Upfront Lipid-Lowering Combination Therapy in High Cardiovascular Risk Patients: A Route to Effective Atherosclerotic Cardiovascular Disease Prevention

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ABSTRACT:

Despite three decades of using statin therapy, 20 years of experience with ezetimbe, and availability of innovative non-statin lipid lowering therapies (LLT), there are still about 70% patients over the low-density lipoprotein cholesterol (LDL-C) goal, with every 5-6th being over the target from the group of very high and extremely high cardiovascular disease (CVD) risk patients. Adding another even every 5th patient at very high CVD risk without any LLT, makes this situation highly frustrating, especially lipid disorders are the most common CVD risk factor with the prevalence of over 60%, with the worst awareness within all cardiovascular risk factors (only about 15% people knows their LDL-C level). To answer this since 2021 there is an approach to apply upfront (immediate) lipid lowering combination therapy of statin and ezetimibe in very high and extremely high-risk patients to be on the LDL-C target as low as possible, but especially as early as possible, enabling to introduce the third line therapy (i.e., bempedoic acid and/or PCSK9 targeted therapy) already after 4-6 weeks. This review discusses the current stage of knowledge and recent data on the group of patients that might benefit the most from the upfront combination LLT, when it should be optimally implemented, and the recent data on its role on LDL-C reduction, cardiovascular and mortality outcomes as well as safety issues.

Key words: statins, ezetimibe, combination therapy, cardiovascular disease, prevention, safety.

LDL-C a cause of IHD global epidemy

Ischemic heart disease (IHD) remains the leading cause of global cardiovascular disease (CVD) mortality, followed by intracerebral hemorrhage and ischemic stroke [1]. In 2019, IHD accounted for 197.2 million (177.7-219.5) prevalent cases and 9.1 million (8.4-9.7) deaths. Globally, high systolic blood pressure (SBP) (54.6%), high low-density lipoprotein cholesterol (LDL-C) (46.6%), and smoking (23.9%) are the three largest IHD risk factors [2]. However, in many countries, the prevalence of lipid disorders may be as high as 60%, and this represents the worst controlled and monitored CVD risk factor [3]. In 2021, 3.81 million (95% CI: 2.17-5.42 million) CV deaths and 3.81 million (95% CI: 2.17-5.42 million) deaths overall were attributed to elevated LDL-C levels [4].

LDL-C time exposure and cardiovascular disease risk

The association between LDL-C levels and atherosclerotic CVD (ASCVD) risk depends on the degree of elevation in LDL-C levels and the duration of exposure to the elevated levels (cholesterol-years concept) [3,5]. A theoretical threshold of LDL-C after exposure, in which IHD is more likely to occur, has been set at about 8000 mg/dl-years; such a threshold is reached at different ages according to the individual LDL-C levels [6]. For example, the hypothetical estimated age of onset of acute coronary syndrome (ACS) in a patient with LDL-C levels of 200 mg/dl, 125 mg/dl and 100 mg/dl is approximately 40, 64 and 80 years, respectively [6]. Hence, in a patient with untreated heterozygous familial hypercholesterolemia (HeFH) or lifestyle-related hypercholesterolemia, the average age of ACS onset is 40-45 and 55-60 years, respectively, and in the general population 70-75 years [6]. In an analysis based on the large Polish ACS Registry it was observed that reaching the threshold >6000 cholesterol-years at the age of 40 (LDL-C levels 150 mg/dl or more) significantly increased the risk of the first myocardial infarction (MI) [5]. It was also showed that elevated LDL-C level is particularly associated with the risk of ASCVD in patients with coronary artery calcium (CAC) score >0 [7].

Incident IHD event risk depends on prior cumulative exposure to LDL-C and, independently, the time course represented by the area under the LDL-C versus age curve. The same area accumulated at a younger age, compared with older age, resulted in a greater increase in the risk of IHD risk [8,9]. Reducing the LDL-C level by 50% reduces CV risk regardless of the duration of dyslipidemia, but the greatest extent of reduction is achieved when the reduction occurs at the earliest possible stage of the disease (start of treatment at the age of 30 - HR = 0.48; 40 - HR = 0.54; 50 - HR = 0.63; 60 - HR = 0.73) [10]. Each 1 mmol/l (40 mg/dl) reduction

in serum LDL-C is associated with a 12% (95% CI: 8–16%) reduction in the risk of major CVD events at year 1, 20% (16–24%) in year 3, 23% (18–27%) in year 5, and 29% (14–42%) in year 7 of lipid-lowering treatment (LLT) [11]. In this context it needs to be emphasized that intensive LLT leading to a reduction in LDL-C levels <40 mg/dl (1 mmol/l) is safe and does not increase the risk of neurocognitive disorders, cancers, hemorrhagic strokes, new-onset diabetes (NOD), haepatobiliary disorders, muscle disorders and cataracts, and still allows for a greater reduction in CV events (OR = 0.82; 95% CI: 0.72-0.94) [12-14].

The increasing knowledge about the impact of exposure to elevated LDL-C levels on ASCVD has led to significant evolution of target LDL-C levels in all cardiovascular risk groups over the years (**Figure 1A**) [15]. Moreover, an additional group of patients has been distinguished - those with extreme cardiovascular risk, in whom the target LDL-C level should be below 40 mg/dl (1 mmol/l) [16,17]. Currently, in the context of LDL-C levels, the rule is "*the lower the better*", which is related to the fact that there is no *plateau* effect in the relationship between reducing LDL-C levels and reducing the risk of ASCVD [3,7,11]. This creates the need to use very intensive LLT in some patients so that they can achieve the target LDL-C level (*the earlier the better*), in accordance with the current guidelines. Currently available LLTs, both based on statins and non-statin drugs (in patients with statin intolerance), allow for a significant reduction of LDL-C in most patients (**Figure 1B**) [3,17].

How to identify patients who benefit the most from intensive LLT?

Statin therapy and LLT in primary prevention is associated with a reduction in the risk of death from any cause by 11%, CV death by 20%, acute coronary syndrome by 38%, stroke by 17%, unstable IHD by 25% and major CV events by 26% [3,18]. In secondary prevention, the effectiveness is even greater and leads to a reduction in the risk of death from any cause by 22%, death from CV causes by 31%, ACS by 38%, the need for coronary revascularization by 44% and cerebrovascular events by 25% [19]. However, the main condition to achieve this is to ensure that the patient reaches their LDL-C goal, which unfortunately only occurs in every 3-4th patient worldwide (irrespective of the CVD risk) and every 5-6th very high-risk patient [3,20]. At the same time, we cannot be LDL-C-centric, and we should always take a comprehensive approach to the amelioration of all CVD risk factors. Similarly important is the effective tackling of therapeutical inertia (risk of underdiagnosis and inadequate intensive therapy) and nonadherence [21]. It seems that the effectiveness of therapy can also be improved by treating the risk as a cardiovascular continuum, applying the concept of the lifetime risk estimation instead of 5-10-year predictions (as it is e.g. in the SCORE2) that usually

underestimate the risk (not adjusting to multiple risk factors) and does not help the patients to understand the risk and be adherent to the administered therapies. Thus there is a large need for revising the approaches to defining and managing risk in primary and secondary prevention [22,23]. The first attempt for this has been made in the recent American Heart Association (AHA) recommendations, which introduced the Predicting Risk of CVD EVENTs (PREVENT) equations among US adults 30 to 79 years of age without known CVD allowing stratifying CVD risk for 10 and 30-year perspective [24]. Nowadays, with sophisticated imaging techniques to be applied we can diagnose very early atherosclerosis (soft/noncalcified atheroma plaques, spotty calcifications, low attenuated plaques, total plaque burden) in coronary arteries. This allows for the optimization of treatment to reverse the atherosclerosis process promptly and effectively, thereby preventing the first event (**Figure 2**) [25]. The pericoronary fat attenuation index (FAI) may be also a reliable indicator of local immune-inflammatory response activation, which is closely related to plaque vulnerability, but we need to have this method more commonly available and more data to confirm its role in CVD risk prediction [26].

Coronary Computed Tomography Angiography (CCTA) and Coronary Artery Calcium (CAC) scoring may play a crucial role in the identification and quantification of ASCVD, thus directing the intensification of preventive interventions through lifestyle changes and risk factor management [25]. In an analysis of very high-risk patients, Budoff *et al.* showed that patients without known coronary artery disease (CAD) with CAC score >300 have a risk of major adverse cardiac events (MACE) similar to post-MI patients [27]. This finding has very practical implications - we should shift the definition of secondary prevention to earlier phases of the atherosclerosis process, then such patients would be considered equivalent to those with established CVD. They would be recommended to receive intensive upfront lipid lowering combination therapy (defined as immediate start lipid disorders therapy with statin and ezetimibe; here at least with a high intensity statin and ezetimibe, or triple therapy – including also bempedoic acid or PCSK9 targeted therapy - for high baseline LDL-C or statin nonadherence patients), which would be expected to substantially reduce the likelihood of a first event.

Such an approach seems logical for very and extremely high-risk patients, but an approach on how to proceed with patients at lower CVD risk should be considered with the concept of the "*power of zero*" (that is CAC score =0). First, it needs to be emphasized that we should not consider CAC-score alone, without a comprehensive view of the other risk factors, risk categories based on SCORE, and CCTA (if accessible) to assess whether or not atherosclerosis is already present in the coronary arteries (soft atheroma plaques, LAP, total coronary plaque

volume). It has recently been shown that this may be already associated with cardiac injury, and low-attenuation plaque burden was independently associated with plasma cardiac troponin I concentration ≥5 ng/L (adjusted odds ratio [aOR] 1.62, 95%CI 1.17 to 2.32, p=0.005) or presence of any visible coronary artery disease (aOR 1.57, 95%CI 1.07 to 2.37, p=0.026) [28]. In another study, the authors confirmed that LAP was the strongest predictor of fatal or nonfatal MI (aHR, 1.60, 95% CI, 1.10–2.34, P=0.014), exceeding other established markers, including CVD risk scores, calcium scoring, and coronary artery stenoses (**Figure 2**) [29,30].

It seems that the approach to the "*power of zero*" for low to moderate risk patients (based on SCORE2), adherent to lifestyle changes, with no subclinical atherosclerosis, may be that no statin is needed imminently. However, a follow-up CCTA and CAC score should be obtained in the next 3-5 years [31]. But the "power of zero" for patients at moderate risk, nonadherent to lifestyle changes, implies reevaluation in 3 years (if possible), and in case of high baseline LDL-C levels and/or family history of premature CVD, statin therapy should be considered, to invest in health as early as possible, and to prevent atherosclerosis progression effectively. For all other categories: symptomatic patients (the recent data suggests that >41% of patients with CAC=0 show coronary atherosclerosis in CCTA [32]), those with confirmed atherosclerosis in CCTA (LAP, noncalcified plaques) statin therapy, high and very high-risk patients, irrespective the lifestyle changes, should be always recommended with suitable intensity to achieve the recommended LDL-C goals. Thus, in all remaining very high and extremely high-risk patients, especially those with established ASCVD and other risk factors, and post-event, double or triple upfront LLT should be recommended [33]. It also seems that available data prompt consideration of upfront combination LLT in very high-risk primary prevention patients with CAC score ≥300 (what implies equivalent risk to post-MI patients), to start effective prevention earlier and to reduce the risk of recurrent MIs, that can appear for many as 20% of patients within 12 months and in 26% in 3 years after the event [34,35]. Waiting for the further progression of atherosclerosis without effective therapy, and without reaching treatment goals increases the risk significantly. Based on the data from the CAC Consortium it was demonstrated that compared to those with no CAC, a CAC score of ≥1000 increased the hazard ratio for CVD 6.8-fold and all-cause mortality 2.9-fold, a significant increase from those with CAC scores of 400–999 [36]. Based on recent data, it has been confirmed that lipid lowering combination therapy significantly increased the likelihood of reaching LDL-C goals (meeting the approach of *the lower the better*) as early as possible (*the earlier the better*), to maintain the reduction (*the longer the better*), to increase adherence, to reduce the risk of adverse effects and discontinuation, and finally to reduce cardiovascular outcomes and mortality [33,37-39]. Until

ongoing studies on this are published, such as the SCOT-HEART 2 trial (*Computed Tomography Coronary Angiography for the Prevention of Myocardial Infarction*; NCT03920176 – to be completed in 2028) that investigates CCTA-guided management compared with current standard of care, or the CorCal trial (*Effectiveness of a Proactive Cardiovascular Primary Prevention Strategy, With or Without the Use of Coronary Calcium Screening, in Preventing Future Major Adverse Cardiac Events;* NCT03439267 –expected to be released later in 2024) that evaluates the effectiveness of a proactive CVD primary prevention strategy, with or without CAC screening, the above mentioned approach seems the most practically reasonable to effectively prevent CVD events (**Figure 2**).

The (upfront) combination LLT – the known and unknown

The abovementioned data clearly shows that the treatment of lipid disorders should be carried out according to the principle "*the earlier the better*", "*the lower the better*" and "*the longer the better*" in the correctly identified patients. Only such treatment allows for a maximum reduction in lifetime LDL-C exposure. Despite evidence of the significant CV benefits and safety of LLT, the percentage of patients achieving target LDL-C levels is very low. In the *Treatment of high and very high risk dyslipidemic pAtients for the prevention of cardiOvasculaR events in Europe - a multInatioNal observatIonal* (SANTORINI) study, which included 9044 patients with high or very high CV risk (coming from 14 Western European countries), it was found that only 20.1% (24% in the high-risk group and 18.6% in the very high-risk group) achieved the therapeutic goal according to the European Society of Cardiology/ European Atherosclerosis Society (ESC/EAS) 2019 guidelines [40,41]. In the extended follow-up of the SANTORINI study, it was observed that monotherapy and combination therapy usage rose from 53.6% and 25.6% to 57.1% and 37.9%, respectively. The largest increase in the use of any combination therapy in the overall group, mostly reflected an increased use of statin and ezetimibe combination in the overall group (17.1 to 26.4%), and high-risk (12.1 to 17.0%) and very-high-risk patients (19.1 to 30.3%). This was a result that after over a year of follow-up mean LDL-C levels decreased from 2.4 mmol/L to 2.0 mmol/L, and goal attainment improved from 21.2% to 30.9%, and was greater with combination therapy compared with monotherapy at follow-up (39.4 vs 25.5%) [42].

The newly updated (2024) recommendations of the International Lipid Expert Panel (ILEP) regarding LLT in patients with established ASCVD and following ACS strongly indicate that combination LLT should be considered upfront in all very high and extremely high-risk patients, emphasizing the importance of its utilization pre-event [43]. What is more, the

recommendations promote the personalization of LLT through upfront combination therapy consisting of reduced dose statin and ezetimibe in very challenging group of patients with metabolic disturbances and statin intolerance [43,44]. This approach is new, because even in the applicable ESC/EAS 2019 guidelines stepwise intensification of LLT is recommended (for at least 8-12 weeks, which means at least 6-12 months in practice), including ACS patients, those with ASCVD and/or diabetes, that should require intensive reduction to reach their LDL-C target as early as possible [41].

In the small prospective Jena auf Ziel—JaZ study, which included 86 patients after ACS, the authors found that after 4-6 weeks, 80% of them achieved the target LDL-C level (<55 mg/dl) as a result of the use of combination of atorvastatin 80 mg + ezetimibe 10 mg. Further intensification of treatment by adding bempedoic acid or a PCSK9 inhibitor. After 12 months of observation, this resulted in 100% of patients reaching the therapeutic goal according to ESC/EAS 2019 [44]. In a study by Lee *et al.,* including 72,050 patients undergoing percutaneous coronary intervention (PCI), the authors investigated the impact of statin monotherapy *versus* upfront statin plus ezetimibe combination therapy on the risk of a composite endpoint, including a 3-year composite event of CV death, ACS, coronary revascularization, hospitalization for heart failure or nonfatal stroke. Upfront combination LLT was associated with a significantly lower risk of the composite endpoint (HR 0.75; 95% CI: 0.70-0.79), a lower risk of treatment discontinuation (HR 0.85; 95% CI: 0.78-0.94) and a lower risk of new onset diabetes (HR 0.80; 95% CI: 0.72-0.88) [46]. Extremely important clinical clues were provided in the analysis by Lewek *et al.,* covering 38,023 patients after ACS, included in the Polish Registry of ACS (PL-ACS) [37]. It was shown that upfront combination therapy (rosuvastatin or atorvastatin + ezetimibe) was associated with a significant reduction of all-cause mortality in comparison with statin monotherapy (OR 0.526; 95% CI: 0.378-0.733), with absolute risk reduction of 4.7% after 3 years (number needed to treat = 21). Importantly, the significant effect of the upfront combination LLT on mortality reduction appeared after only 52 days [37]. A study by Jang *et al.,* with 21,446 ACS patients, also showed a significant advantage of upfront combination treatment, confirming that this approach reduced the risk of ACS, stroke and all-cause mortality by 15% (HR 0.85; 95% CI: 0.78- 0.92) *versus* statin monotherapy [47]. A meta-analysis of 6 randomized clinical trials (RCTs) conducted by Oliveira *et al.,* including 20,574 patients with ACS, confirmed that the use of combined treatment (statin + ezetimibe) brings greater CV benefits: a 7% reduction in the risk of MACE (RR 0.93; 95%CI: 0.90-0.97) and non-fatal ACS by 12% (RR 0.88; 95%CI: 0.81-0.95) [48]. It is also worth mentioning that combination of statin + ezetimibe may also bring significant

benefits in primary prevention (prevention of the first MACE), which was observed in the study by Jun *et al.,* including 69,488 participants, where the combination LLT *versus* statin monotherapy led to a 19% reduction in the ACS risk (HR 0.81; 95%CI: 0,71-0.94) and stroke by 22% (HR 0.78; 95%CI: 0.65-0.93) [49]. In the most recent and largest meta-analysis of 14 studies with 108,353 very high-risk patients Banach *et al.* [50] showed that upfront combination LLT significantly more effectively reduces the LDL-C level from baseline (by -12.96 mg/dL, 95%CI: -17.27 to -8.65, p<0.001), and significantly reduces all-cause mortality (OR 0.81, 95%CI: 0.67 to 0.97, p=0.02), MACE (0.82, 95%CI: 0.69-0.97, p=0.02), and stroke incidence (0.83, 95%CI: 0.75-0.91, p<0.001). The risk of adverse events and the therapy discontinuation rate was comparable between groups and 44% lower for upfront combination LLT in comparison to high intensity statin therapy in the accompanying network meta-analysis [50]. Based on all above results, an attempt at the recommendations indicating group of patients that benefit the most from the upfront combination LLT have been recently prepared by the experts from the Polish Lipid Association (PoLA) [51].

The use of combination LLT is also characterized by a greater lipid-lowering effect compared to increasing the dose of a single drug. A meta-analysis of 14 studies conducted by Zhu *et al.,* including 3,105 participants, compared the effect of adding ezetimibe to a statin *versus* doubling the statin dose on the lipid profile showed that combination of statin plus ezetimibe compared to double-dose statin monotherapy significantly decreased LDL-C, non-HDL-C, TC, and TG levels by 14.16%, 14.01%, 11.06%, and 5.96%, respectively [52]. Ultimately, the use of a high intensity statin with ezetimibe allows for a reduction of LDL-C by approximately 65% [4]. It is worth mentioning that further intensification of LLT by adding a PCSK9-targeted therapy or bempedoic acid allows for lowering LDL-C by 85% and 75%, respectively [4]. This results from the additive/synergistic effect attributable to the different biological mechanisms of action of these drugs (**Figure 3**) [3,53]. An additional benefit of combined LLT also translates to its impact on the volume of atherosclerotic plaque. A meta-analysis of 52 RCTs conducted by Rivera *et al.,* including 9,113 patients on LLT, showed that the combination of a statin with ezetimibe *versus* statin monotherapy reduced percent atheroma volume (PAV) to a greater extent (-4.07% *versus* -1.01%) [54]. It is worth mentioning that each 1% reduction in PAV is associated with a 19% reduction in the odds of MACE (OR 0.81; 95% CI: 0.68-0.96) [55]. Zhang *et al.*, in their meta-analysis, found that the combination of a statin with ezetimibe *versus* statin monotherapy reduced the total atheroma volume (WMD -3.17%; 95%CI: -5.42 to -0.92) to a significantly greater extent [56].

It is important to emphasize that in addition to the benefit of a greater LDL-C reduction, PAV and in the risk of CV events, another important benefit of upfront combination therapy is a lower frequency of discontinuation or dose reduction in those treated with the combination therapy than in the statin monotherapy, including clinically challenging populations, such as elderly patients, and those with diabetes [37,47,57]. The ILEP 2024 recommendations, like European and US guidelines published since 2018, also indicate that combined therapy (statin + ezetimibe) should be used in the form of a fixed dose combination (FDC) where practical to do so [43]. Patients taking a statin with ezetimibe in the form of FDC, compared to those taking two drugs in monotherapy, have an 87% (75–99%) greater chance of being highly adherent. Patients with high adherence have a greater likelihood to be at LDL-C goal and as much as a 55% lower risk of CV outcomes [58]. This translates into greater adherence, compliance, and persistence of LLT, and thus leads to a reduction in lifetime LDL-C exposure (**Figure 4A and B**).

Conclusions: what needs to be done?

Considering the above evidence of the CV benefits resulting from the use of lipid lowering combination therapy, every effort should be made to ensure that as many of the appropriate selected patients as possible (especially those at high, very high and extreme risk) are recommended such a treatment [59,60]. In the above-mentioned SANTORINI study, in the group of patients with high and very high CV risk, only 37.9% used combined LLT [42], but the clinical practice of most of the countries indicates that only 10-20% of patients are prescribed combination therapy, and much less are on the FDC. Well-recognized reasons for non-adherence include lack of patients and physicians' education (digital tools should be more commonly applied [61]), low level and class of recommendation and observed inconsistency in the existing guidelines, resistance to polypharmacy, availability and cost of drugs, and lack of reimbursement/limited access to healthcare [17,43]. Finally, despite this paper mostly refers to the lipid lowering therapy for patients at different cardiovascular risk and atherosclerosis progression, one should remember that lifestyle changes (optimal well-balanced diet, regular physical exertion, avoiding overweight and obesity, smoking and alcohol cessation) should be always a permanent part of the management, synergistically increasing the chance to prevent ASCVD risk [23].

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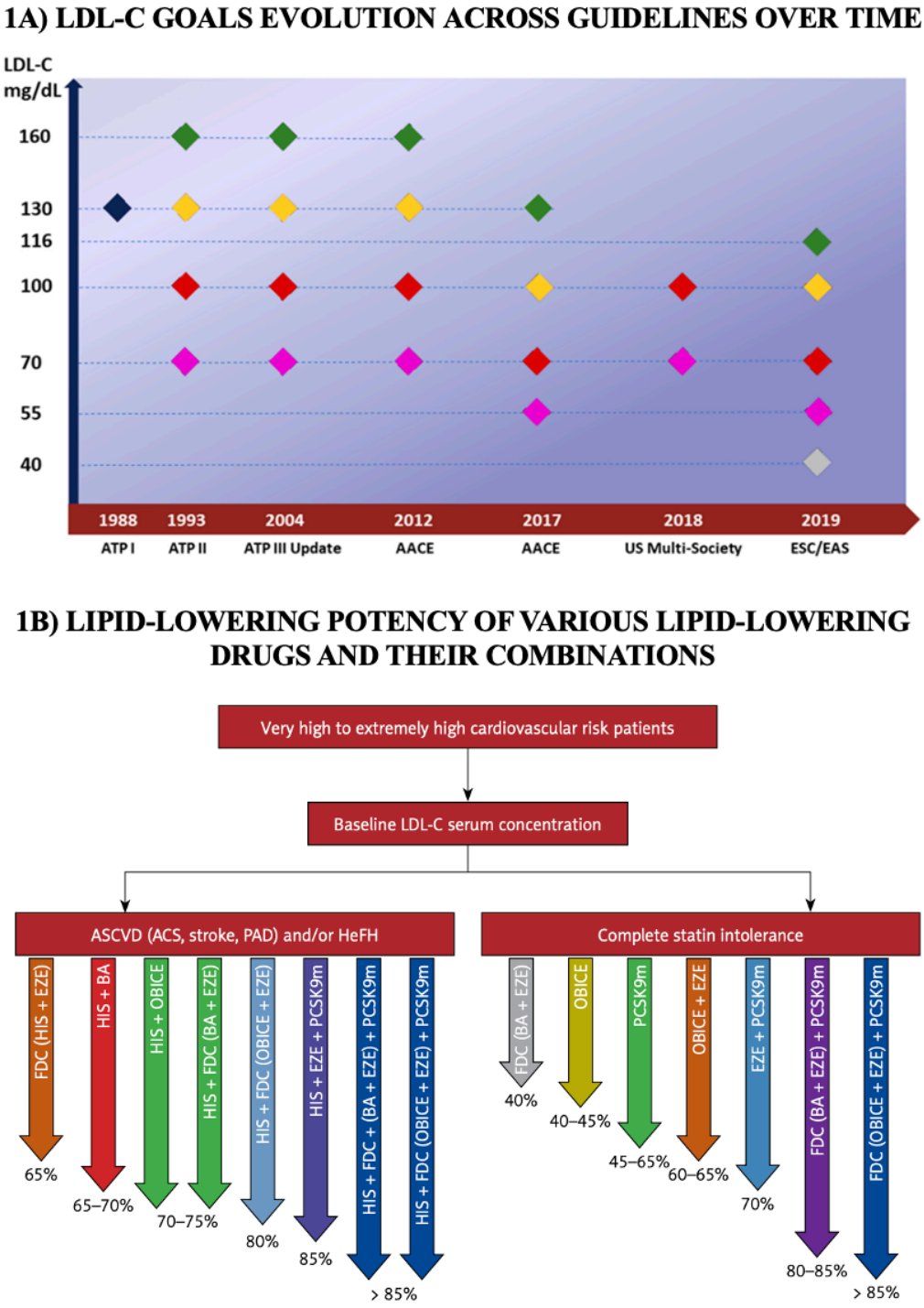

Figure 1. A) LDL-C goals evolution across guidelines over time. Reprinted from [15], license CC-BY – no permission required; **B)** Lipid-lowering combination therapy in very high cardiovascular risk patients now, and the possible prospective combinations, including drugs being under investigations (*for some of the presented combinations the suggested reduction is assumption based on the available data). Reprinted from [3] with permission. *Abbreviations: AACE - American Association of Clinical Endocrinologists; ATP - Adult Treatment Panel; EAS - European Atherosclerosis Society; ESC - European Society of Cardiology; LDL-C - low-density lipoprotein cholesterol; ASCVD – atherosclerotic cardiovascular disease, ACS – acute coronary syndrome, PAD – peripheral artery disease, HeFH - heterozygous familial hypercholesterolemia, FDC – fixed dose combination, HIS – high intensity statin, EZE – ezetimibe, BA – bempedoic acid, OBICE – obicetrapib, PCSK9m – proprotein convertase subtilisin/kexin 9 modulator.*

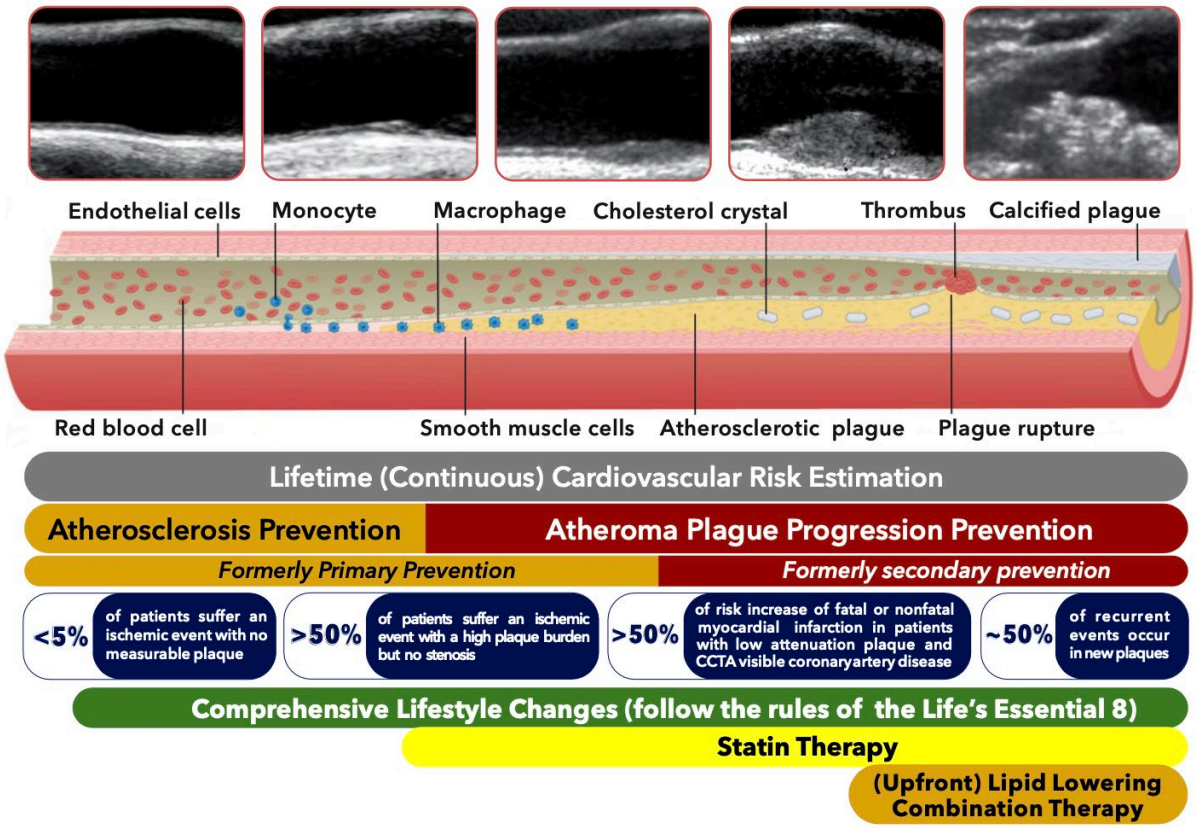

Figure 2. The practical guidance on risk stratification and management of patients at different stages on atherosclerosis process. Modified and redrawn based on Raitakari *et al.* [62] with permission (No.: 5834370924715) and Blaha *et al.* [63] (no permission required). *Abbreviations: CCTA - Coronary Computed Tomography Angiography.*

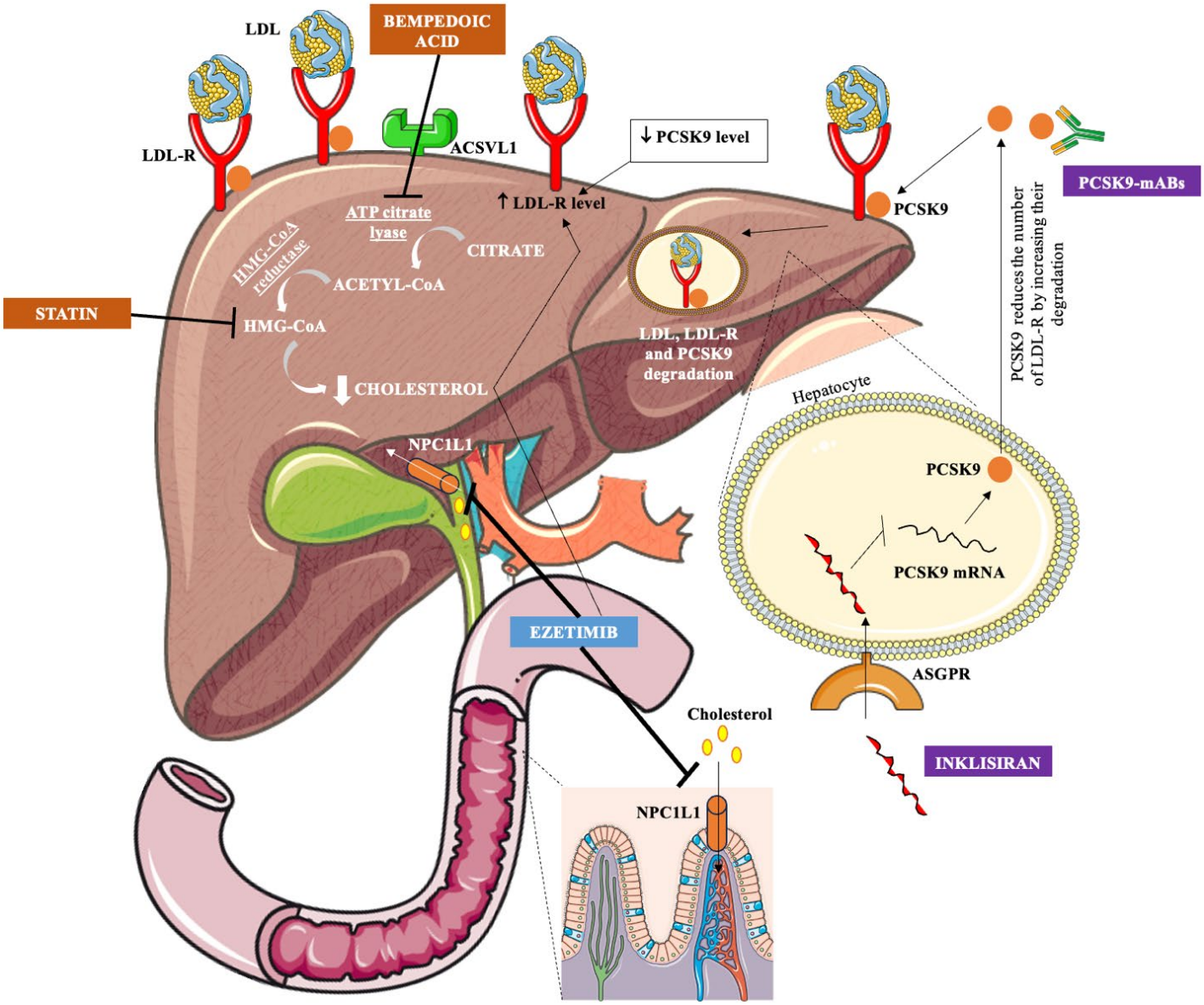

Figure 3. Mechanism of action of the most important lipid-lowering drugs. Based on information from [3,53]. *Abbreviations: LDL – low-density lipoprotein; LDL-R – low-density lipoprotein receptor; ACSVL1 - very long-chain acyl-CoA synthetase; HMG-CoA - β-hydroxy β-methylglutaryl-CoA; NPC1L1 - Niemann-Pick C1-Like 1; PCSK9 - proprotein convertase subtilisin/kexin 9; mAbs – monoclonal antibodies; mRNA – messenger ribonucleic acid*

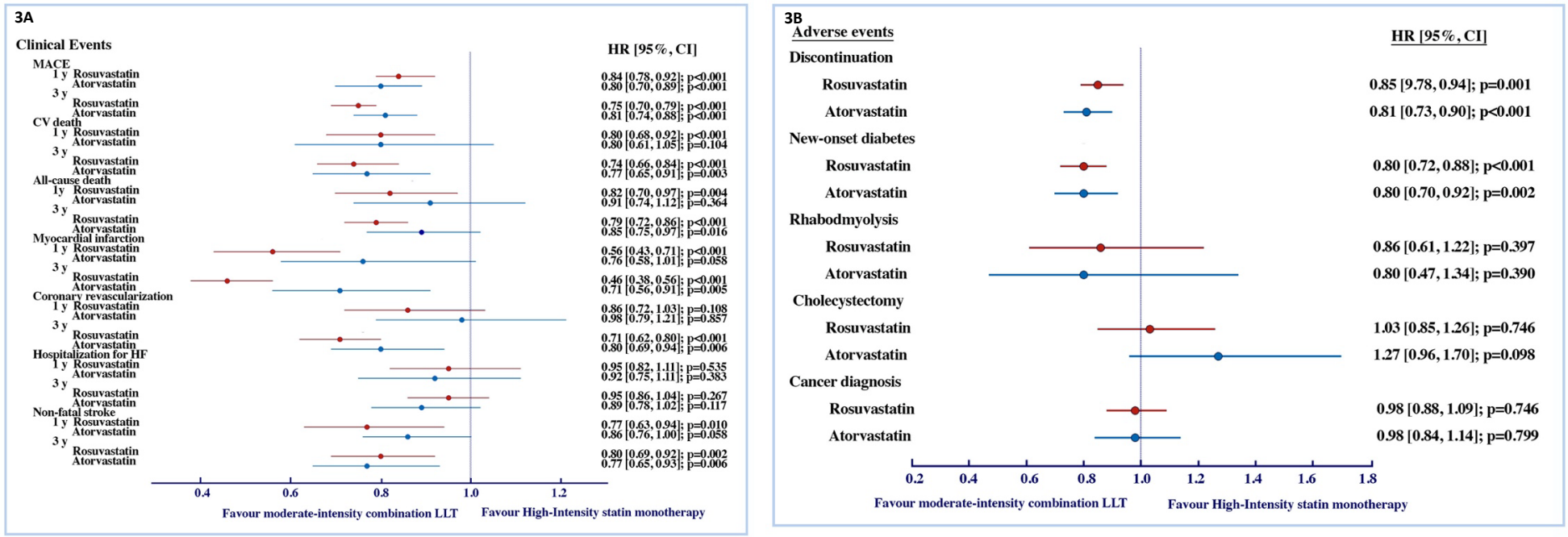

Figure 4A. Effect of upfront lipid lowering combination therapy of moderate intensity rosuvastatin or atorvastatin plus ezetimibe vs high intensity statin therapy [HIS] of rosuvastatin or atorvastatin on cardiovascular and mortality outcomes; **B** – the effect of upfront moderate intensity lipid lowering combination therapy vs HIS on adverse effects and safety parameters. Drawn based on results from Lee SJ, *et al.* J Am Coll Cardiol. 2023;82(5):401-410 [46] and Lee SJ, *et al.* Eur Heart J Cardiovasc Pharmacother. 2023; doi: 10.1093/ehjcvp/pvad083 [64].