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The patient with chronic ischemic heart disease. Role of ranolazine in the management of stable angina

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Abstract. – Ischemic heart disease (IHD) is a major cause of death in Western Countries and accounts for very high costs worldwide. In this review we discussed the pathogenesis, symptoms, diagnosis, prognosis and management of chronic IHD. In particular, we discussed about the percutaneous coronary interventions and coronary artery bypass grafting, as well as to clinical trials that evaluated the advantages of one approach versus another. Pharmacological treatment is among major objectives of the review and for each class of therapeutic agents an evaluation of well-conducted clinical trials is provided. The most important drug classes in IHD treatment are betablockers, calcium channel blockers, nitrates, antiplatelet agents, and ACE-inhibitors. In addition to these agents, also new treatment options are evaluated in patients with stable IHD. Ranolazine, in particular, is a innovative anti-anginal drug with a great successful in the management of patients with refractory angina. A pharmacological as well as clinical profile of this drug is provided.

Key Words:
Stable angina, Ischaemic heart disease, Diagnosis, Prognosis, Drug and surgical treatment, Ranolazine.

Introduction

Ischaemic heart disease (IHD) is characterized by stable angina symptoms over a period of months, years, or even decades and it may represent the first clinical presentation of IHD, or it may follow an acute coronary syndrome (ACS)[1]. Chronic IHD includes three different clinical presentations: *stable angina*, microvascular angina and vasospastic angina. Moreover, it can be known that myocardial ischemia may be silent in all anginal syndromes[1].

In chronic IHD transient myocardial ischemia is mainly caused by obstructive coronary stenoses which reduce coronary flow reserve, thus preventing the matching between myocardial oxygen supply and myocardial oxygen demand when subendocardial coronary flow reserve is exhausted[2]. Symptom severity can be modulated by dynamic vasomotion at the site of stenoses and/or by coronary microvascular dysfunction[1,2].

In *microvascular angina* transient myocardial ischemia is caused by coronary microvascular dysfunction in patients with angiographically normal epicardial coronary arteries, in the absence of any other specific cardiac disease[3,4]. In *vasospastic angina* transient myocardial ischemia is caused by coronary spasm[5].

Furthermore, angina and transient myocardial ischemia may also occur in patients with non atherosclerotic obstructive coronary artery disease, such as congenital abnormalities of coronary arteries, myocardial bridging, coronary arteritis in association with systemic vasculitis and radiation-induced coronary disease[6].

Pathogenesis of Myocardial Ischaemia

Ischaemia is caused by an imbalance between myocardial oxygen supply and consumption. The imbalance can be caused by a primary reduction of myocardial oxygen supply which can be caused by a reduction of coronary blood flow (for instance in presence of occlusive coronary thrombosis or spasm or of severe hypotension) or by a reduction of O_2-carrying capacity (for instance caused by anaemia or carbon monoxide poisoning)[1,2]. The imbalance also occurs when coronary flow reserve is reduced by an increase of coronary vascular resistance caused by critical coronary stenoses, coronary microvascular dysfunction or extracoronary conditions (for instance aortic stenosis)[1-6].

The main causes of myocardial ischemia are:

Stenotic atherosclerotic plaque: a progressive impairment of tissue perfusion due to the growth of the plaque inside the lumen of the vessel causing impairment of blood flow and ischaemia which may lead to angina symptoms[7].

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Occlusive spasm and dynamic stenoses: a paroxysmal and intense occlusive vasoconstriction usually involving a segment of an epicardial coronary artery, which results in transmural myocardial ischaemia. Coronary artery spasm may occur at the site of an obstructive coronary atherosclerotic plaque or in angiographically normal or near normal coronary arteries. In some cases it may involve more segments in the same coronary artery branch or even more than one branch[8-16].

Thrombosis: local thrombosis occurs at the site of eroded or fissured plaques is central to the initiation of myocardial ischaemia in ACS[17].

Microvascular dysfunction: a result of either functional (e.g. endothelial and/or smooth muscle cell dysfunction) or structural (e.g. remodelling of intramural coronary arteries with a reduced lumen to wall ratio) alterations[3,4].

Extracoronary disease: for esample hypertrophic cardiomyopathy, restrictive cardiomyopathy, hypertensive heart disease, aortic stenosis, pulmonary diseases, severe anaemia or hyperthyroidism[6].

Epidemiology of Chronic Ischaemic Heart Disease

Cardiovascular diseases remain a major cause of mortality and morbility in Western countries, although, after peaking in the '60s of the previous Century, a decreasing trend of their incidence has been shown in the last decades, mainly explained by the dramatic improvement in the control of cardiovascular risk factors and preventive medical therapies[18-20]. The exact prevalence and incidence of chronic stable angina in European as well as in other countries, however, is poorly known in the contemporary era due to the lack of recent large-scale epidemiologic studies. In fact, the prevalence and incidence of angina have been always difficult to be assessed adequately, as, in contrast with acute coronary events, that require hospitalization and, therefore, can be more easily identified, the diffusion of angina in the population can be assessed only by means of surveys or questionnaires[21].

However, several previous studies from different cohorts of patients suggested an annual incidence of uncomplicated angina of about 0.5% in Western people with age > 40, although geographic variations are evident[22]. Overall, it can be estimated that between 20.000 and 40.000 patients are affected by angina pectoris in most European Countries. The prevalence of angina increases with aging in both genders. At the age of 45-54 years, indeed, it is around 2-5%, whereas it is 10-20% at the age of 65-74[23].

Interestingly, the prevalence of angina seems to be slightly higher in women than in men through several age decades and countries in the world, with an average ratio of 1.2[24]. However, about 10% to 30% of women with angina symptoms have normal or near normal coronary arteries suggesting a prevalence of microvascular disfunction in the femal gender.

Characteristics of Angina Pectoris

The most typical clinical manifestation of myocardial ischaemia is represented by angina pectoris[25]. The features of chest pain that should be investigated to diagnose and characterize angina pectoris include type, location, irradiation and duration of pain, modalities of pain onset and offset, and response to cessation of effort and nitrate administration. Most patients refer angina symptoms as a constrictive, aching sensation, or pressure or tightness discomfort in the retrosternal area or in the anterior portion of the chest and the area of pain, indicating by the patient with a clenched fist or an open hand in the middle of the chest.

Pain frequently radiates towards the neck, the left shoulder and the medial side of the left arm, and lasts no more than 10-15 minutes. Angina responds promptly to cessation of effort and short-acting nitrates. However, several variants exist to this typical presentation and pain can be represented by a heavy or burning sensation and can radiate towards the epigastrium, the right shoulder or arm, the interscapular area, the jaw and teeth, and, exceptionally, it can also be referred to the upper right abdominal quadrant or to the head[26]. Physical efforts are often the trigger of angina, but angina symptoms may appear during stressful or emotional states, exposure to cold, abundant meals or hypertensive episodes. Angina usually subsides by removing the triggering cause, but short-acting nitrates may be necessary to shorten angina duration. Finally, angina can also occur at rest without any apparent triggering cause.

Furthermore, angina pectoris may be caused by several non-ischaemic cardiac diseases or by extracardiac diseases (Figure 1). In fact, somatic or visceral pain signals may converge on the

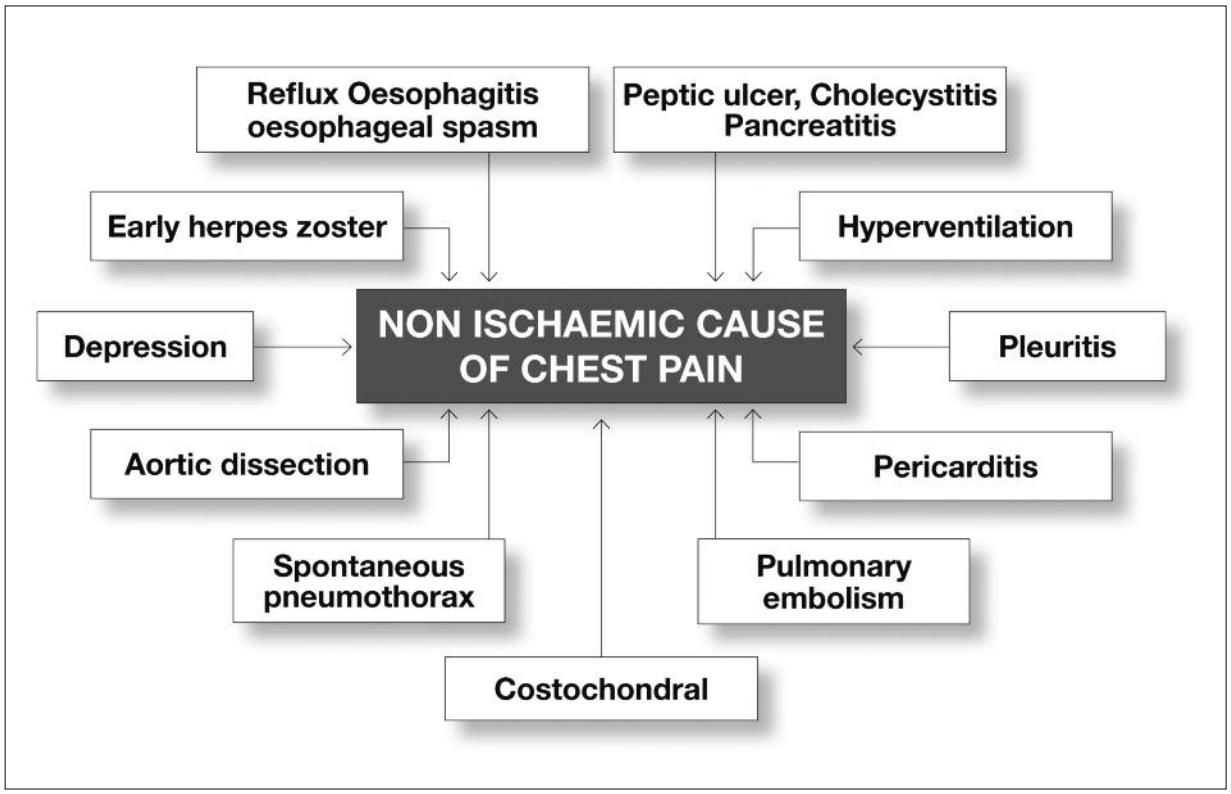

Figure 1. Non ischaemic cause of chest pain.

same neurones in the spinal dorsal horns which also receive cardiac ischaemic pain signals, thus resulting in a pain sensation similar or indistinguishable from angina.

Furthermore, in some patients myocardial ischaemia is expressed by transient symptoms that are different from angina pectoris, including dyspnea, arrhythmias and presyncope or syncope (angina equivalents).

Diagnosis of Chronic IHD

With accord to European Heart Association guidelines[1] and National Institute for Health and Clinical Excellence (NICE) guidelines[27] for the management of patients with stable IHD, the diagnosis of chronic IHD is based on clinical evaluation and non-invasive and invasive tests. A flow chart summarizing the diagnostic work-up in patients with stable angina symptoms is shown in Figure 2.

Clinical Evaluation

The clinical evaluation of patients with angina pectoris is essential for the correct diagnosis of chronic IHD. Stable angina is characterized by a pattern of angina which has remained stable for at least 2 months and it can be the first manifestation of IHD or can appear in patients who had suffered a previous acute coronary event. Typically, stable angina is induced by efforts or conditions that increase myocardial oxygen demand (e.g., emotional and psychological stresses, hypertensive episodes) and is promptly relieved by interrupting the precipitating event or using short-acting nitrates. Moreover, in stable angina myocardial ischaemia can occur reproducibly for a given level of exercise or in specific conditions, suggesting fixed stenoses, or moreover, in most patients the ischaemic threshold is variable, and angina can occasionally occur at rest (mixed angina). This variability can be the result of vasomotion at the site of pliable stenoses, modulating their severity (dynamic stenoses) and/or of vasomotor changes in the coronary microcirculation or collateral vessels[28,29].

The most widely used classification to assess severity of stable angina is the Canadian Cardiovascular Society (CCS) classification[30]. Alternative classifications systems have also been proposed, such as the Duke specific activity index[31] and the Seattle angina questionnaire[32], which may offer better prognostic capability[33].

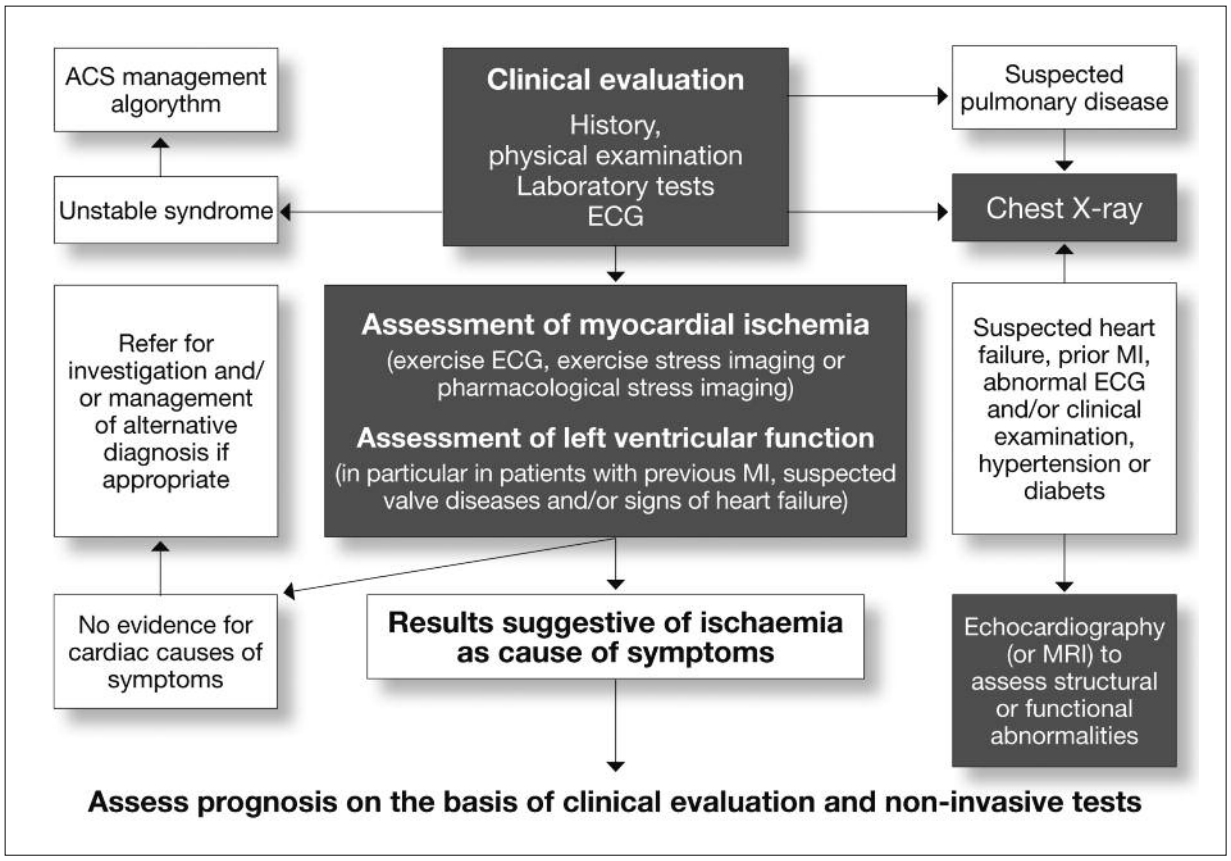

Figure 2. Flow chart summarizing the diagnostic work-up in patients with stable angina symptoms. Modified from ref 1.

Essential is the investigation of cardiovascular risk factors in patients with angina pectoris. For example, findings suggesting lipid disorders (i.e., cutaneous xanthomata, xanthelasma, corneal arcus) can be observed on visual inspection or peripheral pulse examination may reveal bruits and murmurs suggesting arterial stenoses (for example carotid and femoral arteries).

Cardiac physical examination is usually uninformative. However, a rapid pulse may be a clue to thyrotoxicosis or anaemia, which can exacerbate angina pectoris. A third and/or fourth heart sound may be heard during angina because of transient cardiac failure. A transient paradoxical splitting of the second heart sound appears in cases of ischaemia-induced left bundle branch block, whereas a transient systolic murmur may indicate mitral regurgitation following papillary muscle dysfunction, in particular in patients with a dilated left ventricle. Finally, a systolic murmur may suggest that aortic stenosis or hypertrophic cardiomyopathy is a possible cause of angina.

Non-invasive Tests

Laboratory Tests

The laboratory tests can provide information related to possible causes of ischaemia. Haemoglobin and thyroid hormone levels provide information related to possible causes of ischaemia[6]. Serum creatinine is a simple method to evaluate renal function and is recommended at initial evaluation in all patients with suspected angina[34]. Biochemical markers of myocardial damage such as troponin or creatinine kinase myocardial band (measured by the mass assay) should be employed to exclude myocardial injury[17].

Resting Electrocardiogram

In patients with suspected angina pectoris a resting 12-lead electrocardiogram (ECG) should be recorded, although only occasionally it is of diagnostic value. Indeed, resting ECG is normal in about 50% of cases and, when abnormal, will show abnormalities (e.g., minor ST-segment/T wave changes, atrioventricular or intraventricular

conduction disorders, supraventricular or ventricular arrhythmias) that are not sufficiently specific for the diagnosis of IHD because they can be frequently found in several other conditions. However, the detection of pathologic Q/QS waves, even in the absence of any history of previous myocardial infarction (MI), or of typical negative symmetric T waves and/or ST-segment depression, strongly suggests an ischaemic origin of symptoms[1].

Chest X-ray

Chest X-ray has poor diagnostic value in suspected stable angina, although it is routinely performed in these patients. The detection of coronary calcifications, however, is associated with a high probability of obstructive IHD[35].

Echocardiography at Rest

The resting two-dimensional and doppler echocardiography is useful to detect left ventricular (LV) function and it is essential to rule out the possibility of other disorders such as valvular heart disease or hypertrophic cardiomyopathy as a cause of symptoms.

Ambulatory ECG-Holter Monitoring

ECG-Holter monitoring may reveal myocardial ischaemia during normal daily activities[36] in up to 10-15% of patients with stable angina who do not develop diagnostic ST-segment depression during ECG-EST (exercise stress test)[37]. This can occur in patients in whom coronary vasoconstriction plays an important role in the pathogenesis of myocardial ischaemia.

Accordingly, ECG monitoring is more helpful for diagnostic purposes in patients with symptoms suggestive of dynamic stenosis or coronary vasospasm.

ECG Exercise Stress Test (ECG-EST)

Treadmill or bicycle ECG-EST during 12-lead ECG monitoring is the test of choice to diagnose myocardial ischaemia in the majority of patients with suspected chronic IHD[1].

The main diagnostic ECG abnormality during EST consists of a rectilinear or downsloping ST-segment depression ≥ 0.1 mV, persisting for at least 0.06-0.08 seconds after the J-point, in one or more ECG leads[38]. Moreover, it is to be noted that in about 15% of patients diagnostic ST-segment changes appear during the recovery phase, rather than during the active phase, of exercise[39].

Previous studies reported a sensitivity of ECG-EST of 50% and a specificity of 90%[40-43]. The positive predictive value for coronary artery disease of exercise-induced ST-segment depression increases up to 90% if it is accompanied by typical angina pain, if it occurs in the early stages of exercise or persists for more than 5 minutes in the recovery phase, and if it is > 0.2 mV[44].

It is to be noted that bias should be considered for the diagnosis of chronic IHD. This bias consists of considering the presence or absence of obstructive coronary stenoses at angiography as the gold standard for diagnostic accuracy. Indeed, non-invasive stress tests detect myocardial ischaemia, which may be caused by coronary spasm or microvascular dysfunction; or obstructive atherosclerosis does not always cause myocardial ischaemia during stress (e.g., for the presence of well-developed collateral circulation).

The interpretation of ST-segment changes during ECG-EST should be individualized, particularly considering the pre-test probability for the patient to have obstructive coronary artery disease. Indeed, owing to the suboptimal sensitivity and specificity of ECG-EST, pre-test probability influences the predictive value for IHD, according to Bayes theorem[45].

Moreover, the ECG-EST has limited value in patients with basal ECG abnormalities, including left bundle branch block, paced rhythm or Wolff-Parkinson-White syndrome, which preclude a correct interpretation of ST-segment changes.

An important issue with ECG-EST is the diagnosis of obstructive IHD in women, in whom ST-segment depression has been found to have lower specificity than in men. However, when pre-test probability is accurately determined and patients with normal ECG at rest are selected, ECG-EST has the same reliability in women as in men[46].

Stress Tests in Combination With Imaging

Stress imaging techniques have several advantages over conventional ECG-EST, including superior diagnostic performance for the detection of obstructive coronary artery disease, the ability to quantify and localize areas of ischaemia, and the ability to provide diagnostic information in the presence of resting ECG abnormalities or inability of the patient to exercise. These imaging techniques are often preferred in patients with previous percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) because of their ability to localize ischaemia.

Stress imaging techniques, therefore, might be considered as an alternative to standard ECG-EST to detect ischaemia; however, they are more ex-

pensive and time-consuming, and less cost-effective. Thus, for diagnostic purposes they are only indicated in patients with non-conclusive results of ECG-EST or when ECG is not interpretable[1].

Scintigraphic Stress Tests

Exercise myocardial perfusion scintigraphy is a non-invasive method of assessing regional myocardial perfusion and it allows the diagnosis of myocardial ischaemia by showing a reversible reduction of isotope myocardial uptake at peak exercise, as compared to rest, in myocardial regions supplied by stenotic coronary arteries. The three commercially available flow perfusion tracers, ^{201}thallium, and ^{99m}Tc-labelled sestamibi or tetrofosmin, have similar accuracies for the detection of IHD. Exercise myocardial scintigraphy is more sensitive than ECG-EST for IHD detection; in fact, sensitivity has been found to range 70-98%, and specificity 40-90%[1]. Scintigraphic studies are more accurate than ECG-EST in predicting the presence of multivessel IHD and in detecting the location and extent of myocardial ischaemia[1]. Moreover, pharmacological stressors can be used as an alternative to exercise in patients who are unable to exercise adequately, for example elderly patients or patients with peripheral vascular disease or those limited by dyspnea[47,48]. They include the sympathetic agonist dobutamine, which causes an increase of myocardial oxygen consumption simulating physical exercise, and the arteriolar vasodilators dipyridamole and adenosine, which cause subendocardial underperfusion in myocardial regions supplied by stenotic coronary artery branches, because of the coronary blood flow steal phenomenon.

Echocardiographic Stress Tests

Exercise echocardiography is an alternative to exercise myocardial perfusion scintigraphy as a second-tier test to standard ECG-EST, presenting similar indications and advantages, including a more reliable diagnosis of multivessel disease and location of myocardial ischaemia[49]. Diagnosis of IHD on echocardiography is based on the detection of stress test-induced reversible regional LV wall motion abnormalities. Compared with scintigraphy, inconveniences include poor image quality in about 15% of patients, higher operator-dependent interpretation, lower sensitivity, the need for special training for a correct performance and interpretation, and more difficult assessment of ischaemia in the presence of basal LV wall motion abnormalities. Exercise echocardiography, however, also has some advantages over exercise perfusion scintigraphy, including a slightly higher specificity, the possibility of a more extensive evaluation of cardiac anatomy and function, greater availability, lower cost, and a greater safety. Pharmacological stressors are used more frequently than exercise in echocardiography. Indications and stressors for echocardiography are the same as those for pharmacological scintigraphic stress tests (dobutamine and dipyridamole).

Stress Cardiovascular Magnetic Resonance

Cardiovascular magnetic resonance stress testing in conjunction with dobutamine infusion can detect wall motion abonormalities induced by ischaemia[50,51]. Although still in development, the results are already good in comparison with other imaging techniques[52]. However, the restricted availability, the higher costs, and also some difficulties in continuous monitoring of the patient during the stress test, limit at present the utilization of this technique for diagnostic purposes in clinical practice.

Non-Invasive Techniques to Assess Coronary Anatomy

Computed Tomography

Two imaging techniques of this kind include ultra-fast or electron beam computer tomography and multi-detector or multi-slice computer tomography. Both techniques have been validated for quantification of the extent of coronary calcifications, which correlates more closely with the overall burden of plaque than with the location or severity of stenoses[53,54].

Magnetic Resonance Arteriography

Cardiac magnetic resonance (CMR) contrast coronary arteriography also permits the non-invasive assessment of the coronary lumen[55], and, in addition, also holds the potential for plaque characterization[56]. Additional advantages of the technique are that it has a considerable potential for evaluation of the overall cardiac anatomy and function. However, at present it is still an investigational tool not recommended in clinical practice.

Invasive Tests

Coronary Angiography

Obstructive coronary artery disease is ultimately diagnosed by documenting flow-limiting coronary artery stenoses at angiography. Yet, because of the small, but definite, risk of complica-

tions and its cost, coronary angiography cannot be recommended as a routine diagnostic procedure to assess chest pain.

Coronary angiography for diagnostic purposed is indicated in specific subsets of patients including: (1) patients who have a high probability of needing myocardial revascularization; (2) patients at high risk because of resuscitated sudden death or life-threatening ventricular arrhythmias in whom a definitive diagnosis regarding the presence or absence of coronary disease is important in clinical decision making; (3) patients with a non conclusive diagnosis of IHD on non-invasive testing[1].

Prognosis of Patients With Chronic IHD

Prognosis in chronic IHD patients can be derived mainly from clinical evaluation and from non invasive laboratory tests, in particular the assessment of LV function and severity of myocardial ischaemia[1].

Previous studies reported that the severity and frequency of chest pain have prognostic implications. In fact, a low anginal threshold is usually associated with severe coronary flow reserve reduction and symptoms of acute LV dysfunction during angina, possibly indicating extensive myocardial ischaemia, also predict a worse outcome[57].

The presence of peripheral vascular disease identifies patients at increased risk of subsequent cardiovascular events in stable angina[1]. Furthermore, an accurate assessment of cardiovascular risk factors is usefull to establish patient's risk profile[1]. Further laboratory testing, including measures of apolipoproteins, homocysteine, lipoprotein (a), BNP (Brain Natriuretic Peptide) or NT-proBNP, haemostatic abnormalities and markers of inflammation, such as C-reactive protein, has been investigated as parameters to improve current risk prediction[1,58].

Left ventricular ejection fraction (LVEF) is the strongest single predictor of long-term survival in patients with stable IHD. In particular, in the CASS study the 12-year survival rate of patients with LVEF >50%, 35-49%, and <35% were 73%, 54% and 21%, respectively[59]. For this reason, an estimation of LVEF is desirable for risk stratification of patients with stable angina.

The Duke treadmill score[60], which has been prospectively validated in large cohorts of patients, is based on exercise capacity (as exercise duration), severity of myocardial ischaemia (as maximal ST-segment depression) and appearance of angina, and is calculated from the following formula: exercise duration (Bruce protocol, in min)-(5 x ST-segment depression during exercise test, in mm)-(4 x angina index), where the angina index assumes a value of "0" if there is no angina induced by exercise, "1" if non-limiting angina occurs during exercise, and "2" if angina is the reason for stopping the test.

Among patients with suspected IHD, the two-thirds of patients with a Duke score > 5 had a 4-year survival rate of 99% (average annual mortality rate 0.25%), whereas, at the other extreme, the 4% of patients, with a score of -11 or less, had a 4-year survival rate of 79% (average annual mortality rate 5%)[60].

Furthermore, the extent of perfusion defects and/or signs of LV dysfunction on radionuclide scintigraphic tests and the extent of LV wall motion abnormalities on echocardiography, induced by either exercise or pharmacological stressors, have been found to be associated with an adverse clinical outcome in stable IHD patients[61,62].

Frequent transient ischaemic episodes during daily life, detected by ECG Holter monitoring, are also associated with a worse prognosis[63] thus, ECG-Holter might be prognostically helpful in patients unable to undergo EST.

With regard coronary angiography, the simplest and most widely used is the classification into one, two, three, and left main (LM) vessel disease. In the CASS registry of medically treated patients, the 12-year survival rate of patients with normal coronary arteries was 91% compared with 74% for those with single vessel disease, 59% for those with two vessel disease, and 50% for those with three-vessel disease[59]. Patients with severe LM stenosis have a poor prognosis when treated medically and the presence of severe proximal left anterior descending coronary artery (LAD) disease also significantly reduces the survival rate. The 5-year survival rate with three-vessel disease plus ≥ 95% proximal LAD stenosis was reported to be 54% compared with a rate of 79% with three-vessel disease without proximal LAD stenosis[64].

Treatment

According to European Heart Association guidelines (1) and NICE guidelines (27) for the management of patients with stable IHD, clinical management has two main objectives. The first objective is to improve prognosis by preventing the ACS and the development of LV dysfunction; the second objective is to minimize or abolish symptoms using anti-anginal drugs and recurring to myocardial revascularization in patients who do not respond to medical treatment.

The first intervention to improve outcome is acting on cardiovascular risk factors. In particular, a reduction of cardiovascular risk can be performed abolishing smoking, regulating diet, reducing cholesterol and lipoprotein levels, reducing body weight and blood pressure, and performing physical activity[1].

Two flow charts summarizing the treatment of patients with stable angina symptoms are shown in Figures 3 and 4.

Myocardial Revascularization

There are two well-established approaches to revascularization for treatment of chronic stable angina caused by coronary atherosclerosis: percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG). As in the case of pharmacological therapy, the potential objectives of revascularization are to improve survival and to diminish or eradicate symptoms.

Coronary revascularization procedures should be considered when the annual cardiovascular mortality rate is > 2% (patients with low Duke score at treadmill exercise test or with large regions of ischemia at stress imaging or with impaired LV function). In contrast, myocardial revascularization cannot be expected to improve the outcome and, therefore, should not be considered for prognostic purposes, in patients at low risk with annual cardiovascular mortality < 1%.

In the presence of an intermediate risk the choice is difficult and should be carefully discussed with each individual patient, although in this setting diagnostic coronary angiography can add important prognostic information[1].

Myocardial revascularization, however, is indicated, regardless of its effect on the outcome, in patients who remain symptomatic in spite of optimal medical treatment, if the operative risk is acceptable[1].

Percutaneous Coronary Interventions (PCI)

Balloon angioplasty is aimed at restoring blood flow through stenotic coronary arteries by mechanical dilatation through inflation of a balloon catheter steered percutaneously to the narrowed site under fluoroscopic guidance. Following the availability of miniature and highly steerable guidewires, which have permitted access to virtually any branch of the epicardial coronary tree, is possible the application of endovascular metallic scaffolds, called stents. The stent implantation technique itself has been optimized by proper

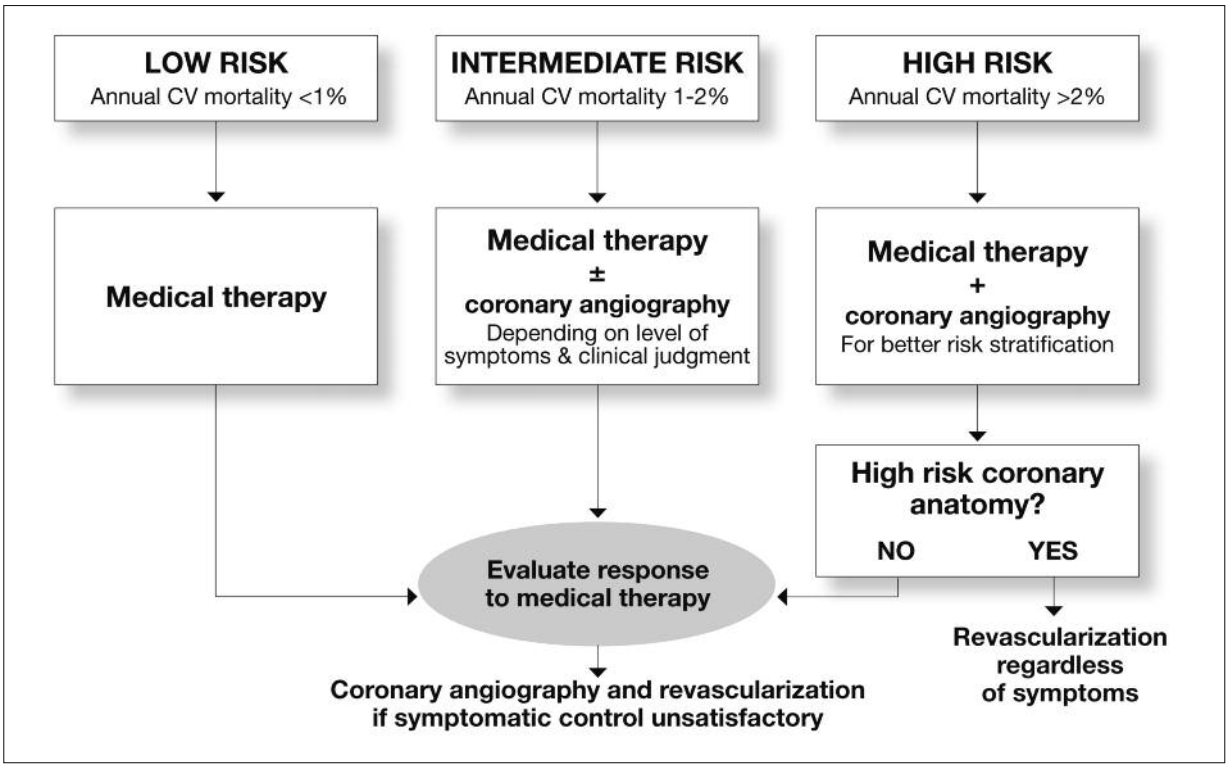

Figure 3. Flow chart summarizing the treatment of patients with stable angina symptoms. Modified from ref 1.

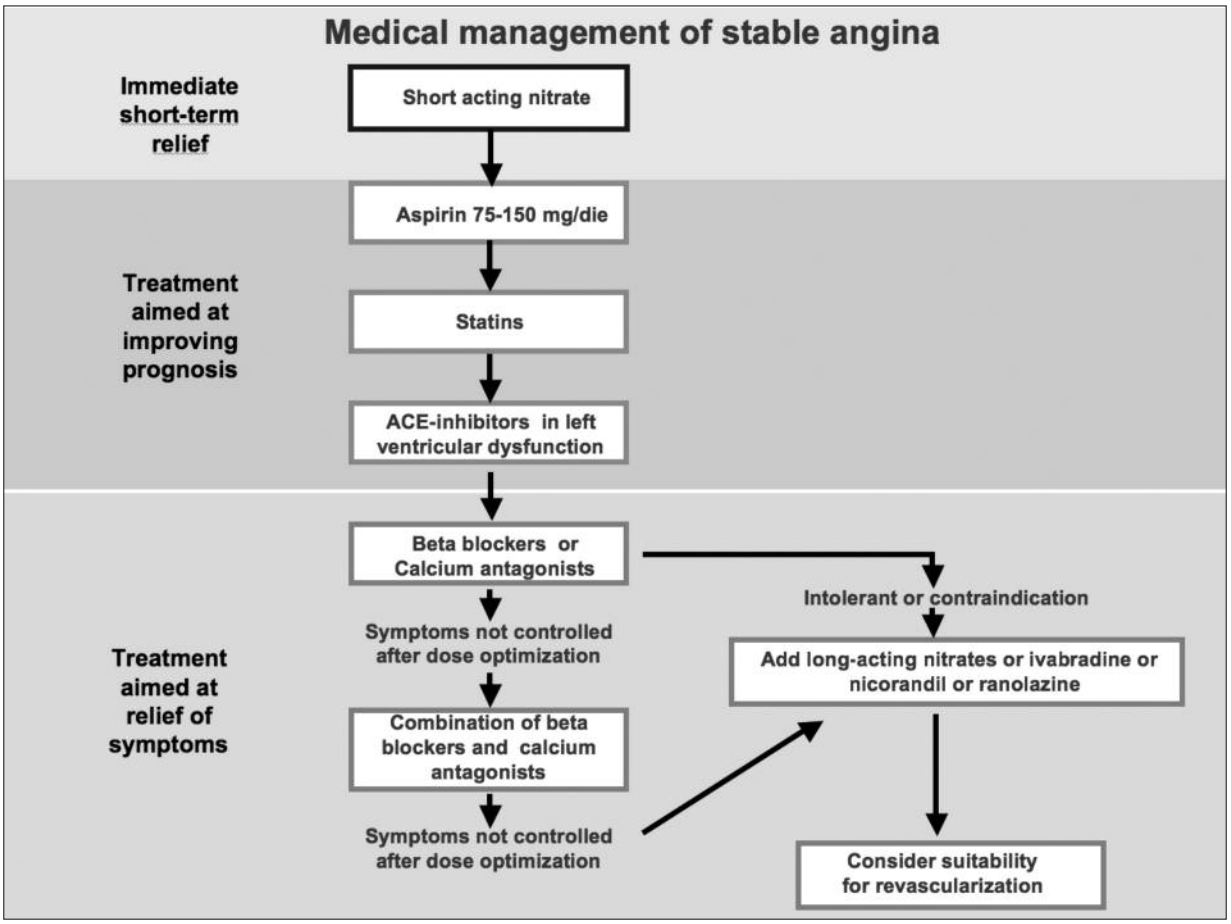

Figure 4. Flow chart summarizing the drug therapy of patients with stable angina symptoms. Extracted from NICE guidelines for the management of patients with stable IHD.

stent expansion and apposition against the wall, as learned from intravascular ultrasound imaging[65].

Stented angioplasty is superior to balloon angioplasty in technical success for the following reasons: (1) plaque fracture and dissection caused by balloon inflation often result in a pseudo-successful procedure while limited luminal enlargement is actually obtained; (2) the dilated lesion shows greater stability after stenting, while abrupt closure within 48 h following balloon treatment is not uncommon (up to 15% in the presence of severe residual dissection); (3) the angiographic result obtainable after stenting is predictable irrespective of stenosis complexity; (4) follow-up studies show a lower restenosis rate with stent implantation[1].

Implantation of bare metal stent (BMS) eliminates vessel shrinkage but at the same time, however, implantation of metallic stents exacerbates neo-intimal proliferation and stent restenosis. Presently, drug-eluting stents (DES) are replacing BMS. These metallic scaffolds are covered with polymers from which less than 0.1 mg of cytotoxic and anti-inflammatory compounds (e.g. paclitaxel, sirolimus, everolimus) are progressively eluted over the first weeks after stent implantation. Three drugs have shown significantly positive effects in prospective randomized trials of DES (paclitaxel, sirolimus, and its derivative everolimus). Both angiographic restenosis rates and the need for repeat intervention due to symptom recurrence have been reduced by over 60%, at least with the use of the currently approved devices[66]. Reported incidence of major adverse cardiac events, including re-interventions, over 9 months ranges between 7.1 and 10.3% with DES stents compared with a range between 13.3 and 18.9 with BMS[67].

A drawback of stent implantation is the risk of stent thrombosis which is associated to a considerably high in hospital mortality[1]. Stent thrombosis rate is about 2% during the first year and

about 0.5% per year thereafter. The risk of stent thrombosis seems higher for DES than for BMS. However, the higher risk of stent thrombosis associated with DES implantation does not translate in a higher rate of MI or mortality[68,69]. Thus, by markedly reducing the high rates of restenosis that would have occurred after BMS implantation, DES may directly reduce the subsequent occurrence of death and nonfatal MI, offsetting the incremental risk of stent thrombosis. Taken together these findings suggest that DES should be utilized in the treatment of coronary lesions at higher risk of restenosis and that their implantation should be followed by a prolonged period of dual antiplatelet therapy[1,68]. There is presently no consensus on the optimal duration of dual antiplatelet therapy after DES but many physicians empirically recommend prolonged treatment up to 1 year, particularly after stenting of complex or multiple lesions[1,68].

Indications for Percutaneous Coronary Interventions

Previous studies showed that PCI compared with medical therapy did not provide substantial survival benefit in stable angina. Trial-based evidence indicates that PCI is more often effective than medical treatment in reducing events that impair quality of life (angina pectoris, dyspnea, need for re-hospitalization, or limitation of exercise capacity)[1].

The ACME trial[70], RITA-2 trial[71] and the AVERT trial[72] showed that in chronic IHD patients PCI resulted in a better control of symptoms of ischaemia and improved exercise capacity compared with medical therapy, with a similar rate of death and MI.

The COURAGE trial has recently confirmed the results of previous trials[73]. This randomized trial involved 2287 patients with significant coronary artery disease and objective evidence of myocardial ischemia, who were randomized to undergo PCI with optimal medical therapy or to receive optimal medical therapy alone. The primary outcome was a combination of death from any cause and nonfatal MI during a median follow-up of 4.6 years. The cumulative primary-event rates were 19.0% in the PCI group and 18.5% in the medical-therapy group.

A very recent meta-analysis, including also the COURAGE trial, found a lower total mortality in patients randomized to PCI as compared to those randomized to medical treatment[74]. However, several limitations, including the inclusion of trials enrolling patients with recent MI make the interpretation of the results difficult. Furthermore, no difference was found with regard to cardiac mortality.

Thus, currently available data suggest that in low- medium-risk patients with stable IHD, medical treatment including aggressive lipid-lowering therapy may be as effective as PCI in reducing major adverse cardiac events, while PCI is associated with a greater improvement in anginal symptoms and is, therefore, a viable option in patients who are symptomatic for angina in spite of optimal anti-anginal treatment[1].

Coronary Artery Bypass Grafting

This surgical technique was initially introduced by Favaloro in 1969 using safenous vein grafts (SVG) interposed between the aorta and epicardial coronary artery branches distal to critical stenoses[75]. Furthermore, large observational studies showed that the use of the left internal mammary artery (LIMA) graft improves survival and reduces the incidence of late MI, recurrent angina, and the need for further cardiac interventions as compared to SVG[76-78].

Over the last 20 years the standard procedure has been to graft the LAD with the LIMA and use SVG for the other epicardial coronary branches. Moreover, there is a significant survival benefit when using bilateral internal mammary artery[79,80]. Other arterial grafts include the radial artery and the right gastroepiploic artery[81,82].

The use of extracorporeal circulation for performing coronary artery surgery remains the most commonly used approach. However, there are risks, including a whole-body inflammatory response and the production of microemboli.

The so-called "off-pump" surgery may lead to a reduction in perioperative mortality and morbidity. The recent introduction of stabilization devices has enabled surgeons to treat patients with three-vessel disease in this way. Randomized trials comparing off-pump with the standard procedure showed no differences in perioperative complication rates and no difference in outcome in the first 1-3 years after surgery[83,84].

A meta-analysis of six studies including 558 patients randomized to on-pump and 532 to off-pump CABG found no significant difference in the combined end-point of death, stroke or MI[85]. A further randomized trial with angiographic follow-up at 3-6 months showed a significant reduction in graft patency (90% vs. 98%) in the

off-pump group[86]. Accordingly, in a recent observational study including 49.830 patients, off-pump surgery was associated with lower in-hospital mortality and complication rates than on-pump CABG, but long-term outcomes were comparable, except for freedom from revascularization, which favoured on-pump CABG[87]. These studies suggest that the use of off-pump surgery should be applied cautiously and selectively to patients with good target vessels and significant comorbidity.

Indications for Coronary Bypass Surgery

In a meta-analysis of surgical trials comparing CABG with medical therapy prognostic benefit of CABG compared with medical therapy has not been found in low-risk patients, while CABG was shown to improve prognosis in those at medium to high-risk[88-90].

Analyses of observational and randomized controlled trial data revealed that the presence of specific coronary artery anatomy is associated with a better prognosis with surgery than with medical treatment. Such disease includes[91-93]:

- Significant LM stenosis;
- Significant proximal stenosis of the three major coronary arteries;
- Significant stenosis of two major coronary arteries, including high-grade stenosis of the proximal LAD

Significant stenosis was defined in these studies as > 70% of major coronary arteries or > 50% of the LM stem. The presence of impaired LV function increases the absolute prognostic advantage of surgery over medical treatment in all categories. This information mainly comes from three major randomized studies, the European Coronary Artery study[94] the Coronary Artery Surgery study[95] and the Veterans Administration study[88].

Percutaneous Interventions Versus Coronary Bypass Surgery

Meta-analysis of trials conducted before 1995, when coronary stenting was rare, revealed no significant differences in the treatment strategy for either death or the combined endpoint of death or MI[96]. The need for subsequent revascularization was significantly higher in the PCI group, and although patients were significantly less likely to have angina one year after bypass surgery than after PCI, by 3 years this difference was no longer statistically significant.

Results from the BARI study, the largest single randomized trial of PCI vs. surgery, not included in this meta-analysis, were nonetheless consistent with these findings, although a survival advantage with bypass surgery was observed in the diabetic subgroup[97]. Compared with the balloon era, angioplasty using BMS has halved the risk difference for repeat revascularization at 1 year, which however remains at 18% after PCI vs. 4.4% after CABG[98,99].

A meta-analysis including trials of stents suggests a mortality benefit with CABG compared with PCI at 5 years which continued to 8 years in patients with multivessel disease. Furthermore, a significantly lower incidence of angina and need for repeat revascularization was shown.

A more recent meta-analysis of four randomized controlled trials of PCI with stents compared with bypass surgery showed no significant difference between the treatment strategies in the primary endpoint of death, MI, or stroke at 1 year[100].

However, observational data on more than 60000 patients from the New York Cardiac Registry indicated that for patients with two or more diseased coronary arteries, CABG was associated with higher adjusted rates of long-term survival compared to stenting[101]. Similar findings were confirmed, more recently, with observational data from the same Registry in the comparison between CABG and DES[102].

The SYNTAX trial enrolled 3075 patients with 3-vessel and/or left main (LM) stem disease; 1800 patients, amenable to similar myocardial revascularization by PCI or CABG, were randomized; 1077 patients who underwent CABG because of contraindications to PCI and 198 who underwent PCI because of contraindications to CABG were followed in registries. The primary end-point was a composite of all cause death, cerebrovascular accident, documented MI or any repeat revascularization at 12 month follow up. The trial failed to demonstrate non inferiority of PCI vs CABG for the primary endpoint which occurred in 13.7% of the PCI group and 5.9% of the CABG group. This difference was mainly driven by a higher repeat revascularization rate (14.7% vs 5.4%), while the rate of death, cerebrovascular accidents or MI was similar (7.7% vs 7.6%, respectively). Interestingly, cerebrovascular accident rate was higher in the CABG group than in PCI group (2.2% vs 0.6%), whereas acute MI rate was higher in the PCI group than in the CABG group (4.8% vs. 3.2%).

Among patients in the CABG registry the primary end-point rate was 8.8%, thus indicating that about one third of patients with 3-vessel and/or left main stem disease were amenable to CABG only and in these patients CABG was associated with an excellent outcome. Among patients in the PCI registry the primary end-point rate was 20.5%. In this patients, however, pre-procedural risk was considerably higher than that of randomized patients. Thus, PCI is a viable option for patients not eligible for CABG, although with a significant increase in the risk of major coronary events. Interestingly, the Authors developed a new score to describe the complexity of coronary lesions which was predictive of the primary outcome. Among patients with a low score (about one third of randomized patients) the rate of the primary end-point was similar in the CABG and PCI groups[103].

With regard diabetic patients, although a direct comparison of PCI with CABG in diabetics is not yet available, subgroup or post hoc analyses of clinical trials have invariably shown a worse outcome with PCI than with CABG[104].

Finally, the following factors should always be taken into consideration for an optimal choise of the modality of myocardial revascularization: (1) risk of periprocedural morbidity and morbidity; (2) likelihood of success, including factors such as technical suitability of lesions for angioplasty or surgical bypass; (3) risk of restenosis or graft occlusion; (4) completeness of revascularization; (5) diabetic status; (6) local hospital experience in cardiac surgery and interventional cardiology; (7) patient's preference.

Medical Therapy

Antiplatelet Agents

Low-dose aspirin

This drug acts has an antithrombotic effect inhibiting irreversibly platelet thromboxane A2 synthesis, which has pro-aggregatory and vasoconstrictive properties. The inhibition is normally complete with chronic dosing >75 mg/day and the optimal dosage appears to be 75-150 mg/die. Aspirin is a mainstay in the treatment and prevention of vascular events[105-107]. The main risk of aspirin therapy are bleeding and the dosage should be the lowest effective one in order to optimize the balance between therapeutic gains and gastrointestinal side-effects during chronic therapy. In particular, the relative risk of suffering an intracranial haemorrhage with aspirin treatment at doses >75 mg/day increases by 30%, but the absolute risk of such complications is less than 1 per 1000 patient years[108].

Thienopyridines

Clopidogrel and ticlopidine are thienopyridines that act as non-competitive ADP receptor antagonists and have antithrombotic effects similar to aspirin. Ticlopidine has been replaced by clopidogrel due to its risk of neutropenia and thrombocytopenia and the occurrence of more symptomatic side-effects. The main study documenting clopidogrel use in stable IHD is the CAPRIE trial[109], which included three equally large groups of patients with previous MI, previous stroke or peripheral arterial disease. This trial showed that, compared with aspirin 325 mg/day, clopidogrel 75 mg/day was slightly more effective in preventing cardiovascular complications in high risk patients. The active metabolite of clopidogrel is formed by hepatic CYP3A4 enzyme and, for this reason, clopidogrel has pharmacological interaction with numerous drug causing a variability of antiplatelet response[110].

Beta Blockers

Beta-blockers are well documented for the prevention of anginal symptoms and ACS in patients with chronic IHD[111-114]. They reduce oxygen demand by reducing heart rate and contractility, and by reducing blood pressure. Commonly used beta-1 blockers with good documentation as anti-anginal drugs are metoprolol, atenolol, and bisoprolol. Side-effects of beta-blockade include bradycardia, hypotension, increased respiratory symptoms in asthma and chronic obstructive pulmonary disease and sexual dysfunction.

Calcium Channel Blockers

Heart rate lowering calcium channel blockers may improve the prognosis in patients with chronic IHD as showed in previous studies[115-119]. Actually, calcium channel blockers may be an optimal alternative to beta blockers in patients with IHD without heart failure who do not tolerate beta blockers.

Angiotensin Converting Enzyme (ACE) Inhibitors

ACE-inhibitors prevent vasoconstriction by inhibiting the production of the vasoactive octapeptide angiotensin II from the decapeptide angiotensin I. This inhibition results in vasodilata-

tion due to lowering of systemic vascular resistance and natriuresis from inhibition of aldosterone secretion. Previous trials showed a significant reduction of cardiovascular events in patients with chronic IHD[120-124]. Actually, the ACE-inhibitors are considered for the treatment of patients with stable angina pectoris and co-existing hypertension, diabetes, heart failure, asymptomatic LV dysfunction or previous MI.

These drugs are generally well tolerated. The most frequent adverse effect is a dry cough, in up to 20% of individuals. Angio-oedema is a comparatively rare but more serious adverse effect. Patients who do not tolerate an ACE-inhibitor should be given an angiotensin receptor blockers[1].

Nitrates

The pain relieving and anti-ischaemic effects of short and long-acting nitrates are mainly related to venodilatation and reduced diastolic filling of the heart which also favours subendocardial perfusion. Long-acting nitrates may be considered if beta-blockers and calcium channel blockers are not tolerated or are contraindicated. Furthermore, they can be considered in people whose symptoms are not controlled by therapy with beta blockers or calcium channel blockers[1].

Nitrates causes dose-dependent vasodilator side-effects, such as headache and flushing. Overdosing may cause postural hypotension and reflexogenic cardiac sympathetic activation with tachycardia, leading to "paradoxical" angina. Tolerance to continuous oral or transdermal nitrates develops rapidly and, in order to overcome this inconvenient, nitrate-free intervals or a modified delivery system designed to provide a period of low blood nitrate concentration have been recommended[125].

It is very important to underscore that in the scientific literature there are no clinical studies showing that long-term treatment with nitrates reduces mortality or the incidence of MI in patients with stable angina. Thus, nitrates are used to reduce angina symptoms without acting on long-term prognosis of patients with IHD[1].

Nicorandil

Adenosine triphosphate-sensitive potassium channels are ubiquitous in the heart and blood vessels and are important modulators of cardiovascular function. Nicorandil is a hybrid compound that comprises a potassium channel opener and a nitrate moiety[126]. Nicorandil has a dual mechanism of action on both preload and afterload, producing a dose-related improvement in haemodynamics. The IONA trial[127] has shown a significant early reduction of major coronary events in stable anginal patients treated with nicorandil when compared with placebo as add-on to conventional therapy. Headache is the most common side effect, usually occurring early on commencement of treatment and disappearing with chronic dosing.

Ivabradine

This drug has negative chronotopic effects acting on sinus node inhibiting the cardiac pacemaker current If. A recent randomized controlled trial showed that ivabradine produces dose-dependent improvements in exercise tolerance and time to ischaemia during exercise in patients with chronic IHD[128]. The main side effect is represented by mild visual disturbances, mainly with the highest dose of ivabradine, which resolve spontaneously or with drug cessation. These may be linked to the presence of retinal ion channels similar to those mediating If[129].

Trimetazidine

A metabolic agent that has been shown to preserve energy balance and prevent disturbance of ion haemostasis during ischaemia. Its specific mechanism of action is unknown but its antianginal effects are attributed to modulatory effects on intracellular calcium. Trimetazidine also stimulates glucose oxidation and acts as a partial fatty acid oxidation inhibitor. Antianginal efficacy has been established with immediate-release formulations of trimetazidine three times daily[130] and, more recently, with a modified-release formulation of trimetazidine 35 mg daily. The most commonly reported adverse effects with clinical doses are fatigue/drowsiness.

Ranolazine: an Innovative Antianginal Drug

Ranolazine is an innovative antianginal drug with a novel mechanism of action that appears to offer freedom from most adverse hemodynamic effects. Ranolazine was approved by the U.S. Food and Drug Administration (FDA) and it was commercialized in Europe from 2009 for the treatment of patients with chronic IHD.

Mechanism of Action of Ranolazine

Furthermore, various studies using animal models have been used suggesting the its mechanism of action is trought the inhibition of the late

sodium current in cardiac myocites [131,132]. During myocardial ischemia, there is a build-up of intracellular sodium, which leads to an increase in intracellular calcium via the sodium-calcium exchanger[133,134]. The disregulation of these ions causes electrical instability, arrhythmias, reduced myocardial contractility, increased mitochondrial dysfunction with reduced adenosine triphosphate, and subsequently, cell injury[135-138]. The proposed novel mechanism of action of ranolazine reduces the size of the sodium and calcium overload that follows myocardial ischemia. By regulating this imbalance in ion shifts, ranolazine may improve myocardial relaxation and reduce LV diastolic stiffness, which in turn can enhance myocardial contractility and perfusion, and it may reduce arrhytmias[131,132].

Pharmacokinetics

Ranolazine is a racemic mixture that contains enantiomeric forms (S-ranolazine and R-ranolazine). Ranolazine is rapidly metabolized in the liver, primarily through the cytochrome P-450 3A enzyme pathway, and in the intestine. More than 70% of the drug is excreted in the urine. This pharmacokinetic profile necessitates careful dosage adjustments in patients who are elderly, who weigh less than 60 kg, and who have mild-to-moderate renal insufficiency or mild hepatic impairment, and in patients who are in New York Heart Association functional class III-IV. Ranolazine is contraindicated in patients with severe renal impairment (glomerular filtration rate, <30 mL/min/1.73 m2) or moderate-to-severe hepatic impairment (Child-Pugh classes B and C) [139].

Due to the dependence of ranolazine on CYP3A metabolic pathways, the coadministration of a wide variety of drugs can affect its clearance. In particular, ketoconazole, a potent CYP3A inhibitor, can raise steady-state concentrations of ranolazine to more than 3 times the expected value. Moderate inhibitors of CYP3A, such as diltiazem and verapamil, should be used with caution. Simvastatin, a weak inhibitor of CYP3A, does not seem to increase ranolazine levels. Macrolide antibiotics, human immunodeficiency virus protease inhibitors, and grapefruit juice, all of which inhibit CYP3A to varying degrees, should be used with caution. Ranolazine also inhibits P-glycoprotein, so it should be used with caution by patients who are taking verapamil, because plasma levels of that drug may increase. Ranolazine has been shown to increase serum digoxin levels by 1.5 times, leading to the recommendation that digoxin dosages may be altered in patients who are taking both drugs[139,140].

Clinical Trials

The initial study of ranolazine versus placebo was performed by Pepine and Wolff[141]. The Authors showed that exercise duration, exercise time until the onset of angina, and exercise time until the development of 1 mm ST-segment depression increased with the use of immediate-release ranolazine.

The first trial on ranolazine was the Monotherapy Assessment of Ranolazine in Stable Angina (MARISA)[142] in which ranolazine was compared with placebo in a double-blinded crossover study of 175 patients. All patients were required to undergo angina-limited ESTs and to discontinue previous antianginal therapy 1 week before randomization to placebo or to twice-daily regimens of 500, 1.000, or 1.500 mg of ranolazine. At peak and trough levels, all 3 ranolazine regimens led to statistically significant increases versus placebo in exercise duration (500 mg, 23.7 s, $p < 0.003$; 1.000 mg, 33.7 s, $p < 0.001$; and 1.500 mg, 45.9 s, $p < 0.001$), in time until the onset of angina (500 mg, 27 s, $p < 0.005$; 1.000 mg, 45.9 s, $p < 0.001$; and 1.500 mg, 59.6 s, $p < 0.001$), and in time until the development of 1 mm ST-segment depression (27.6, 44.5, and 64.6 s, respectively; all $p < 0.001$). Although the 1.500 mg regimen had the greatest effect, the side effect profile was also highest at that dose.

The second study with ranolazine was the Combination Assessment of Ranolazine in Stable Angina (CARISA) trial[143]. Ranolazine response at 750 mg and 1.000 mg twice daily was compared with response to placebo in 823 patients who were already receiving antianginal therapy. Patients in both ranolazine groups showed statistically significant improvement in exercise duration at trough dosing (750 mg, 23.7 s and 10000 mg, 24 s; both $p < 0.03$). Secondary endpoints (exercise duration at 4 hr after dosing, and times to angina, ECG evidence of myocardial ischemia, and frequency of anginal episodes) were also significantly longer in both ranolazine groups than in the placebo groups.

In the third trial, Efficacy of Ranolazine in Chronic Angina (ERICA) [143], ranolazine was evaluated versus placebo in 565 patients in whom angina persisted despite maximal doses of amlodipine (10 mg/d). Patients with a 60% stenosis in at least 1 major coronary artery, a stress-induced defect on perfusion imaging, chronic stable

angina for at least 3 months, and at least 3 anginal episodes per week during a 2 week period were randomized to receive either 1.000 mg of ranolazine twice daily or placebo. The primary endpoint of self-reported anginal episodes per week was lower in the ranolazine group than in the placebo group (mean, 2.9 vs 3.3 episodes; $p < 0.028$). A similar effect was seen in all subgroups, including women, elderly patients (age > 65 yr), and patients on ongoing nitrate therapy. Ranolazine was more beneficial in patients who had more than 4.5 anginal episodes per week than in patients who experienced fewer episodes.

Ranolazine use was also studied in patients with unstable angina and non-ST-elevation MI, in the Metabolic Efficiency with Ranolazine for Less Ischemia in Non-ST-Elevation Acute Coronary Syndromes-Thrombolysis in MI (MERLIN-TIMI) 36 trial[145]. This randomized, double-blinded, placebo controlled, multinational clinical trial involved 6.560 patients who presented within 48 hours of ischemic symptoms and who were treated with either intravenous ranolazine followed by sustained-release oral ranolazine (1-000 mg twice daily) or placebo. Although the investigators found no statistically significant difference between groups in the primary efficacy endpoint, they reported a significant reduction in the endpoint of recurrent ischemia in the ranolazine group. In addition, the study revealed a similar reduction in recurrent ischemic complications in the ranolazine group, specifically in 30 day cardiovascular death, MI, severe recurrent ischemia, and positive Holter monitoring for ischemia ($p = 0.55$). Because the investigations revealed no difference in mortality rates or symptomatic arrhythmia between the 2 groups, but a significant reduction or recurrent ischemia in the ranolazine group (13.9%) compared with placebo group (16%) ($p = 0.03$), the results established the safety of ranolazine as antianginal therapy in a large population.

The Antiarrhythmic Effects of Ranolazine

Although clinical data reported some antiarrhythmic effects of ranolazine, actually it is not indicated for the treatment of arrhythmias in patients with IHD.

The complex nature of ranolazine's antiarrhythmic effects is due to its action of inhibiting the late sodium current and the late rectifying potassium channel. Whereas inhibition of the potassium channel increases the action-potential duration, inhibition of the other 2 channels shortens the action potential[146]. This physiologic effect seems to explain the modest increase in QTC interval that was observed in some clinical trials.

In the CARISA trial, the mean increase in QTC was 6.1 ms in the 750 mg ranolazine group and 9.2 ms in the 1.000 mg group[143]. Similar increases over the baseline QTC interval were seen in the MARISA trial in all 3 trough-dosing regimens[142]. However, none of the 4 major clinical trials produced evidence of increased percentage of torsades de pointes. The absence of this expected effect is partially explained by the absence of early after depolarization and increased dispersion of ventricular repolarization because both of these electrophysiologic events are often needed to initiate malignant ventricular tachyarrhythmias in the presence of a prolonged QT interval.

In a subgroup analysis of the MERLIN-TIMI 36 trial, the Authors showed that, in comparison with placebo, treatment with ranolazine resulted in fewer episodes of ventricular tachycardia that lasted 8 beats or longer, and in fewer episodes of supraventricular tachycardia and new-onset atrial fibrillation. In addition, there were no differences in the incidence of polymorphic ventricular tachycardia or sudden cardiac death, a concern that had arisen after previous observations of prolonged QT intervals[145,147].

Furthermore, previous experimental studies showed that ranolazine has some antiarrhythmic effect on atrial myocytes[148-153]. Infact, in a small study of 7 patients, ranolazine was initiated soon after atrial fibrillation ablation and was found to be useful in maintaining sinus rhythm[154].

Ranolazine in Heart Failure

In patients with IHD, ranolazine increased regional peak filling rate and regional wall thickening during the isovolumetric relaxation period, indicating improved diastolic function. Of note, this improvement was seen without a concomitant decrease in fractional shortening, indicating no negative inotropic effect of the drug. In the subgroup analysis of the MERLIN-TIMI 36 trial that categorized patients with IHD and heart failure, the Authors divided these patients into 2 groups on the basis of BNP levels and they showed that ranolazine reduced the composite endpoint in patients who had elevated BNP levels[155].

Ranolazine and Diabetes Mellitus

The authors of MERLIN-TIMI[156] and CARISA[143] trials have also looked at the effect of ranolazine in patients suffering from diabetes mellitus, as diabetic patients represent a signifi-

cant proportion of patients suffering from ACS. On inspecting the CARISA trial data, they found that ranolazine worked equally well for patients with and without diabetes mellitus. This was true when looking at either reduction of the number of angina episodes suffered weekly or reduction in use of nitroglycerine consumption. On further interest, they showed that at doses of 750 mg and 1000 mg b.d. over a 12 week period, ranolazine reduced the haemoglobin A1c values compared to placebo, by 0.48% and 0.7% for the respective doses. This reduction was sustained long term (up to 2 years) and was greater in insulin-treated patients. Therefore, it appears that ranolazine may have a beneficial role in this particular subgroup of patients and further studies may be useful. Similar data were also reported in the MERLIN TIMI 36 data in which ranolazine significantly reduced haemoglobin A1c values after 4 months of therapy and reduced the recurrence of ischemia in patients with and without diabetes mellitus[156].

Posology

Ranolazine is available in Europe as 375, 500 and 750 mg in prolonged-release formulations. The recommended initial dose for adults is 375 mg b.d. This should be titrated up to 500 mg b.d. after 2 to 4 weeks, until a maximum of 750 mg b.d. is reached [1,27].

Side Effects

As highlighted in the major clinical trials[142-145], the most commonly occurring are dizziness, headache, constipation, nausea and vomiting, and asthenia. However, the trials have also shown that adverse drug reactions are not a major issue and the majority of patients managed to take ranolazine for several years without difficulty. Furthermore, the manufacturers have advised that caution be applied in patients with a history of congenital long QT syndrome, a family history of long QT syndrome, those with prolonged QTc on routine ECGs, and in patients taking drugs that will prolong the QT.

Official Recommendation for Clinical Use of Ranolazine in EU SmPC (Table I)

On the basis of the data from the clinical trials, the FDA approved ranolazine as a first-line agent in the treatment of chronic stable angina, either as a primary agent or an adjunct to ongoing β-blocker and nitrate therapy.

Ranolazine is not approved for the treatment of ACS: the results of the MERLIN-TIMI 36 trial established the safety and tolerability of the drug in a large cohort but did not provide evidence of its benefit in ACS.

Finally, there are insufficient data to support ranolazine treatment in patients with reduced left ventricular systolic function, and it has not been approved for use in that group. Special warnings and precautions for use ranolazine are reported in the Table I.

Other Clinical Manifestation of Chronic IHD

Microvascular Angina

Microvascular angina is typically characterized by: (1) angina predominantly occurring on effort; (2) "ischemic like" ST segment depression during angina or provocative tests; (3) normal coronary

Table I. Special warnings and precautions for use ranolazine.

Caution should be exercised when prescribing ranolazine to patients in whom an increased exposure is expected:

- Concomitant administration of moderate CYP3A4 inhibitors
- Concomitant administration of P-glycoprotein inhibitors
- Mild hepatic impairment
- Mild to moderate renal impairment (creatinine clearance 30-80 ml/min)
- Elderly
- Patients with low weight (≤ 60 kg)
- Patients with moderate to severe cardiac heart failure (NYHA Class III-IV)

Drug-interactions:

- Ranolazine with a dose of 750 mg twice daily increased plasma concentrations of metoprolol by 1.8-fold. Therefore the exposure to metoprolol or other CYP2D6 substrates (e.g. propafenone and flecainide or, to a lesser extent, tricyclic antidepressants and antipsychotics) may be increased during co-administration with ranolazine, and lower doses of these medicinal products may be required.
- Simvastatin metabolism and clearance are highly dependent on CYP3A4. Ranolazine with a dose of 1000 mg twice daily increased plasma concentrations of simvastatin 1.4 to 1.6 fold. Rhabdomyolysis has been associated with high doses of simvastatin. Limit the dose of simvastatin to 20 mg once daily

arteries at angiography; (4) absence of epicardial coronary artery spasm and of cardiac or systemic diseases known to cause microvascular dysfunction[3,4]. This clinical presentation is also usually defined as cardiac syndrome X both in medical literature and clinical practice[157].

The prevalence and incidence of microvascular angina is also poorly known. However, among patients with chest pain suggestive of transient myocardial ischemia who undergo coronary angiography, 10% to 30% are found to have normal or near normal coronary arteries and no evidence of coronary vasospasm[1].

Pathogenesis

There is still debate about whether microvascular dysfunction is the cause of myocardial ischemia and chest pain in patients presenting with angina and normal coronary arteries. A reduced coronary flow reserve, however, has been consistently reported by several studies using different methods and techniques[158-160]. Both an impaired endothelium-dependend and endothelium-independent vasodilator function and an increased vasoconstrictor activity of coronary resistance arteries may be involved. The mechanisms are still incompletely known, but may include abnormal adrenergic activity, insulin resistance, inflammation and, in women, oestrogen deficiency[157]. There is consensus that enhanced pain perception is present in a group of these patients, which could facilitate chest pain even for mild degrees of myocardial ischemia.

Clinical Presentation

In most cases the features of chest pain do not allow to distinguish patients with microvascular angina from those with obstructive coronary atherosclerosis. Some features of angina, however, strongly suggest microvascular angina, including a prolonged duration of chest pain after interruption of effort and a slow or inconstant response to sublingual nitrates.

Diagnosis

Physical examination is typically unremarkable, whereas ECG-EST shows results largely similar to those observed in patients with obstructive IHD and exercise myocardial perfusion scintigraphy is positive in about half of the patients[161]. The absence of LV contractile abnormalities during echocardiographic stress test, despite the induction of chest pain and ST-segment depression[162], strongly suggests microvascular angina, as does the lack of improvement of exercise induced angina and ST segment changes by short-acting nitrates[163].

Furthermore, the assessment of an impairment of coronary flow reserve in these patients may be performed by transthoracic Doppler recording of LAD, contrast stress echocardiography, CMR or positron emission tomography[164-165].

Prognosis

Prognosis of microvascular angina has consistently been shown to be excellent without an increasing in the risk of major cardiac events[166]. However, several patients with microvascular angina show persistence and even worsening of symptoms over time, with angina attacks becoming more frequent, severe, prolonged, and poorly responsive to drug therapy. Symptoms may considerably restrict patient's daily activities and lead to frequent non invasive, and even invasive, diagnostic investigation, as to emergency room and hospital admissions[166-169].

Treatment

Treatment of microvascular angina is initially based on traditional anti-ischemic drugs (beta-blockers, calcium antagonists and nitrates) in variable combination. In patients with persistent symptoms, benefits have been reported in small studies with the addition of ACE-inhibitors (which may counteract the vasoconstrictive and pro-oxidant effects of angiotensin II), xanthine derivatives (which can favour redistribution of myocardial blood flow towards ischemic areas), statins (which may improve endothelial function), and (in pre-menopausal or menopausal women) estrogens (which may also improve endothelial function). In patients with angina refractory to medical treatment and with evidence of increased pain perception imipramine (which inhibits visceral pain transmission) can be added. Electrical neuromodulatory stimulation was found to reduce the number of angina episodes and might be, therefore, considered in this condition[157].

Vasospastic Angina

Variant angina was first described by Prinzmetal et al in 1959[170]. At its onset variant angina may present typical features of an ACS, due to recurrence of chest pain episodes at rest, although the usual typical short duration suggests the vasospastic nature of angina attacks.

There have been no systematic studies assessing the epidemiology of variant angina, but in a recent study, variant angina was the final diagnosis in about 1.5% of patients admitted because of transient angina attacks[171]. The incidence, however, might be higher in Japanese than in Caucasian people[172].

Pathogenesis

Angiographic studies reported that variant angina has its unique mechanism in occlusive/subocclusive epicardial artery spasm, resulting in transient transmural ischemia[173,174]. The pathogenetic mechanisms of coronary artery spasm are unknown, but an aspecific post-receptorial hyperreactivity to multiple vasoconstrictor stimuli of smooth muscle cells in one or more segments of epicardial coronary arteries has been shown to be responsible for the clinical syndrome[175].

Clinical Presentation

Variant angina should be suspected in patients with angina occurring exclusively or predominantly at rest, without any apparent triggering cause. Angina is usually of short duration (2-5 minutes), sometimes recurs in clusters, frequently shows a typical circadian pattern, with a more frequent occurrence in the early morning or in the night hours, and it promptly responds to short-acting nitrates. Several patients present "hot" and "cold" symptomatic phases, with periods of waxing and waning of symptoms lasting weeks or months. In some cases, however, symptoms can persist for years, reappearing when therapy is withdrawn. Effort tolerance is often well preserved, but exercise is a trigger of coronary artery spasm in about 25% of patients.

In some patients severe ventricular tachyarrhythmias may develop during myocardial ischemic episodes caused by coronary artery spasm. These patients may present syncope or pre-syncope associated with angina and are at risk of sudden death[176,177]. Severe bradyarrhythmias (sinus arrest, atrio-ventricular block) may also occur, in particular in patients with inferior transmural ischemia. Prolonged, unrelieved occlusive spasm, on the other hand, may result in acute MI.

Diagnosis

The clinical diagnosis of variant angina can be confirmed by the documentation of transient ST-segment elevation (≥1 mm) on the standard ECG during an anginal attack. When it is difficult to record standard ECG during a chest pain episode, variant angina can be usually diagnosed by 24-48-hour ambulatory ECG monitoring, which allows also to assess the total ischemic burden and the daily distribution of ischemic episodes, most of which are silent[178]. ECG-EST can allow the diagnosis of vasospastic angina in a minority of patients by inducing reversible ST-segment elevation during or in the recovery phase of exercise.

In about 10% of patients a provocative test of coronary artery spasm is necessary to confirm the diagnosis. Provocative tests of spasm can be performed either non invasively or during coronary angiography and are diagnostic when they induce anginal symptoms with typical ST-segment elevation. Non invasive tests are done mainly by administration of intravenous ergonovine, under careful clinical and ECG monitoring. As an alternative, hyperventilation test can be used, although it has a lower sensitivity. Invasive provocative tests of spasm are usually performed by intracoronary infusion of ergonovine or acetylcholine during angiography[1].

Prognosis

In early studies prognosis of variant angina was found to mainly depend on the presence of multivessel IHD[179]. Subsequent studies, however, showed that sudden death and cardiac arrest, as well as acute MI, may occur also in patients with normal or near-normal epicardial arteries[180,181]. High risk includes multivessel spasm, severe ischemia-related brady- or tachy-arrhythmias, prolonged spasm, in particular when not promptly responding to nitrates, and, finally, spasm refractory to high doses of calcium-antagonists.

Importantly, prognosis of variant angina is strictly dependent on the time of diagnosis. Indeed, most events occur within days or months of symptom onset. Thus a prompt diagnosis is mandatory, even because initiation of medical vasodilator therapy is able to effectively prevent recurrence of spasm and significantly improve long-term prognosis[180].

Treatment

Chronic preventive treatment of variant angina is based mainly on the use of calcium channel blockers (e.g., 240-360 mg/day of verapamil or diltiazem, 60-80 mg/day of nifedipine) and long-acting nitrates (isosorbide dinitrate 20-40 mg, or isosorbide mononitrate 10-20 mg, both twice a day). In about 10% of cases coronary artery spasm may be refractory to standard vasodilator

therapy, although refractoriness is usually limited to brief periods in most patients. Use of very high doses of calcium-antagonists and nitrates (i.e. diltiazem 960 mg/day, or verapamil 800 mg/day, each associated with nifedipine 100 mg and isosorbide dinitrate 80 mg) usually control angina attacks in these periods. In the rare cases in which this treatment is insufficient, the addition of the anti-adrenergic drugs guanethidine or clonidine might be helpful.

Possible benefits have also been suggested from the use of anti-oxidant agents and of statins[181]. PCI with stent implantation at the site of spasm (even in the absence of significant stenosis) has also been reported to facilitate control of symptoms and efficacy of drug therapy in these patients[182]. Finally, implantation of an automatic cardioverter defibrillator or a pacemaker is indicated in patients with spasm-related life-threatening tachyarrhythmias or bradyarrhythmias, respectively, when coronary spasm presents a poor or uncertain response to medical therapy.

Anti-Anginal Drugs

Anti-anginal drugs of treatment of patients with chronic IHD include ranolazine, trimetazidine, nicorandil and ivabradine. They can be used in symptomatic patients who do not tolerate beta-blockers or calcium-antagonists. They can also be used in patients who need combination treatment, but are intolerant to the combination of traditional anti-anginal drugs (beta-blockes, calcium channel blocker).

Conclusions

The management of patients with stable IHD has two main objectives: the first objective is to improve prognosis by preventing the ACS and the development of LV dysfunction; the second objective is to minimize or abolish symptoms using anti-anginal drugs or recurring to myocardial revascularization in patients who do not respond to medical treatment. Furthermore, a group of patients with chronic IHD develops angina symptoms refractory to all medical treatment, with a significant reduction of their quality of life. In the clinical practice, ranolazine is a new anti-anginal drug with a great successful in the management of patients with IHD because acting reducing significantly their angina symptoms and improving their quality of life without effecting BP and HR.

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