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Editorial

Novel Bullet for Dyslipidemia and Cardiovascular Disease in the Horizon: Does Genetics Contribute to the Blueprint?

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The development of novel therapy for dyslipidemia and cardiovascular diseases (CVD) had been constrained by some challenges, and several recent approaches have failed for lack of efficacy. Progress had been made by a single, greatest contribution from statins in reducing the risk of CVD. However, the burden of CVD and residual risk remains quite high, and new pathways to prevent and treat the diseases are still needed. Despite this clear unmet need, nevertheless many research institutions have begun to withdraw their efforts in discovering 'the new bullet' for this prevalent diseases[1].

Though statins are effective drugs, their utilization is sometimes fraught with issues, such as failure of adequate lipid control in approximately 30% of cases and intolerance in selected subjects, and also new-onset diabetes issue. Also, the limited efficacy of other drugs such as bile acid sequestrants, fibrates and niacin has urged the search for other novel molecules with better efficacy and safety. [2]As examples, within the past several years, large clinical trials of lipid-altering drugs (niacin)[3,4], as well as new therapeutic options such as cholesteryl ester transfer protein (CETP) inhibitor (dalcetrapib)[5], secreted phospholipase A2 (sPLA2) inhibitor (varespladib)[6], and lipoprotein-associated phospholipase A2 (LpPLA2) inhibitor (darapladib)[7] failed to convey important clinical benefits in reducing CVD outcome.

Regrettably, animal models of atherosclerosis have not reliably convinced at predicting new anti-atherosclerotic therapies that would be effective in human. Further, non-invasive atherosclerosis imaging approaches had not been predictive of clinical outcomes in response to therapy. Dalcetrapib, varespladib and darapladib were all shown, to some extent, to get positive and beneficial effects in animal models and in imaging studies in humans as well, but unfortunately failed in large CVD outcome trials.

In contrast, human genetics can bring forth much greater confidence that a therapeutic targeted to a particular pathway will show clinical benefit in reducing major CVD events[8]. A particular example of this proof of concept is the report about proprotein convertase subtilisin/kexin type 9 (PCSK9). PCSK9 is a serine protease involved in the degradation of the LDL receptor. It binds to the LDL receptor present on the surface of the cell viaclathrin-coated pits and leads to internalization of LDL receptor, leading to degradation and resultant increase in the concentration of LDL cholesterol.[9]A specific mutation in PCSK9 gene namely D374Y was found to cause a gain-of-function, resulting in increased binding of PCSK9 to the LDL receptor and resultant

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degradation. The findings related to inhibition of PCSK9 are burgeoning as an attractive target for reducing LDL-C in both dyslipidemia and CVD.[10,11]

Loss of function mutations in the PCSK9 gene were associated with very low levels of LDL-C and, more importantly, substantial risk reduction for coronary artery disease. [12]This influential finding contributes to a great confidence that pharmacologic inhibition of PCSK9 would not only decrease LDL-C levels, but also reduce the risk of CVD. In the future, we would have unequivocal evidence that inhibition of PCSK9 notably reduces LDL-C in human. [13]Although studies aimed to prove that PCSK9 inhibition improving risk of CVD are still ongoing, there is a high level of hope and confidence based on the human genetics data.

Alternatively, plasma triglycerides (TG) are an interesting case in point. There are ample observational epidemiologic data showing that TG levels is positively associated with increased CVD risk, but there has been uncertainty about the causal nature of this association. However, a recent large study comprehensively addressed the genetic relationships and found that variants associated with TG concentration were associated with CVD risk even after being adjusted for the effects of these variants on LDL-C and HDL-C.[1]This suggests that certain proteins regulating TG metabolism could be potential targets for therapy. For example, a gain-of-function variant in lipoprotein lipase (LPL) is associated with reduced TG concentration (as well as increased HDL-C) and reduced risk of CVD, indicating that increased LPL activity may be atheroprotective. LPL also has several natural inhibitors, including apolipoprotein C-III (apoC-III and gene *APOC3*). A loss-of-function nonsense variant in *APOC3* is associated with reduced TG (and increased HDL-C) as well as reduced coronary atherosclerosis. [14]This suggests that APOC3 may be an attractive target for pharmacologic inhibition.

While it may not be a straightforward proposition to take away statins from their current position as a cholesterol reducing agent and a drug to improve CVD, our new comprehension of this diseases and appropriate harnessing of resources using sound and robust technology could make rapid in roads in our pursuit of the ideal anti-dyslipidemic and CVD bullets in the horizon.[2]

References

1. Rader DJ. New Therapies for Coronary Artery Disease: Genetics provides a blueprint. Scie Trans Medicine 2014; 6: 239: 1 – 4.
2. George M, Selvarajan S, Muthukumar M, Elangovan S. Looking into the Crystal Ball – Upcoming Drugs for Dyslipidemia. J of CardiovascPharmacol Therapeutics 2015; 20(1): 11 – 20.
3. Boden WE, Probstfield JL, Anderson T, et al. AIM-HIGH investigators. Niacin in patients with low-HDL cholesterol levels receiving intensive statin therapy. N Eng J Med 2011; 365: 2255 – 67.
4. Haynes R, Jiang L, Hopewell JC, et al. HPS2-THRIVE Collaborative Group. HPS2-THRIVE randomized placebo-controlled trial in 25,673 high-risk patients of ER niacin/laropirant: Trial design, pre-specified muscle and liver outcomes and reasons for stopping study treatment. Eur Heart J 2013; 34: 1279 – 91.
5. Schwartz GG, Olsson AG, Ballantyne CM, et al. Effects of dalcetrapib in patinets with a recent acute coronary syndrome. N Eng J Med 2012; 367: 2089 – 99.
6. Nicholls SJ, Kastelein JJ, Schwartz GG, et al. VISTA-16 Investigators. Varespladib and cardiovascular events in patients with an acute coronary syndrome: The VISTA-16 randomized clinical trial. J Am Med Assoc 2014; 311: 252 – 62.
7. White HD, Held C, Stewart R, et al. STABILITY Investigators. Darapladib for preventing ischemic events in stable coronary heart disease. N Eng J Med 2014; 370: 1702 – 11.
8. Plenge RM, Scolnick EM, Altshuler D. Validating therapeutic targets through human genetics. Nat Rev Drug Discover 2013; 12: 581 – 94.
9. Sun H, Samarghandi A, Zhang N, et al. Proprotein convertase subtilisin/kexin type 9 interacts with apolipoprotein B and prevents its intracellular degradation, irrespective of the low-density lipoprotein receptor. ArterioscIerThrombVasc Biol. 2012;32(7): 1585 - 95.
10. Shen L, Peng H, Xu D, et al. The next generation of novel low density lipoprotein cholesterol lowering agents: proprotein convertase subtilisin/kexin 9 inhibitors. Pharmacol Res 2013; 73: 27 – 34.
11. Popp Switzer M, Nwosu AC, San Juan Z, et al. Propetein convertase subtilisin/kexin type 9 (PCSK9) and LDL lowering in the contemporary management of dyslipidemia. Cardiovasc Hematol Agents Med Chem2013; 11(4): 281 – 8.
12. Cohen JC, Boerwinkle E, Mosley TH, et al. Sequence variations in PCSK9, low LDL and protection against coronary heart disease. N Eng J Med 2006; 354: 1264 – 72.
13. Stein EA. Low density lipoprotein cholesterol reduction by inhibition of PCSK9. CurrOpinLipidol 2013; 24: 510 – 17.
14. Pollin TI, Damcott CM, Shen H, et al. A null mutation in human APOC3 confers a favorable plasma lipid profile and apparent cardioprotection. Science 2008; 322: 1702 – 05.