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Is there a role for earlier use of combination therapy?

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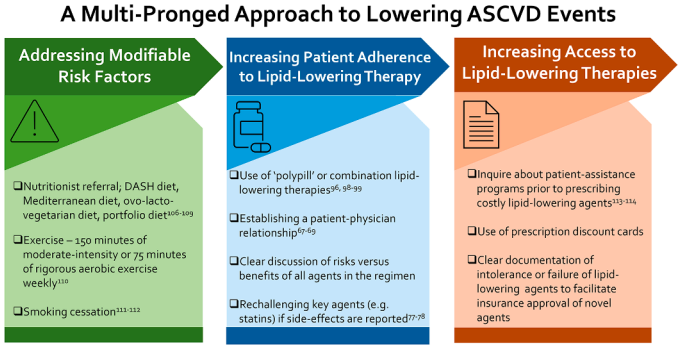
GRAPHICAL ABSTRACT

Central Figure. A Multi-Pronged Approach to Lowering ASCVD Events



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ABSTRACT

As the global population ages and cardiovascular risk factors rise, we can expect a continued increase in atherosclerotic disease. Low-density lipoprotein cholesterol (LDL-C) reduction is a cornerstone of cardiovascular risk reduction with strong, causal evidence indicating that the greatest benefit is derived from early and large decreases in LDL-C. Despite the adoption of statins as the backbone of lipid-therapy regimens, numerous studies and registry analyses reveal our collective inability to achieve LDL-C goals in high-risk patients. Combination therapy with ezetimibe has been shown to result in statistically significant decreases in LDL-C level, atheroma volume, and cardiovascular adverse event rates. A major barrier to implementing an upfront combination therapy approach is the perceived side effects from therapeutic agents although multiple studies show that a therapeutic patient-physician relationship could overcome this issue. Novel agents such as PCSK-9 inhibitors, bempedoic acid, and inclisiran have the potential to achieve similar outcomes although additional research is needed regarding the cost effectiveness of these approaches. Despite these hurdles, there is a role for the newer agents early in the disease course of high-risk patients such as those with markedly elevated LDL-C >190 mg/dL and FH.

The implementation of upfront combination therapy, especially in high-risk patients, will decrease clinical inertia while allowing for earlier consideration of newer, effective agents to decrease cardiovascular burden.

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1. Introduction

As factors such as obesity and an aging population rise, the global atherosclerotic burden is slated to climb to unparalleled levels. In the United States alone, there are close to 930,000 cardiovascular deaths yearly with coronary artery disease (CAD) deemed to be the culprit in approximately 41 % of these cases [1]. Low-density lipoprotein cholesterol (LDL-C) reduction is widely recognized as a pillar of cardiovascular disease prevention. One of the cardinal events in the development of atherosclerotic cardiovascular disease (ASCVD) is the accumulation and aggregation of cholesterol-rich apolipoprotein B (apoB) lipoproteins within the arterial intima. A strong, dose-dependent correlation exists between the LDL-C concentration and likelihood of this intimal retention [2–4]. A large meta-analysis involving 170,000 participants found, that over a five-year period, there was a 22 % log-linear proportional reduction in the risk of a major cardiovascular event per millimole per liter reduction in LDL-C. One millimole reduction was found to reduce all-cause mortality by 10 % (p <0.0001), in large part due to decreased mortality from CAD (RR 0.80, 99 % CI 0.74–0.87, p <0.0001) with benefits extended to other vascular outcomes such as decreased ischemic stroke rate and need for revascularization [5]. Numerous studies have consistently demonstrated decreased rates of adverse cardiovascular outcomes with LDL-C reductions, largely independent of baseline LDL-C level, although some debate persists on whether there are diminishing returns after achieving levels significantly lower than guidelines suggest. [6–12]

A post-hoc analysis of the Stroke Prevention by Aggressive Reduction in Cholesterol (SPARCL) trial compared the degree of LDL-C reduction to ensuing vascular event rates. This randomized, placebo-controlled study primarily focused on cerebrovascular accidents but analyzed coronary events as a secondary composite outcome. Greater than 50 % LDL-C reduction was associated with a 39 % reduction (p = 0.025) in coronary heart disease events and a 48 % reduction (p = 0.0006) in revascularization over a minimum four-year period [13]. The 2018/2019 American Heart Association (AHA)/American College of Cardiology (ACC)/Multisociety Cholesterol guidelines recommend targeting a LDL-C less than 70 mg/dL (1.8 mmol/L) in those with clinical ASCVD with a lower goal of less than 55 mg/dL (1.4 mmol/L) for very-high risk patients [10,14]. Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk – Open Label Extension (FOURIER-OLE) data demonstrated that LDL-C levels could be decreased below 20 mg/dL (0.2 mmol/L) without compromising safety [15].

This review will focus on the possible role of upfront combination therapy in high-risk populations, consideration of limitations of this approach, and earlier roles for new lipid lowering therapies within this framework.

2. Limitations of statin monotherapy in achieving optimal ldl-c reductions

Initiation of high-intensity statin therapy typically leads to halving of LDL-C with associated reductions in mortality and vascular events [5,12,16]. Intravascular ultrasonographic monitoring of coronary atheroma volume has been used to establish the importance of upfront high-intensity statin therapy with multiple studies showing regression of coronary atherosclerosis [17,18]. A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden (ASTEROID) trial examined the impact of atorvastatin 40 mg on coronary atherosclerosis in statin naïve patients. Nearly 80 % of patients experienced disease regression with atheroma in the most diseased subsegments decreasing by a mean of −6.1 mm^3 (97.5 % CI, −6.8 to −4.0 mm^3, p <0.001) corresponding with a 6.8 % median volume reduction [19]. The Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER), a randomized multi-national trial, found that the rates of adverse cardiovascular events were 0.77 and 1.36 per 100 person-years of follow-up in the rosuvastatin and placebo groups, respectively (HR 0.56; 95 % CI 0.46 to 0.69; p<0.00001)[20]. These findings complement those of the Myocardial Ischemic Reduction with Aggressive Cholesterol Lowering (MIRACL) and Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22) trials showing early initiation of statins after an acute coronary syndrome (ACS) event reduced cardiovascular events [21,22]. The various pleiotropic effects (plaque stabilization, anti-inflammatory actions, and improvement of endothelial function) along with their remarkable efficacy in reducing LDL-C and atheroma volume firmly establish this agent as the backbone of lipid lowering therapy regimens [23].

However, statin monotherapy does not consistently lead to the LDL-C reductions needed to optimally reduce adverse cardiovascular events. Of the estimated 1.3 million patients on statin monotherapy, nearly 70 % did not attain their respective LDL-C goal [24].

3. High risk populations – the ideal population for upfront combination therapy

The 2018 AHA/ACC/Multisociety guidelines defines very-high risk as those with a history of multiple major ASCVD events or one major ASCVD event with multiple high-risk conditions such as: age ≥ 65, heterozygous familial hypercholesterolemia (FH), history of percutaneous intervention or coronary artery bypass surgery, diabetes mellitus, chronic kidney disease, current smoking, persistently elevated LDL-C ≥ 100 mg/dL (2.6 mmol/L) despite maximally tolerated statin and ezetimibe, and congestive heart failure [14]. The 2022 ACC Expert Consensus Decision Pathway (EDCP) on the Role of Non-Statin Therapies in the Management of ASCVD addresses these sub-populations but also suggests obtaining coronary calcium (CAC) scores when a patient's overall risk is unclear. Although there is no consensus on a very-high risk CAC score, those with moderate predicted risk with a score greater than 300 Agatston Units or the 75th percentile for their demographic are considered higher risk than initially calculated. These are patients who may benefit from early rather than upfront combination therapy [25].

Of these, heterozygous FH represents a particularly high-risk group with varying, but extremely high, congenital levels of circulating LDL-C with increased risk for premature ASCVD. Although many FH patients benefit from more than one lipid-lowering agent, it has been repeatedly shown that multiple lipid-lowering medications are needed to adequately decrease LDL-C. With a global prevalence of 1 in 200, there are an estimated 1.5 million individuals with FH in the United States alone [26]. Of note, many of the usual risk assessment tools such as Pooled Cohort and Framingham Risk Score lack the strong predictive value in FH as they do in the general population which contributes to undertreatment [27]. The Cascade Screening for Awareness and Detection (CASCADE) registry studied about 1300 FH patients being followed in specialty lipid clinics around the United States. Of those with treated LDL-C, only about 25 % achieved an LDL-C goal less than 100 mg/dL (2.6 mmol/L) with less than 6 % achieving the therapeutic threshold of less than 70 mg/dL (1.8 mmol/L). Of this group, significant coronary disease was reportedly present in 36 % of individuals at the time of enrollment [28]. The Spanish Familial Hypercholesterolemia Cohort (SAFEHEART) study similarly found that only about 11 % of FH patients achieved an LDL-C below 100 mg/dL (2.6 mmol/L) despite the use of statins and ezetimibe [29]. Recent studies showed that the inability to reach LDL-C targets was, largely, a ramification of underutilization of combination therapy. FH patients who were on triple therapy were more likely to achieve a LDL-C less than 70 mg/dL (1.8 mmol/L) with one study demonstrating that those who used ezetimibe (OR 1.41, 95 % CI 1.15 – 1.72) and proprotein convertase subtilisin-kexin type 9 (PCSK-9) inhibitors (OR 6.49, 95 % CI 4.57 – 9.21) in conjunction with a statin were more successful in reaching the LDL-C goal compared to statin monotherapy [30,31].

Independent of FH-defining mutations, those with an LDL-C greater than 190 mg/dL (4.9 mmol/L) show an alarmingly premature risk of

CAD. It is estimated that, in both sexes, this severely elevated LDL-C leads to CAD risks that mirror those in age groups up to thirty years older with average LDL-C [32]. Much like the FH cohorts, these patients were also found to be widely undertreated [33,34]. Sub-analysis of the PINNACLE registry, the largest catalog of outpatient cardiology quality improvement data, showed that only 35 % of this high-risk patient population was on a lipid-lowering regimen that could lead to a minimum of 50 % reduction in levels. This is, in part, because less than a third were on a high-intensity statin. In those without known ASCVD, only one in four were on a high-intensity statin with even lower rates of ezetimibe and PCSK-9 inhibitor use (4.9 % and 0.74 %, respectively) [33].

The GOULD registry, a U.S prospective observational registry study tracking lipid-lowering therapies for ASCVD, revealed that of patients with known disease, two-thirds remained at an LDL-C greater than 70 mg/dL (1.8 mmol/L)[35]. Similarly, of the approximately 1.9 million patients with ASCVD in the PINNACLE registry, 21 % had never been on lipid lowering therapy and nearly 85 % had not achieved an LDL-C therapeutic threshold of less than 70 mg/dL (1.8 mmol/L). Other registry analyses also demonstrate that large numbers of the high to very-high risk patients do not attain the ideal LDL-C goal [28-30,36,37].

Despite demonstration of unsatisfactory LDL-C levels with less than 20 % of ASCVD patients having appropriate lipid-therapy intensification after two years, guidelines continue to advocate for a stepwise approach rather than upfront combination therapy [35]. It may now be time to shift our focus to the benefits of initial or early combination therapy in our highest-risk patients with consideration of earlier use of non-statin therapies as suggested by the aforementioned 2022 ACC EDCP [25]. Patients classified as very-high risk per the 2018 AHA/ACC/Multisociety guidelines may benefit from a upfront combination therapy approach whereas other high-risk patients and those with intermediate-risk but high CAC scores may benefit from evaluation for early combination therapy.

4. The original combination therapy: ezetimibe and statins

Approved in 2002, ezetimibe monotherapy can reduce LDL-C levels by up to 20 % (approximately 25 % when used in conjunction with a statin) but is now primarily used in our current stepwise model for sequential LDL-C reduction [38,39]. The Examination of Potential Lipid-Modifying Effects of Rosuvastatin in Combination with Ezetimibe versus Rosuvastatin Alone (EXPLORER) study was the earliest large-scale, multinational, endeavor that examined the efficacy of dual therapy, consisting of rosuvastatin 40 mg and ezetimibe 10 mg, in very-high risk patients. Although definitions vary, in this study, the designation of very-high risk was determined by the presence of any of the following: presence of CAD, 10-year ASCVD risk >20 %, or LDL >160 mg/dL (4.1 mmol/L) [10,40]. Patients were then assigned to upfront combination therapy or statin monotherapy after an initial lipid-lowering therapy washout period. By week six, average LDL-C levels had declined by 70 % in the combination group compared to 57 % in the rosuvastatin group correlating with a mean reduction from 189 mg/dL (4.9 mmol/L) to 57 mg/dL (1.5 mmol/L). Approximately 80 % of very-high risk patients receiving this combination achieved their optimal LDL-C level compared to 35 % attainment on monotherapy. Myalgia was the most frequently reported symptom affecting about 1–2 % of participants although there were no clinically significant creatine kinase elevations or myopathy. Furthermore, combination therapy related adverse events only led to discontinuation in less than 1 % of patients[40].

The benefits of this regimen extend beyond mere numerical cholesterol improvement. Oftentimes, patients are unable to access healthcare until after a cardiovascular event occurs, thereby implying that many are not reaping the benefits of primary prevention. The Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) studied the consequences of the combination of ezetimibe and simvastatin on over 9000 patients who had been hospitalized with an ACS event. The primary endpoint of cardiovascular mortality, a major coronary event, unstable angina, revascularization, or non-fatal stroke was significantly lower in the combination therapy (32.7 %) as compared to simvastatin monotherapy (34.7 %) with an absolute risk difference of 2.0 % (HR 0.936, 95 % CI 0.89 to 0.99, $p = 0.016$) with the benefit appearing a year after therapy initiation [41]. Although the use of high-intensity statins is preferred, some patients are unable to tolerate this regimen. The Ildong Rosuvastatin and Ezetimibe for Hypercholesterolemia (I-ROSETTE) evaluated LDL-C changes after assigning patients to ezetimibe with varying strengths of rosuvastatin (5 mg to 20 mg) or the same doses of rosuvastatin monotherapy. Patients on combination therapy, at all levels of rosuvastatin strength, experienced greater than 50 % LDL-C reductions as compared to their corresponding doses of rosuvastatin monotherapy. Interestingly, the mean adjusted LDL-C reduction with ezetimibe and rosuvastatin 5 mg rivaled that of rosuvastatin 20 mg monotherapy (−55 % vs −51 %) [42]. The Randomized Comparison of Efficacy and Safety of Lipid-Lowering with Statin Monotherapy Versus Statin/Ezetimibe Combination for High-Risk Cardiovascular Disease (RACING) trial echoed these findings by demonstrating that moderate intensity rosuvastatin in combination with ezetimibe is non-inferior to high intensity rosuvastatin monotherapy [43].

These findings regarding combination therapy efficacy are further supported by intravascular ultrasound examinations that demonstrate combination therapy not only arrests, but regresses atheroma volume at significantly higher percentages than statin monotherapy (78 % versus 58 %, $p = 0.004$) [44].

Given the known efficacious synergy between the two agents, an observational study evaluated mortality in upfront combination therapy (statin plus ezetimibe) versus statin monotherapy in ACS patients using Polish Registry of Acute Coronary Syndromes data (PL-ACS). This small, prospective, observational study had limitations in that it did not specify intensity of atorvastatin/rosuvastatin used and focused solely on secondary prevention. In the context of these limitations, the all-cause mortality rates were lower in the upfront combination group as early as one year (5.9 % versus 3.9 %; $p = 0.041$; ARR 2.4 %) later but the greatest benefit was seen three years after treatment initiation (10.2 % versus 5.5 %; $p = 0.024$; ARR 4.7 %, NNT=21)[45].

The culmination of this data lays the groundwork for a cogent argument regarding the advantage of upfront combination therapy. Implementation of this regimen is not only economically feasible but would lead to less treatment delays and improved adherence [46,47].

5. A different permutation: the role for novel agents

5.1. PCSK-9 inhibitors

The PCSK-9 inhibitors, alirocumab and evolucumab, are monthly to bi-weekly subcutaneous injections capable of reducing LDL-C by over 50 % if administered as monotherapy [48]. In practice, it is used in dual or triple lipid-lowering therapy regimens in efforts to derive maximal benefits. In many prominent studies, patients were antecedently receiving statins thereby allowing them to capture the effectiveness of combination therapy albeit in the context of a stepwise model. The FOURIER study assessed the ability of evolocumab to induce significant LDL-C reductions in ASCVD patients who had not achieved an LDL-C less than 70 mg/dL (1.8 mmol/L). Patients were randomized to evolocumab or placebo but, notably, nearly all the patients were on high-(69.3 %) or moderate-intensity statins (30.4 %) prior to study initiation with minimal changes made to their pre-existing regimen during the study's course. These high-risk patients had a median presenting LDL-C of 92 mg/dL (2.4 mmol/L) and after 48 weeks of evolocumab therapy, LDL-C levels were below 70 mg/dL (1.8 mmol/L) in 87 %, 40 mg/dL (1.0 mmol/L) in 67 %, and 25 mg/dL (0.65 mmol/L) in 42 % of patients with an associated decrease in adverse cardiovascular events (HR 0.85, 95 % CI 0.79 to 0.92, p <0.001)[49]. The subsequent Evaluation of

Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment with Alirocumab (ODYSSEY-OUTCOMES) trial titrated the dose of the PCSK-9 inhibitor to target an LDL-C of 25–50 mg/dL (0.65–1.3 mmol/L). Given that this addition to statin monotherapy led up to a 63 % mean decrease in LDL-C, it bolstered the findings from the preceding FOURIER trial [50]. Much like statins and ezetimibe, PCSK-9 inhibitors induced LDL-C reductions were associated with regression of atherosclerosis. In the Global Assessment of Plaque Regression with a PCSK9 Antibody as Measured by Intravascular Ultrasound (GLAGOV) trial, patients with non-obstructive CAD were treated with evolocumab or placebo with subsequent measurements of their total atheroma volume. Both groups had similar baseline characteristics in terms of total atheroma volume, initial LDL-C values, near 100 % utilization of background statin therapy, and minimal ezetimibe use. After 76 weeks of treatment, a higher percentage of the evolocumab group experienced total atheroma volume regression as compared to placebo which mostly consisted of those on background statin therapy (61.5 % versus 48.9 %; difference 12.5 %; 95 % CI 5.9 % to 19.2 %; p <0.001). A post-hoc analysis on those with baseline LDL-C levels <70 mg/dL (1.8 mmol/L) showed that evolocumab continued to exert a positive impact – treatment group patients had greater than 30 % higher rate of percent atheroma volume regression as compared to placebo (81.2 % versus 48.0 %; between-group difference 33.2 %; 95 % CI 18.6 % to 47.7 %; p <0.001)[51].

Although overall adherence to PCKS9 inhibitors is high, likely given it's convenient biweekly dosing, prompt adoption as part of upfront combination therapy could be a difficult proposition given the high cost of this medication compared to ezetimibe/statin [52,53]. While this argument may hold true for a large portion of the hyperlipidemic population, changing the frame of reference to focus on those with FH and LDL-C levels >190 mg/dL (4.9 mmol/L) opens up the possibility of PCSK-9 inhibitor use as part of personalized combination therapy [54]. Furthermore, although this medication's current role may not involve incorporation into routine upfront combination therapy regimens, upfront initiation of ezetimibe and statin could help clinicians more quickly decide which patients would benefit from the addition of PCSK-9 inhibitors.

6. An earlier role for bempedoic acid and inclisiran

A similar approach can be adopted for bempedoic acid and inclisiran which have both been shown to augment LDL-C reduction in those on maximally tolerated statin therapy. CLEAR Wisdom was a phase 3, randomized, double-blind, placebo-controlled, trial measuring LDL-C after adding bempedoic acid to maximally tolerated statins. After twelve weeks of treatment, bempedoic acid decreased LDL-C levels by 15.1 % versus 2.4 % in the placebo group (p<0.001) with a least-squares mean difference of −17.4 % (95 % CI, −21.0 % to −13.9 %). Post-hoc subgroup analysis showed that similar reductions of 14–15 % occurred in both the low/moderate intensity statin group and the high-intensity statin group with up to 25 % reductions seen in those without underlying statin therapy [55]. The CLEAR Harmony trial is a similarly designed phase 3 clinical trial that primarily focused on the safety of adding bempedoic acid to statin regimens but secondarily evaluated the effects on LDL-C. In this study, nearly 100 % of the patients were on background statin therapy with over 90 % receiving a moderate or high intensity statin. By week 12, there was mean LDL-C reduction of 19.2 mg/dL (0.50 mmol/L) with continued, minimally attenuated effects, until at least week 52 of treatment [56]. Although over 90 % of the patients in both studies did not have FH or a LDL-C >190 mg/dL (baseline prior to statin therapy not reported), the conclusions from these studies can likely be extrapolated to these high-risk groups [57]. One phase 3, double-blinded, U.S based clinical trial examined the effect of a fixed-dose combination (FDC) pill of bempedoic acid 180 mg and ezetimibe 10 mg on LDL-C levels in those on stable statin therapy. Inclusion criteria included requirement of a fasting LDL-C greater than or equal to 100 mg/dL (2.6 mmol/L) in those with ASCVD/FH or 130 mg/dL (3.4 mmol/L) in those with multiple ASCVD risk factors. Over 60 % of participants in all the study groups had FH or were known to have ASCVD. By week 12, nearly 34 % of patients in the FDC group had an LDL-C reduction of 50 % or more versus 0 %, 5.0 %, and 3.7 % in the placebo, ezetemibe 10 mg only, and bempedoic acid 180 mg only groups (p <0.001). Both the high-intensity statin and statin-intolerant subgroups experienced an approximate 39 % LDL-C reduction from baseline with the use of the FDC pill [58].

Inclisiran showed similar efficacy as PCSK-9 inhibitors in inducing LDL-C reduction with the added advantage of less frequent administration. ORION-10 and ORION-11, both of which were randomized, double-blinded, trials demonstrated that inclisiran led to a LDL-C reduction of 51.3 % versus a 1.0 % increase in placebo (between-group difference −52.3 %, 95 % [CI] −55.7 % to −48.8 %; p<0.001) and 45.8 % versus a 4.0 % increase in placebo (between-group difference −49.9 %, 95 % [CI] −53.1 % to −46.6 %; p<0.001), respectively, when added to background statin therapy. Of the approximately 1600 cumulative patients, 89.2 % in ORION-10 and 94.7 % in ORION-11 were on a statin with 68.0 % and 78.6 % tolerating high-intensity statin therapy prior to receiving inclisiran. However, many of these patients were presumably not on combination therapy prior to the study given that ezetimibe use was less than 10 % in both trials [59]. ORION-9, a multinational double-blinded trial, focused specifically on those with genetically confirmed FH or those who met Simon-Broome phenotypic FH criteria. Although the study population was smaller with 482 total patients, the efficacy of inclisiran was redemonstrated with statistically significant results. At day 510, there was an average LDL-C reduction of 39.7 % (95 % CI, −43.7 % to −35.7 %) in the inclisiran group compared to a 8.2 % increase (95 % CI, 4.3 % to 12.2 %) in the placebo group resulting in a between-group difference of −47.9 % (95 % CI, −53.5 % to −42.3 %; p <0.001)[60].

Both bempedoic acid and inclisiran are novel agents that show strong promise regarding incorporation into the stepwise approach especially for very high-risk patients such as those with FH [57,60]. Table 1 sunmmarizes the various lipid-lowering agents that can be used in conjunction with statin therapy.

7. Barriers to implementation

7.1. Clinical inertia

While studies demonstrate efficacy of all the lipid lowering agents on the market, real-world implementation tends to deviate considerably partially due to 'clinical inertia' which is defined as a "failure to initiate or intensify therapy when indicated" [61].

The EU-Wide Cross-Sectional Observational Study of Lipid-Modifying Therapy Use in Secondary and Primary Care (DA VINCI) study revealed that of the high-risk patients on statin monotherapy, less than 30 % of those on high-intensity statins achieved an LDL-C <70 mg/dL (1.8 mmol/L). Despite this demonstrated inadequacy of statin monotherapy, only 9 % and 1 % of patients were on ezetimibe and PCSK-9 inhibitors, respectively [62]. Several other U.S based studies reflect similar findings with one study showing that of over 360,000 PCSK-9 inhibitor eligible patients, less than 0.5 % were prescribed this agent [63–65]. This PCSK9 data along with the previously discussed analysis registries such as GOULD and PINNACLE highlight the prevalence of clinical inertia in our management of high-risk patients [24,35,66].

8. Misattribution of side effects

A patient's experience with lipid lowering therapy plays a large role in its uptake into their medication regimen. An analysis of the Patient and Provider Assessment of Lipid Management (PALM) registry (composed of patients from cardiology, primary care, and endocrinology practices throughout the United States) showed that although a sizable

Table 1
Features of Various Lipid-Lowering Agents for Use in Combination with a Statin.

Lipid-Lowering Agent	Mechanism for LDL Reduction	Method and Frequency of Administration	Additional LDL-C Reduction in Addition to a Statin
Ezetimibe	Binds to Neimann-Pick-C1–1 (a cholesterol transport protein) found on the brush border of enterocytes thereby blocking intestinal absorption of LDL-C[101]	oral, daily[101]	~25 %[41,102
PCSK-9 Inhibitors	PCSK-9 causes degradation of hepatocyte LDL-C receptors. Inhibition of this protein increases LDL-C clearance[50]	subcutaneous injection, every 2–4 weeks[49,50	54–62 %[49,50,103]
Bempedoic Acid	Inhibits ATP citrate lyase (enzyme involved in cholesterol biosynthesis)[56]	oral, daily[56]	14–19 %[55,56
Bempedoic Acid/Ezetimibe Combination Pill	See aforementioned details for both agents above	oral, daily[104]	~36 %[104]
Inclisiran	Small interfering RNA molecule that inhibits hepatic synthesis of PCSK9	subcutaneous injection, every 6 months*[59] *After the initial two doses	50–56 %[59,105]

number of those qualifying for a statin reported never being offered therapy (59.2 %), a large percentage reported discontinuing therapy (30.7 %) or declining a statin (10.1 %). Those warranting a statin for secondary prevention reported lower rates of not being offered a statin (66.5 % versus 47.0 %) but higher rates of discontinuing (42.8 % versus 23.5 %) and declining (10.2 % versus 10.1 %) as compared to those with primary prevention needs. Side effects were the predominant reason underlying the decision to discontinue or decline a statin – approximately 37 % of those who declined and 55 % of those who discontinued did so due to perceived side effects. Those that discontinued a statin cited that it could cause liver damage (61.1 % versus 54.7 % in current users, $p<0.05$) and muscle aches (76.0 % versus 61.1 % in current users, $p<0.001$). While statistically significant differences exist between these groups, high percentages of current users also perceive these to be worrisome side effects which could lead to future discontinuation [67]. A similar analysis of the Understanding Statin Use in America and Gaps in Education (USAGE) database, the largest U.S survey of self-reported statin users, found that 60 % of former statin users reported muscle side effects with 62 % stating that side effects were the primary reason for discontinuation [68].

The prevalence of Statin-Associated Muscle Symptoms (SAMS) has been reported to be as low as 1.5 %−5 % in many randomized studies, but these may underestimate the true percentage as many patients who experience SAMS are excluded from trials [69,70]. There are also mechanistic explanations and demonstrations of CK elevations that underpin some cases of SAMS with the incidence of myopathy and rhabdomyolysis ranging from 1 per 10,000 per year and 1 per 100,000 per year, respectively [70–72]. However, trials showing high rates of SAMS in the statin subgroups also demonstrate nearly as high rates of muscle symptoms in placebo groups indicating that there is a degree of misattribution bias occurring during real-world implementation [20, 73-75]. This misattribution bias risks exacerbation with an upfront combination approach with ezetimibe despite only rare associations with myopathy or SAMS [76]. An N-of-1 trial was conducted on 60 patients who had previously discontinued statins due to experiencing side effects within the first two weeks of initiation. Each patient received a month each of atorvastatin 20 mg, placebo pills, and no treatment with instructions to report daily symptoms. Of those who re-experienced symptoms with a statin, 90 % of the symptom burden was also present when taking placebo. With this re-challenge, half of the patients restarted and were continuing their statin six months after completion of the trial [77].

With many patients willing to retry a statin after initial discontinuation, rechallenging with the same or lower dose can be an attractive option with one retrospective cohort study showing that 92.2 % of rechallenged patients continued with a statin when evaluated 12 months after their initial statin-related event [78]. Another option is switching to alternate-day/intermittent dosing which showed promise in many, initially statin-intolerant, patients albeit compromising the degree of LDL-C reduction [79]. The USAGE data showing that initially hesitant patients expressed willingness to try statins at a physician's recommendation supports patient-centered decision making in the pursuit of improving statin adherence and uptake of a upfront combination therapy approach for our high-risk patients [67,68].

9. Limitations of the novel agents

Statins with and without the addition of ezetimibe have been shown to be cost-effective in most patients with ASCVD, however this may not always hold true with the newer agents such as PCSK-9 inhibitors, bempedoic acid, and inclisiran [46,80-83]. High costs of medications are the root cause of a large proportion of medication non-adherence in patients with cardiovascular disease [84]. Results from financial analyses of PCSK-9 inhibitors have demonstrated a wide range of cost-effectiveness due to variations in the studied population with more favorable cost-effectiveness ratios seen in those with continued high-risk despite standard of care [54,83]. Documentation issues and insurance approval remain significant barriers to PCSK-9 inhibitor usage in the United States [66,85]. Bempedoic acid and inclisiran, both high-cost medications relative to statins and ezetimibe, will likely face the same barriers to usage [86,87]. While awaiting eventual decreases in drug prices and improvements in the healthcare system, identifying high risk patients may benefit from novel agents offers the best chance at optimizing cost effectiveness. It should be noted that for certain newer agents, such as inclisiran, patient assistance programs and other support may be available for eligible patients [25]. Furthermore, documentation of response to upfront/early combination therapy and any intolerance could decrease the administrative burden of insurance appeals for approval when prescribing these new agents.

10. Polypharmacy

While there is no consensus on the definition of polypharmacy, many studies use five or more medications as a threshold [88,89]. Those who would benefit most from upfront and/or early combination therapy are also at risk of having other comorbidities that increase their pill burden and dosing frequency leading to downstream effects on medication adherence [90]. While much of the existing data on cardiovascular polypharmacy examines older individuals, the conclusions remain generalizable to younger populations as we witness rising rates of chronic, cardiovascular risk factors such as diabetes and hypertension in young adults [91,92]. These co-morbid conditions carry their own medication burden with studies such as the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack (ALLHAT) trial showing that over 60 % of patients were prescribed two or more anti-hypertensives [93–95]. A consideration for those with multiple co-morbidities and excessive pill burden is the use of a FDC pill. The use of various FDC iterations consisting of anti-hypertensives, lipid-lowering therapies, and aspirin has shown to be efficacious in improving medication adherence in a number of countries worldwide [96–99]. Furthermore, FDC pills consisting of combinations of lipid-lowering therapies alone such as simvastatin + ezetimibe and bempedoic acid

+ ezetimibe have also shown efficacy [41,58]. While it can decrease therapeutic inertia, use of FDC drugs risks the same misattribution biases that can occur with upfront combination therapy along with loss of therapeutic benefit of all agents if discontinued.

11. Conclusion

The use of upfront combination therapy reduces one step within the stepwise approach, allowing for clinicians to reach for PCSK9 inhibitors and other novel agents more readily and earlier in the disease course. Starting combination lipid-lowering therapy in high-risk patients at diagnosis, will reduce treatment delays by allowing them to experience large reductions in LDL-C by garnering dual therapy benefits in as little as four to five weeks [100]. In those with initial intolerance to statins, establishing a therapeutic patient-physician alliance while determining next steps such as re-challenging or trialing intermittent dosing can lead to improved adherence overall. This, along with adjunctive measures such as addressing modifiable risk factors and increasing access to lipid-lowering therapies, is linked to lowering ASCVD risk **(Central Figure).** To combat clinical inertia, we implore clinicians to preferentially incorporate upfront or early combination lipid-lowering therapy in their management of select high-risk patients rather than the classical stepwise approach.

CRediT authorship contribution statement

Shruti Revankar: Writing – review & editing, Writing – original draft, Conceptualization. **Jong Kun Park:** Writing – review & editing, Writing – original draft, Conceptualization. **Priyanka Satish:** Supervision, Conceptualization. **Anandita Agarwala:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Anandita Agarwala reports was provided by Baylor Scott & White The Heart Hospital Plano. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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