



The Egyptian Association of Vascular Biology and Atherosclerosis (EAVA) Perspectives on the Usage of Inclisiran

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ABSTRACT

Background: Elevation of low-density lipoprotein cholesterol (LDL-c) is still a hugely unmet need in the reduction of atherosclerotic cardiovascular disease. In the published CardioRisk project in Egypt, up to 71% of female participants had dyslipidemia. Control of LDL-c levels and thus improvement of hyperlipidemia is quite often very difficult. With the introduction

of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, the decrease of significant cardiac adverse events, the patient control rate, and the death rate have all been improved. Inhibition of the formation of PCSK9 through inclisiran, which is a novel method of reducing LDL-c and is only given twice per year, seems alluring. After revision of published data, we analyzed the potential advantages of the use of inclisiran.

Conclusion: The Egyptian Association for Vascular Biology and Atherosclerosis (EAVA) analyzed the data necessary for obtaining clear indications for the usage of inclisiran. We propose the addition of inclisiran to statins with or without ezetimibe for patients with documented atherosclerotic cardiovascular disease (ASCVD) or similar risk, familial hypercholesterolemia (FH) with another major risk factor, and very high and high risk diabetes mellitus, who did not reach LDL-c goals and/or with true statin intolerance. Inclisiran is also recommended as upfront therapy, with triple combination, in extreme risk subjects such as those with post acute coronary syndromes (ACS).

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Key Summary Points

Small interfering RNA molecules (siRNA), e.g., Inclisiran, represent an attractive alternative to monoclonal antibodies for lowering proprotein convertase subtilisin/kexin type 9 (PCSK9).

These molecules offer profound lowering of (intra- and extracellular) PCSK9 at a lower-dose frequency and potentially at a lower cost. Inclisiran has undergone evaluation in phases 1, 2, and 3 all within the context of the ORION trials, with good efficacy and safety.

Therefore, the Egyptian Association of Vascular Biology and Atherosclerosis (EAVA) took the responsibility of providing the first Egyptian consensus on the use of Inclisiran in clinical practice.

We propose the addition of inclisiran to statins with or without ezetimibe for patients with documented ASCVD or similar risk, FH with another major risk factor, and very high and high risk DM, who did not reach LDL-c goals and/or with true statin intolerance. Inclisiran is also recommended as upfront therapy, with triple combination, in extreme risk subjects such as those with post ACS.

INTRODUCTION

The role of low-density lipoprotein cholesterol (LDL-c) as an atherogenic particle in the process of atherosclerosis is essential. With that in mind, the reduction of LDL-c in the blood has been proven to lower cardiovascular events and mortality. As treatment guidelines progress, the targets for LDL-c have gone lower and lower [1–3]. This puts a burden on reaching the targets if it was not for the use of ezetimibe and the more recently effective proprotein convertase subtilisin/kexin type 9 (PCSK9) monoclonal

antibodies evolocumab and alirocumab [4]. Physicians designated recurrent cardiovascular events with multivessel or polyvascular disease as a new entity of extreme risk [5]. The high prevalence of premature atherosclerosis among patients with acute coronary syndromes (ACS), in Egypt, as well as in many other countries, may require early initiation of powerful lipid-lowering therapies, such as PCSK9-targeted medications in many very high and high risk subjects [6, 7]. The high prevalence of patients not at their LDL-c goal despite the currently available oral lipid-lowering therapies, mainly due to poor adherence and lack of compliance, makes the infrequent dosage schedules of PCSK9-targeted therapies advantageous [8].

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

THE EGYPTIAN EXPERIENCE WITH LDL-C LOWERING

Data from the Egyptian CardioRisk project [7] indicate the incidence of premature coronary artery disease (CAD) (described as exhibiting ACS before the age of 65 and 55 years in women and men, respectively) is approximately 51% as a result of a significantly greater burden of typical health risks, particularly possible familial hypercholesterolemia and smoking. The current therapy of hypercholesterolemia was studied in the CEPHEUS research program in individuals taking lipid-lowering medications in seven Middle Eastern nations. Results showed that 32.5% of 1043 Egyptian patients [8] met their LDL-c therapeutic target, while those at a greater risk for a cardiovascular incident had a lower chance of doing so. Almost three-quarters of patients in this trial were deemed to be at high or extremely high risk. Only 10% of patients with high risk achieved the treatment objective.

THE REALITY OF LDL-C REDUCTION IN THE ERA OF NOVEL THERAPIES

PCSK9 inhibitors have struggled to penetrate the market. The 2019 European Society of Cardiology (ESC) guidelines and 2018 American Heart Association/American College of Cardiology (AHA/ACC) cholesterol recommendations designate them as essential third-line therapy following ezetimibe and statins. To add to this, the guidelines stated that the pricing of PCSK9 inhibitors must be decreased by between 70% and 85% to fulfill traditional cost-effectiveness benchmarks. Amgen and Sanofi decreased their treatments costs by 60% later in 2018, but use remains considerably below the projections made at the time of their introduction [9].

Research published in 2019 in the *Journal of the American Heart Association* examined lipid-lowering prescription data from 1 January 2015 to 31 March 2017 for about 2.2 million people suffering from dyslipidemia and approximately 940,000 with coronary heart disease (CHD) or CAD. Only 362 (0.02%) individuals with dyslipidemia and 1952 (0.21%) individuals with CAD or CHD had been administered a PCSK9 inhibitor [10].

Despite the enormous unmet need for hyperlipidemia treatments, pharma manufacturers are naturally hesitant to enter the market because of the PCSK9 inhibitors' problematic history. The US Food and Drug Administration (FDA) approved, in February 2020, bempedoic acid as an adjuvant to statin therapy that is maximally tolerated for treating people with established atherosclerotic cardiovascular disease (ASCVD) requiring further LDL-c reduction or heterozygous familial hypercholesterolemia. Bempedoic acid is a prime inhibitor of ATP citrate lyase (ACL) that reduces the levels of LDL-c by blocking the production of cholesterol by the liver. Bempedoic acid lowered the levels of LDL-c by on average 18% when administered in combination with various dosages of statins, compared to placebo, as reported by previous studies [11].

Evinacumab is an angiopoietin-like 3 protein (ANGPTL3) antagonist that is being studied for

the treatment of homozygous familial hypercholesterolemia. ANGPTL3 appears to play a crucial role in lipoprotein metabolism since it inhibits endothelial lipase and lipoprotein lipase. In a phase III clinical study, evinacumab, in comparison with placebo, reduced cholesterol by 49% [12]. The pipeline for lipid-lowering medications is still innovating with many more molecules on the horizon.

INCLISIRAN

Mechanism of Action

Inclisiran is a double-stranded, cholesterol-lowering small interfering ribonucleic acid (siRNA) that is coupled on the sense strand with triantennary *N*-acetylgalactosamine (GalNAc) to enhance the selective reuptake by hepatocytes. Inclisiran employs the RNA interference mechanism in hepatocytes and drives the enzymatic degradation of PCSK9 mRNA (Fig. 1). This promotes the recycling of LDL receptors as well as expressing it on the surface of the hepatocyte cell, which improves LDL-c absorption and decreases LDL-c levels in the blood by inhibiting PCSK9 production [13].

PCSK9 inhibition has not been demonstrated in clinical studies, including the ORION trials, to reduce CRP levels [14]. A relationship between PCSK9 and inflammation was supported by considerable evidence from preclinical research. PCSK9 is induced in several cell lines by pro-inflammatory chemicals like lipopolysaccharide, hepatocyte nuclear factor 1- α , and tumor necrosis factor α [15]. Additionally, PCSK9 is expressed in vascular regions with decreased shear stress and atherosclerotic plaques, predominantly in vascular smooth muscle cells (VSMCs). PCSK9 is related to the size of atherosclerotic plaques, the death of VSMCs, and neointima proliferation [14].

Clinical Efficacy and Safety

In three phase III clinical investigations (Table 1), the 284 mg inclisiran dosage, which is

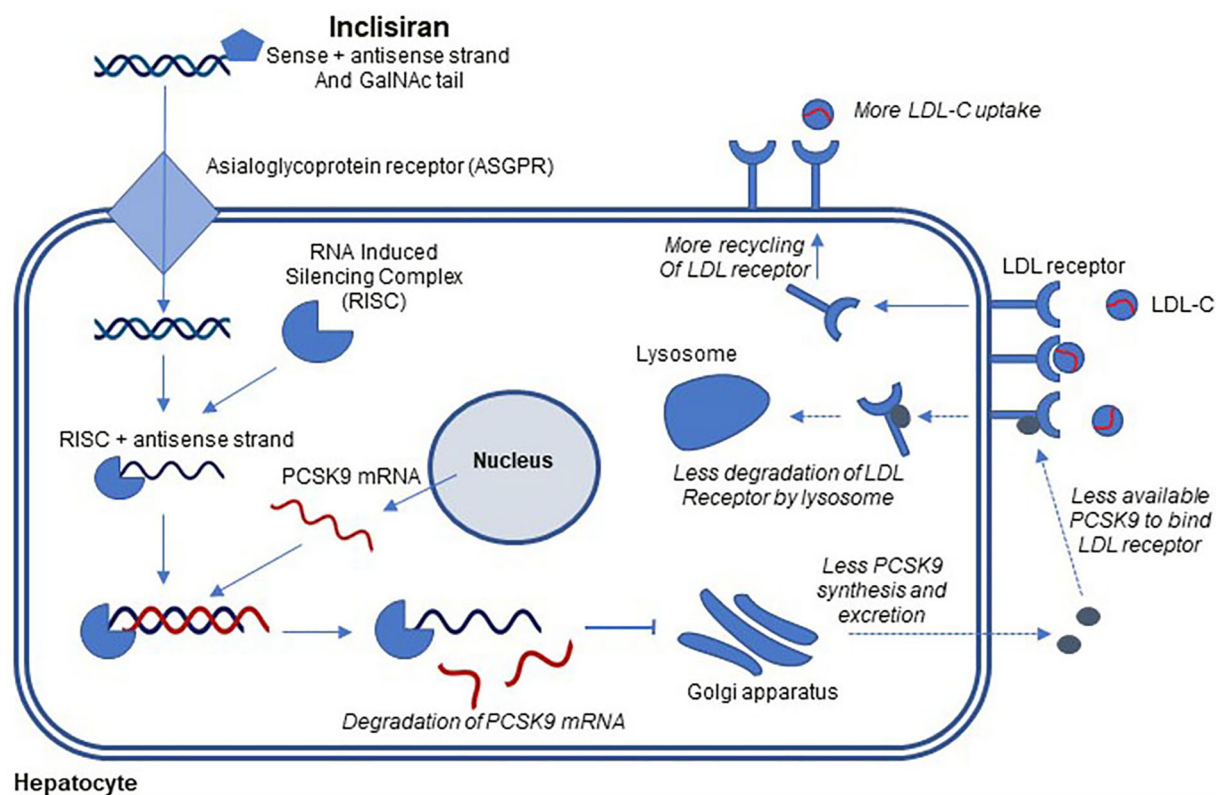


Fig. 1 Simplified overview of mechanism of action by inclisiran. Inclisiran is delivered to the hepatocyte through the asialoglycoprotein receptor (ASGPR). Its antisense strand then binds to the RNA induced silencing complex (RISC). The combination of RISC and the antisense strand then binds PCSK9 messenger RNA (mRNA), leading to degradation of PCSK9 mRNA and less PCSK9 protein

synthesis. PCSK9 directs LDL receptor (LDLR) for degradation by the lysosome. As a result of less PCSK9 protein, more LDLR can be recycled to the hepatic membrane for LDL-c uptake. Adapted with permission from Professor John J.P. Kastelein

comparable to and referred to as 300 mg inclisiran sodium salt, was examined in the following categories of patients [16, 17, 18]:

1. Patients with established ASCVD, whether coronary, peripheral, or cerebral vascular disease
2. ASCVD risk equivalents (familial hypercholesterolemia, type 2 diabetes mellitus, or a 10-year cardiovascular event risk of 20% or higher as determined by the Framingham risk score or similar scores)
3. Heterozygous familial hypercholesterolemia (FH)

Patients using a maximum tolerated dosage of statin with or without concomitant lipid-modifying medication and failing to attain

LDL-c goals required further LDL-c lowering. An estimated 8% of individuals were intolerant to statins. On days 1, 90, 270, and 450, patients received subcutaneous injections of 284 mg inclisiran or placebo. Follow-up was done at 540 days. In the phase 3 pooled evaluation, subcutaneously injected inclisiran reduced LDL-c by 50–55% as early as day 90, and this reduction was sustained over long-term treatment. Reduction in LDL-c started from 2 weeks (reduction by 48%). On day 150, following a second injection, the greatest decrease in LDL-c was seen.

A total of 482 patients with heterozygous FH were randomly assigned individually, in the ORION-9 trial, to either 300 mg inclisiran sodium or placebo. Four total doses were given

Table 1 Summary of main inclisiran trials

Trial	Design	Participants	Intervention	Results
ORION-10	Phase 3, randomized, double-blind, placebo-controlled, parallel group study	1561 adults in the USA with atherosclerotic cardiovascular disease and LDL-c levels at screening 70 mg/dL or higher	Patients were randomly assigned in a 1:1 ratio to receive either inclisiran (284 mg) or placebo, administered by subcutaneous injection on day 1, day 90, and every 6 months thereafter over a period of 540 days	At day 510, inclisiran reduced LDL-c levels by 52.3% with corresponding time-adjusted reductions of 53.8% ($P < 0.001$ for all comparisons vs placebo). Adverse events were generally similar in the inclisiran and placebo groups, although injection-site adverse events were more frequent with inclisiran than with placebo (2.6% vs 0.9%)
ORION-11	Phase 3, randomized, double-blind, placebo-controlled, parallel group study	1617 adults in Europe and South Africa with atherosclerotic cardiovascular disease or an atherosclerotic cardiovascular disease risk equivalent and LDL-c levels at screening 70 mg/dL and 100 mg/dL or higher, respectively	Patients were randomly assigned in a 1:1 ratio to receive either inclisiran (284 mg) or placebo, administered by subcutaneous injection on day 1, day 90, and every 6 months thereafter over a period of 540 days	At day 510, inclisiran reduced LDL cholesterol levels by 49.9% with corresponding time-adjusted reductions of 49.2% ($P < 0.001$ for all comparisons vs placebo). Adverse events were generally similar in the inclisiran and placebo groups, although injection-site adverse events were more frequent with inclisiran than with placebo (4.7% vs 0.5%)
ORION-9	Phase 3, double-blind, randomized, placebo-controlled study	482 adults with diagnosis of heterozygous familial hypercholesterolemia with LDL of at least 100 mg/dL, despite receiving a maximally accepted dose of statin therapy with or without ezetimibe	The patients were assigned in a 1:1 ratio to receive inclisiran sodium (at a dose of 300 mg) or matching placebo, which were both administered as a 1.5-mL subcutaneous injection on days 1, 90, 270, and 450	At day 510, the percentage change in the LDL-c level was a reduction of 39.7% in the inclisiran group and an increase of 8.2% in the placebo group, for a between-group difference of -47.9 percentage points. Adverse events and serious adverse events were similar in the two groups

at baseline, after 3 months, then every 6 months after, with a mean LDL-c decrease, compared to placebo, of 47.9% at the major efficiency timepoint of day 510 and an average time for reduction of LDL-c of 44.3% over the course of the 18-month study [18].

The ORION-10 study investigated 1561 individuals with cardiovascular disease (CVD), whereas the ORION-11 study investigated 1617 patients with CVD or a disease that is equivalent in risk (heterozygous FH, type 2 diabetes, or as a score on the Framingham risk score equal to 10-year 20% risk). From day 0 to day 510, the percentage decrease in LDL-c values in ORION-10 is – 52.3%. After day 90 and up to day 540, the time-adjusted percentage change in LDL-c levels from baseline is – 53.8% to – 54%, and in ORION-11 the inclisiran groups had a 50% reduction in LDL-c levels in comparison with the placebo group. In all the three studies, inclisiran consistently lowered the levels of plasma PCSK9, with no indication that this effect diminished with time. In addition, inclisiran significantly decreased non-high-density lipoprotein cholesterol (non-HDL-c), total cholesterol, triglycerides, and apolipoprotein B and was related to an 18.6–25.6% decrease in lipoprotein (a) [Lp(a)] levels. C-reactive protein (CRP) levels did not change between groups receiving inclisiran, although HDL-c levels rose [17]. In general, inclisiran showed a favorable tolerability and safety profile. Side effects at the site of injection (like bruising, swelling, or redness) were more frequent among the inclisiran group compared to the placebo group, although the majority were moderate, and no severe or chronic side effects were reported. During the 18-month clinical trials, only 2.5% of patients terminated inclisiran owing to side effects. In individuals treated with inclisiran, the rate of treatment termination owing to injection site adverse effects was minimal (0.2% for inclisiran vs 0.0% for placebo).

These findings represent a significant achievement in the advancement of both lipid-lowering medicines and siRNA treatments. While siRNA treatments are now licensed for an uncommon condition, inclisiran is the first siRNA with the possibility to be widely utilized in preventing the prevalence of atherosclerosis.

Are Statins Required with Inclisiran?

When the LDL-c decrease in patients with hypercholesterolemia treated with a statin is inadequate, further medications are often given. Another strategy would be to substitute the statin with a drug that has higher effectiveness in lowering LDL-c than statins, as is the case with inclisiran. A benefit of this strategy is that the person would not need to administer a statin every day. Before this suggestion, however, it is required to conduct a clinical trial to see whether the advantages of inclisiran only are comparable to the advantages of inclisiran with statin medication. We are aware of no such experiment being planned. Similar reasoning applies to the PCSK9 monoclonal antibodies alirocumab and evolocumab, whose benefits for the cardiovascular system were shown in clinical studies alongside statins [19, 20]. Consequently, it is necessary to assess their efficiency with and without a statin. Thus, apart from statin-intolerant cases, statins are and will be an integral part of the management of LDL-c reduction regardless of the added therapies.

Should Ezetimibe Be Used Prior to Considering Inclisiran?

Although isolated studies demonstrated very minimal cardiovascular privileges with ezetimibe [21, 22], it is now widely believed that the cardiovascular advantages of lowering LDL-c are proportional to the length of therapy and the absolute reduction, regardless of the drug utilized to decrease LDL-c [23]. In ORION-9, around 50% of participants took ezetimibe; however, in ORION-10 and ORION-11, just 8% of participants used ezetimibe. Before adding inclisiran or a PCSK9 monoclonal antibody, participants should often be given ezetimibe to establish whether a statin/ezetimibe combination is sufficient to lower LDL-c to the needed levels.

Adherence Issues

Among the benefits of inclisiran over other LDL-c-lowering medications is that it is

delivered twice a year. This should increase adherence and keep LDL-c levels at a low level for a longer period, which is anticipated to enhance clinical results. Comparatively, adherence to statins, which must be taken daily, varies from 35% to 70%, and lower levels of adherence and treatment duration are related to poorer clinical results [24]. Typically, PCSK9 monoclonal antibodies are injected every 2 weeks. At 180 days, the dropout rate for these drugs was 43%, which might be attributed to poor tolerability, unwillingness to administer injections, or expense [25]. Thus, as inclisiran is a twice-per-year dosage, this theoretically may improve adherence.

Economics of Inclisiran

The price of PCSK9 monoclonal antibodies has been one of the primary issues restricting their adoption [26]. Their usage is frequently subject to prior permission and co-payments and as a result many prescriptions are never completed [27]. To prevent this from occurring with inclisiran, the subject cost must be less than that of PCSK9 monoclonal antibodies. The price must be affordable and acceptable to many subjects and their health care providers. The cost and cost-effectiveness of inclisiran are still to be determined on a country-to-country basis. However, we do think that a partnership between any governmental sector and the industry (such as the UK NHS inclisiran funding model) [28] for tackling cardiovascular disease through partial or complete coverage of the cost will ease access to this therapy.

Pharmacokinetics of Inclisiran

As a result of the unique mechanism of action of inclisiran, it selectively binds to receptors on the liver and thus theoretically and clinically does not affect other organs. Its half-life in the bloodstream is 9 h and it completely disappears from blood in 48 h being completely diffused in liver tissue, even though its LDL-c-lowering effect persists. There are no long-term data on the safety of the family of PCSK9-modifying

therapies till now; however, the usage of these drugs has not raised any concerns to date [29].

PCSK-9-Targeted Therapies in Context

Coexisting with statin therapy, monoclonal antibodies against PCSK9 provide significant cardiovascular benefits. In participants with ASCVD, evolocumab reduced the risk of myocardial infarction, cardiovascular mortality, hospitalization for unstable angina, stroke, or coronary revascularization by 1.5 percentage points for a reduction in LDL-c of approximately 60% (11.3% in the placebo group vs 9.8% in the evolocumab group over follow-up period of 2.2-year; relative risk reduction, 13%) [19]. For a comparable reduction in LDL cholesterol, cardiovascular events (nonfatal myocardial infarction, mortality from CHD, unstable angina requiring hospitalization, or nonfatal or fatal stroke) were reduced by 1.6 percentage points with alirocumab in participants with recent ACS (9.5% vs 11.1% in the placebo group over a period of 2.8 years; relative risk reduction, 14%) [20].

Presently, there are no published data about the cardiovascular advantages of inclisiran, and if benefits do occur, their magnitude relative to that of PCSK9 antibodies is unknown. ORION-3 is an extension of the ORION-1 trial (NCT02597127), which compared inclisiran to placebo in subjects with ASCVD. In ORION-3 (NCT03060577), the LDL-c lowering impact of inclisiran is compared to that of evolocumab [30]; however, cardiovascular results are not being assessed. Even though the ORION-3 trial has been done, the findings have not yet been released [31]. In addition to trials evaluating the LDL-c effects of PCSK9 monoclonal antibodies and inclisiran, trials comparing cardiovascular outcomes are necessary.

Cardiovascular Outcome Trials with Inclisiran

The purpose of the ORION-4 clinical study is to evaluate the impact of inclisiran on cardiovascular outcomes (first incidence of CHD mortality, myocardial infarction, fatal or nonfatal

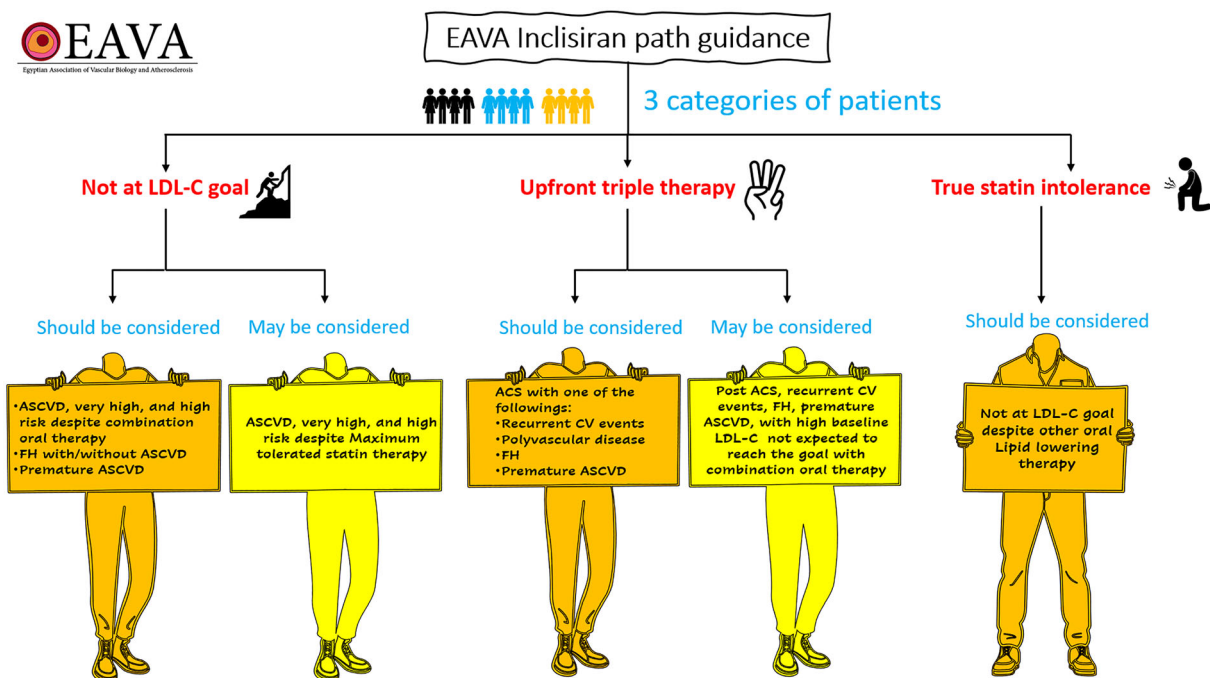


Fig. 2 EAVA path guidance for the potential indications of inclisiran in clinical practice

ischemic stroke, or urgent coronary revascularization surgery) in 15,000 individuals with CVD. It began in October 2018, although completion is not anticipated until December 2026 [32]. To our knowledge, there are no ongoing clinical studies comparing inclisiran to PCSK9 monoclonal antibodies for cardiovascular outcomes.

CONCLUSIONS

The EAVA's recommendations for potential indications of inclisiran in clinical practice are summarized in Fig. 2.

Having revised the evidence from the studies and trials provided for inclisiran PCSK9 monoclonal antibodies, and statins, we can conclude that inclisiran use:

Should be considered in:

1. Those who are not at LDL-c goal despite maximally tolerated statin therapy and ezetimibe with any of the following:
 - ASCVD, very high, or high risk according to the ESC 2019 guidelines [1]

- FH with/without ASCVD
- Premature ASCVD

2. Upfront triple therapy together with statins and ezetimibe in patients experiencing ACS plus any of the following:

- Recurrent CV events
- Polyvascular disease
- Multivessel CAD
- FH
- Premature ASCVD

3. Patients with true statin intolerance who are not at LDL-c goal despite other oral lipid-lowering therapy

May be considered in:

1. Those who are not at LDL-c goal and having ASCVD, very high, and high risk according to the ESC 2019 guidelines [1], despite maximum tolerated *statin* therapy, before adding ezetimibe
2. Upfront triple therapy together with statins and ezetimibe in patients with post-ACS, recurrent CV events, FH, premature ASCVD, polyvascular disease, or multivessel CAD, with high baseline LDL-c not expected to

reach the goal with combination oral therapy alone

Considering the Egyptian environment of clinical practice, we do think that not only cardiologists should be the authoritative prescribers of inclisiran. This ought to be a collaborative multidisciplinary work between cardiologists, clinical lipidologists, internists, and clinical endocrinologists.

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Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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