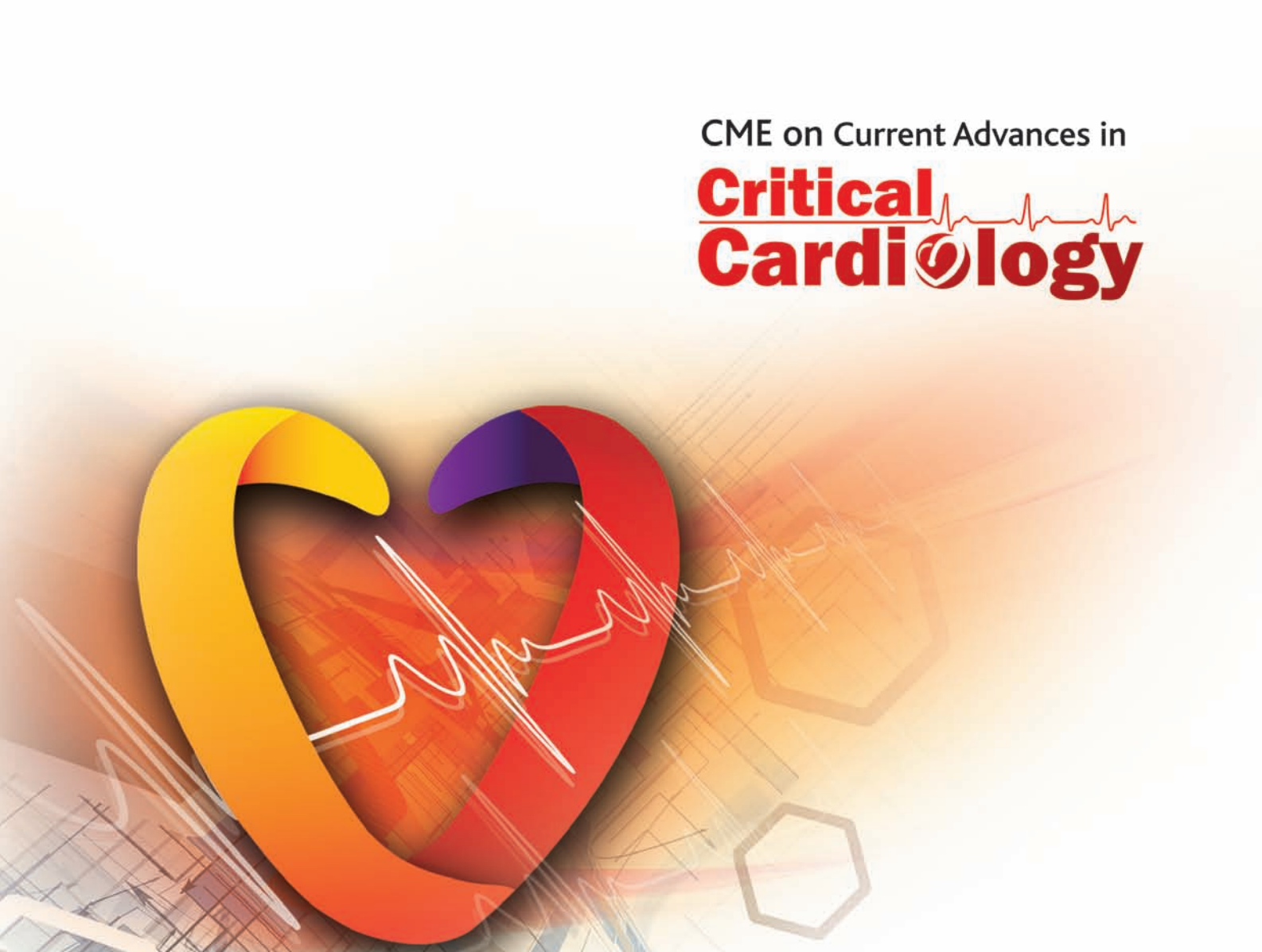
CME on Current Advances in

Critical Cardiology



Module 1

Current Advances in DYSLIPIDEMIA

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Table of Contents

SECTION 1

Dyslipidemia and cardiovascular risk 4

SECTION 2

Dyslipidemia: An emerging epidemic in India 12

SECTION 3

Current advances in dyslipidemia management 18

SECTION 1

Dyslipidemia and cardiovascular risk

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OVERVIEW

The epidemic of cardiovascular (CV) diseases is spreading across continents, contributing to significant morbidity and mortality in both the developed and developing countries. World Health Organization (WHO) estimates that CV diseases account for 17.7 million deaths each year, amounting to 31% of all global deaths.[1] Dyslipidemia is one of the most prominent risk factors for CV diseases. Specifically, high levels of LDL-cholesterol and triglycerides, and low levels of HDL-cholesterol engender high CV risk. These lipoprotein abnormalities can either occur in isolation or in combination with other defects of lipid metabolism.[2] The exact magnitude of CV risk depends on the pattern of lipoprotein abnormalities and its underlying cause.[3]

Dyslipidemia has a genetic basis. Additionally, several secondary causes of dyslipidemia are known (Table 1).[3] Targeting LDL-cholesterol through lifestyle modifications and/or statin therapy, remains the primary means of treating dyslipidemia and its associated CV risk. Patients intolerant to statin therapy and those who are unable to attain their target LDL goals on statin therapy alone, often require additional lipid therapy. Several non-statin drugs are currently available, which are used either alone or in combination with statins to maximize treatment efficacy and optimize lipid control.[3,4]

LDL-CHOLESTEROL FOR CV RISK ASSESSMENT

Dyslipidemia is an established cause of CV diseases. The role of LDL-cholesterol, a measure of total cholesterol content of LDL particles, is significant in this regard. Since the past several years, LDL-cholesterol has been regarded a traditional risk factor for coronary artery disease (CAD), and an independent predictor of CV risk. Persistently elevated LDL-cholesterol promotes atherosclerosis progression, and therefore contributes to coronary events.[5] In fact, a linear relationship between LDL-cholesterol and incidence of coronary events has

Table 1: Important secondary causes of dyslipidemia

- Metabolic syndrome
- Obesity
- Type 2 diabetes
- Hypothyroidism
- Renal diseases
- Polycystic ovary syndrome
- Drugs (such as corticosteroids, beta-blockers, antipsychotics, immunosuppressants)
- Diet (high calories, high fat or trans-fat content in the diet, alcohol)

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been documented, especially in high-risk patients with hypercholesterolemia.[6] Recently, it has emerged that elevated LDL-cholesterol levels can also contribute to the development of complex coronary bifurcation lesions, which are associated with low procedural success and long-term adverse cardiac events.[7,8] These observations strongly support LDL-cholesterol as the primary lipid marker for CV risk assessment, and the main target for initiation and adjustment of lipid-lowering therapies. Indeed, targeting LDL-cholesterol using statin therapy has remained the "gold standard" treatment strategy for dyslipidemia and its associated CV risk.[2]

Recent emergence of the concept of "residual CV risk" prompted several investigators to re-consider merits of using LDL-cholesterol as the primary treatment target for dyslipidemia. Residual CV risk refers to persistence of significant risk of CV events despite optimization of LDL-cholesterol at or below the recommended targets. This phenomenon indicates that in addition to LDL-cholesterol, several other lipid- and non-lipid factors also influence CV risk that can be targeted by lipid therapies for maximizing treatment benefits.[9] Some alternate lipid markers of residual CV risk include HDL-cholesterol, triglycerides, non-HDL-cholesterol, apoprotein(B) [apo(B)], and lipoprotein(a) [Lp(a)].[9,10]

ALTERNATE RESIDUAL CV RISK MARKERS

HDL-cholesterol

Extensive epidemiological data has established an inverse relationship between HDL-cholesterol and CV risk. Low HDL-cholesterol is an independent risk factor for CV diseases.[11,12] These observations fuelled interest in therapeutic options that could increase HDL-cholesterol, and thereby reduce potential risk of CV events. Lifestyle modifications, such as aerobic exercises, dietary changes, and smoking cessation, can favorably influence levels of HDL-cholesterol. In addition, several pharmacological agents, including niacin and fibrates can increase HDL-cholesterol.[13] Intriguingly, some recent gene studies and intervention trials[11,12] casted serious apprehensions on the role of HDL-cholesterol as a target for lipid-lowering therapy, showing that therapeutically increasing HDL-cholesterol does not always lead to unequivocal improvement in CV outcomes.

The recently introduced concept of HDL functionality can largely explain this discrepancy. It is now increasingly becoming clear that HDL quality, which is defined as the composition and function of different HDL subfractions, is also an important determinant of its atheroprotective nature.[14-16] In fact, HDL function is believed to be a better predictor of CV risk than its plasma concentration.[16] Therefore, measurement of HDL concentration alone may not reliably indicate CV risk.[15] Additionally evaluating its functional properties and addressing defects in HDL function through appropriate therapeutic intervention is apparently a more rational approach for reduction of CV risk. Unfortunately, even though some laboratory assays for evaluation of HDL function are currently available, they remain unvalidated and cannot be routinely used in clinical practice.[16] Recently, an expert working committee[10] recommended that despite its shortcomings, HDL-cholesterol concentration remains a good predictor of CV risk; however, it should not be used as a therapeutic target for lipid-lowering therapies. Clinical trials of HDL-raising therapies have in fact been negative (i.e., no reduction in CV events).[17-20] This is why the expert working committee says it should not be used as a therapeutic target.

Triglycerides

An association between triglyceride levels and CV risk was proposed more than six decades back, although its veracity has since been shrouded in controversy.[21] Early clinical studies showed that high triglyceride levels increased CV risk, although the association became insignificant after adjusting for LDL-cholesterol and/or total cholesterol. These studies, therefore, could not convincingly establish triglycerides as an independent risk factor for CV disease.[22] Two recent studies,[23,24] however, showed that genetically-elevated triglycerides and triglyceride-rich lipoproteins were indeed associated with increased risk of ischemic heart disease (IHD). Another recent report[25] reiterated that elevated fasting and non-fasting triglyceride levels