World Journal of Cardiology

Online Submissions: http://www.wjgnet.com/esps/
bpgoffice@wjgnet.com
doi:10.4330/wjc.v6.i4.130

*World J Cardiol* 2014 April 26; 6(4): 130-139
ISSN 1949-8462 (online)


TOPIC HIGHLIGHT

WJC 6th Anniversary Special Issues (2): Coronary artery disease

# Myocardial ischemia is a key factor in the management of stable coronary artery disease

Kohichiro Iwasaki

Kohichiro Iwasaki, Department of Cardiology, Okayama Kyokuto Hospital, Okayama 703-8265, Japan
Author contributions: Iwasaki K contributed to the concept, design, and analysis and interpretation of the data; Iwasaki K also drafted the article, revised it critically for important intellectual content, and approved the final version to be published.
Correspondence to: Kohichiro Iwasaki, MD, Department of Cardiology, Okayama Kyokuto Hospital, 567-1 Kurata, Naka-ku, Okayama 703-8265, Japan. kiwasaki@kyokuto.or.jp
Telephone: +81-86-2763231 Fax: +81-86-2741028
Received: September 2, 2013 Revised: November 16, 2013
Accepted: March 3, 2014
Published online: April 26, 2014

## Abstract

Previous studies demonstrated that coronary revascularization, especially percutaneous coronary intervention (PCI), does not significantly decrease the incidence of cardiac death or myocardial infarction in patients with stable coronary artery disease. Many studies using myocardial perfusion imaging (MPI) showed that, for patients with moderate to severe ischemia, revascularization is the preferred therapy for survival benefit, whereas for patients with no to mild ischemia, medical therapy is the main choice, and revascularization is associated with increased mortality. There is some evidence that revascularization in patients with no or mild ischemia is likely to result in worsened ischemia, which is associated with increased mortality. Studies using fractional flow reserve (FFR) demonstrate that ischemia-guided PCI is superior to angiography-guided PCI, and the presence of ischemia is the key to decision-making for PCI. Complementary use of noninvasive MPI and invasive FFR would be important to compensate for each method's limitations. Recent studies of appropriateness criteria showed that, although PCI in the acute setting and coronary bypass surgery are properly performed in most patients, PCI in the non-acute setting is often inappropriate, and stress testing to identify myocardial ischemia is performed in less than half of patients. Also, some studies suggested that revascularization in an inappropriate setting is not associated with improved prognosis. Taken together, the presence and the extent of myocardial ischemia is a key factor in the management of patients with stable coronary artery disease, and coronary revascularization in the absence of myocardial ischemia is associated with worsened prognosis.



**Key words:** Coronary artery bypass surgery; Coronary revascularization; Fractional flow reserve; Myocardial ischemia; Myocardial perfusion imaging; Percutaneous coronary intervention

**Core tip:** Studies of myocardial perfusion imaging demonstrate that, for patients with moderate to severe ischemia, revascularization is the preferred therapy for survival benefit. For patients with no to mild ischemia, medical therapy is the main choice, and revascularization is associated with increased mortality probably because of worsened ischemia. Studies using fractional flow reserve demonstrate that ischemia-guided percutaneous coronary intervention (PCI) is superior to angiography-guided PCI, and the presence of ischemia is the key factor in decision-making for PCI. Thus, myocardial ischemia is a key factor in the management of patients with stable coronary artery disease.

Iwasaki K. Myocardial ischemia is a key factor in the management of stable coronary artery disease. *World J Cardiol* 2014; 6(4): 130-139 Available from: URL: http://www.wjgnet.com/1949-8462/full/v6/i4/130.htm DOI: http://dx.doi.org/10.4330/wjc.v6.i4.130

## INTRODUCTION

Coronary artery disease is a leading cause of mortality and morbidity in developing and developed countries[1-5]. In approximately half of patients with newly diagnosed coronary artery disease, the first presentation is either acute myocardial infarction or sudden cardiac death[6,7].

The development of percutaneous coronary intervention (PCI) has enhanced the management of patients with acute coronary syndrome, and the prognosis of these patients has been considerably improved[8-15]. However, in patients with stable coronary artery disease, coronary revascularization decreases angina symptoms but does not significantly prevent cardiac death or myocardial infarction[16-21]. Recent studies suggest that the presence and extent of myocardial ischemia determine the prognosis of patients with stable coronary artery disease. Coronary revascularization is associated with improved prognosis in patients with moderate or severe ischemia, but is associated with worsened prognosis in patients with no or mild ischemia[22,23]. In this article, studies with myocardial perfusion imaging (MPI) and fractional flow reserve (FFR) on the effects of coronary revascularization on prognosis are reviewed.

## CLINICAL OUTCOMES UTILIZING REVASCULARIZATION AND AGGRESSIVE DRUG EVALUATION TRIALS

Previous studies demonstrated that coronary revascularization does not significantly decrease the incidence of cardiac death and myocardial infarction in patients with stable coronary artery disease[16-21]. In particular, the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) study had a tremendous impact on our management of patients with stable coronary artery disease[24]. COURAGE trial is a randomized trial involving 2287 patients who had objective evidence of myocardial ischemia and significant coronary artery disease. The investigators assigned 1149 patients to undergo PCI with optimal medical therapy (PCI group) and 1138 to receive optimal medical therapy (OMT group) alone. The 4.6-year cumulative primary outcome (death from any cause and nonfatal myocardial infarction) rates were 19.0% in the PCI group and 18.5% in the OMT group (HR for the PCI group: 1.05; 95%CI: 0.87-1.27; $P$ = 0.62). There were no significant differences between the PCI group and the OMT group in the composite of death, myocardial infarction, and stroke (20.0% *vs* 19.5%, HR = 1.05; 95%CI: 0.87-1.27; $P$ = 0.62); hospitalization for acute coronary syndrome (12.4% *vs* 11.8%, HR = 1.07; 95%CI: 0.84-1.37; $P$ = 0.56); or myocardial infarction (13.2% *vs* 12.3%, HR = 1.13; 95%CI: 0.89-1.43; $P$ = 0.33). They concluded that as an initial management strategy in patients with stable coronary artery disease, PCI did not reduce the risk of death, myocardial infarction, or other major cardiovascular events when added to OMT.

However, the COURAGE Trial Nuclear Substudy tells another story[25]. This study enrolled 314 patients who underwent MPI performed before treatment and 6 to 18 mo after randomization. At follow-up, the reduction in ischemic myocardium was greater with PCI than with OMT (-2.7% *vs* -0.5%; $P < 0.0001$). More PCI patients exhibited significant ischemia reduction (33% *vs* 19%; $P = 0.0004$), especially patients with moderate to severe pretreatment ischemia (78% *vs* 52%; $P = 0.007$). Patients with ischemia reduction had lower ischemia-unadjusted risk of death or myocardial infarction ($P = 0.037$; risk-adjusted $P = 0.26$), particularly if baseline ischemia was moderate to severe ($P = 0.001$; risk-adjusted $P = 0.08$). Death or myocardial infarction rates ranged from 0% to 39% for patients with no residual ischemia to ⩾ 10% residual ischemia on follow-up MPI ($P = 0.002$; risk-adjusted $P = 0.09$). Thus this study showed that adding PCI to OMT resulted in a greater reduction in ischemia compared with OMT alone, although the effect of PCI on death or myocardial infarction was borderline significant probably because of the small number of patients.

## MPI

MPI is the most commonly used test to assess the presence and the extent of myocardial ischemia. Many studies demonstrated that the presence and extent of myocardial ischemia was closely related to adverse cardiac events[26-36]. Hachamovitch *et al*[36] identified 5183 patients who underwent MPI and were followed up for the occurrence of cardiac death or myocardial infarction. Over a mean follow-up of 642 ± 226 d, 119 cardiac deaths and 158 myocardial infarctions occurred, giving an annual cardiac death rate of 3.0% and annual myocardial infarction rate of 2.3%. In patients with no [summed stress score (SSS) 0-3], mild (SSS 4-8), moderate (SSS 9-13), and severe (SSS > 13) ischemia, the annual cardiac death rate was 0.3%, 0.8%, 2.3%, and 2.9%, respectively. Similarly, in patients with no, mild, moderate, and severe ischemia, the annual myocardial infarction rate was 0.5%, 2.7%, 2.9%, and 4.2%, respectively. Thus increased myocardial ischemia is associated with more frequent cardiac events.

Many studies also showed that coronary revascularization has a beneficial effect in patients with moderate to severe ischemia[22,23,37]. Hachamovitch *et al*[22] studied 10627 patients without known coronary artery disease who underwent MPI and were followed up for 1.9 ± 0.6 years. Within 60 d after MPI, 671 patients underwent revascularization therapy and 9956 patients underwent medical therapy (MT). On the basis of the Cox proportional hazards model predicting cardiac death, patients undergoing MT demonstrated a survival advantage over patients undergoing revascularization in the setting of no or mild ischemia (% total myocardial ischemia less than 10%), whereas patients undergoing revascularization had an increasing survival benefit over patients undergoing MT when moderate ischemia (% total myocardial ischemia 11%-20%) to severe ischemia (% total myocardial ischemia more than 20%) was present. In 2011, the same

authors expanded their sample to 12329 patients and studied the interaction between the extent of ischemia and myocardial scar after revascularization on patient survival[23]. In the absence of prior coronary artery disease, increasing amounts of ischemia were associated with lower HRs with early revascularization. In the setting of little or no ischemia, early revascularization was associated with an approximately 50% greater risk than MT, whereas, with increasing ischemia, a progressive improvement in risk with early revascularization compared with MT was found. In the setting of extensive ischemia (> 20% myocardium), a 30% reduction in risk of all-cause death was present with the use of early revascularization compared with MT. Equipoise between the two strategies was present with approximately 10%-15% of the myocardium ischemic. As for patients with < 10% fixed defect, the risk reduction was 12.5% with MT and for patients with prior revascularization but no prior myocardial infarction it was 7.5%. Thus, these studies demonstrate that for patients with moderate to severe ischemia, revascularization is the preferred therapy for survival benefit, whereas for patients with no to mild ischemia MT is the main choice and revascularization is associated with increased mortality.

## WHY IS CORONARY REVASCULARIZATION IN PATIENTS WITH NO OR MILD ISCHEMIA ASSOCIATED WITH INCREASED MORTALITY?

There is some evidence that revascularization in patients with no or mild ischemia is not associated with improved ischemia, but rather associated with worsened ischemia. Safley *et al*[38] identified 301 patients who underwent PCI for chronic total occlusion and in whom MPI was performed within 12 ± 3 mo before PCI and a follow-up study within 12 ± 3 mo after PCI. The change in % ischemia was +5.39% ($P = 0.006$), -1.70% ($P = 0.008$), -6.32% ($P < 0.001$), and -16.26% ($P < 0.001$) in patients with no/minimal (< 5% ischemic myocardium), mild (5%-9.9%), moderate (10%-16%), and severe (> 16%) ischemia, respectively. The percentage of patients with improved ischemic myocardium ≥ 5% was 0%, 34.7%, 68.5%, and 86.7% in patients with no/minimal, mild, moderate, and severe ischemia, respectively ($P < 0.001$). The percentage of patients with worsened ischemic myocardium ≥ 5% was 87.3%, 34.7%, 19.2%, and 9.2% in patients with no/minimal, mild, moderate, and severe ischemia, respectively ($P < 0.001$). Kaplan-Meier survival in patients with *vs* without improvement in ischemia showed a survival advantage in patients with improved ischemic myocardium ≥ 5% (87% *vs* 78%, $P = 0.018$). Receiver operating characteristics curve (ROC) analysis identified a 12.5% ischemic burden as the optimal cut-point to predict improvement in ischemia following PCI (sensitivity 80%, specificity 80%). This 12.5% ischemic burden is almost the same as that in the 2011 study by Hachamovitch *et al*[23]. Also ROC analysis identified a 6.25% ischemic burden as the optimal cut-point to predict worsening in ischemia following PCI (sensitivity 75%, specificity 80%). Thus, this study demonstrated that revascularization had no survival benefit and harms patients with no to mild ischemia, although the study was limited to patients who underwent PCI for chronic total occlusion.

Myocardial infarction associated with PCI (periprocedural myocardial infarction) is classified as type 4a by the third universal definition of myocardial infarction[39]. The prevalence of periprocedural myocardial infarction is 7.3% to 17.9% defined by CK-MB isoenzyme elevation > 3x upper limit of normal (ULN) and 15.0% to 44.2% defined by cardiac troponin > ULN[40-55]. The results of several studies suggested that any elevation in CK-MB was associated with reduced long-term survival and that there was a direct correlation between the magnitude of myonecrosis and mortality. Other studies have shown that only large myocardial infarctions were predictive of a poor long-term outcome[40-46]. Similarly, some studies showed that the serum concentration of cardiac troponin was an independent predictor of survival, others did not[47-55]. However two recent meta-analyses concluded that an elevated cardiac troponin levels after PCI does provide prognostic information[56,57]. Risk factors of periprocedural myocardial infarction are those which identify patients with increasing atherosclerotic disease burden, increased thrombotic risk, and with neurohormonal activation that predispose to either macrovascular complications (side branch occlusion or macroembolization) or microvascular obstruction (distal embolization of microparticles)[58].

In the era of coronary angioplasty, many studies reported that numerous "false positive" reversible perfusion defects occurred early after angioplasty, possibly as a result of inadequate early vessel remodeling or sustained abnormalities of coronary vasomotor tone. However, a significant percentage of patients showed persistent abnormalities in the later period[59-66]. In one study, 76% of patients without prior myocardial infarction showed improvement in perfusion abnormalities after angioplasty, but only 34% had completely reversible ischemia[60]. In the other study of 15 patients 1 to 2 wk after angioplasty, 7 had a reversible perfusion defect, of whom only 4 subsequently normalized by 4 to 6 wk[61]. These studies suggested that an improved or normalized perfusion abnormality does not necessarily occur after coronary angioplasty in every patient. Taken together, revascularization in patients with no or mild ischemia is likely to result in worsened ischemia, which is associated with increased mortality.

## ISCHEMIA-GUIDED REVASCULARIZATION

There are some studies which showed that the ischemia-

guided (IG) strategy resulted in a better prognosis[67-70]. Farzaneh-Far *et al*[67] identified 1425 consecutive patients with coronary artery disease who underwent two serial MPI. They were followed for a median of 5.8 years after the second MPI. Patients were included in the PCI or coronary artery bypass graft (CABG) group on the basis of the first revascularization procedure occurring within 60 d of the first MPS scan. Thus patients were divided into a MT group, PCI group, and CABG group. The incidence of patients with worsening of the ischemic myocardium by ⩾ 5% was more frequent in the MT group (15.6%) compared with the PCI (6.2%) and CABG groups (6.7%) ($P < 0.001$). After adjustment for established predictors, ⩾ 5% ischemia worsening remained a significant independent predictor of death or myocardial infarction (HR = 1.634; $P = 0.0019$). Thus, this study showed that ischemia worsening was an independent predictor of death or myocardial infarction, and revascularization was associated with more frequent improvement in myocardial ischemia compared with MT.

Kim *et al*[68] studied the importance of IG revascularization. From a registry of 5340 patients with multivessel coronary artery disease, comprising 2587 PCI and 2753 CABG. MPI was performed in 42.3% of patients and IG revascularization was performed in 17.3%. The MPI was defined as abnormal if the SSS was 3 or greater. The incidence of major adverse cardiac and cerebrovascular events (MACCE) was significantly lower in the IG group than in the non-IG group [16.2% *vs* 20.7%, adjusted HR (aHR) = 0.73; 95%CI: 0.60-0.88; $P = 0.001$], primarily driven by the lower repeat revascularization rate (9.9% *vs* 22.8%, aHR = 0.66; 95%CI: 0.49-0.90; $P = 0.009$). Subgroup analysis showed that IG reduced the risk of MACCE in PCI patients (17.4% *vs* 22.8%, aHR = 0.59; 95%CI: 0.43-0.81; $P = 0.001$) but not in CABG patients (16.0% *vs* 18.5%, aHR = 0.87; 95%CI: 0.67-1.14; $P = 0.31$). Thus IG revascularization with MPI, particularly in PCI-treated patients, seems to decrease the risk of repeat revascularization and MACCE in patients with multivessel disease. Taken together, these studies suggest that the IG strategy is associated with improved prognosis.

## FFR

FFR (the ratio of maximal blood flow in a stenotic artery to normal maximal flow), is now a gold standard for invasive assessment of coronary artery stenosis[71-80]. In Fractional Flow Reserve *vs* Angiography in Multivessel Evaluation (FAME) study, investigators randomly assigned 1005 patients with multivessel coronary artery disease to PCI with implantation of drug-eluting stents guided by angiography alone or guided by FFR measurements in addition to angiography[81]. Patients assigned to angiography-guided PCI underwent stenting of all indicated lesions, whereas those assigned to FFR-guided PCI underwent stenting of all indicated lesions only if the FFR was 0.80 or less. The primary endpoint was the rate of death, nonfatal myocardial infarction, and repeat revascularization at 1 year. The number of indicated lesions per patient was 2.7 ± 0.9 in the angiography group and 2.8 ± 1.0 in the FFR group ($P = 0.34$). The number of stents used per patient was 2.7 ± 1.2 and 1.9 ± 1.3, respectively ($P < 0.001$). The 1-year event rate was 18.3% in the angiography group and 13.2% in the FFR group ($P = 0.02$). The rate of death and myocardial infarction was 11.1% in the angiography group and 7.3% in the FFR group ($P = 0.04$). Pijls *et al*[82] reported the 2-year follow-up results of the FAME study. The 2-year rates of mortality or myocardial infarction were 12.9% in the angiography-guided group and 8.4% in the FFR-guided group ($P = 0.02$). Combined rates of death, nonfatal myocardial infarction, and revascularization were 22.4% and 17.9%, respectively ($P = 0.08$). For lesions deferred on the basis of FFR > 0.80, the rate of myocardial infarction was 0.2% and the rate of revascularization was 3.2% after 2 years, which is a very low rate. Thus, routine measurement of FFR in patients with multivessel coronary artery disease who undergo PCI with drug-eluting stents significantly reduced the rate of death, nonfatal myocardial infarction, and repeat revascularization for up to 2 years.

Tonino *et al*[83] studied the angiographic *vs* functional severity of coronary artery stenosis in the FAME study. Of the 1414 lesions (509 patients) in the FFR-guided arm of the FAME study, 1329 were successfully assessed by the FFR. Before FFR measurement, these lesions were categorized into 50%-70%, 71%-90%, and 91%-99% diameter stenosis by visual assessment. In the category 50%-70% stenosis, only 35% were functionally significant. In the category 71%-90% stenosis, 80% were functionally significant and in the category of subtotal stenoses, 96% were functionally significant. Of all 509 patients with angiographically defined multivessel disease, only 235 (46%) had functional multivessel disease.

In FAME 2 study, investigators enrolled patients with stable coronary artery disease for whom PCI was being considered, and assessed all stenoses by measuring FFR[84]. Patients in whom at least one stenosis was functionally significant (FFR ⩽ 0.80) were randomly assigned to FFR-guided PCI plus the best available MT (PCI group), or the best available MT alone (MT group). Patients in whom all stenoses had an FFR of more than 0.80 were entered into a registry and received the best available MT. The primary endpoint was a composite of death, myocardial infarction, or urgent revascularization. Recruitment was halted prematurely after enrollment of 1220 patients (888 who underwent randomization and 332 enrolled in the registry) because of a significant between-group difference in the percentage of patients who had a primary endpoint event: 4.3% in the PCI group and 12.7% in the MT group (HR with PCI: 0.32; 95%CI: 0.19-0.53; $P < 0.001$). The difference was driven by a lower rate of urgent revascularization in the PCI group than in the MT group (1.6% *vs* 11.1%; HR = 0.13; 95%CI: 0.06-0.30; $P < 0.001$). Among patients in the registry, 3.0% had a primary endpoint event, which was not significantly different from the PCI group. Thus, in

patients with stable coronary artery disease and functionally significant stenoses, FFR-guided PCI plus the best available MT, as compared with the best available MT alone, decreased the need for urgent revascularization. In patients without ischemia, the outcome appeared to be favorable with the best available MT alone. The main reason why there was no significant difference in death and myocardial infarction between the PCI group and MT group seems to be the relatively small number of patients and short-term follow-up period (mean duration of follow-up was 213 ± 128 d in the PCI group and 214 ± 127 d in the MT group).

Pijls *et al*[80] explain why FFR-guided PCI decreases the rate of death and myocardial infarction in the FAME study. From many studies it is known that the death and myocardial infarction rates are less than 1% per year for a functionally nonsignificant stenosis if treated appropriately by medication, between 5% and 10% per year for a functionally significant stenosis if only treated by medication, and approximately 3% per year for a stented lesion whether it was functionally significant or not. Thus, stenting a functionally significant stenosis improves outcome, but stenting a functionally nonsignificant stenosis worsens outcome. Taken together, these studies suggest that IG PCI is superior to angiography-guided PCI, and the presence of ischemia is the key to the decision-making for PCI.

## APPROPRIATENESS CRITERIA

For many years, the American College of Cardiology (ACC) and American Heart Association (AHA) have jointly published and updated guidelines for PCI and CABG[85,86]. Recently, the ACC Foundation/Society for Cardiovascular Angiography and Interventions/Society for Thoracic Surgeons/American Association for Thoracic Surgery/AHA/American Society of Nuclear Radiology released appropriateness criteria for coronary revascularization to serve as a supplement to the ACC/AHA guideline documents[87].

Hannan *et al*[88] studied the appropriateness of PCI and CABG performed in New York for patients without acute coronary syndrome or previous CABG. Of the 8168 patients undergoing CABG, 90.0% were appropriate for revascularization, 1.1% were inappropriate, and 8.6% were uncertain. Of the 33970 PCI patients, 28% lacked sufficient information to be rated. Of the patients who could be rated, 36.1% were appropriate, 14.3% were inappropriate, and 49.6% were uncertain. A total of 91% of the patients undergoing PCI who were classified as inappropriate had one- or two-vessel disease without proximal left anterior descending artery disease, and had no or minimal anti-ischemic MT. Chan *et al*[89] studied 500154 patients enrolled in the National Cardiovascular Data Registry. For 355417 patients with acute indications, 98.6% were classified as appropriate, 1.1% as inappropriate, and 0.3% as uncertain. For 144737 patients with nonacute indications, 50.4% were classified as appropriate, 11.6% as inappropriate, and 38.0% as uncertain. The majority of inappropriate PCIs for nonacute indications were performed in patients with no angina (53.8%), low-risk ischemia on noninvasive stress testing (71.6%), or suboptimal (≤ 1 medication) antianginal therapy (95.8%). Furthermore, although variation in the proportion of inappropriate PCI across hospitals was minimal for acute procedures, there was substantial hospital variation for nonacute procedures (mean hospital rate for inappropriate PCI, 10.8%; interquartile range, 6.0%-16.7%).

Lin *et al*[90] studied the frequency and predictors of stress testing prior to elective PCI in a Medicare population of 23887 patients. Only 44.5% of patients underwent stress testing within 90 d prior to elective PCI. There were wide regional variations among the hospital referral regions, with stress testing ranging from 22.1% to 70.6% (mean, 44.5%, interquartile range 39.0%-50.9%). Female sex [adjusted OR (aOR) = 0.91; 95%CI: 0.86-0.97], age 85 years or older (aOR = 0.83; 95%CI: 0.72-0.95), a history of congestive heart failure (aOR = 0.85; 95%CI: 0.79-0.92), and prior cardiac catheterization (aOR = 0.45; 95%CI: 0.38-0.54) were associated with a decreased likelihood of prior stress testing. Thus, these studies demonstrated that, although PCI in the acute setting and CABG are properly performed in most patients, PCI in the nonacute setting is often inappropriate, and stress testing to identify myocardial ischemia is performed in less than half of patients.

Some studies also showed that revascularization in an inappropriate setting is not associated with improved prognosis. Ko *et al*[91] assessed the appropriateness of coronary revascularization (PCI or CABG) and examined its association with longer-term outcomes. In 1625 patients with stable coronary artery disease, coronary revascularization was performed in only 69% in the appropriate category, 45% in the inappropriate category, and 54% in the uncertain category. In patients in the appropriate category, coronary revascularization was associated with a lower adjusted hazard of death or acute coronary syndrome (aHR = 0.61; 95%CI: 0.42-0.88; $P$ = 0.0087) at 3 years compared with MT. No significant differences in death or acute coronary syndrome were observed between coronary revascularization and MT in the inappropriate category (aHR = 0.99; 95%CI: 0.48-2.02) and the uncertain category (aHR = 0.57; 95%CI: 0.28-1.16; $P$ = 0.12).

## FUTURE PERSPECTIVE

Both MPI and FFR clearly identify the presence or absence of myocardial ischemia, and IG revascularization is associated with improved prognosis. However, the FFR value which is concordant with a 10% ischemic myocardium by MPI remains to be determined. A cut-off value of 0.75 was determined by the positive or negative results of three noninvasive stress tests; bicycle exercise test, thallium scintigraphy, and stress echocardiography with dobutamine[92]. A FFR value between

0.75 and 0.80 is deemed to be in the gray zone. MPI has limitation in identification of the highest risk subsets, left main coronary artery disease and three-vessel coronary artery disease, because of "balanced ischemia"[93-98]. One study showed that in patients with left main coronary artery disease, MPI results were normal in 5% and low-risk in 10% of patients[93]. The other study showed that in patients with triple-vessel coronary artery disease, MPI results were normal in 12% and single-vessel in 28% of patients[94].

Some studies compared MPI and FFR in patients with multivessel coronary artery disease. Ragosta *et al*[99] performed angiography, FFR, and MPI in 36 patients (88 arteries), and determined the association between FFR and perfusion for each vascular zone. Concordance between angiography, FFR, and MPI was seen in 61 of 88 zones (69%). Discordance was seen in the remaining 27 zones (31%), and was predominantly related to the finding of a FFR < 0.75 or total occlusion despite no defect on MPI. Melikian *et al*[100] performed MPI and FFR in 67 patients (201 vessels) with angiographic two- or three-vessel coronary artery disease. In 42% of patients, MPI and FFR detected identical ischemic areas (mean number of areas 0.9 ± 0.8 for both, $P = 1.00$). In the remaining 36% MPI underestimated the number (MPI = 0.46 ± 0.6, FFR = 2.0 ± 0.6, $P < 0.001$) and in 22% overestimated the number (MPI = 1.9 ± 0.8, FFR = 0.5 ± 0.8, $P < 0.001$) in comparison with FFR. Thus, MPI has poor concordance with FFR and tends to underestimate or overestimate the functional importance of coronary stenosis in comparison with FFR in patients with multivessel disease. In patients with multivessel coronary artery disease, FFR is the preferred method to identify myocardial ischemia. Therefore, complementary use of noninvasive MPI and invasive FFR would be important to compensate for each method's limitations.

## CONCLUSION

MPI studies demonstrate that for patients with moderate to severe ischemia, revascularization is the preferred therapy for survival benefit. For patients with no to mild ischemia, MT is the main choice and revascularization is associated with increased mortality probably because of worsened ischemia. FFR studies demonstrate that IG PCI is superior to angiography-guided PCI, and the presence of ischemia is the key to decision-making for PCI. Studies of appropriateness criteria demonstrate that, although CABG and emergency PCI are appropriately performed in most patients, use of elective PCI is often inappropriate. Some studies also suggest that revascularization in an inappropriate setting is not associated with improved prognosis. Taken together, myocardial ischemia is a key factor in the management of patients with stable coronary artery disease.

## REFERENCES


1 **National Cholesterol Education Program (NCEP) Expert Panel on Detection,** Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation* 2002; **106**: 3143-3421 [PMID: 12485966]

2 **Ohira T**, Iso H. Cardiovascular disease epidemiology in Asia: an overview. *Circ J* 2013; **77**: 1646-1652 [PMID: 23803294 DOI: 10.1253/circj.CJ-13-0702]

3 **Hata J**, Kiyohara Y. Epidemiology of stroke and coronary artery disease in Asia. *Circ J* 2013; **77**: 1923-1932 [PMID: 23842096 DOI: 10.1253/circj.CJ-13-0786]

4 **WHO**. Statistical Information System. Causes of death: Mortality and health statsu. WHO data and statistics. Accessed Novomber 12, 2013. Available from: URL: http: //www.who.int/research/en/

5 **WHO**. The global burden of disease. Accessed Novomber 12, 2013. Available from: URL: http: //www.who.int/topics/global_burden_of_disease/en/

6 **Schatzkin A**, Cupples LA, Heeren T, Morelock S, Kannel WB. Sudden death in the Framingham Heart Study. Differences in incidence and risk factors by sex and coronary disease status. *Am J Epidemiol* 1984; **120**: 888-899 [PMID: 6239541]

7 **Gibbons RJ**, Jones DW, Gardner TJ, Goldstein LB, Moller JH, Yancy CW. The American Heart Association's 2008 Statement of Principles for Healthcare Reform. *Circulation* 2008; **118**: 2209-2218 [PMID: 18820173 DOI: 10.1161/CIRCULATIONAHA.108.191092]

8 **Keeley EC**, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. *Lancet* 2003; **361**: 13-20 [PMID: 12517460 DOI: 10.1016/S0140-6736(03)12113-7]

9 Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomised trials of more than 1000 patients. Fibrinolytic Therapy Trialists' (FTT) Collaborative Group. *Lancet* 1994; **343**: 311-322 [PMID: 7905143]

10 **Hochman JS**, Sleeper LA, Webb JG, Sanborn TA, White HD, Talley JD, Buller CE, Jacobs AK, Slater JN, Col J, McKinlay SM, LeJemtel TH. Early revascularization in acute myocardial infarction complicated by cardiogenic shock. SHOCK Investigators. Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock. *N Engl J Med* 1999; **341**: 625-634 [PMID: 10460813 DOI: 10.1056/NEJM199908263410901]

11 **Zahn R**, Schiele R, Schneider S, Gitt AK, Wienbergen H, Seidl K, Voigtländer T, Gottwik M, Berg G, Altmann E, Rosahl W, Senges J. Primary angioplasty versus intravenous thrombolysis in acute myocardial infarction: can we define subgroups of patients benefiting most from primary angioplasty? Results from the pooled data of the Maximal Individual Therapy in Acute Myocardial Infarction Registry and the Myocardial Infarction Registry. *J Am Coll Cardiol* 2001; **37**: 1827-1835 [PMID: 11401118 DOI: 10.1016/S0735-1097(01)01264-5]

12 **Schömig A**, Neumann FJ, Kastrati A, Schühlen H, Blasini R, Hadamitzky M, Walter H, Zitzmann-Roth EM, Richardt G, Alt E, Schmitt C, Ulm K. A randomized comparison of antiplatelet and anticoagulant therapy after the placement of coronary-artery stents. *N Engl J Med* 1996; **334**: 1084-1089 [PMID: 8598866 DOI: 10.1056/NEJM199604253341702]

13 **Kastrati A**, Mehilli J, Dirschinger J, Schricke U, Neverve J, Pache J, Martinoff S, Neumann FJ, Nekolla S, Blasini R, Seyfarth M, Schwaiger M, Schömig A. Myocardial salvage after coronary stenting plus abciximab versus fibrinolysis plus abciximab in patients with acute myocardial infarction: a randomised trial. *Lancet* 2002; **359**: 920-925 [PMID: 11918909

DOI: 10.1016/S0140-6736(02)08022-4]
14 **Stone GW**. Angioplasty strategies in ST-segment-elevation myocardial infarction: part I: primary percutaneous coronary intervention. *Circulation* 2008; **118**: 538-551 [PMID: 18663102 DOI: 10.1161/CIRCULATIONAHA.107.756494]
15 **Stone GW**. Angioplasty strategies in ST-segment-elevation myocardial infarction: part II: intervention after fibrinolytic therapy, integrated treatment recommendations, and future directions. *Circulation* 2008; **118**: 552-566 [PMID: 18663103 DOI: 10.1161/CIRCULATIONAHA.107.739243]
16 **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 [PMID: 1345754 DOI: 10.1056/NEJM199201123260102]
17 **Hueb WA**, Bellotti G, de Oliveira SA, Arie S, de Albuquerque CP, Jatene AD, Pileggi F. 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 artery stenoses. *J Am Coll Cardiol* 1995; **26**: 1600-1605 [PMID: 7594092 DOI: 10.1016/0735-1097(95)00384-3]
18 Coronary angioplasty versus medical therapy for angina: the second Randomised Intervention Treatment of Angina (RITA-2) trial. RITA-2 trial participants. *Lancet* 1997; **350**: 461-468 [PMID: 9274581 DOI: 10.1016/S0140-6736(97)07298-X]
19 **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 [PMID: 9180111 DOI: 10.1016/S0735-1097(97)00097-1]
20 **Pitt B**, Waters D, Brown WV, van Boven AJ, Schwartz L, Title LM, Eisenberg D, Shurzinske L, McCormick LS. 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 [PMID: 10395630 DOI: 10.1056/NEJM199907083410202]
21 **TIME Investigators**. Trial of invasive versus medical therapy in elderly patients with chronic symptomatic coronary-artery disease (TIME): a randomised trial. *Lancet* 2001; **358**: 951-957 [PMID: 11583747 DOI: 10.1016/S0140-6736(01)06100-1]
22 **Hachamovitch R**, Hayes SW, Friedman JD, Cohen I, Berman DS. Comparison of the short-term survival benefit associated with revascularization compared with medical therapy in patients with no prior coronary artery disease undergoing stress myocardial perfusion single photon emission computed tomography. *Circulation* 2003; **107**: 2900-2907 [PMID: 12771008 DOI: 10.1161/CIRC.0000072790.23090.41]
23 **Hachamovitch R**, Rozanski A, Shaw LJ, Stone GW, Thomson LE, Friedman JD, Hayes SW, Cohen I, Germano G, Berman DS. Impact of ischaemia and scar on the therapeutic benefit derived from myocardial revascularization vs. medical therapy among patients undergoing stress-rest myocardial perfusion scintigraphy. *Eur Heart J* 2011; **32**: 1012-1024 [PMID: 21258084 DOI: 10.1093/eurheartj/ehq500]
24 **Boden WE**, O'Rourke RA, Teo KK, Hartigan PM, Maron DJ, Kostuk WJ, Knudtson M, Dada M, Casperson P, Harris CL, Chaitman BR, Shaw L, Gosselin G, Nawaz S, Title LM, Gau G, Blaustein AS, Booth DC, Bates ER, Spertus JA, Berman DS, Mancini GB, Weintraub WS. Optimal medical therapy with or without PCI for stable coronary disease. *N Engl J Med* 2007; **356**: 1503-1516 [PMID: 17387127 DOI: 10.1056/NEJMoa070829]
25 **Shaw LJ**, Berman DS, Maron DJ, Mancini GB, Hayes SW, Hartigan PM, Weintraub WS, O'Rourke RA, Dada M, Spertus JA, Chaitman BR, Friedman J, Slomka P, Heller GV, Germano G, Gosselin G, Berger P, Kostuk WJ, Schwartz RG, Knudtson M, Veledar E, Bates ER, McCallister B, Teo KK, Boden WE. 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 [PMID: 18268144 DOI: 10.1161/CIRCULATIONAHA.107.743963]
26 **Brown KA**, Boucher CA, Okada RD, Guiney TE, Newell JB, Strauss HW, Pohost GM. Prognostic value of exercise thallium-201 imaging in patients presenting for evaluation of chest pain. *J Am Coll Cardiol* 1983; **1**: 994-1001 [PMID: 6833659 DOI: 10.1016/S0735-1097(83)80100-4]
27 **Ladenheim ML**, Pollock BH, Rozanski A, Berman DS, Staniloff HM, Forrester JS, Diamond GA. Extent and severity of myocardial hypoperfusion as predictors of prognosis in patients with suspected coronary artery disease. *J Am Coll Cardiol* 1986; **7**: 464-471 [PMID: 3950226 DOI: 10.1016/S0735-1097(86)80454-5]
28 **Machecourt J**, Longère P, Fagret D, Vanzetto G, Wolf JE, Polidori C, Comet M, Denis B. Prognostic value of thallium-201 single-photon emission computed tomographic myocardial perfusion imaging according to extent of myocardial defect. Study in 1,926 patients with follow-up at 33 months. *J Am Coll Cardiol* 1994; **23**: 1096-1106 [PMID: 8144775 DOI: 10.1016/0735-1097(94)90597-5]
29 **Iskander S**, Iskandrian AE. Risk assessment using single-photon emission computed tomographic technetium-99m sestamibi imaging. *J Am Coll Cardiol* 1998; **32**: 57-62 [PMID: 9669249 DOI: 10.1016/S0735-1097(98)00177-6]
30 **Berman DS**, Hachamovitch R, Kiat H, Cohen I, Cabico JA, Wang FP, Friedman JD, Germano G, Van Train K, Diamond GA. Incremental value of prognostic testing in patients with known or suspected ischemic heart disease: a basis for optimal utilization of exercise technetium-99m sestamibi myocardial perfusion single-photon emission computed tomography. *J Am Coll Cardiol* 1995; **26**: 639-647 [PMID: 7642853 DOI: 10.1016/0735-1097(95)00218-S]
31 **Hachamovitch R**, Berman DS, Kiat H, Cohen I, Cabico JA, Friedman J, Diamond GA. Exercise myocardial perfusion SPECT in patients without known coronary artery disease: incremental prognostic value and use in risk stratification. *Circulation* 1996; **93**: 905-914 [PMID: 8598081 DOI: 10.1161/01/CIR.93.5.905]
32 **Hachamovitch R**, Berman DS, Kiat H, Bairey CN, Cohen I, Cabico A, Friedman J, Germano G, Van Train KF, Diamond GA. Effective risk stratification using exercise myocardial perfusion SPECT in women: gender-related differences in prognostic nuclear testing. *J Am Coll Cardiol* 1996; **28**: 34-44 [PMID: 8752792 DOI: 10.1016/0735-1097(96)00095-2]
33 **Marwick TH**, Shaw LJ, Lauer MS, Kesler K, Hachamovitch R, Heller GV, Travin MI, Borges-Neto S, Berman DS, Miller DD. The noninvasive prediction of cardiac mortality in men and women with known or suspected coronary artery disease. Economics of Noninvasive Diagnosis (END) Study Group. *Am J Med* 1999; **106**: 172-178 [PMID: 10230746]
34 **Chatziioannou SN**, Moore WH, Ford PV, Fisher RE, Lee VV, Alfaro-Franco C, Dhekne RD. Prognostic value of myocardial perfusion imaging in patients with high exercise tolerance. *Circulation* 1999; **99**: 867-872 [PMID: 10027807 DOI: 10.1016/S0002-9343(98)00388-X]
35 **O'Keefe JH**, Bateman TM, Ligon RW, Case J, Cullom J, Barnhart C, Spertus J. Outcome of medical versus invasive treatment strategies for non-high-risk ischemic heart disease. *J Nucl Cardiol* 1998; **5**: 28-33 [PMID: 9504870 DOI: 10.1016/S1071-3581(98)80007-X]
36 **Hachamovitch R**, Berman DS, Shaw LJ, Kiat H, Cohen I, Cabico JA, Friedman J, Diamond GA. Incremental prognostic value of myocardial perfusion single photon emission computed tomography for the prediction of cardiac death: differential stratification for risk of cardiac death and myocardial infarction. *Circulation* 1998; **97**: 535-543 [PMID: 9494023 DOI:

10.1161/01/CIR.97.6.535]
37 **Moroi M**, Yamashina A, Tsukamoto K, Nishimura T; J-ACCESS Investigators. Coronary revascularization does not decrease cardiac events in patients with stable ischemic heart disease but might do in those who showed moderate to severe ischemia. *Int J Cardiol* 2012; **158**: 246-252 [PMID: 21342709 DOI: 10.1016/j.ijcard.2011.01.040]
38 **Safley DM**, Koshy S, Grantham JA, Bybee KA, House JA, Kennedy KF, Rutherford BD. Changes in myocardial ischemic burden following percutaneous coronary intervention of chronic total occlusions. *Catheter Cardiovasc Interv* 2011; **78**: 337-343 [PMID: 21413136 DOI: 10.1002/ccd.23002]
39 **Thygesen K**, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, Thygesen K, Alpert JS, White HD, Jaffe AS, Katus HA, Apple FS, Lindahl B, Morrow DA, Chaitman BA, Clemmensen PM, Johanson P, Hod H, Underwood R, Bax JJ, Bonow RO, Pinto F, Gibbons RJ, Fox KA, Atar D, Newby LK, Galvani M, Hamm CW, Uretsky BF, Steg PG, Wijns W, Bassand JP, Menasché P, Ravkilde J, Ohman EM, Antman EM, Wallentin LC, Armstrong PW, Simoons ML, Januzzi JL, Nieminen MS, Gheorghiade M, Filippatos G, Luepker RV, Fortmann SP, Rosamond WD, Levy D, Wood D, Smith SC, Hu D, Lopez-Sendon JL, Robertson RM, Weaver D, Tendera M, Bove AA, Parkhomenko AN, Vasilieva EJ, Mendis S; ESC Committee for Practice Guidelines (CPG). Third universal definition of myocardial infarction. *Eur Heart J* 2012; **33**: 2551-2567 [PMID: 22922414 DOI: 10.1093/eurheartj/ehs184]
40 **Ellis SG**, Chew D, Chan A, Whitlow PL, Schneider JP, Topol EJ. Death following creatine kinase-MB elevation after coronary intervention: identification of an early risk period: importance of creatine kinase-MB level, completeness of revascularization, ventricular function, and probable benefit of statin therapy. *Circulation* 2002; **106**: 1205-1210 [PMID: 12208794 DOI: 10.1161/01/CIR.0000028146.71416.2E]
41 **Tardiff BE**, Califf RM, Tcheng JE, Lincoff AM, Sigmon KN, Harrington RA, Mahaffey KW, Ohman EM, Teirstein PS, Blankenship JC, Kitt MM, Topol EJ. Clinical outcomes after detection of elevated cardiac enzymes in patients undergoing percutaneous intervention. IMPACT-II Investigators. Integrilin (eptifibatide) to Minimize Platelet Aggregation and Coronary Thrombosis-II. *J Am Coll Cardiol* 1999; **33**: 88-96 [PMID: 9935014 DOI: 10.1016/S0735-1097(98)00551-8]
42 **Stone GW**, Mehran R, Dangas G, Lansky AJ, Kornowski R, Leon MB. Differential impact on survival of electrocardiographic Q-wave versus enzymatic myocardial infarction after percutaneous intervention: a device-specific analysis of 7147 patients. *Circulation* 2001; **104**: 642-647 [PMID: 11489768 DOI: 10.1161/hc3101.093902]
43 **Jeremias A**, Baim DS, Ho KK, Chauhan M, Carrozza JP, Cohen DJ, Popma JJ, Kuntz RE, Cutlip DE. Differential mortality risk of postprocedural creatine kinase-MB elevation following successful versus unsuccessful stent procedures. *J Am Coll Cardiol* 2004; **44**: 1210-1214 [PMID: 15364321 DOI: 10.1016/j.jacc.2004.06.051]
44 **Ioannidis JP**, Karvouni E, Katritsis DG. Mortality risk conferred by small elevations of creatine kinase-MB isoenzyme after percutaneous coronary intervention. *J Am Coll Cardiol* 2003; **42**: 1406-1411 [PMID: 14563583 DOI: 10.1016/S0735-1097(03)01044-1]
45 **Ghazzal Z**, Ashfaq S, Morris DC, Douglas JS, Marshall JJ, King SB, Weintraub WS. Prognostic implication of creatine kinase release after elective percutaneous coronary intervention in the pre-IIb/IIIa antagonist era. *Am Heart J* 2003; **145**: 1006-1012 [PMID: 12796756 DOI: 10.1016/S0002-8703(03)00095-4]
46 **Brener SJ**, Ellis SG, Schneider J, Topol EJ. Frequency and long-term impact of myonecrosis after coronary stenting. *Eur Heart J* 2002; **23**: 869-876 [PMID: 12042008 DOI: 10.1053/euhj.2001.2976]
47 **Ricciardi MJ**, Davidson CJ, Gubernikoff G, Beohar N, Eckman LJ, Parker MA, Bonow RO. Troponin I elevation and cardiac events after percutaneous coronary intervention. *Am Heart J* 2003; **145**: 522-528 [PMID: 12660677 DOI: 10.1067/mhj.2003.2]
48 **Nallamothu BK**, Chetcuti S, Mukherjee D, Grossman PM, Kline-Rogers E, Werns SW, Bates ER, Moscucci M. Prognostic implication of troponin I elevation after percutaneous coronary intervention. *Am J Cardiol* 2003; **91**: 1272-1274 [PMID: 12745120 DOI: 10.1016/S0002-9149(03)00283-2]
49 **Gruberg L**, Fuchs S, Waksman R, Pichard AD, Kent KM, Laird JR, Wu H, Elsayyad S, Allen CM, Satler LF. Prognostic value of cardiac troponin I elevation after percutaneous coronary intervention in patients with chronic renal insufficiency: a 12-month outcome analysis. *Catheter Cardiovasc Interv* 2002; **55**: 174-179 [PMID: 11835642 DOI: 10.1002/ccd.10081]
50 **Fuchs S**, Kornowski R, Mehran R, Lansky AJ, Satler LF, Pichard AD, Kent KM, Clark CE, Stone GW, Leon MB. Prognostic value of cardiac troponin-I levels following catheter-based coronary interventions. *Am J Cardiol* 2000; **85**: 1077-1082 [PMID: 10781755 DOI: 10.1016/S0002-9149(00)00699-8]
51 **Bertinchant JP**, Polge A, Ledermann B, Genet L, Fabbro-Peray P, Raczka F, Brunet J, Poirey S, Wittenberg O, Pernel I, Nigond J. Relation of minor cardiac troponin I elevation to late cardiac events after uncomplicated elective successful percutaneous transluminal coronary angioplasty for angina pectoris. *Am J Cardiol* 1999; **84**: 51-57 [PMID: 10404851 DOI: 10.1016/S0002-9149(99)00191-5]
52 **Garbarz E**, Iung B, Lefevre G, Makita Y, Farah B, Michaud P, Graine H, Vahanian A. Frequency and prognostic value of cardiac troponin I elevation after coronary stenting. *Am J Cardiol* 1999; **84**: 515-518 [PMID: 10482147 DOI: 10.1016/S0002-9149(99)00369-0]
53 **Kini AS**, Lee P, Marmur JD, Agarwal A, Duffy ME, Kim MC, Sharma SK. Correlation of postpercutaneous coronary intervention creatine kinase-MB and troponin I elevation in predicting mid-term mortality. *Am J Cardiol* 2004; **93**: 18-23 [PMID: 14697460]
54 **Natarajan MK**, Kreatsoulas C, Velianou JL, Mehta SR, Pericak D, Goodhart DM. Incidence, predictors, and clinical significance of troponin-I elevation without creatine kinase elevation following percutaneous coronary interventions. *Am J Cardiol* 2004; **93**: 750-753 [PMID: 15019884 DOI: 10.1016/j.amjcard.2003.11.069]
55 **Cavallini C**, Savonitto S, Violini R, Arraiz G, Plebani M, Olivari Z, Rubartelli P, Battaglia S, Niccoli L, Steffenino G, Ardissino D; Italian 'Atherosclerosis, Thorombosis, and Vascular Biology' and 'Society for Invasive Cardiology-GISE' Investigators. Impact of the elevation of biochemical markers of myocardial damage on long-term mortality after percutaneous coronary intervention: results of the CK-MB and PCI study. *Eur Heart J* 2005; **26**: 1494-1498 [PMID: 15741227 DOI: 10.10931/eurheartj/ehi173]
56 **Nienhuis MB**, Ottervanger JP, Bilo HJ, Dikkeschei BD, Zijlstra F. Prognostic value of troponin after elective percutaneous coronary intervention: A meta-analysis. *Catheter Cardiovasc Interv* 2008; **71**: 318-324 [PMID: 18288753 DOI: 10.1002/ccd.21345]
57 **Testa L**, Van Gaal WJ, Biondi Zoccai GG, Agostoni P, Latini RA, Bedogni F, Porto I, Banning AP. Myocardial infarction after percutaneous coronary intervention: a meta-analysis of troponin elevation applying the new universal definition. *QJM* 2009; **102**: 369-378 [PMID: 19286891 DOI: 10.1093/qjmed/hcp005]
58 **Lansky AJ**, Stone GW. Periprocedural myocardial infarction: prevalence, prognosis, and prevention. *Circ Cardiovasc Interv* 2010; **3**: 602-610 [PMID: 21156928 DOI: 10.1161/CIRCINTERVENTIONS.110.959080]
59 **Hirzel HO**, Nuesch K, Gruentzig AR, Luetolf UM. Short- and long-term changes in myocardial perfusion after percutaneous transluminal coronary angioplasty assessed by

thallium-201 exercise scintigraphy. *Circulation* 1981; **63**: 1001-1007 [PMID: 6781790 DOI: 10.1161/01.CIR.63.5.1001]
60 **Cloninger KG**, DePuey EG, Garcia EV, Roubin GS, Robbins WL, Nody A, DePasquale EE, Berger HJ. Incomplete redistribution in delayed thallium-201 single photon emission computed tomographic (SPECT) images: an overestimation of myocardial scarring. *J Am Coll Cardiol* 1988; **12**: 955-963 [PMID: 2971086 DOI: 10.1016/0735-1097(88)90461-5]
61 **Miller DD**, Verani MS. Current status of myocardial perfusion imaging after percutaneous transluminal coronary angioplasty. *J Am Coll Cardiol* 1994; **24**: 260-266 [PMID: 8006276 DOI: 10.1016/0735-1097(94)90572-X]
62 **Kanemoto N**, Hör G, Kober G, Kaltenbach M. Quantitative evaluation of exercise T1-201 myocardial scintigraphy before and after transluminal coronary angioplasty. A preliminary report. *Jpn Heart J* 1983; **24**: 891-907 [PMID: 6231390 DOI: 10.1536/ihj.24.891]
63 **Lim YL**, Okada RD, Chesler DA, Block PC, Boucher CA, Pohost GM. A new approach to quantitation of exercise thallium-201 scintigraphy before and after an intervention: application to define the impact of coronary angioplasty on regional myocardial perfusion. *Am Heart J* 1984; **108**: 917-925 [PMID: 6237567 DOI: 10.1016/S0002-8703(84)90455-1]
64 **Miller DD**, Liu P, Strauss HW, Block PC, Okada RD, Boucher CA. Prognostic value of computer-quantitated exercise thallium imaging early after percutaneous transluminal coronary angioplasty. *J Am Coll Cardiol* 1987; **10**: 275-283 [PMID: 2955023 DOI: 10.1016/S0735-1097(87)80008-6]
65 **Manyari DE**, Knudtson M, Kloiber R, Roth D. Sequential thallium-201 myocardial perfusion studies after successful percutaneous transluminal coronary artery angioplasty: delayed resolution of exercise-induced scintigraphic abnormalities. *Circulation* 1988; **77**: 86-95 [PMID: 2961482 DOI: 10.1161/01.CIR.77.1.86]
66 **Kostkiewicz M**, Jarosz W, Tracz W, Przewłocki T, Pieniazek P, Podolec P, Wójcik J. Thallium-201 myocardial perfusion imaging in patients before and after successful percutaneous transluminal coronary angioplasty. *Int J Cardiol* 1996; **53**: 299-304 [PMID: 8793585 DOI: 10.1016/0167-5273(05)02552-9]
67 **Farzaneh-Far A**, Phillips HR, Shaw LK, Starr AZ, Fiuzat M, O'Connor CM, Sastry A, Shaw LJ, Borges-Neto S. Ischemia change in stable coronary artery disease is an independent predictor of death and myocardial infarction. *JACC Cardiovasc Imaging* 2012; **5**: 715-724 [PMID: 22789940 DOI: 10.1016/j.jcmg.2012.01.019]
68 **Kim YH**, Ahn JM, Park DW, Song HG, Lee JY, Kim WJ, Yun SC, Kang SJ, Lee SW, Lee CW, Moon DH, Chung CH, Lee JW, Park SW, Park SJ. Impact of ischemia-guided revascularization with myocardial perfusion imaging for patients with multivessel coronary disease. *J Am Coll Cardiol* 2012; **60**: 181-190 [PMID: 22789882 DOI: 10.1016/j.jacc.2012.02.061]
69 **Hachamovitch R**, Rozanski A, Hayes SW, Thomson LE, Germano G, Friedman JD, Cohen I, Berman DS. Predicting therapeutic benefit from myocardial revascularization procedures: are measurements of both resting left ventricular ejection fraction and stress-induced myocardial ischemia necessary? *J Nucl Cardiol* 2006; **13**: 768-778 [PMID: 17174808 DOI: 10.1016/j.nuclcard.2006.08.017]
70 **Aldweib N**, Negishi K, Hachamovitch R, Jaber WA, Seicean S, Marwick TH. Impact of repeat myocardial revascularization on outcome in patients with silent ischemia after previous revascularization. *J Am Coll Cardiol* 2013; **61**: 1616-1623 [PMID: 23500275 DOI: 10.1016/j.jacc.2013.01.043]
71 **Kern MJ**, Lerman A, Bech JW, De Bruyne B, Eeckhout E, Fearon WF, Higano ST, Lim MJ, Meuwissen M, Piek JJ, Pijls NH, Siebes M, Spaan JA. Physiological assessment of coronary artery disease in the cardiac catheterization laboratory: a scientific statement from the American Heart Association Committee on Diagnostic and Interventional Cardiac Catheterization, Council on Clinical Cardiology. *Circulation* 2006; **114**: 1321-1341 [PMID: 16940193 DOI: 10.1161/CIRCULATIONAHA.106.177276]
72 **Kern MJ**, Meier B. Evaluation of the culprit plaque and the physiological significance of coronary atherosclerotic narrowings. *Circulation* 2001; **103**: 3142-3149 [PMID: 11425782 DOI: 10.1161/01.CIR103.25.3142]
73 **Bishop AH**, Samady H. Fractional flow reserve: critical review of an important physiologic adjunct to angiography. *Am Heart J* 2004; **147**: 792-802 [PMID: 15131533 DOI: 10.1016/j.ahj.2003.12.009]
74 **Pijls NH**. Optimum guidance of complex PCI by coronary pressure measurement. *Heart* 2004; **90**: 1085-1093 [PMID: 15310716 DOI: 10.1136/hrt.2003.032151]
75 **Tobis J**, Azarbal B, Slavin L. Assessment of intermediate severity coronary lesions in the catheterization laboratory. *J Am Coll Cardiol* 2007; **49**: 839-848 [PMID: 17320741 DOI: 10.1016/j.jacc.2006.10.055]
76 **Spaan JA**, Piek JJ, Hoffman JI, Siebes M. Physiological basis of clinically used coronary hemodynamic indices. *Circulation* 2006; **113**: 446-455 [PMID: 16432075 DOI: 10.1161/CIRCULATIONAHA.105.587196]
77 **De Bruyne B**, Sarma J. Fractional flow reserve: a review: invasive imaging. *Heart* 2008; **94**: 949-959 [PMID: 18552231 DOI: 10.1136/hrt.2007.122838]
78 **Kern MJ**, Samady H. Current concepts of integrated coronary physiology in the catheterization laboratory. *J Am Coll Cardiol* 2010; **55**: 173-185 [PMID: 20117397 DOI: 10.1016/j.jacc.2009.06.062]
79 **Park SJ**, Ahn JM, Kang SJ. Paradigm shift to functional angioplasty: new insights for fractional flow reserve- and intravascular ultrasound-guided percutaneous coronary intervention. *Circulation* 2011; **124**: 951-957 [PMID: 21859982 DOI: 10.1161/CIRCULATIONAHA.110.012344]
80 **Pijls NH**, Sels JW. Functional measurement of coronary stenosis. *J Am Coll Cardiol* 2012; **59**: 1045-1057 [PMID: 22421298 DOI: 10.1016/j.jacc.2011.09.077]
81 **Tonino PA**, De Bruyne B, Pijls NH, Siebert U, Ikeno F, van' t Veer M, Klauss V, Manoharan G, Engstrøm T, Oldroyd KG, Ver Lee PN, MacCarthy PA, Fearon WF. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. *N Engl J Med* 2009; **360**: 213-224 [PMID: 19144937 DOI: 10.1056/NEJMoa0807611]
82 **Pijls NH**, Fearon WF, Tonino PA, Siebert U, Ikeno F, Bornschein B, van't Veer M, Klauss V, Manoharan G, Engstrøm T, Oldroyd KG, Ver Lee PN, MacCarthy PA, De Bruyne B. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention in patients with multivessel coronary artery disease: 2-year follow-up of the FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) study. *J Am Coll Cardiol* 2010; **56**: 177-184 [PMID: 20537493 DOI: 10.1016/j.jacc.2010.04.012]
83 **Tonino PA**, Fearon WF, De Bruyne B, Oldroyd KG, Leesar MA, Ver Lee PN, Maccarthy PA, Van't Veer M, Pijls NH. Angiographic versus functional severity of coronary artery stenoses in the FAME study fractional flow reserve versus angiography in multivessel evaluation. *J Am Coll Cardiol* 2010; **55**: 2816-2821 [PMID: 20579537 DOI: 10.1016/j.jacc.2009.11.096]
84 **De Bruyne B**, Pijls NH, Kalesan B, Barbato E, Tonino PA, Piroth Z, Jagic N, Möbius-Winkler S, Rioufol G, Witt N, Kala P, MacCarthy P, Engström T, Oldroyd KG, Mavromatis K, Manoharan G, Verlee P, Frobert O, Curzen N, Johnson JB, Jüni P, Fearon WF. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. *N Engl J Med* 2012; **367**: 991-1001 [PMID: 22924638 DOI: 10.1056/NEJMoa1205361]
85 **Levine GN**, Bates ER, Blankenship JC, Bailey SR, Bittl JA, Cercek B, Chambers CE, Ellis SG, Guyton RA, Hollenberg SM, Khot UN, Lange RA, Mauri L, Mehran R, Moussa ID, Mukherjee D, Nallamothu BK, Ting HH. 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention:

a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. *Circulation* 2011; **124**: e574-e651 [PMID: 22064601 DOI: 10.1161/CIR.0b013e31823ba622]

86 **Hillis LD**, Smith PK, Anderson JL, Bittl JA, Bridges CR, Byrne JG, Cigarroa JE, Disesa VJ, Hiratzka LF, Hutter AM, Jessen ME, Keeley EC, Lahey SJ, Lange RA, London MJ, Mack MJ, Patel MR, Puskas JD, Sabik JF, Selnes O, Shahian DM, Trost JC, Winniford MD. 2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation* 2011; **124**: e652-e735 [PMID: 22064599 DOI: 10.1161/CIR.0b013e31823c074e]

87 **Patel MR**, Dehmer GJ, Hirshfeld JW, Smith PK, Spertus JA. ACCF/SCAI/STS/AATS/AHA/ASNC 2009 Appropriateness Criteria for Coronary Revascularization: A Report of the American College of Cardiology Foundation Appropriateness Criteria Task Force, Society for Cardiovascular Angiography and Interventions, Society of Thoracic Surgeons, American Association for Thoracic Surgery, American Heart Association, and the American Society of Nuclear Cardiology: Endorsed by the American Society of Echocardiography, the Heart Failure Society of America, and the Society of Cardiovascular Computed Tomography. *Circulation* 2009; **119**: 1330-1352 [PMID: 19131581 DOI: 10.1161/CIRCULATIONAHA.108.191768]

88 **Hannan EL**, Cozzens K, Samadashvili Z, Walford G, Jacobs AK, Holmes DR, Stamato NJ, Sharma S, Venditti FJ, Fergus I, King SB. Appropriateness of coronary revascularization for patients without acute coronary syndromes. *J Am Coll Cardiol* 2012; **59**: 1870-1876 [PMID: 22595405 DOI: 10.1016/j.jacc.2012.01.050]

89 **Chan PS**, Patel MR, Klein LW, Krone RJ, Dehmer GJ, Kennedy K, Nallamothu BK, Weaver WD, Masoudi FA, Rumsfeld JS, Brindis RG, Spertus JA. Appropriateness of percutaneous coronary intervention. *JAMA* 2011; **306**: 53-61 [PMID: 21730241 DOI: 10.1001/jama.2011.916]

90 **Lin GA**, Dudley RA, Lucas FL, Malenka DJ, Vittinghoff E, Redberg RF. Frequency of stress testing to document ischemia prior to elective percutaneous coronary intervention. *JAMA* 2008; **300**: 1765-1773 [PMID: 18854538 DOI: 10.1001/jama.300.15.1765]

91 **Ko DT**, Guo H, Wijeysundera HC, Natarajan MK, Nagpal AD, Feindel CM, Kingsbury K, Cohen EA, Tu JV. Assessing the association of appropriateness of coronary revascularization and clinical outcomes for patients with stable coronary artery disease. *J Am Coll Cardiol* 2012; **60**: 1876-1884 [PMID: 23062534 DOI: 10.1016/j.jacc.2012.06.056]

92 **Pijls NH**, De Bruyne B, Peels K, Van Der Voort PH, Bonnier HJ, Bartunek J Koolen JJ, Koolen JJ. Measurement of fractional flow reserve to assess the functional severity of coronary-artery stenoses. *N Engl J Med* 1996; **334**: 1703-1708 [PMID: 8637515 DOI: 10.1056/NEJM199606273342604]

93 **Berman DS**, Kang X, Slomka PJ, Gerlach J, de Yang L, Hayes SW, Friedman JD, Thomson LE, Germano G. Underestimation of extent of ischemia by gated SPECT myocardial perfusion imaging in patients with left main coronary artery disease. *J Nucl Cardiol* 2007; **14**: 521-528 [PMID: 17679060 DOI: 10.1016/j.nuclcard.2007.05.008]

94 **Lima RS**, Watson DD, Goode AR, Siadaty MS, Ragosta M, Beller GA, Samady H. Incremental value of combined perfusion and function over perfusion alone by gated SPECT myocardial perfusion imaging for detection of severe three-vessel coronary artery disease. *J Am Coll Cardiol* 2003; **42**: 64-70 [PMID: 12849661 DOI: 10.1016/S0735-1097(03)00562-X]

95 **Zaacks SM**, Ali A, Parrillo JE, Barron JT. How well does radionuclide dipyridamole stress testing detect three-vessel coronary artery disease and ischemia in the region supplied by the most stenotic vessel? *Clin Nucl Med* 1999; **24**: 35-41 [PMID: 9890491 DOI: 10.1097/00003072-1999901000-00008]

96 **Beller GA**. Underestimation of coronary artery disease with SPECT perfusion imaging. *J Nucl Cardiol* 2008; **15**: 151-153 [PMID: 18371582 DOI: 10.1016/j.nuclcard.2008.01.012]

97 **Shiba C**, Chikamori T, Hida S, Igarashi Y, Tanaka H, Hirose K, Ohtaki Y, Usui Y, Miyagi M, Hatano T, Yamashina A. Important parameters in the detection of left main trunk disease using stress myocardial perfusion imaging. *J Cardiol* 2009; **53**: 43-52 [PMID: 19167637 DOI: 10.1016/j.jjcc.2008.08.010]

98 **Potter BJ**, Dorais M, Mansour S, Orlicka K, Gobeil F, Rinfret S. Effectiveness of myocardial perfusion scintigraphy to predict coronary anatomy in patients with non-ST elevation acute coronary syndrome. *Am J Cardiol* 2009; **104**: 644-647 [PMID: 19699338 DOI: 10.1016/j.amjcard.2009.04.051]

99 **Ragosta M**, Bishop AH, Lipson LC, Watson DD, Gimple LW, Sarembock IJ, Powers ER. Comparison between angiography and fractional flow reserve versus single-photon emission computed tomographic myocardial perfusion imaging for determining lesion significance in patients with multivessel coronary disease. *Am J Cardiol* 2007; **99**: 896-902 [PMID: 17398179 DOI: 10.1016/j.amjcard.2006.11.035]

100 **Melikian N**, De Bondt P, Tonino P, De Winter O, Wyffels E, Bartunek J, Heyndrickx GR, Fearon WF, Pijls NH, Wijns W, De Bruyne B. Fractional flow reserve and myocardial perfusion imaging in patients with angiographic multivessel coronary artery disease. *JACC Cardiovasc Interv* 2010; **3**: 307-314 [PMID: 20298990 DOI: 10.1016/j.jcin]

**P- Reviewers**: Goldhammer E, Maurizio T, Skowasch D
**S- Editor**: Ma YJ **L- Editor**: A **E- Editor**: Liu SQ

Published by **Baishideng Publishing Group Co., Limited**
Flat C, 23/F., Lucky Plaza,
315-321 Lockhart Road, Wan Chai, Hong Kong, China
Fax: +852-65557188
Telephone: +852-31779906
E-mail: bpgoffice@wjgnet.com
http://www.wjgnet.com