

# A consensus statement on lipid management after acute coronary syndrome

European Heart Journal: Acute Cardiovascular Care  
2018, Vol. 7(6) 532–543

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DOI: 10.1177/2048872616679791

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## Abstract

In patients admitted for acute coronary syndrome (ACS), the guidelines of the European Society of Cardiology give a Class I, Level A recommendation for the prescription of high-intensity statins to be initiated as early as possible, regardless of the low-density lipoprotein cholesterol (LDL-C) level. Although statins are widely prescribed after ACS, the intensity of therapy and the proportion of patients achieving target LDL-C values are often not in line with recommendations due to a lack of compliance with guidelines by the physicians, a lack of compliance with treatment or poor tolerance by patients, and poor dose adaptation. In this context, a group of French physicians came together to define strategies to facilitate and improve the management of lipid-lowering therapy after ACS. This paper outlines the scientific rationale for the use of statins at the acute phase of ACS, the utility of ezetimibe, the measurement of LDL-C during the course of ACS, the opportunities for detecting familial hypercholesterolaemia and the results of the consensus for the management of lipid-lowering therapy, illustrated in two decision-making algorithms.

## Keywords

Acute coronary syndrome, statins, ezetimibe, lipid-lowering therapy, familial hypercholesterolaemia, LDL cholesterol

Date received: 2 June 2016; accepted: 23 October 2016

## Introduction

In patients with acute coronary syndrome (ACS), the guidelines of the European Society of Cardiology (ESC) give a Class I, Level A recommendation for the prescription of high-intensity statins to be initiated as early as possible, regardless of the level of low-density lipoprotein cholesterol (LDL-C).<sup>1,2</sup> The recommended target is LDL-C <70 mg/dL or a reduction of at least 50% if the baseline LDL-C is between 70 and 135 mg/dL; if this cannot be achieved, then the addition of ezetimibe is suggested with a Class IIa, Level B recommendation.<sup>1,3,4</sup>

However, these guidelines are only partially implemented in usual practice. There are several reasons for this phenomenon, including insufficient treatment intensity, poor patient compliance and the side-effects associated with high doses of statins. Although statins are widely prescribed after ACS, the intensity of therapy and the proportion of patients achieving target LDL-C values are often not

in line with the guidelines. An observational study performed in 2008 and 2009 in Europe of 11,104 patients treated with statins for secondary prevention reported that,

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immediately post-ACS, 47.4% of patients had a median statin dose equivalent to 20 mg simvastatin per day and only 61.5% of patients had an LDL-C at or below the recommended target (<100 mg/dL (2.6 mmol/L) in 2007).<sup>5</sup> In the second Dyslipidemia International Study, data from the French cohorts showed that, compared with the 2007 cohort, there was a significant increase in statin intensity in 2012, but only 34% of patients achieved the target LDL-C level post-ACS.<sup>6</sup>

The up-titration of lipid-lowering therapy (LLT) according to the LDL-C target is uncommon during follow-up<sup>7</sup> and adequate prescription at discharge is a predictor of the long-term use of statins.<sup>8</sup> Maintaining a prescription of high-intensity statins over the longer term can be problematic, as illustrated by an American registry reporting in 2015 that only 27% of patients with a coronary artery disease (CAD) event received high-intensity statins post-discharge.<sup>9,10</sup> Intolerance is also a frequent cause of the discontinuation of statins, although specific management could help to avoid interruptions to treatment.<sup>11,12</sup> Lack of treatment compliance is widespread and represents another common cause of statin discontinuation<sup>13</sup>; this is probably compounded by the media encouraging patients to stop taking statins even when they are well tolerated.<sup>14</sup> In addition to patient compliance and statin tolerance, physician inertia regarding the biological monitoring of LDL-C and treatment adaptation was found to exist in a large international registry, where no statin prescription or no increase in statin intensity was often observed 6–36 months after ACS.<sup>15</sup>

Although the precise clinical consequences of statin discontinuation, either through intolerance or lack of compliance, are not known, an estimation put forward after the statin controversy regarding the number of events that discontinuation could engender was alarming.<sup>16,17</sup> During hospitalization for ACS, very high LDL-C levels should prompt a suspicion of familial hypercholesterolaemia (FH),<sup>18</sup> although it is likely that the diagnostic work-up of FH in France is incomplete given the number of cases of FH observed compared with other European countries.<sup>18</sup>

In this context, a group of French clinicians proposed the definition of strategies to facilitate and improve the management of LLT in patients with ACS and compliance with ESC guidelines. Based on the area of expertise of each individual clinician and ensuring a balanced geographical representation from across France (Figure 1), four lipidologists and 30 cardiologists (of whom the majority are directly involved in the management of ACS in public or private hospitals) (see full participant list in Appendix) were invited to participate in writing this consensus statement on the management of LLT. The group recognizes the importance of all secondary prevention treatments, including cardiac rehabilitation, but this document focuses on the available lipid-lowering strategies, outlines the scientific justification for the use of statins during the acute phase of ACS, the

utility of ezetimibe, the measurement of plasma LDL-C during the course of ACS, the opportunities for detecting FH and the results of the consensus for the management of LLT, illustrated in two decision-making algorithms.

## **I. Scientific rationale for the prescription of high-intensity statins, as early as possible at the acute phase of ACS, as recommended by the ESC guidelines<sup>1,2</sup> based on the results of clinical trials validating the use of high-intensity statin treatment in patients with ACS and on the benefit yielded by early treatment initiation**

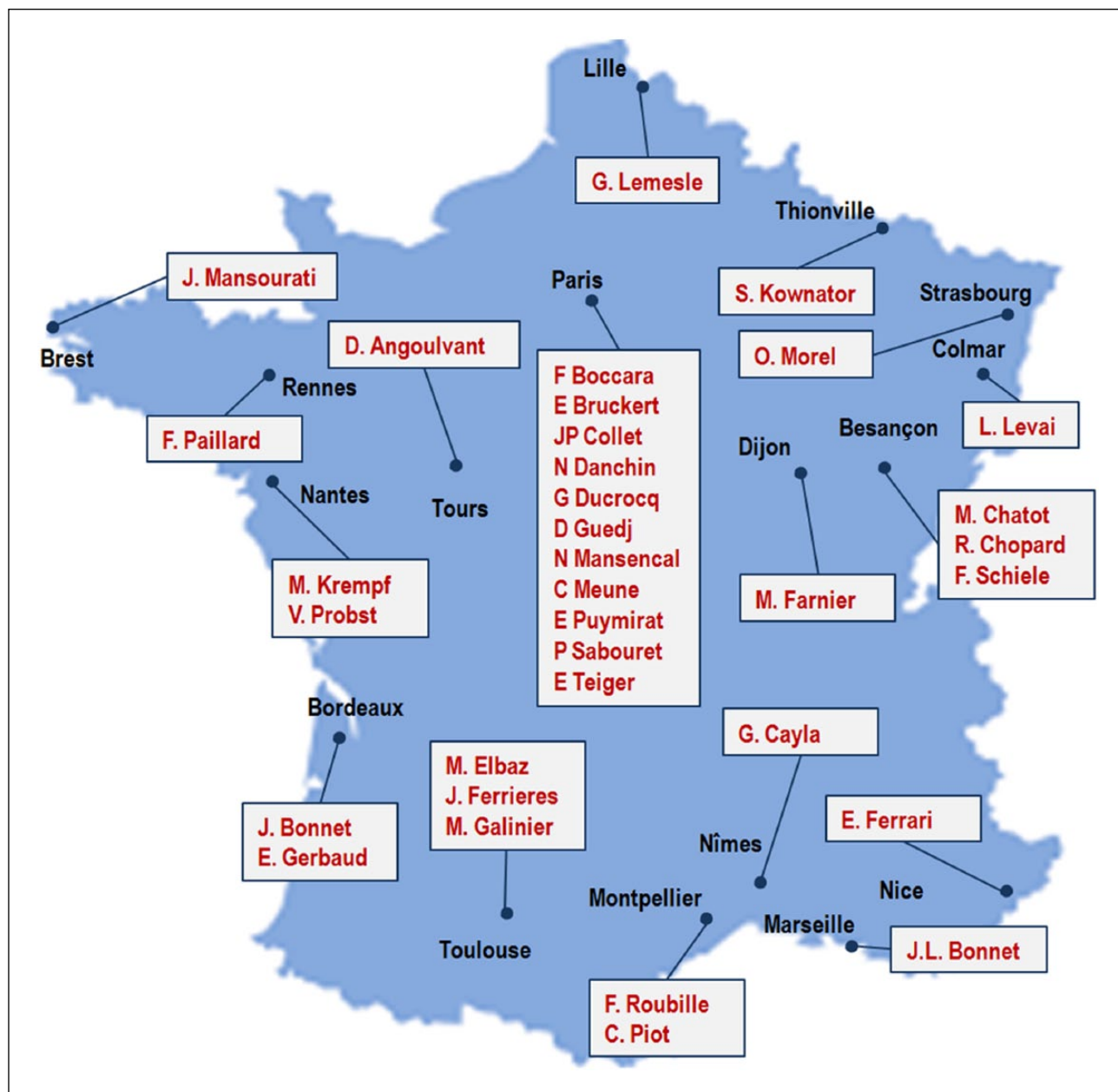
### *a. Statins and ACS*

Since the publication of the 4S study,<sup>19</sup> a large number of prescription modalities have been tested in patients with stable CAD and ACS. The experimental data indicate that statins may have early beneficial effects by improving endothelial function,<sup>20</sup> decreasing platelet aggregability and thrombus formation<sup>21</sup> and reducing vascular inflammation.<sup>22</sup> Each of these mechanisms has an important role in ACS. Statins may exert these additional effects beyond their cholesterol-lowering effect, which makes them amenable to the supplementary treatment of ACS.<sup>23</sup> A Cochrane review published in 2011 questioned the initiation of statins before hospital discharge after ACS, regardless of the baseline LDL-C level.<sup>24</sup> In line with two previous meta-analyses,<sup>25,26</sup> the Cochrane review concluded that early statin therapy reduced the combined endpoint of death, recurrent ischaemia and recurrent myocardial infarction (MI) at 6 months of treatment and thereafter. A second Cochrane meta-analysis<sup>27</sup> published in 2014 concluded that the initiation of statin therapy within 14 days following ACS produced favourable trends. Although it did not significantly reduce death, MI or stroke up to 4 months after the index event, the early initiation of statin therapy significantly reduced the occurrence of unstable angina at 4 months following ACS.

### *b. Use of high-intensity statins*

In the context of ACS, the PROVE-IT TIMI 22 trial<sup>28</sup> tested atorvastatin 80 mg versus pravastatin 40 mg and the A-to-Z study<sup>29</sup> tested 80 mg versus 40 mg of simvastatin per day. Compared with lower intensity statins, the use of high doses of statins was associated with a reduction in vascular mortality and in overall mortality when the results of these studies were pooled.<sup>30</sup>

In an open-label, randomized study,<sup>31</sup> when compared with conventional medical treatment, the use of atorvastatin



**Figure 1.** Geographical representation of the affiliations of the French Group.

80 mg per day was associated with a 44% reduction in death, MI and stroke. As a result, the current guidelines recommend the use of high-intensity statins, regardless of LDL-C level, after ACS.<sup>1</sup>

### *c. Initiation of statins as early as possible*

In a meta-analysis<sup>32</sup> bringing together the results of 20 clinical trials, the rapid administration of statins at a high intensity after ACS was shown to yield a benefit compared with later prescription. Two strategic periods were defined: the

first month and beyond the first month after the ACS. At 1 month, the rate of MI was significantly lower in the group receiving early statins (odds ratio 0.67, 95% confidence interval 0.53–0.84,  $p=0.0007$ ) with a trend towards a reduction in overall mortality ( $p=0.06$ ) and a significant reduction in major adverse cardiac events (MACE). There was a statistically significant relation between the time of statin initiation and the occurrence of MACE – namely, cardiovascular death, MI and coronary revascularization. The earlier statins were introduced after ACS, the better the prognosis.<sup>32</sup>

## 2. Scientific rationale for the prescription of ezetimibe at the acute phase of ACS as recommended by the ESC guidelines<sup>1</sup>

### a. Ezetimibe: a specific mechanism of action

Ezetimibe is a specific inhibitor of the intestinal absorption of cholesterol of both dietary and biliary origin. It blocks the Niemann-Pick C1-Like 1 (NPC1L1) protein, which is involved in the intestinal uptake of cholesterol.<sup>33</sup> NPC1L1 inhibition reduces the quantity of cholesterol available for incorporation into chylomicrons. In response to the reduced quantity of cholesterol arriving in the liver and delivered via chylomicron remnants, there is an increase in the synthesis of LDL-C receptors and, consequently, an increase in the clearance of LDL-C from the blood. In parallel, there is an increase in the hepatic synthesis of cholesterol and therefore ezetimibe as a monotherapy only moderately reduces the level of LDL-C. Ezetimibe should thus be associated with a statin because these two drug classes have complementary and additive mechanisms of action.

Although ezetimibe monotherapy reduced LDL-C from 17 to 22% compared with a placebo in various studies,<sup>34</sup> numerous randomized studies have shown that, when co-administered with a statin, the additional reduction in LDL-C was on average between 25 and 30%.<sup>35–37</sup> The addition of ezetimibe to statin therapy has repeatedly been shown to decrease LDL-C more than when the statin dose is doubled. The results from several studies suggest that the reduction in LDL-C is greater when ezetimibe is associated with a statin in patients who did not achieve the target LDL-C level under statin therapy, probably through the selection of patients who were poorer responders to statin monotherapy.<sup>37</sup>

### b. Ezetimibe: recent genetic evidence in favour of a clinical benefit

Evidence of cardiovascular prevention through the inhibition of NPC1L1, complementary to that observed with statin therapy, has been provided by studies investigating genetic mutations that inactivate NPC1L1 and that were associated with protection against CAD<sup>38</sup>; 15 mutations that inactivate NPC1L1 have been identified. Heterozygous patients who have one of these mutations have an LDL-C level 12 mg/dL lower than non-carriers and their risk of CAD is significantly reduced (–53%).<sup>39</sup> The analysis of Mendelian randomization has shown that polymorphisms of the genes for HMGCoA reductase and NPC1L1 associated with modest reductions in LDL-C also reduce the risk of CAD.<sup>40</sup> This study also shows an additive effect in terms of protection against CAD when NPC1L1 and HMGCoA reductase polymorphisms simultaneously act to reduce

LDL-C. These genetic findings strongly suggest that the association of ezetimibe with a statin should yield a benefit in terms of cardiovascular prevention.

### c. Ezetimibe in association with a statin: cardiovascular benefit demonstrated in post-ACS patients

The IMPROVE-IT study, which included 18,144 patients hospitalized for ACS, showed that the addition of ezetimibe to statin therapy yielded a clinical benefit.<sup>41</sup> In this study, simvastatin 40 mg alone was compared with an association of ezetimibe 10 mg and simvastatin 40 mg in patients with relatively low levels of LDL-C. In the simvastatin 40 mg group, the average LDL-C was around 70 mg/dL, i.e. the target level recommended for this category of patients. The addition of ezetimibe made it possible to achieve an additional 24% reduction in LDL-C to reach an average level of 53 mg/dL. The primary composite endpoint, including cardiovascular death, non-fatal MI, unstable angina requiring re-hospitalization, coronary revascularization ( $\geq 30$  days after randomization) or non-fatal stroke, was reduced by 6.4% ( $p=0.016$ ) after an average follow-up of almost 7 years. A secondary endpoint consisting of death from cardiovascular causes, non-fatal MI and non-fatal stroke was reduced by 10% ( $p=0.003$ ). The additional cardiovascular benefit was almost exactly that expected based on the Cholesterol Treatment Trialists' meta-analysis modelling the relationship between LDL-C reduction and the risk of MACE.<sup>42</sup> In the IMPROVE-IT study, the benefit of the simvastatin 40 mg/ezetimibe 10 mg combination on recurrent events was also demonstrated, with a risk reduction of 12%.<sup>43</sup> Overall, there was a 9% reduction in total events (first and recurrent events) ( $p=0.007$ ). The IMPROVE-IT study also confirmed the safety of ezetimibe administered in association with a statin. The IMPROVE-IT trial was the first to show a clinical benefit when a second lipid-lowering drug was added to statins. In line with the genetic data, IMPROVE-IT also confirmed – if there was any need to – that LDL-C plays a crucial part in atherosclerosis.<sup>44</sup>

## 3. New insights regarding lipid profiles at the acute phase of ACS

### a. Utility of dosing lipid levels

The Interheart and Euroaspire studies<sup>45,46</sup> confirmed the importance of lipid parameters in patients with ACS and interventional studies with statins have shown the utility of treating lipid abnormalities. There is therefore no longer any question about the need to correct abnormal lipid parameters in patients with CAD. The guidelines of the American Heart Association<sup>47</sup> recommend the prescription of a high-intensity statin to all patients aged <75 years who present with CAD, initially without specifying target

cholesterol levels. This ‘fire and forget’ strategy, in which LDL-C measurement during the acute phase of ACS has no impact on the prescription, with blanket high-intensity treatment for all patients, was subsequently modified in the recent ACC Expert Consensus Decision Pathway.<sup>48</sup> This document underlined the need to measure the LDL-C level to fine-tune risk estimation and therapy intensity. Three arguments were advanced in favour of performing a lipid profile during the acute phase of an ACS:

- US recommendations propose that the LDL-C level should be reduced by 50% by means of a high-intensity statin. To achieve this target, it is necessary to know the baseline LDL-C value.
- The IMPROVE-IT study showed the utility of achieving LDL-C levels below the target stipulated in European Guidelines (70 mg/dL) using ezetimibe. Although no new target LDL-C has been specifically defined, a strategy associating statins and ezetimibe can clearly be considered depending on the LDL-C level at admission and taking into account the likely effect of high-intensity statin therapy on the LDL-C value.
- In all patients, especially younger patients, elevated LDL-C levels (>190 mg/dL without pre-treatment) should systematically prompt the physician to look for FH, to initiate appropriate prevention and to detect the disease in other family members.

### ***b. Variability in cholesterol levels in the days following ACS***

The validity of the measurement of LDL-C at the acute phase of ACS remains debatable following several small studies after an acute infectious or vascular event.<sup>49–52</sup> A 10–20% reduction in total cholesterol, LDL-C or high-density lipoprotein cholesterol, together with a 20–30% increase in triglycerides, has repeatedly been reported. Lipid parameters usually return to prior levels after an average of 3 months. Several mechanisms have been proposed to explain this phenomenon, such as an increase in LDL-C receptors or disturbances of the proteins involved in the metabolism of high-density lipoprotein cholesterol. These data were revisited in a sub-study of the LUNAR trial testing rosuvastatin and atorvastatin at different doses in ACS.<sup>53</sup> Among 507 patients with varying levels of risk (ST segment elevation MI, non-ST segment elevation MI or unstable angina), the LUNAR study confirmed a 2% reduction in LDL-C in the 24 h after admission, followed by a 6% increase by day 4.<sup>53</sup> In the LATIN study, a 6–10% reduction in LDL-C was also observed at the acute phase, with a return to baseline values observed 3 months later.<sup>54</sup> There was no significant influence of direct LDL-C measurement compared with indirect calculation, with excellent correlation between the two methods, although in patients

with very elevated triglycerides the reliability of indirect calculation using the Friedewald equation remains debatable. Any variations in LDL-C during hospitalization are minor, with fluctuations ranging from 2 to 10% and therefore performing a lipid profile at admission provides reliable results.

### ***c. No need for fasting measurement***

The lack of variability in total cholesterol, and particularly LDL-C, has also been validated irrespective of the time of the patient’s last meal.<sup>52,55</sup> Even by calculating LDL-C using the Friedewald equation, very high triglyceride levels (around 300 mg/dL) would have to be reached before observing small variations that are non-significant in clinical terms. In a specific analysis of the effect of fasting or non-fasting LDL measurements in the National Health and Nutrition Survey (including 16,161 participants), it was shown that fasting status had no impact on LDL-C levels.<sup>56</sup> A Danish cohort of 90,000 participants also showed that the LDL-C calculation was unchanged, irrespective of whether the patient was fasting or had just eaten. LDL-C levels have been shown to vary with the season, age and sex, but do not influence either the diagnosis of hypercholesterolaemia or medical decisions in the context of ACS.<sup>57</sup> Therefore LDL-C can be measured in patients with ACS regardless of their fasting status. As a consequence, the European Atherosclerosis Society (EAS) and the European Federation of Clinical Chemistry and Laboratory Medicine have published a joint consensus statement on the use of non-fasting blood collection for the diagnosis of lipid disturbances or treatment follow-up.<sup>58</sup>

### ***d. Familial hypercholesterolaemia***

Familial hypercholesterolemia is a relatively common autosomal dominant genetic disease (around 1 in 300–500 live births for the heterozygous form). It results from mutations mainly affecting the gene coding for LDL receptors (60%), but also, less commonly, the gene coding for Apo lipoprotein B (10%) and PCSK9 (<5%). The mutation is unknown in around 20% of patients. The risk of transmission when one parent is a heterozygous carrier is 50%. The heterozygote form is therefore fairly common and needs to be detected because, in the absence of treatment, it exposes the carrier to a risk of CAD 13 times higher than that of the general population.<sup>59</sup> Statins have made it possible to considerably reduce these events as long as treatment is initiated early. The screening and treatment of families identified through patients admitted to coronary care units is therefore a major challenge. The work-up should investigate a family history of early vascular disease and the clinical examination should look for characteristic features such as xanthomas (Figure 2). An LDL-C value >130 mg/dL with statin therapy or >190 mg/dL in patients without statin



**Figure 2.** The *Mona Lisa* by Leonardo da Vinci (left panel) and an *Elderly Lady* by Frans Hals (right panel). Cutaneous markers of familial hypercholesterolaemia, such as possible xanthoma and xanthelasma, are easily recognizable, even by non-physicians.

therapy suggests FH. The diagnosis of FH is very likely for LDL-C values  $>250$  mg/dL. The different diagnostic elements for FH are clearly outlined in FH risk score algorithms.<sup>18</sup>

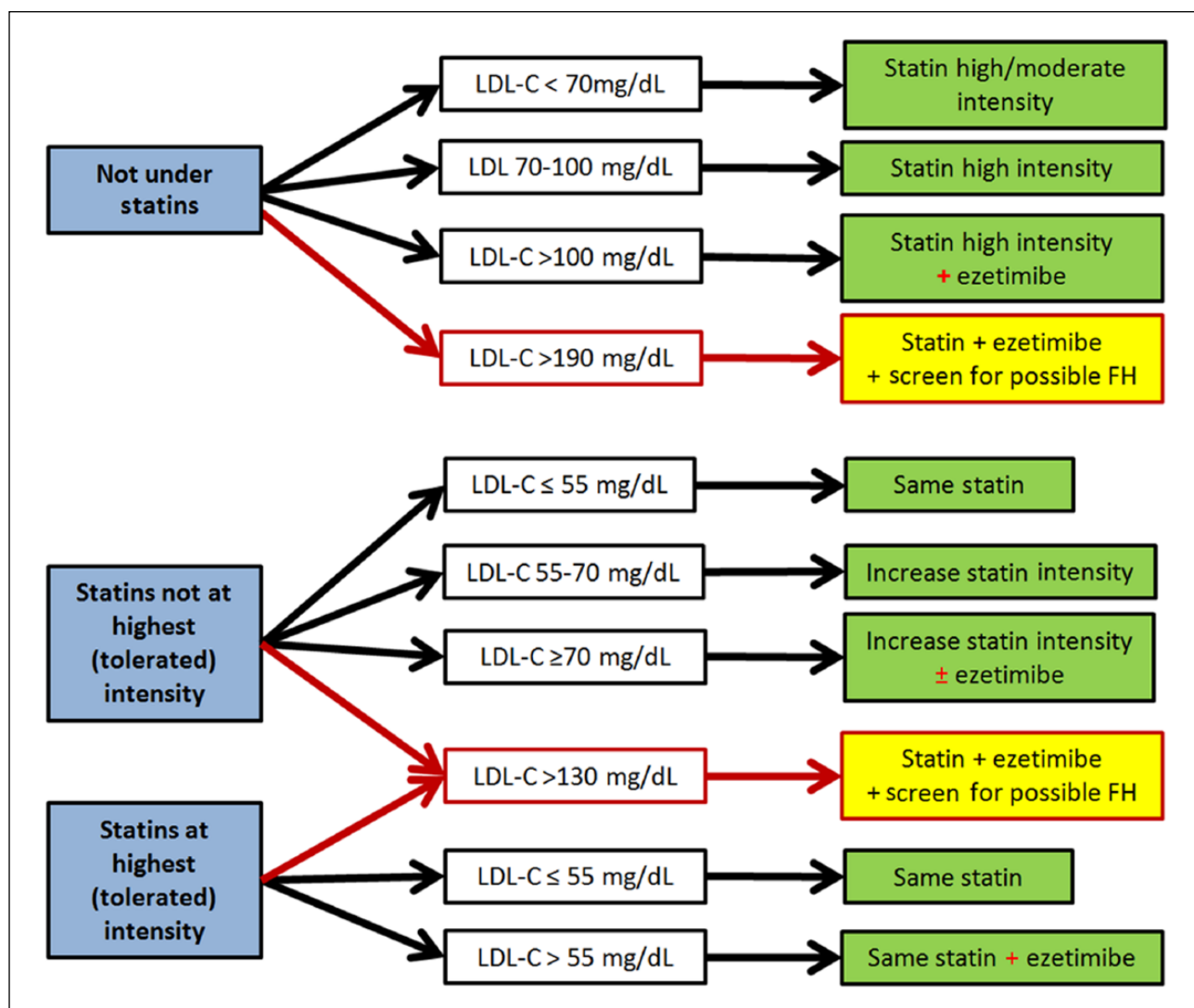
#### 4. Methods and results of this Consensus

To achieve a consensus on how to interpret lipid profile results and on which LLT to use, our group held discussions during live meetings and exchanged at length via the internet. Two questionnaires were prepared and circulated to obtain the opinion of all the members of our group without the usual constraints related to physical presence at a meeting, variations in speaking time or referral to external sources of information. The algorithms proposed here are therefore the final result of a consensus-building process by a group that is not necessarily representative of the whole population of French physicians. Nonetheless, all the members of this group have practical clinical experience in prescribing secondary prevention therapy and the majority of cardiologists in the group are involved in the emergency management of ACS in routine practice; all are regularly called on to provide recommendations for general practitioners regarding the prescription of LLT. The lipidologists in the group contributed to the description of protocols for increasing or decreasing treatments as well as the management of statin intolerance and the detection of FH.

##### a. Scientific rationale of the proposals

The scientific rationale for the proposals made here is based on the evidence of efficacy presented in this paper and/or on the guidelines of the ESC.

- The introduction of a high-intensity statin (i.e. atorvastatin  $\geq 40$  mg or rosuvastatin  $\geq 20$  mg) generally leads to an average reduction of 50% in LDL-C; 35% with moderate-intensity statins and 30% with low-intensity statins.<sup>60</sup>
- Wide individual variations exist, with the result that estimating the effect of a statin on LDL-C is hazardous at best. Some patients are ‘good responders’, with a reduction  $>50\%$  in LDL-C, whereas others respond less well, achieving reductions  $<50\%$ .<sup>61,62</sup>
- Doubling the statin dose has a predictable effect – namely, an additional 6% reduction in LDL-C. Conversely, halving the statin dose leads to a 6% increase in LDL-C.<sup>60</sup>
- An estimation of the theoretical LDL-C in the absence of statins can be made using the reverse calculation, with the same limits as those associated with the introduction of a statin.<sup>63</sup>
- Changing the type of statin has a predictable effect on the level of LDL-C based on studies of statin bioequivalence.<sup>63</sup>
- Adding ezetimibe to statin therapy yields a predictable 20% reduction in LDL-C.<sup>28,41</sup>
- In the IMPROVE-IT study, patients with an LDL-C of 55 mg/dL had a more favourable clinical outcome than those with an LDL-C of 70 mg/dL.<sup>41</sup> Patients were included if they had an LDL-C between 50 and 125 mg/dL without statins or between 50 and 100 mg/dL under simvastatin 40 mg (or equivalent).
- Patients who are intolerant to high-intensity statins may be able to tolerate less intensive treatment (reduced dose and/or change in the type of statin). The addition of ezetimibe is generally well tolerated.<sup>11</sup>
- Intolerance to statin therapy requires confirmation and re-challenge is recommended.<sup>12</sup>



**Figure 3.** Decision algorithm at admission.

- Lack of compliance may be due to intolerance and can be detected during the first weeks after the introduction of statin therapy.<sup>64</sup>
- The efficacy and safety of low LDL-C levels (<40 mg/dL) is widely assumed, but not definitively proven.
- The probability that a patient has FH is high when the LDL-C level exceeds 190 mg/dL in the absence of statin therapy. Given the efficacy of statins, the threshold for a high probability of FH is 130 mg/dL in patients treated with statins.<sup>18</sup> In patients with a confirmed diagnosis of FH, PCSK9 inhibition can be considered using either alirocumab<sup>65</sup> or evolucumab<sup>66</sup> when LDL-C levels are still elevated under high-intensity statins and ezetimibe.

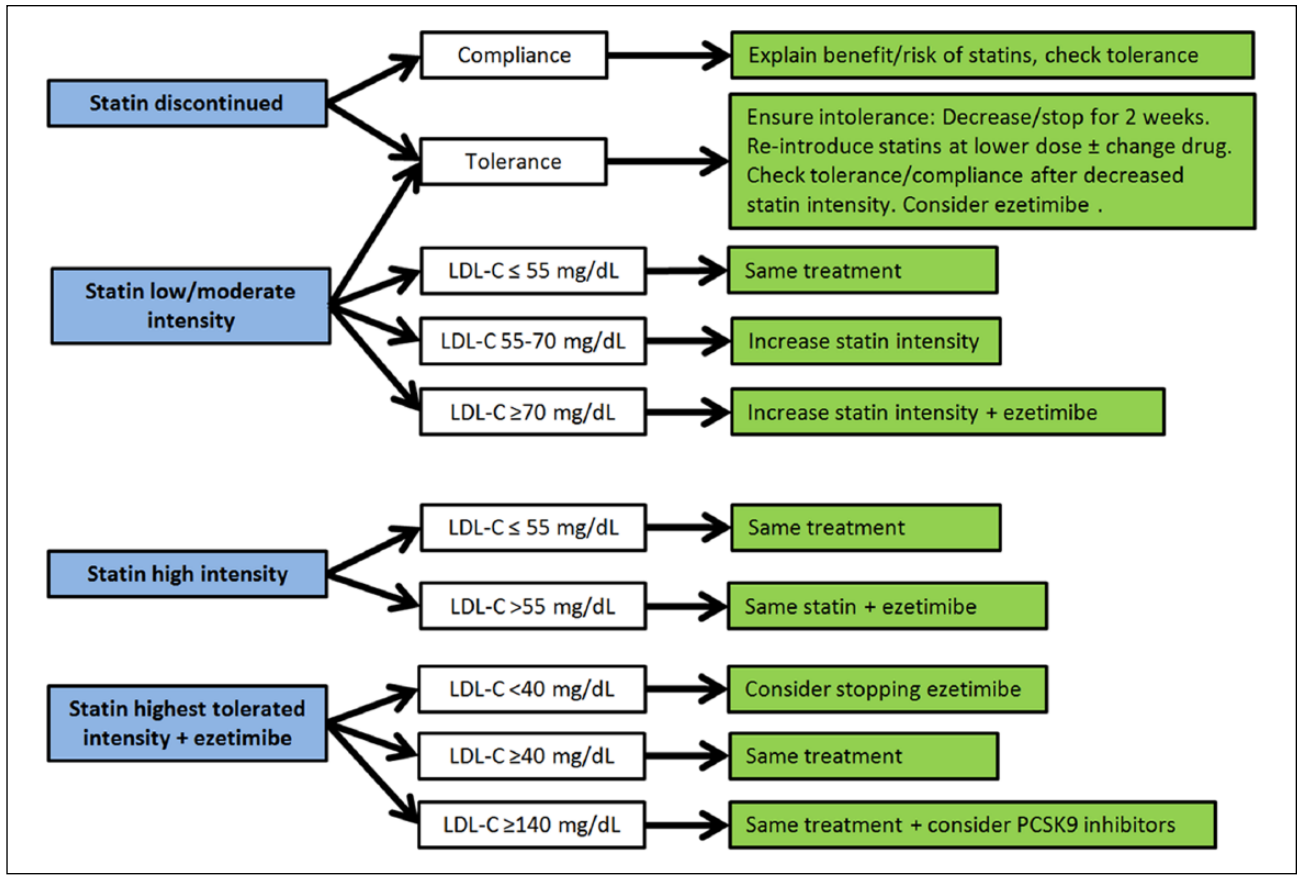
### *b. Algorithm for in-hospital prescription*

The algorithm for in-hospital prescription in the context of ACS takes into account a wide variety of clinical situations,

prior treatment regimens and LDL-C levels. Two situations are distinguished at admission, depending on the existence (or not) of prior statin therapy.

In a patient admitted without prior statin therapy, which is about 70% of all patients, the statin intensity can be modulated depending on the admission LDL-C level (Figure 3).

- In patients with an admission LDL-C <70 mg/dL, the prescription of a high-intensity statin is strongly encouraged. Nevertheless, moderate-intensity statins can be considered, given the greater risk of intolerance with high-intensity doses and the current lack of scientific evidence supporting a target LDL-C <55 mg/dL.
- In patients with an admission LDL-C <100 mg/dL, a high-intensity statin is probably sufficient to achieve a target LDL <70 mg/dL and probably close to 55 mg/dL.



**Figure 4.** Decision algorithm at follow-up.

- In patients with an admission LDL-C >100 mg/dL, the probability of achieving an LDL-C <70 mg/dL with treatment is high; however, the probability of achieving an LDL-C <55 mg/dL is low. This situation corresponds to the conditions of the IMPROVE-IT study, where the patients were included if LDL-C was 50–125 mg/dL without statins and the addition of 10 mg ezetimibe, in addition to statin therapy, yielded a 6.4% reduction in the risk of death, stroke and recurrent MI.
- In patients with admission LDL-C >190 mg/dL without any LLT, the presence of FH should be actively investigated.

In patients already treated with statins at admission, the same principles should be followed to adjust therapy appropriately.

- Pursuing treatment at the same dose associated with reinforced lifestyle changes or increasing statin intensity with the addition of ezetimibe can be considered for LDL-C values >55 mg/dL. The likely course of LDL-C values under treatment can be calculated fairly accurately using the ‘6% rule’ by doubling the dose.

- In patients already receiving statin therapy, LDL-C values >130 mg/dL should prompt suspicion of FH (Figure 3).

### c. Prescription algorithm at 4–8 weeks

The second algorithm (Figure 4) is to be used 4–8 weeks after discharge and assumes that the patient attends a consultation again (although not necessarily by the cardiologist) and that appropriate instructions were given regarding medical follow-up when the patient was discharged.

This algorithm takes into consideration biological efficacy, tolerance and compliance with treatment. Treatment modifications can be proposed according to the treatment at follow-up.

- In patients who have stopped taking statins at follow-up, intolerance and compliance need specific management. In cases of non-compliance, an explanation of the risk–benefit ratio of statins should be given because disinformation is a common cause for a lack of compliance with statins. In cases of intolerance, a strategy of careful history-taking should be adopted to determine whether the symptoms are consistent with the effects of statin. Discontinuation

and re-challenge with lower intensity statins is then recommended, if necessary using statins with a long half-life given two to three times a week. In statin-intolerant patients, the use of ezetimibe in association with low-intensity statins, or even alone, can help to lower LDL-C pending the approval of other non-statin drugs such as PCSK9 inhibitors.<sup>48</sup>

- Treatment should be pursued without any change in patients with low to moderate statin intensity when LDL-C is <55 mg/dL and without statin intolerance. Otherwise, when LDL-C is 55–70 mg/dL, an increase in statin dose and, if LDL-C is >70 mg/dL, an increase in statin intensity by the addition of ezetimibe is proposed.
- A decrease in treatment intensity is proposed by interrupting ezetimibe if LDL-C is <40 mg/dL in patients with a combination of high-intensity statins and ezetimibe.
- If the LDL-C target is not reached with the highest tolerable statin and ezetimibe treatment, PCSK9 inhibitors may be considered in addition to LLT.<sup>4</sup> So far, no clear LDL-C threshold has been defined for adding PCSK9 inhibitors in the setting of ACS. However, a recent ESC/EAS consensus statement proposed criteria for the consideration of PCSK9 inhibition before the results of the ongoing cardiovascular endpoint trials.<sup>67</sup> In this consensus statement, considering the 50% reduction in LDL-C usually observed with these drugs, the threshold proposed for patients in secondary prevention is an LDL-C level >140 mg/dL (or >100 mg/dL for patients with a rapid progression of atherosclerotic cardiovascular disease) under maximally tolerated statin and ezetimibe. The application of this strategy may depend on the national availability and reimbursement of PCSK9 inhibitors.

## Conclusions

The decision algorithms proposed in this consensus document are simple, cover the majority of clinical situations commonly observed in routine practice and aim to improve the quality of care. It should be noted, however, that neither the feasibility of applying these strategies in routine practice nor their efficacy in terms of clinical outcome has been determined. The strategies recommended here are in line with the indications for statins and ezetimibe in France, are in conformity with the guidelines of the ESC and incorporate the results of the most recent clinical trials. In this regard, these algorithms are probably applicable in the majority of European countries subject to the availability and indications of statins and ezetimibe. Other lipid-lowering therapies not addressed in these algorithms may be of clinical utility in specific cases, but were not incorporated here to preserve the simplicity of the algorithms.

## Conflicts of interest

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article. M. Krempf has received honoraria from AstraZeneca, Amgen, Abbott, Boehringer, Chiesi, Menarini, MSD, Novo Nordisk, Sanofi-Regeneron and Unilever. J. Ferrières has received honoraria from Amgen, MSD, Novartis and Sanofi. P. Sabouret declares consulting or lecture fees from Astra Zeneca, Bristol Myers Squibb, Daiichi-Sankyo, Eli-Lilly, Novartis and MSD. G. Ducrocq reports speaker and/or consulting fees from Astra Zeneca, Biotronik, BMS, Daiichi-Sankyo and Lilly; membership of advisory board for Lilly; CEC for Sanofi and Philips; DSMB for Abbot and MicroPort; and travel fees from Astra Zeneca. M. Farnier has received grants, consulting fees and/or honoraria and delivered lectures for Abbott/Mylan, Akcea/Ionis, Amgen, Astra Zeneca, Eli-Lilly, Genzyme, Kowa, Merck and Co, Pfizer, Roche, Sanofi/Regeneron and Servier. E. Puymirat declares fees for lectures and/or consulting from Amgen, Astra Zeneca, Bayer, BMS, Daiichi-Sankyo, MSD, Eli-Lilly, The Medicines Company, St Jude Medical and Servier. F. Roubille reports speaker fees from Amgen, Sanofi Aventis and MSD. F. Schiele has received support from/participated in speaker's bureau for Amgen, Merck, Pfizer, Eli-Lilly, Daiichi-Sankyo and Sanofi. He has received honoraria from Amgen, Merck, Pfizer, Eli-Lilly, Daiichi-Sankyo, BMS and Sanofi. He has received study honoraria as representative of a research association from Amgen, MSD, Sanofi, Pfizer and BMS. E. Bruckert has received honoraria from AstraZeneca, Amgen, Genfit, MSD, Sanofi-Regeneron, Unilever, Danone, Aegerion, Chiesi, MEDA-Rottapharm, Lilly and Ionis-Pharmaceutical. J.L. Bonnet declares honoraria from Astra Zeneca and Bristol Myers Squibb. M. Elbaz reports an unrestricted grant for research from Boston Scientific, speaker fees and consulting with Daiichi-Sankyo, Astra Zeneca and MSD. M. Galinier reports honoraria from Amgen, Air Liquide, Astra Zeneca, Bayer, BioMérieux, Boehringer Ingelheim, Bristol Myers Squibb, Novartis, Pfizer, Roche Diagnostic, Sanofi Aventis, Servier, Thoratec and Vifor Pharma. J. Bonnet reports honoraria from MSD, Genzyme and Sanofi Aventis. J.P. Collet reports research grants to the institution or consulting/lecture fees from, AstraZeneca, Bayer, Bristol Myers Squibb, Daiichi-Sankyo, Eli-Lilly, Fédération Française de Cardiologie, Lead-Up, Medtronic, MSD, Sanofi Aventis and WebMD. No other author has any conflict of interest to declare.

## Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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