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OPTIMAL USE OF LIPID-LOWERING THERAPY AFTER ACUTE CORONARY SYNDROMES:

A Position Paper endorsed by *the International Lipid Expert Panel (ILEP)*

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ABBREVIATIONS:

ACS	Acute coronary syndromes
ASCVD	atherosclerotic cardiovascular disease
EAPCI	European Association of Percutaneous Cardiovascular Interventions
EAS	European Atherosclerosis Society
ESC	European Society of Cardiology
IHD	Ischaemic heart disease
LDL-C	low density lipoprotein cholesterol
LLT	Lipid-lowering therapy
PCSK9	Proprotein convertase subtilisin/kexin type 9
PCSK9I	Proprotein convertase subtilisin/kexin type 9 inhibitor.
SCORE	Systematic COronary Risk Evaluation

ABSTRACT:

Atherosclerotic cardiovascular disease (ASCVD) and consequent acute coronary syndromes (ACS) are substantial contributors to morbidity and mortality across Europe. Much of these diseases burden is modifiable, in particular by lipid-lowering therapy (LLT). Current guidelines are based on the sound premise that with respect to low density lipoprotein cholesterol (LDL-C), "*lower is better for longer",* and the recent data have strongly emphasized the need of also "*the earlier the better*". In addition to statins, which have been available for several decades, the availability of ezetimibe and inhibitors of proprotein convertase subtilisin/kexin type 9 (PCSK9) are additional very effective approach to LLT, especially for those at very high and extremely high cardiovascular risk. LLT is initiated as a response to an individual's calculated risk of future ASCVD and is intensified over time in order to meet treatment goals. However, in real-life clinical practice goals are not met in a substantial proportion of patients. This Position Paper complements existing guidelines on the management of lipids in patients following ACS. Bearing in mind the very high risk of further events in ACS, we propose practical solutions focusing on immediate combination therapy in strict clinical scenarios, to improve access and adherence to LLT in these patients. We also define an 'Extremely High Risk' group of individuals following ACS, completing the attempt made in the recent European guidelines, and suggest mechanisms to urgently address lipid-medicated cardiovascular risk in these patients.

Key words: combination therapy, effectiveness, ezetimibe, PCSK9 inhibitors, safety, statins.

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1. INTRODUCTION

Atherosclerotic cardiovascular disease (ASCVD), results in myocardial ischaemia, and is a substantial contributor to morbidity and mortality across Europe and worldwide[1]. In 2017, about 34.9 million people were estimated to live with ischaemic heart disease (IHD) in 54 European Society of Cardiology (ESC) member countries, resulting in an estimated cost of €59 billion in 2015[2]. The median number of age-standardized disability adjusted life-years (DALYs) due to CVD, was 4530 per 100 000 inhabitants of ESC member countries, of which 54% were attributable to IHD[2]. The European Association of Percutaneous Cardiovascular Interventions (EAPCI) have reported an annual median of 2478 percutaneous coronary intervention (PCI) procedures per million people[3]. Much of this disease burden is modifiable, in particular by lipid-lowering therapy (LLT)[4, 5]. In addition, to statins and ezetimibe, the availability of proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9is) presents an additional opportunity to reduce the risk of ASCVD. These new agents are more expensive than other LLTs, and therefore should be prioritised for use in those patients who are most likely to benefit from them. These are particularly patients at very high risk of ASCVD, including many who have already experienced an acute coronary syndrome (ACS)[6, 7].

Multiple sources of evidence demonstrate that an individual's lifetime exposure to low density lipoprotein cholesterol (LDL-C) determines their risk of ASCVD[4, 8]. In patients who have had a myocardial infarction, poor adherence to statin therapy is common, and is associated with worse outcomes [9, 10], attainment of treatment targets is poor[11], and higher-intensity LLT results in fewer ASCVD events than less-intensive treatment[12,13]. Whilst primary prevention uses prediction tools such as Systematic COronary Risk Evaluation (SCORE) to grade risk[14], post ACS patients are categorised as 'very high risk' in current ESC/European Atherosclerosis Society (EAS) dyslipidaemia guidelines[15], although they are in fact a heterogeneous group, in which risk factors can be used to identify those individuals at more

than the highest risk of further ASCVD events[16]. Those individuals with the highest absolute risk, are likely to receive the largest benefit from the innovative treatment with PCSK9 inihibitors[5]

Taking these facts into account, there is an urgent need to ensure that guideline-directed LLT is prescribed to all ACS patients, and to ensure that those individuals at greatest risk of recurrent events can access the most efficacious LLT without delay, thereby reducing their exposure to elevated LDL-C. It is especially important as the recent ESC/EAS guidelines in many places are more academic than clinical, and in many countries it is not possible to be on target <55 mg/dl (1.4 mmol/l) for very high risk and <40 (1.0 mmol/l) for the extremely high risk patients not due to lack of knowledge or nonadherence, but simply due to lack of availability of effective LLT. In many countries of Central and Southern Europe (represented by the experts in this Position Paper) not only are PCSK9 inhibitors limited and reimbursed only for very selected groups of patients, but even the availability of all statins and ezetimibe is sometimes limited and e.g., can be prescribed only by the specialists and without co-payment only for selected indications. These are arguments for giving an opportunity for much more ACS patients to achieve LDL-C target but also it is a loud call-for-action to support the experts in those countries in their negotiations with the healthcare providers and insurers to allow them to use all available therapies for those patients.

2. GUIDELINE CONTEXT

The use of LLT in ACS is covered in the 2019 ESC/EAS guidelines for the management of dyslipidaemias[15], a wide-ranging document, which deals with a range of primary and secondary prevention scenarios. The guidelines are based on sound principles of LDL-C reduction: the earlier the better, the lower the better, the longer the better[17,18], and strong recommendation for cardiac rehabilitation programmes[15,19,20]. The importance and benefit of early access to

statin therapy is hightlighted[14,21-23]. The guidelines recommend intensification of statin therapy and addition of ezetimibe, if treatment targets are not met (Class IIa)[15]. Furthermore, if the LDL-C goal is not achieved after 4 - 6 weeks despite maximally tolerated statin therapy and ezetimibe, addition of a PCSK9 inhibitor is recommended (Class 1)[15]. These guidelines for the first time also suggested the possibility of introduction of PCSK9 inhibitors for ACS patients during hospitalization (Class IIa). However due to the reimbursement criteria in most countries, this recommendation is simply not applicable.

Nevertheless, this incremental approach of adding drugs after failing to meet targets does not allow for the fact that the proportional lipid reduction achievable with current treatments is predictable[15], and in many cases with very high baseline LDL-C, monotherapy is extremely unlikely to enable patients to reach their treatment targets[24-26]. This results in delay to target attainment and unnecessary further exposure to LDL-C. Furthermore, the guidelines treat all ACS patients (*"Documented ASCVD, either clinical or unequivocal on imaging. Documented ASCVD includes previous ACS (MI or unstable angina), stable angina, coronary revascularization (PCI, CABG, and other arterial revascularization procedures), stroke and TIA, and peripheral arterial disease.)* as 'very high risk', without allowing for variability within this group[15].

There is therefore a strong argument to initiate therapy with multiple drugs (double or even triple therapy) immediately during hospitalization or during the visit, in the highest-risk patients - an approach which is already used in the management of hypertension[24-27].

3. OVERARCHING AIM

This Position Paper complements existing guidelines on the management of lipids in patients after ACS. Bearing in mind the very high risk of further events in patients with ACS, we propose practical approaches to improve access and adherence to LLT in these patients. We also adopt the definition of an '*Extremely High Risk'* group of individuals following ACS and

suggest strategies to urgently address lipid-medication of cardiovascular risk in these patients. The position paper is based entirely on evidence relating to the clinical effectiveness of LLTs, rather than pharmacoeconomic evaluations.

4. DEVELOPMENT OF POSITION PAPER

The ACS EuroPath Central & South European Countries Project started with a videoconference meeting in June 2020 between members of the Steering Committee (comprised of International Lipid Expert Panel members), and representatives from Bosnia & Herzegovina, Croatia, Czech Republic, Greece, Hungary, Poland, Romania, Slovakia and Slovenia who discussed current clinical practice, including availability of hypolipidemic drugs, data gathering (ACS registries), organization of healthcare systems as a way to understand unmet needs, identification of post ACS patients most in need for LLT intensification, and strategies for optimal lipid management. In a second (December 2020) videoconference, representatives from each country gave an update of lipid-lowering practice in their region, with a particular focus on areas for improvement. Members of the steering committee summarized the information and presented draft practice recommendations, which could be universally applicable in all states. These recommendations were discussed during the videoconference. All participants were also able to engage in online discussion *via* a web forum before, during and after the meeting. The consensus from these discussions was basis for drafting this Position Paper, which was then refined by consensus amongst Steering Committee members.

5. CURRENT SITUATION IN EUROPE

Information relating to the current status of post-ACS therapy with respect to access to LLT, procedures for intensification of therapy, lipid measurement, follow-up and rehabilitation

were collected for all countries participating in the development of the Position Paper (**Table 1**) and are summarised below.

5.1. Availability of drugs and reimbursement

In most countries represented, statins are widely available, usually with very little or no requirement for co-payment. However, there are still countries in which prescribing even with co-payment is only possible for specific clinical indications – sometimes based on not up-to-date Evidence Based Medicine (EBM), and lipid-lowering drugs might be prescribed only by specialists. Access to ezetimibe is restricted in some countries (for example statin intolerance must be demonstrated), and in few countries prescription of ezetimibe is still limited only to selected specialists (cardiologists, endocrinologists). Very strict restrictions are still common for PCSK9 inhibitors. Many guidelines and policies require ezetimibe to be used, as a precondition for prescribing PCSK9 inhibitors therapy. In this situation, lack of access to ezetimibe effectively precludes PCSK9 therapy.

5.2. Intensification of drug therapy

Intensification of lipid-lowering therapy following discharge, is a common problem, particularly when primary care is responsible for this task. As a result, rates of achieving LDL-C target values are low, and the recent data clearly showed that only 18% of patients achieved LDL-C level of 55 mg/dl (1.4 mmol/l)[28]. The recent data also clearly showed that in most cases only combination therapy with statins, ezetimibe and PCSK9 inhibitors might allow to be on target for most patients at very high and extremely high cardiovascular risk[29]. A variety of reasons were provided for the failure to intensify statin therapy – many of which fell under the heading of 'therapeutic inertia'. Some countries reported a very hostile anti-statin movement in public media, a problem which has been observed elsewhere[30]. Unusual and non-evidence-based practices by GPs (such as regularly reducing the statin doses or

recommending an annual 'statin holiday') were also reported. Statins are strongly susceptible to the 'drucebo effect', whereby the expectation of adverse effects (particularly muscle pain), rather than the pharmacological effect of the drug causes the patients to experience adverse effects[31-33]. In light of this, it was reported that some primary care physicians (but also cardiologists and other specialists) prescribe lower doses of statin then indicated, because they believe that this will reduce the adverse effects, and they fear that any adverse effect will lead to treatment cessation. In situations of polypharmacy, it was reported that patients and doctors often prioritised the use of other medicines for CVD over statins. There is also a phenomenon called '*deprescription*' of statins, especially observed in geriatrics patients. Another issue, that needs to be at least briefly mentioned is statin loading before, during or after vascular interventions. One should remember that high-dose statin pretreatment is recommended for PCI and CABG according to current guidelines, and statin discontinuation should be avoided during acute CV events and vascular interventions[34.]

5.3. Lipid measurement and reference values

It was apparent that universal measurement of plasma lipids on admission to hospital is not a routine practice in all countries. The elements of the lipid report varied in their complexity. In several countries, a problem arose from a mismatch between the laboratory definition of 'normal' values with a patient' target values according to the guidelines and based upon their risk profile. This was believed to contribute to reduced motivation to increase LLT dosage and even treatment cessation in patients who consequently thought that LLT was no longer necessary.

5.4. Follow-up and cardiac rehabilitation

Common problems were identified with respect to the availability of, and patients' engagement in cardiac rehabilitation programmes. In Poland, the KOS (comprehensive care programme for ACS patients)[35,36] had relatively good results (still needs to be optimized, especially concerning LDL-C regular monitoring), but similar services are not universally available in all countries. There was significant variability in the extent to which interventional cardiologists were involved in follow-up coordinated care. This highlighted the need for a standardised pathway for acute therapy and discharge and pointed out that objective quality control measures were required to evaluate rehabilitation services.

6. RECOMMENDATIONS

The recommendations for optimal LLT in ACS are presented below, as a main treatment pathway, with additional pathways for a small number of specific clinical practice scenarios. The pathways are based upon the principles of LDL-C reduction: *The earlier the better, the lower the better, the longer the* better[17]. The pathways are also firmly based in the /EAS guidelines for the management of dyslipidaemias[15], albeit with a greater emphasis on reducing delays in lipid-lowering, particularly in those individuals at the greatest risk of recurrent events.

The main pathway for optimal LLT post ACS can be divided into 3 sections (**Figure 1**):

- *Diagnosis and stratification*
- *Target-driven LLT*
- *Support and follow-up*

In the diagnosis and stratification stage, some patient groups are identified for special pathways. These include patients with familial hypercholesterolaemia (FH) (either heterozygous (HeFH), or homozygous (HoFH)) or extremely high ASCVD risk (Section 6.1.1; **Figure 2**), statin intolerance (Section 6.1.2; **Figure 3**) and those who have LDL-C >120mg/dl

(3.0mmol/l) despite at least 8 weeks of combination therapy with high-intensity statin and ezetimibe (Section 6.1.2; **Figure 4**).

All other patients can be managed by a three-stage target-driven approach to LLT. In statin-treated patients with LDL<100 mg/dl (2.5 mmol/l), statin therapy has to be intensified to maximally tolerated dose. In statin naïve patients with LDL-C <120 mg/dl (3.0 mmol/l), therapy with high doses of atorvastatin or rosuvastatin should be commenced. In each case a reduction of LDL-C by 50% (target <55 mg/dl [1.4 mmol/l]) is aimed for. In statin treated patients with LDL-C 100-300 mg/dl (2.5-7.5 mmol/l), or statin naïve patients with LDL-C 120-300 mg/dl (3-7.5 mmol/l), maximally tolerated statin therapy should be combined with ezetimibe, to obtain a 50-80% reduction in LDL-C (target <55 mg/dl [1.4 mmol/l]). In any patient with LDL-C >300mg/dl (7.5 mmol/l) on admission, >80% reduction in LDL-C is required to reach the target of <55 mg/dl (1.4 mmol/l). Therefore, triple therapy (statin + ezetimibe + PCSK9 inhibitor) might be initiated in hospital. All patients should be followed-up after 4-6 weeks, and treatment should be intensified if necessary (or if it has not been already intensified) to reach the target. Once the LDL-C target (<55 mg/dl [1.4 mmol/l]) has been achieved, less frequent follow-up is acceptable. In case of ineffectiveness of such a treatment the patient should be referred to a lipidologist.

6.1. Special Pathways

The diagnosis and stratification stage identifies groups of patients who need care which differs from the standard pathway. Advice relating to these groups is provided below.

6.1.1. Extreme cardiovascular risk

The current ESC/EAS dyslipidaemia guidelines (2019) include all ACS patients to a 'very high risk' category. However, these guidelines are incomplete concerning the definition of extremely high-risk patients. Based upon recent statements made by ILEP[37], and the joint

recommendations of the Polish Society of Laboratory Diagnostics (PSLD) and the Polish Lipid Association (PoLA)[38], the following definition of 'extremely high risk' is proposed (based on the numerous data from trials with PCSK9 inhibitors)[6,7,39].

Patients fulfilling any of the following criteria (not being on the LDL-C target despite intensive/maximally tolerated statin therapy and ezetimibe) should be considered to be at 'extremely-high' risk:

- *Recurrent MI + previous vascular event in the last 2 years*
- *ACS + multivessel disease (MVD)*
- *ACS + polyvascular disease*
- *ACS + familial hypercholesterolaemia (FH)*
- *ACS + diabetes mellitus (DM) + at least one additional risk factor (including hsCRP ≥3 mg/L and/or chronic kidney disease with eGFR <60 ml/min/1.73m^2 and/or lipoprotein(a) >50 mg/dl).*

The extremely high-risk nature of this group demands a lower target for LDL-C (<40 mg/dl [1 mmol/l]). In order to minimise delay to achieve this lipid target in these individuals and bearing in mind the potential difficulties in attaining the lower target, initial immediate dual therapy should be considered, using maximally-tolerated statin therapy and ezetimibe. A PCSK9 inhibitor can be prescribed at follow-up if the target is not met (**Figure 2**). Taking into account the limited data concerning the group of extremely high-risk patients (based on the subgroup analyses), the prospective validation of these groups is still necessary.

6.1.2. Statin intolerance

If complete statin intolerance has been confirmed using objective criteria (it refers usually only to 3-5% of patients with statin therapy)[40-42] the treatment should proceed immediately using non-statin LLT (**Figure 3**). In the case of partial statin intolerance, the main pathway

(**Figure 1**) allows for combination therapy with a maximally tolerated statin dose and additional LLTs. In this situation, consideration should be given to early initiation of additional LLTs in combination with a low dose of statin, rather than delaying target attainment by slow gradual upward titration of the statin dose. Such an approach allows to reduce the risk of LDL-C visit to visit variability and significant increase of recurrent CVD events[43,44].

6.1.3. Patients on maximal statin and ezetimibe therapy

In accordance with the (Class IIa) recommendation of the ESC/EAS dyslipidaemia guidelines, in ACS patients who have not attained LDL-C target levels despite taking a maximally tolerated statin dose and ezetimibe in pre-hospital period, consideration should be given to the initiation of PCSK9 inhibitor therapy during hospitalisation[15].

6.2. Support and follow-up

Particular consideration should be given to communication at the interface of secondary and primary care, with the aim of maximising adherence to the treatment pathway, follow-up and escalation of LLT. A standardised discharge letter should be used for all patients. It is particularly important to include personal LDL-C goals and specific instructions about how and when treatment should be escalated if treatment targets are not achieved. Furthermore, the letter should describe the process of regular monitoring (including tele-monitoring, e-visits, e-advice, e-prescriptions, e-referrals). An example of such a discharge letter content is presented in the **Table 2.**

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Table 1: Summary of current approaches to LLT and challenges in participating countries. *1. Availability of ACS registry; 2. Availability of special guidelines on how to manage ACS patients; 2. Statin availability (free to all, free but only in the special clinical scenarios, not available like in Bosnia, etc.)*; *3. Ezetimibe availability (as above, with the clear information on who might prescribe this)*; *4. PCSK9 inhibitors restrictions*; *5. Unmet needs/gaps*; *6. Educational needs / critical needs for improvement.*

Country	ACS Registry	ACS Guidance	Statin availability			Ezetimibe availability			PCSK9I availability	Unmet Needs	Educational / Critical Needs
			Initiation	Co-payment*	Restrictions**	Initiation	Co-payment*	Restrictions**			
Bosnia & Herzegovina (Federation B&H)	NO	NO	GPs & Specialists	NO	NO	Specialist	YES (no reimbursement)	NA	Not reimbursed (may become available for highest risk patients during 2021)	Ensuring adequate use of LDL-C lowering drugs	Ensuring LDL-Goal is communicated in discharge letter
Bosnia & Herzegovina (Republic Srpska)	NO	NO	Specialist	YES (50%)	YES	Specialist	YES (no reimbursement)	YES			
Croatia	YES	YES	GPs & Specialists	NO	YES	Specialists	NO	YES	Initiation restricted to specialists ACS (with max statin + EZE) HeFH No co-payment	Consistent achievement of LDL-C target	Education for GPs and patients regarding targets
Czech Republic	YES	YES	GPs & Specialists	NO	NO	GPs & Specialists	NO	NO	Reimbursement restricted to specialist centres (LDL-C >2.5 mmol/L with max statin plus EZE)	Follow-up referrals for optimal lipid management	Continuous education at all levels
Greece	NO	YES	GPs & Specialists	YES (small)	NO	GPs & Specialists	YES (small)	NO	Initiation restricted to specialists Secondary prevention, primary in FH (with LDL targets unmet) No co-payment	Need for consistent approach	Dissemination of national consensus paper
Hungary	YES	YES	GPs & Specialists	YES (max €3/ month)	NO	Specialists	YES (max €2/ month)	YES	Initiation restricted to specialists Approval on named-patient basis Post-ACS (with max statin and EZE and unmet LDL-C targets) Co-payment: (€7/ month)	Ensuring LDL-C is measured for all patients during index hospitalisation Structured follow-up of patients by cardiologist and GPs	Ensuring LDL-Goal is communicated in discharge letter Improve patient knowledge regarding importance of LDL-C reduction
Poland	YES	YES	GPs & Specialists	Yes (small)	NO	GPs & Specialists	Yes (small)	NO	Initiation restricted to specialists	Increase proportion of	National and local education

									FH (with additional restrictions) Very high/extreme risk after AMI (with additional restrictions)	patients referred to comprehensive care programme	campaigns for doctors
Romania	NO	YES	GPs & Specialists	YES (10%)	NO	Specialists	50%	YES	Initiation restricted to specialists Eligibility based upon current lipid-lowering therapy and unlet LDL-c targets Fully reimbursed	Ensuring LDL-C is measured for all patients during index hospitalisation Consistent achievement of LDL-C target	Ensuring LDL-Goal is communicated in discharge letter Improve patient knowledge regarding importance of LDL-C reduction
Slovakia	YES	YES	GPs & Specialists	YES (small)	NO	Specialists	YES (small)	YES	Initiation restricted to specialists Treatment must be approved in advance by insurance company Restricted to defined patient population with very high LDL-C threshold Fully reimbursed	Therapeutic inertia	Patient education to counter misinformation and improve adherence
Slovenia	YES	NO	GPs & Specialists	NO (generics only)	NO	GPs & Specialists	YES	YES	Initiation restricted to specialists 2° prevention (with max statin and EZE) 1° prevention (HeFH) Statin intolerance (2 statins) Fully reimbursed (No co-payment within restrictions) Patients followed in PCSK9 registry	Standard pathway for ACS	Educational needs for patients National survey (for quality control)

**Is co-payment necessary when drugs are prescribed within restrictions, **Is reimbursement restricted to specific patient groups. Abbreviations: AMI, Acute Myocardial Infarction; EZE, Ezetimibe; HeFH, heterozygous familial hypercholesterolaemia; NA, not applicable.*

Table 2. Suggested wording of a discharge letter of a post-ACS patient.

- Follow-up with a GP within 7 days after discharge.
- Follow-up with a cardiologist; first follow-up after discharge within 4 weeks after discharge.
- Healthy lifestyle, regular adequate physical activity according to tolerance and concomitant conditions, heart-healthy diet, no smoking (!), regular check-ups of blood pressure and lipid levels (1st after 4-6 weeks, 2nd after 8-12 weeks, 3rd after 6 months, 4th after 12 months, forthcoming check-ups depending on the targets achievements – at least once a year).
- Dual antiplatelet therapy for 12 months.
- Monitoring of liver (especially in case of symptoms) and renal tests, glycaemia, creatine kinase in 4-6 weeks.
- Intensive/maximally tolerated statin treatment (maximum dose of atorvastatin or rosuvastatin preferably), check of plasma lipid levels in 4-6 weeks with adjustment of lipid lowering treatment to meet the LDL-C goal that is set at <55 mg/dl/40 mg/dl (1.4 mmol/L/1.0 mmol/L).
- If the abovementioned target LDL-C level AND at the same time a reduction of at least 50% (compared to the baseline value) cannot be reached, the patient should be offered treatment with a PCSK9 inhibitors.
- Risk factor control, goal attainment and patients´ adherence to therapies must be regularly checked (also with e-visits/e-advises), at least once monthly during the first 3 month and then in 3-6 months periods.

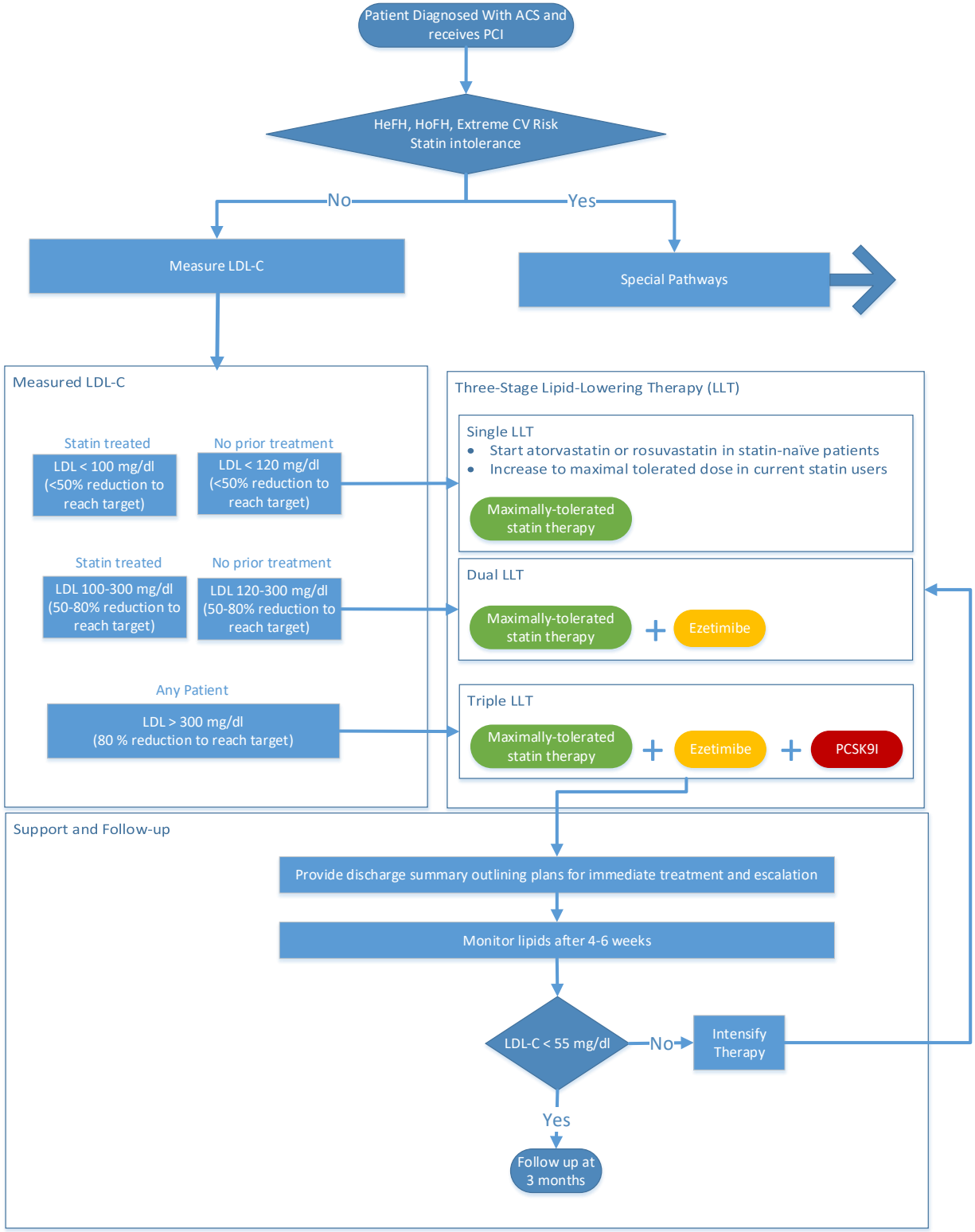

Figure 1: Overall pathway of optimal lipid-lowering therapy post-acute coronary syndrome (ACS). The pathway is divided into three Stages: (1) Diagnosis and stratification, (2) Target-driven lipid-lowering therapy, (3) Support and follow-up. Special pathways are provided for specific treatment groups including those with extreme cardiovascular (CV) risk (as defined in this document), familial hypercholesterolaemia, statin intolerance or elevated LDL-C despite dual therapy with maximally tolerated statin and ezetimibe.

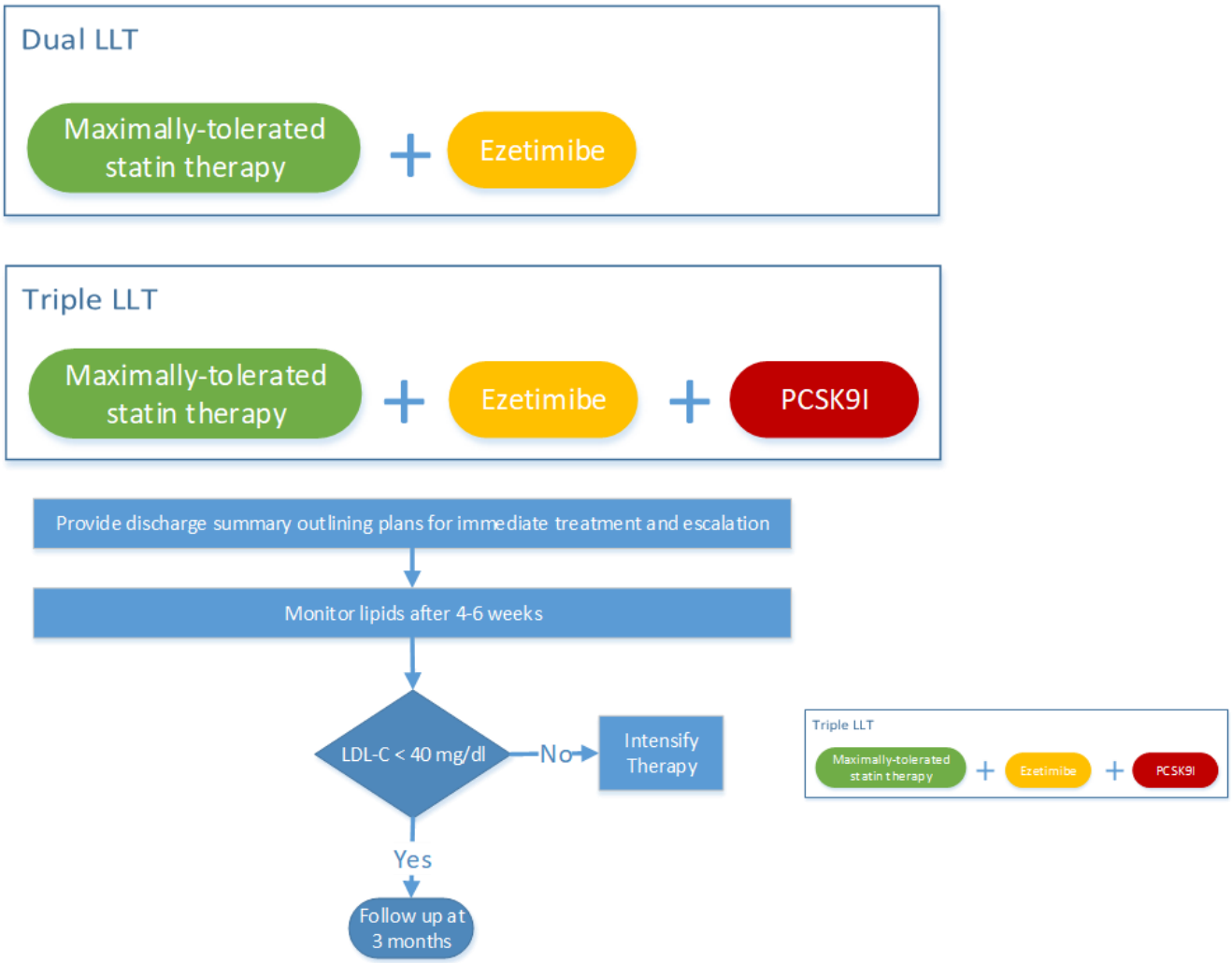

Figure 2: Special pathway for patients with extreme cardiovascular (CV) risk (Recurrent myocardial infarction (MI) + previous vascular event in last 2 years; Acute coronary syndrome (ACS) + multivessel disease (MVD); ACS + Polyvascular disease; ACS + familial hypercholesterolaemia (FH); ACS + diabetes mellitus (DM) + at least one additional risk factor). Consider immediate initiation of Dual lipid-lowering therapy (LLT) and intensify if necessary (IIbC)

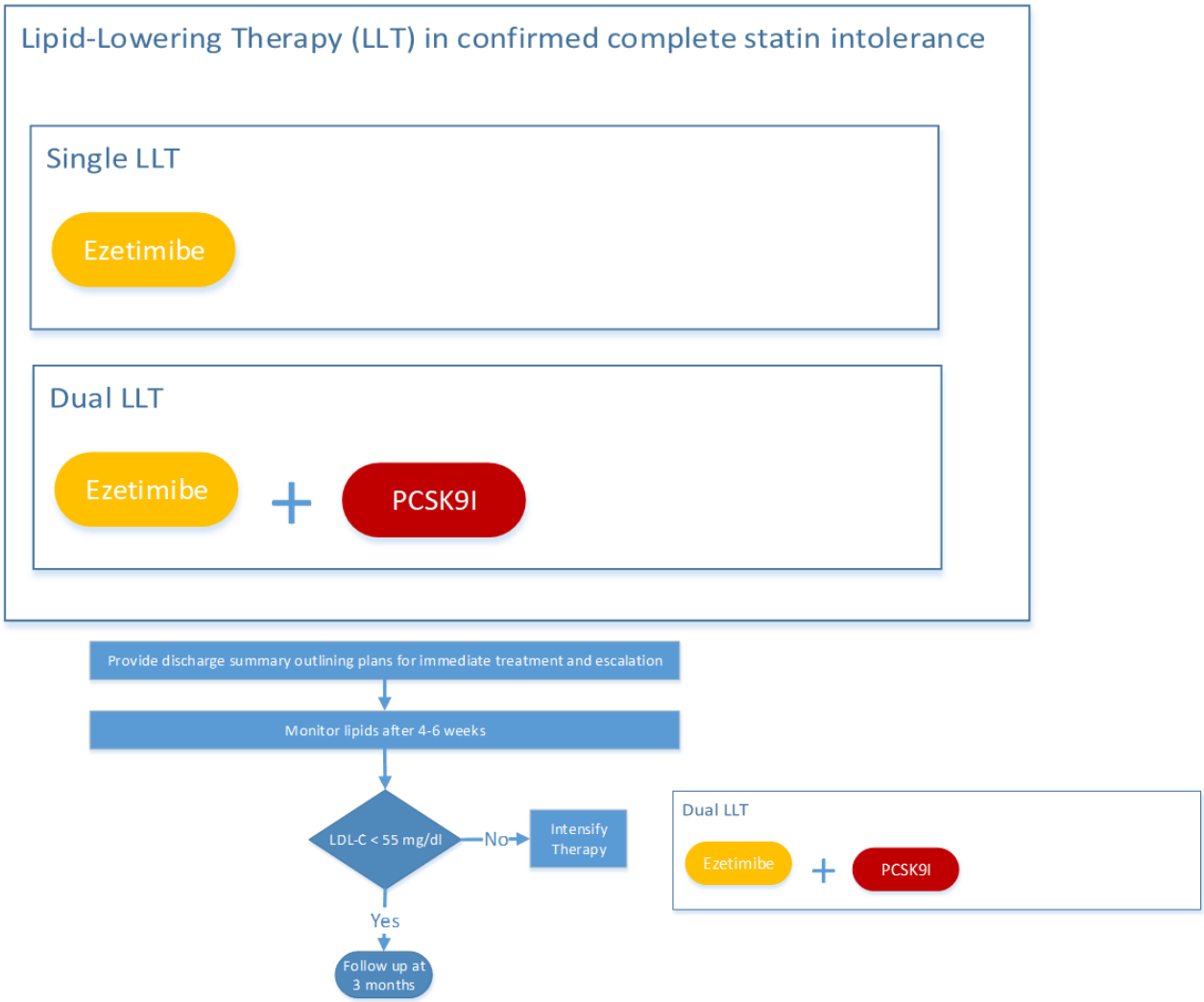

Figure 3: Special pathway for participants with objectively confirmed complete statin intolerance. Initiate ezetimibe monotherapy and intensify if necessary.

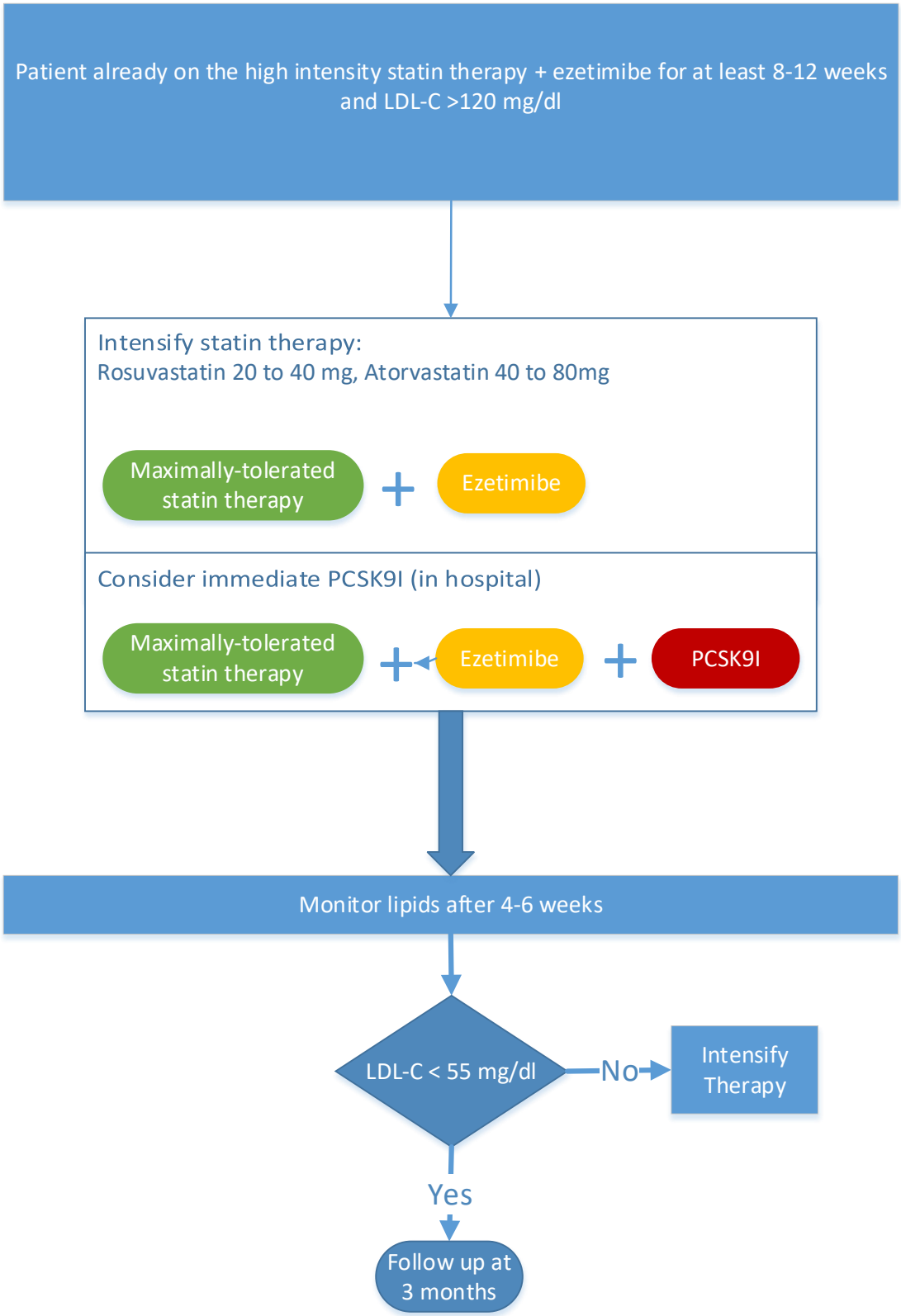

Figure 4: Special pathway: Patients already taking statin therapy and ezetimibe for at least 8 weeks prior to admission, statin therapy should be intensified if possible, and immediate treatment with a PCSK9i should be considered.