higher LDL cholesterol (22% higher, 95% CI 11–23; p=3×10−12) and plasma triglycerides (19% higher, 95% CI 12–25; p=3×10−12) as well as increased risk for CAD (Odds Ratio 2.84; 95% CI 1.35–2.51; p=0.001). Beyond rare mutations, FH mutation carriers had higher cumulative exposure to LDL cholesterol than noncarriers and an additional analysis of 6 common LPL variants noted a 51% increase in risk of CAD (95% CI 39–64; p=1.1×10−25) per standard deviation increase in triglycerides.

Interpretation: In our series, about 46.6% carry a damaging mutation in the LPL pathway genes that are associated with higher plasma triglycerides as well as increased risk for CAD. Impaired clearance of triglyceride-rich lipoproteins by the LPL gene appears to be a causative mediator of human atherosclerosis

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P2994 | BENCH

Deletion of fatty acid binding protein-4 and -5 reduce triglyceride absorption in small intestine of mice

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Elevated blood triglyceride concentration is strongly correlated with increased risk for cardiovascular disease and associated with high-fat diet consumption. Fatty acid binding protein-4 and -5 are intracellular receptors that mediate metabolic disorders such as diabetes, diet-induced obesity, and atherosclerosis. We previously showed that FABP4/5 are expressed in capillary endothelial cells of heart and skeletal muscle to facilitate fatty acid transport from blood to intra-cellular fluid. Mice with double deficient of FABP4/5 (DKO mice) have reduction of fatty acid uptake in heart and skeletal muscle compared to wild-type mice (WT mice). However, the level of triglyceride and free fatty acid (FFA) on serum of DKO mice are not reduced under feeding condition despite the reduced uptake of fatty acids. We hypothesize that FABP4/5 contribute to triglyceride absorption in the small intestine of mice. To test triglyceride absorption of small intestine in long term, ketogenic diet were exposed to WT and DKO mice for six weeks. Triglyceride serum was increased in WT mice and not changed in DKO mice during ketogenic diet. This results suggesting triglyceride absorption in small intestine of DKO mice. Next, we measured the capacity of acute triglyceride absorption by given intragastric olive oil. Triglyceride serum levels were lower in DKO mice compared to WT mice after 2, 4 and 6 hours of intragastric oil, which was followed by reduced levels of TG-rich lipoproteins, chylomicron and very large density lipoprotein, as well as reduced of triglyceride concentration in lymph vessel. The levels of triglyceride were still lower in DKO mice even after injection of tyloxapol, a lipoprotein lipase inhibitor and ruled out the possibility of disruption in peripheral tissues. Oil red O staining revealed less number and size of lipid droplets in small intestine of DKO mice, suggested low triglyceride formation and accumulation in small intestine. We noticed that FABP4/5 proteins are expressed in capillary endothelium of small intestine, adipose tissue and lymph vessel, suggesting that FABP4/5 play role in triglyceride absorption in an unexpected mechanism. Together, our data implying that the lack of VEGF-B appears to be dispensable in lipid metabolism.

Conclusions: Here, we report an unexpected finding that VEGF-D knockout leads to grossly elevated cholesterol and triglyceride levels in chylomycin particles. Furthermore VEGF-B, in combination with VEGF-D knockout, rescues hyperlipidemia and altered chylomicron metabolism that is induced by VEGF-D knockout alone. These findings clearly highlight the importance of VEGFs as the major modifiers of lipid metabolism.

P2995 | BEDSIDE

Risk factors for aortic stenosis and aortic valve replacement in 1.2 million UK women

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Background: There are no medical therapies to prevent or slow the progression of non-rheumatic aortic stenosis, and data on risk factors for the disease are limited. Studies have shown similarities to coronary atherosclerosis.

Purpose: To conduct a prospective study of associations between established cardiovascular risk factors and non-rheumatic aortic stenosis, and to compare the magnitudes of these associations with those for coronary heart disease.

Methods: A population-based cohort of 1.2 million UK women, average age 56 (SD 5) years at recruitment, was followed for an average of 16 (SD 2.5) years by electronic record linkage to routinely-collected databases of hospital admissions and deaths. We used Cox proportional hazards regression to estimate multivariable adjusted associations of established cardiovascular risk factors (smoking, strenuous physical activity, body mass index, height, education and socioeconomic deprivation, and being treated for hypertension, high cholesterol, or diabetes) with incident non-rheumatic aortic stenosis, aortic valve replacement, and coronary heart disease.

Results: Among women with no record of cardiovascular disease at recruitment, there were 8752 with a record of aortic stenosis during follow-up, of whom 3088 had an aortic valve replacement in the same or a subsequent hospital admission. Risks of aortic stenosis and aortic valve replacement were strongly associated with higher body mass index, smoking, and being treated for hypertension, high cholesterol, or diabetes (P<0.001 for each). Relative risks were similar to those for coronary heart disease, except that high body mass index was associated with substantially greater relative risks of aortic stenosis than of coronary heart disease (RR for ≥35 kg/m2 compared to 20–24.9 kg/m2: 4.46, 95% CI 4.05–4.90, versus 1.86, 95% CI 1.81–1.91, respectively; P=0.001 for heterogeneity).

Conclusion: Established cardiovascular risk factors are potentially modifiable risk factors for aortic stenosis. Obesity is a major risk factor for aortic stenosis and aortic valve replacement.

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P2996 | BEDSIDE

Antithrombotic strategies in patients with aortic bio prosthesis, what is the optimal treatment

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Background: After aortic valve replacement with bioprosthesis (SAVR) antithrombotic treatment with initial warfarin or aspirin alone is recommended. No randomized study has compared different antithrombotic regimes after transcatheter aortic valve replacement (TAVR).

Purpose: Evaluate efficacy of different antithrombotic treatments on the risks of death, ischemic stroke and intracerebral bleeding after SAVR and TAVR, respectively.

Results: VEGF-D KO x LDLR−/−/−ApoB100/100 mice showed normal lipid absorption but elevated plasma cholesterol and triglyceride levels in chylomycin and large VLDL particles. These large particles cannot freely penetrate through endothelium of arteries, which lead to an anti-atherogenic phenotype. Interestingly, VEGF-B/D KO x LDLR−/−/−ApoB100/100 mice displayed reduced lipid absorption and normal plasma cholesterol and triglyceride levels. The combination induced VEGF-D knockout in addition to VEGF-D seems to rescue hyperlipidaemia and altered chylomicron metabolism induced by VEGF-D knockout. Additionally, VEGF-B/D KO x LDLR−/−/−/−ApoB100/100 mice exhibited significantly reduced LDL turnover leading to accelerated atherogenesis. VEGF-B knockout alone in LDLR−/−/−/−/−ApoB100/100 mice had no major effect on body weight, indicating that the lack of VEGF-B appears to be dispensable in lipid metabolism.

CONCLUDING THE VALVULAR HEART DISEASE PUZZLE