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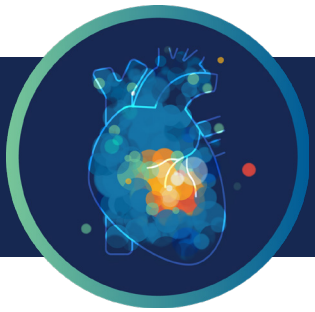
EXPERT INSIGHTS: Q&A WITH PROF. KAUSIK K RAY



Professor Kausik K Ray, FMedSci

Professor of Public Health; Honorary Consultant Cardiologist; Director of ICTU-Global, Imperial Clinical Trials Unit; Chief Clinical Officer and Head of Trials – Discover Now; NIHR ARC National Lead of Cardiovascular Disease; President European Atherosclerosis Society

Should we continue to use Body Mass Index (BMI) as a reliable measure of obesity?

BMI is imperfect in certain ethnic groups but it is the most widely used so at least for now it is reasonable although waist hip ratio is probably better across ethnicities.

This was a high risk ASCVD cohort enrolled to SELECT. However, there was no requirement for subjects to be taking maximally tolerated lipid lowering therapy and/or to have attained guideline mandated LDL-C targets as a pre-requisite for entry into the trial. Do you see this as a major confounder when interpreting the trial outcomes?

This is not a major limitation because baseline levels of lipids, blood pressure, and other measures of risk were in line with real world data. Furthermore, these are balanced at baseline between the groups (active treatment vs placebo) so these do not affect the relative risk reduction observed.

The study population was predominantly male and predominantly Caucasian. Are we able to extrapolate the results of this trial to women and under-represented ethnic groups?

The effect was consistent across subgroups with no evidence of a statistical interaction so the results are generalizable.

On a more general note, what are your thoughts on how we can achieve better gender parity and racial diversity in large cardiovascular outcomes trials?

We need to actively recruit those patients in regions of the world where they exist rather than simply going to where the market is. We need to have more female Principal Investigators and allow for increase in sample size to account for lower event rates in some groups like women.

Death from cardiovascular causes, as a confirmatory secondary endpoint, was not significantly different between semaglutide vs. placebo. Do you have any thoughts on why this might have come to pass?

This may be due to misclassification where for instance the cause is likely to be cardiovascular but there isn't enough information to say this for certain so this may be put down as unknown. This also occurred during the pandemic where some deaths attributable to a cardiovascular cause may not have been due to atherosclerosis, but instead caused by thrombotic complications associated with COVID-19. As such these events in the SELECT trial may not have been modifiable by GLP-1 exposure. This results in the dilution of the potential impact of GLP-1 on CV deaths if a large proportion of CV deaths were unlikely to be modifiable by the effects of GLP-1.

How would you summarise the key points from the SELECT trial in plain language, if a patient were to ask you about it in clinic?

In patients with atherosclerotic cardiovascular disease and obesity (but without diabetes), semaglutide reduces weight/ BMI and reduces the occurrence of adverse events associated with heart disease, such as death from heart-related causes, heart attack and stroke. The benefit appears early before significant weight loss suggesting this is related at least in part to a direct benefit of semaglutide per se.