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ANMCO position paper on the management of hypercholesterolaemia in patients with acute coronary syndrome

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Patients suffering from acute coronary syndrome (ACS) present a high risk of recurrence and new adverse cardiovascular events after hospital discharge. Elevated plasma LDL-cholesterol (LDL-C) levels have been shown to be a causal factor for the development of coronary heart disease, and robust clinical evidence has documented that LDL-C levels decrease linearly correlates with a reduction in cardiovascular events. Recent studies have also demonstrated the safety and efficacy of an early and significant reduction in LDL-C levels in patients with ACS. In this position paper, Italian Association of Hospital Cardiologists proposes a decision algorithm on early adoption of lipid-lowering strategies at hospital discharge and short-term follow-up of patients with ACS, in the light of the multiple evidence generated in recent years on the treatment of hypercholesterolaemia and the available therapeutic options, considering current reimbursement criteria.

Introduction

Six years after the publication of the position paper of the Italian Association of Hospital Cardiologists (ANMCO) on the management of hypercholesterolaemia after acute coronary syndrome (ACS)[1] and the inter-society consensus

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document on the diagnostic-therapeutic pathway on hypercholesterolaemia and cardiovascular risk in Italy,[2] ANMCO decided to publish this position paper in the light of the multiple and solid evidence generated in recent years on the treatment of hypercholesterolaemia and the new therapeutic options available.

Patients suffering from an ACS have a high risk of new short- and long-term adverse cardiovascular events after hospital discharge.[3,4] Elevated plasma levels of LDL-cholesterol (LDL-C) have unequivocally been shown to be a causative factor in the development of coronary artery disease (CAD), and strong clinical evidence has documented that decreasing LDL-C levels linearly correlates with a reduction in cardiovascular (CV) events.[5,6] A meta-analysis involving 26 trials and ~170 000 patients (most of whom had documented CAD and a history of ACS) showed that each 1.0-mmol/L (~39 mg/dL) reduction in LDL-C was associated with a 20% relative reduction per year of adverse events, including coronary death, non-fatal myocardial infarction, coronary revascularization, and ischaemic stroke.[6] This observation is further supported by Mendelian randomization studies which showed that subjects with genetic mutations associated with a reduction in LDL-C had a substantially reduced development of CV disease.[7,8] Recent studies have also suggested that there is no threshold beyond which LDL-C reduction is not associated with clinical benefits. In fact, approval trials of monoclonal proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor antibodies have demonstrated a reduction in adverse atherothrombotic events even at LDL-C levels never reached (<40 mg/dL), with a favourable safety profile.[9]

LDL-cholesterol in patients with acute coronary syndrome

The systemic inflammatory response that is associated with ACS induces significant spontaneous changes in LDL-C levels, even in the absence of any cholesterol-lowering treatment. Indeed, clinical studies carried out in ACS before the widespread use of revascularization showed a spontaneous reduction in LDL-C values of around 30%.[10] Subsequent investigations in patients with ACS who underwent pharmacological or mechanical reperfusion procedures revealed minor changes, with an average reduction in LDL-C of ~10%.[11,12] Typically, LDL-C values are significantly reduced within the first 24 h after admission and reach their minimums ~7 days after clinical onset.[11,12] Therefore, it is appropriate to assess LDL-C levels as early as possible in the course of hospitalization as a reference value and support for the choice of cholesterol-lowering therapy. In this regard, it is important to point out that average LDL-C values during hospitalization for ACS in patients not previously treated with statins (statin naive) range between 120 and 130 mg/dL.[5,13] Significantly lower levels (90–110 mg/dL) are to be found in patients admitted to hospital for ACS despite ongoing treatment with statins.[5,13]

Clinical benefits of early initiation of oral cholesterol-lowering agents in acute coronary syndrome

Several observational studies and small trials with mechanistic endpoints have evaluated the benefit of early administration of statins in patients with ACS.[14,15] The large Global Registry of Acute Coronary Events study recruited ~20 000 patients with ACS and compared CV events among patients who had not started a statin treatment during index hospitalization with those who had started but stopped it or with those who had continued it during hospitalization.[16] The latter group was found to have a significantly lower risk of death and stroke (odd ratio (OR) 0.66; 95% confident intervals (CI) 0.56–0.77). Furthermore, patients who started statin treatment during hospitalization but discontinued it for whatever reason had a similar risk of CV events as those who had not started any statin treatment (OR 1.02; 95% CI 0.74–1.41).[16] An analysis of the Euro Heart Survey on ACS[17] subsequently showed in 8197 patients that initiation of statin therapy within 24 h of hospital admission was associated with an improvement in CV outcome and all-cause mortality at 7 and 30 days even after adjustment for multiple variables (hazard ratio (HR) 0.90; 95% CI 0.60–1.3). More recently, an analysis of the SWEDEHEART registry conducted on more than 40 500 patients with ACS followed for about four years showed that a 50% reduction in LDL-C compared with baseline, achieved with high-intensity statins prescribed during hospitalization, was associated with a significant reduction in composite CV endpoints such as mortality, myocardial infarction and stroke, lower all-cause mortality, and a reduced incidence of hospitalization for stroke, heart failure, and coronary revascularization.[18] Several randomized clinical trials have also demonstrated the benefit of early initiation of statin therapy in patients with ACS[19-29] (*Table 1*). It is worth mentioning among others the Myocardial Ischaemia Reduction with Aggressive Cholesterol Lowering (MIRACL) trial, in which 3086 patients with ACS without ST-segment elevation were randomized within four days after the acute event to atorvastatin 80 mg or placebo for 16 weeks.[21] The primary endpoint, a composite of resuscitated cardiac arrest death and hospitalization for recurrent symptomatic myocardial ischaemia, was significantly reduced by early use of atorvastatin (HR 0.84, 95% CI 0.70–1.00, $P = 0.048$). Subsequently, the PROVE IT study (The Pravastatin or Atorvastatin with Aggressive Cholesterol Lowering)[5] demonstrated in 4162 patients with ACS < 10 days, an additional benefit of high-intensity cholesterol-lowering therapy using atorvastatin 80 mg compared with conventional therapy with pravastatin 40 mg. Indeed, at 2 years the composite endpoint consisting of mortality, myocardial infarction, and hospitalization for unstable angina or revascularization was significantly reduced by the use of the high-intensity statin (HR 0.84, 95% CI 0.74–0.95, $P = 0.005$).

However, it seems important to emphasize that the benefit of early statin therapy in ACS appears to be dependent on the patient's residual clinical risk and baseline LDL-C levels. In a sub-analysis of the PROVE IT-TIMI 22 trial (Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction 22), the benefit of intensive cholesterol-lowering treatment with atorvastatin 80 mg over pravastatin 40 mg was progressively reduced as baseline LDL-C levels decreased in statin-naïve ACS patients.[30]

Ezetimibe is a potent inhibitor of intestinal absorption of free cholesterol[31] (*Figure 1*). In the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) study, the combination of ezetimibe with the maximal dose of simvastatin led to a reduction in the risk of CV death, major coronary events, and non-

Table 1 Main characteristics of randomized clinical trials that compared early statin use vs. placebo or usual care in patients with acute coronary syndrome

Trial	Statin	Control	No. of patient	Statin administration (average, days)
LAMIL[19]	Pravastatin	Placebo	69	2
PAIS[20]	Pravastatin	Placebo	99	2
MIRACL[21]	Atorvastatin	Placebo	3086	3
PTT[22]	Pravastatin	Trattamento attivo	164	1
LIPS[23]	Pravastatin	Placebo	824	2
PACT[24]	Pravastatina	Placebo	3408	1
ESTABLISH[25]	Atorvastatin	Active treatment	70	1
Macin *et al.*[26]	Atorvastatin	Placebo	90	2
Ren *et al.*[27]	Simvastatin	Placebo	86	<3
FACS[28]	Fluvastatin	Placebo	156	1
ARMYDA-ACS[29]	Atorvastatin	Placebo	171	11

In all studies, the statin was administered within three days after symptom onset.

ARMYDA, Atorvastatin for Reduction of MYocardial Damage During Angioplasty; LAMIL, Lipid Acute Myocardial Infarction Lowering; PAIS, Pravastatin in Acute Ischaemic Syndromes; PTT, Pravastatin Turkish Trial; PACT, Pravastatin in Acute Coronary Treatment; LIPS, Lescol Intervention Prevention Study; MIRACL, Myocardial Ischaemia Reduction with Aggressive Cholesterol Lowering; FACS, Fluvastatin in the first-line therapy of Acute Coronary Syndrome.

fatal stroke in ~18 000 patients with recent ACS (<10 days after admission).[32] These benefits were particularly relevant in higher risk ACS populations such as those with diabetes mellitus or previous surgical revascularization.[33,34] It is important to consider that the benefit of adding ezetimibe to the statin in ACS also appears to be relative to the LDL-C concentration at the time of admission. In a recent post-hoc analysis of the Heart Institute of Japan-PRoper level of lipid lOwering with Pitavastatin and Ezetimibe in acute coRonary syndrome (HIJ-PROPER) study,[35] a multicentre prospective randomized open-label study comparing two cholesterol-lowering treatments in ~1730 patients with ACS in 19 Japanese hospitals, the addition of ezetimibe to pivastatin produced greater CV benefits when LDL-C levels at hospital admission were above 130 mg/dL.[36]

Bempedoic acid is a once-daily orally administered propharmaceutical that is rapidly converted in the liver to its active metabolite by a synthetase present only in hepatocytes and not in skeletal muscle, thus being associated with a lower risk of potential muscle-related adverse events (e.g. myalgia and myopathy) than statins.[37] Bempedoic acid acts by inhibiting ATP citrate lyase, a cytosolic enzyme located within the enzymatic cascade leading to cholesterol synthesis (*Figure 1*). The LDL-C-lowering benefits of bempedoic acid were evaluated in the extensive CLEAR [Cholesterol Lowering via Bempedoic Acid, an adenosinetriphosphate citrate lyase (ACL)-Inhibiting Regimen] study programme. These studies have shown that a dosage of 180 mg bempedoic acid in addition to statin therapy at the maximum tolerated dose resulted in an additional reduction in LDL-C levels of 15–20%.[38–40] The impact of bempedoic acid on CV events is being evaluated in the CLEAR OUTCOMES trial, which recently completed the enrolment of 14 014 patients intolerant to statins and high CV risk or known CV disease. The results were reported to be positive in terms of reduction of adverse CV events. However, to date, no specific data are available on the impact of bempedolic acid on LDL-C reduction and related clinical effects after a recent ACS, and trials conducted so far have excluded this type of patients.

Role of circulating proprotein convertase subtilisin/kexin type 9 in patients with acute coronary syndrome

Proprotein convertase subtilisin/kexin type 9 is a protein involved in the regulation of LDL receptor degradation present on hepatocyte cell membranes. Recent data suggest that circulating levels of PCSK9 are increased within hours from ACS onset and correlate with increased antiplatelet aggregation, vulnerability of coronary plaque, elevated inflammatory markers, and increased long-term CV events.[41] Different evidence suggest that PCSK9 exerts deleterious effects on coronary plaques through different mechanisms including oxidation of LDL-C and direct modification of plaque composition[42,43] through the production of cytokines and pro-inflammatory molecules.[44–47] Conversely, in coronary plaque, inhibition of PCSK9 reduces the amount of macrophages and necrotic core content and promotes apoptosis.[48] In addition, cardiac ischaemia activates upregulation of PCSK9 synthesis and causes dynamic changes in enzyme levels.[49] In an animal study, the plasma concentration of PCSK9 was increased at 12–96 h after acute myocardial infarction with a peak at 48 h. In addition, hepatic messenger RNA (mRNA) expression of PCSK9 was increased ~2.2-fold at 12 h and 4.1-fold at 24 h.[49] These observations provide a rationale for considering PCSK9 inhibition at an early stage of ACS as it may not only produce a more rapid reduction in LDL-C levels but may also exert an early effect on the stabilization of activated coronary plaques.[41]

Clinical studies on anti-proprotein convertase subtilisin/kexin type 9 agents

The monoclonal antibodies alirocumab and evolocumab, administered subcutaneously 1 or 2 times a month, selectively inhibit the PCSK9 protein, ensuring increased LDL receptor efficiency and drastically reducing circulating LDL-C levels (*Figure 1*). They have been evaluated in

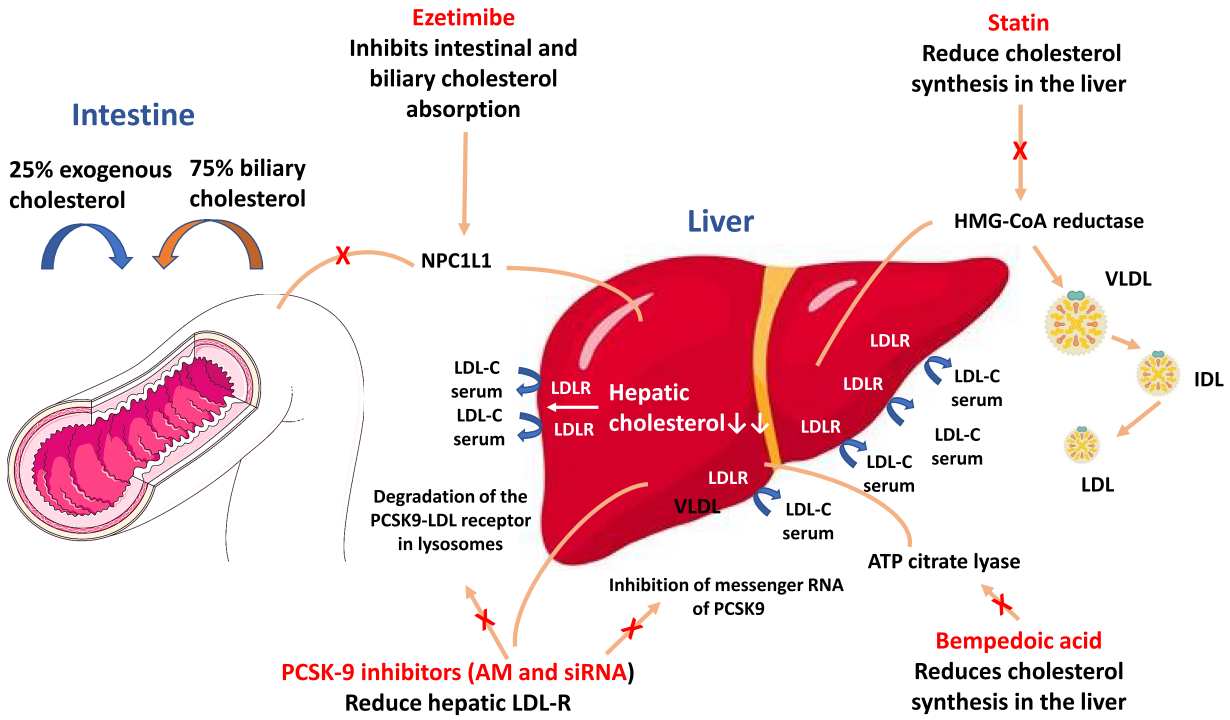

Figure 1 Main agents available for LDL-cholesterolreduction. AM, monoclonal antibodies; HMG-CoA hydroxymethylglutaryl-CoA; IDL, intermediate density lipoprotein; LDL, low-density lipoprotein; LDL-R, LDL receptor; NPC1L1, Niemann-Pick C1-Like 1; siRNA, small interfering RNA; VLDL, very low-density lipoprotein.

numerous randomized Phase 2 and 3 clinical trials in the ODYSSEY and PROFICIO (Programme to Reduce LDL-C and Cardiovascular Outcomes Following Inhibition of PCSK9 in Different Populations) research programmes, respectively.[50] The largest randomized Phase 3 trials, FOURIER and ODYSSEY OUTCOMES, included patients with baseline LDL-C > 70 mg/dL despite optimized cholesterol-lowering therapy, and evaluated the effects of evolocumab in high-risk patients with known CAD and alirocumab in patients with recent ACS, respectively.[51,52] Both drugs resulted in a significant reduction in the primary composite endpoint that included death from CV causes, myocardial infarction, stroke, and coronary revascularization.[51,52] A recent meta-analysis that included 39 randomized clinical trials and ~66 500 patients treated with alirocumab or evolocumab and followed up for ~2 years confirmed that PCSK9 inhibition is associated with a significant reduction in myocardial infarction, ischaemic stroke, and coronary revascularization compared with placebo, although a significant reduction in death from all causes and CV mortality was not found.[50] However, a prolonged open-label follow-up analysis in patients treated with evolocumab (FOURIER-OLE) evaluated at a mean of 5 years showed a significant benefit of PCSK9 inhibition not only in terms of major CV events but also in CV mortality in the absence of major side effects.[53] Importantly, a pre-specified analysis of the FOURIER trial, which included 5711 patients with recent myocardial infarction (<12 months prior to randomization), showed that these patients may benefit from a greater absolute risk reduction with PCSK9 inhibition than patients with previous myocardial infarction >12 months after randomization.[54] In the ODYSSEY OUTCOMES trial, the use of alirocumab on top of optimized cholesterol-lowering therapy was associated with a 22% improvement in survival among patients with at least 3 years of follow-up available.[55,56] This benefit was most pronounced in patients with baseline LDL-C levels ≥100 mg/dL, who had a 29% reduction in relative mortality risk.[55] Furthermore, the use of alirocumab was associated with an ~25% reduction in lipoprotein(a) levels in patients with ACS, consistent with previous evidence obtained with evolocumab in patients with known CAD.[57,58] This is particularly relevant as in post-ACS the reduction in lipoprotein(a) achieved with PCSK9 inhibitors is independently associated with a reduction in CV events, which is particularly evident with high basal lipoprotein(a) levels.[57,58]

Another way to reduce PCSK9 levels is to inhibit its gene expression by neutralizing its mRNA through short interfering molecules (small interfering RNA) (*Figure 1*). In this sense, inclisiran is a double-stranded ribonucleic acid, administered subcutaneously once every 6 months, which exerts a sustained effect of reducing PCSK9 synthesis in hepatocytes.[59,60] In the recent ORION-10 (Inclisiran for Participants With Atherosclerotic Cardiovascular Disease and Elevated Low-Density Lipoprotein Cholesterol) and ORION-11 (Inclisiran for Subjects With ACSVD or ACSVD-Risk Equivalents and Elevated Low-Density Lipoprotein Cholesterol) studies, inclisiran was compared with placebo on top of optimal cholesterol-lowering therapy in patients with known CAD or risk factor equivalents and elevated LDL-C levels (≥70 or ≥100 mg/dL, respectively).[61] LDL-C levels were halved with inclisiran compared with placebo, with no significant differences in safety apart

from minor skin reactions at the injection site. The ongoing ORION-4 (Inclisiran on Clinical Outcomes Among People With Cardiovascular Disease) study will evaluate the impact of inclisiran on ~15 000 patients with known CAD, including those with previous stroke, although ACS with symptom onset <4 weeks will be excluded from randomization.[62] The VICTORION-INCEPTION study is evaluating the efficacy of early administration of inclisiran in ~380 patients with recent ACS (within 5 weeks) and LDL-C > 70 mg/dL in terms of LDL-C percentage reduction and achievement of lipid targets at 1-year follow-up compared with standard therapy.

Studies on the early administration of proprotein convertase subtilisin/kexin type 9 inhibitors in acute coronary syndrome

In the EVOPACS (Evolocumab for Early Reduction of LDL Cholesterol Levels in Patients With Acute Coronary Syndromes) study, the efficacy and safety of evolocumab were assessed during the acute phase of ACS in 308 patients.[63] These patients were randomized to receive placebo or evolocumab 420 mg in addition to high-intensity statin therapy. Evolocumab was associated with a 40% reduction in LDL-C levels and enabled 90% of the treated patients to reach the LDL-C target value of 55 mg/dL at 1 month compared with 11% of those who received statin alone (*P* 0.001). In the Evolocumab in Acute Coronary Syndrome (EVACS) study, patients with ACS without ST-segment elevation were enroled and treated with evolocumab SQ 420 mg or placebo within 24 h after the acute event.[64] At hospital discharge, 65% of patients treated with evolocumab reached the recommended LDL-C target (<55 mg/dL), compared with 24% of patients randomized to statin treatment alone. Finally, the recently published EPIC-STEMI study confirmed that alirocumab also significantly reduced LDL-C levels at 6 weeks compared with control when administered acutely during primary angioplasty for acute ST-segment elevation myocardial infarction, in the absence of side effects.[65]

Effects of cholesterol-lowering therapies on volume and plaque characteristics in acute coronary syndrome

A large atheroma extension measured by intravascular ultrasonography (IVUS), a large lipid extension measured by near-infrared spectroscopy (NIRS), and the presence of a fibrous cap of thin plaque assessed by optical coherence tomography (OCT) have been associated with an increased risk of CV events.[66] The investigation of the so-called vulnerable plaques appears to be of particular importance in patients with ACS since wide natural history studies of ACS have shown that after coronary angioplasty the recurrence of CV events is equally related to culprit lesions treated during the acute phase and to lesions on non-culprit coronary arteries at the index hospitalization.[66] In this context, the identification of thin-cap fibroatheroma diagnosed by IVUS with virtual histology was found to be an independent predictor of late CV events in non-culprit lesions.[66] Several studies have shown that the early administration of cholesterol-lowering therapies in ACS activates a plaque-modifying, anti-platelet process and results in improved endothelial function. High-intensity statin therapy has been shown in several experimental studies to prevent the evolution of coronary atheroma extension and to positively influence plaque composition by reducing the lipid content, increasing the thickness of the fibrous cap and thus reducing plaque vulnerability in patients with ACS.[67-69] More recently, the GLAGOV (GLobal Assessment of Plaque ReGression with a PCSK9 AntibOdy as Measured by IntraVascular Ultrasound) trial documented that the addition of evolocumab to statin treatment in patients with CAD reduced the progression of coronary atherosclerosis as measured by IVUS at 76 weeks.[70] These benefits in terms of reduction and stabilization of atherosclerotic plaque were subsequently confirmed in the HUYGENS (High-Resolution Assessment of Coronary Plaques in a Global Evolocumab Randomized Study) study, which evaluated the effects of evolocumab in a population of patients with ACS without ST-segment elevation by OCT.[71] In the randomized, multicentre, double-blind ODYSSEY J-IVUS trial, the use of alirocumab vs. placebo for 14 weeks stabilized atherosclerotic plaque in high CV risk and statin intolerant patients with a concomitant reduction in parietal inflammation assessed by PET/CT.[72] Recently, the PACMAN-AMI trial (Effects of the PCSK9 Antibody Alirocumab on Coronary Atherosclerosis in Patients With Acute Myocardial Infarction) enroled 300 patients undergoing coronary angioplasty for ACS and evaluated the effects of early administration of 150 mg alirocumab on coronary atherosclerosis assessed by multimodality intracoronary imaging (IVUS, NIRS, and OCT) of non-culprit lesions compared with placebo.[73] At 52 weeks, the coronary plaque volume was significantly reduced in the alirocumab group compared with placebo (between-group difference, −1.21%; 95% CI, −1.78% to −0.65%; $P < 0.001$). Favourable changes were also observed in secondary endpoints that included a greater reduction in lipid burden assessed by NIRS and a greater increase in fibrotic cap plaque assessed by OCT. All these qualitative and quantitative changes in coronary plaque characteristics were directly correlated with LDL-C levels.[73]

Guidelines' recommendations on LDL-cholesterol targets

Guidelines for the treatment of hypercholesterolaemia have been updated in recent years by both North American and European cardiology societies and both have further intensified the approach to LDL-C reduction for secondary prevention.[74,75] However, the different guidelines differ in the LDL-C levels to be achieved (≤70 mg/dL in the US vs. ≤55 mg/dL in Europe).[74,75] Both guidelines recommend in patients with ACS the assessment of target reached within 4 weeks and the achievement of this target in a stepwise approach by first recommending the use of high-intensity statins and subsequently the addition of ezetimibe and PCSK9 inhibitors as second or third line based on several factors (baseline LDL-C, statin naive, recurrent events, etc.). In the American guidelines, the first approach to LDL-C reduction is the statin at the maximum tolerated dose (Class I) and, if

the target is not reached, the addition of ezetimibe or the PCSK9 inhibitor (Class IIa) is recommended.[74] European guidelines recommend starting the statin at the highest intensity or highest tolerated dosage as soon as possible regardless of LDL-C values in order to reduce levels by ≥50% from baseline with a target of ≤55 mg/dL (Class I, Level A).[75] If the target (baseline LDL-C halving and ≤55 mg/dL in secondary prevention or ≤40 mg/dL in patients with recurrent events in the last 2 years) has not been reached at a 4-6-week assessment, the combination with ezetimibe (Class I, Level B) and, after a further 4-6 weeks, the addition of a PCSK9 inhibitor (Class I, Level A) as a third-line therapy is suggested.[75] For patients, on the other hand, who are hospitalized for ACS and are not on target for LDL-C levels despite treatment with statins at the highest tolerated dose and ezetimibe or for patients with recurrences of ACS in the last 2 years (extreme risk), the addition of the PCSK9 inhibitor can be considered already during hospitalization for the acute event (Class II, Level C).[75]

Achieving lipid targets in the real world

Despite the clear demonstrated benefits in terms of reduction of CV events of cholesterol-lowering therapies in patients with ACS and the increased number of available drugs,[76] there remains an important real-world gap from the LDL-C targets recommended by international guidelines, due to underuse of LDL-C-lowering drugs. The reasons for this underuse of lipid-lowering drugs are many and include the side effects and perceived risk of statins, geographic and gender disparities, different health care protocols and systems, costs, and therapeutic inertia. In the DA VINCI study, which evaluated the use of lipid-lowering therapies in several European countries, the majority of patients with atherosclerotic CV disease were receiving a moderate-intensity statin monotherapy (44%) or a high-intensity statin monotherapy (38%).[77] Only 9% of patients were treated with a combination of statin and ezetimibe and 1% with a drug combination including a PCSK9 inhibitor.[77] Consequently, the LDL-C

Ldlc	AB 180 Eze 10 36%*	Ato 40mg 45%*	Alirocumab 75mg 50%*	Ato 80mg 55%*	Rosu 20mg 55%*	Simva40/10 55%*	Ato 40/10 56%*	Ato80/10 61%*	Simva 80/10 61%*	Alirocumab 150 62%*	Evolocumab 140 62%*	Rosu20/10 62%*	Rosu 40mg 63%*	AB 180 Eze 10 Ato20 63%*	Rosu40/10 70%*	Rosu 20 o Ato 40 + iPCSK9 75%*	Rosu 20 o Ato 40/ Eze10+iPCSK9 85%*
230 - 200	147 - 128	126 - 110	115 - 100	103 - 90	103 - 90	103 - 90	101 - 88	90 - 78	90 - 78	87 - 76	87 - 76	87 - 76	85 - 74	85 - 74	69 - 60	57 - 50	34 - 30
200 - 170	128 - 109	110 - 93	100 - 85	90 - 76	90 - 76	90 - 76	88 - 75	78 - 66	78 - 66	76 - 65	76 - 65	76 - 65	74 - 63	74 - 63	60 - 51	50 - 42	30 - 25
170 - 140	109 - 90	93 - 77	85 - 70	76 - 63	76 - 63	76 - 63	75 -62	66 - 55	66 - 55	65 - 53	65 - 53	65 - 53	63 - 52	63 - 52	51 - 42	42 - 35	25 - 21
140 -110	90 - 70	77 - 60	70 - 51	63 - 49	63 - 49	63 - 49	62 - 48	55 - 43	55 - 43	53 - 42	53 - 42	53 - 42	52 - 41	52 - 41	42 - 33	35 - 27	21 - 16
110 - 80	70 - 51	60 - 44	55 - 40	49 - 36	49 - 36	49 - 36	48 - 35	43 - 31	43 - 31	42 - 30	42 - 30	42 - 30	41 - 30	41 - 30	33 - 24	27 - 20	16 - 12

	LDL>100
	100<LDL>70
	70<LDL>55
	<55

Figure 2 Estimated reduction of LDL-cholesterol levels with various combinations of the main cholesterol-lowering drugs. *Relative LDL-cholesterol reduction reported in the summary of product characteristics. AB, bempedoic acid; Ato, atorvastatin; Rosu, rosuvastatin; Sinva, sinvastatin.

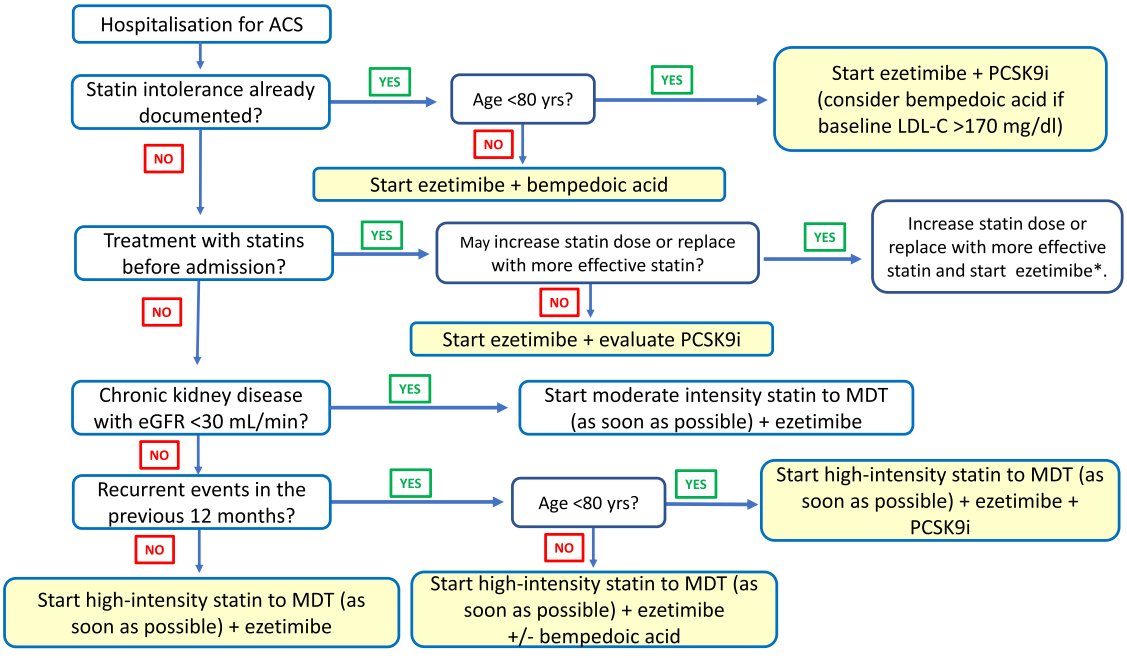

Figure 3 Initiation of cholesterol-lowering therapy during hospitalization in patient with acute coronary syndrome. *Also evaluate PCSK9 inhibitor addition in case of recurrent event. eGFR, estimated glomerular filtration rate; MDT, maximum tolerated dose; PCSK9i, PCSK9 inhibitors.

target recommended by international guidelines was achieved in a low percentage of cases. Other European survey data[78] and drug prescription data from Germany or Poland also suggested that ~20% of very high-risk patients achieved the previous guideline recommended target (≤70 mg/dL).[79,80] Even from analysis of Italian registries on ACS or very high-risk patients, where more than 85% of patients were discharged on statin therapy alone, attainment of the LDL-C target of <70 mg/dL was achieved in approximately half of patients.[81-83]

Proposed algorithm and intervention strategies

The patient with ACS requires a personalized therapeutic intervention, aimed at achieving the lipid targets clearly outlined in the guidelines. Indeed, LDL-C must be halved from baseline and brought below the threshold of 55 mg/dL.[75] In clinical practice, the physician must take into account all elements that may cause side effects and adverse reactions, remembering that most undesirable events occur when using high doses of statins, such as, for example, patients with hypothyroidism, chronic kidney disease, or vitamin D deficiency.[84] With the premise that any therapeutic strategy appears reasonable for the purpose of reducing LDL-C and that the early approach is safe and leads to a faster attainment of the target,[85] an intensive approach of cholesterol-lowering strategies is proposed, in compliance with the recommendations of the European guidelines and the criteria for drugs reimbursement. In this regard, the June 2022 update of the AIFA monitoring registers for PCSK9-inhibiting monoclonal antibodies allows these drugs to be used in secondary prevention for patients aged ≤80 years with LDL-C levels ≥ 70 mg/dL after a single LDL-C detection in case of recent AMI (last 12 months) or multiple CV events or with demonstrated intolerance to statins and/or ezetimibe. It is also important to consider that studies conducted over the past decades have made it possible to accurately quantify the estimated mean LDL-C reduction for each drug used. This makes possible to reliably predict the LDL-C levels that can be achieved with different therapeutic strategies by generating a simplified treatment algorithm for patients with ACS (*Figure 2*). In the proposed algorithm, statin therapy in ACS statin-naive patients should start during hospitalization as early as possible and should include the use of high-intensity statins, which provide at least a 50% reduction in LDL-C, in combination with ezetimibe[86,87] (*Figure 3*). In ACS patients on statin therapy, the drug and dosage in use prior to the event should first be considered. In patients with ACS with a history of established intolerance to statin treatment, it is reasonable to prescribe ezetimibe 10 mg/day and a PCSK9 inhibitor (*Table 2*); in addition, if the patient has high baseline LDL-C values (>150 mg/dL), it seems reasonable to immediately consider a combination with bempedoic acid (*Figure 3*). In patients with ACS and a history of chronic renal disease, associated with a glomerular filtration rate < 30 mL/min, it seems appropriate to consider the use of the combination of ezetimibe 10 mg with a moderate-intensity statin (*Table 3*) in order to reduce the risk of possible side effects or adverse reactions. In patients with at least one ACS event in the year prior to the index admission for ACS, it is reasonable, in subjects <80 years of age and especially if baseline LDL-C is > 150 mg/dL, to start with the triple therapy consisting of a high-intensity statin at the maximum tolerated dosage, ezetimibe and a PCSK9 inhibitor.[87] In patients over 80 years of age, it is possible to replace the PCSK9 inhibitor with bempedoic acid, bearing in mind that the average age of patients enroled in clinical trials of bempedoic acid to date is 65 years, so particular care is suggested in the use of this drug in older patients, especially when used in combination with high-dose statins.[88] In all cases it is however recommended to start treatment with a high-intensity statin and ezetimibe from discharge (*Figure 3*). Obviously, in order to improve therapeutic adherence, it is desirable to favour pre-constituted statin and ezetimibe combinations.[89] Lipid-lowering therapies should be continued indefinitely after discharge, taking care to verify the achievement and maintenance of the recommended lipid target over time (LDL-C reduced by 50% and <55 mg/dL). A first check of the LDL-C can be carried out 4 weeks after discharge, or according to the 'diagnostic-therapeutic care pathways' in force at the individual facility (*Figure 4*). Subsequent controls must be defined in relation to clinical needs. At each check-up, the patient's adherence to the prescriptions and the possible occurrence of side effects or adverse reactions correlated to lipid-lowering therapies must be checked.[1] In patients aged < 80 years who, at the first check-up, despite treatment with the maximum

Table 2 Options of currently and soon to be available cholesterol-lowering strategies in statin-intolerant patients and estimated LDL-cholesterol reduction

	Estimated reduction in LDL-cholesterol levels	
	>35%	>60%
Currently available options		Ezetimibe 10 + Alirocumab/ Evolocumab[a]
Soon available options	Bempedoic acid 180 + Ezetimibe 10	Bempedoic acid 180 + Ezetimibe 10 + Anti-PCSK9[a] Ezetimibe 10 + Inclisiran

[a]Monoclonal antibodies (alirocumab or evolocumab) or siRNA (inclisiran).

Table 3 Type and dosages of high- and moderate-intensity statins

High-intensity statins[a]	Moderate-intensity statins[b]
Atorvastatin 40-80 mg Rosuvastatin 20-40 mg	Atorvastatin 10-20 mg Rosuvastatin 5-10 mg Simvastatin 20-40 mg Pravastatin 40-80 mg Lovastatin 40 mg Fluvastatin 80 mg Pitavastatin 2-4 mg

[a]Daily dose reduces LDL-C by ~50%.
[b]Daily dose reduces LDL-C by ~30-49%.

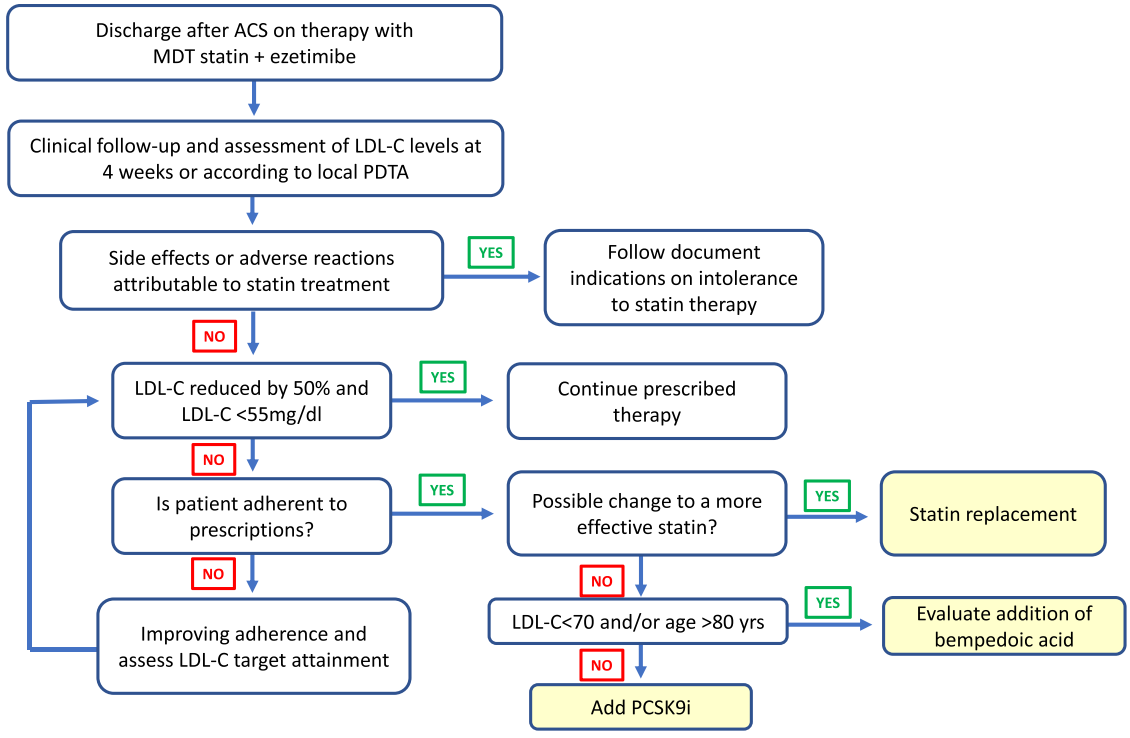

Figure 4 Management of cholesterol-lowering treatment after hospital discharge for acute coronary syndrome in patients already treated with the statin/ezetimibe combination. ACS, acute coronary syndrome; LDL-C, LDL-cholesterol; MDT, maximum tolerated dose; PDTA, diagnostic-therapeutic care pathway.

tolerated dose of a high-intensity statin do not reach the target and have LDL-C values > 70 mg/dL, the addition of a PCSK9 inhibitor should be considered (*Figure 4*). In elderly patients (≥ 80 years) with LDL-C values between 55 and 70 mg/dL, the addition of bempedoic acid[88] can be considered (*Figure 4*). If side effects or adverse reactions develop during statin treatment, a reduction of the statin dosage may be considered. This measure ensures a lower risk of side effects and improved therapeutic adherence. The management of these patients, however, must conform to the suggestions of the ANMCO document on the diagnostic-therapeutic pathway in patients with hypercholesterolaemia and intolerance to statin therapy.[90]

Extreme risk and elderly patients

There are two groups of patients who have precise indications for lipid-lowering therapy intensification in guidelines and regulatory bodies, namely patients with infarct recurrence (extreme risk) and elderly patients. These two types of patients are increasingly encountered in secondary prevention, thanks also to the improvement in treatment of ACS, which has led to a lengthening of life expectancy with a concomitant worsening of clinical conditions and an increase in comorbidities. Patients with ACS recurrence within 1-2 years after the index event constitute 10-20% of patients admitted for ACS and have an extremely higher short- and medium-term risk of CV events and mortality than patients with no history of ACS events.[91] In the EYESHOT POST-MI study which included ~1600 patients with myocardial infarction in 165 Italian cardiology centres, 13% had a history of 2 and 5% more than three infarct events. The latter had more risk factors and were older than patients at their first ACS event.[92] According to registries conducted in cardiology intensive care units, patients aged ≥ 75 years represent ~30% of patients with an ST-segment elevation ACS and 40% of those without ST-segment elevation ACS.[3,93-95] These data underestimate the true number of elderly patients with ACS since more than 17% of these patients are admitted to non-cardiac wards.[96] Elderly patients constitute a group of patients at high risk and clinical complexity that requires geriatric and interdisciplinary evaluation in order to pursue a holistic approach and optimize therapeutic strategies on the basis of individual biological vulnerability.[96]

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No new data were generated or analysed in support of this research.

References

1. Colivicchi F, Gulizia MM, Arca M, Abrignani M, Perna GP, Mureddu GF *et al*. Position paper ANMCO: Gestione clinica dell'ipercolesterolemia dopo sindrome coronarica acuta. *G Ital Cardiol* 2016;**17**:456–461.
2. Gulizia MM, Colivicchi F, Ricciardi G. Documento di consenso intersocietario ANMCO/ISS/AMD/ANCE/ARCA/FADOI/GICR-IACPR/SICI-GISE/SIBioC/SIC/SICOA/SID/SIF/SIMEU/SIMG/SIMI/SISA Colesterolo e rischio cardiovascolare: percorso diagnostico-terapeutico in Italia. *G Ital Cardiol* 2016;**17**:3S–57S.
3. De Luca L, Marini M, Gonzini L, Boccanelli A, Casella G, Chiarella F *et al*. Contemporary trends and age-specific sex differences in management and outcome for patients with ST-segment elevation myocardial infarction. *J Am Heart Assoc* 2016;**5**:e004202.
4. De Luca L, Cicala SD, D'Errigo P. Impact of age, gender and heart failure on mortality trends after acute myocardial infarction in Italy. *Int J Cardiol* 2022;**348**:147–151.
5. Cannon CP, Braunwald E, McCabe CH, Rader DJ, Rouleau JL, Belder R *et al*. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med* 2004;**350**:1495–1504.
6. Cholesterol Treatment Trialists Collaboration; Baigent C, Blackwell L, Emberson J *et al*. 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.
7. Ference BA, Ginsberg HN, Graham I, Ray KK, Packard CJ, Bruckert E *et al*. Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis sSociety Consensus Panel. *Eur Heart J* 2017;**38**:2459–2472.
8. Ference BA, Yoo W, Alesh I, Mirowska KK, Mewada A, Khan J *et al*. Effect of long-term exposure to lower low density lipoprotein cholesterol beginning early in life on the risk of coronary heart disease. *J Am Coll Cardiol* 2012;**60**:2631–2639.
9. Sabatine MS, Wiviott SD, Im K, Murphy SA, Giugliano RP. Efficacy and safety of further lowering of low-density lipoprotein cholesterol in patients starting with very low levels: a meta-analysis. *JAMA Cardiol* 2018;**3**:823–828.
10. Fyfe T, Baxter RH, Cochran KM, Booth EM. Plasma-lipid changes after myocardial infarction. *Lancet* 1971;**2**:997–1001.
11. Fresco C, Maggioni AP, Signorini S, Merlini PA, Mocarelli P, Fabbri G *et al*. Variations in lipoprotein levels after myocardial infarction and unstable angina: the LATIN trial. *Ital Heart J* 2002;**3**:587–592.
12. Pitt B, Loscalzo J, Ycas J, Raichlen JS. Lipid levels after acute coronary syndromes. *J Am Coll Cardiol* 2008;**51**:1440–1445.
13. Briel M, Schwartz GG, Thompson PL, de Lemos JA, Blazing MA, van Es GA *et al*. Effects of early treatment with statins on short-term clinical outcomes in acute coronary syndromes: a meta-analysis of randomized controlled trials. *JAMA* 2006;**295**:2046–2056.
14. Heeschen C, Hamm C, Laufs U Snapinn S, Böhm M, White HD *et al*. Withdrawal of statins increases event rates in patients with acute coronary syndromes. *Circulation* 2002;**105**:1446–1452.
15. Aronow H, Topol E, Roe M, Houghtaling P. Effect of lipidlowering therapy on early mortality after acute coronary syndromes: an observational study. *Lancet* 2001;**357**:1063–1068.
16. Spencer FA, Allegrone J, Goldberg RJ, Gore JM, Fox KA, Granger CB *et al*. Association of statin therapy with outcomes of acute coronary syndromes: the Grace Study. *Ann Intern Med* 2004;**140**:857–866.
17. Lenderink T, Boersma E, Gitt A, Zeymer U, Wallentin R, van de Werf F *et al*. Patients using statin treatment within 24 h after admission for ST-elevation acute coronary syndromes had lower mortality than non-users: a report from the First Euro Heart Survey on Acute Coronary Syndromes. *Eur Heart J* 2006;**27**:1799–1804.
18. Schubert J, Lindahl B, Melhus H Renlund H, Leosdottir M, Yari A *et al*. Low-density lipoprotein cholesterol reduction and statin intensity in myocardial infarction patients and major adverse outcomes: a Swedish nationwide cohort study. *Eur Heart J* 2021;**42**:243–252.
19. Kesteloot H, Claeys G, Blanckaert N, Lesaffre E. Time course of serum lipids and apolipoproteins after acute myocardial infarction: modification by pravastatin. *Acta Cardiol* 1997;**52**:107–116.
20. Hartog FD, Van Kalmthout P, Van Loenhout T, Schaafsma HJ, Rila H, Verheugt FW *et al*. Pravastatin in acute ischaemic syndromes: results of a randomised placebo-controlled trial. *Int J Clin Pract* 2001;**55**:300–304.
21. Schwartz G, Olsson A, Ezekowitz M, Rifai N, Sasiela WJ, Szarek M *et al*. Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes: the MIRACL Study: a randomized controlled trial. *JAMA* 2001;**285**:1711–1718.
22. Kayikcioglu M, Can L, Kultursay H, Payzin S, Turkoğlu C *et al*. Early use of pravastatin in patients with acute myocardial infarction undergoing coronary angioplasty. *Acta Cardiol* 2002;**57**:295–302.
23. Serruys P, De Feyter P, Macaya C Kokott N, Puel J, Vrolix M, Branzi A *et al*. Fluvastatin for prevention of cardiac events following successful first percutaneous coronary intervention: a randomized controlled trial. *JAMA* 2002;**287**:3215–3222.
24. Okazaki S, Yokoyama T, Miyauchi K, Shimada K, Kurata T, Sato H *et al*. Early statin treatment in patients with acute coronary syndrome: demonstration of the beneficial effect on atherosclerotic lesions by serial volumetric intravascular ultrasound analysis during half a year after coronary event: the Establish Study. *Circulation* 2004;**110**:1061–1068.
25. Thompson P, Meredith I, Amerena J, Campbell TJ, Sloman J, Harris P *et al*. Effect of pravastatin compared with placebo initiated within 24 hours of onset of acute myocardial infarction or unstable angina: the Pravastatin in Acute Coronary Treatment (PACT) Trial. *Am Heart J* 2004;**148**:e2.
26. Macin S, Perna E, Farias E, Franciosi V, Cialzeta JR, Brizuela M *et al*. Atorvastatin has an important acute anti-inflammatory effect in patients with acute coronary syndrome: results of a randomized, double-blind, placebo-controlled study. *Am Heart J* 2005;**149**:451–457.
27. Ren HZ, Ma LL, Wang LX. Effect of simvastatin on plasma interleukin-6 in patients with unstable angina. *Clin Invest Med* 2009;**32**:E280–E284.
28. Ostadal P, Alan D, Vejvoda J, Macek M, Hajeck P, Mates M *et al*. Fluvastatin in the first-line therapy of acute coronary syndrome: results of the multicenter, randomized, doubleblind, placebo-controlled trial (the FACS-Trial). *Trials* 2010;**11**:61.
29. Patti G, Pasceri V, Colonna G, Miglionico M, Fischetti D, Sardella G *et al*. Atorvastatin pretreatment improves outcomes in patients with acute coronary syndromes undergoing early percutaneous coronary intervention: results of the ARMYDA-ACS randomized trial. *J Am Coll Cardiol* 2007;**49**:1272–1278.
30. Giraldez RR, Giugliano RP, Mohanavelu S, Murphy SA, MacCabe C, Cannon C *et al*. Baseline low-density lipoprotein cholesterol is an important predictor of the beneft of intensive lipid-lowering therapy: a PROVE IT-TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Terapy-Trombolysis In Myocardial Infarction 22) analysis. *J Am Coll Cardiol* 2008;**52**:914–920.
31. Sudhop T, Lutjohann D, Kodal A Igel M, Tribble D, Shah S *et al*. Inhibition of intestinal cholesterol absorption by ezetimibe in humans. *Circulation* 2002;**106**:1943–1948.
32. Cannon CP, Blazing MA, Giugliano RP, McCagg A, White J, Theroux P *et al*. Ezetimibe added to statin therapy after acute coronary syndromes. *N Engl J Med* 2015;**372**:2387–2397.
33. Eisen A, Cannon CP, Blazing MA, Bohula E, Park J, Murphy SA *et al*. The benefit of adding ezetimibe to statin therapy in patients with prior coronary artery bypass graft surgery and acute coronary syndrome in the IMPROVE-IT trial. *Eur Heart J* 2016;**37**:3576–3584.
34. Giugliano RP, Cannon CP, Blazing MA, Nicolau JC, Corbalán R, Špinar J *et al*. Benefit of adding ezetimibe to statin therapy on cardiovascular outcomes and safety in patients with versus without diabetes mellitus: results from IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial). *Circulation* 2018;**137**:1571–1582.
35. Hagiwara N, Kawada-Watanabe E, Koyanagi R, Arashi H, Yamaguchi J, Nakao K *et al*. Low-density lipoprotein cholesterol targeting with pitavastatin + ezetimibe for patients with acute coronary syndrome and dyslipidaemia: the HIJ-PROPER study, a prospective, open-label, randomized trial. *Eur Heart J* 2017;**38**:2264–2276.
36. Im J, Kawada-Watanabe E, Yamaguchi J, Arashi H, Otsuki H, Matsui Y *et al*. Baseline low-density lipoprotein cholesterol predicts the benefit of adding ezetimibe on statin in statin-naïve acute coronary syndrome. *Sci Rep* 2021;**11**:7480.
37. Pinkosky SL, Newton RS, Day EA, Ford RJ, Lhotak S, Austin RC *et al*. Liver-specific ATP-citrate lyase inhibition by bempedoic acid decreases LDL-C and attenuates atherosclerosis. *Nat Commun* 2016;**7**:13457.
38. Ray KK, Bays HE, Catapano AL, Lalwani ND, Bloedon L, Sterling L *et al*. Safety and efficacy of bempedoic acid to reduce LDL cholesterol. *N Engl J Med* 2019;**380**:1022–1032.

39. Goldberg AC, Leiter LA, Stroes ESG, Baum S, Hanselman J, Bloedon L *et al*. Effect of bempedoic acid vs placebo added to maximally tolerated statins on low-density lipoprotein cholesterol in patients at high risk for cardiovascular disease: the CLEAR Wisdom randomized clinical trial. *JAMA* 2019;**322**:1780–1788.
40. Di Minno A, Lupoli R, Calcaterra I, Poggio P, Forte F, Spadarella G *et al*. Efficacy and safety of bempedoic acid in patients with hypercholesterolemia: systematic review and meta-analysis of randomized controlled trials. *J Am Heart Assoc* 2020;**9**:e016262.
41. Navarese EP, Kolodziejczak M, Kereiakes DJ, Tantry U, O'Connor C, Gurbel PA. Proprotein convertase subtilisin/kexin type 9 Monoclonal antibodies for acute coronary syndrome: a narrative review. *Ann Intern Med* 2016;**164**:600–607.
42. Ding Z, Liu S, Wang X Deng X, Fan Y, Shahanawaz J *et al*. Cross-talk between LOX-1 and PCSK9 in vascular tissues. *Cardiovasc Res* 2015;**107**: 556–567.
43. Wu CY, Tang ZH, Jiang L, Li XF, Jiang ZS, Liu LS. PCSK9 siRNA inhibits HUVEC apoptosis induced by ox-LDL via Bcl/Bax-caspase9- caspase3 pathway. *Mol Cell Biochem* 2012;**359**:347–358.
44. Tang Z, Jiang L, Peng J, Wei D, Wu C, Pan L *et al*. PCSK9 siRNA suppresses the inflammatory response induced by oxLDL through inhibition of NF-B activation in THP-1-derived macrophages. *Int J Mol Med* 2012;**30**:931–938.
45. Chi H, Messas E, Levine RA, Graves DT, Amar S. Interleukin-1 receptor signaling mediates atherosclerosis associated with bacterial exposure and/or a high-fat diet in a murine apolipoprotein E heterozygote model: pharmacotherapeutic implications. *Circulation* 2004;**110**: 1678–1685.
46. Sawamura T, Kume N, Aoyama T Moriwaki H, Hoshikawa H, Aiba Y *et al*. An endothelial receptor for oxidized low-density lipoprotein. *Nature* 1997;**386**:73–77.
47. Ehara S, Ueda M, Naruko T, Haze K, Itoh A, Otsuka M *et al*. Elevated levels of oxidized low density lipoprotein show a positive relationship with the severity of acute coronary syndromes. *Circulation* 2001; **103**:1955–1960.
48. Kuhnast S, van der Hoorn JW, Pieterman E, van de Hoek A, Sasiela W, Gusarova V *et al*. Alirocumab inhibits atherosclerosis, improves the plaque morphology, and enhances the effects of a statin. *J Lipid Res* 2014;**55**:2103–2112.
49. Zhang Y, Liu J, Li S Xu RX, Sun J, Tang Y *et al*. Proprotein convertase subtilisin/kexin type 9 expression is transiently upregulated in the acute period of myocardial infarction in rat. *BMC Cardiovasc Disord* 2014;**14**:192.
50. Guedeney P, Giustino G, Sorrentino S, Claessen BE, Camaj A, Kalkman DN *et al*. Efficacy and safety of alirocumab and evolocumab: a systematic review and meta-analysis of randomized controlled trials. *Eur Heart J* 2019:ehz430 doi: 10.1093/eurheartj/ehz430 ahead of print.
51. Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott S, Murphy SA *et al*. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N Engl J Med* 2017;**376**:1713–1722.
52. Schwartz GG, Steg PG, Szarek M, Bhatt DL, Bittner VA, Diaz R *et al*. Alirocumab and cardiovascular outcomes after acute coronary syndrome. *N Engl J Med* 2018;**379**:2097–2210.
53. O'Donoghue ML, Giugliano RP, Wiviott SD, Atar D, Keech A, Kuder JF *et al*. Long-Term evolocumab in patients with established atherosclerotic cardiovascular disease. *Circulation* 2022;**146**:1109–1119.
54. Gencer B, Mach F, Murphy SA, De Ferrari GM, Huber K, Lewis BS *et al*. Efficacy of evolocumab on cardiovascular outcomes in patients with recent myocardial infarction: a prespecified secondary analysis from the FOURIER Trial. *JAMA Cardiol* 2020;**5**:1–6.
55. Steg PG, Szarek M, Bhatt DL, Bittner VA, Brégeault MF, Dalby AJ *et al*. Effect of alirocumab on mortality after acute coronary syndromes. *Circulation* 2019;**140**:103–112.
56. Bays HE. Alirocumab, decreased mortality, nominal significance, p values, Bayesian statistics, and the duplicity of multiplicity. *Circulation* 2019;**140**:113–116.
57. Bittner VA, Szarek M, Aylward PE, Bhatt DL, Diaz R, Edelberg JM *et al*. Effect of alirocumab on lipoprotein(a) and cardiovascular risk after acute coronary syndrome. *J Am Coll Cardiol* 2020;**75**:133–144.
58. Raal FJ, Giugliano RP, Sabatine MS, Koren MJ, Blom D, Seidah N *et al*. PCSK9 inhibition-mediated reduction in Lp(a) with evolocumab: an analysis of 10 clinical trials and the LDL receptor's role. *J Lipid Res* 2016;**57**:1086–1096.
59. Fitzgerald K, White S, Borodovsky A, Bettencourt BR, Strahs A, Clausen V *et al*. A highly durable RNAi therapeutic inhibitor of PCSK9. *N Engl J Med* 2017;**376**:41–51.
60. Ray KK, Landmesser U, Leiter LA, Kallend D, Dufour R, Karakas M *et al*. Inclisiran in patients at high cardiovascular risk with elevated LDL cholesterol. *N Engl J Med* 2017;**376**:1430–1440.
61. Ray KK, Wright RS, Kallend D, Koenig W, Leiter LA, Raal FJ *et al*. Two phase 3 trials of inclisiran in patients with elevated LDL cholesterol. *N Engl J Med* 2020;**382**:1507–1519.
62. Stoekenbroek RM, Kallend D, Wijngaard PL, Kastelein JJ. Inclisiran for the treatment of cardiovascular disease: the ORION clinical development program. *Future Cardiol* 2018;**14**:433–444.
63. Koskinas KC, Windecker S, Pedrazzini G, Mueller C, Cook S, Matter CM *et al*. Evolocumab for early reduction of LDL cholesterol levels in patients with acute coronary syndromes (EVOPACS). *J Am Coll Cardiol* 2019;**74**:2452–2462.
64. Leucker TM, Blaha MJ, Jones SR, Vavuranakis MA, Williams MS, Lai H *et al*. Effect of evolocumab on atherogenic lipoproteins during the peri- and early postinfarction period: a placebo-controlled, randomized trial. *Circulation* 2020;**142**:419–421.
65. Mehta SR, Pare G, Lonn EM, Jolly SS, Natarajan M, Pinila-Echeverri N *et al*. Effects of routine early treatment with PCSK-9 inhibitor in patients undergoing primary percutaneous coronary intervention for ST-segment elevation myocardial infarction: a randomized, double-blind, sham-controlled trial. *EuroIntervention*; doi: 10.4244/EIJ-D-22-00735. Published online ahead of print 19 September 2022.
66. Stone GW, Maehara A, Lansky AJ, de Bruine B, Cristea E, Mintz GS *et al*. A prospective natural-history study of coronary atherosclerosis. *N Engl J Med* 2011;**364**:226–235.
67. Schartl M, Bocksch W, Koschyk D, Voelker V, Karsch K, Kreuzer J *et al*. Use of intravascular ultrasound to compare effects of different strategies of lipid-lowering therapy on plaque volume and composition in patients with coronary artery disease. *Circulation* 2001;**104**:387–392.
68. Kawasaki M, Sano K, Okubo M, Ito Y, Murata I, Tsuchiya k *et al*. Volumetric quantitative analysis of tissue characteristics of coronary plaques after statin therapy using three-dimensional integrated backscatter intravascular ultrasound. *J Am Coll Cardiol* 2005;**45**: 1946–1953.
69. Nakamura D, Shimamura K, Capodanno D, Attizzani G, Fineschi M, Musumeci G *et al*. Fate of nonculprit plaques in patients with STEMI undergoing primary PCI followed by statin therapy: a serial Optical coherence tomography analysis from the OCTAVIA study. *JACC Cardiovasc Imaging* 2017;**10**:827–829.
70. Nicholls SJ, Puri R, Anderson T, Ballantyne CM, Cho L, Kastelein JJ *et al*. Effect of evolocumab on progression of coronary disease in statin-treated patients: the GLAGOV randomized clinical trial. *JAMA* 2016;**316**:2373–2384.
71. Nicholls SJ, Kataoka Y, Nissen SE, Prati F, Windecker S, Puri R, Hucko T *et al*. Effect of evolocumab on coronary plaque phenotype and burden in statin-treated patients following myocardial infarction. *JACC Cardiovasc Imaging* 2022;**15**:1308–1321.
72. Hoogeveen RM, Opstal TSJ, Kaiser Y, Stiekema LCA, Kroon J, Knoll RJ *et al*. PCSK9 Antibody alirocumab attenuates arterial wall inflammation without changes in circulating inflammatory markers. *JACC Cardiovasc Imaging* 2019;**12**:2571–2573.
73. Räber L, Ueki Y, Otsuka T, Losdat S, Häner JD, Lonborg J *et al*. Effect of alirocumab added to high-intensity statin therapy on coronary atherosclerosis in patients with acute myocardial infarction: the PACMAN-AMI randomized clinical trial. *JAMA* 2022;**327**:1771–1781.
74. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS *et al*. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. *Circulation* 2019;**139**:e1082–e1143.
75. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L *et al*. 2019 ESC/EAS guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J* 2019;**41**: 111–188.
76. Claessen BE, Guedeney P, Gibson CM, Gibson CM, Angiolillo DJ, Cao D *et al*. Lipid management in patients presenting with acute coronary syndromes: a review. *J Am Heart Assoc* 2020;**9**:e018897.
77. Ray KK, Molemans B, Schoonen WM, Giovas P, Bray S, Kiru G *et al*. EU-wide crosssectional observational study of lipid-modifying therapy

use in secondary and primary care. *Eur J Prev Cardiol* 2021;**28**: 1279–1211.
78. De Backer G, Jankowski P, Kotseva K Mirrakhimov E, Reiner Ž, Rydén L *et al*. Management of dyslipidaemia in patients with coronary heart disease: results from the ESC-EORP EUROASPIRE V survey in 27 countries. *Atherosclerosis* 2019;**285**:135–146.
79. Fox KM, Tai MH, Kostev K, Hatz M, Qian Y, Laufs U. Treatment patterns and low-density lipoprotein cholesterol (LDL-c) goal attainment among patients receiving high- or moderate-intensity statins. *Clin Res Cardiol* 2018;**107**:380–388.
80. Dyrbus K, Gasior M, Desperak P, Nowak J, Osadnik T, Banach M. Characteristics of lipid profile and effectiveness of managemnt of dyslipidaemia in patients with acute coronary syndromes—data from the TERCET registry with 19,287 patients. *Pharmacol Res* 2019;**139**: 460–466.
81. De Luca L, Arca M, Temporelli PL, Meessen J, Riccio C, Bonomo P *et al*. Current lipid lowering treatment and attainment of LDL targets recommended by ESC/EAS guidelines in very high-risk patients with established atherosclerotic cardiovascular disease: insights from the START registry. *Int J Cardiol* 2020;**316**:229–235.
82. Silverio A, Benvenga RM, Piscione F, Gulizia MM, Maessen J, Colivicchi F *et al*. Prevalence and predictors of out-of-target LDL cholesterol 1 to 3 years after myocardial infarction. A subanalysis from the EYESHOT post-MI registry. *J Cardiovasc Pharm Therap* 2020;**26**:149–157.
83. Colivicchi F, Gulizia MM, Arca M, Temporelli PL, Gonzini L, Venturelli V *et al*. Lipid lowering treatment and eligibility for PCSK9 inhibition in post-myocardial infarction patients in Italy: insights from two contemporary nationwide registries. *Cardiovasc Ther* 2020;**2020**: 3856242.
84. Pasternak RC, Smith SC, BaireyMerz CN, Grundy SM, Cleeman JI, Lenfant C. ACC/AHA/NHLBI clinical advisory on the use and safety of statins. *Stroke* 2002;**33**:2337–2341.
85. Ray KK, Reeskamp LF, Laufs U, Banach M, Mach F, Tokgözoğlu LS *et al*. Combination lipid-lowering therapy as first-line strategy in very high-risk patients. *Eur Heart J* 2022;**43**:830–833.
86. Bilato C, Caldarola P, Musumeci G. Il controllo del rischio lipidico nel paziente con malattia coronarica nella pratica clinica: i risultati della consensus BEST. *G Ital Cardiol* 2023.
87. Zuin M, Rigatelli G, Caldarola P Colivichi F, Roncon L, Bilato C *et al*. Efficacia nel mondo reale delle attuali strategie per la riduzione del colesterolo LDL dopo sindrome coronarica acuta. Cambiare il paradigma di trattamento. *G Ital Cardiol* 2023;**24**:30–40.
88. Colivicchi F, Di Fusco SA, Gabrielli D. Acido bempedoico: una nuova opportunità terapeutica per la cura dell'ipercolesterolemia. *G Ital Cardiol* 2021;**22**:301–310.
89. De Luca L, Corsini A, Uguccioni M, Colivicchi F. Statins plus ezetimibe in the era of proprotein convertase subtilisin/kexin type 9 inhibitors. *Kardiol Pol* 2020;**78**:850–860.
90. Gulizia MM, Colivicchi F, Arca M. Position paper ANMCO: Percorso diagnostico-terapeutico nel paziente con ipercolesterolemia e intolleranza alla terapia con statine. *G Ital Cardiol* 2016;**17**:447–455.
91. De Luca L, Paolucci L, Nusca A, Putini R, Mangiacapra F, Natale E *et al*. Current management and prognosis of patients with recurrent myocardial infarction. *Rev Cardiovasc Med* 2021;**22**:731–740.
92. De Luca L, Colivicchi F, Gabrielli D, Lucci D, Grippo G, Piemonte F *et al*. Incidence, characteristics, and management of patients with recurrent myocardial infarctions: insights from the EYESHOT POST-MI. *J Interv Cardiol* 2022;**2022**:4593325.
93. De Luca L, Leonardi S, Cavallini Cl. Contemporary antithrombotic strategies in patients with acute coronary syndrome admitted to cardiac care units in Italy: the EYESHOT study. *Eur Heart J Acute Cardiovasc Care* 2015;**4**:441–452.
94. De Luca L, Olivari Z, Bolognese L, Lucci D, Gonzini L, Di Chiara A *et al*. A decade of changes in clinical characteristics and management of elderly patients with non-ST elevation myocardial infarction admitted in Italian cardiac care units. *Open Heart* 2014;**1**:e000148.
95. Schoenenberger W, Radovanovic D, Windecker S. Temporal trends in the treatment and outcomes of elderly patients with acute coronary syndrome. *Eur Heart J* 2016;**37**:1304–1311.
96. Morici N, De Servi S, De Luca L, Crimi G, Montalto C, De Rosa R *et al*. Management of acute coronary syndromes in older adults. *Eur Heart J* 2022;**43**:1542–1553.