Review Article

Chronic Stable Angina: Percutaneous Coronary Intervention or Medication?

Dimitrios Maragiannis, George Lazaros, Manolis Vavuranakis, Christina Chrysohoou, Stavroula Athanassopoulou, Athanassios Patialiakas, Christodoulos Stefanadis

1st Cardiology Department, School of Medicine, University of Athens, Hippokration Hospital, Athens, Greece

Key words:
Coronary artery disease, stable angina, treatment, prognosis.

Manuscript received:
October 2, 2009;
Accepted:
January 13, 2010.

Address:
George Lazaros

31 Achilleos St.
175 62 P. Faliro
Athens, Greece
e-mail:
glaz35@hotmail.com

Coronary artery disease is a worldwide hazard today and stable angina is one of its commonest manifestations.[1,2] The diagnosis of chronic stable angina is based on the presence of anginal symptoms, a positive exercise test for myocardial ischaemia, and confirmation of coronary artery atherosclerosis by coronary angiography.[3]

However, the optimum treatment of these patients has been a controversial issue in recent years.[2,4] Recent studies, or meta-analyses thereof, have still not fully determined the usefulness of invasive treatment of the coronary arteries with percutaneous coronary intervention (PCI) in comparison with medication. While PCI is known to reduce the incidence of death and myocardial infarction in patients who suffer from acute coronary syndromes, the same benefit does not appear to extend to patients who have stable coronary artery disease.[5,6]

As the availability of non-invasive methods of diagnosing coronary artery disease steadily increases, asymptomatic patients are often referred for PCI. However, a necessary condition for any preventive therapy is that it should combat a threat —which in the case of stable coronary artery disease is acute myocardial infarction and death— with an acceptable cost.

Review of relevant published studies

One of the first studies to compare the effectiveness of PCI in patients with stable angina, compared to medication alone, was the ACME trial (Veterans Affairs Angioplasty Compared to MEdicine).[7] The patients in that study had known one-vessel disease and a positive exercise test, and were followed for a total of six months. The investigators found greater improvement of symptoms and better exercise tolerance in the PCI group, although the incidence of death and myocardial infarction was similar in the two groups. PCI, however, was associated with a greater cost and a higher complication rate.

The ACME 2 trial studied men with two-vessel disease, stable angina, and a positive stress test, who were treated with either PCI or medication, and the results were compared with those from the previous study of men with one-vessel disease.[8] The study showed that angioplasty was less effective in controlling symptoms in patients with two-vessel disease and stable angina than in those with one-vessel disease.

The ACIP study (Asymptomatic Cardiac Ischaemia Pilot) included patients who were either without symptoms or had symptoms controlled with medication, with asymptomatic ischaemia on 24-hour Holter monitoring and a positive exercise

test.[9,10] The study showed, over a two-year follow up, that these patients had a better prognosis when they were reperfused either with angioplasty or surgically.

The AVERT trial (Atorvastatin VErsus Revascularisation Treatment) was designed to examine the effect of aggressive lipid-lowering treatment on the incidence of ischaemic symptoms.[11] The study enrolled 341 patients with mild to moderate stable angina and good left ventricular contractility, who were followed for 18 months and were treated either with angioplasty or with medication—the latter included 80 mg atorvastatin per day. The findings of the study showed that medication achieved a reduction in anginal complaints similar to that achieved by angioplasty.

In the MASS study (Medicine, Angioplasty, or Surgery Study), 214 patients with stable angina and good left ventricular function, with >80% stenosis of the proximal anterior descending coronary artery branch, were followed for 5 years.[12] The patients were treated with either angioplasty or drugs. Although anginal episodes were reduced in the PCI group, there was no difference in the "hard" endpoints such as myocardial infarction and death.

The ALKK[13] study (Arbeitsgemeinschaft Leitende Kardiologische Krankenhausärzte) enrolled 300 patients with mild or no angina after a recent myocardial infarction (one to six weeks previously) and one-vessel disease, who were followed for 56 months. In these stable patients it was shown that PCI in the culprit artery was associated with a lower use of nitrates and a better prognosis.

In the RITA-2 trial (Second Randomised Intervention Treatment of Angina), 1018 patients without angina who had angiographically documented coronary artery disease were initially treated with only medication or PCI.[14,15] Over a seven-year follow up, the PCI group had fewer anginal episodes and greater exercise tolerance, although there was no reduction in acute infarctions or death. It should be noted, however, that 35.4% of the patients in the medication group ultimately underwent reperfusion during the study period.

The TIME study (Trial of Invasive versus Medical therapy in the Elderly) included patients aged more than 75 years who had angina that was refractory to at least two anti-anginal drugs.[16-19] The aim of the study was to investigate the effect of medication alone, or in combination with PCI, in reducing major adverse cardiovascular events (death, non-fatal myocardial infarction, hospitalisation for angina with or without reperfusion) and improving the patients' quality of life, over a six-month follow up. The study demonstrated a small early improvement in quality of life in the group who underwent PCI. Over a four-year follow up there was no difference in mortality between the two groups. Therefore, invasive treatment could be used in elderly patients with refractory angina in order to relieve their symptoms, without promising any prolongation of life.

Hambrecht et al studied 101 patients with stable one-vessel coronary artery disease (angiographic stenosis >75%), who were either treated with PCI or followed an exercise regimen (20 min daily on a bicycle ergometer).[20] The patients also had angina (Canadian Cardiovascular Society, CCS class I to III) and myocardial ischaemia documented by a non-invasive test. In this study it was found that patients who exercised showed a clinical improvement by one CCS class in comparison with the PCI group, as well as a longer interval free of cardiac events, at half the cost.

A sub-analysis of the DANAMI study (DANish Acute Myocardial Infarction study), including 1008 patients who had undergone thrombolysis because of an acute myocardial infarction and had residual ischaemia (silent or symptomatic), showed that invasive treatment reduced the risk of non-fatal reinfarction, as well as hospital admissions for unstable angina.[21]

The INSPIRE (adenosine sestamibi SPECT Post-Infarction Evaluation) study followed 205 stable patients after acute myocardial infarction, with ejection fraction >35% and with high-risk criteria on myocardial adenosine scintigraphy (adenosine SPECT).[22] The aim of the study was to investigate the possible benefit of intensive drug therapy compared with PCI as regards the reduction in scintigraphically monitored ischaemia. It was found that optimal drug treatment had results comparable with those of reperfusion as regards the reduction in scintigraphic perfusion defect.

In the MASS II study, 611 patients with stable angina on a substrate of multi-vessel coronary artery disease (>70% stenosis in proximal segments of the coronary arteries) and documented myocardial ischaemia on exercise testing were treated either with medication alone or with PCI.[23-26] A comparison of the groups revealed no difference in cardiac deaths or total mortality. However, the PCI group had a significantly lower incidence of anginal episodes.

The SWISSI II (SWiss International Study on Silent Ischemia) trial included 201 patients with a recent myocardial infarction and silent ischaemia.[27] The patients were treated either with medication alone

or with PCI and were followed for a mean period of about ten years. The PCI arm showed a benefit in terms of reduced cardiovascular events.

Of particular importance were the results of the recent COURAGE study (Clinical Outcomes Utilising Revascularisation and Aggressive Drug Evaluation).[28] This study was carried out from 1999 to 2004 and included 2287 patients with stable angina and objective evidence of myocardial ischaemia, who were treated with medication either alone or in conjunction with PCI. One limitation of the study was the relatively small number of women included (15%). Patients with left main disease, a strongly positive exercise test, refractory angina CCS class IV, drug-refractory heart failure or cardiogenic shock, or an ejection fraction <30% were excluded, as were those who had undergone reperfusion during the previous six months or who had a coronary anatomy unsuitable for PCI. The patients in this study had either >70% stenosis in the proximal segment of an epicardial coronary artery together with findings of myocardial ischaemia on exercise testing or the resting ECG, or >80% stenosis and typical angina. However, one quarter of the patients did not have anginal symptoms. The mean follow up was 4.6 years. Angina in the medication group improved at one year, with a further benefit at five years. Although angina improved more in the PCI group initially, the difference was not statistically significant after five years. It should be taken into consideration that by the end of the study about a third of the patients in the medication group had undergone reperfusion because of treatment-refractory angina or because of a worsening of ischaemia on a non-invasive ischaemia test. In the COURAGE study, drug-eluting stents were implanted in only 2.7% of the patients. Finally, the study showed that there was no reduction in mortality in patients treated with PCI, while the benefit in terms of symptom relief in the PCI arm was blunted with the passage of time.

Weintraub et al found that patients with stable angina who were treated with angioplasty showed a better state of health as determined by special questionnaires.[29] However, this small difference did not persist beyond 36 months.

Gu et al studied 80 patients with stable angina and angiographically documented multi-vessel coronary artery disease,[30] 31 of whom were treated with PCI and 41 with medication alone. No benefit was seen in terms of major cardiovascular events in either group.

In a sub-study of selected patients from COURAGE who were evaluated in serial myocardial perfusion tests with the use of myocardial perfusion single photon emission computed tomography (MPS), the addition of PCI to drug treatment resulted in a further reduction in imaging-documented ischaemia; in particular, the benefit was greater in those with a bigger initial ischaemic burden.[31]

A Japanese study of patients with stable angina and chronic low-risk coronary artery disease showed that the combination of PCI with medication reduced cardiovascular events over a 3.3-year follow up to a greater degree than medication alone.[32]

In a meta-analysis of 17 studies of patients with stable coronary artery disease, it was found that a strategy of PCI therapy improved expected survival in comparison with medication.[33]

The recent BARI 2D study[34] (Bypass Angioplasty Revascularisation Investigation) was not able to show a benefit from PCI in terms of mortality and cardiovascular events in diabetic patients with chronic coronary artery disease and angina (>70% stenosis of a major coronary artery, or >50% stenosis and a positive exercise test), confirming and reinforcing the results of the COURAGE trial.[28]

Finally, a recent meta-analysis by Trikalinos et el[35] of all the studies from the last 20 years concerning the treatment of chronic coronary artery disease with PCI showed that, in a total of 25,388 patients, despite the technological advances, PCI did not reduce the incidence of fatal myocardial infarction or death compared to drug treatment alone.

The designs and outcomes of the most important of the preceding studies are summarised in Table 1.

Reasons for the results so far – weakness of studies

A recent publication by Katritsis et al,[36] concerning the effect of PCI on prognosis in patients with stable coronary artery disease, points out the relatively short follow-up period in most studies, with the exception of SWISSI II (10.2 years) and COURAGE (4.6 years). The same article also mentions that the myocardial ischaemia was not confirmed by an invasive examination in most investigations.

We also know that it is mainly the characteristics of the atheromatous plaque, rather than the degree of stenosis (which was used as the indication for PCI in most studies), that determine the risk of plaque rupture and the occurrence of an acute coronary syndrome, and hence the prognosis of the coronary patient. Patients with stable angina have mainly stable

Table 1. Design and outcomes of the main studies comparing percutaneous coronary intervention (PCI) with medication in patients with chronic stable angina.

Study	Patients	Follow up	Outcome
ACME Parisi AF et al.[7] (1992)	One-vessel disease + ischaemia on exercise test	6 months	Greater improvement of symptoms and better exercise tolerance in PCI group
ACIP Davies RF et al.[10] (1997)	Asymptomatic or symptomatic with ischaemia on 24-hour Holter or positive exercise test	2 years	Better prognosis in reperfusion group
MASS Hueb WA et al.[12] (1999)	Stable angina and >80% stenosis in proximal part of anterior descending	5 years	Reduction of angina episodes in PCI group
ALKK Zeymer U et al.[13] (2003)	No or mild angina after recent myocardial infarction	56 months	Improved prognosis in PCI group
RITA-2 Henderson RA et al.[14] (2003)	Without angina, with angiographically documented coronary artery disease	7 years	Reduction of angina episodes and increased exercise tolerance in PCI group
TIME Pfisterer M et al.[16] (2004)	Refractory to at least two angina drugs	4 years	Early small improvement in quality of life in PCI group
INSPIRE Mahmarian JJ et al.[22] (2006)	Post-infarction with high-risk criteria on myocardial adenosine scintigraphy	62 days	Optimum medication resulted in results comparable with reperfusion in reduction of perfusion defect
DANAMI Madsen JK et al.[21] (2007)	Post-infarction with residual myocardial ischaemia	2.4 years	Reduction of reinfarctions and hospitalisations in PCI group
SWISSI II Erne P et al.[27] (2007)	Post-infarction or with silent ischaemia and one- or two-vessel coronary artery disease	10.2 years	Benefit as regards major cardiovascular events in PCI group
MASS II Hueb W et al.[25] (2007)	Stable angina with multi-vessel disease and documented myocardial ischaemia	5 years	Significant reduction in anginal episodes in PCI group
COURAGE Boden WE et al.[28] (2007)	Stable angina and findings of myocardial ischaemia	4.6 years	No reduction in mortality or major cardiovascular events in PCI group
Gu Y et al.[30] (2008)	Stable angina and >70% stenosis of one vessel	24 months	No benefit in terms of cardiovascular events in PCI group
Shaw LJ et al.[31] (2008)	Sub-study of COURAGE patients	6-18 months	Reduction of ischaemia as documented by myocardial scintigraphy in PCI group
Nishigashi K et al.[32] (2008)	Stable angina and low-risk coronary artery disease	3.3 years	Reduction in acute coronary events in PCI group
Katritsis DG et al.[36] (2008)	Meta-analysis of 17 studies		Improved survival in reperfusion group
BARI 2D Frye RL et al.[34] (2009)	Diabetics with chronic coronary artery disease	5 years	No benefit as regards mortality and cardiovascular events in PCI group
Trikalinos TA et al.[35] (2009)	Meta-analysis of 61 studies	Last 20 years	No reduction in incidence of myocardial infarction or death in PCI group

plaques with a thick fibrous cap, small fatty cores, more smooth muscle cells, fewer macrophages, and more collagen.[37,38]

At the same time, significant progress in modern drug treatments has greatly improved prognosis through the introduction of new medications (thienopyridines, statins, angiotensin-converting enzyme inhibitors) for patients with coronary artery disease, many of which were not available and were not used in most of the trials. Also, compliance with the drug regimen was not the same, not only in different studies, but also in different groups of a given study.

There has also been significant progress in the techniques, methods and materials used in modern PCI of the coronary arteries. However, many of the abovementioned studies used either plain old balloon angioplasty, or bare-metal stents, whereas drug-eluting stents were only used in a small percentage of the patients who were treated invasively. More specifically, as mentioned previously, in the COURAGE trial drug-eluting stents were only used in 2.7% of the patients. On the other hand, in a recent study by Horst et al it appeared that drug-eluting stents are superior in the first year after their implantation, as re-

gards restenosis, mortality, myocardial infarction, and cerebrovascular stroke, but that those differences are blunted after the first year.[39-41]

Special notice should be taken of the lack of homogeneity among the patient populations in the different studies, mainly as regards the angiographic extent of the underlying coronary artery disease and the different severity of the clinical syndrome.

All the above factors provide a rationale for the lack of any consensus among the findings of different studies, while it appears that in order to draw safe conclusions regarding the effectiveness of the two methods of treatment it is essential to perform case-by-case risk stratification for future events. Also, it seems that knowledge of the coronary anatomy is a necessary prerequisite for the choice of the appropriate treatment modality.

Guidelines for PCI in patients with chronic stable angina

The guidelines for the treatment of stable angina issued by the European Society of Cardiology in 2006 state that PCI has a Class IIa indication for improvement of prognosis in a patient with reversible ischaemia on functional testing and frequent ischaemic episodes during daily activities.[42] Coronary artery angioplasty is indicated (Class I) for improvement of symptoms in patients with one-vessel coronary artery disease who are eligible for invasive treatment and have symptoms that are not controlled by medication (and in whom the periprocedural risk does not exceed the expected benefit). In multi-vessel disease, without high-risk coronary artery anatomy in patients with moderate to severe symptoms, angioplasty improves symptoms and also has a Class I indication. Angioplasty has a class IIa indication in patients with only one-vessel disease, eligible for invasive treatment, with mild to moderate symptoms that are not tolerated. In multi-vessel disease with mild to moderate symptoms, PCI also has a Class IIa indication when the patient cannot tolerate the symptoms.

The corresponding guidelines of the American College of Cardiology and the American Heart Association recommend PCI with a Class IIa indication in patients with asymptomatic ischaemia or angina in CCS class I or II, with one or more significant stenoses in one or two coronary arteries that supply a moderate to large region of viable myocardium, or are associated with a moderate or severe degree of ischaemia on non-invasive examination.[43-45] PCI received a Class IIa indication in patients with asymptomatic ischaemia, or CCS class I or II angina and restenosis after angioplasty in an artery that supplies a large region of viable myocardium, or in the presence of high-risk criteria on non-invasive examination. Angioplasty is also recommended in patients with asymptomatic ischaemia, or angina of CCS class I or II, with significant stenosis of the left main coronary artery (>50%) that cannot be treated surgically (Class IIa). In patients with CCS class III angina, angioplasty is recommended in those with one-vessel disease or multi-vessel disease who have one or more significant stenoses in one or more arteries suitable for PCI (Class IIa indication). It is also recommended in those with angina CCS class III with significant left main coronary artery disease who cannot undergo surgery, or in surgically treated coronary arteries with multiple stenoses in grafts that are not susceptible to reoperation (Class IIa).

Conclusions

Previous studies, notably COURAGE, and meta-analyses have shown that PCI of the coronary arteries as documented does not improve mortality or the risk of myocardial infarction in patients with chronic stable angina. The controversy continues to grow, however, since some new meta-analyses show an improvement in survival[33,46] for patients in this category who undergo PCI, while others do not.[35]

It appears, however, that in the initial treatment of patients with chronic stable angina who are considered to be at low or medium risk, medication and lifestyle changes are sufficient in most cases, especially if the symptoms do not significantly affect their quality of life.[47]

In every case where a therapeutic strategy must be laid out, it is essential to take into account features such as symptomatology, quality of life, sex, race, ejection fraction, compliance with medication, prognosis based on non-invasive tests for myocardial ischaemia, angiographic findings, and the characteristics of the atheromatous plaque.

It is very important to keep in mind that the two approaches are not in opposition, but are complementary, with a view to achieving the optimum therapy of the coronary patient. In any case, we know from the results of studies that a significant percentage of patients who are initially treated with medication will eventually undergo invasive treatment.

The need to design new large trials to examine the treatment of patients with chronic stable angina

is still compelling. In adequately risk-stratified patients who are to be enrolled in such studies, optimal and maximal drug treatment should be administered, based on the guidelines. In the PCI arm the most modern techniques and materials must be used with a view to maximising reperfusion and minimising the ischaemic burden.[48,49] Only through this approach will it be possible to evaluate the effectiveness of each method in relation to the hard endpoints of death and non-fatal myocardial infarction.

References

1. Yusuf S, Reddy S, Ounpuu S, Anand S. Global burden of cardiovascular diseases: part 1: general considerations, the epidemiologic transition, risk factors, and impact of urbanization. Circulation. 2001: 104: 2746-2453.
2. Opie LH, Commerfold PJ, Gersh BJ. Controversies in stable coronary artery disease. Lancet. 2006; 367: 69-78.
3. Abrams J. Clinical practice. Chronic stable angina. N Engl J Med. 2005; 352: 2524-2533.
4. Vaina S, Stefanadis C. Treatment of multi-vessel coronary artery disease. What is the optimal revascularisation approach? What do we know, what will we learn? Hellenic J Cardiol. 2007; 48: 1-4.
5. Mehta SR, Cannon CP, Fox KAA, et al. Routine vs selective invasive strategies in patients with acute coronary syndromes: a collaborative meta-analysis of randomized trials. JAMA. 2005; 293: 2908-2917.
6. Kastrati A. Meta-analysis of PCI vs medical therapy in patients with stable and unstable angina [Internet]. Paper presented at: Transcatheter Cardiovascular Therapeutics; October 20-25, 2007 [cited 2008 April 30]; Washington, DC. Available from: http://www.tctmd.com/show.aspx?id=65674.
7. Parisi AF, Folland ED, Hartigan P. A comparison of angioplasty with medical therapy in the treatment of single-vessel coronary artery disease. Veterans Affairs ACME Investigators. N Engl J Med. 1992; 326: 10-16.
8. Folland ED, Hartigan PM, Parisi AF. Percutaneous transluminal coronary angioplasty versus medical therapy for stable angina pectoris: outcomes for patients with double-vessel versus single-vessel coronary artery disease in a Veterans Affairs Cooperative randomized trial. Veterans Affairs ACME Investigators. J Am Coll Cardiol. 1997; 29: 1505-1511.
9. Pepine CJ, Sharaf B, Andrews TC, et al. Relation between clinical, angiographic and ischemic findings at baseline and ischemia-related adverse outcomes at 1 year in the Asymptomatic Cardiac Ischemia Pilot study. ACIP Study Group. J Am Coll Cardiol. 1997; 29: 1483-1489.
10. Davies RF, Goldberg AD, Forman S, et al. Asymptomatic Cardiac Ischemia Pilot (ACIP) study two-year follow-up: outcomes of patients randomized to initial strategies of medical therapy versus revascularization. Circulation. 1997; 95: 2037-2043.
11. Pitt B, Waters D, Brown WV, et al. Aggressive lipid-lowering therapy compared with angioplasty in stable coronary artery disease. Atorvastatin versus Revascularization Treatment Investigators. N Engl J Med. 1999; 341: 70-76.
12. Hueb WA, Soares PR, Almeida De Oliveira S, et al. Five-year follow-up of the medicine, angioplasty, or surgery study (MASS): A prospective, randomized trial of medical therapy, balloon angioplasty, or bypass surgery for single proximal left anterior descending coronary artery stenosis. Circulation. 1999; 100: II107-113.
13. Zeymer U, Uebis R, Vogt A, et al. Randomized comparison of percutaneous transluminal coronary angioplasty and medical therapy in stable survivors of acute myocardial infarction with single vessel disease: a study of the Arbeitsgemeinschaft Leitende Kardiologische Krankenhausärzte. Circulation. 2003; 108: 1324-1328.
14. Henderson RA, Pocock SJ, Clayton TC, et al. Seven-year outcome in the RITA-2 trial: coronary angioplasty versus medical therapy. J Am Coll Cardiol. 2003; 42: 1161-1170.
15. Rita-2 Trial Participants. Coronary angioplasty versus medical therapy for angina: the second Randomised Intervention Treatment of Angina (RITA-2) trial. Lancet. 1997; 350: 461-468.
16. Pfisterer M. Long-term outcome in elderly patients with chronic angina managed invasively versus by optimized medical therapy: four-year follow-up of the randomized Trial of Invasive versus Medical therapy in Elderly patients (TIME). Circulation. 2004; 110: 1213-1218.
17. Kaiser C, Kuster GM, Erne P, et al. Risks and benefits of optimised medical and revascularisation therapy in elderly patients with angina—on-treatment analysis of the TIME trial. Eur Heart J. 2004; 25: 1036-1042.
18. Pfisterer M, Buser P, Osswald S, et al. Outcome of elderly patients with chronic symptomatic coronary artery disease with an invasive vs optimized medical treatment strategy: one-year results of the randomized TIME trial. JAMA. 2003; 289: 1117-1123.
19. Trial of invasive versus medical therapy in elderly patients with chronic symptomatic coronary-artery disease (TIME): a randomised trial. Lancet. 2001; 358: 951-957.
20. Hambrecht R, Walther C, Möbius-Winkler S, et al. Percutaneous coronary angioplasty compared with exercise training in patients with stable coronary artery disease: a randomized trial. Circulation. 2004; 109: 1371-1378.
21. Madsen JK, Nielsen TT, Grande P, et al. Revascularization compared to medical treatment in patients with silent vs. symptomatic residual ischemia after thrombolyzed myocardial infarction—the DANAMI study. Cardiology. 2007; 108: 243-251.
22. Mahmarian JJ, Dakik HA, Filipchuk NG, et al. An initial strategy of intensive medical therapy is comparable to that of coronary revascularization for suppression of scintigraphic ischemia in high-risk but stable survivors of acute myocardial infarction. J Am Coll Cardiol. 2006; 48: 2458-2467.
23. Soares PR, Hueb WA, Lemos PA, et al. Coronary revascularization (surgical or percutaneous) decreases mortality after the first year in diabetic subjects but not in nondiabetic subjects with multivessel disease: an analysis from the Medicine, Angioplasty, or Surgery Study (MASS II). Circulation. 2006; 114: I420-424.
24. Hueb W, Soares PR, Gersh BJ, et al. The medicine, angioplasty, or surgery study (MASS-II): a randomized, controlled clinical trial of three therapeutic strategies for multivessel coronary artery disease: one-year results. J Am Coll Cardiol. 2004; 43: 1743-1751.
25. Hueb W, Lopes N, Gersch B, et al. Five year follow-up of the Medicine, Angioplasty, or Surgery Study (MASS II): a randomised controlled clinical trial of 3 therapeutic strategies for multivessel coronary artery disease. Circulation. 2007; 115: 1082-1089.

26. Daemen J, Boersma E, Flather M, et al. Long term safety and efficacy of percutaneous intervention with stenting and coronary artery bypass Surgery for Multivessel Coronary Artery Disease. A metanalysis with a 5-year patient-level data from the ARTS, ERACI II, MASS II and SOS trials. Circulation. 2008; 118: 1146-1154.
27. Erne P, Schoenenberger AW, Burckhardt D, et al. Effects of percutaneous coronary interventions in silent ischemia after myocardial infarction: the SWISSI II randomized controlled trial. JAMA. 2007; 297: 1985-1991.
28. Boden WE, O'Rourke RA, Teo KK, et al. Optimal medical therapy with or without PCI for stable coronary disease. N Engl J Med. 2007; 356: 1503-1516.
29. Weintraub WS, Spertus JA, Kolm P, et al. Effect of PCI on quality of life in patients with stable coronary disease. N Engl J Med. 2008; 359: 677-687.
30. Gu Y, Hu Y, Hu L, Cheng Z, Li L. Outcome of patients with stable angina pectoris treated with or without percutaneous coronary intervention. Cardiol J. 2008; 15: 226-229.
31. Shaw LJ, Berman DS, Maron DJ, et al. Optimal medical therapy with or without percutaneous coronary intervention to reduce ischemic burden: results from the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial nuclear substudy. Circulation. 2008; 117: 1283-1291.
32. Nishigaki K, Yamazaki T, Kitabatake A, et al. Percutaneous coronary intervention plus medical therapy reduces the incidence of acute coronary syndrome more effectively than initial medical therapy only among patients with low risk coronary artery disease a randomized comparative multicenter study. JACC Cardiovasc Interv. 2008; 1: 469-479.
33. Schömig A, Mehilli J, de Waha A, Seyfarth M, Pache J, Kastrati A. A meta-analysis of 17 randomized trials of a percutaneous coronary intervention-based strategy in patients with stable coronary artery disease. J Am Coll Cardiol. 2008; 52: 894-904.
34. Frye RL, August P, Brooks MM, et al; for the BARI 2D Study Group. A randomized trial of therapies for type 2 diabetes and coronary artery disease. N Engl J Med. 2009; 360: 2503-2515.
35. Trikalinos TA, Alsheikh-Ali AA, Tatsioni A, Nallamothu BK, Kent DM. Percutaneous coronary interventions for nonacute coronary artery disease: a quantitative 20-year synopsis and a network meta-analysis. Lancet. 2009; 373: 911-918.
36. Katritsis DG, Meier B. Percutaneous coronary intervention for stable coronary artery disease. J Am Coll Cardiol. 2008; 52: 889-893.
37. Shah PK. Mechanisms of plaque vulnerability and rupture. J Am Coll Cardiol. 2003; 41 (4 Suppl S): 15S-22S.
38. Falk E, Shah PK, Fuster V. Coronary plaque disruption. Circulation. 1995; 92: 657-671.
39. Horst B, Rihal CS, Holmes DR, et al. Comparison of drug eluting stents and bare metal stents for stable coronary artery disease. JACC Cardiovasc Interv. 2009; 2: 321-328.
40. Toutouzas K, Patsa C, Vaina S, et al. A preliminary experience report: Drug-eluting stents versus coronary artery bypass surgery in patients with a single lesion in the proximal left anterior descending artery suffering from diabetes mellitus and chronic stable angina. Hellenic J Cardiol. 2008; 49: 65-71.
41. Toutouzas K, Markou V, Drakopoulou M, Mitropoulos I, Tsiamis E, Stefanadis C. Patients with type two diabetes mellitus: increased local inflammatory activation in culprit atheromatous plaques. Hellenic J Cardiol. 2005; 46: 283-288.
42. Fox K, Garcia MAA, Ardissino D, et al. Guidelines on the management of stable angina pectoris: executive summary: The Task Force on the Management of Stable Angina Pectoris of the European Society of Cardiology. Eur Heart J. 2006; 27: 1341-1381.
43. Gibbons RJ, Abrams J, Chatterjee K, et al. ACC/AHA 2002 guideline update for the management of patients with chronic stable angina—summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients With Chronic Stable Angina). Circulation. 2003; 107: 149-58.
44. Smith SC Jr, Feldman TE, Hirshfield JW Jr, et al. ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/SCAI Writing Committee to Update 2001 Guidelines for Percutaneous Coronary Intervention). Circulation 2006; 113: e166-286.
45. King SB 3rd, Smith SC Jr, Hirshfeld JW Jr, et al. 2007 focused update of the ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention: a report of the American College of Cardiology/American Heart Association Task Force on Practice guidelines. J Am Coll Cardiol. 2008: 51: 172-209.
46. Katritsis DG, Ioannidis JPA. Percutaneous coronary intervention versus conservative therapy in nonacute coronary artery disease: a meta-analysis. Circulation. 2005; 111: 2906-2912.
47. Coylewright M, Blumenthal RS, Post W. Placing COURAGE in context: review of the recent literature on managing stable coronary artery disease. Mayo Clin Proc. 2008; 83: 799-805.
48. Stefanadis CI. Expanding the boundaries of interventional cardiology. Hellenic J Cardiol. 2009; 50: 235-236.
49. Spanos VN, Toutouzas PK. The ever increasing role of percutaneous interventions in coronary revascularisation. Hellenic J Cardiol. 2010; 51: 512-517.