ANMCO/GICR-IACPR/SICI-GISE Consensus Document: the clinical management of chronic ischaemic cardiomyopathy

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Stable coronary artery disease (CAD) is a clinical entity of great epidemiological importance. It is becoming increasingly common due to the longer life expectancy, being strictly related to age and to advances in diagnostic techniques and pharmacological and non-pharmacological interventions. Stable CAD encompasses a variety of clinical and anatomic presentations, making the identification of its clinical and anatomic features challenging. Therapeutic interventions should be defined on an individual basis according to the patient’s risk profile. To this aim, management flow charts have been reviewed based on sustainability and appropriateness derived from recent evidence. Special emphasis has been placed on non-pharmacological interventions, stressing the importance of lifestyle changes, including smoking cessation, regular physical activity, and diet. Adherence to therapy as an emerging risk factor is also discussed.

Definitions and clinical profiles

For a clear definition of chronic ischaemic cardiopathy (CIC), the most correct approach is to identify the groups of patient suffering from the condition (Figure 1). Among these we can undoubtedly include those who have had prior cardiovascular events, patients who have already undergone percutaneous coronary intervention (PCI) or surgical coronary artery bypass grafting (CABG), and also those patients in whom, despite having no history of acute myocardial infarction (AMI), there are findings of necrosis on the electrocardiogram (ECG) or of localized akinesia on the ECG.

The condition of post-AMI stability is currently defined after 1 year, as established by the EuroHeart Survey. The same interval applies to all patients who have suffered acute ischaemic events.

It is, however, a far more complex issue to consider other subsets, i.e. those of the patients who do not belong to the previous groups and have angina symptoms, evidence of ischaemia at baseline or after an induction test or a coronary angiogram or computed tomography (CT) angiogram finding of coronary stenosis.

The most recent European guidelines concerning CIC include both the known and the suspected form of the condition and therefore characterize different groups of patients: those who are symptomatic for angina or equivalents; those who are asymptomatic but are known to have coronary disease, occlusive or otherwise; and those who report for the first-time symptoms that they have been experiencing for several months (Table 1).

Clinical overview

Angina is one of the main clinical presentations of CIC. The diagnosis of angina is purely clinical and is based on a number of characteristics, such as quality, duration, site, and the precipitating and triggering factors. The various types are:

- Exertional;
- Varying (transient alteration in blood supply due to coronary vasospasm or platelet aggregation, in the absence or presence of atherosclerotic plaques); and
- Cardiac syndrome X (with anatomically normal coronary arteries, caused by a microcirculation disorder, with a good long-term prognosis).

The definition of stable angina uses exclusion criteria (i.e. without the characteristics of unstable angina: onset at rest, appearance <1–2 months previously or with a worsening evolution).

Clinical epidemiology and natural history

Although the survival of patients with CIC is rapidly improving, this condition is the first cause of death due to
cardiovascular disease in both men and women, in whom it is responsible for 27% of deaths. An epidemiological description of CIC is difficult for a number of reasons:

- The data obtained from various randomized controlled trials often do not reflect the real-life patient population.
- Because of the multi-form nature of stable angina, prevalence and incidence vary according to the diagnostic criteria used.

For epidemiological purposes, in order to identify and stage angina symptoms, it is possible to use dedicated questionnaires such as the Rose Angina Questionnaire. There are various other questionnaires or assessment scales that are useful above all for quantifying the severity and incidence of symptoms on patients’ quality of life. These include:

- the angina classification devised by the Canadian Cardiovascular Society (CCSA), which is similar to the New York Heart Association (NYHA) classification for decompensated heart failure;
- the Multidimensional Seattle Angina Questionnaire (SAQ);
- the HeartQoL; and
- the ANMCO Cardiotest (Table 2).

**Incidence**

In Italy, the annual incidence of hospitalization for myocardial infarction (MI) is estimated to be approximately 100,000 cases. The number of isolated CABG procedures carried out in heart surgery units has dropped over time, and the number of PCI procedures has consequently progressively increased.

Incidence

| Table 2 | The ANMCO cardiotest |
|-----------------|------------------------|
| **ANMCO Cardiotest** | **Score** |
| 1. During the past 3 months, when performing your daily activities, have you experienced a feeling of tightness around your chest, chest pain or breathlessness: - while getting dressed or having a bath? - while walking or doing household chores? - only if going upstairs, carrying heavy loads or walking quickly? | NO □ 0 YES □ 3 |
| 2. Over the past month, have you felt of tightness around the chest, chest pain or breathlessness: - become more frequent than in the past - occurred several times over the past two weeks? | NO □ 0 YES □ 3 |
| 3. Have you had to take under the tongue medication (carvinol, Tsetineline, Nei spray) for these disorders? | NO □ 0 YES □ 2 |
| 4. Have you taken medication in the past two weeks? | NO □ 0 YES □ 3 |
| **TOTAL SCORE** | ——— |

N.B. An overall score of 23 indicates that the symptoms are not optimally controlled and, therefore, cardiovascular reassessment is required.

The data available suggest an annual incidence of angina pectoris of 1% in Western male populations aged 45-65 years, with a slightly higher incidence among women. The incidence of stable angina increases progressively with age. However, in men, there is a peak around 55-65 years of age.

**Prevalence**

It is estimated that prevalence in Western countries is 30,000-40,000 cases per million inhabitants. In Italy, we can use the data of the Osservatorio Epidemiologico Cardiovascolare [Cardiovascular, Epidemiology Database (OEC)] and, more recently, those of the OEC/Health Examination Survey, according to which, 30,000 patients per million inhabitants have stable angina, with a higher prevalence among women and on the increase in both sexes.

It is estimated, in any case, that in Italy there are approximately 5,000,000 patients with coronary disease, of whom 1,500,000 with stable angina.

**Prognosis and related variables**

Patients who survive acute coronary syndrome (ACS) or AMI remain at risk of events. In one sub-analysis of the GRACE Registry, total mortality 5 years after ACS was 19.8%, whereas the incidence of new AMIs, stroke, and revascularization procedures was 9.3, 7.7, and 17%, respectively.

The real-life data are slightly more pessimistic, as shown by the Primary Prevention Study.

**Instrumental diagnosis**

**Laboratory diagnostics**

Laboratory diagnostics is useful for determining a possible cause of ischaemia, in order to evaluate cardiovascular risk and for prognostic stratification, by means of the evaluation of:

- haemoglobin and white blood cell levels;
- creatininemia and estimated glomerular filtration rate using the Cockroft-Gault or Modification of Diet in Renal Disease formula;
- glycaemia and glycated haemoglobin (HbA1c);
- total cholesterolamia, HDL, LDL, and triglyceride levels are essential for the assessment of cardiovascular risk, the indication for anti-dystipidaemia treatment, and for assessing the results obtained with treatment;
- myocardial necrosis marker (troponin, preferably with high sensitivity) in the event of a destabilization of the clinical situation; and
- assessment of the thyroid hormones free triiodothyronine, free thyroxine, and thyroid stimulating hormone.

**Instrumental diagnostics for the purpose of prognostic stratification**

Patients with recent acute coronary syndrome

The prognostic stratification of patients with stable angina must take into account the presence or absence of a recent acute episode. Early risk assessment is essential. The variables with a documented prognostic value after an ACS have differing weights: the conventional risk factors have a
poorer long-term predictive capacity than the left ventricular damage parameters. The prognostic indicators after ACS are left ventricular dysfunction, decompensated heart failure (DHF) and, to a lesser extent, the determinants of thrombotic risk.

Patients with an ejection fraction (EF) of <40% and patients with an EF of between 40% and 45%, but with an associated remodelling predictor (either mild mitral insufficiency, restrictive diastolic filling, high asynergy score, or non-dilated ventricle), represent a high-risk subgroup. In the follow-up, it is therefore important to guarantee serial echocardiographic monitoring.

The prognostic importance of the DHF that develops during hospitalization for AMI is well known. It is therefore important to achieve a diagnosis of DHF, which is often underestimated, before the patient is discharged for ACS, as shown by the BLITZ-4 study. DHF developing after an ACS is also associated with an unfavourable prognosis.

In a younger population, the incidence of CHF 1 year after discharge was lower (12.2%); however, the development of DHF was associated with an increase in mortality at 1 year that was four times that of those patients who did not develop it. The indicators of DHF are max Killip class, echocardiographic EF, predictors of remodelling, use of loop diuretics, and, lastly, brain natriuretic peptide level variation.

As far as thrombotic risk is concerned, elements such as initial clinical presentation, the ECG tracing, and biomarkers are strongly predictive of recurrent ischaemic events. In addition, old age, co-morbidities including diabetes mellitus, renal insufficiency, prior stroke/transient ischaemic attack (TIA), peripheral or carotid arterial disease, prior AMI are associated with an increased risk of recurrent ischaemic events.

Scores such as GRACE and TIMI are certainly of help. For patients undergoing a coronary angiogram, certain angiographic parameters can also be used, such as the number of coronary arteries affected by significant stenosis or incomplete revascularization, which increase the risk of recurrence. There are also other scores based on angiographic parameters, such as the SYNTAX, Clinical SYNTAX, SYNTAX II, and ACUITY-PCI scores. These thromboembolic risk assessment parameters must be included in the patient’s discharge papers so that he/she can be referred to a diversified secondary prevention programme (Table 3).

Patients without recent acute coronary syndrome or coronary index event
Clinical assessment, followed by non-invasive instrumental diagnostics that make it possible to evaluate ventricular function and response to stress tests and the severity of the coronary disease, through to invasive imaging, represent the key elements for the stratification of cardiovascular risk.

Risk stratification by clinical assessment. The patient’s history and physical examination provide prognostic information of great importance regarding the risk factors that are known to be predictive of an unfavourable outcome. Other important factors include renal dysfunction, peripheral arterial disease, prior MI, decompensated heart failure, and the severity of angina (Table 4).

| Table 3 | Variables to be considered for patient stratification with recent acute coronary syndrome |
|---|---|
| Predictors of mortality | 
| High Killip class | 
| Ejection fraction < 40% | 
| Ejection fraction ≥ 40 to < 45% with | 
| (i) Restrictive diastolic filling pattern | 
| (ii) Mitral insufficiency | 
| (iii) High WMSI and no ventricular dilation | 
| Significant BNP alteration | 
| Use of loop diuretics | 
| Predictors of recurrence of ischaemia | 
| Peripheral arterial disease or prior stroke/TIA | 
| History of angina or prior myocardial infarction | 
| Diabetes mellitus | 
| Multi-vessel coronary disease | 
| Incomplete revascularisation | 
| Non-revascularized patients | 
| BNP, brain natriuretic peptide; TIA, transient ischaemic attack; WMSI, wall motion score index. | 

In this phase, the presence of ECG alterations at rest, such as evidence of prior MI, left branch bundle block, left anterior hemiblock, left ventricular hypertrophy, second- and third-degree atrioventricular block, or atrial fibrillation, identifies those patients at a higher risk.

Risk stratification by ventricular function assessment. Left ventricular function is the most important predictive factor of long-term survival. The data of the CASS study showed that 12-year survival in patients with EF > 50, between 35-49%, and <35% was 73, 54, and 21% (P < 0.0001), respectively.

The presence of diastolic dysfunction identifies those patients with the worst prognosis in both the early and the later phases.

Special attention must be dedicated to hypertensive and diabetic patients, in whom the ECG makes it possible to identify the presence of hypertrophy and systolic and diastolic left ventricular dysfunction. Asymptomatic ventricular dysfunction is not rare and consequently a resting echocardiogram is recommended for all patients suspected of having stable angina.

Risk stratification by stress testing. The prognostic information that can be obtained through ischaemia induction tests, combined if necessary with imaging techniques, regards not merely the demonstration of ischaemia but also the evaluation of the ischaemic threshold, the extent and the severity of the ischaemia, and functional capacity. In order to predict future events, induction tests must be completed with a clinical assessment. More specifically, symptomatic patients with suspected or confirmed coronary disease should have an induction test for prognostic stratification and the results should constitute the basis for therapeutic decision making for those patients who are candidates for revascularization.

Exercise electrocardiogram. The contribution of the exercise ECG in the risk stratification of symptomatic patients with confirmed or suspected coronary disease has been
extensively demonstrated. For example, the prognosis of patients with a normal exercise ECG and low clinical risk for severe coronary disease is excellent. The exercise test parameters of greatest prognostic value are exercise capacity, blood pressure (BP) response, and the finding of stress-induced ischaemia. One important prognostic indicator is work capacity, which can be measured according to the maximum duration of the exercise, maximum metabolic equivalent level achieved, maximum load expressed in watts, maximum heart rate, and the pressure rate product (heart rate × BP). Indeed, in patients with known coronary disease, 5-year survival is greater in those with greater stress tolerance.

The Duke treadmill score is the most commonly used score for the exercise test, as its prognostic value has been extensively proven. Stress echocardiography. The stress echocardiogram (both physical, which is always recommended due to the greater information it offers, and pharmacological) is effective for the stratification of the risk of future cardiovascular events. Stress myocardial perfusion scintigraphy. It has been demonstrated that a normal scintigraphy study is highly predictive of a favourable prognosis, with an incidence of death and MI at 1 year of <1%. Conversely, the presence of extensive perfusion defects is an unfavourable factor. Patients with reversible stress-induced perfusion defects >10% of the whole myocardium are at high risk and should have a coronary angiogram as soon as possible.

Stress cardiac magnetic resonance. Single studies have shown that there is an independent association between the absence of ischaemia on dobutamine cardiac magnetic resonance and the absence of events during follow-up (up to 3 years). Similar data have also been obtained with adenosine.

**Risk stratification by coronary anatomy assessment.** Computed tomography coronary angiography. Prospective studies have established the independent prognostic value of CT coronary angiogram, due to both the presence and the extent of coronary lesions and the presence of non-occlusive atherosclerotic plaques. Its negative predictive power is especially important. However, international recommendations suggest performing an additional pre-coronary angiogram ischaemia test for patients at high risk on the basis of the CT angiogram but with uncertain symptoms, which gives this technique an ambiguous role.

**Follow-up and the timing of check-ups**

The follow-up strategies in patients with stable angina are often inadequate. While low-risk patients are often subject to unnecessary assessments, high-risk patients have a lower probability of accessing appropriate checks.

For the first year after ACS, where the programme should be individualized and clearly defined in the discharge extract, guidance is provided in a recent international consensus. Another multidisciplinary document has also been produced for patients who recently underwent PCI, which identifies three strategies with decreasing levels of follow-up intensity. For further details and for the three different flow charts, reference should be made to the document in question.

In patients with stable angina and no recent index event, follow-up should focus primarily on secondary prevention, patients’ functional status and on symptoms. In this context, the main player is the general practitioner who should monitor treatment compliance, risk factor correction, and the appearance of new symptoms. On the basis of clinical elements, the cardiologist should establish the most suitable clinical and/or instrumental workup, a specialist consultation with an ECG and routine blood chemistry tests are often sufficient for identifying patients at low risk or at high risk for whom there is an indication for a coronary angiogram without other preliminary investigations, thereby identifying those patients at intermediate risk in whom further instrumental investigations are justified. For clinically stable patients with no recent acute event, a cardiologist consultation with ECG and blood chemistry tests once a year are adequate. After an efficacious elective PCI, the first check-up should take place after ~3 months and thereafter, in the absence of new clinical events, within 1 year.

**Table 4 The Euro Heart Survey prognostic score (Daly)**

| Risk factor                  | Score contribution | Individual score |
|------------------------------|--------------------|------------------|
| Co-morbidity                 |                    |                  |
| No                           | 0                  |                  |
| Yes                          | 86                 |                  |
| Diabetes                     |                    |                  |
| No                           | 0                  |                  |
| Yes                          | 57                 |                  |
| Angina score                 |                    |                  |
| Class I                      | 0                  |                  |
| Class II                     | 54                 |                  |
| Class III                    | 91                 |                  |
| Duration of symptoms         |                    |                  |
| ≥6 months                    | 0                  |                  |
| <6 months                    | 80                 |                  |
| Abnormal ventricular function|                    |                  |
| No                           | 0                  |                  |
| Yes                          | 114                |                  |
| ST depression or T wave inversion on resting electrocardiogram | 0 | |
| Yes                          | 34                 |                  |
|                              | Total              |                  |

The prognostic value of the stress test combined with imaging techniques is greater than that of pharmacologically induced stress tests as it provides information on symptoms and exercise tolerance.
A recent document published by the ANMCO Prevention Area provided guidance on the timing of instrumental investigations. 51

For resting echocardiograms, after the first 6 months from the AMI, where it is useful to monitor the ventricular function and remodelling, its repetition (especially at annual intervals) is of no use in stable patients. 52

Repeating the routine stress test (<2 years from the previous test) is not indicated unless there are changes in the symptoms experienced. After revascularization, in asymptomatic patients, there is no indication to repeat the ischaemia induction test before 2 years in the case of PCI and sooner than 5 years in the case of CABG, except when revascularization is incomplete or new symptoms appear. 53
This applies for both stress ECGs and ischaemia induction tests using imaging techniques.

On the other hand, in the presence of suspected ischaemic symptoms, the CT angiogram can be used to confirm graft patency. 54

**Lifestyle and pharmacological therapy**

**Smoking**

Smoking is a strong independent risk factor in patients with ischaemic cardiopathy.

To resume smoking doubles the risk of having another event at 1 year, whereas stopping smoking leads to a reduction in the risk that is greater than any pharmacological intervention. 55-58

Tobacco dependency is a chronic, relapsing condition. Given these characteristics, smoking addiction requires constant treatment, through counselling, support, and pharmacological therapy. 59-61
The use of medicinal products can be effective, especially in the presence of frequent and violent withdrawal symptoms and those most commonly used are varenicline, bupropion, and nicotine. At the current time, treatment with varenicline is that which has yielded the greatest success. In literature, cutting back on the number of cigarettes has not been associated with a clear reduction in effects.

It is therefore fundamental that smoking be evaluated systematically and objectively using the Fagenstrom test. Counselling should be introduced while the patient is still in hospital and continued at each outpatient clinic appointment. The family environment should also be stimulated to create a smoking-free home.

For patients with high-grade addictions and those who experience frequent relapses, predefined, privileged programmes should be implemented in intensive secondary prevention clinics, ambulatory rehabilitation centres, or in dedicated anti-smoking centres (Table 5).

**Diet**

A correct diet modulates a number of cardiovascular risk factors, thereby playing a crucial role in the prevention of ischaemic relapses. In patients with cardiovascular conditions, the protective effect of the ‘Mediterranean diet’ has been known for some time now.

On the basis of the cornerstones of the ESC guidelines, in accordance with the results of GISSI-Prevenzione study, the following guidelines can be considered (Table 6):

| Table 5  | Suggestions to improve smoking cessation |
|----------|-----------------------------------------|
| 1. Inform all patients on the risks connected to smoking |
| 2. Systematically investigate smoking habits in all patients |
| 3. Assess the degree of dependency using the Fagenstrom test |
| 4. Refer all patients to counselling, also providing adequate training for nursing staff |
| 5. Tell patients that they should go back to their general practitioner if they start smoking again |

| Table 6  | An organic approach to change the lifestyle |
|----------|---------------------------------------------|
| 1. Diet plays an important role in chronic ischaemic cardiomyopathy, as it interferes positively with all the main risk factors, such as diabetes, hypertension, and dyslipidaemia |
| 2. All patients and their families must be informed of the need to follow a correct diet |
| 3. Information must be provided using simple and straightforward language |

**Exercise**

We now have a great amount of evidence supporting the prescription of regular ‘moderate’ exercise, not merely for the prevention of ischaemic heart disease but also as part of a treatment programme after MI, angioplasty, and CABG. 3,62-64 Clinical studies have provided irrefutable evidence on exercise’s capacity to improve physical performance and reduce cardiovascular and all-cause morbidity and mortality. 65,66

The guidelines of all European and American scientific societies therefore include exercise (Class 1A) as one of the cornerstones of secondary prevention, 3,67 recommending between 30 and 60 min of aerobic exercise several times a week, even better once a day. In patients who recently had ACS, aerobic exercise should be recommended at an early phase as part of a structured rehabilitative cardiology programme.

Physical exercise has direct and indirect effects on the cardiovascular system. 68-70 The indirect benefits include a reduction in risk factors, including reduction in stress. The direct benefits include a reduction in heart rate and BP and an increase in cardiac contractility. An increase in coronary blood flow has also been reported. The reduction in resting heart rate is perhaps the most obvious effect of regular physical exercise. The increase in cardiac contractility reduces the dimensions of the ventricles, by reducing wall tension, thereby promoting the perfusion of critical areas of the myocardium.

**Diabetes**

Type 1 diabetes mellitus (DM1) and type 2 diabetes mellitus (DM2) are associated with a significant increase in cardiovascular risk, 71-73 as well as a worse prognosis in patients with CIC, 74 which therefore exposes diabetics to a risk that is similar to that of patients with prior AMI. 75

There is no certain information available regarding the effects of close glycaemic monitoring on the prevention of...
macrovascular complications. To this end, the Action to Control CArdiovascular Risk in Diabetes (ACCORD) study observed a slight increase in mortality in the arm receiving intensive treatment.76

There is, however, a clear positive effect of intensive glycaemia treatment on cardiovascular complications in young diabetic patients, in the absence of chronic vascular alterations secondary to poor glycaemic control.77

However, the greater effects of cardiovascular prevention occur when intensive glycaemic control is combined with an effective control of the other risk factors.78

The medicinal products that act on glycaemia can be broken down into three classes:

1. medicinal products that increase blood insulin levels: insulin, fast and slow insulin analogues, sulfonylureas, metformin, and DipePTyl Peptidase-4 inhibitors;
2. medicinal products that increase insulin sensitivity (metformin and pioglitazone); and
3. glucose absorption inhibitors that work on an intestinal level (carbamide) and on a renal tubule level (sodium glucose co-transporter-2 (SGLT-2) inhibitors).

However, none of the glycaemia-lowering agents have been seen to significantly reduce cardiovascular risk,79 with the exception of metformin in overweight subjects.80

Only recently, empagliflozin, an SGLT-2 inhibitor used in diabetic patients at high cardiovascular risk, was seen to reduce the rates of cardiovascular mortality and non-fatal infarction and stroke, when added to standard therapy.81

Moreover, although close glycaemia monitoring (HbA1c <6.5-7%) is preferable in young subjects with a short history of diabetes, it can be harmful in elderly patients. One aspect of crucial importance would appear to be the treatment of hypercholesterolaemia, with the aim of reaching the target for high-risk patients with an LDL cholesterol value below 70 mg/dL.

Arterial hypertension

Arterial hypertension in Italy is still the second cause of reduced life expectancy. However, the recent ESH/ESC guidelines recommend a target pressure of <140/90 mmHg for all patients, regardless of the risk level,82 therefore including those with CIC. The criticism of the above is based on the following assumptions: it has been proved that the relationship between BP and cardiovascular events is linear and continuous without thresholds for values <115/70 mmHg83; various studies show a reduction in cardiovascular events in the intensive treatment strategy (BP <130 mmHg) compared with the conservative strategy (BP <140 mmHg) without any paradox effect of increase in risk at the lowest systolic BP values achieved.

The optimal BP level in hypertensive patients with cardiovascular events is controversial, especially given the presumed reduction in survival for a significant drop in arterial BP, the so-called J-curve phenomenon, which appears to be important in the elderly people84; however, this remains a subject for debate.85,86

Of the trials designed specifically to evaluate the benefit of intensive BP monitoring (<130 mmHg) in patients with a history of coronary events, the results were positive for the EUROPA87 and CAMELOT88 studies, but negative in the PREVENT, ACTION, and PEACE studies.89-91

In this context, the recent article of Vidal-Petiot et al.92 published in Lancet puts in evidence that it seems to exist a clear J-curve both for systolic and, more importantly, for diastolic BP. These data suggest that in patients with stable coronary artery disease (CAD) and hypertension, a very intensive treatment likely to determinate systolic BP values <120 mmHg and diastolic BP values <70 mmHg were associated with adverse cardiovascular outcomes, also with an increase in mortality.

These observations support the idea that the relationship between a reduction in BP and mortality only interests certain subgroups, and actually, only has a prognostic weight for elderly patients.84,93

In addition, in one meta-analysis of 147 trials, the weight of pharmacological treatment was evident in both primary and secondary prevention, regardless of the clinical or epidemiological settings.94 On the basis of a series of experiences, a recent joint American Heart Association/American College of Cardiology/American Society of Hypertension95 consensus document states that (i) a lower systolic BP is associated with a lower risk of stroke; (ii) the achievement of diastolic BP values between 70 and 79 mmHg would seem to be safe; (iii) a target BP <130/80 mmHg may be appropriate in certain subjects with CIC, prior AMI, stroke or TIA, or ischaemic equivalents, such as carotid atherosclerosis, peripheral arterial disease or abdominal aortic aneurysm (Office B, evidence level B). The recent (Systolic Blood Pressure Intervention Trial (SPRINT) study96 further supports this evidence (Table 7).21

Dyslipidaemia

The role of LDL cholesterol (C-LDL), as both a marker of cardiovascular risk and a therapeutic target, is well known. Statins were seen to be capable of significantly reducing C-LDL with an absolutely favourable risk-benefit assessment.97-100 Lowering mortality and the recurrence of ischaemic events, data that are confirmed by registry studies101 and meta-analyses102,103; however, the higher the basic risk and the levels of C-LDL, the greater the benefit of treatment. For these reasons, the C-LDL target recommended by European guidelines for patients with CIC is 70 mg/dL, or, should this not be possible, a reduction of at least 50%.11,12,104 Statins should be prescribed at the recommended maximum dose or, in any case, the maximum tolerable dose in order to meet the target.104 The use of statins and ezetimibe, the advantages of which were shown by the IMPROVE-IT study105 and implemented by [Italian Medicines Agency] in its circular no.13 must be considered if the statins are not tolerated or if the target is not achieved.104

The very recent American guidelines, on the other hand, have criticized the benefit of achieving specific targets for C-LDL.106 This strategy has been strongly disputed.107 Indeed, treatment compliance is significantly greater in patients with a strategy addressing a specific target.108 A more extensive consideration of the approach to patients...
with dyslipidaemia after acute coronary syndrome and on the emerging role of PCSK9 inhibitors is dealt with in the ANMCO documents currently being published, which should be consulted.

Therefore, from now on, physicians must be aware of the importance of achieving and maintaining the recommended lipid targets.\textsuperscript{109} Non-HDL cholesterol would also appear to have a prognostic importance\textsuperscript{110} and its recommended target value is 100 mg/dL in patients with CIC. In the recent ANMCO/GICR/GISE consensus document,\textsuperscript{21} the Panel agreed that the C-LDL and HDL targets of 70 mg/dL and 100 mg/dL, respectively, remain a fundamental objective to be met and maintained in secondary prevention schemes.

| Table 7 Subgroups of patients in secondary prevention schemes (prior cardiovascular event) for whom it would appear reasonable to set lower blood pressure targets (<130 mmHg) than the usual standard (<140 mmHg) (more intensive therapeutic regimen) |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| Clinical condition | Target (mean BP achieved) | Outcome | Main (level of) evidence | Reference |
| Prior stroke or TIA (5665 patients) | (143 vs. 149 mmHg) | Recurrence of cerebrovascular events | Incidence of non-fatal stroke reduced by 29%, absolute benefit of 29 events per 1000 subjects/3 years | PATS Collaborating Group. Chin Med J (Engl) 1995; 108: 710-717. |
| Prior stroke or TIA (6106 patients) | (132 vs. 141 mmHg) | Recurrence of cerebrovascular events | Reduced incidence of stroke (~28%) and major vascular events (~26%) | PROGRESS Collaborative Group. Lancet 2001;358:1033-1041. |
| High-risk non-diabetic hypertensive patients (1111), >55 years of age with uncontrolled arterial blood pressure (SBP >150 mmHg) despite therapy - additional risk factor. | <130 vs. <140 mmHg | Prevalence of LV hypertrophy on the ECG at 2 years | The drop in BP <130 mmHg did not cause any increase in cardiovascular events (no J-curve effect) | Cardio-Sis Study Group. Lancet 2009;374:525-533. |
| Chronic ischemic cardiomyopathy (subgroup with cardiovascular events vs. subgroup without prior cardiovascular events) | <130 vs. <140 mmHg | Reduction in the composite secondary endpoint of CV events and all-cause mortality. | Parallel reduction in the composite secondary endpoint of CV events and all-cause mortality. | The European Trial on reduction of cardiac events with perindopril in stable coronary artery disease Investigators. Lancet 2003;362:782-788. |
| Chronic ischemic cardiomyopathy (13655 subjects): \* 64% with prior AMI \* 61% with coronary disease, \* 55% prior revascularization | (126 vs. 133 mmHg) | Total mortality, non-fatal AMI, unstable angina, non-resuscitated cardiac arrest | 20% reduction in the RR of the composite endpoint | Cardio-Sis Study Group. Hypertension. 2014;63:475-482. |
| Normal LVEF Subjects at high cardiovascular risk (20% with prior CV event) | <120 vs. <140 mmHg | AMI, ACS, stroke, cardiac insufficiency or death by cardiovascular causes | Reduction (~25%) in the composite endpoint, and reduction (~27%) in total mortality | The SPRINT Research Group. N Engl J Med 2015;373:2103-2116. |
| Chronic ischemic cardiomyopathy: \* Prior AMI \* Prior stroke or TIA \* Ischemic cardiomyopathy equivalents: \* carotid atherosclerosis \* peripheral arterial disease \* abdominal aortic aneurysm | <130 mmHg | Class IIa; evidence level: B | | A Scientific Statement from the American Heart Association, American College of Cardiology, and American Society of Hypertension Journal of the American College of Cardiology, 2015;65: 1998-2038 |

TIA, transient ischaemic attack; BP, blood pressure; SBP, systolic blood pressure; LV, left ventricle; CV, cardiovascular; ECG, electrocardiogram, AMI, acute myocardial infarction; RR, relative risk, ACS, acute coronary syndrome.
On the other hand, no specific target is currently indicated for triglycerides.\textsuperscript{1,104}

**Anti-thrombotic therapy**

**Anti-platelet therapy.** Anti-platelet therapy in patients with CIC has the aim of preventing the risk of ischaemic events, spontaneous or secondary to revascularisation and stenting procedures.

However, it is important to achieve a careful balance between thrombotic and haemorrhagic risk.\textsuperscript{111}

Acetylsalicylic acid (ASA) remains the anti-platelet agent of election in chronic treatment. Monotherapy with ASA at the optimal dose of 75-150 mg/day has been seen to reduce mortality, the incidence of MI, and stroke in patients with CIC, and therefore, it should be initiated and continued indefinitely as soon as the diagnosis has been established.\textsuperscript{112}

In case of allergy or intolerance, ASA should be replaced by clopidogrel at a dose of 75 mg/dL.\textsuperscript{113}

In patients with CIC undergoing coronary angioplasty and stenting, there is an indication for dual anti-platelet therapy (DAT) with ASA and clopidogrel. In patients who are not on treatment with ASA, in the case of coronary angioplasty, it is appropriate to administer a loading dose of 150-300 mg by mouth or 80-150 mg i.v. prior to the procedure, followed by maintenance doses of 75-100 mg a day.\textsuperscript{114} Despite the absence of definitive evidence, in clinical practice, pre-PCI treatment with Clopidogrel is common, at least in patients with non-high haemorrhagic risk. In the case of pre-treatment, a loading dose of 300 mg should be administered at least six hours before the procedure or 600 mg at least two hours beforehand.\textsuperscript{115}

In patients with CIC, it is recommended that DAT be continued for 1 month after procedures with bare metal stents and for 6 months after those involving drug-eluting stents. For new-generation drug-eluting stents, it is possible to contemplate a reduction on the duration of DAT to <6 months in the presence of significant haemorrhagic risk (or in the case of clinically relevant bleeds). It is, in any case, considered reasonable to not suspend DAT earlier than 3 months, except in the case of severe bleeding.\textsuperscript{116,117}

It would appear reasonable to continue DAT for longer than 6 months, e.g. 12 months or even longer, in patients at a high-risk of thrombosis and low risk of haemorrhage\textsuperscript{118}:

- in the case of multiple stents, stents on the proximal left anterior descending artery or left main coronary artery and
- in the presence of diabetes or a history of AMI.

DAP for 30 months reduces intra-stent thrombosis and MI with an increase in moderate bleeds and consequently should only be considered for patients with a low risk of haemorrhage but a high risk of ischaemia. A score is available in order to identify those who may benefit from this strategy: http://www.daptsstudy.org/.

In the presence of ASA allergy or intolerance and the need for double-platelet therapy, it is possible to consider the empirical use of another cyclo-oxidase inhibitor (COX-1), indobufen, at a dose of 200 mg/b.i.d., combined with clopidogrel.

For patients with CIC not undergoing coronary angioplasty or stenting, there is no indication for DAT.

There are few data available on the use of prasugrel and ticagrelor in patients with CIC and it must take into account the aforesaid balance between thrombotic and haemorrhagic risk.\textsuperscript{119}

The only study available at the current time is the PEGASUS study,\textsuperscript{120} which showed that both doses of ticagrelor reduce the rate of cardiovascular mortality, MI, and stroke, but with a higher number of TIMI major bleeds among patients treated with ticagrelor than with placebo (P < 0.001 for both doses vs. placebo). Therefore, for long-term treatment, the lower dose presents equal advantages and better tolerance.

The data of a sub-analysis of the PEGASUS study show that,\textsuperscript{121} in patients with a high thrombotic risk, it may be appropriate to continue treatment with ticagrelor after the first year or, in any case, to recommence within 30 days of suspension, whereas recommencing it after more than 1 year increases bleeds but does not produce any benefit.

The efficacy and safety profiles of ticagrelor were also seen to be similar in both sexes.\textsuperscript{121}

Lastly, the data regarding treatment with ticagrelor in patients with kidney disease are extremely interesting.\textsuperscript{122}

In the PEGASUS study, the relative reduction in the risk of ischaemic events with ticagrelor was seen to be similar for all estimated glomerular filtration rate (eGFR) categories. The relative risk of TIMI major bleeding was also seen to be similar, whereas TIMI minor bleeding increased with a worsening in renal function (P-trend = 0.007). Therefore, patients with severe but non-end-stage renal dysfunction (diyalised patients were excluded from the study) benefited from a greater reduction in absolute risk for ischaemic events with an increase in risk for TIMI major bleeding similar to that of patients with normal eGFR.

Another novel aspect of anti-thrombotic therapy is constituted by vorapaxar (an antagonist of the protease-activated receptor PAR-1 for thrombin), a compound that was tested in the TRAP 2P-TIMI50 study,\textsuperscript{123} with a reduction in ischaemic events but an increase in moderate or severe bleeds and, in addition, a significant increase in intracranial haemorrhages and TRACER,\textsuperscript{124} where the use of vorapaxar was associated with a reduction in the same composite endpoint if used in combination with clopidogrel and as monotherapy.

In short, the above data show that in patients at a high risk of thrombosis, a high risk of ischaemic events persists even in the first few years of what we call CIC. This risk can be reduced using the new forms of anti-thrombotic therapy or by prolonging therapies already used with success in the previous clinical phase, i.e. in the year after an acute coronary syndrome. The use of long-term anti-platelet therapies that are more potent that ASA monotherapy, in patients with CIC nevertheless exposes them to an increase in haemorrhagic complications, which must always be taken into careful consideration when choosing treatment options and regularly reassessed in the follow-up period.

**Anti-ischaemic therapy**

The ESC guidelines for the pharmacological treatment of angina and myocardial ischaemia recommend, as first-line
therapy, the use of short-acting nitrates (taken via the sublingual route) in order to control symptoms (Class I Level B) and the use of beta-blockers and/or calcium channel blockers in order to control heart rate and symptoms (Class I Level A).

As second-line therapy, it is recommended to combine long-acting nitrates (long-acting transdermal or oral products) or ivabradine or nicorandil or ranolazine, depending on heart rate, BP, and the respective tolerance of the various medicinal products (Class IIa Level B).

It is also indicated, in the case of necessity for co-morbidity or intolerance, to use a second-line therapy as first-line in certain patients (Class I Level C) and to also use beta-blockers in asymptomatic patients, provided they have a large inducible ischaemia area (>10%; Class IIa Level C).

In patients with vasospastic angina, it is recommended to use calcium channel blockers or nitrates and to avoid beta-blockers (Class IIa Level B).

**Beta-blockers.** Recent data provided by registries, such as the REACH and the Kaiser Permanente Northern California registries, do not show a lower risk of cardiovascular events, using beta-blockers in stable CAD. In particular, in the REACH, authors concluded that the use of beta-blockers is not protective in reducing mortality both in patients with prior MI and in whom with known CAD without MI, with a reduction, on the other hand, of the rate of recurrent MI and angina. Andersson et al. observed a lower rate of cardiac events, and also a reduction in mortality, associated with the use of beta-blockers, only in the setting of patients with a prior AMI.

For these controversial data, beta-blockers are not indicated for the reduction of cardiac events by ESC guideline of stable CAD of 2013 but only for control of symptoms. Nevertheless, beta-blockers remain a cornerstone for the treatment of this condition in clinical practice and are indicated for reducing events in the presence of decompen-sated heart failure or post-infarction left ventricular dysfunction with EF <40%.

**Calcium channel blockers.** The rationale recommended by the ESC for calcium channel blockers lies, for amlodipine, in the demonstration of efficacy on the tolerance to use in combination with beta-blockers obtained in the CASIS study and for verapamil on the results of the APSIS study in which an equivalence was observed between metoprolol and verapamil in terms of mortality and non-fatal cardiovascular events.

Therefore, given the absence of recent evidence, the ESC’s recommendations should be considered for a use of verapamil in the replacement of beta-blockers, when they are contraindicated or not tolerated, and for amlodipine in combination with beta-blockers.

**Nitrates.** The ESC guidelines on CIC affirm that routine use of long-lasting nitrates must be critically reassessed in all patients, given the tolerance and the ever-increasing evidence concerning the relationship between long-lasting nitrates and endothelial dysfunction.

Therefore, long-lasting nitrates have lost evidence in symptom prophylaxis (IIb), whereas short-acting nitrates remain the choice of election (IB guideline). However, in Italy, about 70% of general practitioners prescribe long-acting nitrates as the treatment of election, which is far higher than the value for Europe, where 44% of prescriptions regard prescriptions for new anti-angina products (ivabradine and ranolazine).

**Ivabradine.** The use of ivabradine in patients with stable ischemic cardiomyopathy was trialled in different studies with positive results. In particular, Borer et al. tested the drug vs. placebo, while Tardif et al. in the INITIATIVE trial and Ruzylo et al. compared ivabradine with atenolol and amlodipine, respectively, showing a non-inferiority profile in terms of efficacy and safety.

In the SIGNIFY study conducted in patients with CIC without decompen-sated heart failure, with an EF >40% and high a heart rate >70 b.p.m., the sinus rhythm with the addition of ivabradine in comparison with standard therapy did not improve outcomes. However, Tendera et al. observed a consistent improvement in self-reported quality of life parameters related to anginapectoris, in particular with a reduction of symptoms frequency and of disease perception. Furthermore, the failure of this study can be partially explained by an excessive decreasing of heart rate, related to the high-dose regime of ivabradine and concomitant use of verapamil and diltiazem.

According to these observations, the association of ivabradine with verapamil and diltiazem is contraindicated for the synergic effect in reducing the heart rate.

These data do not influence the results obtained previously in populations with stable ischemic angina and decompen-sated heart failure or left ventricular dysfunction.

Indeed, in the BEAUTIFUL study, in the predefined subgroup of patients with heart rates >70 b.p.m., treatment with ivabradine reduced the secondary endpoints: hospitalization for fatal and non-fatal MI and myocardial revascularisation. Furthermore, in the subgroup with a heart rate >70 b.p.m. and limiting angina, the same medicinal product also reduced the primary endpoint.

The SHIFT study found that for 67.5% of patients with CIC and decompen-sated heart failure, the medicinal product caused a reduction in the primary composite endpoint of cardiovascular mortality or hospitalization for a worsening in decompen-sated heart failure, due primarily to the reduction in hospitalization for a worsening in decompensated heart failure.

Lastly, in the ASSOCIATE study, ivabradine combined with atenolol was seen to significantly prolong the duration of exercise compared with the placebo.

Ultimately, the use of ivabradine should be considered, in combination with beta-blockers, for patients with CIC and decompen-sated heart failure or left ventricular dysfunction, or as the treatment of election in the case of a contraindication to beta-blockers.

**Ranolazine.** Recently, the RIVER-PCI study, a trial with a number of limitations and without the statistical power to show a reduction in angina symptoms, conducted on patients with chronic angina and incomplete revascularization gave conflicting results by showing an improvement in the
frequency of evident angina at 6 months in diabetics treated with ranolazine and in the more symptomatic patients; however, in both cases the advantage disappeared at 12 months.

Previously, in the MERLIN-TIMI 36 study, ranolazine was seen to reduce recurrent ischaemia after non-ST segment elevation MI,\textsuperscript{141} though without the effects on the composite primary endpoint of cardiovascular mortality, MI, and recurrent ischaemia.

Among the previous studies on the influence of ranolazine on tolerance to exercise, the CARISA study showed that ranolazine in combination with beta-blockers, diltiazem, or amlodipine\textsuperscript{142} compared with placebo obtained a 24\% increase in the duration of exercise without prolonging the time of ST-segment depression onset.

To conclude, the use of ranolazine in chronic ischaemic cardiomyopathy should be considered in combination with beta-blockers and/or calcium channel blockers, especially in patients with severe angina and in diabetics,\textsuperscript{143} or as the treatment of election in patients with contraindications to the use of beta-blockers, taking caution in patients with NYHA Class III–IV decompensated heart failure.

**Conclusions.** In patients with chronic ischaemic cardiomyopathy, anti-ischaemic pharmacological therapy must envisage (Figures 2–4):

- extensive beta-blocker use;
- a critical review of long-acting nitrates and calcium channel blockers;
- the use of ranolazine to control symptoms; and
- the use of ivabradine in patients with decompensated heart failure or left ventricular dysfunction, both as second-line therapy and, sometimes, as first-line treatment.

**Treatment compliance**

**Prescriptive inertia and therapeutic compliance.** There is widespread underuse of the pharmacological treatments recommended in the guidelines for the treatment of CIC.\textsuperscript{144–146} This results in failure to achieve therapeutic objectives and stems from a combination of organizational factors and patient behaviour.\textsuperscript{144–146} The clinical management of the main risk factors would, in any case, appear to be inadequate in current clinical practice, partly due to physicians’ clinical and therapeutic inertia, characterized by:\textsuperscript{147}.

- failure to prescribe the recommended treatments;
- prescription of reduced, potentially inadequate doses; and
- the absence of adequate intervention and effective treatment adjustments.

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**Figure 2** Patient with angina who is not controlled by beta-blocker. HR, heart rate; LA, long-acting; SR, sinus rhythm; LV, left ventricle.

**Figure 3** Patient with angina and contraindications to use of beta-blockers. HR, heart rate; LA, long acting; SR, sinus rhythm; LV, left ventricle.

**Figure 4** Algorithm for optimal management of symptomatic treatment of patients with stable chronic ischaemic cardiomyopathy. HR, heart rate; LA, long-acting; SR, sinus rhythm; LV, left ventricle.
All of this constitutes a key aspect in cardiovascular prevention, by representing an ‘additional hidden risk factor’.148

Patients are considered to be ‘treatment compliant’ when they take 80% of the medication prescribed, ‘partially compliant’ if they take between 20% and 70%, and ‘non-compliant’ if they take <20%.

Dimensions of the phenomenon. Non-compliance is thought to involve 50–60% of patients in primary cardiovascular prevention schemes and 30–40% of those in secondary prevention schemes.148,149

Studies conducted in the USA and Canada suggest that lipid-lowering treatment with statins is interrupted in 30–40% of cases within just 6 months of first prescription.150 Similar data have also been recorded in Italy.151 In clinical studies, the interruption of treatment or intermittent use are determined by a number of factors, which can be divided into 5 categories (Table 8).

Clinical assessment. The evaluation of treatment compliance is usually performed in a direct talk with the patient. This assessment is highly subjective and involves a possible 20–30% overestimate of the real use of medicinal products.148,152 On the contrary, however, problems of non-compliance can be better identified using questionnaires (example in Table 9).

Intervention to improve compliance. Intervention to improve compliance can be broken down into four types153 (Table 10):

1. Intervention regarding prescription, with simplification and modification of drug posology and doses.
2. Patient awareness schemes.
3. Initiatives aimed at changing patients’ individual behaviour.
4. ‘Complex and combined’ initiatives split into different levels and implemented through multidisciplinary integrated approaches.

Overall, the quality of communication and congruous duration of clinical meetings between health care professionals (doctors and nurses) and patients represent the key elements that condition compliance.

Myocardial revascularization

Indications for coronary angiography and coronary angioplasty

Coronary angiography is an invasive technique allowing a direct assessment of the coronary tree. In this context, the radial approach reduces haemorrhagic complications and allows earlier patient mobilization than the femoral approach.

The application of coronary angiography and coronary angioplasty (PCI) should be guided by angina symptoms.

The diagnosis of angina is a ‘clinical’ diagnosis. As indicated in European guidelines,3 it is important to stress that the diagnosis of angina must be primarily clinical, consisting of thorough medical history collection, in order to evaluate symptoms in their full complexity.

The distinction between stable and instable angina is not always well defined in the real world.

There is often a diagnostic delay (>1 month), which can lead to a completely different approach to patient management, by changing the diagnosis from unstable angina to stable angina. In these cases of angina of (relatively) recent onset, a coronary angiogram could be considered as the first investigation.

| Table 8 | Non-compliant factors associated with therapeutic prescriptions |
|---------|---------------------------------------------------------------|
| Patient related | Related to clinical condition | Therapy related | Health service related | Related to socio-economic system |
| • Old age | • Chronic illness | • Frequent administration | • Poor prescribing physician authoritativeness | • Poor academic record |
| • Female | • Multiple co-morbidities | • High number of medicinal products | • Inadequacy of information on the condition and medicinal products | • No spouse |
| • Cognitive, sight or hearing deficits | • Efficacy cannot be assessed | • Uncertainty as to the duration of treatment | • Low income |
| • Depression | • Side effects | • Limited time dedicated to the patient | • Need to contribute to medical expenses |

| Table 9 | Morisky Medication Adherence Scale |
|---------|----------------------------------|
| Morisky scale | |
| (1) Have you ever forgotten to take your medication? | |
| (2) Are you occasionally a bit careless about taking your medication? | |
| (3) When you feel better, do you ever interrupt your therapy? | |
| (4) When you feel worse, do you ever interrupt your therapy? | |
| Each positive response has a score of 0, and each negative response a score of 1. Patients with scores of 0–2 are considered non-compliant, those with scores of 3–4 are considered compliant. | |
| Adapted from Morisky et al.154 | |
The assessment of coronary anatomy has an essential role in prognostic stratification. According to European guidelines, PCI should be guided by coronary anatomy and a 50% stenosis on the left anterior descending artery should be treated, even in patients with atherosclerosis or silent ischaemia (Class I guideline). A recent sub-analysis of the COURAGE trial showed that the anatomical situation assessed by angiogram and EF are predictors of events rather than the size of inducible ischaemia. This said, high-risk patients were excluded from the COURAGE study.

The pretest probability mentioned in European guidelines before proceeding with a coronary angiogram, has certain obvious limits: In accordance with this definition, only male subjects aged >70 years, with typical angina, should be candidates for a coronary angiogram, without having first performed induction tests. In all other cases, a preventive demonstration of ischaemia is indicated. In this model, the only determinants indicated by European guidelines are age, gender, and the typicality of symptoms. These data that dictate pretest probability originate from databases that were not created ad hoc for this diagnostic doubt and they do not always contemplate the presence of clinical risk factors, which undoubtedly increase pretest probability.

The evidence concerning coronary CT as a surrogate for the invasive approach are not univocal and, in addition, no gains in terms of costs were seen in the PROMISE study, which compared coronary CT with functional stress tests in subjects with suspected stable angina.

Nowadays, no coronary angiographic assessment can be considered from a merely anatomical standpoint, but also from a functional one, with an assessment of the fractional flow reserve (FFR). The FFR assessment is an invasive technique that allows the identification of coronary lesions that are functionally significant, despite being angiographically intermediate. European guidelines recommend (Class I) the use of FFR in all cases in which there is an indication for a coronary angiogram without any evidence of ischaemia in the non-invasive tests. Method validation refers to the FAME 1 and 2 trials. Despite the significant critical elements of the above trials, a number of studies have effectively confirmed the validity of the method.

A recent meta-analysis of Johnson showed that a FFR-guided strategy reduces the indication for PCI by 50%, despite significantly reducing both adverse events and angina symptoms. The reliability of FFR has also been seen in left main coronary artery lesions, intra-stent restenosis, CABG, residual stenosis in patients with acute coronary syndrome, and in patients with multi-vessel coronary disease.

At the current time, the procedural risks associated with coronary angiograms and coronary angioplasties are extremely low. One recent American registry (2008-10) reported a cumulative incidence of vascular complications associated with elective diagnostic and interventional procedures performed via a femoral access of 0.8%. Furthermore, in one dedicated study, the radial approach was shown to reduce the incidence of bleeding and vascular complications compared with the femoral approach, especially for major bleeds, by 73%.

The COURAGE study does not reflect the real-world setting and enrolled patients known to have coronary disease. In the COURAGE study, PCI is not associated with a reduction in the risk of death, MI, or other major cardiovascular events compared with optimized medical therapy. However, the trial population was not representative of the real world, as randomization was only performed after patients considered to be at a high risk on the basis of their angiogram findings had been excluded from the study.

The main objective of PCI in stable angina could be (even just) that of providing relief from angina symptoms, by improving the quality of life, despite having a neutral effect on survival.

Angina symptoms and silent ischaemia are important prognostic factors in stable coronary disease, especially if they occur at low loads. In this context, the use of coronary angiography and, even, of PCI could have a merely symptomatic purpose. Although it would not seem to affect mortality, PCI makes it possible to treat ischaemia, improve the quality of life and exercise capacity, and improve prognosis in patients already on optimum medical therapy. This was demonstrated by the RITA-2 and COURAGE trials.

On the basis of these considerations, in accordance with the document issued by GISE, the panel of experts agrees in affirming that:

- in patients with typical angina and multiple cardiovascular risk factors, the first approach can be coronary angiography (Figure 5). Patients with typical angina but at intermediate risk and those with atypical symptoms...
symptoms at high or intermediate risk should have an imaging procedure before proceeding with a coronary angiogram;
• PCI could be indicated in patients with single-vessel coronary disease with critical stenosis and angina with or without evidence of inducible ischaemia (Figures 5 and 6);
• PCI could be indicated in patients with single-vessel coronary disease with intermediate stenosis and evidence of inducible ischaemia (Figure 7);
• In patients with single- or multi-vessel coronary disease with intermediate stenosis in the absence of inducible ischaemia, PCI is indicated if FFR is < 0.80.

Coronary artery bypass grafting
Introduction
The aspects that influence the decision-making process in CIC with an indication for CABG are:

1. benefits expected from the revascularization procedure;
2. site, extent, and complexity of the coronary lesions, which can be evaluated by SYNTAX score and derivatives that are rarely used in clinical practice;
3. the extent of the ischaemic area, left ventricular function, in association with CAD and heart valve disease or with other structural defects;
(4) type of patient, bearing in mind that the risk scores such as the logistic EuroSCORE and STS may overestimate or underestimate the effective risk;
(5) characteristics of the heart surgery facility;
(6) technical elements such as: (i) the use of the double mammary technique, (ii) on-pump bypass vs. off-pump bypass, (iii) complete revascularisation, and (iv) duration of extracorporeal circulation; and
(7) pre-procedural discussion with the patient to establish his/her wishes.

This information, together with the waiting time before the procedure, the mean post-operative hospitalization time and the need for rehabilitation, should be given to the patient in a clear and detailed manner.

**Expected benefit of revascularization obtained by coronary artery bypass grafting**

The aim of coronary artery revascularization is to improve both symptoms and prognosis.

The persistence of angina symptoms, despite optimum medical therapy, concerns about 50% of patients and worsens the quality of life.

**Prognosis is related to the severity of the coronary disease, in terms of the number and the type of vessels involved, the extent of the ischaemic area (>10% of the left ventricle), and ventricular function. These elements represent a strong indication for coronary revascularization** (Table 11).

**Site and size of the coronary lesions**

The anatomical indication for CABG is related to three aspects: lesions on the left main coronary artery (LMCA), lesions on the proximal left anterior descending artery (LAD), and the size and complexity of coronary diseases with a high SYNTAX score.

The most recent relevant European guidelines identify those patients with an indication for CABG. The superiority of CABG over medical therapy, in large, complex lesions, is based on the results of a meta-analysis of the most important randomized clinical trials, which showed a clear reduction in mortality at 5, 7, and 10 years in patients treated with CABG vs. medical therapy, which is more evident in patients with LMCA disease and three-vessel coronary disease.
The study that had the greatest impact on the type of revascularization is the SYNTAX Trial, which confirmed the superiority of CABG vs. PCI in terms of the need for revascularization; however, the two strategies are equivalent with regard to mortality, stroke, and infarction. New-generation stents [everolimus-eluting stents (EES)] were studied in the BEST trial, which reconfirmed the superiority of CABG vs. PCI with EES in patients with multi-vessel disease with complex lesions.\(^{177}\)

| Table 12 | Indications for coronary artery bypass grafting |
|----------|-----------------------------------------------|
| Class\(^a\) | Level\(^b\) |
| Left main coronary artery stenosis | I | B |
| SYNTAX score >32 | I | B |
| Left main coronary artery stenosis with | I | B |
| SYNTAX score 23–32 | I | A |
| Three-vessel coronary disease with | I | A |
| SYNTAX score 23–32 | I | A |
| Three-vessel coronary disease with | I | A |
| SYNTAX score >32 | | |
| Three-vessel coronary disease in | | |
| diabetics | | |
| | | |

Adapted from Windecker et al.\(^{111}\) \(^{a}\)Recommendation class. \(^{b}\)Evidence class.

Myocardial revascularization vs. medical therapy
Myocardial revascularization must not be intended as an alternative to optimal medical therapy (OMT), rather, when indicated, as an essential part of the overall treatment of a patient with CIC, with the aim of further improving prognosis and/or symptoms.

The indication for revascularization in order to improve the prognosis of the individual patient must be based on coronary anatomy, left ventricular function, and the size of the ischaemic area. As far as symptoms are concerned, no solid data are available to support or refute revascularization with a view to prognostic improvement.

Coronary anatomy
More than 50% stenosis of the left main coronary artery: in studies comparing medical therapy and CABG,\(^{179,180}\) the prognostic benefit of revascularization was so evident as to make this anatomical condition an absolute indication for revascularization.

Multi-vessel disease: the evidence obtained by studies comparing CABG and medical therapy\(^{176,181-183}\) have shown an improvement in the survival of revascularized patients only in the presence of three-vessel disease or two-vessel disease involving the proximal left anterior descending artery. The most recent study, the MASS II study, confirmed the prognostic benefit of revascularization, in particular with CABG.\(^{184}\) The recommendation of European guidelines for revascularization of patients with two or three-vessel disease with reduced left ventricular function or decompen- sation is of Class IA.\(^{110}\)

Stenosis of the proximal left anterior descending artery: the presence of critical stenosis in the proximal portion of the left anterior descending artery is prognostically unfavourable; however, there are few studies in this setting. The European guidelines based on the data available,\(^{176,184-186}\) nevertheless, provide a IA recommendation for revascularization in this patient subgroup.\(^{110}\)

Left ventricular function
The presence of a left ventricular dysfunction, in particular an EF of between 35% and 49%, when associated with three-vessel disease pinpoints those patients who could benefit from myocardial revascularization,\(^{176,182-184}\) as shown in the recent STICH trial.\(^{179}\)

Size of the ischaemic area
In the presence of an ischaemic area >10% of the area of the left ventricle revascularization improves and tailored to suit patient needs. The heart team is also responsible for establishing:

- prognostic stratification and clinical classification;
- the technical aspects of the procedure; and
- the waiting time, which should be no more than 2 weeks in the presence of angina with a CCS of three, left main CAD or equivalent, three-vessel coronary disease or depressed left ventricular function;

After this procedure and once the patient’s consent has been obtained, the patient can be put on the waiting list for CABG.

Patient and SCORES
Although even the most recent scores (Logistical EuroSCORE II and STS score) are ineffective for global patient assessment, they are certainly useful for communications between the various members of the heart team and the scientific community.

Characteristics of the heart surgery facility and relations with the heart surgeon
The relationship between the cardiologist and heart surgeon is of paramount importance to the management of patients with chronic ischaemic cardiomyopathy and indications for revascularization; in this context, the heart team must be functional to the institution in which it works

The extent of the ischaemic area, left ventricular function, association of CAD with heart valve disease or with other structural heart defects
Myocardial perfusion scintigraphy is the gold standard for evaluating the extent of the ischaemic area in patients with CIC; coronary revascularization is recommended if the ischaemic area is >10%.\(^ {154}\)

In clinical practice, the stress echocardiogram is the most commonly used imaging test.

Left ventricular dysfunction with EF <35% is a known mortality risk factor; indeed, two studies have confirmed the advantage of revascularization in these patients.\(^ {178}\)

The concomitance of heart valve disease associated with critical stable coronary disease is an indication for combined surgery.

The extent of the ischaemic area is

In the presence of an ischaemic area >10% of the area of the left ventricle revascularization improves.
Table 13 Indications for revascularization in patients with stable ischaemic cardiomyopathy

| Indications to improve prognosis | Classa | Levelb |
|---------------------------------|---------|---------|
| More than 50% stenosis of left main coronary artery | I | A |
| More than 50% stenosis of the proximal left anteriodescending artery | I | A |
| Two- and three-vessel coronary disease with LV dysfunction or decompenated heart failure | I | A |
| Last patent vessel with >50% stenosis | I | C |
| Substantiated large area of ischaemia (>10% of LV) | I | B |

Table 13 lists the indications for revascularization for patients with CIC, taken from the 2013 and 2014 European guidelines. 1,110

Coronary angioplasty vs. coronary artery bypass grafting

The optimal revascularization strategy in patients with chronic ischaemic cardiomyopathy that does not respond to medical therapy or with a significantly sized area of ischaemia was, for many years, considered to be that of surgery. However, the arrival of coronary angioplasty (especially after the advent of drug-eluting stents) has cast doubt on this concept.

The studies. The two most recent studies comparing the two revascularization strategies, the SYNTAX and the FREEDOM studies, redefined the evidence in this sense and deserve a special mention:

• in the SYNTAX study, for which the primary endpoint was death, infarction, stroke, or need for another revascularization procedures, a particular benefit in favour of CABG would seem to emerge in patients with three-vessel coronary disease, in whom a significant reduction in mortality, infarction, and the need for revascularization without an increase in strokes was seen. Another score has been defined that if high or intermediate identifies those patients who benefit most from CABG, unlike a score lower than 23, in which the two revascularization techniques would appear to be equivalent. Conversely, in patients with left main coronary artery stenosis not associated with three-vessel coronary disease, surgical reduction did not reduce either mortality or infarctions, but only the need for revascularization. Two meta-analyses, one of which was published in the JACC and the other in Circulation Journal came to different conclusions. 192,193

• in the FREEDOM study, the results at 5 years showed a significant reduction in the primary endpoint in patients treated with CABG. Again in this study, patients treated with BPAC had a significant excess of stroke.

The registry studies. Registry data, however, tell a different tale. A study conducted on patients with multi-vessel coronary disease treated with CABG or PCI with second-generation drug EES was recently published. 194 At about 3 years, there was no difference in mortality, but a significant increase, in the patients treated with PCI, of the risk of infarction and the need for new revascularization counterbalanced by the significant reduction in the risk of stroke in patients treated with PCI.

The guidelines. On the basis of the SYNTAX study, the ESC guidelines on myocardial revascularization in patients with CIC narrowed the indications for PCI and widened the recommendations for CABG, by assigning a stronger indication for CABG in patients with three-vessel disease, in patients with two-vessel coronary disease involving the proximal left anterior descending artery and in those cases with stenosis of the left main coronary artery in whom the SYNTAX score is >22. The only patients for whom there is a preferential indication for PCI are those with single- and two-vessel coronary disease without the involvement of the proximal left anterior descending artery. 110 It should be noted that the CABG vs. PCI with second-generation stents registry was published after the ESC guidelines.

To conclude, the tendency, in recent years, towards a reduction in PCIs and an increase in CABG could change direction with a more widespread adoption of second generation stents, thanks also to ongoing trials, such as the ISCHEMIA study and studies using modern drug-eluting stents.

Special populations

Elderly patients

The number of elderly patients with ischaemic cardiomyopathy is undergoing a constant increase. 8 Coronary disease in the elderly requires special attention, given the tendency to be more aggressive and widespread.

Most of the cardiovascular risk factors are also present in old age. 1 Moreover, pharmacological and non-pharmacological treatments must take into account aspects concerning treatment compliance and persistence, especially in patients taking many different drugs, the co-morbidities that are most common in the elderly and, lastly, the exclusion of this group of patients from trials. 3
Lifestyle correction remains important, and individualized strategies would be preferable. Dyslipidaemia requires compliance with the same targets as for young patients and the use of statins must be recommended.

Once again with regard to BP monitoring, the benefits identified in young subjects are also expected in the elderly population. However, although the most recent guidelines recommend maintaining a maximum BP of <140 mmHg and a minimum of <90 mmHg in all hypertensive patients, there is no specific evidence for the elderly, for whom the only value provided is a maximum BP of <160 mmHg.

The guidelines recommend annual flu vaccination in elderly patients with CIC.

As far as anti-platelet therapy is concerned, current recommendations suggest a similar use to that of the young population with greater attention dedicated to the gastric damage caused by aspirin and the greater risk of bleeding.

With regard to anti-ischaemic therapy in the elderly people, treatment is similar to that of younger patients with the difference that the likelihood of adverse events is greater, in the same way as there is a higher risk of both haemorrhagic and renal complications, due to the need for invasive procedures. When choosing the revascularization strategy, PCI is often preferable to CABG. In this sense, the TIME study provides evidence as to how interventional therapy can improve symptoms and quality of life compared with medical therapy.

Lastly, ranolazine and ivabradine have been seen to be safe and efficacious in the elderly at the recommended doses, provided they are used with caution in subjects with severe kidney disease.

Women
The female population presents a delay of between 10 and 20 years compared with the male population in the clinical onset of coronary disease. There is evidence that women present greater hypercoagulability, more extensive endothelial dysfunction and smaller vessels, a situation that is further influenced by hormonal and genetic factors. We must also reconsider the opinion that female coronary disease is anatomically less severe than in males, as shown by the WISE study.

Women are characterized by a higher intrahospital complication rate during acute coronary syndrome and invasive procedures. In addition, treatment compliance is poorer and the incidence of depression higher, with a consequent worsening in prognosis.

There has been a great deal of debate on the possibility that hormone replacement therapy might improve the prognosis of chronic ischaemic cardiomyopathy in women. The results of the PEPI and HERS studies are not conclusive.

Diabetic patients
Diabetic patients are a high-risk population, with poorer prognosis.

As far as revascularization strategies are concerned, the BARI Trial compared CABG and PCI with OMT vs. OMT alone, without yielding evidence as to the superiority of either of the two strategies. In addition, in this study, no significant details were observed between glycaemia-lowering medication based on insulin-sensitizing drugs and insulin therapy. As regards the comparison between CABG and PCI in diabetic patients, almost all studies indicate surgical revascularization as being superior, but with an increase in the incidence of non-fatal stroke. As regards PCI, the use of drug-eluting stents vs. bare metal stents reduces the risk of restenosis without modifying cardiovascular mortality and all-cause mortality.

Patients with chronic kidney disease
Chronic kidney disease (CKD) is one of the most common important co-morbidities and one that often poses complex implications in terms of management. CKD is present in ~20% of patients with CIC. The latter condition is, in turn, very common among nephropathic patients. The unfavourable prognostic role of CKD is proportionate to the reduction in GFR, with a higher risk to be attributed to those with a GFR of <15 mL/min/1.73 m² or who are on dialysis. Subjects with CKD also present multiple risk factors that promote particularly aggressive and accelerated atherosclerosis. Vascular calcification is particularly common in the advanced stages of CKD. Statin therapy improves outcome in patients with Stages 2 and 3 CKD and slows down disease progression.

In these patients, caution is required when using iodinated contrast medium and when adapting posology to a reduction in glomerular filtration rate for those medicinal products that are excreted primarily via the kidneys. Generally speaking, the treatments to be used in subjects with CKD and CIC are the same as in the remaining population.

Given the aggressiveness of atherosclerosis in these patients, risk factor treatment must be intensive.

It is necessary to choose statins with the least possible renal excretion in the most advanced forms of CKD, and the simvastatin–ezitimibe combination has been seen to be both efficacious and safe.

As far as ranolazine is concerned, FDA recommends regular GFR monitoring in subjects with moderate/severe CKD.

The data concerning revascularization treatment would appear to be controversial. In general, CABG entails higher periprocedural mortality, a higher probability of starting dialysis in patients with CKD but also a better long-term outcome than treatment with angioplasty.

Patients with chronic lung disease
CIC and chronic lung disease are two conditions that are often associated, in part because they share two extremely important risk factors (age and smoking). In addition, the presence of chronic lung disease is included in all the main patient stratification scores for ischaemic cardiomyopathy (EuroSCORE, SYNTAX, and STS). The data in our possession suggest that the causes of death in patients with chronic lung disease are very often cardiovascular. In addition, the cardiovascular morbidity in patients with COPD is very high, as shown by the Lung Health Study. In this study, a relationship was observed between pulmonary function and risk of cardiovascular death. After all, COPD is known to be an independent risk factor in patients with CIC, leading to a worse prognosis in patients with acute MI treated...
with both PCI and CABG. Restrictive pulmonary disease in particular would appear to be that with the worst prognosis. However, the same study showed that patients with even severe COPD should not be denied the possibility of surgical revascularization.

As far as chronic therapy is concerned, the evidence available currently on cardioselective beta-blockers, which used to be contraindicated, actually improve survival in patients with COPD and ischaemic cardiomyopathy. Similar results were obtained with renin–angiotensin system inhibitors and statins that, in addition to reducing mortality, have also been seen to slow down the deterioration in pulmonary function.

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