square (the measured effect) on a horizontal line (the 95% confidence interval) around the main finding. The size of the square reflects the weight of that study, the length of the horizontal line represents the uncertainty of the estimate of the effect for this study.

The main measure of effect commonly used in meta-analysis is the relative risk (RR) or odds ratio (OR). A relative risk of 2 implies that the defined endpoint happens twice as often in the treated group as in the controls. A relative risk of 0.5 implies 50% reduction in the event in the intervention group compared to the control group. The vertical line in the diagram corresponds to a relative risk of 1 (no effect of treatment), squares on the left side of this vertical line favour treatment, squares on the right side favour control. The diamond represents the combined relative risk of all studies included.

The benefits of meta-analyses are obvious; results from individual clinical trials (especially when they are small) may not be significant, but aggregating studies in a systematic way allows results to appear in a distinctive way i.e. if a particular treatment confers significant benefits for a specific group of patients.

Individual studies may contain too few patients in subgroups of interest or detect only small clinical effects. Systematic aggregations of data from many studies lead to more powerful results to uncover these small effects, especially when the investigator is searching for effects in specific subgroups.

The advantage of meta-analyses also lies in the transparency and openness with which they allow the readers to determine the reasonableness of the decision taken and their likely impact on the final estimate of effect size.

As with all research techniques, there may be flaws in the conduct and interpretation of meta-analyses. One problem can be the heterogeneity of the different trials included. This heterogeneity depends on upon which extent the author mixes studies of different kind and nature (patient groups, interventions applied). This is an unavoidable fact concerning meta-analysis, but the question is not whether it is present but to which extent it is tolerated by the author and whether its extent seriously undermines the conclusions. Therefore a profound literature review is performed to generalize over the differences in primary search. The present analysis includes only studies with comparable patient groups, treatment and endpoints so the differences between the studies are reduced to a minimum.

Another weakness, which can be easily overcome by meta-analysis carried out on a rigorous systematic review, are bias, by offering an unbiased synthesis of the empirical data.

One more known possible deficiency is to ignore qualitative differences between studies respectively the study quality in general. A good meta-analysis does not ignore these differences, the effect of a study quality is coded as a moderator, so the

differences can be seen and low quality studies can be removed from the analysis. It is in the responsibility of every author to only use good quality studies.

For the trials of the present meta-analysis, a quality score was used and only studies with a high score were included.

Some critics argue that a meta-analysis is a garbage-in, garbage-out procedure: of course, a meta-analysis is only as good as the set of studies upon which it is based on. The validity and quality of the meta-analysis depends mainly on a well-executed systematic review with complete coverage of all relevant studies on which it is based. This meta-analysis uses explicit and objective criteria for inclusion or rejection of studies so only high quality trials with comparable attributes are included. In this meta-anaylsis, only randomized controlled trials are included and randomized trials are, in their vast majority, published regardless the significance of the result. Additionally, a good meta-analysis actively seeks unpublished findings and grey literature like reports or conference proceedings and by no means disregards them.

Another point of criticism is the fact that most meta-analyses are concerned with dichotomous outcomes (e.g. alive/dead). To fit in, data from individual studies have to be selected and discarded, in which may result in a loss of information. Therefore, it is useful to perform meta-analysis on problems where the answers with yes/no are possible without a loss of information such as the endpoints ‘’mortality’’ or ‘’myocardial infarction’’ used in this meta-analysis.

Additionally, an aspect which should not be neglected is the good cost-benefit ratio of meta-analyses. With a comparatively low investment, which can be achieved by the re-use of already existing data, new relevant information can be achieved at rather low costs. (Handbook of the Cochrane Collaboration, 2013)

All in all, meta-analyses offer a more systematic and quantitative approach to reviewing important therapeutic questions, a wide variety of questions can be investigated and new knowledge can be gained.

2.2 Clinical trial selection

We intended to retrieve all randomized trials comparing a PCI-based invasive treatment strategy with a medical treatment strategy in patients with coronary artery disease and symptoms or signs of ischemia. Trials that included patients with acute coronary syndromes (with or without ST-segment elevation on ECG, with or without troponin or cardiac enzyme elevations) within the first one week from presentation were excluded from this meta-analysis.

The search was performed for the period between January 1st, 1980 through December, 2012 and involved the PubMed database, U.S. National Institute of Health (www.clinicaltrials.gov), proceedings of the American Heart Association, American College of Cardiology, and European Society of Cardiology as well as internet-based sources of information on results of clinical trials in cardiology (www.cardiosource.com/clinicaltrials, www.theheart.org, www.clinicaltrialresults.com, and www.tctmd.com), Cochrane Central Register of Controlled Trials (http://www.mrw.interscience.wiley.com/cochrane/cochrane_clcentral_articles_fs.html). Other data sources included reference lists of retrieved articles, and pertinent reviews and editorials from leading medical journals.

22 randomized clinical trials were identified that assigned patients with no acute coronary syndromes to an invasive, PCI-based treatment strategy or medical only treatment strategy (Bech et al., 2001, Boden et al., 2007, Dakik et al., 1998, Davies et al. 1997, Erne et al.,2007, Folland et al., 1997, Hambrecht et al., 2004, Henderson et al, 2003, Hochmann et al., 2006, Hueb et al., 1999, Madsen et al., 2007, Marhmarian et al., 2006, Parisi et al., 1992, Pfisterer et al., 2004, Pitt et al., 1999, Sievers et al., 1993, Hueb et al., 2007, Steg et al., 2004, Zeymer et al., 2003, Dagenais et al., 2011, Pijls et al., 2007, Nishigaki et al., 2008).

In two of these trials (Hochman et al., 2006, Steg et al., 2004), neither symptoms nor signs of myocardial ischemia were a prerequisite for enrolment of patients in the study; thus, they were excluded from the present meta-analysis.

Of the 20 trials included, one was published in abstract form (Sievers et al., 1993) and 19 as full articles mostly presenting updated, extended follow-up (Bech et al., 2001, Boden et al., 2007, Dakik et al., 1998, Davies et al. 1997, Erne et al.,2007, Folland et al., 1997, Hambrecht et al., 2004, Henderson et al, 2003, Hueb et al., 1999, Madsen et al., 2007, Marhmarian et al., 2006, Parisi et al., 1992, Pfisterer et al., 2004, Pitt et al., 1999, Hueb et al., 2007, Zeymer et al., 2003, Dagenais et al., 2011, Pijls et al., 2007, Nishigaki et al., 2008).

In two trials (Hueb et al., 1999, Hueb et al., 2007), patients were randomly assigned to one of three treatment groups: PCI, medical treatment or aorto-coronary bypass surgery (CABG); for both these trials, the CABG treatment arm was not included in this meta-analysis. However, patients who were randomly assigned to the PCI-based strategy or medical treatment group but received CABG were not excluded from this meta-analysis.

2.3 Outcome variables and data extraction

The primary end point of this meta-analysis was all-cause death within the longest follow-up period that was published by the investigators. Other outcomes of interest were death due to cardiac causes and myocardial infarction. The definition of the end point of myocardial infarction is shown in Table 1. Data abstracted included patients and trial characteristics, outcome measures and details regarding the two treatment groups.

2.4 Statistical analysis

All trials included in this meta-analysis were prospective, randomized trials. Baseline characteristics were evenly distributed between the 2 treatment groups in all trials. The actual treatment received was clearly shown for all trials. In all but 2 trials the analysis was performed on the basis of the "intention-to-treat" principle. In the 2 trials that did not follow this principle, a total of 5 patients were excluded after randomization (Dakik et al., 1998, Pfisterer et al., 2004).

Treatment effect could not be assessed for trials in which the event of interest was not observed in any of the treatment groups. For trials in which only one of the treatment groups had no events of interest, the treatment effect estimate and its standard error were approximated from 2x2 contingency tables after adding 0.5 to each cell (Sterne et al., 2001). We used the Cochran Q-test to assess heterogeneity across trials. Also, we calculated the I^2 statistic to measure the consistency between trials with values of 25%, 50%, and 75% defining the cut-off points for identifying low, moderate and high degrees of heterogeneity, respectively (Higgins et al., 2003).

Treatment effects from individual trials were pooled using both the fixed effects Mantel-Haenszel model (Mantel et al., 1959) and the random effects DerSimonian and Laird model (DerSimonian et al., 1986). Several additional analyses were carried out to assess potential bias regarding the primary end point of the study.

First, sensitivity analyses were performed by comparing the treatment effects obtained with each trial removed consecutively from the analysis with the overall treatment effects. Second, the Egger's test was used to assess publication bias (Egger et al., 1997). Third, a funnel plot was constructed to graphically illustrate the relation between treatment effect size and sample size of the individual trials.

All *P*-values are two-sided. Statistical significance was assumed for $P<0.05$. Statistical analysis was performed using the Stata software, version 9.2 (Stata Corp, College Station, Tex).

3 Results

A total of 20 randomized trials including 9679 patients were analyzed (Bech et al., 2001, Boden et al., 2007, Dakik et al., 1998, Davies et al. 1997, Erne et al.,2007, Folland et al., 1997, Hambrecht et al., 2004, Henderson et al, 2003 , Hueb et al., 1999, Madsen et al., 2007, Marhmarian et al., 2006, Parisi et al., 1992, Pfisterer et al., 2004, Pitt et al., 1999, Sievers et al., 1993, Hueb et al., 2007, Zeymer et al., 2003, Dagenais et al., 2011, Pijls et al., 2007, Nishigaki et al., 2008). Overall, average age of the patients was 61 years, 21% of them were women, 52% had incurred myocardial infarction and the average length of follow-up was 53 months. 92% of the patients in the PCI-based strategy group received revascularization, 13 trials performed angioplasty with stenting. Drug-eluting stents were only used in two trials (Boden et al., 2007, Dagenais et al., 2011). In the medical treatment group, 25% of the patients received non-protocol revascularization early or at some point of time during follow-up.

Table 2 shows inclusion and exclusion criteria as well as the primary end point in individual trials. Table 3 shows main characteristics of the patients in each trial.

In the PCI group, 365 patients died as compared to 415 patients in the medical treatment group, which corresponds to a non-significant 10% reduction in the odds ratio of all-cause death (Odds ratio, 0.90; 95% CI, 0.77 to 1.04;). See Fig. 3. There was no inconsistency across the trials (I^2=0%, P=0.73 for heterogeneity across the trials). The sensitivity analysis yielded odds ratios that were not significantly different from the overall odds ratio (P≥0.59). Figure 2A displays the funnel plot of publication bias, which was not statistically significant on the basis of the Egger's test. Figure 2B shows that there was no relation between sample size and treatment effect size.

Patients with acute coronary syndromes were excluded from the studies included in this meta-analysis. However, all but one trial (Hueb et al., 1999) had included patients with previous myocardial infarction in a proportion ranging from 25 to 100%. In 4 of the 5

trials that included only patients with previous myocardial infarction (Dakik et al., 1998, Madsen et al., 2007, Mahmarian et al, 2006, Zeymer et al., 2003), myocardial infarction was recent (<4 weeks) according to current guidelines (Thygesen et al., 2007).

In the remaining trial (Erne et al., 2007), the time interval from myocardial infarction was on average >8 weeks. When calculation regarding all-cause death was confined to the 4 trials enrolling patients with recent myocardial infarction, PCI was associated with an odds ratio of 0.65 (95% CI, 0.37 to 1.12) from the random effects model. When calculation was confined to the remaining 16 trials, PCI was associated with an odds ratio of 0.93 (95% CI, 0.79 to 1.09) from the random effects model. In addition, the exclusion of the 4 trials in which CABG was allowed as a treatment option in the PCI-based group (Davies et al., 1997, Madsen et al., 2007, Mahmarian et al., 2006, Pfisterer et al., 2004) did not make any difference in treatment effect regarding all-cause mortality: PCI was associated with an odds ratio of 0.90 (95% CI 0.76 to 1.06) from the random effects model.

The cardiac cause of death was reported in 16 trials (Bech et al., 2001, Boden et al., Dakik et al., Erne et al., 2007, Hambrecht et al., 2004, Henderson et al., 2003, Hueb et al., 1999, Mahmarian et al., 2006, Pfisterer et al., 2004, Pitt et al., 1999, Sievers et al, 1993, Zeymer et al., 2003, Hueb et al., Dagenais et al., 2011, Pijls et al., 2007, Nishigaki et al. 2008). In the PCI group, 159 patients died due to cardiac causes as compared to 191 patients in the medical treatment group, (OR, 0.81; 95% CI, 0.61 to 1.09). There was a slight inconsistency across the trials (I^2=22%). See Fig. 4.

In the PCI group, 418 patients had nonfatal myocardial infarction after randomization as compared to 446 patients in the medical treatment group (OR, 0.92; 95% CI, 0.70 to 1.2). (Figure 5). However, there was a moderate inconsistency of treatment effects across the trials (I^2=55 %). We also calculated the odds ratios for the composite cardiac death or nonfatal myocardial infarction. PCI was associated with an odds ratio of 0.88 (95% CI, 0.64 to 1.22) from the random effects model.

Table 2. Inclusion, Exclusion Criteria and End Point Definitions of the included Trials

Trial	Inclusion Criteria	Exclusion Criteria	Primary End Point	MI Definition
Sievers et al, 1993	Previous non-Q wave MI; single vessel disease of a major coronary artery and no angina in daily life under medication	Previous Q-wave MI, positive stress test at 50 watt, diabetes mellitus	6 mo exercise stress test	NR
ACME 1 Folland et al., 1997	Stable angina, markedly positive stress test, or MI within 3 months, stenosis >70% in the proximal 2/3 of a single vessel	Medically refractory unstable angina pectoris, previous PCI, left main artery stenosis >50%, >70% stenosis at more than one artery, EF<30	Death, MI, recurrent hospitalization for cardiac disease, non-protocol revascularization	New Q-waves, hospital admission for chest pain with serum enzyme changes
ACME 2 Folland et al., 1997	Stable angina, markedly positive stress test, or MI within 3 months, stenosis >70% in the proximal 2/3 of 2 vessels	Medically refractory unstable angina pectoris, previous PCI, left main artery stenosis >50%, >70% stenosis at more than 2 arteries, EF<30	Death, MI, recurrent hospitalization for cardiac disease, revascularization	New Q-waves, hospital admission for chest pain with serum enzyme changes
ACIP Davies et al., 1997	Stable patients either free of angina or with symptoms that could be well controlled by medical therapy, by stress test, at least 1 episode of asymptomatic ischemia during 24h-ECG; angiographically documented coronary artery disease	Recent MI (within 4 weeks), unstable angina, CCS IV, NYHA III or IV, PCI within 6 months, CABG within 3 months, left main artery stenosis >50%	Death, death or MI, hospitalization for a cardiac condition (including non-protocol revascularization)	NR
Dakik et al., 1998	Stable survivors of MI, large total (>20%) and ischemic (>10%) left ventricular perfusion defect size	Clinical instability, EF <35%, 3-vessel disease, >50% left main artery stenosis	Reduction of LV perfusion defect	Rise in creatinine kinase-MB with new ST-changes and/or chest pain
AVERT Pitt et al., 1999	LDL >115mg/dl, Triglycerides <500mg. MI or unstable angina >14 days, CCS I, II angina or asymptomatic, stenosis >50%	Age >80years, MI or unstable angina pectoris within previous two weeks, triple-vessel disease, left main artery stenosis, EF <40%	Ischemic events (cardiac death, cardiac arrest, MI, cerebrovascular accident, non-protocol revascularization, worsening angina requiring hospitalization)	NR

MASS **Hueb et al., 1999**	Stable angina, normal EF, inducible ischemia; stenosis >80% before first diagonal branch <12mm in length	Prior revascularization, Q-wave MI, left ventricular dysfunction, total occluded or tortuous or calcified lesions, >50% stenosis of left main artery	Cardiac death, MI, refractory angina requiring hospitalization	New Q-waves with creatinine kinase-MB enzyme rise >3 times its normal value
Bech et al., 2001	CCS I or higher class angina, no evidence of reversible ischemia (non-invasive testing previous 2 months either negative, inconclusive or not performed), significant de novo stenosis >50%	Total occlusion, Q-wave MI or unstable angina, small target vessel <2.5 mm	All-cause death, MI, revascularization, procedure-related complication	New Q-waves or increase of serum creatinine kinase levels to >2 times the normal limit
ALKK **Zeymer et al., 2003**	Stable patients 8 to 42 days after ST-segment elevation MI; CCS I, II angina pectoris, significant stenosis or occlusion of native infarct-related artery	CCS III, IV angina, >70% stenosis in non-infarct vessels, indication for CABG	Survival free of reinfarction, (re)intervention, CABG, readmission for severe angina	NR
RITA 2 **Henderson et al., 2003**	Stable or unstable angina leading to admission, last episode at least 7 days before enrolment, single or multivessel disease, stenosis in at least one artery, >50% stenosis in two or >70% stenosis in one projection	Left main artery disease, previous revascularization, recent (<7 days) acute coronary syndrome	All-cause death or MI	New Q-waves or convincing clinical history associated with typical ECG changes and serum activities
TIME **Pfisterer et al., 2004**	Age >75 years with chronic CCS II angina or higher, chest pain refractory to at least 2 antianginal drugs	Acute MI within previous 10 days	Quality of life, major adverse cardiac events (death, MI, acute coronary syndrome)	Clinical event with significant ECG and enzyme changes
Hambrecht et al., 2004	CCS I-III angina with documented ischemia during stress test, one native coronary artery stenosis >75%	Age >70 years, acute coronary syndrome, recent MI (<2 months), EF<40%, revascularization within past 12 months, left main artery stenosis >25% or high-grade stenosis of left anterior descending artery	Angina-free exercise capacity, a composite of cardiac death, MI, stroke, revascularization, worsening angina	NR
DANAMI **Madsen et al., 2007**	Inducible post-infarct ischemia, ability to perform a symptom limited bicycle exercise	Drug resistant angina pectoris, previous revascularization procedure	Death, reinfarction, admission with unstable angina	New Q-waves in at least two ECG leads
INSPIRE **Mahmarian et al., 2006**	Stable survivors of MI, total perfusion defect size >20% ischemic defect size >10% (by adenosine SPECT), EF >35	Cardiogenic shock, recurrent chest pain, acute coronary syndrome with primary PCI, NYHA class III, IV	Reduction of LV perfusion defect	NR

MASS II **Soares et al., 2006**	Documented ischemia (stress testing or CCS II or III angina), proximal multivessel coronary stenosis >70%	Age >80 years, unstable angina, acute MI, EF <40%, previous revascularization, single vessel disease, left main artery stenosis >50%	Overall mortality, MI, refractory angina requiring revascularization	New Q-waves, symptoms compatible with MI and creatine kinase MB >3 times the upper limit
SWISSI II **Erne et al., 2007**	First MI within preceding 3 months, no chest pain at maximal symptom-limited exercise test, sign of silent ischemia (confirmed by stress imaging), 1 or 2 vessel disease	3 vessel CAD coronary lesons noz technically amendable tp PCI	Survival free of major adverse cardiac events (cardiac death, MI, symptom-driven revascularization	Typical chest pain, ST-segment elevation, typical increase of cardiac enzymes
COURAGE **Boden et al., 2007**	CCS I, II angina or initial CCS IV angina stabilized medically, stable post-MI, objective evidence of ischemia, stenosis >70% in at least one proximal coronary artery and objective evidence of ischemia or at least 1 stenosis >80% and classic angina without provocative testing	Age >69 years, persistent CCS IV angina, markedly positive stress test, refractory heart failure or cardiogenic shock, EF <30%, revascularization within 6 months, unprotected left main artery stenosis >50%	Composite of death from any cause or MI and symptom-driven revascularization	Acute coronary syndrome with new Q-waves or positive cardiac markers
DEFER **Pijls et al., 2007**	Angiography with >50% stenosis in native coronary artery and FFR ≥0.75, no evidence of reversible ischemia by noninvasive testing within the previous 2 mo	Total occlusion of the target artery, Q-wave infarction, unstable angina, or small target arteries	Composite of all-cause mortality, MI, CABG, PCI, and any proce-dure-related complica-tion requiring major in-tervention or prolonged hospital stay	Clinical episode of typocal chst pain with development of new pathologicQ waves on the ECG or increase of serum kreatinine kinase leves twice the normal
JSAP **Nishigaki et al., 2008**	≥75% (or ≥60% on quantitative coronary angiography) 1 or 2 vessel CAD, inducible ischemia on stress testing or ST depression or T-wave inversion on resting EKG	Three vessel CAD, left main or ostial LAD disease, total occlusion, ACS, LVEF <50%, tendency to bleed, disseminated intravascular coagulation, severe pneumonia, creatinine >1.5 mg/ dL, graft stenosis, low-risk CAD where PCI or medical therapy had already been prescribed	Composite of all-cause mortality, ACS, stroke, emergent hospitalization requiring intensive care	Two new abnormal Q waves in 2 or more ECG leads, ECG changes compatible with non-Q-wave infarction and 2 cardiac enzyme levels twice the normal
BARI 2D **Dagenais et al., 2011**	≥50% stenosis of major coronary artery with positive stress test or ≥70% stenosis of major coronary artery with classic angina and type 2 diabetes mellitus	Immediate revascularization, left main disease, creatinine >2 mg/dL, glycated hemoglobin >13%, class III or IV heart failure, hepatic dysfunction, PCI, or CABG in previous 12 mo	All-cause mortality	Doubling of cardiac markers, evidence of ischemia (ECG or imaging)

ACIP denotes Asymptomatic Cardiac Ischemia Pilot study; ACME, Angioplasty Compared to Medicine study; ALKK, Study of the Arbeitsgemeinschaft Leitende Kardiologische Krankenhausärzte; AVERT, Atorvastatin versus Revascularization Treatment study; BARI 2D, Bypass Angioplasty Revascularization Investigation 2 Diabetes; CABG, aorto-coronary bypass surgery; CCS, Canadian Cardiovascular Society; COURAGE, Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation study; DANAMI, Danish Multicenter Randomized Study of Invasive Versus Conservative Treatment in Patients With Inducible Ischemia After Thrombolysis in Acute Myocardial Infarction study; DEFER, Percutaneous Coronary Intervention of Functionally Nonsignificant Stenosis Study; ECG, Electrocardiographie; EF, ejection fraction; INSPIRE, Adenosine Sestamibi Post-Infarction Evaluation study; JSAP, Japanese Stable Angina Pectoris Study Investigators; MASS, Medicine, Angioplasty, or Surgery Study; MI, myocardial infarction; NR, not reported; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; RITA 2, Second randomized Intervention Treatment of Angina study; SWISSI II, Swiss Interventional Study on Silent Ischemia Type II; TIME, Randomized Trial of Invasive Versus Medical Therapy in Elderly Patients.

Table 3. Main Characteristics of the Trials

Trial	Year of Most Recent Publication	Enrolment Period	Total No. of Patients	Mean Age (Years)	Women (%)	Previous MI (%)	Protocol Revascularizations in PCI Group (%) Total (CABG)	Use of Stents in PCI Group (%)	Non-protocol Revascularizations in Medical Group (%) Total (CABG)	Length of Follow-Up (months)
Sievers et al.	1993	NR	88	56	NR	55	100 (0)	0	20 (5)	24
ACME 1 Folland et al.	1997	1987-1990	227	60	0	34	96 (0)	0	41 (11)	60
ACME 2 Folland et al.	1997	1987-1990	101	60	0	45	100 (0)	0	40 (30)	60
ACIP Davies et al.	1997	1991-1993	558	62	14	40	89 (41)	0	29 (22)	24
Dakik et al.	1998	1995-1996	44	54	41	100	100 (0)	29	9 (9)	12
AVERT Pitt et al.	1999	1995-1996	341	58	16	42	94 (0)	30	12 (1)	20

MASS **Hueb et al.**	1999	1988-1991	144	65	42	0	100 (0)	0	17 (11)	60
Bech et al.	2001	NR	181	61	36	25	100 (0)	46	7 (0)	24
ALKK **Zeymer et al.**	2003	1994-1997	300	57	13	100	93 (0)	16	24 (NR)	52
RITA 2 **Henderson et al.**	2003	1992-1996	1018	58	18	47	93 (0)	8	35 (12)	84
TIME **Pfisterer et al.**	2004	1996-2000	301	80	42	47	71 (20)	44	42 (NR)	48
Hambrecht et al.	2004	1997-2001	101	60	0	46	100 (0)	100	6 (0)	12
DANAMI **Madsen et al.**	2006	1990-1994	1008	57	18	100	82 (29)	0	20 (NR)	28
INSPIRE **Mahmarian et al.**	2006	1999-2002	205	64	24	100	67 (26)	39	26 (10)	60
MASS II **Soares et al.**	2006	1995-2000	408	60	32	46	95 (0)	72	24 (15)	60

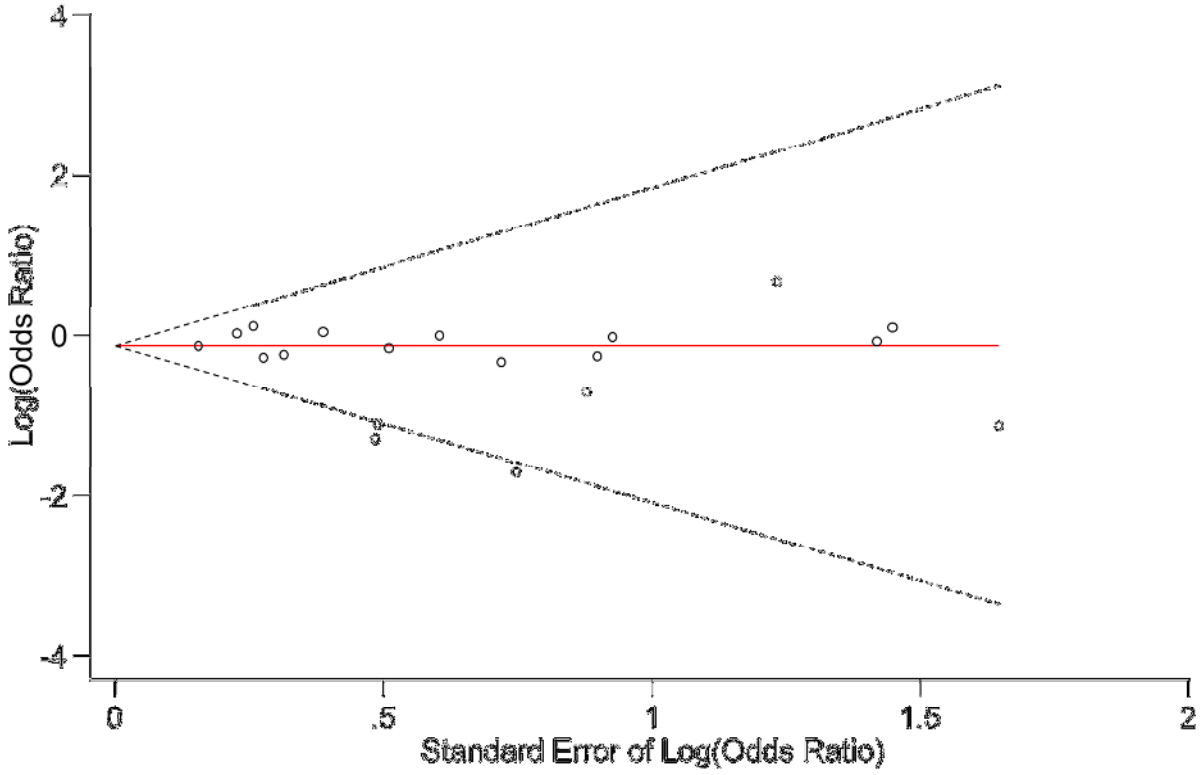
SWISSI II **Erne et al.**	2007	1991-1997	201	55	12	100	100 (0)	0	44 (NR)	122
COURAGE **Boden et al.**	2007	1991-2004	2287	61	15	38	96 (0)	88	31 (7)	54
DEFER **Pijls et al.**	2007	1997-1998	181	61	36	25	NR	46	NR	60
JSAP **Nishigaki et al.**	2008	2002-2004	380	64	25	14	91(0)	76	36 (0)	3.3
BARI 2D **Dagenais et al.**	2011	2001-2005	1605	62	35	30	95(0)	91	42(0)	60

ACIP denotes Asymptomatic Cardiac Ischemia Pilot study; ACME, Angioplasty Compared to Medicine study; ALKK, Study of the Arbeitsgemeinschaft Leitende Kardiologische Krankenhausärzte; AVERT, Atorvastatin versus Revascularization Treatment study; BARI 2D, Bypass Angioplasty Revascularization Investigation 2 Diabetes; CABG, aorto-coronary bypass surgery; CCS, Canadian Cardiovascular Society; COURAGE, Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation study; DANAMI, Danish Multicenter Randomized Study of Invasive Versus Conservative Treatment in Patients With Inducible Ischemia After Thrombolysis in Acute Myocardial Infarction study; DEFER, Percutaneous Coronary Intervention of Functionally Nonsignificant Stenosis Study; ECG, Electrocardiographie; EF, ejection fraction; INSPIRE, Adenosine Sestamibi Post-Infarction Evaluation study; JSAP, Japanese Stable Angina Pectoris Study Investigators; MASS, Medicine, Angioplasty, or Surgery Study; MI, myocardial infarction; NR, not reported; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; RITA 2, Second randomized Intervention Treatment of Angina study; SWISSI II, Swiss Interventional Study on Silent Ischemia Type II; TIME, Randomized Trial of Invasive Versus Medical Therapy in Elderly Patients.

Figure 2. Assessment of Publication Bias and Relation Between Sample Size of the Trial and Treatment Effect

A) Funnel Plot for Assessment of Publication Bias of Trials Comparing the Percutaneous Coronary Based Strategy with Medical Treatment Strategy Regarding Mortality.

The circles correspond to the treatment effects from individual trials; the red line shows the summary estimate and the diagonal lines show the expected 95% confidence intervals around the summary estimate. Note that there is no evident asymmetry of the points in relation of the summary estimate that might indicate a relevant publication bias.



B) Graph Showing the Relation between Sample Size of the Trial and Treatment Effect Regarding Mortality.

Both treatment effect and sample size are shown on a logarithmic scale. Note the lack of evident relation between sample size and observed treatment effect.

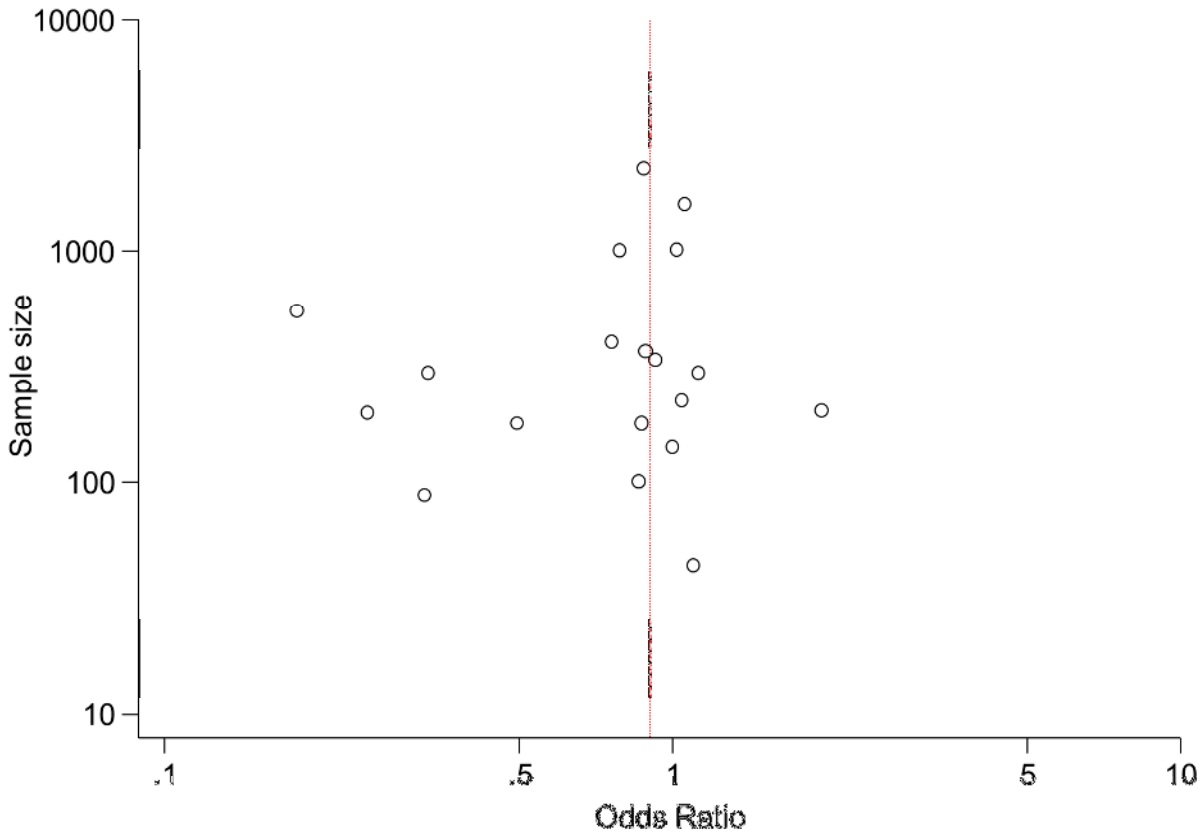


Figure 3 Odds Ratios for Mortality in Individual Trials Comparing the PCI-based with the Medical Treatment Strategy

Pooled odds ratios are also shown. OR = odds ratio PCI = percutaneous coronary intervention

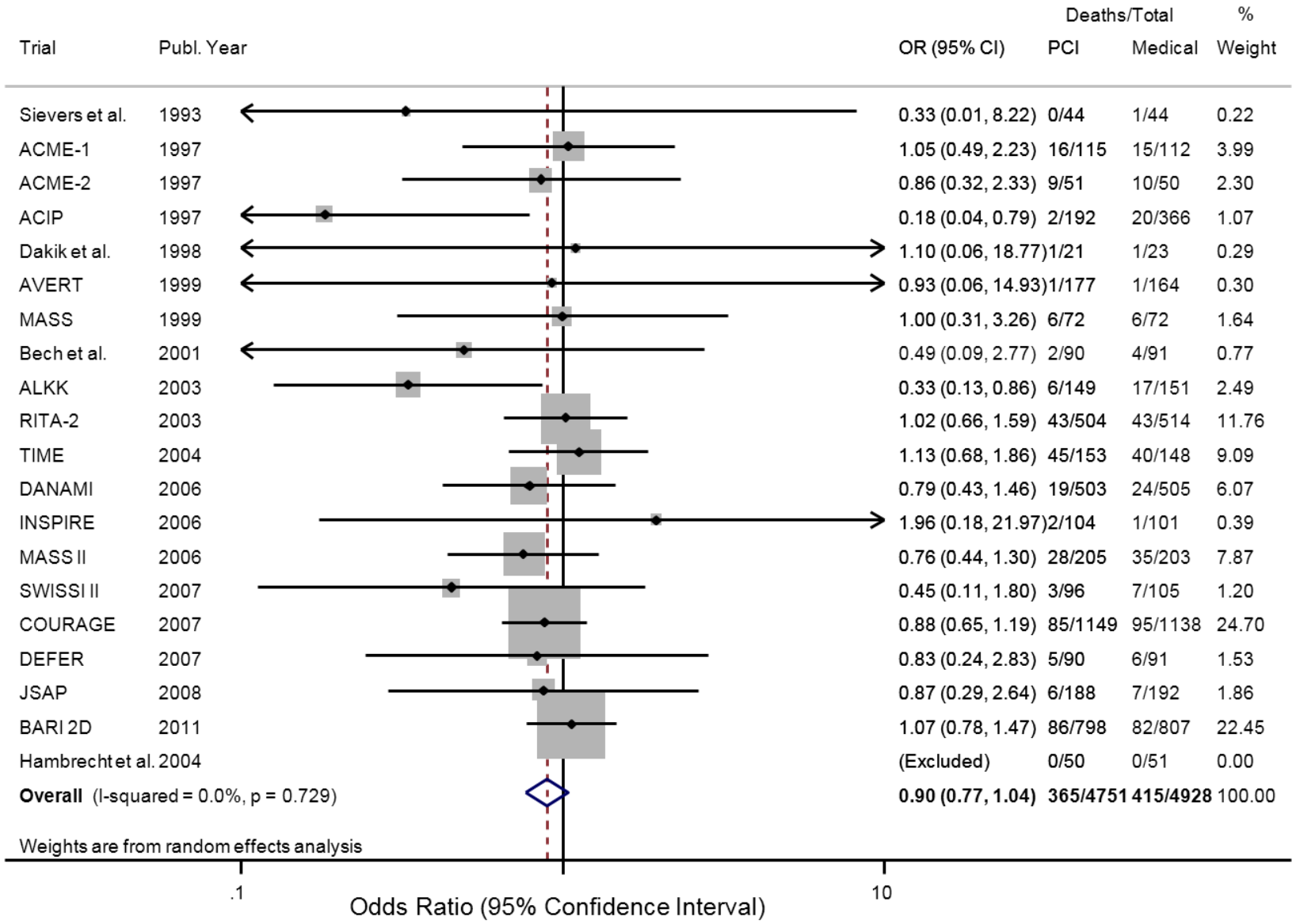


Figure 4 Odds Ratios for Cardiac Death in Individual Trials Comparing the PCI-based with the Medical Treatment Strategy

Pooled odds ratios are also shown. OR = odds ratio PCI = percutaneous coronary intervention

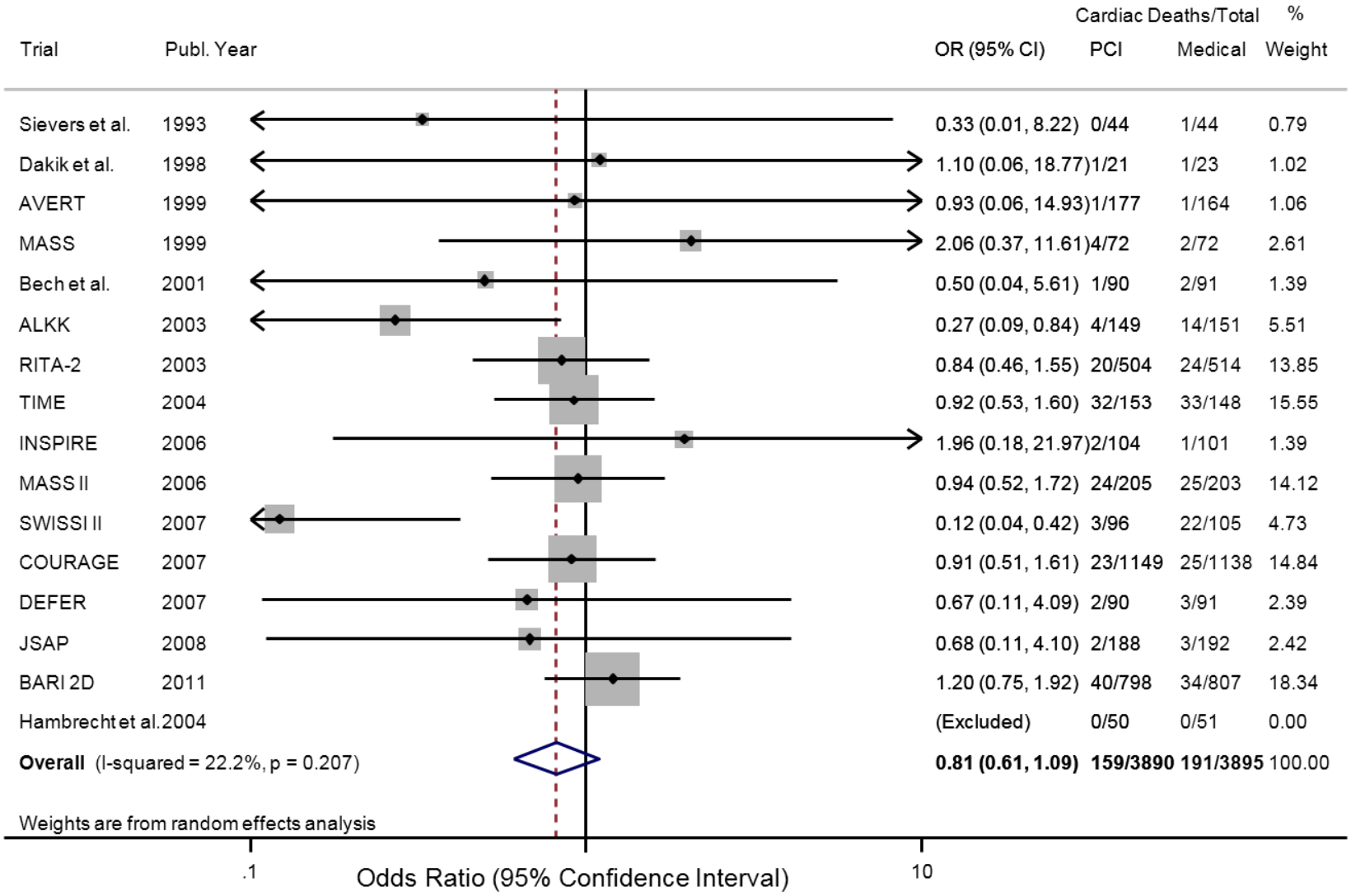
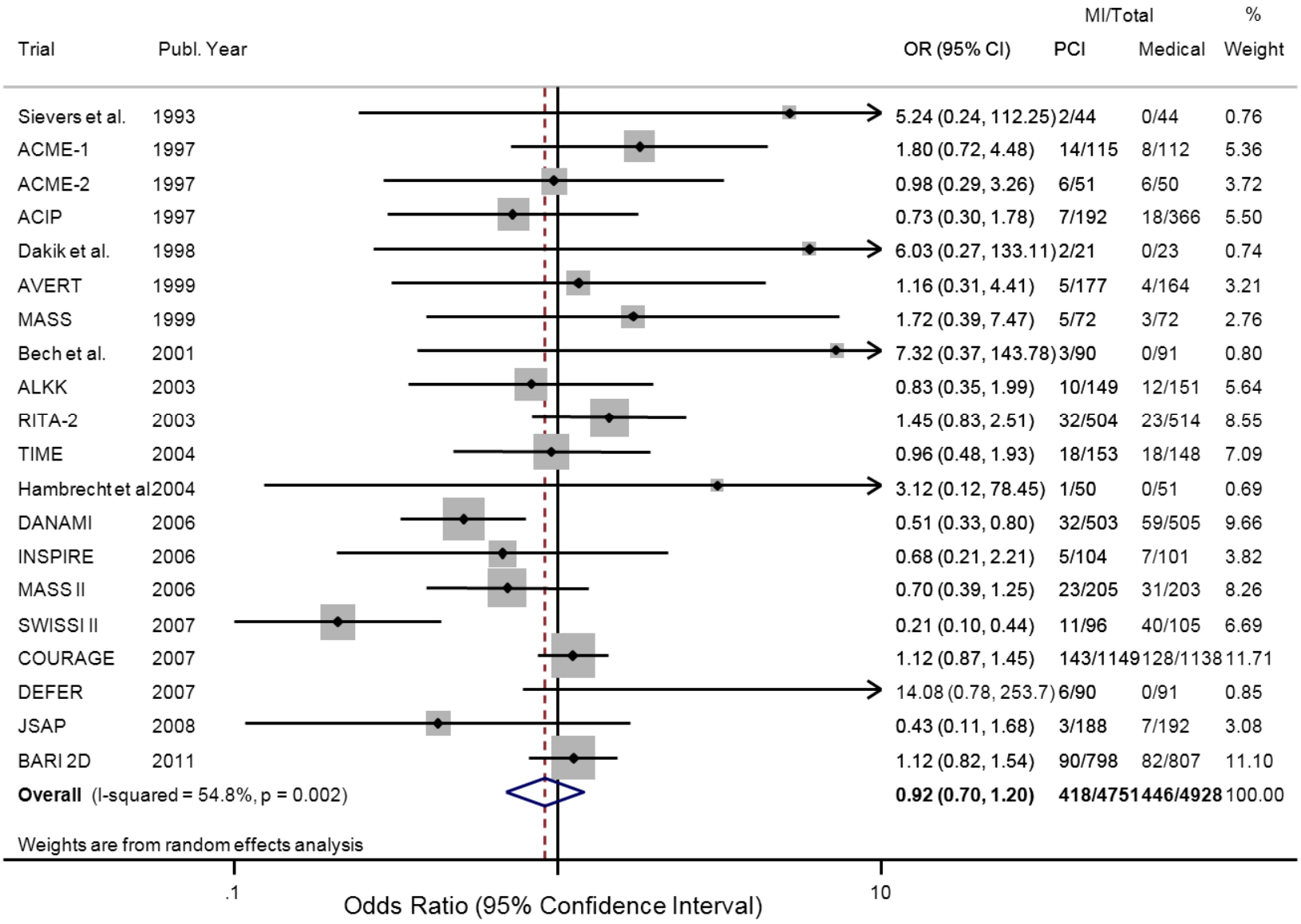


Figure 5 Odds Ratios for MI in Individual Trials Comparing the PCI-based with the Medical Treatment Strategy

Pooled odds ratios are also shown. OR = odds ratio MI = nonfatal myocardial infarction PCI = percutaneous coronary intervention



4 Discussion

In this most updated analysis, we pooled together the results from 20 randomized trials on the value of a PCI-based treatment strategy in 9679 patients with stable coronary artery disease. Treatment effect size was calculated from random effects models. The primary analysis focused on mortality within an average follow-up period of 53 months.

We observed no statistically significant differences regarding the outcomes overall mortality, cardiac death or non-fatal myocardial infarction with PCI compared to OMT. However, the point estimates for all endpoints favored PCI. The effect size was not statistically dependent on any specific trial characteristics including sample size and length of follow-up. However, the effect appeared to be greater among in patients with a recent (<4 weeks) myocardial infarction, in whom there was an approximate 35% reduction in the odds of death with PCI, as compared to patients without recent myocardial infarction in whom the odds of death with PCI was reduced by 10%.

Well-defined inclusion criteria relevant to the question to be addressed and comprehensive accounting for all studies meeting those criteria are crucial to the success of the meta-analysis. The present meta-analysis intended to include all studies that investigated the relative merits of PCI in patients with stable coronary artery disease and symptoms or signs of ischemia. Two randomized trials have evaluated the role of PCI patients with persistent occluded infarct-related vessel after myocardial infarction, mostly without any clues of ischemia (Hochman et al., 2006, Steg et al., 2004). In essence, this was done with the objective of assessing the “open-artery” hypothesis. The present meta-analysis did not include the latter 2 trials due to the absence of ischemia criterion. The same was done by Katritsis and Ioannidis in their initial and updated version (Katritsis et al. 2005 and 2007) of meta-analysis as well as in the analysis from Pursnani (Pursnani et al.2012). In contrast to the latter, we included trials that enrolled stable post recent infarct patients with symptoms or signs of ischemia (Dakik et al.,

1998, Madsen et al., 2007, Mahmarian et al., 2006, Zeymer et al., 2003) as well as all trials that used CABG instead of PCI in 20 to 41% of the patients in the PCI-based strategy group (Davies et al., 1997, Madsen et al., 2007, Mahmarian et al., Pfisterer et al., 2004). In these trials, the form of invasive treatment therapy was selected after randomization and their exclusion from our meta-analysis would have violated the “intention-to-treat” principle. Thus, the present study constitutes a consistent and comprehensive investigation of available evidence by meta-analytical methods.

It is important to note that the included randomized trials and, consequently, the entire present meta-analysis, should not be considered as a head-to-head comparison of 2 mutually exclusive treatment strategies. On the contrary, all of them evaluated the value of the PCI-based strategy as an addition to medical therapy, because patients in both study arms received medical treatment.

Furthermore, 25% of the patients assigned to medical treatment only, did receive revascularization at some point of time during follow-up. This might have blunted differences in survival between the two treatment groups in a way that cannot be predicted. Finally, individual patient data were not available for this study, which precluded several subgroup analyses. In particular, we were not able to assess the influence of the severity of ischemia at baseline on the potential benefit with PCI.

Whereas there was consistency across trials in the treatment effect size regarding all-cause mortality, there was a slight inconsistency with respect to cardiac death and a moderate inconsistency regarding myocardial infarction. This is a new clue of both the difficulties arising from pooling together results that partly depend on event definition and the robustness of all-cause mortality as an end point in the evaluation of treatment strategies.

However, although the slight decrease in the risk of nonfatal myocardial infarction should not be overstated, even the lack of an increased risk of this adverse event in the PCI group may be considered a positive finding when combined with the reduced overall mortality observed with this strategy. Apparently, the PCI-based strategy is not associated with a increased risk of large myocardial infarctions leading to cardiac death

and, at least, no increase in the long-term risk of smaller, nonfatal myocardial infarctions despite the known finding of myocardial injury that some patients incur early after the procedure.

Another aspect that should be considered is that enrolment of patients was extended over a 19-year period, time in which major developments have been recorded both in the pharmacological and interventional treatment of coronary artery disease.

In fact, the year of completion of patient enrollment did not have a significant impact on the overall result as shown by the meta-regression analysis. Obviously, patients of both study arms have benefited from advances in drug therapy. Bare-metal stents were used in less than half of the patients included in the present meta-analysis and drug-eluting stents were implanted in an irrelevant number of patients. Although no advantage in survival has been attributed to both bare-metal and drug-eluting stents (Brophy et al., 2003, Kastrati et al., 2007), this does not exclude that future advances in both pharmacological and interventional treatment of patients with coronary artery disease may reduce or further accentuate the difference in mortality observed in this meta-analysis.

The recently published FAME-2 trial compared revascularization with the use of drug-eluting stents followed by optimal medical therapy with medical therapy alone in patients with stable coronary artery disease and evidence of a functionally significant stenosis, assessed by fractional flow reserve.

The trial was stopped early by the data and safety monitoring board because of a markedly reduced need for urgent revascularization in patients treated with drug-eluting stents, as compared with those who received optimal medical therapy alone (1.6% vs. 11.1%, $P<0.001$) (de Bruyne et al., 2012). The risk of death or myocardial infarction did not differ significantly between groups. It is noteworthy that 50% of urgent revascularizations were triggered by myocardial infarction or unstable angina.

In conclusion, in stable patients with coronary artery disease and symptoms or signs of myocardial ischemia, no statistically significant benefit of PCI regarding overall-

mortality or the incidence of cardiac death or non-fatal MI when compared to an optimal medical therapy alone could be detected.

However, the point estimates for overall-mortality and cardiac death favored PCI and was most prominent in trails with longer follow-up. This justifies the performance of new randomized clinical trials sufficiently powered for evaluating the impact of state-of-the-art PCI on long-term mortality.

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