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CONSENSUS DOCUMENT

2024 consensus document of the Italian Society of Arterial Hypertension (SIIA) and the Italian Society of Cardiovascular Prevention (SIPREC): update on LDL cholesterol lowering in patients with arterial hypertension

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Abstract

Hypertension and hypercholesterolemia often occur in the same individuals, increasing the risk of major cardiovascular (CV) outcomes, including myocardial infarction, stroke, CV death, as well as other CV complications. Concomitant management of these condition now represent a crucial step to reduce individual global CV risk and improve CV disease prevention in daily clinical practice. Given the high prevalence of hypertension and hypercholesterolemia in general population and their impact on health status, several pharmacological options are currently available to achieve the recommended therapeutic targets. These drugs, mostly including statins, ezetimibe, bempedoic acid, proprotein convertase subtilisin/kexin type 9 (PCSK-9) inhibitors and inclisiran, can be used either in monotherapies or in combination therapies, with different clinical indications, therapeutic efficacy and tolerability profile. Decision among different drug classes and dosages, as well as choice between monotherapy or combination therapy (fixed or free), largely depend on individual global CV risk profile and therapeutic targets of low-density lipoprotein (LDL) cholesterol levels to be achieved under pharmacological therapy. The present consensus document represents an update of the previous document published on 2022 and endorsed by the Italian Society of Hypertension (SIIA) and the Italian Society of Cardiovascular Prevention (SIPREC). Here we propose a novel paradigm for the treatment of the patients with hypertension and hypercholesterolemia at high or very high cardiovascular risk. In addition, the pharmacological properties, and the clinical efficacy of novel agents recently approved for a tailored therapy of hypercholesterolemia in patients with atherosclerotic CV disease, including PCSK9 inhibitors and bempedoic acid, will be summarized.

Keywords Hypertension · Dyslipidaemia · Blood pressure · Total cholesterol · Low-density lipoprotein cholesterol · Statins · Ezetimibe · Bempedoic acid · PCSK9i · Inclisiran · Cardiovascular risk · Cardiovascular mortality

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1 Introduction

It is worldwide recognised that arterial hypertension and dyslipidaemia represent the leading risk factors for cardiovascular (CV) disease and their management is of crucial importance in both primary and secondary CV prevention. This is of particular importance, if we consider that hypertension and dyslipidaemia often coexist, and synergically conspire in raising the severity of CV risk, beyond that implied by simply adding the effect of these two risk factors together in the same individual [1].

This concept has been fully recognised and integrated into the main international guidelines on the management of arterial hypertension and hypercholesterolemia, which in fact recommend different treatment goals not only on the basis of the absolute values of the individual risk factor, but rather on the basis of the individual global CV risk profile [2, 3]. For these reasons, assessment of full lipid profile and identification of LDL-C values are mandatory steps in each hypertensive patient's work-up for properly estimating global CV risk profile [2].

Indeed, available clinical studies homogenously indicates that low-density lipoprotein cholesterol (LDL-C) is a major causal factor for atherosclerotic CV disease, remarking the "cause-effect" relationship between LDL-C lowering and CV risk reduction [4]. Findings from multiple meta-analyses and individual randomized clinical trials demonstrated that lipid-lowering medications, including statins and non-statin-based treatments, led to a linear relative risk reduction of CV events that is proportional to the entity of LDL-C reduction. Such effect was obtained independently of baseline LDL-C levels, both in primary and in secondary prevention, and without any J-shaped curve effect, thus advocating the so-called "the lower the better" paradigm [5, 6]. More recently, clinical trials performed with ezetimibe or proprotein convertase subtilisin/kexin type 9 (PCSK-9) inhibitors accumulated evidence in supporting the causal role of LDL-C reduction for CV protection [6]. In recent years, bempedoic acid has become an additional therapeutic option that addresses the clinical need for LDL-C lowering treatment that can be used on a large scale, is cost-effective and easy to administer. The results of trials performed with bempedoic acid showed that this drug not only confirmed efficacy and safety in reducing LDL-C levels, but also significantly reduced major CV events in a population of "statin-intolerant" patients at high CV risk [7].

In the light of these recent findings, this consensus document from the Italian Society of Arterial Hypertension (SIIA) and the Italian Society of Cardiovascular Prevention (SIPREC) aims to provide an update on LDL-C lowering therapies in patients with hypertension and hypercholesterolemia, with a focus on the main clinical scenarios in which the use of bempedoic acid treatment may be a useful therapeutic option. The present consensus document represents an update of the previous 2022 SIIA document for the clinical management of hypertensive patients with hypercholesterolemia and high or very high CV risk [8].

2 Current guidelines on hypertension and dyslipidemias: targeting the risk

Hypertension and hypercholesterolemia are both major, and often coexisting CV risk factors, as extensively recognized by the European Society of Hypertension (ESH), the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS) guidelines [2, 3, 9]. Their treatment needs to be simultaneous rather than isolated, and interventions, both non-pharmacological and pharmacological, should be preferred and actively promoted, having demonstrated to provide broader, multifaceted beneficial effects on global CV risk reduction [2, 3, 9].

Targeting individual CV risk is the ultimate goal of the combined management of these two conditions and should be prioritized to replace the obsolete "silos" approach in which risk factors is managed separately [10]. However, in view of the distinct conceptual differences between hypertension and dyslipidemia, some clarifications are needed to effectively harmonize the approach to CV-lowering treatment.

First, dyslipidemia and hypertension have a different relationship with CV risk. In the case of hypercholesterolemia, individual global CV risk is defined by TOT-C levels; conversely, treatment goals are defined by achieved LDL-C levels [2, 3, 9]. In the case of hypertension, target blood pressure (BP) levels are defined by age and health status according to 2023 ESH guidelines [2] and by global CV risk profile according to 2024 ESC guidelines [11]. In both conditions, however, CV risk is influenced by the presence of other major risk factors and/or by CV, cerebrovascular and kidney chronic diseases. Treatment initiation is generally started when BP levels are above 140 mmHg for systolic BP and/or 90 for diastolic BP. However, in individuals at very high CV risk, BP lowering is initiated at high-normal levels [2]. In addition, guidelines suggest that the detection of the presence and extent of atherosclerosis by different imaging techniques may represent a tool to identify individuals with longer exposure to risk factors and at a higher risk of events.

Second, the well-recognized statement "the lower, the better" applies to LDL-C levels, but only partially to the treatment of hypertension. While guidelines generally recommend a BP target of less than 130/80 mmHg, with particular caution in some populations, such as the elderly or

frail people, they also argue against deliberate intensive treatment to lower BP below 120/70 mmHg [2].

Third, in younger patients, i.e. those aged less than 40 years, reducing LDL-C is more controversial than BP lowering. In fact, SCORE2, the most widely used CV risk calculator in Europe, and a reference for dyslipidemia guidelines and LDL-C therapeutic targets, is highly dependent on age [12–14].

Although this reflects the static effect of older age as a major CV risk factor, it is shortcoming in terms of early prevention. Indeed, it overlooks the notion that early exposure implies a higher cumulative burden of disease later in life [15]. ESH guidelines recommend starting BP lowering treatment even in young patients (> 18 years, whose CV risk is generally low, low-to-moderate), if their BP is above the diagnostic threshold for hypertension [2]. Conversely, LDL-C lowering treatment is more controversial, as the 2019 guidelines focus on CV risk calculation, and the 2021 ESC guidelines on CV prevention do not generally recommend risk factor treatment other than lifestyle intervention in low-to-moderate risk conditions and in those younger than 50 years [3]. In Europe, cumulative risk calculators, such as the LIFE-CVD model/LIFE-CVD2 model could be used appropriately in individuals at low-to-moderate risk and in an age range of 35-90 years [16, 17].

On the basis of these considerations, he general principles recommended are: (1) classification into CV risk categories, with complementary risk assessment via SCORE2/SCORE2-OP or SCORE2-Diabetes [12–14]; (2) in very high risk individuals, if antihypertensive medications are well tolerated, start BP treatment even at high-normal levels and use the lowest LDL-C target; (3) if not at very high risk, start BP treatment at > 140/90 mmHg and use appropriate LDL-C target; (4) if risk is low-to-moderate in younger patients (< 50 years o 40?), start BP treatment at > 140/90 mmHg and consider LDL-C treatment based on the individual burden of risk factors and lifetime risk calculators as LIFE-CVD model. Table 1 summarizes this approach.

3 Real-world data: where are we now?

Current United States [18] and European [9] guidelines on hypercholesterolemia recommend a progressively more intensive lipid lowering approach leading to LDL-C normalization in all individuals affected by hypercholesterolemia. In the hypertensive population, the 2023 ESH guidelines [2]

Table 1 Harmonized BP and LDL treatment approach based on global CV risk stratification proposed by European guidelines

Hypertension disease staging	Other risk factors, HMOD, CVD or CKD	BP (mmHg) grading			
		High-normal SBP 130-139 DBP 85-89	Grade 1 SBP 140-159 DBP 90-99	Grade 2 SBP 160-179 DBP 100-109	Grade 3 SBP ≥ 180 DBP ≥ 110
Stage 1	No other risk factors	LDL < 116 BPt start: no BPt target < 130/80	LDL < 116 BPt start: yes BPt target < 130/80	LDL < 100 BPt start: yes BPt target < 130/80	LDL < 70/50%b BPt start: yes BPt target < 130/80
	1 or 2 risk factors	LDL < 116 BPt start: no BPt target < 130/80	LDL < 100 BPt start: yes BPt target < 130/80	LDL < 100 or < 70 BPt start: yes BPt target < 130/80	LDL < 70/50%b BPt start: yes BPt target < 130/80
	≥3 risk factors	LDL < 116 or < 100 BPt start: no BPt target < 130/80	LDL < 100 or < 70/50%b BPt start: yes BPt target < 130/80	LDL < 70/50%b BPt start: yes BPt target < 130/80	LDL < 70/50%b BPt start: yes BPt target < 130/80
Stage 2	HMOD, CKD grade 3, or diabetes mellitus	LDL < 100 or < 70/50%b BPt start: no BPt target < 130/80	LDL < 70/50%b BPt start: yes BPt target < 130/80	LDL < 70/50%b BPt start: yes BPt target < 130/80	LDL < 55/50%b BPt start: yes BPt target < 130/80
Stage 3	Established CVD or CKD grade ≥4	LDL < 55/50%b BPt start: yes BPt target < 130/80	LDL < 55/50%b BPt start: yes BPt target < 130/80	LDL < 55/50%b BPt start: yes BPt target < 130/80	LDL < 55/50%b BPt start: yes BPt target < 130/80

50%b: reduction of at least 50% from baseline values. In the absence of diabetes mellitus, CKD or CVD, complementary cardiovascular risk assessment with SCORE2/SCORE2-OP (depending on the age) and, when needed, with LIFE-CVD2 model is recommended. Please note that some recommendations may differ in specific populations (e.g. frail elderly, patients younger than 50 years). BPt: Blood pressure treatment; CKD: chronic kidney disease; CVD: cardiovascular disease. LDL units are expressed as mg/dL; BP units are expressed as mmHg. Light green: low risk; light orange: moderate risk; light red: high risk; bright red: very high risk

emphasize the concept that hypertension and dyslipidemia are highly prevalent in the general population and often coexist, contributing to CV risk in an additive way [19].

Both SIIA [8] SIPREC [20] strongly support the need for an adequate control of these conditions, and sharply define the routes for reaching BP and LDL-C normalization in the vast majority– if not all– patients with either hypertension or dyslipidemia, or both. In contrast to these recommendations [8, 20], real world data from patients taking lipid lowering drugs [21] in secondary prevention showed a mean achieved serum LDL-C level that was largely above the goal of 55 mg/dL despite of the addition of PCSK9 inhibitors. Concordantly, the open label extension (median follow up of about 5 years) of the FOURIER-OLE trial [22] demonstrated that approximately 20% of patients in secondary prevention did not achieve the recommended LDL-C therapeutic goal (< 55 mg/dL) despite the prescription of the PCSK9 inhibitor evolocumab. Similar findings were observed in an open label trial with inclisiran [23] and, although data on achieved serum LDL-C concentrations were not clearly reported, in the open label extension of the ODISSEY OUTCOMES trial performed with alirocumab [24]. These data appear surprising, since PCSK9 inhibition is known to reduce serum LDL-C concentration by approximately 60%. Thus, it is evident that real-world analysis is of key importance to explore our ability to normalize serum LDL-C concentration in the daily clinical practice.

In this context, the above mentioned open-label extension trials confirm that the majority of hypercholesterolemic patients was also affected by hypertension while showing that prescription of a high intensity statin + ezetimibe was not common and, in some instances, even rare. This is the evident cause of an insufficient LDL-C control in daily practice. Concordantly, an Italian observational study showed that– despite PCSK9 prescription and excellent patient adherence– the LDL-C target was achieved only in about 60% of treated patients [25]. Again, the vast majority (72.6%) of these patients were simultaneously affected by hypertension and dyslipidemia, and the insufficient LDL-C control was mostly due to inadequate prescriptions of either high intensity statins or high intensity statin + ezetimibe. Bempedoic acid, a novel lipid lowering agent that does not induce muscle adverse events and that demonstrated good efficacy and safety profiles in the real-world setting [26], will probably attenuate this gap but it is not expected to favor LDL-C control in the whole hypercholesterolemic (hypertensive) population.

In keeping to this, two recent surveys conducted in Portugal [27] and Italy [28] demonstrated that LDL-C and BP control is markedly worsened when hypertension and hypercholesterolemia coexist. We are now expected to use all the most recent inputs coming from clinical trials in the daily clinical practice, but real-world evidence suggest that this approach is probably outdated and should be implemented with meaningful and rigorous observational studies [29]. Indeed, real world data can generate robust evidence in favor or against clinical trials [30]. Obviously, interpretation of real world evidence should be independent and objective. In addition, the sources of real world data are often heterogeneous and vary from controlled open label follow up studies [22–24] to electronic health records, claims and billing data, registries, wearable device data, social media data, data from smartphone apps and smartwatch [31]. This information needs to be systematically validated but provides invaluable insights into the efficacy, safety, costs and meaning of medical treatments and interventions. Clinical trials, especially those obtained by applying randomization, will be also extremely useful, to test the interventions as it happens in a clinical trial though using real-world clinical practice settings (Fig. 1) [32].

Fig. 1 Current timeline from drug discovery to in-human phase 1 trials and ultimately approval and launch. In the next future clinical trials will follow suggestions and evidence deriving from arterial intelligence and in silico pharmacology and be supported by real world studies both before and after (angle arrow) drug approval and launch. Starting from phase 3, in-human studies, are expected to be based on a pragmatic rather than an explanatory approach. AI, Artificial Intelligence; RWE, Real world evidence; *Phase 3 trials are expected to be mainly «pragmatic», as in the original definition provided by Schwartz and Lellouch in 1967 [77], and then revised in 2009 [78], providing evidence for adoption of the intervention into real-world clinical practice

4 LDL-lowering drugs, established classics: statins and ezetimibe

Statins are reversible inhibitors of 3-hydroxy-3-methyl-Coenzyme A reductase, able to reduce the LDL-C levels by a 30-55% (depending on dose and intensity of the molecule). A large meta-analysis carried out by the Cholesterol Treatment Trialists' Collaboration and including individual data from 174,149 participants (among whom 46,675 women, 27%) concluded that statin therapy had similar absolute effects on one-year lipid concentrations in both men and women, reducing LDL-C by about 40 mg/dL in statin vs. control trials and approximately 20 mg/dl for more-intensive vs. less-intensive therapy. The proportional reductions in major CV events per 38 mg/dL reduction in LDL-C were comparable between women (rate ratio [RR] 0.84, 99% CI 0.78–0.91) and men (RR 0.78, 99% CI 0.75–0.81). No adverse effects on cancer incidence or non-CV mortality rates were observed in both sexes. These overall benefits resulted in reductions in all-cause mortality with statin therapy for both women (RR 0.91, 99% CI 0.84-0.99) and men (RR 0.90, 99% CI 0.86–0.95; adjusted heterogeneity $p = 0.43$) [5]. Practical suggestions could help to maintain adherence to the treatment with statins, which is usually very low, even in high-risk patients (Table 2) [33]. Recent literature suggest that the maximally tolerated dose of highly effective statins (rosuvastatin, atorvastatin) should prescribed as first treatment in all high-risk subjects [34].

The onset of the non-statin drug era can be traced back to 2002, when it was issued the Food and Drug Administration (FDA) approval of ezetimibe, an inhibitor of the Niemann–Pick C1-like 1 transporter on enterocytes. This mechanism of action specifically blocks the intestinal absorption of dietary and biliary cholesterol without interfering with the absorption of fat-soluble nutrients. Ezetimibe has favorable pharmacological characteristics that may contribute to its safety and tolerability profile. These included low incidence of myalgia and/or increased transaminases (0.1–1%) and myopathy (< 0.1%). Its pharmacokinetics are not significantly affected by age, sex, or race, and no dosage adjustment is required for patients with mild hepatic impairment or mild-to-severe renal impairment. Due to its extensive glucuronidation and minimal affinity for hepatic isoenzymes and transporters, ezetimibe is relatively resistant to metabolic drug-drug interactions, as shown by the absence of clinically relevant interactions with statins. At the recommended dose of 10 mg/day, ezetimibe has been shown to reduce LDL-C levels by approximately 18%, with an additional 25% reduction when combined with statins [35].

A meta-analysis of 26 randomized controlled trials involving 23,499 participants concluded that adding ezetimibe to statins reduces the risk of non-fatal myocardial infarction (MI) (RR 0.88, 95% CI 0.81 to 0.95; a reduction from 105/1000 to 92/1000, 95% CI 85 to 100) and non-fatal stroke (RR 0.83, 95% CI 0.71 to 0.97; a reduction from 32/1000 to 27/1000, 95% CI 23 to 31). The addition of ezetimibe to statins also reduces the need for coronary revascularization (RR 0.94, 95% CI 0.89 to 0.99; a reduction from 196/1000 to 184/1000, 95% CI 175 to 194). Regarding safety, adding ezetimibe to statins has little-to-no impact on the risk of hepatopathy (RR 1.14, 95% CI 0.96 to 1.35). No significant differences were observed between treatment groups regarding the risk of myopathy, rhabdomyolysis, cancer, gallbladder-related disease, or discontinuation due to adverse events [34].

Table 2 Clinical tricks to improve adherence to statin treatment

Clinical tricks to improve adherence to statin treatment
Clearly explaining the individual estimated cardiovascular risk
Clearly explaining efficacy and safety of the proposed treatment
Checking liver transaminases, gamma-GT and CPK before starting statin treatment
Checking (and managing) factors favouring statins-related adverse events before starting statin treatment (i.e. liver diseases, severe chronic kidney disease, hypothyroidism, low vitamin D,…)
In patients with moderate risk, starting with low-dosed statins associated with ezetimibe (even with alternate daily doses), slowly increasing dose to the maximally tolerated one
Moving statins to morning intake, when they associate statin use with the incidence of night adverse events (cramps, nightmares)

5 LDL-lowering drugs, "new" drugs: bempedoic acid and PCSK9i

A major therapeutic boost in the lipid lowering field came from the broader availability of non-statin alternatives, such as ezetimibe and proprotein convertase subtilisin/kexin type 9 (PCSK-9) inhibitors (both monoclonal antibodies and small interfering RNA) [36]. Finally, the CV benefit of the newly approved bempedoic acid, an oral adenosine triphosphate citrate lyase inhibitor that lowers LDL-C, was demonstrated by the solid finding that this compound is able to reduce major adverse CV events in both primary and secondary prevention [36].

5.1 PCSK9 inhibitors and inclisiran

5.1.1 Pharmacology

PCSK9, mainly synthesized and secreted by the liver, is a key regulator of circulating levels of LDL-C because of its ability to downregulate the hepatic expression of the LDL receptor. The rational to develop a PCSK9 inhibitor is based on different issues from genetic, epidemiology that together

with the role of PCSK9 in the pathogenesis of atherosclerosis strongly support PCSK9 as a pharmacological target for preventing hypercholesterolemia and CV risk [37]. PCSK9 inhibitors mAbs (Evolocumab and Alirocumab), are human monoclonal antibodies that interfere with the extracellular pathway by neutralizing circulating PCSK9 due to the interaction between PCSK9 (catalytic domain) and LDL receptor (EGF-A domain) to negate PCSK9's activity against LDLR recycling thus preventing its binding to the LDL receptor and its degradation. Alternatively, inclisiran, a small interfering RNA (siRNA) that inhibits hepatic synthesis of PCSK9, affects both extracellular and intracellular PCSK9 signaling pathways [38]. Inclisiran is a stabilized double-stranded ribonucleic acid siRNA, conjugated to an N-acetylgalactosamine (GalNAc) and designed to target selectively hepatic PCSK9 mRNA [36]. Direct inhibition of PCSK9 by mAbs or decrease in PCSK9 levels by inclisiran both lead to increase in LDL receptor recycling rates and the number of LDLR on the cell surface, to a prolonged functional lifespan of the LDL receptor and thus to lowering of LDL-C levels.

Both drug classes provide further reduction in LDL-C levels (up to 50%) beyond those achieved with statin therapy. Numerically, mAbs against PCSK9 achieve marginally superior LDL-C reduction (≈ 60%) as compared to the siRNA (≈ 50%), although head-to-head comparisons are required to confirm between-class differences in efficacy [36].

5.1.2 Clinical efficacy

The correlation between LDL-C reduction and CV events has been documented for both evolocumab [39] and alirocumab [40]; the specific randomized clinical trials, as well as their open-label extension, have also confirmed the safety and tolerability of both mAbs. In the FOURIER study [39], enrolling patients with documented atherosclerotic CV diseases, evolocumab reduced major adverse cardiac events by 15%, an effect primarily driven by reduced rates of MI (− 27%), stroke (− 21%) and coronary revascularization (− 22%). The benefit was also demonstrated in the open-label extension (FOURIER-OLE) in which 6635 of these patients were transitioned to open-label evolocumab regardless of initial treatment allocation in the parent trial and were followed up with for an additional median of 5 years [41]. Long-term achievement of lower LDL-C levels, down to < 20 mg/dL was associated with a lower risk of CV outcomes with no significant safety concerns [36]. Relative to alirocumab, the ODYSSEY OUTCOMES trial [40] showed a reducing in major CV events by 15% when compared to placebo in patients with recent acute coronary syndrome. This benefit was evident irrespective of age and independent of baseline eGFR, across a broad range above 30 mL/min/1.73 m^2, with larger relative risk reductions in patients with eGFR > 60 mL/min/1.73 m^2 [1].

The potential CV benefits of inclisiran are under investigation in two ongoing trials ORION-4 (NCT03705234) and VICTORION-2 PREVENT (NCT05030428) [42].

5.2 Bempedoic acid

5.2.1 Pharmacology

Bempedoic acid is a direct and competitive inhibitor of adenosine triphosphate citrate lyase (ACLY) [36, 43]. To manifest its direct and competitive inhibitory effect on cholesterol synthesis, bempedoic acid requires its transformation from a prodrug (8-hydroxy-2,2,4,14-tetramethyl-pentadecanedioic acid) to an active metabolite catalyzed by enzyme "very long-chain acyl-CoA synthetase-1 (ACSVL1)" which occurs in hepatocytes and leads to the genesis of the powerful direct and competitive inhibitor, bempedoic acid-CoA [1]. As documented by a series of in vitro and in vivo preclinical data, the inhibition of ACLY determines a reduction of cholesterol synthesis in the liver which translates into an increased expression of the LDL receptor. Thus, bempedoic acid reduces LDL-C (20–25%), non-HDL-C (19%), apo B (15%) and total cholesterol (16%) in patients with hypercholesterolemia or mixed dyslipidemia [1]. The selective action of bempedoic acid at the hepatic level on the endogenous synthesis of cholesterol represents a strong rationale, from a pharmacological point of view, for the combination with ezetimibe, inhibitor of cholesterol intestinal absorption, in the same pharmaceutical formulation [1]. This combination is very effective in the treatment of high and very high CV risk patients who require significant reductions in LDL-C. In fact, the combination of bempedoic acid, ezetimibe and statins, reduces by 63% the LDL-C levels [44] with an additional 30% with PCSK9 inhibitor [1]. Altogether, bempedoic acid may help to control cholesterol levels either as monotherapy or in combination with existing lipid-lowering therapy in a broad spectrum of patients at high CV risk as proposed recently by Banach [45]. This position paper of the International Lipid Expert Panel (ILEP) summarizes the recent evidence around the efficacy and safety of bempedoic acid and presents practical recommendations for its use, which complements the 'lower-is-better-for-longer' approach to lipid management, which is applied across international guidelines for the management of CV risk.

5.2.2 Clinical efficacy

Bempedoic acid has been approved for clinical use following the positive results of 4 randomized phase 3 studies

(CLEAR Harmony [46], CLEAR Wisdom [47], CLEAR Tranquility [48], CLEAR Serenity [48], and its clinical efficacy was confirmed in 2023 with the and CLEAR Outcomes trial [7]. The CLEAR Outcomes study enrolled a total of 13,970 patients who underwent randomization (between December 2016 and August 2019); 6992 were assigned to the bempedoic acid group (180 mg) and 6978 to the placebo group. The median duration of follow-up was 40.6 months. The primary endpoint (death from CV causes, non-fatal MI, nonfatal stroke, or coronary revascularization) occurred in 11.7% of participants taking bempedoic acid and 13.3% of those taking a placebo (HR = 0.87; 95%CI, 0.79-0.96) with a number-needed-to-treat (NNT) of 63. This benefit was in line with the CTTC endpoint calculation, which predicts an HR of 0.846 for 26.1 mg/dL in LDL-C reduction. There was no significant difference in rates of death between the two study arms. The key secondary endpoint (fatal or non-fatal MI occurred in 3.7% of patients given bempedoic acid and in 4.8% of those given placebo (HR = 0.77; 95% CI, 0.66–0.91). Bempedoic acid was superior to placebo to reduce coronary revascularization by 19% (HR = 0.81; 95% CI, 0.72–0.92).

A simplified therapeutic algorithm was proposed in the previous 2022 SIIA consensus document [8]. On the basis of the most recent evidence from RCTs, an updated therapeutic approach can be proposed for achieving the recommended therapeutic LDL-C targets in patients with hypertension and dyslipidaemia. The novel algorithm proposes different approaches based on either the absence (Fig. 2) or the presence (Fig. 3) of documented statin intolerance, or the presence of very high CV risk profile or previous atherosclerotic CV diseases (Fig. 4). Attained LDL-C reductions that can be achieved with different therapeutic approaches, both in monotherapies and in various combinations therapies, are also illustrated in Fig. 4 (Table 3).

6 The role of LDLc in cardiovascular risk profile: additional benefits in patients with hypertension

Elevated systolic BP and LDL-C levels are listed as two major risk factors for CV diseases and all-cause mortality [49], being responsible for up to 10.8 and 3.8 million global deaths in 2021 [50], respectively. Hypertension and hypercholesterolemia often coexist [51], which may be due both to the high prevalence of the two risk factors in the general population and to their shared genetic-based pathophysiological mechanisms. Regarding this last point, a Mendelian randomization study tested the association between 24 LDL-C single-nucleotide polymorphisms and hypertension using counted genetic risk scores and weighted genetic risk scores [52]. In this study of 11,378 normotensive and 8,158 hypertensive subjects, the risk of hypertension increased as LDL-C increased, thus confirming the existence of causal effects between LDL-C and hypertension [52]. Additional mechanistic links into the pathophysiological association between hypercholesterolemia and hypertension have been proposed, including overactivation of the renin–angiotensin system, increased activity of endothelin-1, systemic endothelial dysfunction and arterial stiffening [51].

The detrimental interplay between hypertension and hypercholesterolemia is further supported by several lines of evidence showing that increased LDL-C levels impair

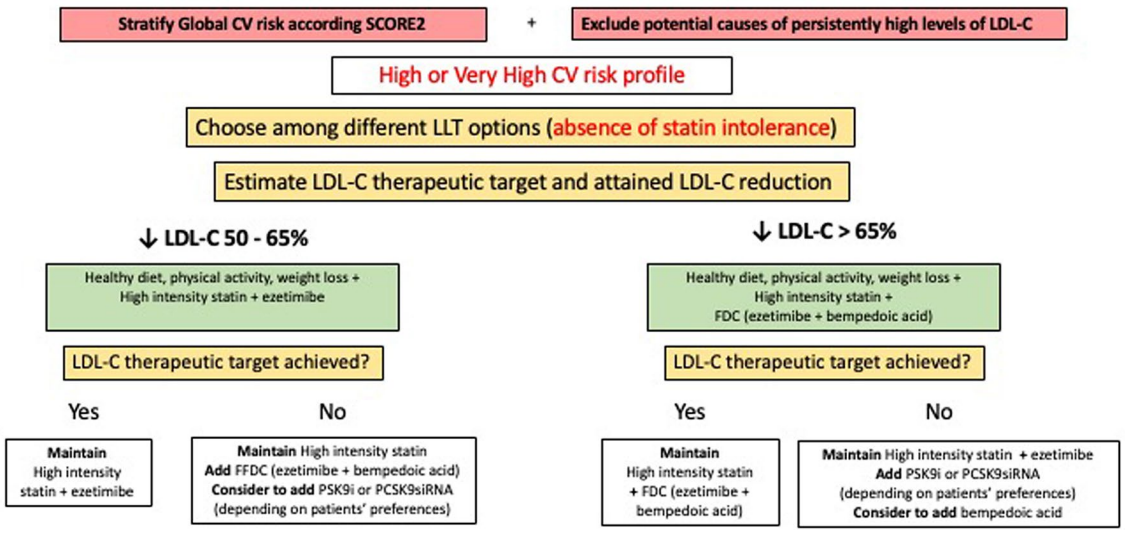

Fig. 2 Proposed therapeutic algorithm for achieving the recommended LDL-C therapeutic targets in patients without statin intolerance. Modified from reference num [79]. In figure: CV, cardiovascular; LDL-C, low density lipoprotein cholesterol; FDC, fixed dose combination; PCSK9, proprotein convertase subtilisin/kexin type 9.

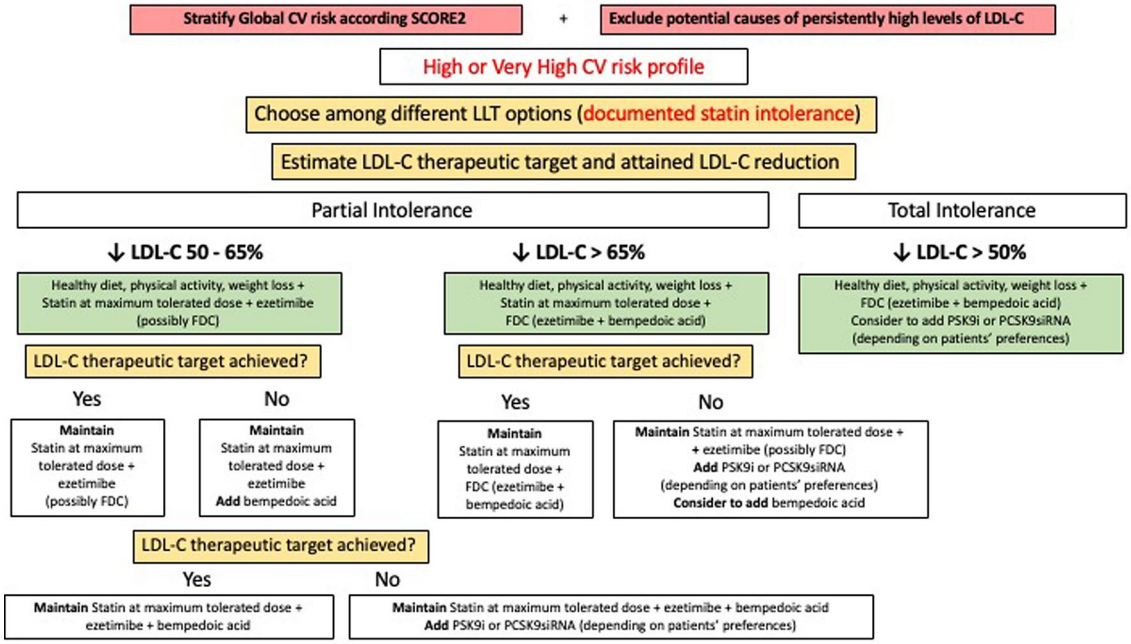

Fig. 3 Proposed therapeutic algorithm for achieving the recommended LDL-C therapeutic targets in patients with very high CV risk profile or previous atherosclerotic CV diseases (ASCVD). Modified from reference num [79]. CV, Cardiovascular; LDL-C, Low density lipoprotein cholesterol; FDC, Fixed dose combination; PCSK9, Proprotein convertase subtilisin/kexin type 9.

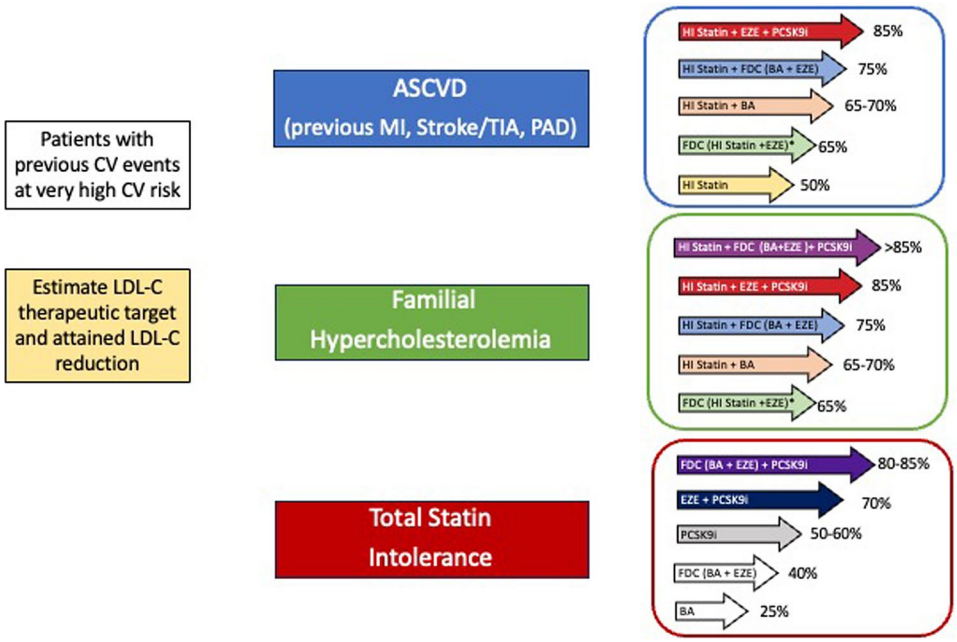

Fig. 4 Estimated LDL-C reductions that can be achieved with different therapeutic approaches, both in monotherapies and in various combinations therapies. In figure: CV, cardiovascular; LDL-C, low density lipoprotein cholesterol; FDC, fixed dose combination; MI, myocardial infraction; BA, bempedoic acid; EZE, ezetimibe; HI, high intensity; PCSK9, proprotein convertase subtilisin/kexin type 9.

arterial function and promote atherosclerosis in patients with hypertension and vice versa [53]. Furthermore, a synergistic interaction between hypertension and hypercholesterolemia in promoting ischemic heart disease and stroke has been demonstrated [54, 55]; thus, indicating that the CV risk is higher in patients with both disorders than the combined risk of hypertension and hypercholesterolemia alone.

Based on the strong and frequent synergistic detrimental impact of hypertension and hypercholesterolemia, translating into an extremely high attributable CV risk, prompt, efficient and durable control of both risk factors (especially when combined in the same subject) appears mandatory. In this regard, a meta-analysis of 7 studies, including 27,020 patients with 857 major CV events and 725 deaths, clearly concluded that CV risk reduction with BP lowering drugs

Table 3 Estimated LDL-C reductions that can be achieved with different therapeutic approaches, both in monotherapies and in various combinations therapies, based on the available data from randomized clinical trials

Lipid-lowering treatment options	Estimated LDL-C reduction (%)*
BA	~25
BA + statin	~18
BA + EZE	~40
BA + EZE + statin	~75
BA + EZE + PCSK9i	83
Low-intensity statin + BA	~40–45
Low-intensity statin + EZE + BA	~55–60
Moderate-intensity statin + BA	~50–55
Moderate-intensity statin + EZE + BA	64
Moderate-intensity statin + Inclisiran	~70
Moderate-intensity statin + PCSK9i	~75
High-intensity statin + EZE	~65
High-intensity statin + BA	~68
High-intensity statin + EZE + BA	~70–75
High-intensity statin + Inclisiran	~75
High-intensity statin + PCSK9i	~80
High-intensity statin + EZE + Inclisiran	~81
High-intensity statin + EZE + PCSK9i	~85
High-intensity statin + EZE + BA + Inclisiran	85
High-intensity statin + EZE + BA + PCSK9i	> 85

The size of LDL-C reduction for some recommended combinations is an assumption and needs to be confirmed. Modified from reference num [44].

BA, Bempedoic acid; EZE, Ezetimibe; LDL-C, Low-density lipoprotein cholesterol; LLT, Lipid-lowering therapy; PCSK9, Proprotein convertase subtilisin/kexin type 9.

*Statistical significance

was evident in patients taking statins; similarly, the relative risk reduction with statins was confirmed in patients receiving BP lowering drugs [56]. In this meta-analysis, the combined relative effects of BP drugs and statins on CV events were multiplicative [56]. This result is in line with several lines of evidence. First, lifelong genetic exposure to lower LDL-C and systolic BP levels was associated with lower CV risk in Mendelian randomization analysis [57]. Second, genetically proxied medications of combined lipid-lowering and antihypertensive drugs have an independent and additive effects on CV diseases [58]. Third, considering the putative CV benefits of reducing both LDL-C and blood-pressure, the results of the ASCOT-LLA trial confirms the beneficial effect on CV prognosis of adding a statin to BP-lowering treatment regimen in patients with hypertension [59]. Fourth, the inclusion of statins and BP -lowering agents into a fixed single pill combination increases the effectiveness of the combination therapy on each risk factor, improves treatment adherence and CV risk as well [60–62]. Fifth, statin treatment has the potential to minimally lower BP levels [63].

The frequent coexistence of two highly detrimental risk factors for CV disease, the availability of pharmacological strategies to reach an optimal control of both BP and LDL-C levels, the positive results gained from genetic studies and randomized clinical trials altogether is strongly support an evidence that goes in the same direction: that is, the development of effective strategies for the combined control of hypertension and hypercholesterolemia.

7 Beyond LDL-C: potential benefits of the new lipid lowering drugs in the hypertensive patients

Lipid-lowering therapies, mostly statins, have demonstrated to provide several clinical advantages, beyond LDL-C reduction, in a broad range of high-risk patients, including those with hypertension, in terms of reduced CV morbidity and mortality, independently by age, gender, ethnicity. concomitant CV risk factors and comorbidities. These beneficial effects provided by statins are based on large, randomized controlled clinical trials, which enrolled patients at different risk profile across the CV continuum. Indeed, most patients included in these trials also had hypertension, and BP elevation is one of the most frequently associated risk factors in patients with dyslipidaemia, also in the setting of clinical practice.

As an example, in the Collaborative Atorvastatin Diabetes Study (CARDS) trial, which enrolled patients with type 2 diabetes without previous CV events, who were randomized to atorvastatin 10 mg versus placebo, the proportion of patients with hypertension was about 84% [64]. In the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE- IT) trial, which enrolled patients who had been hospitalized for acute coronary syndrome within the preceding 10 days, about 61% of patients treated with either simvastatin monotherapy or a combination of simvastatin plus ezetimibe was also affected by hypertension [65].

Over the last decade, novel therapeutic approaches have been developed and tested in genetic and human studies for the clinical management of patients with hypercholesterolemia. These novel lipid lowering therapies can interfere with key enzymatic steps of cholesterol metabolism, that have been demonstrated to play a causative role in the development and progression of atherosclerotic diseases, at both coronary and peripheral levels. Specifically, these new lipid lowering therapies are based on RNA-targeted approaches, which included antisense oligonucleotides (ASO), siRNA, and novel genome editing techniques, and can interfere with

several atherogenic lipoproteins, such as PCSK9, apolipoprotein A (Apo(a)), and apolipoprotein C3 (APOC3) [66]. The adoption of these LLTs has demonstrated to produce dramatic reduction in LDL-C levels in patients at high and very high CV risk profile, most of whom were affected by hypertension.

Among these LLTs, PCSK9 inhibitors (alirocumab and evolocumab) induce the degradation of the LDL receptors located on the surface of hepatocytes, thus increasing the removal of LDL particles from the blood, and significantly reducing LDL-C levels by an average of 60% in individuals at high or very high CV risk. Beyond their therapeutic effects on LDL-C levels, PCSK9 inhibitors have demonstrated to provide additional, non-lipid-lowering properties, such as the improvement of endothelial function, the reduction of inflammatory markers, and platelet aggregation and activation, which may contribute in the reduction of risk of atherosclerotic diseases [67]. They also demonstrated to reduce the risk of cardiovascular morbidity and mortality in two large, randomized controlled clinical trials [39, 40].

Although no prespecified sub-analysis was performed on patients with hypertension included in these two large clinical trials, a recent pooled analysis from 10 phase 3 ODYSSEY trials [68], including about 5000 patients with heterozygous familial hypercholesterolemia or non–familial hypercholesterolemia, treated with maximum tolerated dose of statins, confirmed the beneficial effects of alirocumab in reducing LDL-C levels and achieving the recommended therapeutic targets compared to placebo, particularly in the subgroup of patients with hypertension. Interestingly, in this analysis it was reported no suggestion of higher levels of PCSK9 among participants with vs without hypertension, in line with previous study [69]. However, the clinical efficacy of this drug was particularly evident and statistically significant in patients with than in those without hypertension.

PCSK9i therapy has been also associated with sustained improvements in endothelial function, arterial stiffness, and microvascular function, independently from concomitant lipid lowering therapies, as confirmed by recent clinical study [70] and meta-analysis [71]. Preliminary data also suggested a potential beneficial effect of PCSK9 inhibitor evolocumab in reducing serum aldosterone levels [72], thus contributing to lowering BP levels, in high CV risk patients.

Finally, the clinical efficacy and safety of the siRNA, inclisiran, was tested in the double-blind, randomized, placebo-controlled clinical trials, which included adult patients with familial hypercholesterolemia (ORION-9) [73] and non–familial hypercholesterolemia and atherosclerotic disease (ORION-10), and atherosclerotic CV disease or an atherosclerotic CV disease risk equivalent (ORION-11) [74]. Proportions of patients with hypertension in these trials were 42%, 90% and 80%. Also in this case, new lipid lowering therapies produced significantly greater reductions of LDL-C levels compared to placebo, independently by age, gender, and additional risk factors, without any significant increased risk of adverse events or side effects, as also demonstrated by recent pooled analyses of these trials [75, 76].

Although no specific clinical trials or predefined sub-analyses have been conducted in hypertensive populations, the use of novel lipid lowering therapies, including PCSK9 inhibitors or siRNA, or both, have demonstrated to provide additional benefits to the primary and secondary prevention of CV complications, mostly coronary events, in those patients with hypertension and dyslipidaemia, who have either failed to achieve the target values of LDL-C with statins or any other lipid lowering therapies, or those who have documented statin intolerance. Several other randomized clinical trials are ongoing to confirm the beneficial effects provided by these new lipid lowering therapies and to test other therapeutic targets, such as lipoprotein (a) or other lipoproteins [66].

8 Conclusion

In conclusion, statins today represent the first-line intervention to reduce the atherosclerotic burden driven by raised levels of LDL-C. However, considering the opportunity of reducing LDL-C to very low levels to mitigate the CV risk in very-high risk patients, statin monotherapy is not sufficient in most cases to achieve the required benefit. Combination with ezetimibe, PCSK9 inhibitors (mAbs and siRNA), and the most recent bempedoic acid, should all be considered as first line strategy for an optimal LDL-C-lowering action for the prevention of CV disease.

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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval No request to local Ethic Committee has been made, given the descriptive nature of the manuscript (systematic review).

Human and animal rights This article does not contain any studies

involving human participants performed by any of the authors. All procedures performed in clinical trials discussed in this manuscript and involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants involved in the clinical trials, according to the study protocols.

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