MEDICAL TREATMENT IN MULTI VESSELS CORONARY DISEASE

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Post-acute and chronic phases after acute coronary syndrome (ACS) present with several challenges for patients and physicians alike. Guidelines have been developed to help physician in the decision making process, but at times they are at variance from more recent studies and the current clinical practice.

Prognosis after myocardial infarction

After ACS patients remain at risk for adverse cardiovascular events: according to the GRACE Registry[1] at 5 years after ACS total and cardiovascular mortality were 20% and 13%; new myocardial infarctions (MI), stroke and need for revascularization occurred respectively in 9%, 8% and 17%. Patients with stable angina on the other hand have a yearly mortality rate between 1% and 2.5%,[2] and a rate of 0.6%-2.7% of adverse coronary events.[3,4] Every day clinical practice seems to

depict a bleaker picture: the Primary Prevention Study reported survival for patients with previous MI and stable angina of 34% and 53% respectively.[5] The prognosis of chronic ischemic heart disease varies considerably according to the baseline anatomical, clinical and functional characteristics as well as the choice of therapeutic intervention. After ACS patients can be divided in two basic categories: patients with high risk of heart failure, presenting a negative evolution from the immediate post-acute phase characterized by progressive unfavorable remodeling; and patients at high risk for new thrombotic events leading to recurrent ischemia or anew necrosis. There are some angiography-derived parameters known to be associated with high risk of ischemic recurrence, such as the number of coronary vessels with significant stenosis and the incomplete revascularization. Recently, the SYNTAX score has been devised to characterize coronary anatomy according to the number and the complexity of the coronary lesions, deriving a score for each lesion and a total score for the patient. This system has provided important standardization in the definition of coronary anatomy but has the limitation of not taking into account other important variables such as the ejection fraction, the myocardial vitality of the coronary territory and the presence of co-morbidity, such renal insufficiency and chronic obstructive pulmonary disease. The ARTS-II study and the ACUITY trial brought convincing evidence supporting the use of scoring system which combine clinical and angiographic parameters as the most useful in predicting a prognosis and re-affirmed that diabetes mellitus, renal insufficiency, peripheral arterial disease, history of angina or previous MI and multi vessels disease are associated with a very high residual cardiovascular risk.

Therapy of MI in patients with multi vessels disease according to Guidelines

According to the 2015 ESC Guidelines[6], in patients after non-ST-elevation MI (NSTEMI) are recommended lifestyle modification measures and optimal medical therapy to improve the long-term prognosis. With IA recommendation are included: high-dose statins; ACE-inhibitors/ARB in

diabetes, systolic dysfunction or hypertension; beta-blockers particularly in patients with ejection fraction <40%; the latter recommendation has been recently challenged in Randomized Clinical Trials (RTC) after NSTEMI without systolic dysfunction.

The 2014 American Heart Association Guidelines[7] confirmed the need for risk factor control and change in lifestyle. Beta-blockers without intrinsic sympathycomimetic activity (metoprolol succinate, bisoprolol, carvedilol) are recommended for NSTEMI with decreased ejection fraction after clinical stabilization and in absence of contraindications. Non-dyhidropyridinic calcium antagonists are recommended for patients with recurrent angina when beta-blockers are contraindicated in patients without significant left ventricular dysfunction. ACE-inhibitors and anti-aldosterone drugs preserve their usual indications; with the level IIB recommendation ACE-inhibitors are given in all patients with multiple site atherosclerotic disease; as a second line anti angina treatment, for symptoms control, nitrates and ranolazine are also recommended.

The 2013 AHA Guidelines[8] for ST elevation MI (STEMI) are similar in the recommendation for beta-blockers, ACE-inhibitors, antialdosterone drugs and statins to the NSTEMI Guidelines but there is no mention of calcium antagonists. For anterior MI there is a IA recommendation for ACE-inhibitor, whereas the level drops to IIB level for the use of ACE-inhibitor in all other acute MI patients.

There is wide agreement in all Guidelines as to the usefulness of cardiac rehabilitation to help in control of cardiovascular risk factor and compliance to the medical treatment, especially in patients with a high risk profile. There are no specific indications as to the proper treatment for patients with multi vessels disease.

Pharmacological therapy of MI during the post-acute and chronic phases

Antiplatelets and cholesterol lowering drugs

Dual antiplatelet therapy and statins are the most effective drugs in terms of improving the prognosis after MI. In this field, the most topical issues are the choice of the molecule to be given, the duration of treatment, the need for different associations, and the LDL cholesterol target to be aimed for; these therapies are treated extensively in other parts of this volume.

Beta-blockers

One of the major and controversial innovation in 2013 ESC Guidelines[2] has been the withdrawal of beta-blockers as drugs able to improve prognosis, whereas, in the 2006 edition, received a class IA recommendation after MI. Presently they received a class IIaC recommendation only in patients with documented residual ischemia >10%. In the AHA Guidelines for chronic ischemic heart disease[9] beta-blockers received a class IB recommendation for the first 3 years after the MI and a class IIbC in the long term[10] (Table 1).

This action has been taken following publication of studies documenting that beta-blockers did not have a significant effect in decreasing cardiovascular events in patients without left ventricular dysfunction. In the REACH Registry[11] patients who received beta-blockers did not have reduction in the risk of cardiovascular events at 44 months' mean follow up. This study though lacked of specific information as to the beta-blocking molecule utilized and its dose; ventricular function was also not considered. Data remain very discordant: in a large sample study beta-blockers significantly reduced mortality for cardiovascular causes[12], while a meta-analysis comparing trials performed before and after the advent of coronary reperfusion, concluded that, in the post-reperfusion era, beta-blockers have no impact on mortality, but increase risk of heart failure and cardiogenic shock[13]. However, both AHA and ESC Guidelines recommend starting beta-blocker treatment during hospitalization to reduce ischemia, re-infarction and complex ventricular arrhythmias. According to COMMIT/CCS-2[14], beta-blockers should be started later in patients with acute ventricular dysfunction, hypotension or at high risk of cardiogenic shock (Table 1).

To support the therapeutic value of beta-blockers there is the demonstration of a favorable prognosis associated with low resting heart rate: in 2005 was proved that a resting heart rate ≤62 bpm was an independent predictor of lower mortality.[15] Similarly it was demonstrated that for each 10 beats reduction of resting heart rate there was 20% decrease in all cause mortality, 30% of cardiovascular mortality, 39% of sudden death and 21% of non fatal MI.[16]

Calcium-antagonists

Non dyhidropyridinic calcium antagonists (CA) are effective in reducing cardiovascular risk in patients after MI without left ventricular dysfunction by decreasing the heart rate. Data for this class of drugs derive from somewhat dated studies and in clinical practice they are now used when there are absolute contraindication to beta-blockers such as in patients with COPD and reversible bronchoconstriction.

Dyhidropyridinic CA are attested in Guidelines efficacy both at a single drug and in association with beta-blockers, [17] when they have demonstrated, although in a few older studies, to provide for a better exercise tolerance and a trend toward a lower rate of cardiovascular events.[18]

ACE/ARB

There is ample evidence of the beneficial effect of ACE-inhibitor after MI with reduction of mortality and cardiovascular events in patients with left ventricular dysfunction, without the same uniformity of data in patients with preserved ejection fraction. ACE-inhibitors are also effective in the post MI remodeling process.

The evidence that angiotensin receptor blockers (ARB) are non-inferior to ACE-inhibitors in reducing morbidity and mortality after MI stems from the VALIANT study, conducted in patients with reduced EF.

Nitrates

Various nitrates formulations are widely used in clinical practice after MI. The ESC Guidelines for chronic ischemic heart disease debate against the routine use of nitrates in the long-term. In fact, besides the notorious tolerance phenomenon, there is evidence suggesting that long-term use of nitrates is associated with endothelial dysfunction. Fifteen years ago was observed that patients chronically assuming long acting nitrates after ACS had a worst prognosis.[18] During the following years numerous evidences became available tightening the isosorbide-5-mononitrate (I5MN) to endothelial dysfunction through a mechanism mediated by a production of oxygen free radical.[19] Recent animal experiments documented an increased expression of endothelin-1 activating adenin dinucleotidefosphate vascular and phagocites oxidase with production of oxygen free radicals.[20]
Accordingly, the Guidelines gives to long acting nitrates a class IIB recommendation for symptoms control and class IA for the same purpose to short acting nitrates. Despite these recommendations Italian doctors still prescribe long acting nitrates in over 70% of the patients.

Ivabradine

Ivabradine is a specific inhibitor of the I*f* channels in the sinus atrial node that reduces angina and ameliorates exercise tolerance. It is used in patients with sinus rhythm to decrease the heart rate in a dose-dependent fashion, thus decreasing myocardial ischemia without affecting systemic blood pressure, myocardial contractility, intra-cardiac conduction or ventricular repolarization.
In patients with heart failure and ischemic heart disease, the drug provided for a significant reduction of the risk of cardiovascular death and recurrent hospital admission.
In 2014 the SIGNIFY trial[21], designed to evaluate the effectiveness of this drug in patients with chronic stable ischemic heart disease without heart failure, showed that patients taking the drug did not have significant reduction in cardiovascular deaths or non fatal MI, despite significant reduction in heart rate of 10 bpm. In treated patients with moderate to severe degrees of angina, instead, there

was evidence for an increase in cardiovascular deaths and non fatal MI, and development of symptomatic bradycardia and atrial fibrillation. Several hypotheses were raised to explain these data: too high dose of the drug (10 mg bid), the absence of correlation between reduction of heart rate and reduction of events in patients with preserved EF, the deleterious effect of the association of ivabradine with calcium antagonists such as verapamil.[22]

Accordingly, whether an adjustment of the beta-blockers dosage is recommended before starting ivabradine in patients without left ventricular dysfunction, ivabradine is very useful after MI in patients with systolic dysfunction for symptomatic treatment of ischemic heart disease.[23]

Ranolazine

Ranolazine is useful in reducing angina symptoms in patients with chronic myocardial ischemia due to its ability to block the slow entry current of sodium in the cells thus reducing the sodium and calcium intracellular overload and consumption of ATP and oxygen thus reducing the electrical and mechanical dysfunction brought by ischemia. The efficacy of this drug in improving symptoms control was proven in the registration studies. In the MERLIN-TIMI36[24], conducted in patients with ACS / NSTEMI, ranolazine had significantly reduced episodes of recurrent ischemia compared with placebo but not mortality, but in the subgroup of patients with previous diagnosis of angina, the primary end point (cardiovascular death, MI, or recurrent ischemia) was significantly reduced in the treated group.

Other studies demonstrated the efficacy of this drug in patients with diabetes mellitus and in women in particular. Accordingly, the drug is used in combination with other drugs when those are not sufficient for symptoms control or when beta-blockers or calcium antagonists are contraindicated.

The RIVER-PCI trial[25] failed to demonstrate an effect of this drug on the prognosis thus raising inappropriate doubts on its efficacy in symptomatic patients after coronary revascularisation. However, it arose critical considerations on the trial design and the conclusions derived from it,

partly raised by the same authors. For these reasons, the therapeutic indication of ranolazine in symptomatic chronic ischemic heart disease remains completely unchanged.

Non pharmacological therapy

Too often underestimated, but of fundamental importance, is the organization of a secondary prevention program that follows the patient after discharge from the hospital, with provision for tailored treatment and follow up and education about disease and therapy. To support this concept, the OASIS 5[26] demonstrated that just 6 months after discharge patient in optimal medical therapy had a 3.8 time risk of death, recurrent infarct or stroke when they resumed the smoking habit and did not follow diet and physical activity recommendation as compared to patients who did.

As indicated by The Italian Consensus Document of the National Cardiologists Associations[27] patients with a high risk profile (see for example the multivessels disease) should be referred to Cardiac Rehabilitation and secondary prevention programs. In reality STEMI and NSTEMI patients who are referred to rehabilitation in Italy are still a small part (less than 17% in the Blitz4 Quality ANMCO Registry).

The compliance with pharmacological treatment is also very important but in clinical practice up to 50% of the patients failed to follow their drug regimen during the first year after MI. According to the CRUSADE-ACTION Registry, explanations could be absence of a follow-up planning or rehabilitation program and lack of adequate instructions to the patients about the goal of the treatment prescribed. This has also being emphasized by the Agency for Healthcare Research and Quality of the United States that in "medication reconciliation" deals also with the fact that many patients after discharge continue to assume prescriptions given by other doctors before the event; this, in some situations, could contribute to pharmacological interaction causing side effect at time even severe or ineffectiveness of the new treatment.

Accordingly, implementing those strategies in a well thought out simple and effective program designed to assist the patients in a long term could be as valuable as the drugs prescribed. [28]

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Table 1: International Guidelines recommendations for beta-blockers therapy.

	STEMI	NSTEMI-UA	Stable CAD
American Heart Association/American College of Cardiology	Start treatment during the first 24 hours if no contraindications (see text) ***Class I evidence B***	As for STEMI ***Class I evidence A***	After acute MI continue treatment for the next 3 years if EF normal ***Class I evidence B*** After acute MI if EF normal: chronic treatment ***Class IIb evidence C*** If EF <40% : chronic treatment ***Class I evidence A*** As treatment for symptoms relief ***Class I evidence A***
European Society of Cardiology	Start treatment during the first hospitalization if no contraindication (see text) than continue indefinitely ***Class IIa evidence B*** If EF <40% start treatment as soon as feasible than continue indefinitely ***Class I evidence A***	Start treatment during the first hospitalization if no contraindication (see text) than continue indefinitely ***Class I evidence B*** Contraindicated with vasospastic angina ***Class IIa evidence B***	Microvascular angina ***Class I evidence B*** As treatment for symptoms relief ***Class I evidence A*** <u>Not present in secondary prevention</u>