European Heart Journal Supplements (2017) **19** (Supplement D), D163–D189
The Heart of the Matter
doi:10.1093/eurheartj/sux021

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

Carmine Riccio (Coordinator)[1]*, Michele Massimo Gulizia, FACC, FESC (Coordinator)[2], Furio Colivicchi, FACC, FESC (Coordinator)[3], Andrea Di Lenarda, FACC, FESC (Coordinator)[4], Giuseppe Musumeci[5], Pompilio Massimo Faggiano[6], Maurizio Giuseppe Abrignani[7], Roberta Rossini[5], Francesco Fattirolli[8], Serafina Valente[9], Gian Francesco Mureddu[10], Pier Luigi Temporelli[11], Zoran Olivari[12], Antonio Francesco Amico[13], Giancarlo Casolo, FACC, FESC[14], Claudio Fresco[15], Alberto Menozzi[16], and Federico Nardi, FACC, FESC[17]

[1]*Cardiovascular Science Department, A.O. Sant'Anna e San Sebastiano, Via Palasciano, 1 81100 Caserta, Italy*
[2]*Department of Cardiology, Ospedale Garibaldi-Nesima, Azienda di Rilievo Nazionale e Alta Specializzazione "Garibaldi", Catania, Italy*
[3]*CCU Unit, Department of Cardiology, Presidio Ospedaliero San Filippo Neri, Rome, Italy*
[4]*Cardiovascular Center, Azienda Sanitaria Universitaria Integrata, Trieste, Italy*
[5]*Cardiology Department, A.O. Santa Croce e Carle, Cuneo, Italy*
[6]*Cardiology Unit, Civili, Spedali, Brescia, Italy*
[7]*CCU Unit, Department of Cardiology, Ospedale Civile Sant'Antonio Abate, Erice, Trapani, Italy*
[8]*Cardiac Rehabilitation Unit, AOU Careggi, Florence, Italy*
[9]*Intensive Integrated Cardiology Department, AOU Careggi, Florence, Italy*
[10]*Cardiology and Cardiac Rehabilitation Department, A.O. San Giovanni-Addolorata, Rome, Italy*
[11]*Cardiac Rehabilitation Unit, Fondazione Salvatore Maugeri, Veruno, Novara, Italy*
[12]*Department of Cardiology, Ospedale Ca' Foncello, Treviso, Italy*
[13]*CCU-Cardiology Unit, Ospedale San Giuseppe da Copertino Hospital, Copertino, Lecce, Italy*
[14]*Cardiology Unit, Nuovo Ospedale Versilia, Lido di Camaiore, Lucca, Italy*
[15]*Cardiology Unit, A.O.U. Santa Maria della Misericordia, Udine, Italy*
[16]*Cardiology Unit, Azienda Ospedaliera Universitaria di Parma, Parma, Italy*
[17]*Cardiology Unit, Ospedale Castelli, Verbania, Italy*

Revised by: Roberto Caporale, Marco Malvezzi Caracciolo, Giovanna Geraci, Alfredo Marchese, Roberto Pedretti, and Guerrino Zuin

Consensus Document Aproval Faculty in appendix

*Corresponding author. Tel: 0823 232362, Fax: 0823 232362, Email: carmine.riccio@tin.it

KEYWORDS
Drug therapy;
Lifestyle modification;
Percutaneous coronary intervention;
Stable coronary artery disease

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 anatomical 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*).[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.[2] 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[3] 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*).

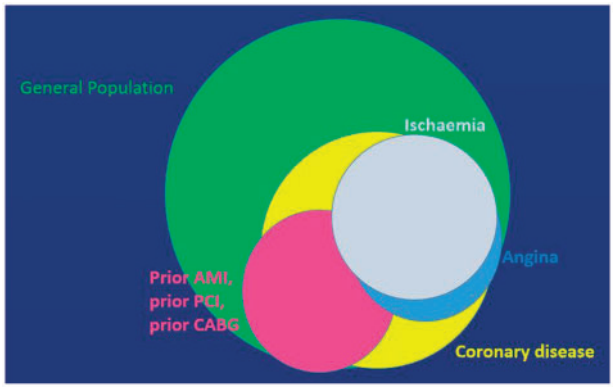

Figure 1 The complex interrelationships between the various components of chronic ischaemic cardiomyopathy.

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

Table 1 Operative definition of chronic ischaemic cardiopathy

- Symptomatic patients with stable angina (or equivalents).
- Patients who are asymptomatic but have clinical or instrumental evidence of prior myocardial infarction or acute coronary syndrome (for over a year).
- Patients who are asymptomatic but have a confirmed diagnosis of occlusive coronary disease (e.g. patients who have already had percutaneous coronary intervention or coronary artery bypass grafting or with coronary angiogram findings of significant stenosis or evidence of ischaemia on the induction tests).

cardiovascular disease in both men and women, in whom it is responsible for 27% of deaths.[4]

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[5];
- the Multidimensional Seattle Angina Questionnaire (SAQ);
- the HeartQoL; and
- the ANMCO Cardiotest[6] (*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.

Table 2 The ANMCO cardiotest

	ANMCO Cardiotest	Score	
1.	During the past 3 months, when performing yor 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 NO ☐ 0 NO ☐ 0	YES ☐ 3 YES ☐ 2 YES ☐ 1
2.	Over the past month, have the feeling 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 NO ☐ 0	YES ☐ 3 YES ☐ 2
3.	Have you had to take under the tongue medication (carvasin, Trinitrine, Nati 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 ≥3** indicates that the symptoms are not optimally controlled and, therefore, cardiological 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.[4,7] The incidence of stable angina increases progressively with age.[7] However, in men, there is a peak around 55–65 years of age.[8]

Prevalence

It is estimated that prevalence in Western countries is 30 000–40 000 cases per million inhabitants.[9] 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.[10]

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.[11]

The real-life data[2,7] are slightly more pessimistic, as shown by the Primary Prevention Study.[12]

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[13,14];
- creatininaemia and estimated glomerular filtration rate using the Cockroft–Gault or Modification of Diet in Renal Disease formula[15];
- glycaemia and glycated haemoglobin (HbA1c)[16,17].
- total cholesterolaemia, HDL, LDL, and triglyceride levels are essential for the assessment of cardiovascular risk, the indication for anti-dyslipidaemia treatment, and for assessing the results obtained with treatment[18,19];
- 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.[20] The prognostic indicators after ACS are left ventricular dysfunction, decompensated heart failure (DHF) and, to a lesser extent, the determinants of thrombotic risk.[21]

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.[22,23] 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.[24]

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.[25-27] Scores such as GRACE and TIMI[28,29] 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,[30] Clinical SYNTAX, SYNTAX II, and ACUITY-PCI scores.[31,32] 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*).

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.

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.[33]

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.[33] Other important factors include renal dysfunction, peripheral arterial disease, prior MI, decompensated heart failure, and the severity of angina (*Table 4*).

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[34] 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.[35]

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[36] 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

Table 4 The Euro Heart Survey prognostic score (Daly)

Score sheet to calculate risk score for patients presenting with stable angina		
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		
No	0	
Yes	34	
		Total =

extensively demonstrated. For example, the prognosis of patients with a normal exercise ECG and low clinical risk for severe coronary disease is excellent.[37] 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.[38]

The Duke treadmill score is the most commonly used score for the exercise test, as its prognostic value has been extensively proven.[39]

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.[40,41]

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%.[42] 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.[43] 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.

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).[44] Similar data have also been obtained with adenosine.[45]

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.[46]

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.[47]

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.[48,49]

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 intersociety consensus.[21] 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.[3,50] 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.

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*).

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.

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*):

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[1] 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, mitiglinides, glucagon-like peptide-1 analogues 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 (acarbose) 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 SLGT-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 mmHg[83]; 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 people[84]; 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 EUROPA[87] and CAMELOT[88] 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 by *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 Hypertension[95] 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 (Class IIB, evidence level B). The recent (Systolic Blood Pressure Intervention Trial (SPRINT) study[96] 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 studies[101] and meta-analyses[102,103]; 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%.[1,5,104] 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 study[105] and implemented by AIFA [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

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 patientst)	(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	Reduction in the prevalence of LV hypertrophy. Parallel reduction in the composite secondary endpoint of CV events and all-cause mortality.	**Cardio-Sis** Study Group. *Lancet* 2009;374:525–533.
Chronic ischaemic 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.	The drop in BP < 130 mmHg did not cause any increase in cardiovascular events (no J-curve effect)	**Cardio-Sis** Study Group. *Hypertension*. 2014;63:475–482.
Chronic ischaemic cardiomyopathy (13 655 subjects): • 64% with prior AMI • 61% with coronary disease, • 55% prior revascularization Normal LVEF	(126 vs. 133 mmHg)	Total mortality, non-fatal AMI, instable angina, non-resuscitated cardiac arrest	20% reduction in the RR of the composite endpoint	The European Trial on reduction of cardiac events with perindopril in stable coronary artery disease Investigators. *Lancet* 2003;362:782–788.
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 ischaemic cardiomyopathy: • Prior AMI • Prior stroke or TIA • Ischaemic 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.

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.[109]

Non-HDL cholesterol would also appear to have a prognostic importance[110] and its recommended target value is 100 mg/dL in patients with CIC. In the recent ANMCO/GICR/GISE consensus document,[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.

On the other hand, no specific target is currently indicated for triglycerides.[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.[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.[112] In case of allergy or intolerance, ASA should be replaced by clopidogrel at a dose of 75 mg/dL.[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.[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.[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.[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[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.daptstudy.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-oxygenase 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.[119]

The only study available at the current time is the PEGASUS study,[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,[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.[121]

Lastly, the data regarding treatment with ticagrelor in patients with kidney disease are extremely interesting.[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 (dialysed 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,[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,[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[125] and the Kaiser Permanente Northern California registries,[126] 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.*[126] 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[3] 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 decompensated heart failure or post-infarction left ventricular dysfunction with EF <40%.[127]

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[128] and for verapamil on the results of the APSIS study[129] 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 ischaemic cardiomyopathy was trialled in different studies with positive results. In particular, Borer *et al.*[130] tested the drug vs. placebo, while Tardif *et al.*[131] in the INITIATIVE trial and Ruzyllo *et al.*[132] compared ivabradine with atenolol and amlodipine, respectively, showing a non-inferiority profile in terms of efficacy and safety.

In the SIGNIFY study[133] conducted in patients with CIC without decompensated 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.*[134] observed a consistent improvement in self-reported quality of life parameters related to angina pectoris, 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 ischaemic cardiomyopathy and decompensated heart failure or left ventricular dysfunction.

Indeed, in the BEAUTIFUL[135] 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.[136]

The SHIFT study[137] found that for 67.5% of patients with CIC and decompensated heart failure, the medicinal product caused a reduction in the primary composite endpoint of cardiovascular mortality or hospitalization for a worsening in decompensated heart failure, due primarily to the reduction in hospitalization for a worsening in decompensated heart failure.[138]

Lastly, in the ASSOCIATE study,[139] 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 decompensated 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,[140] 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,[141] though without the effects on the composite primary endpoint of cardiovascular mortality, MI, and recurrent ischaemia.

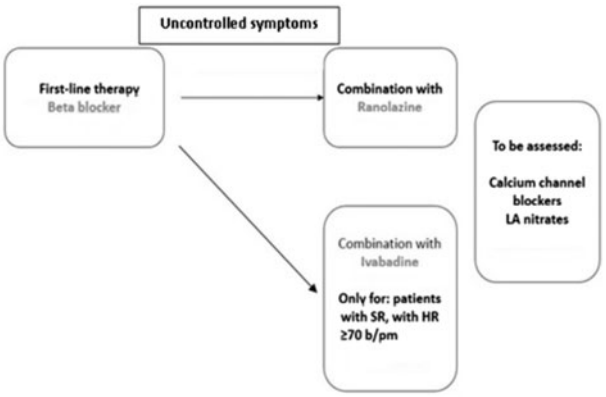

Figure 2 Patient with angina who is not controlled by beta-blocker. HR, heart rate; LA, long-acting; SR, sinus rhythm; LV, left ventricle.

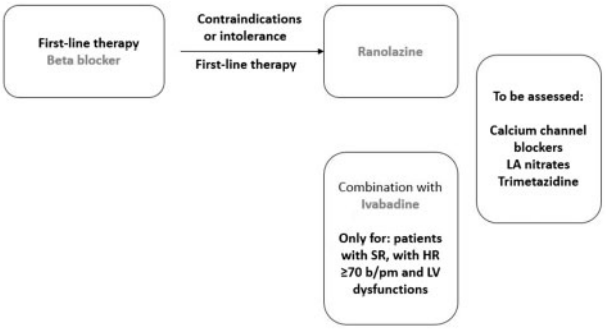

Figure 3 Patient with angina and contraindications to use of beta-blockers. HR, heart rate; LA, long acting; SR, sinus rhythm; LV, left ventricle.

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[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,[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.[144-146] This results in failure to achieve therapeutic objectives and stems from a combination of organizational factors and patient behaviour.[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[147]:

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

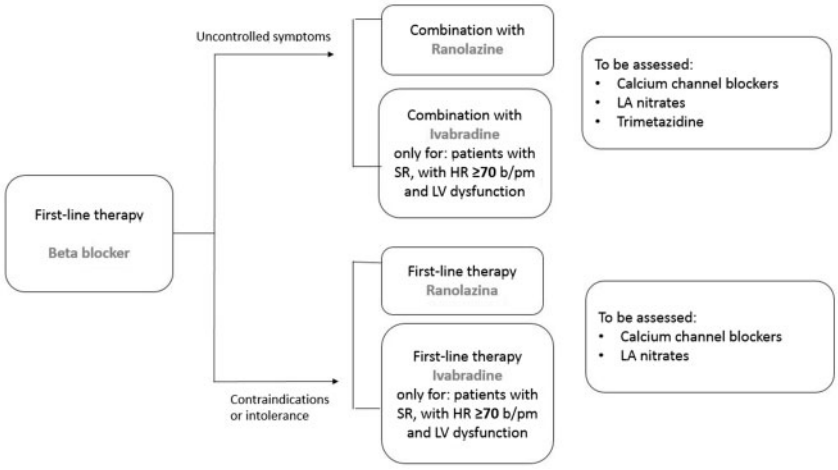

Figure 4 Algorithm for optimal management of symptomatic treatment of patients with stable chronic ischaemic cardiomyopathy. HR, heart rate; LA, long-acting; SR, sinus rhythm; LV, left ventricle.

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 • Female • Cognitive, sight or hearing deficits • Depression	• Chronic illness • Multiple co-morbidities	• Frequent administration • High number of medicinal products • Efficacy cannot be assessed • Side effects	• Poor prescribing physician authoritativeness • Inadequacy of information on the condition and medicinal products • Uncertainty as to the duration of treatment • Limited time dedicated to the patient • Follow-up frequency	• Poor academic record • No spouse • Low income • 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]

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 types[153] (*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 angiogram 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 10 Intervention intended to improve compliance with prescriptions

Changes to therapeutic prescriptions	Training initiatives	Behavioural intervention	Complex intervention
• Reduction in the number of doses • Transdermal administration • Adapt treatment regimen to patient s lifestyle • Facilitate access to medication stocks	• Audiovisual material • Information sheets • Telephone contacts • Mailing	• Short motivational counselling • Frequent check-ups after the beginning of therapy • Use of reminder aids (calendars, diaries, pillboxes, and alarms) • Scheduled residual pill counts • Home visits	• Combination of two or more initiatives belonging to the other categories

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).[3] A recent sub-analysis of the COURAGE trial[154] 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.[155]

The pretest probability mentioned in European guidelines[3] 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.[2] 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.[156,157]

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[3] 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.[158,159] 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.[160] 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.[161–165]

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%.[166] Furthermore, in one dedicated study,[167] 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,[155] 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.[168,169] 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.[171–174] This was demonstrated by the RITA-2 and COURAGE trials.[174,175]

On the basis of these considerations, in accordance with the document issued by GISE,[50] 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

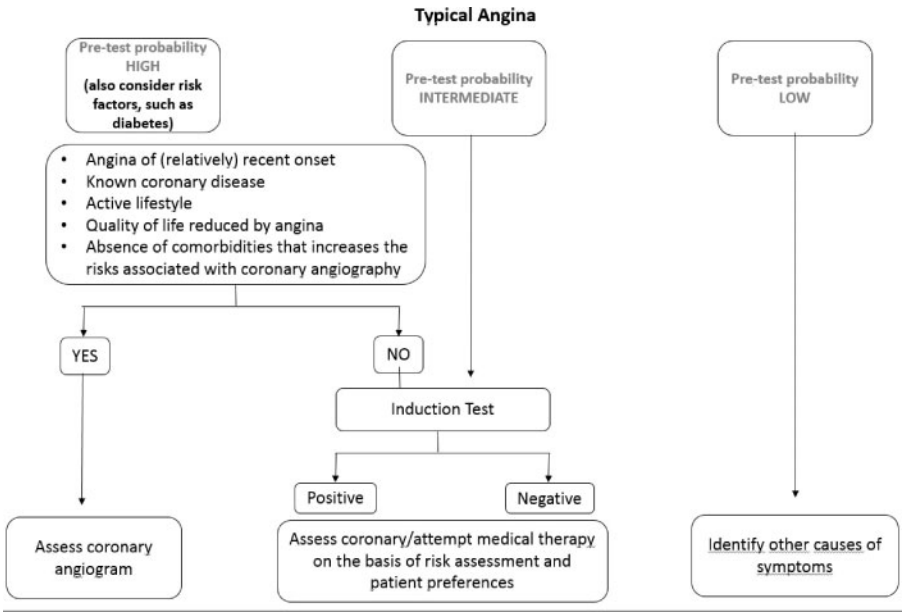

Figure 5 Indications for coronary angiogram in patients with typical angina (coronary artery disease).

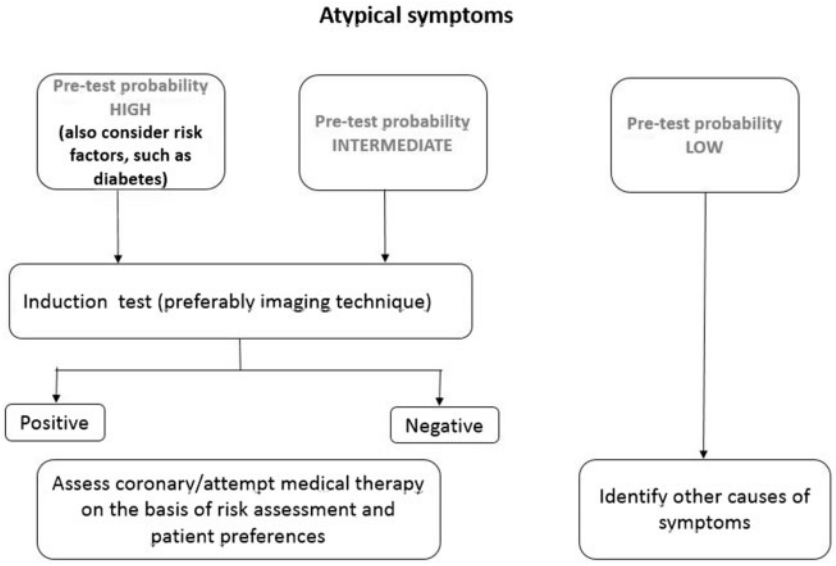

Figure 6 Indications for coronary angiogram in patients with atypical symptoms.

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;

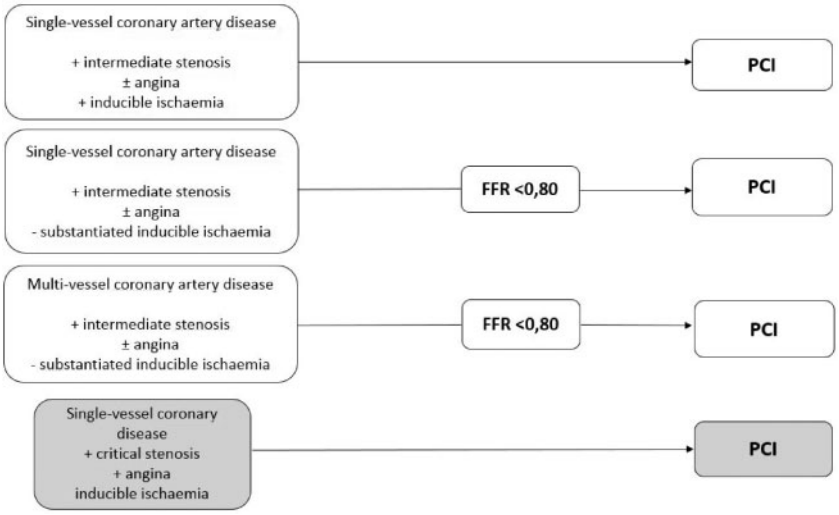

Figure 7 Indications for coronary angioplasty (percutaneous coronary intervention) fractional flow reserve. The white boxes contain the recommendations in agreement with European guidelines; the grey boxes contain the consensus recommendations.

Table 11 Indications for revascularisation in patients with stable angina or silent ischaemia

	Class[a]	Level[b]
More than 50% stenosis of left main coronary artery[c]	I	A
More than 50% stenosi of the proximal left anteriori descending artery	I	A
Two- or three-vessel coronary artery disease with left ventriucular EF $<$ 40%	I	B
Substantiated myocardial ischaemia $>$10% of the left ventricle	I	B
Stenosis $>$50% of only patent vessel[c]	I	C

CAD, coronary artery disease; EF, ejection fraction.
Adapted from Windecker *et al.*[111]
[a]Recommendation class.
[b]Evidence class.
[c]With substantiated ischaemia or fractional flow reserve prognostic reasons $\leq$0.80, if stenosis $<$90%.

(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[110] (*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,[176] 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.

Table 12 Indications for coronary artery bypass grafting

	Class[a]	Level[b]
Left main coronary artery stenosis SYNTAX score >32	I	B
Left main coronary artery stenosis with SYNTAX score 23–32	I	B
Three-vessel coronary disease with SYNTAX score 23–32	I	A
Three-vessel coronary disease with SYNTAX score >32	I	A
Three-vessel coronary disease in diabetics	I	A

Adapted from Windecker *et al.*[111]
[a]Recommendation class.
[b]Evidence class.

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 shows the indications for CABG according to the ESC 2014 guidelines in Class I evidence Levels A and B.[110]

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.

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 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.

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 decompensation 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

Table 13 Indications for revascularization in patients with stable ischaemic cardiomyopathy

	Class[a]	Level[b]
Indications to improve prognosis		
More than 50% stenosis of left main coronary artery	I	A
More than 50% stenosis of the proximal left anteriordescending artery	I	A
Two- and three-vessel coronary disease with LV dysfunction or decompensated heart failure	I	A
Last patent vessel with >50% stenosis	I	C
Substantiated large area of ischaemia (>10% of LV)	I	B
Indications for improving symptoms that are refractory to optimal medical therapy		
Each >50% symptom-related stenosis		

DCH, decompensated heart failure; LV, left ventricle.
Adapted from Montalescot *et al.*[3] and Windecker *et al.*[111]
[a]Recommendation class.
[b]Evidence class.
[c]With fractional flow reserve of 0.80.

prognosis,[43,154,187,188] and this also applies for patients with silent ischaemia,[187] as revealed by the COURAGE study.[154] In the European guidelines, revascularization has Class IB recommendation.[110]

Last patent vessel but with >50% stenosis: even in the absence of evidence, this anatomical context would appear to have such a high risk as to a warrant Class IC indication.[110]

As far as an improvement in symptoms is concerned, for those patients who continue to experience symptoms even in the presence of OMT, revascularization with CABG or PCI is able to improve quality of life.[176,189] In the European guidelines, revascularization has Class IA recommendation.[110]

Table 13 lists the indications for revascularization for patients with CIC, taken from the 2013 and 2014 European guidelines.[3,110]

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.[190,191] 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 comorbidities 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.[195]

As far as anti-platelet therapy is concerned, current recommendations suggest a similar use to that of the younger 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[196] 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.[197] 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.[198]

Women are characterized by a higher intrahospital complication rate during acute coronary syndrome and invasive procedures.[8,199,200] 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[201] and HERS studies are not conclusive.[202]

Diabetic patients

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

As far as revascularization strategies are concerned, the BARI Trial[203] 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.[190,204–208] As regards PCI, the use of drug-eluting stents vs. bare metal stents reduces the risk of restenosis[208] without modifying cardiovascular mortality and all-cause mortality.[209]

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 $\sim$20% of patients with CIC. The latter condition is, in turn, very common among nephropathic patients.[1,3] 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 m^2 or who are on dialysis.[210] 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.[211]

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.[212,213]

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.[214] In addition, the cardiovascular morbidity in patients with COPD is very high, as shown by the Lung Health Study.[215] 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.[216] 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.[216] Similar results were obtained with renin–angiotensin system inhibitors[217] and statins[218] that, in addition to reducing mortality, have also been seen to slow down the deterioration in pulmonary function.

Consensus Document Approval Faculty

Alunni Gianfranco, Amodeo Vincenzo, Angeli Fabio, Aspromonte Nadia, Audo Andrea, Azzarito Michele, Battistoni Ilaria, Bianca Innocenzo, Bisceglia Irma, Bongarzoni Amedeo, Bonvicini Marco, Cacciavillani Luisa, Calculli Giacinto, Caldarola Pasquale, Capecchi Alessandro, Caretta Giorgio, Carmina Maria Gabriella, Casazza Franco, Cassin Matteo, Casu Gavino, Cemin Roberto, Chiarandà Giacomo, Chiarella Francesco, Chiatto Mario, Cibinel Gian Alfonso, Ciccone Marco Matteo, Cicini Maria Paola, Clerico Aldo, D'Agostino Carlo, De Luca Leonardo, De Luca Giovanni, De Maria Renata, Del Sindaco Donatella, Di Fusco Stefania Angela, Di Tano Giuseppe, Egidy Assenza Gabriele, Egman Sabrina, Enea Iolanda, Francese Giuseppina Maura, Gabrielli Domenico, Giardina Achille, Gregorio Giovanni, Iacoviello Massimo, Khoury Georgette, Ledda Antonietta, Lucà Fabiana, Macera Francesca, Marini Marco, Mascia Franco, Masson Serge, Maurea Nicola, Mazzanti Marco, Mennuni Mauro, Menotti Alberto, Mininni Nicola, Molon Giulio, Moreo Antonella, Moretti Luciano, Mortara Andrea, Murrone Adriano, Navazio Alessandro, Nicolosi Gian Luigi, Oliva Fabrizio, Oreglia Jacopo, Parato Vito Maurizio, Parrini Iris, Patanè Leonardo, Pini Daniela, Pino Paolo Giuseppe, Pirelli Salvatore, Procaccini Vincenza, Pugliese Francesco Rocco, Pulignano Giovanni, Radini Donatella, Rao Carmelo Massimiliano, Rasetti Gerardo, Roncon Loris, Ruggieri Maria Pia, Rugolotto Matteo, Sanna Fabiola, Sauro Rosario, Scalvini Simonetta, Scherillo Marino, Severi Silva, Sicuro Marco, Silvestri Paolo, Sisto Francesco, Tarantini Luigi, Themistoclakis Sakis, Uguccioni Massimo, Urbinati Stefano, Vatrano Marco, Vianello Gabriele, and Vinci Eugenio.

Conflict of interest: none declared.

References

1. Perk J, De Backer G, Gohlke H, et al. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). *Eur Heart J* 2012;**33**:1635–1701.
2. Daly CA, De Stavola B, Sendon JL, Tavazzi L, Boersma E, Clemens F, Danchin N, Delahaye F, Gitt A, Julian D, Mulcahy D, Ruzyllo W, Thygesen K, Verheugt F, Fox KM. Predicting prognosis in stable angina: results from the Euro heart survey of stable angina: prospective observational study. *BMJ* 2006;**332**:262–267.
3. Montalescot G, Sechtem U, Achenbach S, et al. 2013 ESC guidelines on the management of stable coronary artery disease. The Task Force on the management of stable coronary artery disease of the European Society of Cardiology. *Eur Heart J* 2013;**34**:2949–3003.
4. National Institutes of Health/National Heart, Lung, and Blood Institute. *Morbidity & Mortality: 2012 Chart Book on Cardiovascular, Lung, and Blood Diseases*. Bethesda, MD: National Heart, Lung, and Blood Institute; 2012.
5. Kaul P, Naylor CD, Armstrong PW, Mark DB, Theroux P, Dagenais GR. Assessment of activity status and survival according to the Canadian Cardiovascular Society angina classification. *Can J Cardiol* 2009;**25**:225–231.
6. Bolognese L, De Luca L, Fattirolli F, Valle R. La cardiopatia ischemica cronica: il problema della valutazione dei sintomi. Una proposta dell'Associazione Nazionale Medici Cardiologi Ospedalieri (ANMCO). *G Ital Cardiol* 2013;**14**:155–163.
7. Hemingway H, Langenberg C, Damant J, Frost C, Pyörälä K, Barrett-Connor E. Prevalence of angina in women versus men a systematic review and meta-analysis of international variations across 31 countries. *Circulation* 2008;**117**:1526–1536.
8. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK. Heart disease and stroke statistics—2015 update. A report from the American Heart Association. *Circulation* 2015;**131**:e29–322.
9. Maddox TM, Reid KJ, Spertus JA, Mittleman M, Krumholz HM, Parashar S, Ho PM, Rumsfeld JS. Angina at 1 year after myocardial infarction: prevalence and associated findings. *Arch Intern Med* 2008;**168**:1310–1316.
10. Giampaoli S, Vanuzzo D. Gruppo del Progetto Osservatorio Epidemiologico Cardiovascolare/Health Examination Survey. La salute cardiovascolare degli italiani. Terzo Atlante Italiano delle Malattie Cardiovascolari—Edizione 2014. *G Ital Cardiol* 2014;**15**:7S–31S.
11. Fox KAA, Carruthers KF, Dunbar DR, Graham C, Manning JR, De Raedt H, Buysschaert I, Lambrechts D, Van de Werf F. Underestimated and under-recognized: the late consequences of acute coronary syndrome (GRACE UK-Belgian Study). *Eur Heart J* 2010;**31**:2755–2764.
12. Rosengren A, Wilhelmsen L, Hagman M, Wedel H. Natural history of myocardial infarction and angina pectoris in a general population sample of middle-aged men: a 16-year follow-up of the Primary Prevention Study, Göteborg, Sweden. *J Intern Med* 1998;**244**:495–505.
13. Lipšic E, Asselbergs FW, van der Meer P, Tio RA, Voors AA, van Gilst WH, Zijlstra F, van Veldhuisen DJ. Anaemia predicts cardiovascular events in patients with stable coronary artery disease. *Neth Heart J* 2005;**13**:254–258.
14. Madjid M, Fatemi O. Components of the complete blood count as risk predictors for coronary heart disease: in-depth review and update. *Tex Heart Inst J* 2013;**40**:17–29.
15. Jurkovitz OT, Abramson JL, Vaccarino LV, Weintraub WS, McClellan WM. Association of high serum creatinine and anemia increases the risk of coronary events: results from the prospective community-based atherosclerosis risk in communities (ARIC) study. *J Am Soc Nefrol* 2003;**11**:2919–2935.
16. Bartnik M, Ryden L, Malmberg K, Ohrvik J, Pyorala K, Standl E, Ferrari R, Simoons M, Soler-Soler J; Euro Heart Survey Investigators. Oral glucose tolerance test is needed for appropriate classification of glucose regulation in patients with coronary artery disease: a report from the Euro Heart Survey on Diabetes and the Heart. *Heart* 2007;**93**:72–77.
17. Ravipati G, Aronow W, Chul A, Sujata K, Saulle LN, Weiss BA. Association of hemoglobin A1c level with the severity of coronary artery disease in patients with diabetes mellitus. *Am J Cardiol* 2006;**7**:968–969.
18. Bhat DL, Steg PG, Hirsh AT, for REACH Registry Investigators. International prevalence, recognition, and treatment of cardiovascular risk factors in outpatients with atherothrombosis. *JAMA* 2006;**295**:180–189.
19. Urbinati S, Olivari Z, Gonzini L. Secondary prevention after acute myocardial infarction: drug adherence, treatment goals, and predictors of health lifestyle habits. The BLITZ-4 Registry. *Eur J Prev Cardiol* 2014;**22**:1548–1556.

20. Berton G, Cordiano R, Cavuto F, Giacomini G, De Toni R, Palatini P. Predictors of ten-year event-free survival in patients with acute-myocardial infarction (from the Adria, Bassano, Conegliano, and Padova Hospitals [ABC] study on myocardial infarction. *Am J Cardiol* 2012;**109**:966–975.
21. Greco C, Bovenzi FM, Berti S, et al. Documento ANMCO/GICR-IACPR/GISEL'organizzazione dell'assistenza nella fase post-acuta delle sindromi coronariche. *G Ital Cardiol* 2014;**15**:3S–27S.
22. Di Chiara A, Fresco C, Savonitto S, Greco C, Lucci D, Gonzini L, Mafrici A, Ottani F, Bolognese L, De Servi S, Boccanelli A, Maggioni AP, Chiarella F. BLITZ-2 Investigators. Epidemiology of non-ST elevation acute coronary syndromes in the Italian cardiology network: the BLITZ-2 study. *Eur Heart J* 2006;**27**:393–405.
23. Kashani A, Giugliano RP, Antman EM, et al. Severity of heart failure, treatments, and outcomes after fibrinolysis in patients with ST-elevation myocardial infarction. *Eur Heart J* 2004;**25**:1702–1710.
24. Ezekowitz JA, Kaul P, Bakal JA, Armstrong PW, Welsh RC, McAlister FA. Declining in-hospital mortality and increasing heart failure incidence in elderly patients with first myocardial infarction. *J Am Coll Cardiol* 2009;**53**:13–20.
25. Thune JJ, Signorovitch JE, Kober L, McMurray JJ, Swedberg K, Rouleau J, Maggioni A, Velazquez E, Califf R, Pfeffer MA, Solomon SD. Predictors and prognostic impact of recurrent myocardial infarction in patients with left ventricular dysfunction, heart failure, or both following a first myocardial infarction. *Eur J Heart Fail* 2011;**13**:148–153.
26. Arnold SV, Smolderen KG, Kennedy KF, Li Y, Shore S, Stolker JM, Wang TY, Jones PG, Zhao Z, Spertus JA. Risk factors for rehospitalization for acute coronary syndromes and unplanned revascularization following acute myocardial infarction. *J Am Heart Assoc* 2015;**4**:e001352.
27. Wilson PW, D'Agostino R Sr, Bhatt DL, Eagle K, Pencina MJ, Smith SC, Alberts MJ, Dallongeville J, Goto S, Hirsch AT, Liau CS, Ohman EM, Röther J, Reid C, Mas JL, Steg PGREACH Registry. An international model to predict recurrent cardiovascular disease. *Am J Med* 2012;**125**:695–703.
28. Fox KA, Dabbous OH, Goldberg RJ, Pieper KS, Eagle KA, Van de Werf F, Avezum A, Goodman SG, Flather MD, Anderson FA Jr, Granger CB. Prediction of risk of death and myocardial infarction in the six months after presentation with acute coronary syndrome: prospective multinational observational study (GRACE). *BMJ* 2006;**333**:1091.
29. Antman EM, Cohen M, Bernink PJ, McCabe CH, Horacek T, Papuchis G, Mautner B, Corbalan R, Radley D, Braunwald E. The TIMI risk score for unstable angina/non-ST elevation MI: a method for prognostication and therapeutic decision making. *JAMA* 2000;**284**:835–842.
30. Sianos G, Morel MA, Kappetein AP, Morice MC, Colombo A, Dawkins K, van den Brand M, Van Dyck N, Russell ME, Mohr FW, Serruys PW. The SYNTAX score: an angiographic tool grading the complexity of coronary artery disease. *EuroIntervention* 2005;**1**:219–227.
31. Garg S, Sarno G, Garcia-Garcia HM, Girasis C, Wykrzykowska J, Dawkins KD; Serruys PWARTS-II Investigators. A new tool for the risk stratification of patients with complex coronary artery disease: the Clinical SYNTAX Score. *Circ Cardiovasc Interv* 2010;**3**:317–326.
32. Palmerini T, Genereux P, Caixeta A, Cristea E, Lansky A, Mehran R, Della Riva D, Fahy M, Xu K, Stone GW. A new score for risk stratification of patients with acute coronary syndromes undergoing percutaneous coronary intervention: the ACUITY-PCI (Acute Catheterization and Urgent Intervention Triage Strategy-Percutaneous Coronary Intervention) risk score. *JACC Cardiovasc Interv* 2012;**5**:1108–1116.
33. Hjemdahl P, Eriksson SV, Held C, Forslund L, Nasman P, Rehnqvist N. Favourable long term prognosis in stable angina pectoris: an extended follow up of the angina prognosis study in Stockholm (APSIS). *Heart* 2006;**92**:177–182.
34. Emond M, Mock MB, Davis KB, Fisher LD, Holmes DR Jr, Chaitman BR, Kaiser GC, Alderman E, Killip T 3rd. Long-term survival of medically treated patients in the Coronary Artery Surgery Study (CASS) Registry. *Circulation* 1994;**90**:2645–2657.
35. Temporelli PL, Giannuzzi P, Nicolosi GL, Latini R, Franzosi MG, Gentile F, Tavazzi L, Maggioni APGISSI-3 Echo Substudy Investigators; Doppler-derived mitral deceleration time as a strong prognostic marker of left ventricular remodeling and survival after acute myocardial infarction: results of the GISSI-3 Echo Substudy. *J Am Coll Cardiol* 2004;**43**:1646–1653.
36. Raymond I, Pedersen F, Steensgaard-Hansen F, Green A, Busch-Sorensen M, Tuxen C, Appel J, Jacobsen J, Atar D, Hildebrandt P. Prevalence of impaired left ventricular systolic function and heart failure in a middle aged and elderly urban population segment of Copenhagen. *Heart* 2003;**89**:1422–1149.
37. Miller TD, Roger VL, Hodge DO, Gibbons RJ. A simple clinical score accurately predicts outcome in a community-based population undergoing stress testing. *Am J Med* 2005;**118**:866–872.
38. Ashley EA, Myers J, Froelicher V. Exercise testing in clinical medicine. *Lancet* 2000;**356**:1592–1597.
39. Mark DB, Shaw L, Harrell FE Jr, Hlatky MA, Lee KL, Bengtson JR, McCants CB, Califf RM, Pryor DB. Prognostic value of a treadmill exercise score in outpatients with suspected coronary artery disease. *N Engl J Med* 1991;**325**:849–853.
40. Chelliah R, Anantharam B, Burden L, Alhajiri A, Senior R. Independent and incremental value of stress echocardiography over clinical and stress electrocardiographic parameters for the prediction of hard cardiac events in new-onset suspected angina with no history of coronary artery disease. *Eur J Echocardiogr* 2010;**11**:875–882.
41. Marwick TH, Case C, Vasey C, Allen S, Short L, Thomas JD. Prediction of mortality by exercise echocardiography: a strategy for combination with the duke treadmill score. *Circulation* 2001;**103**:2566–2571.
42. Brown KA. Prognostic value of thallium-201 myocardial perfusion imaging. A diagnostic tool comes of age. *Circulation* 1991;**83**:363–381.
43. Hachamovitch R, Hayes SW, Friedman JD, Cohen I, Berman DS. Comparison of the short-term survival benefit associated with revascularization compared with medical therapy in patients with no prior coronary artery disease undergoing stress myocardial perfusion single photon emission computed tomography. *Circulation* 2003;**107**:2900–2907.
44. Korosoglou G, Elhmidi Y, Steen H, Schellberg D, Riedle N, Ahrens J, Lehrke S, Merten C, Lossnitzer D, Radeleff J, Zugck C, Giannitsis E, Katus HA. Prognostic value of high-dose dobutamine stress magnetic resonance imaging in 1,493 consecutive patients: assessment of myocardial wall motion and perfusion. *J Am Coll Cardiol* 2010;**56**:1225–1234.
45. Jahnke C, Nagel E, Gebker R, Kokocinski T, Kelle S, Manka R, Fleck E, Paetsch I. Prognostic value of cardiac magnetic resonance stress tests: adenosine stress perfusion and dobutamine stress wall motion imaging. *Circulation* 2007;**115**:1769–1776.
46. Min JK, Dunning A, Lin FY, Achenbach S, Al-Mallah M, Budoff MJ, Cademartiri F, Callister TQ, Chang HJ, Cheng V, Chinnaiyan K, Chow BJ, Delago A, Hadamitzky M, Hausleiter J, Kaufmann P, Maffei E, Raff G, Shaw LJ, Villines T, Berman DS. CONFIRM Investigators. Age- and sex-related differences in all-cause mortality risk based on coronary computed tomography angiography findings results from the International Multicenter CONFIRM (Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter Registry) of 23,854 patients without known coronary artery disease. *J Am Coll Cardiol* 2011;**58**:849–860.
47. Meijboom WB, van Mieghem CA, Mollet NR, Pugliese F, Weustink AC, van Pelt N, Cademartiri F, Nieman K, Boersma E, de Jaegere P, Krestin GP, de Feyter PJ. 64-slice computed tomography coronary angiography in patients with high, intermediate, or low pretest probability of significant coronary artery disease. *J Am Coll Cardiol* 2007;**50**:1469–1475.
48. Mudrick DW, Shah BR, McCoy LA, Lytle BL, Masoudi FA, Federspiel JJ, Cowper PA, Green C, Douglas PS. Patterns of stress testing and diagnostic catheterization after coronary stenting in 250 350 medicare beneficiaries. *Circ Cardiovasc Imaging* 2013;**6**:11–19.
49. Safavi KC, Li SX, Dharmarajan K, Venkatesh AK, Strait KM, Lin H, Lowe TJ, Fazel R, Nallamothu BK, Krumholz HM. Hospital variation in the use of noninvasive cardiac imaging and its association with downstream testing, interventions, and outcomes. *JAMA Intern Med* 2014;**174**:546–553.

50. Marchese A, Rossini R, Basile M, Bedogni F, Danzi GB, Musumeci G, Paradies V, Piccaluga E, Sardella G, Varbella F, Giordano A, Berti S; Italian Society of Invasive Cardiology. [Position paper of the Italian Society of Invasive Cardiology (SICI-GISE) on indications for coronary angiography in patients with stable angina]. *G Ital Cardiol* 2015;**16**:582–589.
51. Cherubini A, Mureddu GF, Temporelli PL, Frisinghelli A, Clavario P, Cesana F, Fattirolli F. Appropriatezza delle procedure diagnostiche in prevenzione cardiovascolare: di che cosa possiamo fare a meno? *G Ital Cardiol* 2014;**15**:582–589.
52. Douglas PS, Garcia MJ, Haines DE, Lai WW, Manning WJ, Patel AR, Picard MH, Polk DM, Ragosta M, Ward RP, Weiner RB; American College of Cardiology Foundation Appropriate Use Criteria Task Force; American Society of Echocardiography; American Heart Association; American Society of Nuclear Cardiology; Heart Failure Society of America; Heart Rhythm Society; Society for Cardiovascular Angiography and Interventions; Society of Critical Care Medicine; Society of Cardiovascular Computed Tomography; Society for Cardiovascular Magnetic Resonance. ACCF/ASE/AHA/ASNC/HFSA/HRS/SCAI/SCCM/SCCT/SCMR 2011 appropriate use criteria for echocardiography. A report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, American Society of Echocardiography, American Heart Association, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, Society of Critical Care Medicine, Society of Cardiovascular Computed Tomography, Society for Cardiovascular Magnetic Resonance American College of Chest Physicians. *J Am Soc Echocardiogr* 2011;**24**:229–267.
53. Wolk MJ, Bailey SR, Doherty JU, Douglas PS, Hendel RC, Kramer CM, Min JK, Patel MR, Rosenbaum L, Shaw LJ, Stainback RF, Allen JM; American College of Cardiology Foundation Appropriate Use Criteria Task Force. ACCF/AHA/ASE/ASNC/HFSA/HRS/SCAI/SCCT/SCMR/STS 2013 multimodality appropriate use criteria for the detection and risk assessment of stable ischemic heart disease: a report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, American Heart Association, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, Society for Cardiovascular Magnetic Reso-nance, and Society of Thoracic Surgeons. *J Am Coll Cardiol* 2014;**63**:380–406.
54. Taylor AJ, Cerqueira M, Hodgson JM, Mark D, Min J, O'Gara P, Rubin GD; American College of Cardiology Foundation Appropriate Use Criteria Task Force.; Society of Cardiovascular Computed Tomography.; American College of Radiology.; American Heart Association.; American Society of Echocardiography.; American Society of Nuclear Cardiology.; North American Society for Cardiovascular Imaging.; Society for Cardiovascular Angiography and Interventions.; Society for Cardiovascular Magnetic Resonance.; Kramer CM, Berman D, Brown A, Chaudhry FA, Cury RC, Desai MY, Einstein AJ, Gomes AS, Harrington R, Hoffmann U, Khare R, Lesser J, McGann C, Rosenberg A, Schwartz R, Shelton M, Smetana GW, Smith SC Jr. ACCF/SCCT/ACR/AHA/ASE/ASNC/NASCI/SCAI/SCMR 2010 appropriate use criteria for cardiac computed tomography. A report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, the Society of Cardiovascular Computed Tomography, the American College of Radiology, the American Heart Association, the American Society of Echocardiography, the American Society of Nuclear Cardiology, the North American Society for Cardiovascular Imaging, the Society for Cardiovascular Angiography and Interventions, and the Society for Cardiovascular Magnetic Resonance. *J Am Coll Cardiol* 2010;**56**:1864–1894.
55. Critchley J, Capewell S. Smoking cessation for the secondary prevention of coronary heart disease. *Cochrane Database Syst Rev* 2004;CD003041.
56. Gerber Y, Rosen LJ, Goldbourt U, Benyamini Y, Drory Y; Israel Study Group on First Acute Myocardial Infarction. Smoking status and long-term survival after first acute myocardial infarction. A population-based cohort study. *J Am Coll Cardiol* 2009;**54**:2382–2387.
57. Critchley JA, Capewell S. Mortality risk reduction with smoking cessation in patients with coronary heart disease. A systematic review. *JAMA* 2003;**290**:86–97.
58. Shah AM, Pfeffer MA, Hartley LH, Moyé LA, Gersh BJ, Rutherford JD, Lamas GA, Rouleau JL, Braunwald E, Solomon SD. Risk of all-cause mortality, recurrent myocardial infarction and heart failure hospitalization associated with smoking status following myocardial infarction with left ventricular dysfunction. *Am J Cardiol* 2010;**106**:911–916.
59. Wood DA, Kotseva K, Connolly S, Jennings C, Mead A, Jones J, Holden A, De Bacquer D, Collier T, De Backer G, Faergeman O; EUROACTION Study Groupon behalf of EUROACTION Study Group. Nurse-coordinated multidisciplinary, family-based cardiovascular disease prevention programme EUROACTION for patients with coronary heart disease and asymptomatic individuals at high risk of cardiovascular disease: a paired, cluster-randomised controlled trial. *Lancet* 2008;**371**:1999–2012.
60. Hajek P, Stead LF, West R, Jarvis M, Hartmann-Boyce J, Lancaster T. Relapse prevention interventions for smoking cessation. *Cochrane Database Syst Rev* 2013;**8**:CD003999.
61. PHS Guideline Update Panel, Liaisons, and Staff. Treating tobacco use and dependence: 2008 update U.S. Public Health Service Clinical Practice Guideline executive summary. *Respir Care* 2008;**53**:1217–1222.
62. Paffenbarger RS Jr, Hyde RT, Wing AL, Hsieh CC. Physical activity, all-cause mortality, and longevity of college alumni. *N Engl J Med* 1986;**314**:605–613.
63. Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F, Bax JJ, Borger MA, Brotons C, Chew DP, Gencer B, Hasenfuss G, Kjeldsen K, Lancellotti P, Landmesser U, Mehilli J, Mukherjee D, Storey RF, Windecker S, Baumgartner H, Gaemperli O, Achenbach S, Agewall S, Badimon L, Baigent C, Bueno H, Bugiardini R, Carerj S, Casselman F, Cuisset T, Erol Ç, Fitzsimons D, Halle M, Hamm C, Hildick-Smith D, Huber K, Iliodromitis E, James S, Lewis BS, Lip GY, Piepoli MF, Richter D, Rosemann T, Sechtem U, Steg PG, Vrints C, Luis Zamorano J; Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology, et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2016;**37**:267–315.
64. Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC), Steg PG, James SK, Atar D, Badano LP, Blömstrom-Lundqvist C, Borger MA, Di Mario C, Dickstein K, Ducrocq G, Fernandez-Aviles F, Gershlick AH, Giannuzzi P, Halvorsen S, Huber K, Juni P, Kastrati A, Knuuti J, Lenzen MJ, Mahaffey KW, Valgimigli M, van 't Hof A, Widimsky P, Zahger D. Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC). ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation The Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC). *Eur Heart J* 2012;**33**:2569–2619.
65. Blair SN, Kohl HW 3rd, Paffenbarger RS Jr, Clark DG, Cooper KH, Gibbons LW. Physical fitness and all-cause mortality. A prospective study of healthy men and women. *JAMA* 1989;**262**:2395–2401.
66. Blair SN, Kampert JB, Kohl HW 3rd, Barlow CE, Macera CA, Paffenbarger RS Jr, Gibbons LW. Influences of cardiorespiratory fitness and other precursors on cardiovascular disease and all-cause mortality in men and women. *JAMA* 1996;**276**:205–210.
67. Fihn SD, Gardin JM, Abrams J, Berra K, Blankenship JC, Dallas AP, Douglas PS, Foody JM, Gerber TC, Hinderliter AL, King SB 3rd, Kligfield PD, Krumholz HM, Kwong RY, Lim MJ, Linderbaum JA, Mack MJ, Munger MA, Prager RL, Sabik JF, Shaw LJ, Sikkema JD, Smith CR Jr, Smith SC Jr, Spertus JA, Williams SV, Anderson JL; American College of Cardiology Foundation/American Heart Association Task Force. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians,

American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *Circulation* 2012;**126**:e354–e471.
68. Shephard RJ, Balady GJ. Exercise as cardiovascular therapy. *Circulation* 1999;**99**:963–972.
69. Wen CP, Wai JP, Tsai MK, Yang YC, Cheng TY, Lee MC, Chan HT, Tsao CK, Tsai SP, Wu X. Minimum amount of physical activity for reduced mortality and extended life expectancy: a prospective cohort study. *Lancet* 2011;**378**:1244–1253.
70. UN. *2011 High Level Meeting on Prevention and Control of Non-Communicable Diseases. General Assembly.* New York, NY: United Nations; 2011.
71. Krolewski AS, Kosinski EJ, Warram JH, Leland OS, Busick EJ, Asmal AC, Rand LI, Christlieb AR, Bradley RF, Kahn CR. Magnitude and determinants of coronary artery disease in juvenile-onset, insulin-dependent diabetes mellitus. *Am J Cardiol* 1987;**59**:750–755.
72. Laing SP, Swerdlow AJ, Slater SD, Burden AC, Morris A, Waugh NR, Gatling W, Bingley PJ, Patterson CC. Mortality from heart disease in a cohort of 23000 patients with insulin-treated diabetes. *Diabetologia* 2003;**46**:760–765.
73. Gu K, Cowie CC, Harris MI. Diabetes and decline in heart disease mortality in US adults. *JAMA* 1999;**281**:1291–1297.
74. Alderman EL, Corley SD, Fisher LD, Chaitman BR, Faxon DP, Foster ED, Killip T, Sosa JA, Bourassa MG. Five-year angiographic follow-up of factors associated with progression of coronary artery disease in the Coronary Artery Surgery Study (CASS). CASS Participating Investigators and Staff. *J Am Coll Cardiol* 1993;**22**:1141–1154.
75. Haffner SM. Coronary heart disease in patients with diabetes. *N Engl J Med* 2000;**342**:1040–1042.
76. Gerstein HC, Miller ME, Byington RP, Goff DC Jr, Bigger JT, Buse JB, Cushman WC, Genuth S, Ismail-Beigi F, Grimm RH Jr, Probstfield JL, Simons-Morton DG, Friedew Ald WT. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med* 2008;**358**:2545–2559.
77. Nathan DM, Cleary PA, Backlund JY, Genuth SM, Lachin JM, Orchard TJ, Raskin P, Zinman B. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *N Engl J Med* 2005;**353**:2643–2653.
78. Gaede P, Lund-Andersen H, Parving HH, Pedersen O. Effect of a multifactorial intervention on mortality in type 2 diabetes. *N Engl J Med* 2008;**358**:580–591.
79. Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, Peters AL, Tsapas A, Wender R, Matthews DR. Management of hyperglycaemia in type 2 diabetes: a patient-centered approach. Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetologia* 2012;**55**:1577–1596.
80. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998;**352**:854–865.
81. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, Mattheus M, Devins T, Johansen OE, Woerle HJ, Broedl UC, Inzucchi SE; EMPA-REG OUTCOME Investigators EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 2015;**373**:2117–2128.
82. Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Böhm M, Christiaens T, Cifkova R, De Backer G, Dominiczak A, Galderisi M, Grobbee DE, Jaarsma T, Kirchhof P, Kjeldsen SE, Laurent S, Manolis AJ, Nilsson PM, Ruilope LM, Schmieder RE, Sirnes PA, Sleight P, Viigimaa M, Waeber B, Zannad F, Redon J, Dominiczak A, Narkiewicz K, Nilsson PM, Burnier M, Viigimaa M, Ambrosioni E, Caufield M, Coca A, Olsen MH, Schmieder RE, Tsioufis C, van de Borne P, Zamorano JL, Achenbach S, Baumgartner H, Bax JJ, Bueno H, Dean V, Deaton C, Erol C, Fagard R, Ferrari R, Hasdai D, Hoes AW, Kirchhof P, Knuuti J, Kolh P, Lancellotti P, Linhart A, Nihoyannopoulos P, Piepoli MF, Ponikowski P, Sirnes PA, Tamargo JL, Tendera M, Torbicki A, Wijns W, Windecker S, Clement DL, Coca A, Gillebert TC, Tendera M, Rosei EA, Ambrosioni E, Anker SD, Bauersachs J, Hitij JB, Caulfield M, De Buyzere M, De Geest S, Derumeaux GA, Erdine S, Farsang C, Funck-Brentano C, Gerc V, Germano G, Gielen S, Haller H, Hoes AW, Jordan J, Kahan T, Komajda M, Lovic D, Mahrholdt H, Olsen MH, Ostergren J, Parati G, Perk J, Polonia J, Popescu BA, Reiner Z, Rydén L, Sirenko Y, Stanton A, Struijker-Boudier H, Tsioufis C, van de Borne P, Vlachopoulos C, Volpe M, Wood DA. 2013 ESH/ESC Guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J* 2013;**34**:2159–2219.
83. Lewington S, Clarke R, Qizilbash N, Peto R, Collins RProspective Studies Collaboration.; Age-specific relevance of usual blood pressure to vascular mortality: ameta-analysis of individual data of one million adults in 61 prospective studies. *Lancet* 2002;**360**:1903–1913.
84. Aronow WS, Fleg JL, Pepine CJ, Artinian NT, Bakris G, Brown AS, Ferdinand KC, Forciea MA, Frishman WH, Jaigobin C, Kostis JB, Mancia G, Oparil S, Ortiz E, Reisin E, Rich MW, Schocken DD, Weber MA, Wesley DJ, Harrington RA; ACCF Task Force. ACCF/AHA 2011 expert consensus document on hypertension in the elderly: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents. *Circulation* 2011;**123**:2434–2506.
85. Denardo SJ, Gong Y, Nichols WW, Messerli FH, Bavry AA, Cooper-Dehoff RM, Handberg EM, Champion A, Pepine CJ. Blood pressure and outcomes in very old hypertensive coronary artery disease patients: an INVEST substudy. *Am J Med* 2010;**123**:719–726.
86. Angeli F, Reboldi G, Verdecchia P. Hypertension and the J-curve phenomenon: implications for tight blood pressure control. *Hypertens Res* 2013;**36**:109–111.
87. The European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease Investigators. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised, double-blind, placebo-controlled, multicentre trial (the EUROPA study). *Lancet* 2003;**362**:782–788.
88. Nissen SE, Tuzcu EM, Libby P, Thompson PD, Ghali M, Garza D, Berman L, Shi H, Buebendorf E, Topol EJ. Effect of antihypertensive agents on cardiovascular events in patients with coronary disease and normal blood pressure: the CAMELOT study: a randomized controlled trial. *JAMA* 2004;**292**:2217–2225.
89. Pitt B, Byington RP, Furberg CD, Hunninghake DB, Mancini GB, Miller ME, Riley W. Effect of amlodipine on the progression of atherosclerosis and the occurrence of clinical events. PREVENT Investigators. *Circulation* 2000;**102**:1503–1510.
90. Poole-Wilson PA, Lubsen J, Kirwan BA, van Dalen FJ, Wagener G, Danchin N, Just H, Fox KA, Pocock SJ, Clayton TC, Motro M, Parker JD, Bourassa MG, Dart AM, Hildebrandt P, Hjalmarson A, Kragten JA, Molhoek GP, Otterstad JE, Seabra-Gomes R, Soler-Soler J, Weber S. Effect of long-acting nifedipine on mortality and cardiovascular morbidity in patients with stable angina requiring treatment (ACTION trial): randomised controlled trial. *Lancet* 2004;**364**:849–857.
91. The PEACE Trial Investigators. Angiotensin-converting-enzyme inhibition in stable coronary artery disease. *N Engl J Med* 2004;**351**:2058–2068.
92. Vidal-Petiot E, Ford I, Greenlaw N, Ferrari R, Fox KM, Tardif JC, Tendera M, Tavazzi L, Bhatt DL, Steg PG; CLARIFY Investigators. Cardiovascular event rates and mortality according to achieved systolic and diastolic blood pressure in patients with stable coronary artery disease: an international cohort study. *Lancet* 2016;2142–2152.
93. Messerli FH, Mancia G, Conti CR, Hewkin AC, Kupfer S, Champion A, Kolloch R, Benetos A, Pepine CJ. Dogma disputed: can aggressively lowering blood pressure in hypertensive patients with coronary artery disease be dangerous? *Ann Intern Med* 2006;**144**:884–893.
94. Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. *BMJ* 2009;**338**:b16652009.
95. Rosendorff C, Lackland DT, Allison M, Aronow WS, Black HR, Blumenthal RS, Cannon CP, de Lemos JA, Elliott WJ, Findeiss L. Treatment of hypertension in patients with coronary artery disease a scientific statement from the American Heart Association,

American College of Cardiology, and American Society of Hypertension. *J Am Coll Cardiol* 2015;**65**:1998–2038.
96. The SPRINT Research Group. A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med* 2015;**373**:2103–2116.
97. Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994;**344**:1383–1389.
98. Sacks FM, Pfeffer MA, Moye LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial Investigators. *N Engl J Med* 1996;**335**:1001–1009.
99. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N Engl J Med* 1998;**339**:1349–1357.
100. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20536 high-risk individuals: a randomised placebo controlled trial. *Lancet* 2002;**360**:7–22.
101. Kulik A, Brookhart MA, Levin R, Ruel M, Solomon DH, Choudhry NK. Impact of statin use on outcomes after coronary artery bypass graft surgery. *Circulation* 2008;**118**:1785–1792.
102. Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C, Kirby A, Sourjina T, Peto R, Collins R, Simes R; Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet* 2005;**366**:1267–1278.
103. Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, Bhala N, Peto R, Barnes EH, Keech A, Simes J, Collins R. Cholesterol Treatment Trialists' (CTT) Collaboration, Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials. *Lancet* 2010;**376**:1670–1681.
104. European Association for Cardiovascular Prevention & Rehabilitation, Reiner Z, Catapano AL, De Backer G, Graham I, Taskinen MR, Wiklund O, Agewall S, Alegria E, Chapman MJ, Durrington P, Erdine S, Halcox J, Hobbs R, Kjekshus J, Filardi PP, Riccardi G, Storey RF, Wood D; ESC Committee for Practice Guidelines (CPG) 2008-2010 and 2010-2012 Committees. ESC/EAS Guidelines for the management of dyslipidaemias: the Task Force for the Management of Dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). *Eur Heart J* 2011;**32**:1769–1818.
105. Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, Darius H, Lewis BS, Ophuis TO, Jukema JW, De Ferrari GM, Ruzyllo W, De Lucca P, Im K, Bohula EA, Reist C, Wiviott SD, Tershakovec AM, Musliner TA, Braunwald E, Califf RM; IMPROVE-IT Investigators; for the IMPROVE-IT Investigators. Ezetimibe added to statin therapy after acute coronary syndromes. *N Engl J Med* 2015;**372**:2387–2397.
106. Goff DC Jr, Lloyd-Jones DM, Bennett G, Coady S, D'Agostino RB, Gibbons R, Greenland P, Lackland DT, Levy D, O'Donnell CJ, Robinson JG, Schwartz JS, Shero ST, Smith SC Jr, Sorlie P, Stone NJ, Wilson PW, Jordan HS, Nevo L, Wnek J, Anderson JL, Halperin JL, Albert NM, Bozkurt B, Brindis RG, Curtis LH, DeMets D, Hochman JS, Kovacs RJ, Ohman EM, Pressler SJ, Sellke FW, Shen WK, Smith SC Jr, Tomaselli GF; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 ACC/AHA Guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 2014;**129(25 Suppl 2)**:S49–S73.
107. Catapano AL, Averna M, Faggiano P, Novo S, a nome della Federazione Italiana di Cardiologia e della Società Italiana per lo Studio dell'Arteriosclerosi, con l'endorsement della European Society of Atherosclerosis e della European Association of Cardiovascular Prevention and Rehabilitation. Nuove linee guida americane 2013 ACC/AHA sul trattamento del colesterolo plasmatico per ridurre il rischio cardiovascolare aterosclerotico: confronto con le raccomandazioni ESC/EAS per la gestione delle dislipidemie. *G Ital Cardiol* 2014;**15**:19–20.
108. Wei L, MacDonald TM, Watson AD, Murphy MJ. Effectiveness of two statin prescribing strategies with respect to adherence and cardiovascular outcomes: observational study. *Pharmacoepidemiol Drug Saf* 2007;**16**:385–392.
109. Degli Esposti L, Sangiorgi D, Arca M, Vigna GB, Buda S, Degli Esposti E. Raggiungimento del target terapeutico nei soggetti avviati al trattamento con statine in pratica clinica. Risultati dallo studio STAR (Statins Target Assessment in Real practice). *Monaldi Arch Chest Dis* 2011;**76**:160–167.
110. Robinson JG, Wang S, Smith BJ, Jacobson TA. Meta-analysis of the relationship between non-high-density lipoprotein cholesterol reduction and coronary heart disease risk. *J Am Coll Cardiol* 2009;**53**:316–322.
111. Windecker S, Kolh P, Alfonso F, Collet JP, Cremer J, Falk V, Filippatos G, Hamm C, Head SJ, Jüni P, Kappetein AP, Kastrati A, Knuuti J, Landmesser U, Laufer G, Neumann FJ, Richter DJ, Schauerte P, Sousa Uva M, Stefanini GG, Taggart DP, Torracca L, Valgimigli M, Wijns W, Witkowski A. 2014 ESC/EACTS Guidelines on myocardial revascularization. *Eur Heart J* 2014;**35**:2541–2619.
112. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 2002;**324**:71–86.
113. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events. *Lancet* 1996;**348**:1329–1339.
114. Patrono C, Andreotti F, Arnesen H, Badimon L, Baigent C, Collet JP, De Caterina R, Gulba D, Huber K, Husted S, Kristensen SD, Morais J, Neumann FJ, Rasmussen LH, Siegbahn A, Steg PG, Storey RF, Vande Werf F, Verheuqt F. Antiplatelet agents for the treatment and prevention of atherothrombosis. *Eur Heart J* 2011;**32**:2922–2932.
115. Steinhubl SR, Berger PB, Mann JT 3rd, Fry ET, DeLago A, Wilmer C, Topol EJ; CREDO Investigators. Clopidogrel for the Reduction of Events During Observation. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. *JAMA* 2002;**288**:2411–2420.
116. Palmerini T, Sangiorgi D, Valgimigli M, Biondi-Zoccai G, Feres F, Abizaid A, Costa RA, Hong MK, Kim BK, Jang Y, Kim HS, Park KW, Mariani A, Della Riva D, Genereux P, Leon MB, Bhatt DL, Bendetto U, Rapezzi C, Stone GW. Short- versus long-term dual antiplatelet therapy after drug-eluting stent implantation: an individual patient data pairwise and network meta-analysis. *J Am Coll Cardiol* 2015;**65**:1092–1102.
117. Colombo A, Chieffo A, Frasheri A, Garbo R, Masotti-Centol M, Salvatella N, Oteo Dominguez JF, Steffanon L, Tarantini G, Presbitero P, Menozzi A, Pucci E, Mauri J, Cesana BM, Giustino G, Sardella G. Second-generation drug-eluting stent implantation followed by 6- versus 12-month dual antiplatelet therapy: the SECURITY randomized clinical trial. *J Am Coll Cardiol* 2014;**64**:2086–2097.
118. Mauri L, Kereiakes DJ, Yeh RW, Driscoll-Shempp P, Cutlip DE, Steg PG, Normand SL, Braunwald E, Wiviott SD, Cohen DJ, Holmes DR Jr, Krucoff MW, Hermiller J, Dauerman HL, Simon DI, Kandzari DE, Garratt KN, Lee DP, Pow TK, Ver Lee P, Rinaldi MJ, Massaro JM; DAPT Study Investigators. Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents. *N Engl J Med* 2014;**371**:2155–2166.
119. Trenk D, Stone GW, Gawaz M, Kastrati A, Angiolillo DJ, Müller U, Richardt G, Jakubowski JA, Neumann FJ. A randomized trial of prasugrel versus clopidogrel in patients with high platelet reactivity on clopidogrel after elective percutaneous coronary intervention with implantation of drug-eluting stents: results of the TRIGGER-PCI (Testing Platelet Reactivity In Patients Undergoing Elective Stent Placement on Clopidogrel to Guide Alternative Therapy With Prasugrel) study. *J Am Coll Cardiol* 2012;**59**:2159–2164.
120. Bonaca MP, Bhatt DL, Cohen M, Steg PG, Storey RF, Jensen EC, Magnani G, Bansilal S, Fish MP, Im K, Bengtsson O, Oude Ophuis T, Budaj A, Theroux P, Ruda M, Hamm C, Goto S, Spinar J, Nicolau JC, Kiss RG, Murphy SA, Wiviott SD, Held P, Braunwald E, Sabatine MS; PEGASUS-TIMI 54 Steering Committee and Investigators. Long-term use of ticagrelor in patients with prior myocardial infarction. *N Engl J Med* 2015;**372**:1791–1800.

121. Bonaca MP, Bhatt DL, Steg PG, Storey RF, Cohen M, Im K, Oude Ophuis T, Budaj A, Goto S, López-Sendón J, Diaz R, Dalby A, Van de Werf F, Ardissino D, Montalescot G, Aylward P, Magnani G, Jensen EC, Held P, Braunwald E, Sabatine MS. Ischaemic risk and efficacy of ticagrelor in relation to time from P2Y12 inhibitor withdrawal in patients with prior MI: insights from PEGASUS-TIMI 54. Eur Heart J 2016;**37**:1133–1142.
122. Magnani G, Storey RF, Steg G, Bhatt DL, Cohen M, Kuder J, Im K, Aylward P, Ardissino D, Isaza D, Parkhomenko A, Goudev AR, Dellborg M, Kontny F, Corbalan R, Medina F, Jensen EC, Held P, Braunwald E, Sabatine MS, Bonaca MP. Efficacy and safety of ticagrelor for long-term secondary prevention of atherothrombotic events in relation to renal function: insights form the PEGASUS-TIMI 54 trial. Eur Heart J 2016;**37**:400–408.
123. Morrow DA, Braunwald E, Bonaca MP. Vorapaxar in the secondary prevention of atherothrombotic events. *N Engl J Med* 2012;**366**:1404–1413.
124. Tricoci P, Lokhnygina Y, Huang Z, Van de Werf F, Cornel JH, Chen E, Wallentin L, Held C, Aylward PE, Moliterno DJ, Jennings LK, White HD, Armstrong PW, Harrington RA, Strony J, Mahaffey KW. Vorapaxar with or without clopidogrel after non-ST-segment elevation acute coronary syndromes: Results from the thrombin receptor antagonist for clinical event reduction in acute coronary syndrome trial. *Am Heart J* 2014;**168**:869–877.
125. Bangalore S, Steg G, Deedwania P, Crowley K, Eagle KA, Goto S, Ohman EM, Cannon CP, Smith SC, Zeymer U, Hoffman EB, Messerli FH, Bhatt DL; REACH Registry Investigators; for the REACH Registry Investigators. Beta-blocker use and clinical outcomes in stable outpatients with and without coronary artery disease. *JAMA* 2012;**308**:1340–1349.
126. Andersson C, Shilane D, Go AS, Chang TI, Kazi D, Solomon MD, Boothroyd DB, Hlatky MA. Beta-blocker therapy and cardiac events among patients with newly diagnosed coronary heart disease. *J Am Coll Cardiol* 2014;**64**:247–252.
127. The CAPRICORN Investigators. Effect of carvedilol on outcome after myocardial infarction in patients with left-ventricular dysfunction: the CAPRICORN randomised trial. *Lancet* 2001;**357**:1385–1390.
128. Davies RF, Habibi H, Klinke WP, Dessain P, Nadeau C, Phaneuf DC, Lepage S, Raman S, Herbert M, Foris K; for CASIS Investigators. Effect of amlodipine, atenolol and their combination on myocardial ischemia during treadmill exercise and ambulatory monitoring. *J Am Coll Cardiol* 1995;**3**:619–625.
129. Rehnqvist N, Hjemdahl P, Billing E, Björkander I, Eriksson SV, Forslund L, Held C, Näsman P, Wallén NH. Effects of metoprolol vs verapamil in patients with stable angina pectoris The Angina Prognosis Study in Stockholm (APSIS). *Eur Heart J* 1996;**17**:76–81.
130. Borer JS, Fox K, Jaillon P, Lerebours G; Ivabradine Investigators Group. Antianginal and antiischemic effects of ivabradine, an If inhibitor, in stable angina: a randomized, double-blind, multicentered, placebo-controlled trial. *Circulation* 2003;**107**:817–823.
131. Tardif JC, Ford I, Tendera M, Bourassa MG, Fox K; for the INITIATIVE Investigators. Efficacy of ivabradine, a new selective If inhibitor, compared with atenolol in patients with chronic stable angina. *Eur Heart J* 2005;**26**:2529–2536.
132. Ruzyllo W, Tendera M, Ford I, Fox KM. Antianginal efficacy and safety of ivabradine compared with amlodipine in patients with stable effort angina pectoris: a 3-month randomised, double-blind, multicentre, noninferiority trial. *Drugs* 2007;**67**:393–405.
133. Fox K, Ford I, Steg PG, Tardif JC, Tendera M; for the SIGNIFY Investigator. Ivabradine in stable coronary artery disease without clinical heart failure for the SIGNIFY Investigators. *N Engl J Med* 2014;**371**:1091–1099.
134. Tendera M, Chassany O, Ferrari R, Ford I, Steg PH, Tardif JC, Fox K; on behalf of the SIGNIFY Investigators. Quality of life with ivabradine in patients with angina pectoris. The study assessing the morbidity–mortality benefits of the if inhibitor ivabradine in patients with coronary artery disease quality of life substudy. *Circulation* 2016;**9**:31–38.
135. Fox K, Ford I, Steg PG, Tendera M, Ferrari R; on behalf of BEAUTIFUL Investigators. Ivabradine for patients with stable coronary artery disease and left-ventricular systolicular dysfunction (BEAUTIFUL): a randomised, double-blind, placebo-controlled trial. *Lancet* 2008;**372**:807–816.
136. Fox K, Ford I, Steg PG, Tendera M, Robertson M, Ferrari R; BEAUTIFUL Investigators. Relationship between ivabradine treatment and cardiovascular outcomes in patients with stable coronary artery disease and left ventricular systolic dysfunction with limiting angina: a subgroup analysis of the randomized, controlled BEAUTIFUL Trial. *Eur Heart* 2009;**30**:2337–2345.
137. Swedberg K, Komajda M, Böhm M, Borer JS, Ford I, Dubost-Brama A, Lerebours G, Tavazzi L; SHIFT Investigators; on behalf of the SHIFT Investigators. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. *Lancet* 2010;**376**:875–885.
138. Mc Alister FA, Natasha W, Ezekowitz JA, Leung AL, Armstrong PW. Meta-analysis: blocker dose, heart rate reduction, and death in patients with heart failure. *Ann Intern Med* 2009;**150**:784–794.
139. Tardif JC, Ponikowski P, Kahan T; for ASSOCIATE Study Investigators. Efficacy of the I(f) current inhibitor ivabradine in patients with chronic stable angina receiving beta-blocker therapy: a 4-month, randomized, placebo-controlled trial. *Eur Heart J* 2009;**30**:540–548.
140. Weisz G, Genereux P, Inguez A; for the RIVER-PCI Investigators, et al. Ranolazine in patients with incomplete revascularisation after percutaneous coronary intervention (RIVER-PCI): a multicentre, randomised, double-blind, placebo-controlled trial. *Lancet* 2015 [Epub ahead of print].
141. Morrow DA, Scirica BM, Karwatowska-Prokopczuk E, Murphy SA, Budaj A, Varshavsky S, Wolff AA, Skene A, McCabe CH, Braunwald E; MERLIN-TIMI 36 Trial Investigators. Effects of ranolazine on recurrent cardiovascular events in patients with non-ST-elevation acute coronary syndromes the MERLIN-TIMI 36 randomized trial. *JAMA* 2007;**297**:1775–1783.
142. Chaitman BR, Pepine CJ, Parker JO, Skopal J, Chumakova G, Kuch J, Wang W, Skettino SL, Wolff AA; Combination Assessment of Ranolazine In Stable Angina (CARISA) Investigators. Effects of ranolazine with atenolol, amlodipine or diltiazem on exercise tolerance and angina frequency in patients with severe angina. *JAMA* 2004;**291**:309–316.
143. Page RL, Ghushchyan V, Read RA, Hartsfield CL, Koch BR, Nair KV;. Comparative effectiveness of Ranolazine versus traditional therapiesbin chronic stable angina pectoris and concomitant diabetes mellitus and impact in health care resource utilization and cardiac interventions.. *AM J Cardio* 2015;**116**:1321–1328.
144. Kotseva K, Jennings CS, Turner EL, Mead A, Connolly S, Jones J, Bowker TJ, Wood DA; ASPIRE-2-PREVENT Study Group. ASPIRE-2-PREVENT: a survey of lifestyle, risk factor management and cardioprotective medication in patients with coronary heart disease and people at high risk of developing cardiovascular disease in the UK. *Heart* 2012;**98**:865–871.
145. Vedin O, Hagström E, Stewart R, Brown R, Krug-Gourley S, Davies R, Wallentin L, White H, Held C. Secondary prevention and risk factor target achievement in a global, high-risk population with established coronary heart disease: baseline results from the STABILITY study. *Eur J Prev Cardiol* 2013;**20**:678–685.
146. EUROASPIRE Investigators. Patients with coronary artery disease and diabetes need improved management: a report from the EUROASPIRE IV survey: a registry from the EuroObservational Research Programme of the European Society of Cardiology. *Cardiovasc Diabetol* 2015;**14**:133.
147. Phillips LS, Branch WT, Cook CB, Doyle JP, El-Kebbi IM, Gallina DL, Miller CD, Ziemer DC, Barnes CS. Clinical inertia. *Ann Intern Med* 2001;**135**:825–834.
148. Colivicchi F, Abrignani MG, Santini M. Therapeutic non-adherence: the hidden risk factor. *G Ital Cardiol* 2010;**11**:124S–127S.
149. Ho PM, Bryson CL, Rumsfeld JS. Medication adherence: its importance in cardiovascular outcomes. *Circulation* 2009;**119**:3028–3035.
150. De Vera MA, Bhole V, Burns LC, Lacaille D. Impact of statin adherence on cardiovascular disease and mortality outcomes: a systematic review. *Br J Clin Pharm* 2014;**78**:684–698.
151. Colivicchi F, Guido V, Ficili S, Ammirati F, Tubaro M, Santini M. Withdrawal of statin therapy is associated with an adverse outcome after non-ST elevation acute coronary syndrome. *Eur Heart J* 2004;**25**:49.
152. Patel MX, David AS. Medication adherence: predictive factors and enhancement strategies. *Psychiatry* 2004;**10**:41–45.

153. Morisky DE, Green LW, Levine DM. Concurrent and predictive validity of aself-reported measure of medication adherence. *Med Care* 1986;**24**:67–74.
154. Shaw LJ, Berman DS, Maron DJ, Mancini GB, Hayes SW, Hartigan PM, Weintraub WS, O'rourke RA, Dada M, Spertus JA, Chaitman BR, Friedman J, Slomka P, Heller GV, Germano G, Gosselin G, Berger P, Kostuk WJ, Schwartz RG, Knudtson M, Veledar E, Bates ER, McCallister B, Teo KK, Boden WE. Optimal medical therapy with or without percutaneous coronary intervention to reduce ischemic burden: results from the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial nuclear substudy. *Circulation* 2008;**117**:1283–1291.
155. Boden WE, O'Rourke RA, Teo KK, Hartigan PM, Maron DJ, Kostuk WJ, Knudtson M, Dada M, Casperson P, Harris CL, Chaitman BR, Shaw L, Gosselin G, Nawaz S, Title LM, Gau G, Blaustein AS, Booth DC, Bates ER, Spertus JA, Berman DS, Mancini GB, Weintraub WS. Optimal medical therapy with or without PCI for stable coronary disease. *N Eng J Med* 2007;**356**:1503–1516.
156. Abbara S, Arbab-Zadeh A, Callister TQ, Desai MY, Mamuya W, Thomson L, Weigold WG. SCCT guidelines for performance of coronary computed tomographicangiography: a report of the Society of Cardiovascular Computed Tomography Guidelines Committee. *J Cardiovasc Comput Tomogr* 2009;**3**:190–204.
157. Douglas PS, Hoffmann U, Patel MR; for the PROMISE Investigators, et al. Outcomes of anatomical versus functional testing for coronary artery disease. *New Engl J Med* 2015;**372**:1291–1300.
158. Tonino PA, De Bruyne B, Pijls NH, Siebert U, Ikeno F, Van' T Veer M, Klauss V, Manoharan G, Engstrøm T, Oldroyd KG, Ver Lee PN, MacCarthy PA, Fearon WF; FAME Study Investigators. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. *N Engl J Med* 2009;**360**:213–224.
159. De Bruyne B, Fearon WF, Pijls NH, Barbato E, Tonino P, Piroth Z, Jagic N, Mobius-Winckler S, Rioufol G, Witt N, Kala P, MacCarthy P, Engström T, Oldroyd K, Mavromatis K, Manoharan G, Verlee P, Frobert O, Curzen N, Johnson JB, Limacher A, Nüesch E, Jüni P; FAME 2 Trial Investigators. Fractional flow reserve-guided PCI for stable coronary artery disease FAME 2 trial investigators. *N Engl J Med* 2014;**371**:1208–1217.
160. Johnson NP, Tóth GG, Lai D, Zhu H, Açar G, Agostoni P, Appelman Y, ArslanF Barbato E, Chen SL, Di Serafino L, Domínguez-Franco AJ, Dupouy P, Esen AM, Esen OB, Hamilos M, Iwasaki K, Jensen LO, Jiménez-Navarro MF, Katritsis DG, Kocaman SA, Koo BK, López-Palop R, Lorin JD, Miller LH, Muller O, Nam CW, Oud N, Puymirat E, Rieber J, Rioufol G, Rodés-Cabau J, Sedlis SP, Takeishi Y, Tonino PA, Van Belle E, Verna E, Werner GS, Fearon WF, Pijls NH, De Bruyne B, Gould KL. Prognostic value of fractional flow reserve: linking physiologic severity to clinical outcomes. *J Am Coll Cardiol* 2014;**64**:1641–1654.
161. Hamilos M, Muller O, Cuisset T, Ntalianis A, Chlouverakis G, Sarno G, Nelis O, Bartunek J, Vanderheyden M, Wyffels E, Barbato E, Heyndrickx GR, Wijns W, De Bruyne B. Long-term clinical outcome after fractional flow reserve-guided treatment in patients with angiographically equivocal left main coronary artery stenosis. *Circulation* 2009;**120**:1505–1512.
162. Park SJ, Ahn JM, Pijls NH, De Bruyne B, Shim EB, Kim YT, Kang SJ, Song H, Lee JY, Kim WJ, Park DW, Lee SW, Kim YH, Lee CW, Park SW. Validation of functional state of coronary tandem lesions using computational flow dynamics. *Am J Cardiol* 2012;**110**:1578–1584.
163. Krüger S, Koch KC, Kaumanns I, Merx MW, Hanrath P, Hoffmann R. Clinical significance of fractional flow reserve for evaluation of functional lesion severity in stent restenosis and native coronary arteries. *Chest* 2005;**128**:1645–1649.
164. Ntalianis A, Sels JW, Davidavicius G, Tanaka N, Muller O, Trana C, Barbato E, Hamilos M, Mangiacapra F, Heyndrickx GR, Wijns W, Pijls NH, De Bruyne B. Fractional flow reserve for the assessment of nonculprit coronary artery stenoses in patients with acute myocardial infarction. *JACC CardiovascInterv* 2010;**3**:1274–1281.
165. Nam CW, Mangiacapra F, Entjes R, Chung IS, Sels JW, Tonino PA, De Bruyne B, Pijls NH, Fearon WF; Fame Study Investigators Functional SYNTAX score for risk assessment in multivessel coronary artery disease. *J Am Coll Cardiol* 2011;**58**:1211–1218.
166. Smilowitz NR, Kirtane AJ, Guiry M, GrayWA Dolcimascolo P, Querijero M, Echeverry C, Kalcheva N, Flores B, Singh VP, Rabbani L, Kodali S, Collins MB, Leon MB, Moses JW, Weisz G. Practices and complications of vascular closure devices and manual compression in patients undergoing elective transfemoral coronary procedures. *Am J Cardiol* 2012;**110**:177–182.
167. Jolly SS, Amlani S, Hamon M, Yusuf S, Mehta SR. Radial versus femoral access for coronary angiography or intervention and the impact on major bleeding and ischemic events: a systematic review and meta-analysis of randomized trials. *Am Heart J* 2009;**157**:132–140.
168. Botman KJ, Pijls NH, Bech JW, Aarnoudse W, Peels K, van Straten B, Penn O, Michels HR, Bonnier H, Koolen JJ. Percutaneous coronary intervention or bypass surgery in multivessel disease? A tailored approach based on coronary pressure measurement. *Catheter CardiovascInterv* 2004;**63**:184–191.
169. Sajadieh A, Nielsen OW, Rasmussen V, Hein HO, Hansen JF. Prevalence and prognostic significance of daily-life silent myocardial ischaemia in middle-aged and elderly subjects with no apparent heart disease. *Eur Heart J* 2005;**26**:1402–1409.
170. Bucher HC, Hengstler P, Schindler C, Guyatt GH. Percutaneous transluminal coronary angioplasty versus medical treatment for non-acute coronary heart disease: meta-analysis of randomised controlled trials. *BMJ* 2000;**321**:73–77.
171. Mukherjee D, Moliterno DJ. Effectiveness of PCI for non-acute coronary artery disease. *Lancet* 2009;**373**:870–872.
172. Rossini R, D'elia E, Ferrero P. Stable angina: what the European guidelines say or do not say. *G ItalCardiol* 2014;**15**:209–214.
173. Rossini R, Musumeci G, Navarese EP, Tarantini G. Coronary artery disease: to cath or not to cath? When and how best to cath: those are the remaining questions. *Am J Cardiovasc Dis* 2013;**3**:27–38.
174. Mancini J, et al. Predicting outcome in the COURAGE Trial (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation). *J Am Coll Cardiol Intv* 2014;**7**:195–201.
175. Coronary angioplasty versus medical therapy for angina: the second Randomised Intervention Treatment of Angina (RITA-2) trial. RITA-2 trial participants. *Lancet* 1997;**350**:461–468.
176. Yusuf S, Zucker D, Passamani E, Peduzzi P, Takaro T, Fisher LD, Kennedy JW, Davis K, Killip T, Norris R, Morris C, Mathur V, Varnauskas E, Chalmers TC. Effect of coronary artery bypass graft surgery on survival: overview of 10-year results from randomised trials by the Coronary Artery Bypass Graft Surgery Trialists Collaboration. *Lancet* 1994;**344**:563–570.
177. Park S-J, Ah J-M, Kim Y-H, Park D-W, Yun S-C, Lee J-Y, Kang S-J, Lee S-W, Lee CW, Park S-W, Choo SJ, Chung CH, Lee JW, Cohen DJ, Yeung AC, Ho Hur S, Seung KB, Ahn TH, Moon Kwon H, Lim D-S, Rha S-W, Jeong M-H, Lee B-K, Tresukosol D, Sheng Fu G, Ong TK; for the BEST Trial Investigators. Trial of everolimus-eluting stents or bypass surgery for coronary disease. *N Engl J Med* 2015;**372**:1204–1212.
178. Velazquez EJ, Lee KL, Deja MA, Jain A, Sopko G, Marchenko A, Ali IS, Pohost G, Gradinac S, Abraham WT, Yii M, Prabhakaran D, Szwed H, Ferrazzi P, Petrie MC, O'connor CM, Panchavinnin P, She L, Bonow RO, Rankin GR, Jones RH, Rouleau JL. Coronary-artery bypass surgery in patients with left ventricular dysfunction. *N Engl J Med* 2011;**364**:1607–1616.
179. Takaro T, Hultgren HN, Lipton MJ, Detre KM. The VA cooperative randomized study of surgery for coronary arterial occlusive disease II. Subgroup with significant left main lesions. *Circulation* 1976;**54**:III107–III117.
180. Caracciolo EA, Davis KB, Sopko G, Kaiser GC, Corley SD, Schaff H, Taylor HA, Chaitman BR. Comparison of surgical and medical group survival in patients with left main equivalent coronary artery disease. Long-term CASS experience. *Circulation* 1995;**91**:2335–2344.
181. Myers WO, Schaff HV, Gersh BJ, Fisher LD, Kosinski AS, Mock MB, Holmes DR, Ryan TJ, Kaiser GC. Improved survival of surgically treated patients with triple vessel coronary artery disease and severe angina pectoris. A report from the Coronary Artery Surgery Study (CASS) registry. *J Thorac Cardiovasc Surg* 1989;**97**:487–495.
182. Varnauskas E. Twelve-year follow-up of survival in the randomized European Coronary Surgery Study. *N Eng J Med* 1988;**319**:332–337.
183. Alderman EL, Fisher LD, Litwin P, Kaiser GC, Myers WO, Maynard C, Levine F, Schloss M. Results of coronary artery surgery in patients with poor left ventricular function (CASS). *Circulation* 1983;**68**:785–795.
184. Hueb W, Lopes N, Gersh BJ, Soares PR, Ribeiro EE, Pereira AC, Favarato D, Rocha AS, Hueb AC, Ramires JA. Ten-year follow-up survival of the Medicine, Angioplasty, or Surgery Study (MASS II): a

randomized controlled clinical trial of 3 therapeutic strategies for multivessel coronary artery disease. *Circulation* 2010;**122**:949–957.
185. Dzavik V, Ghali WA, Norris C, Mitchell LB, Koshal A, Saunders LD, Galbraith PD, Hui W, Faris P, Knudtson ML; Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease (APPROACH) Investigators. Long-term survival in 11,661 patients with multivessel coronary artery disease in the era of stenting: a report from the Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease (APPROACH) Investigators. *Am Heart J* 2001;**142**:119–126.
186. Smith PK1, Califf RM, Tuttle RH, Shaw LK, Lee KL, Delong ER, Lilly RE, Sketch MH Jr, Peterson ED, Jones RH. Selection of surgical or percutaneous coronary intervention provides differential longevity benefit. *Ann Thorac Surg* 2006;**82**:1420–1428.
187. Davies RF, Goldberg AD, Forman S, Pepine CJ, Knatterud GL, Geller N, Sopko G, Pratt C, Deanfield J, Conti CR. Asymptomatic Cardiac Ischemia Pilot (ACIP) study two-year follow-up: outcomes of patients randomized toinitial strategies of medical therapy versus revascularization. *Circulation* 1997;**95**:2037–2043.
188. Hachamovitch R, Rozanski A, Shaw LJ, Stone GW, Thomson LE, Friedman JD, Hayes SW, Cohen I, Germano G, Berman DS. Impact of ischaemia and scar on the therapeutic benefit derived from myocardial revascularization vs. medical therapy among patients undergoing stress-rest myocardial perfusion scin- tigraphy. *Eur Heart J* 2011;**32**:1012–1024.
189. Pursnani S, Korley F, Gopaul R, Kanade P, Chandra N, Shaw RE, Bangalore S. Percutaneous coronary intervention vs. optimal medical therapy in stable coronary artery disease: a systematic review and meta-analysis of randomized clinical trials. *Circ Cardiovasc Interv* 2012;**5**:476–490.
190. Serruys PW, Morice MC, Kappetein AP, Colombo A, Holmes DR, Mack MJ, Ståhle E, Feldman TE, van den Brand M, Bass EJ, Van Dyck N, Leadley K, Dawkins KD, Mohr FW; SYNTAX Investigators. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. *N Engl J Med* 2009;**360**:961–972.
191. Mohr FW, Morice M-C, Pieter Kappetein A, Feldman TE, Ståhle E, Colombo A, Mack MJ, Holmes DR Jr, Morel M-A, Van Dyck N, Houle VM, Dawkins KD, Serruys PW. Coronary artery bypass graft surgery versus percutaneous coronary intervention in patients with three-vessel disease and left main coronary disease: 5-year follow-up of the randomised, clinical SYNTAX trial. *Lancet* 2013;**381**:629–638.
192. Capodanno D, Stone GW, Morice MC, Bass TA, Tamburino C. Percutaneous coronary intervention versus coronary artery bypass graft surgery in left main coronary artery disease. *J Am Coll Cardiol* 2011;**58**:1426–1432.
193. Alam M, Huang HD, Shahzad SA, Kar B, Virani SS, Rogers PA, Paniagua D, Bozkurt B, Palacios I, Kleiman NS, Jneid H. Percutaneous coronary intervention vs. coronary artery bypass graft surgery for unprotected left main coronary artery disease in the drug-eluting stents era–an aggregate data meta-analysis of 11,148 patients. *Circ J* 2013;**77**:372–382.
194. Bangalore S, Guo Y, Samadashvili Z, Blecker S, Xu J, Hannan EL. Everolimus-eluting stents or bypass surgery for multivessel coronary disease. *N Engl J Med* 2015;**372**:1213–1222.
195. Ciszewski A, Bilinska ZT, Brydak LB, Kepka C, Kruk M, Romanowska M, Ksiezycka E, Przyluski J, Piotrowski W, Maczynska R, Ruzyllo W. Influenza vaccination in secondary prevention from coronary ischaemic events in coronary artery disease: FLUCAD study. *Eur Heart J* 2008;**29**:1350–1358.
196. Pfisterer M. Long-term outcome in elderly patients with chronic angina managedinvasively versus by optimized medical therapy: four-year follow-up of the randomized Trial of Invasive versus Medical therapy in Elderly patients (TIME). *Circulation* 2004;**110**:1213–1218.
197. Kannel WB, Wilson PW. Risk factors that attenuate the female coronary disease advantage. *Arch Intern Med* 1995;**155**:57–61.
198. Merz CN, Kelsey SF, Pepine CJ, Reichek N, Reis SE, Rogers WJ, Sharaf BL, Sopko G; for the WISE Study Group. The Women's Ischemia Syndrome Evaluation (WISE) study: protocol design, methodology and feasibility report. *J Am Coll Cardiol* 1999;**33**:1453–1461.
199. Hine C, Fenton S, Hughes AO. Coronary heart disease and physical activity in South Asian women: local context and challenges. *Health Educ J* 1995;**54**:431–443.
200. Aldea GS, Gaudiani JM, Shapira OM, Jacobs AK, Weinberg J, Cupples AL, Lazar HL, Shemin RJ. Effect of gender on postoperative outcomes and hospital stays after coronary artery bypass grafting. *Ann Thorac Surg* 1999;**67**:1097–1103.
201. Effects of estrogen or estrogen/progestin regimens on heart disease risk factors in postmenopausal women. The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial. The Writing Group for the PEPI Trial. *JAMA* 1995;**273**:199–208.
202. Hulley S, Grady D, Bush T, Furberg C, Herrington D, Riggs B, Vittinghoff E. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/progestin Replacement Study (HERS) Research Group. *JAMA* 1998;**280**:605–613.
203. The Bari 2D Study Group A randomized trial of therapies for type 2 diabetes and coronary artery disease. *N Engl J Med* 2009;**360**:2503–2515.
204. Farkouh ME, Domanski M, Sleeper LA, Siami FS, Dangas G, Mack M, Yang M, Cohen DJ, Rosenberg Y, Solomon SD, Desai AS, Gersh BJ, Magnuson EA, Lansky A, Boineau R, Weinberger J, Ramanathan K, Sousa JE, Rankin J, Bhargava B, Buse J, Hueb W, Smith CR, Muratov V, Bansilal S, King S 3rd, Bertrand M, Fuster V; FREEDOM Trial Investigators. Strategies for multivessel revascularization in patients with diabetes. *N Engl J Med* 2012;**367**:2375–2384.
205. Hlatky MA, Boothroyd DB, Bravata DM, Boersma E, Booth J, Brooks MM, et al. Coronary artery bypass surgery compared with percutaneous coronary interventions for multivessel disease: a collaborative analysis of individual patient data from ten randomised trials. *Lancet* 2009;**373**:1190–1197.
206. Bansilal S, Farkouh ME, Hueb W, Ogdie M, Dangas G, Lansky AJ, Cohen DJ, Magnuson EA, Ramanathan K, Tanguay JF, Muratov V, Sleeper LA, Domanski M, Bertrand ME, Fuster V. The Future REvascularization Evaluation in patients with Diabetes mellitus: optimal management of Multivessel disease (FREEDOM) trial: clinical and angiographic profile at study entry. *Am Heart J* 2012;**164**:591–599.
207. Kapur A, Hall RJ, Malik IS, et al. Randomized comparison of percutaneous coronary intervention with coronary artery bypass grafting in diabetic patients. 1-year results of the CARDia (Coronary Artery Revascularization in Diabetes) trial. *J Am Coll Cardiol* 2010;**55**:432–440.
208. Boyden TF, Nallamothu BK, Moscucci M, Chan PS, Grossman PM, Tsai TT, Chetcuti SJ, Bates ER, Gurm HS. Meta-analysis of randomized trials of drug-eluting stents versus bare metal stents in patients with diabetes mellitus. *Am J Cardiol* 2007;**99**:1399–1402.
209. Stettler C, Allemann S, Wandel S, Kastrati A, Morice MC, Schömig A, Pfisterer ME, Stone GW, Leon MB, de Lezo JS, Goy JJ, Park SJ, Sabaté M, Suttorp MJ, Kelbaek H, Spaulding C, Menichelli M, Vermeersch P, Dirksen MT, Cervinka P, De Carlo M, Erglis A, Chechi T, Ortolani P, Schalij MJ, Diem P, Meier B, Windecker S, Jüni P. Drug eluting and bare metal stents in people with and without diabetes: collaborative network metaanalysis. *BMJ* 2008;**337**:a1331.
210. Manjunath G, Tighiouart H, Ibrahim H, MacLeod B, Salem DN, Griffith JL, Coresh J, Levey AS, Sarnak MJ. Level of kidney function as a risk factor for atherosclerotic cardiovascular outcomes in the community. *J Am Coll Cardiol* 2003;**41**:47–55.
211. Baigent C, Landray MJ, Reith C, Emberson J, Wheeler DC, Tomson C, Wanner C, Krane V, Cass A, Craig J, Neal B, Jiang L, Hooi LS, Levin A, Agodoa L, Gaziano M, Kasiske B, Walker R, Massy ZA, Feldt-Rasmussen B, Krairittichai U, Ophascharoensuk V, Fellstrom B, Holdaas H, Tesar V, Wiecek A, Grobbee D, de Zeeuw D, Gronhagen-Riska C, Dasgupta T, Lewis D, Herrington W, Mafham M, MajoniWWallendszus K, Grimm R, Pedersen T, Tobert J, Armitage J, Baxter A, Bray C, Chen Y, Chen Z, Hill M, Knott C, Parish S, Simpson D, Sleight P, Young A, Collins R. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. *Lancet* 2011;**377**:2181–2192.
212. Ashrith G, Lee VV, Elayda MA, Reul RM, Wilson JM. Short- and long-term outcomes of coronary artery bypass grafting or drug-eluting stent implantation for multivesselcoronary artery disease in patients with chronic kidney disease. *Am J Cardiol* 2010;**106**:348–353.
213. Ashrith G, Elayda MA, Wilson JM. Revascularization options in patients with chronic kidney disease. *Tex Heart Inst J* 2010;**37**:9–18.

214. McGarvey LP, John M, Anderson JA, Zvarich M, Wise RA; TORCH Clinical Endpoint Committee. Ascertainment of cause-specific mortality in COPD: operations of the TORCH Clinical End Point Committee. *Thorax* 2007;**62**:411–415.
215. Curkendall SM, DeLuise C, Jones S, Lanes S, Stang MR, Goehring JE, She D. Cardiovascular disease in patients with chronic obstructive pulmonary disease. Saskatchewan Canada cardiovascular disease in COPD patients. *Ann Epidemiol* 2006;**16**:63–70.
216. O'Boyle F, Mediratta N, Chalmers J, Al-Rawi O, Mohan K, Shaw M, Poullis M. Long-term survival of patients with pulmonary disease undergoing coronary artery bypass surgery. *Eur J Cardiothorac Surg* 2013;**43**:697–703.
217. Hawkins NM, Huang Z, Pieper KS, Solomon SD, Kober L, Velasquez EJ, et al. Valsartan in acute myocardial infarction Trial Investigatros. Chronic obstructive pulmonary disease is an independent predictor of death but not atherosclerotic events in patients with acute myocardial infarction: analysis of the Valsartan in Acute Myocardial Infarction Trial (VALIANT). *Eur J Heart Fail* 2009;**11**:292–298.
218. Mancini GB, Etminan M, Zhang B, Levesque LE, Fitzgerard JM, Brophy JM. Reduction of morbidity and mortality by statins, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers in patients with chronic obstructive pulmonary disease. *J Am Coll Cardiol* 2006;**47**:2554–2560.