REVIEW

Treatment decisions for stable coronary artery disease

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Summary: Progress has occurred in all aspects of treatment of stable coronary artery disease. The vast majority of studies suggest that optimal medical treatment is not inferior to percutaneous coronary intervention (PCI), while coronary artery bypass grafting (CABG) offers better results than both, in left main and/with proximal left anterior descending artery, in multivessel disease involvement. However, with the use of 3rd generation drug eluting stents, results are becoming more balanced with both approaches. Diabetes mellitus is a factor of preference of CABG over PCI. Current treatment is based on these findings and is directed towards the improvement of both symptoms and prognosis.
Keywords: angina pectoris, coronary artery bypass surgery, coronary artery disease, percutaneous coronary intervention
Glossary of abbreviations: CAD: coronary artery disease, PCI: percutaneous coronary interventions, CABG: coronary artery bypass grafting, pts: patients, OMT: optimal medical therapy, AP: angina pectoris, MI: myocardial infarction

BACKGROUND

Angina pectoris (AP) is the main symptom of myocardial ischaemia and is usually caused by atherosclerotic obstructive coronary artery disease (CAD). AP can have significant impact on quality of life, restricting daily work and leisure activities. The aim of management of stable AP is (i) to eliminate or minimize symptoms, thus improve quality of life, but also importantly to (ii) reduce long-term morbidity and mortality (prognosis). For treatment to be considered satisfactory both purposes should be fulfilled. Management options include optical medical therapy (OMT) and revascularization using percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG)[1,2].

MEDICAL THERAPY

Drug treatment

oMT consists of one, two or more anti-anginal drugs to treat symptoms plus drugs for secondary prevention of cardiovascular disease. β-blockers and/or calcium channel blockers constitute the first line treatment. Recently Bangalore S et al, concluded that in patients (pts) with recent MI (one year or less), beta-blocker use was associated with a lower incidence of cardiovascular death, nonfatal MI, nonfatal stroke, hospitalization for atherothrombotic events or a revascularization procedure. However, significant reservations have recently been voiced as regards β-blocker use in pts without a previous MI by these authors[3]. In a *post hoc* analysis of the CHARISMA trial, they found a 31% reduced risk of the primary composite outcome among patients using β-blockers, with a prior MI; this was driven by a roughly 40% reduced risk of new MI. However, in non-prior MI patients, the known atherothrombotic disease group and the risk-factors only group, no advantage was seen. In the latter group β-blockers were actually associated with a trend toward an increased risk of stroke[4].

In addition to these two drug categories, long acting nitrates, nicorandil, trimetazidine or ranolazine which acts on the cellular level[5], may reduce myocardial ischaemia, provide symptom relief and possibly improve prognosis. Ranolazine has been found to reduce the extent of myocardial ischaemia, by the use of scintigraphy[6].

Administration of ivabradine in patients (pts) in whom heart rate is not adequately controlled (<70 bpm) did not improve the primary endpoint (composite of cardiovascular death or nonfatal MI) which occurred in 6.8% of the ivabradine group and 6.4% of the placebo group (p=0.20). It was associated with an increase in the incidence of the primary end point among pts with activity-limiting AP but not among those without activity-limiting AP[7].

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The drugs for secondary prevention of cardiovascular disease are aspirin (starting from 75 mg and taking into account the risk of bleeding), statins and antihypertensive drugs for optimal lipid and blood pressure lowering[8]. Clopidogrel can be used as an alternative in case of aspirin intolerance[9].

REVASCULARIZATION FOR STABLE CAD

The main indications for revascularization are persistence of symptoms, despite OMT, and an improvement of prognosis, according to the Guidelines of the *European Society of Cardiology* (ESC) on the management of CAD[10]. Ischaemic burden at non-invasive testing has a significant role in survival of pts with stable AP: Asymptomatic pts with a significant mass of ischaemic myocardium have been shown to obtain a prognosis benefit from revascularization[11,12].

OMT versus PCI

The seminal COURAGE RCT randomized 2287 pts with known CAD and evidence of myocardial ischaemia to OMT alone or to OMT and PCI. At a median follow-up of 4.6 years, there was no significant difference in death, MI, stroke or hospitalization for unstable angina. After 1 year the PCI group had fewer symptoms of angina; however, at 3 years, there was no longer any difference between the 2 groups. After 5 years 21% of the PCI group and 33% of the OMT alone group had received additional revascularization (p<0.001). In this study, 31% of the pts had 1 vessel disease, 39% 2 vessel disease and 30% 3 vessel disease. Only 31% had proximal left anterior descending coronary artery (LAD) disease. Pts with left main disease were excluded and most pts had normal left ventricular function[13].

In a small nuclear substudy of the COURAGE trial, 100 pts with >10% ishaemic myocardium diagnosed with myocardial perfusion single photon emission computed tomography, had a lower risk of death or myocardial infarction (MI) with PCI[14].

Additional efforts are being directed towards establishing if certain subgroups of pts can be benefited by OMT or invasive therapy. In the recent FAME study, measurement of fractional flow reserve (FFR) in pts with multivessel CAD undergoing PCI with drug-eluting stents, significantly reduced the rate of the composite end point of death and repeat revascularization at 1 year[15]. Recently, the use of FFR has been upgraded to a Class IA classification in multi-vessel PCI in the ESC Guidelines on coronary revascularization[10].

Similarly, Muller et al, evaluated the long-term clinical outcome of pts with an angiographically intermediate LAD stenosis in whom revascularization was based on FFR; In 730 pts with a 30% to 70% isolated stenosis in the proximal LAD, when FFR was ≥0.80, the pts were treated medically (medical group); when FFR was <0.80, the pts underwent a revascularization procedure (13% CABG and 87% PCI). The 5-year survival of the medical group was compared with that of a reference population. The 5-year survival estimate was 92.9% in the medical group versus 89.6% in the controls (p = 0.74)[16].

Most previous meta-analyses have reported no mortality benefit, increased periprocedural MI and reduced need for repeat revascularization with PCI[17-19].

In a very recent meta-analysis of all randomized clinical trials from 1970 to 2011, initial coronary stent implantation with medical therapy was compared to OMT alone, to determine the effect of stenting on death, nonfatal MI, unplanned revascularization, and persistent angina. Eight trials enrolling 7229 pts were identified. Three trials enrolled stable pts after MI, whereas 5 studies enrolled pts with stable angina and/or ischemia on stress testing. Mean follow-up was 4.3 years. The respective event rates with stent implantation and medical therapy were similar for death, nonfatal MI, unplanned revascularization and persistent angina. Initial stent implantation for stable CAD showed no evidence of benefit compared with initial medical therapy for prevention of the above endpoints[20,21].

OMT versus CABG

In an older meta-analysis of seven randomized clinical trials, reduced mortality rates were found in pts with left main disease, 3 vessel disease (particularly when the proximal LAD was involved) and impaired LV function who underwent CABG, as compared to OMT alone[22]. The benefits of CABG may be even greater if one considers that most pts in the older trials had low severity of CAD and only 10% of CABG patients received an internal thoracic artery graft, which is the most important prognostic component of CABG[23]. A more recent meta-analysis reported a significant reduction in the hazard ratio for death with CABG versus OMT (HR 0.62, 95% CI 0.50-0.77). Revascularization was not associated with a significant reduction in nonfatal myocardial infarction compared with OMT[24].

PCI versus CABG

According to two meta-analyses, the treatment of isolated LAD stenosis with PCI or CABG has the same endpoints concerning mortality, MI or cerebrovascular

events. There is a significant increase in recurrent angina (three-fold) and revascularization (five-fold), with PCI, at 5 years follow-up[25,26].

More than 15 randomised clinical trials for multivessel CAD, compare PCI to CABG. Most pts in these trials had 1 or 2 VD (vascular diseases), with normal LV function and without proximal LAD disease. Meta-analysis of these trials reported superiority of CABG with a five-fold reduction in the need for revascularization and survival benefit in pts >65 years old (HR 0.82) and in those with diabetes (HR 0.70)[27].

In a recent observational study the ACCF National Cardiovascular Data Registry and the STS Adult Cardiac Surgery Database were linked, concerning patients 65 years of age or older who had two or three-vessel CAD without AMI. In a period from 2004 to 2008, 86,244 underwent CABG and 103,549 underwent PCI. The median follow-up period was 2.67 years. At 1 year, there was no significant difference in adjusted mortality between the groups (6.24% in the CABG group as compared with 6.55% in the PCI group). At 4 years, there was lower mortality with CABG than with PCI (16.4% vs. 20.8)[28].

In the MASS II study, 611 pts with multivessel disease were included and OMT versus PCI versus CABG were compared. At 5 years' follow-up the composite primary endpoint (total mortality, Q wave myocardial infarction, refractory angina requiring revascularization) occurred in 36% of pts receiving OMT, 33% of pts who underwent PCI and 21% of pts who underwent CABG (p=0.003), with revascularization rates of 9%, 11% and 4% respectively (p=0.02)[29].

In the important SYNTAX trial, 1800 pts with three-vessel or left main CAD underwent CABG or PCI (paclitaxel-eluting stent were used) in a 1:1 ratio. Equivalent anatomical revascularization could be achieved with either treatment. At 12-months after randomization the rate of repeat revascularization was 13.5% in the PCI group vs. 5.9% in the CABG group, P<0.001. The two groups had similar rates of death from any cause or MI. Pts with low or intermediate SYNTAX scores in the CABG and the PCI group had similar rates of major adverse cardiac or cerebrovascular events, whereas in high scores, the event rate was significantly increased in the PCI group. This study concerned that CABG remains the standard of care for pts with three-vessel or left main CAD[30].

From the 5-year SYNTAX trial outcomes investigators concluded that major adverse cardiac and cerebrovascular events (MACCE) were 26.9% in the CABG group and 37.3% in the PCI group (p<0 0001).

Myocardial infarction and repeat revascularization were significantly higher with PCI versus CABG. All-cause death and stroke were not significantly different between groups. In patients with low SYNTAX scores MACCE was similar in the CABG and PCI groups (p=0.43). In the CABG group with left main coronary disease 31% had MACCE versus 36.9% in the PCI group (p=0.12); however, in pts with intermediate or high SYNTAX scores, MACCE was significantly increased with PCI (intermediate score, 25.8% of the CABG group vs 36.0% of the PCI group; p=0.008; high score, 26.8% vs 44.0%; p<0.0001). Thus, CABG should remain the standard of care for pts with high or intermediate SYNTAX scores. For pts with less complex disease (low SYNTAX scores) or left main coronary disease (low or intermediate SYNTAX scores), PCI is an acceptable alternative. All pts with complex multivessel coronary artery disease should be reviewed and discussed by both a cardiac surgeon and interventional cardiologist to reach consensus on optimum treatment[31]. Goldenberg and Kornowski, also mentioned the importance of the SYNTAX score in treatment decisions for multivessel CAD[32]. However, an important question has not been adequately answered yet: Is the need for repeat revascularization driven by stent-restenosis or appearance of new stenotic lesions in areas not covered by the stents? In the very recent study of Cassese et al, in 10004 pts followed for 4 years, stent restenosis observed in 26.4% of pts, was a major determinant of long-term mortality, even in asymptomatic pts. However, the number of vessels presenting with new lesions was not mentioned[33].

In recent years, the use of DES has increased. Park et al, evaluated 3,042 pts with multivessel disease who received DES (1547 pts) or underwent CABG (1495 pts) with complete follow-up data for a median 5.6 years; 5-year risk of death and the combined risk of death, myocardial infarction, or stroke were similar between groups. However, the rates of revascularization were significantly higher in the DES group (HR: 2.93; 95% CI: 2.20 to 3.90, p <0.001). Similar results were obtained in comparisons of DES with CABG for high-risk clinical and anatomic subgroups with diabetes mellitus, abnormal ventricular function, age 65 years or more, and 3-vessel and left main disease. Mortality benefit with DES implantation was noted in pts with 2-vessel disease (with proximal LAD 319 pts, without proximal LAD 549 pts), relative to CABG (HR: 0.57; 95% CI: 0.36 to 0.92, p = 0.02)[34].

The *American College of Cardiology Foundation* (ACCF) and the *Society of Thoracic Surgeons* (STS) compared

long-term survival after PCI and CABG. They linked databases to assess data for years 2004 through 2008. They included pts 65 years or older, with 2 or 3 vessel disease without an acute MI; 86244 pts underwent CABG and 103549 PCI. At a 4 years the mortality for CABG was lower than that of PCI (16.4% vs 20.8%; risk ratio, 0.79; 95% CI, 0.76 to 0.82)[35].

Third generation DES are currently used more widely. In the very recent Dutch Peers study the use of 3rd generation DES provided excellent clinical outcomes with both zotarolimus-eluting and everolimus-eluting stents[36].

These excellent results raise an important question whether older generation DES or bare metal stents should continue being used. Many authors point out that even with the use of 2nd generation DES, dual antiplatelet drug therapy can safely be stopped at 6 months after stent implantation[37].

Moreover, questions are continuously being raised whether BMS are really safer as regards late stent thrombosis. Thus, in a secondary analysis of the DAPT trial in the 2014 AHA Scientific Sessions, Dr Dean Kereiakes actually found a lower thrombosis rate at 12 months with DES (1.7%) than with BMS (2.6%), p<0.001 for non-inferiority, p<0.01 for difference. Results appear similar across all DES types. In BMS, extended (30 months) DAPT vs 12 months therapy showed a non significant advantage as regard thrombosis prevention[38]. To us, these results should support the abandonment of BMS for the future, since at 12 months they offer no greater safety for DAPT discontinuation than DES.

All in all 4 trials were presented in the AHA 2014 Scientific Sessions. In the large DAPT study population, which included fewer BMS and more DES, 30 months DAPT was associated with fewer stent thromboses, than with 12 months. Importantly ischaemic events increased markedly in the 3 months that thienopyridine was stopped, regardless of when that occurred, leading to suggestions that treatment should maybe continue longer, even for life. Dr Giles Montalescot, a thrombosis expert, summarizes the results of the 4 trials as follows: There is no common rule for duration of DAPT, it has to be individualized. If the patient had a new-generation stent and you want to stop DAPT early at 6 months you probably can. If the patient has multiple ishaemic factors or the Taxus stent in the left main, he should continue DAPT for a long time, maybe for ever.

Left main stenosis

In this challenging entity CABG is still considered the best approach. However, PCI is being increasingly considered as a viable alternative. The 5 year SYNTAX results have already been discussed[31].

In a meta-analysis of 10 studies of 3773 pts with left main stenosis (including two randomized clinical trials and the MAIN-COMPARE registry), death, myocardial infarction, and stroke were similar in the PCI and CABG-treated patients at 1 year, 2 years and 3 years. Target vessel revascularization was significantly higher in the PCI group at 1 year, 2 years and 3 years. There was no difference in mortality in PCI versus CABG-treated patients at 1 year, 2 years and 3 years. The need for repeat revascularization was 4 times greater in patients who underwent PCI[39].

In a more recent meta-analysis Capodanno et al, identified 1611 patients with left main coronary artery disease, from 4 randomized clinical trials. PCI was associated with a nonsignificantly higher 1-year rate of major adverse cardiac and cerebrovascular events [death, MI, target vessel revascularization (TVR) and stroke] compared with CABG (14.5% vs. 11.8%; p = 0.11), driven by increased TVR (11.4% vs. 5.4%; p <0.001). Conversely, stroke occurred less frequently with PCI (0.1% vs. 1.7; p = 0.013). There were no significant differences in death (3.0% vs. 4.1%; p = 0.29) or MI (2.8% vs. 2.9; p = 0.95)[40].

Patients with diabetes

In the BARI 2D Study Group, 2368 pts with type 2 diabetes and heart disease were randomly assigned to undergo either revascularization (PCI or CABG) with OMT, or OMT alone. In pts receiving PCI, there was no significant difference in primary end points between this and the OMT group. However, in pts receiving CABG, major cardiovascular events were significantly lower in the revascularization (22.4%) than in OMT group (30.5%, P=0.01)[41].

In the prospective, randomized FREEDOM trial, pts with diabetes and multivessel coronary artery disease were assigned to undergo either PCI with drug-eluting stents or CABG. They were followed for a minimum of 2 years (median among survivors, 3.8 years). The primary outcome measure was a composite of death from any cause, nonfatal myocardial infarction, or nonfatal stroke. From 2005 through 2010, 1900 patients were enrolled. The primary outcome occurred more frequently in the PCI group (P=0.005), with 5-year rates of 26.6% in the PCI group and 18.7% in the CABG group. The benefit of CABG was driven by differences

in rates of both myocardial infarction (P<0.001) and death from any cause (P=0.049). Stroke 5-year rates were 2.4% in the PCI group and 5.2% in the CABG group (P=0.03). For pts with diabetes and advanced coronary artery disease, CABG was superior to PCI in that it significantly reduced rates of death and myocardial infarction, with a higher rate of stroke[42].

In a subgroup analysis of the FREEDOM trial, long-term clinical outcomes after revascularization in pts with insulin-treated diabetes mellitus (ITDM) were compared with pts not treated with insulin. A total of 1,850 subjects had an index revascularization procedure performed: 956 underwent PCI with drug-eluting stents (DES), and 894 underwent CABG. A total of 602 pts (32.5%) had ITDM (PCI/DES n = 325, 34%; CABG n = 277, 31%). Subjects were classified according to ITDM versus non-ITDM, with comparison of PCI/DES versus CABG for each group. Interaction analyses were performed for treatment by diabetes mellitus (DM) status alone and for treatment by DM status by coronary lesion complexity. The overall 5-year event rate of death/stroke/MI was significantly higher in ITDM versus non-ITDM patients (28.7% vs. 19.5%, p <0.001); it persisted even after adjustment for multiple baseline factors, angiographic complexity, and revascularization treatment group (death/stroke/MI hazard ratio [HR]: 1.35, 95% confidence interval [CI]: 1.06 to 1.73, p = 0.014). With respect to the primary composite endpoint, CABG was superior to PCI/DES in both DM types and the magnitude of treatment effect was similar (interaction p = 0.40) for ITDM (PCI vs. CABG HR: 1.21; 95% CI: 0.87 to 1.69) and non-ITDM patients (PCI vs. CABG HR: 1.46; 95% CI 1.10 to 1.94), even after adjusting for the angiographic SYNTAX score level. Thus, in pts with diabetes and multivessel coronary artery disease, the rate of major adverse cardiovascular events (death, MI, or stroke) is higher in patients treated with insulin than in those not treated with insulin[43].

Appropriateness Criteria- A new concept
Recently, the *American College of Cardiology Foundation,* the *Society for Cardiovascular Angiography and Interventions,* the *Society of Thoracic Surgeons,* and the *American Association for Thoracic Surgery,* conducted an update of the appropriate use criteria (AUC) for coronary revascularization[44]. In the initial document[45], 180 clinical scenarios were developed to mimic patient presentations encountered in everyday practice and included information on symptoms, extent of medical therapy and risk level as assessed by non-invasive testing and coronary anatomy.

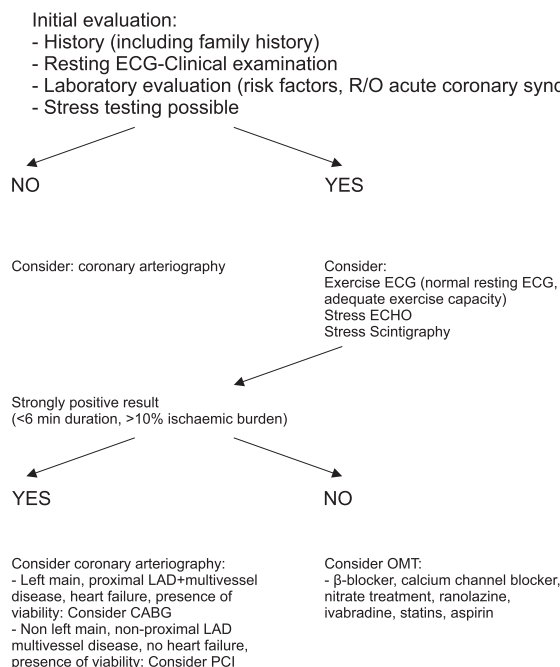**DIAGNOSTIC AND PROGNOSTIC STRATIFICATION**

Figure 1. Chronic stable coronary artery disease (angina).

In general, as seen with the prior AUC, the use of coronary revascularization for pts with acute coronary syndromes and combinations of significant symptoms and/or ischemia is appropriate. In contrast, revascularization of asymptomatic pts, or pts with low-risk findings on noninvasive testing and minimal medical therapy, are viewed less favorably. They suggest that CABG remains an appropriate method of revascularization for pts with high burden of CAD. However, additionally, they suggest that PCI may have a role in revascularization of pts with high burden of CAD. The primary objective of the appropriate use criteria is to improve physician decision making and patient education regarding expected benefits from revascularization. Inappropriate revascularization may be harmful to pts and generate unwarranted costs to the healthcare system, whereas appropriate revascularization procedures can improve patient clinical outcomes.

The Heart Team
For difficult cases, such as patients with heart failure or renal insufficiency, guidelines propose arbitration by a Heart Team which would consist of an interventional cardiologist and a cardiac surgeon[46]. Their recommendations may seem time consuming and somewhat timid to many interventionists. Moreover, these two problems, could have been taken into account before

the patient comes to the catheterization laboratory and necessary preparations can be instituted. Still, the concept of the Heart Team is very useful, and should emphasize the need for a team approach in the management of our pts.

In the following graph we summarize the chronic stable CAD (angina) diagnostic and prognostic stratification adapting from recent ESC guidelines[10]. We tried to make it as simple as possible.

AUTHORS' CONCLUSIONS-REFLECTIONS

Our reflections after presenting all these data are the following: In stable CAD, all pts should have a functional test before coming to catheterization. A large ischaemic burden should alert to probability of left main, proximal LAD and/or 3 vessel disease. The last ESC revascularization guidelines[10] favor stress scintigraphy and echocardiography and do not mention exercise electrocardiography at all. Still, in a male patient with a normal resting ECG, a typical history of angina at exercise and good exercise capacity, it is quite reliable. A "strongly positive" exercise test (<6 min duration, >2 mm ST depression) would obviate any further non-invasive test and direct him straight to coronary arteriography, anticipating the need for invasive therapy[47].

After coronary arteriography is performed, in pts with non-main, non-proximal LAD disease, without evidence of extensive ischaemia by non-invasive testing, if OMT adequately controls symptoms, it is the treatment of choice. Otherwise, the simpler PCI would be preferable to CABG, which however we would still prefer in left main, multivessel disease with proximal LAD stenosis and chronic heart failure with presence of viability. Finally, it should be underlined that in pts with CAD all three treatment modalities can be applied, frequently more than once during their lifetime, with the aim of improving their quality of life and survival. One aspect that is understressed is that OMT should be continued indefinitely with undiminished zeal after PCI or CABG. Thus, all 3 treatments should be considered complementary rather than competing[48].

Conflict of interest: none declared.

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