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Epigenetic actions of RVX-208 to lower the Major Adverse Cardiovascular Events (MACE) in patients with Diabetes Mellitus (DM) and Cardiovascular Diseases (CVD)

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Background & Aim: RVX-208 binds selectively to the second ligand domain of Bromodomain and Extra-Terminal (BET) proteins and inhibits their activity. Each BET protein has two bromodomains that bind acetylated lysine in histones. When a BET protein binds ligand, it recruits transcriptional machinery to DNA and thereby modifies gene activity. Analysis of pooled data from two phase trials: SUSTAIN and ASSURE revealed a 55% relative risk reduction (RRR) of MACE in RVX-208 treated patients (n=331) vs. placebo (n=168). But in those with DM, RVX-208 treatments lead to a 77% RRR of MACE vs. placebo. RVX-208 increased production of ApoA-I yielding more High-Density Lipoprotein (HDL) particles. While these effects should lower MACE, the magnitude was more than expected, prompting studies to identify properties of RVX-208 beyond its effects on ApoA-I/HDL. **Methods:** Plasma biomarkers from SUSTAIN and ASSURE trials were analyzed. Microarray data from RVX-208 treated Primary Human Hepatocytes (PHH) or Human Whole Blood (HWB) were used to identify differentially expressed genes, and guide measurements of specific proteins in clinical samples to confirm key findings. **Results:** Biomarkers from the trials showed significant increases ($p<0.05$, unless specified) between RVX-208 vs. placebo in: HDL-c (+3 mg/dL), ApoA-I (+7.5 mg/dL), large HDL (+0.7 umol/L), HDL size (+0.1 nm), and total HDL particles (+1.8 umol/L, $p<0.07$). Glucose in all patients (n=499) or in those with DM (n=192) given RVX-208 or placebo was unchanged vs. baseline. In patients with DM (n=119) and low HDL (<40 mg/dL), RVX-208 reduced glucose by -0.3 mmol/L but in placebo it increased +0.9 mmol/L. These modest changes do not predict the MACE reductions. Thus microarrays were used to survey PHH and HWB exposed to RVX-208. In PHH, RVX-208 decreased expression of genes in pathways for "cholesterol and fatty acid synthesis", innate immunity and glucose processing. Most profound were, effects on complement and coagulation pathways, where RVX-208 down regulated expression of 19/26 and 20/33 genes respectively. These data were confirmed by RT-PCR of key mRNAs. Furthermore, specific complement and coagulation proteins were found to be decreased in plasma from the trials (range 7-12% vs. baseline). Microarrays from HWB exposed ex-vivo to RVX-208 identified pathways with known roles in atherogenesis including: Pro-inflammatory signaling, cell-cell interactions and extracellular matrix organization. RVX-208 significantly down regulated several pro-atherogenic genes (43/56) but unregulated anti-atherogenic genes (9/17), that control monocyte recruitment, migration and activation, macrophage function, inflammatory signaling and plaque stability to suggest an overall anti-atherosclerotic benefit. **Conclusion:** RVX-208 treatment is associated with marked MACE reductions in SUSTAIN and ASSURE patients and especially in those with DM. RVX-208 modifies cellular epigenetic to impact multiple biological processes that underlie CVD. Combined effects of RVX-208 on reverse cholesterol transport, vascular inflammation, innate immunity, atherosclerosis and thrombosis may explain its efficacy in reducing MACE. These data provide the foundation for the recently initiated phase 3 on RVX-208.

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A multidisciplinary approach to investigating diabetes risk in Asians

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Type 2 diabetes (T2D) is an increasing global health challenge and a potential threat to economic growth, particularly in developing countries. East Asians are known to have higher insulin sensitivity but a much lower insulin response than Caucasians or Africans. For example, Chinese develop diabetes at a relatively lower body mass index (BMI) and younger age than their western counterparts. Thus, understanding the biological mechanism(s) in T2D pathogenesis and identifying high-risk populations are of critical importance in curtailing the growing burden of diabetes in Asian countries and worldwide. Over the last decade, we have conducted a series of studies on T2D, applying nutritional, genetic and molecular epidemiological approaches to investigate the contribution of genetics, nutrition, and other lifestyle factors in the development of T2D. We have identified genetic susceptibility markers, metabolites and dietary factors that are associated with the risk of developing diabetes. In addition, we have launched a new research initiative to investigate the role of the microbiome in diabetes risk. Much of our research has been based on two large population-based cohort studies, the Shanghai Women's Health Study and the Shanghai Men's Health Study.

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