

A Naturally Randomized Trial Comparing the Effect of Long-Term Exposure to Lower LDL-C, Lower SBP, or Both on the Risk of Cardiovascular Disease

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Disclosures

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Declaration of Interest

- Research contracts (MSD)
- Amgen
- Esperion Therapeutics)
- Consulting/Royalties/Owner/ Stockholder of a healthcare company (MSD)
- Esperion Therapeutics
- Celera
- Ionis Pharmaceuticals)



Background

- Persons with ideal risk factor profiles have a very low lifetime risk of CVD
 - fewer than 5% of persons are able to maintain ideal risk factor profiles
- Mendelian randomization studies have shown that LDL-C and SBP each have both causal and cumulative effects on the risk of CVD
- Because LDL-C and SBP have cumulative effects over time, a simplified prevention strategy that focuses on promoting long-term exposure to both lower LDL-C and lower SBP may be a very effective prevention strategy
- **The causal effect of combined exposure to LDL-C and SBP on CVD is unknown**
 - Prospective epidemiologic studies suggest the effect may be more than additive but less than multiplicative
 - A recent 2x2 factorial randomized trial (HOPE-3) suggested the benefit of combined LDL-C and SBP lowering was not greater than LDL lowering alone

Purpose and key points about methods

Purpose

- To estimate the causal effect of combined exposure to lower LDL-C and lower SBP on the risk of cardiovascular events
- To estimate the potential clinical benefit of a parsimonious prevention strategy that focuses on promoting long-term exposure to the combination of one mmol/L lower LDL-C and 10 mmHg lower SBP

Methods

- We used genetic LDL and BP scores as instruments to “naturally randomize” 102,000 study participants to lower LDL-C, lower SBP, both or neither using a 2x2 factorial Mendelian randomization study design
- The genetic scores were not used to predict risk, but instead were used merely as convenient instruments to “naturally randomize” study participants
- The study therefore evaluated the unconfounded causal effect of random allocation to lower LDL, lower SBP and combined exposure to both on the risk of cardiovascular events in a manner analogous to a long-term randomized trial

Results

- A total of 14,368 major vascular events (MVE: CHD death, MI, stroke or coronary revascularizations) occurred during up to 32 years of follow-up
- When present together, lower LDL and lower SBP had independent, multiplicative and cumulative causal effects on the risk of CV events
- Long-term exposure to the combination of 1 mmol/L lower LDL-C and 10 mmHg lower SBP was associated with an 86.1% (OR: 0.139, 95%CI:0.114-0.170, $p=1.6 \times 10^{-83}$) lower risk of MVE
- Combined exposure to lower LDL and lower SBP was associated with a significantly greater reduction in the risk of MVE as compared to lower LDL alone ($p=1.4 \times 10^{-14}$) and to lower SBP alone ($p=1.8 \times 10^{-23}$)
- The effect of combined exposure to lower LDL-C and lower SBP was consistent across multiple different cardiovascular end points (including CHD death)
- The effect was similar in men & women; smokers & non-smokers; diabetics & non-diabetics; persons with LDL-C above and below 3.5 mmol/L, and persons with SBP above and below 120 mmHg

Conclusions

- LDL-C and SBP have independent, multiplicative and cumulative causal effects on the risk of cardiovascular events
- Because their effects are multiplicative and cumulative, long-term exposure to the combination of modestly lower LDL-C and SBP has the potential to dramatically reduce the lifetime risk of cardiovascular events, even among persons with apparently normal cholesterol and blood pressure levels
- Our study confirms that cardiovascular events are largely preventable
- The prevention of cardiovascular disease can be substantially improved and simplified by designing prevention programs that focus on promoting long-term exposure to combination of lower LDL-C and lower SBP beginning in early adulthood