Editorial

Differential residual dyslipidemia/cardiovascular risk after statin treatment between Asian-Indians and western whites. Call for action

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In this issue of Indian Heart Journal, the Dyslipidemia Residual and Mixed Abnormalities IN spite of Statin therapy (REMAINS) Study is published.\(^1\) This is a prospective, multicenter, observational cohort study that investigated changes in lipid parameters between baseline (pre-statin therapy) and after statin therapy or other lipid lowering treatments amongst adult patients hospitalized for their first acute coronary syndrome (ACS).\(^1\) REMAINS included 474 patients who were treated with various doses of a statin, mainly high dose atorvastatin, during their hospitalization for an ACS.\(^1\) The primary outcome was changes in lipid profile during the 12-week period until the end of study (EOS).\(^1\) Comparisons between baseline lipid values and those at the EOS showed that low-density lipoprotein cholesterol (LDL-C) levels were controlled at a satisfactory degree, while high-density lipoprotein cholesterol (HDL-C) levels decreased and there were no major difference in the levels of TG (baseline TG levels were high, either alone or along with other lipid levels).\(^1\) Thus, the conclusions of the REMAINS study were that though statin therapy is effective in lowering LDL-C, according to current guidelines and standards of care, in patients with atherogenic dyslipidemia (AD), residual dyslipidemia still remains; this should be controlled to maximize clinical benefit.\(^1\) In addition, the study reports that the number of patients with AD was great at baseline (suggesting a causal association between AD and ACS) and remained high even after statin treatment (suggesting residual dyslipidemia and consequently higher cardiovascular disease (CVD) risk than those with frank hypercholesterolemia, which were treated effectively with a statin).\(^1\)

Despite the effort to effectively manage all modifiable CVD risk factors, a degree of CVD risk still remains, even after controlling for arterial hypertension, diabetes mellitus (DM), smoking, sedentary life style, and attain targets for LDL-C levels with a statin, according to current guidelines and standards of care.\(^2\) Thus, patients with AD remain at risk for vascular events, even after effective statin treatment; this is considered as residual CVD risk (RCVDR).\(^2\) RCVDR is attributed mainly to mixed-combined AD, characterized by elevated triglyceride (TG), low HDL-C levels, and increased numbers of small-dense LDL particles.\(^2\) AD is common in patients with type 2 diabetes mellitus (T2DM), obesity or the metabolic syndrome (MetS), and contributes to both macrovascular and microvascular RCVDR.\(^2\)

It has been reported that AD is more often amongst Asian Indians than in western whites.\(^3\) As shown in Fig. 1 frank hypercholesterolemia with increased LDL-C is more prevalent in US and Europe, while mixed hyperlipidemia is more prevalent in Asia and Africa, inducing a greater risk for CVD than the sole increase of LDL-C. As a result of this the rates of CVD have accelerated dramatically in South East Asian Countries, especially in urban areas,\(^3\) driven to a significant degree by the metabolic consequences of obesity-dysglycemia-dyslipidemia, such as T2DM and AD, which are common among South Asians, even in those that are permanently living in the UK.\(^3\)

One of the potential mechanisms proposed to explain this difference is that South Asians have a reduced capacity to store fatty acids in their less developed primary adipose tissue compartment (superficial subcutaneous adipose tissue), which results in earlier utilization of the secondary adipose tissue compartments (deep subcutaneous adipose tissue and visceral or intra-abdominal adipose tissue).\(^3\) Intra-abdominal fat accumulation or ectopic fat depositions (non-alcoholic fatty liver disease, pericardial/epicardial, perivascular, intra-muscular, peripertacic, and perirenal) have also adverse effects on adipokines, glucose metabolism (increase insulin
resistance), low grade inflammation, and liver fibrosis, which in turn are substantial risk factors for the development of T2DM, AD (mainly due to increased adipocyte transmembrane flux of fatty acids), or CVD.\textsuperscript{3} This can explain why the waist to hip ratio of South Asians is greater than that in whites at similar body mass index (BMI), and why AD, MetS, and T2DM are more prevalent in South Asians than in western whites for the same BMI.\textsuperscript{3,4} All the above suggest that truncal obesity in developing regions, such as South East Asia and especially India, plays a pivotal role in shaping MetS, T2DM, AD, and CVD rates, because its burden seems to be greater in these areas (Asia, Africa, and Middle East) than in the developed world (US and Europe).\textsuperscript{4}

The above conclusions are important because they bring about the issue of AD and residual dyslipidemia, especially in India, which seems to have a higher prevalence of these disorders than those recorded in western countries.\textsuperscript{3,5} These conclusions also pave the way for an effective treatment of residual dyslipidemia, and RCVDR even during the acute phase of an ACS.\textsuperscript{1} Up to now, there is only one study addressing this issue: The study (Acute Coronary Syndrome Israeli Surveys Data) included 8982 patients that had an ACS from 2000 to 2010, and received a statin.\textsuperscript{6} Of these, 8545 (95%) received statin monotherapy and 437 (5%) received a statin/ibrate combination.\textsuperscript{6} The primary endpoint was the 30-day incidence of major adverse cardiovascular events (MACE) and the secondary the 12 month MACE incidence.\textsuperscript{6} Overall, there were significantly lower MACEs at 30 days in the statin/ibrate group in comparison to statin monotherapy group (p = 0.001).\textsuperscript{6} However, in specific subgroups, the differences were even greater. Indeed, in patients with high TGs and in those with low HDL-C at baseline, the reduction of MACEs was more than 50% and in patients with T2DM this reduction was almost 80%.\textsuperscript{6} The 12 month MACE difference was 46% [hazards ratio (HR) = 0.54, 95% confidence interval (CI) 0.32–0.94] in favor of the statin/ibrate combination.\textsuperscript{6} These results suggest that, following confirmation by at least one prospective study, the administration of the statin/ibrate combination is useful in patients with residual dyslipidemia even during the acute phase of an ACS.\textsuperscript{6}

However, the clinical benefits of the statin/ibrate combinations have been reported in the past and comprise in keeping CVD morbidity and mortality at very low levels in patients with mixed hyperlipidemia, both in primary and secondary CVD prevention.\textsuperscript{7} Moreover, a subgroup analysis of The Action to Control Cardiovascular Risk in Diabetes (ACCORD) Lipid Trial suggests that the statin/ibrate treatment reduces CVD morbidity and mortality by 31% more than statin monotherapy in patients with AD.\textsuperscript{9} Additional post-trial follow-up of ACCORD patients for a total period of nine years\textsuperscript{7} revealed findings similar to the initial ACCORD findings: the addition of fenofibrate to simvastatin displayed a 27% further reduction in CVD events in patients with T2DM and AD compared to a statin monotherapy (HR = 0.73; 95% CI: 0.56–0.95) for AD patients, but had no effect on patients with frank hypercholesterolemia (HR = 0.99; 95% CI: 0.86–1.13; interaction p = 0.048).\textsuperscript{7} Finally, a meta-analysis of all major fibrate trials revealed a 35% (95% CI: 22–46%) reduction in MACE in the subgroups with AD and a not significant one by 6% (95% CI: –5% to 16%) in the subgroups without AD.\textsuperscript{10}

All the above suggest that the statin/ibrate combination is very useful and substantially reduces RCVDR in patients with AD but has no effect on patients with frank hypercholesterolemia and should not be prescribed in these patients. Overall, if the significant clinical benefit of fenofibrate administration on microvascular complications of DM (retinopathy, nephropathy, neuropathy, and amputations) is taken into consideration the entire benefit on life expectancy and quality of life in patients with T2DM and AD is enormous. Another very important conclusion of the REMAINS study is that data from India suggest that the prevalence of both AD and residual dyslipidemia after statin treatment is higher than that of western white patients included in studies performed in US or Europe (Fig. 1),\textsuperscript{1,5} mainly due to abnormal lipid deposition.\textsuperscript{7} Thus, there is a need for local guidelines for the diagnosis and the treatment of MetS (mainly based on waist to hip ratio and not on BMI or waist circumference) with specific recommendations adjusted to South East Asia criteria. Moreover, suggestions for treating residual dyslipidemia should be included in these local guidelines, mainly adopting the statin/ibrate combinations, because the problem for India

Fig. 1 – Mixed-AD has a higher prevalence in developing regions. This is obvious from the differences between the percent prevalence of frank hypercholesterolemia across 4 different regions according to WHO (http://www.who.int/gho/ncd/risk_factors/cholesterol_text/en/), in the upper panel (A), and the percent population-attributable coronary risk due to dyslipidemia across 4 different regions in the INTERHEART study (reference 4), in the lower panel (B). The differences are attributed in part to the high prevalence of mixed-AD (high TGs and low HDL-C) in Africa and SE Asia, which has not been included in the WHO evaluation of frank hypercholesterolemia prevalence.
is too big to ignore. Thus, fresh guidelines relevant to this part of the world are required to fill this void of the existing guidelines.11

Conflicts of interest

This editorial was written independently. The authors did not receive financial or professional help with the preparation of the manuscript. The authors have given talks, attended conferences, and participated in advisory boards and trials sponsored by various pharmaceutical companies.

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