Should we consider low LDL-C a marker of in-hospital bleeding in patients with ACS undergoing PCI?

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In patients with acute coronary syndrome (ACS) undergoing percutaneous coronary intervention (PCI), there is increasing awareness of the need to balance the benefits of antithrombotic therapy against the risks of major bleeding.[1] Non-CABG-related major bleeding is reported to occur in up to 1-3% of patients with ACS treated with dual antiplatelet therapy (DAPT) per annum and is independently associated with mortality. Major bleeding may be more frequent in East Asian populations, with contemporary data indicating up to 3% per annum major bleeding with DAPT.[2] Moreover, registry-based contemporary data suggest that bleeding in 'real-world' clinical practice may be more prevalent, with up to 4-5% of patients with ACS experiencing in-hospital bleeding.[3]

A number of studies have assessed ways of mitigating the bleeding risk in ACS patients undergoing PCI, by reducing the potency or duration of DAPT. However, a significant challenge is identifying which patients are at increased bleeding risk, as many patient-related characteristics shown to increase bleeding risk also increase ischaemic risk, including advancing age, chronic kidney disease, anaemia, and white blood cell count.[1] There are currently no reliable, easily available, validated biomarkers to specifically identify patients at excess bleeding risk.

In this issue, Dr. Yang and colleagues(ref) report an association between admission serum low density lipoprotein cholesterol (LDL-C) and major in-hospital bleeds in a large Chinese nationwide registry involving 42,378 ACS patients treated with PCI from 2014-2019 receiving intensive antithrombotic therapy. Major bleeding was defined as the composite of (1) Bleeding Academic Research Consortium type 3b-3c and type 5 bleeding; (2) Thrombolysis In Myocardial Infarction (TIMI) major bleeding; and (3) PLATelet inhibition and patient Outcomes (PLATO) life-threatening major bleeding. The authors of this retrospective analysis report a nonlinear association between LDL-C levels and major in-hospital bleeds or net clinical outcome, with higher risk of bleeding, including haemorrhagic stroke, associated with lower LDL-C levels, after controlling for 48 baseline covariates A threshold for the increased risk of adverse outcomes in this population was identified at LDL-C <70 mg/dL. Whilst the normal/high and low LDL-C groups differed with regards to most baseline risk factors, the association of low-LDL-C with bleeding held after propensity score matching. Most

patients were on clopidogrel as part of DAPT, and use of ticagrelor in 32% of patients enhanced the low LDL-C-associated bleeding risk, compared to clopidogrel. Roughly a third of patients received a glycoprotein IIb/IIIa inhibitor (an unusually high rate especially in an East Asian population who are prone to bleeding), yet subgroup analysis suggests that admission LDL-C <70 mg/dL was only associated with non-procedural bleeds, predominantly gastrointestinal. Notwithstanding the limitations of a retrospective analysis, this is the first very large cohort study indicating an adverse association of low LDL-C levels with excess bleeding in Chinese patients with ACS, and the findings are worthy of further discussion.

A causative relationship between LDL-C levels and increased bleeding risk cannot be inferred from this study which is observational by design and may be prone to confounding or reverse causality. Whilst propensity score matching was performed with a large number of covariate adjustments, this does not entirely neutralise the marked differences between the two cohorts (those with low LDL-C vs. normal or high-LDL-C) suggesting that LDL-C alone cannot explain the excess bleeding and that the latter is likely multifactorial. Indeed, patients with low LDL-C had multiple risk factors for increased bleeding, compared to those with higher LDL-C, including more advanced age, lower body mass index (BMI) and more frequent renal failure, and were more often treated pre-hospital with aspirin and a P2Y$_{12}$ inhibitor. The lower BMI of patients with low LDL-C compared to that of patients with normal or high LDL-C levels is an important limitation, as low body weight is a strong harbinger of bleeding and other adverse outcomes (obesity paradox).[1,4] Thus, lower LDL-C might be a proxy for a sicker cohort with more comorbidities, or of patients who may, perhaps, have been pre-treated with high dose statins, thereby identifying those with pre-established cardiovascular disease. Indeed, patients with lower LDL-C had more often undergone prior PCI than the higher LDL-C counterparts (17.5% vs 6.6%) and P2Y$_{12}$ inhibitors were used more often before admission (25.6% vs 15.0%). Residual questions relate to the reliability of bleeding event diagnosis, as this was performed locally and not centrally adjudicated, and the generalisability to non-Chinese populations. Some previous studies in predominantly Western populations have identified low LDL-C as a predictor of bleeding in chronic coronary syndrome.[5]

Findings from other studies support a possible causal association, reporting a relationship between lower levels of non-HDL cholesterol, in particular low LDL-C levels, and an increased risk of intracranial haemorrhage (ICH).[6] In particular, in Chinese individuals, there appears to be an inverse association between LDL-C level and ICH, confirmed by genetic analyses and by LDL-C-lowering trials.[7] Recent data from 316,428 individuals enrolled in the UK Biobank, together with 1,286 patients with ICH and matched controls, showed that genetically elevated LDL levels were associated with lower risk of ICH, with one standard deviation increase in total cholesterol (odds ratio [OR] = 0.92) or LDL-C (OR = 0.88) significantly inversely associated with ICH risk.[8] A nested case-control study within the prospective China Kadoorie Biobank involving ~5,000 patients with ICH showed that elevated LDL-C level was inversely associated with risk of ICH.[7] In the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial, which focused on high dose atorvastatin for secondary prevention after a first stroke or transient ischaemic attack, *post hoc* analysis revealed an unexpected increment in ICH with active treatment compared to placebo, although no relationship with entry LDL-C levels were observed.[9]

The above relation remains controversial, given the reported safety of very low (<30 mg/dL) LDL-C levels in a setting of non-intensive antithrombotic therapy. A recent meta-analysis of RCTs did not find an association between low LDL-C and haemorrhagic stroke, in line with previous others.[10] The use of the PCSK-9 inhibitor alirocumab in over 18,000 patients with recent ACS, whilst significantly reducing LDL-C, did not increase the risk of ICH during a 2.8-year follow-up.[11]

Could this association of low LDL-C with bleeding be causal with a plausible mechanism? Histopathologic studies have suggested that lower cholesterol concentrations may increase permeability of the vessel walls.[12] In a mechanistic *in vitro* study, cholesterol depletion reduced mean platelet volume, granularity, platelet ATP release and inhibited platelet aggregation by altering platelet ultrastructure critical in mediating secretion.[13] In a small study of patients with coronary disease undergoing apheresis, a 58% reduction in LDL-C was also associated with a 52% reduction in

fibrinogen and lipoprotein(a) and a significant reduction in shear-stress dependent platelet adhesion.[14] In a single-blind crossover study to assess the effect of lipoprotein apheresis compared to sham apheresis on markers of thrombosis and fibrinolysis, lipoprotein apheresis reduced shear-induced occlusive platelet thrombus formation and enhanced endogenous fibrinolysis, without corresponding changes with sham.[15] In addition, lipoprotein apheresis, but not sham, reduced von Willebrand factor and fibrinogen, with no change in D-dimer, thrombin/antithrombin complex, or thrombin generation assay with either apheresis or sham.

The paper by Dr. Yang and colleagues should stimulate further prospective studies to examine the relationship between serum LDL-C and bleeding, especially among patients receiving intensive antithrombotic therapy as well as those managed without percutaneous intervention. A longer-term analysis, including the DAPT treatment period, or in patients on oral anticoagulation, would also be important. Furthermore, this study included exclusively Chinese patients; since bleeding risk is acknowledged to be higher in East Asians compared to those from other ethnic backgrounds, further analysis to examine this possible association in other populations would be important. Importantly, as shown in a large Swedish national database registry of patients with ST-elevation ACS, the absence of well-recognised modifiable risk factors for ACS (hypertension, diabetes, hypercholesterolaemia, and smoking) identifies a cohort at high mortality risk.[16]

While the magnitude of benefit of LDL-C reduction in patients with ACS undergoing PCI should trump concerns over lipid lowering strategies (the average in-hospital TIMI major bleeding rates were below 1.5 and 2% in the lowest LDL-C categories), low LDL-C on admission among ACS patients undergoing PCI may be a marker of increased susceptibility to bleeding during intensive antithrombotic therapy. Thus, every effort should be made to reduce the risk of bleeding, including with the use of gastrointestinal prophylaxis, radial rather than femoral artery access, good blood pressure control, anticoagulant or parenteral antiplatelet dosing adjusted to weight and renal-function, and careful choice of antithrombotic drugs.

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