PCSK9 inhibitors and incident type 2 diabetes mellitus: a systematic review and meta-analysis with over 96,000 patients-years

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Disclosures: Authors have nothing to disclose
Declaration of interest

- I have nothing to declare
Declaration of interest

- Authors declare no competing interests
Genetic variants of PCSK9 demonstrate its importance in regulating LDL levels

PCSK9 Gain of Function (GoF) = **Less** LDL-Rs\(^{1,3,5}\)

PCSK9 Loss of Function (LoF) = **More** LDL-Rs\(^{1,4,5}\)

Mutations in the human PCSK9 gene that lead to a loss of PCSK9 function are found in 1–3% of the population\(^{1–3}\)

Reduction of LDL-C and cardiovascular events with PCSK9 inhibitors and statins

Ference BA et al. Eur Heart J 2017; August 14 (In press)
PCSK9 loss-of-function genetic variant is associated with pre-diabetes and diabetes.
High cholesterol content in pancreatic beta cell trigger impaired insulin secretion

Inclusion criteria

(i) Study design: phase 2 or 3 RCT;

(ii) Study population: participants with familial or non-familial hypercholesterolemia;

(iii) Study intervention: participants in the treatment group received PCSK9i versus control group, who received placebo with or without other lipid-lowering therapy;

(iv) Treatment duration: 12 weeks or longer.
**Identification**
- Records identified through database searching  
  \( n = 133 \)
- Additional records identified through other sources  
  \( n = 3 \)

**Screening**
- Records after duplicates removal  
  \( n = 100 \)

**Elegibility**
- Records screened  
  \( n = 100 \)
- Records excluded  
  \( n = 2 \)
- Full-text articles excluded, with reasons  
  \( n = 39 \)
  - No incident data of DM  
  - Study design publication  
  - Duplicate data  
  - No RCT  
  - Phase 1 RCT  
  - RCT with other aims  
  - Homozygous for FH

**Inclusion**
- Full-text articles assessed for eligibility  
  \( n = 59 \)
- Studies included in qualitative synthesis  
  \( n = 20 \)

**Studies included in quantitative synthesis** 
(meta-analysis)  
\( n = 20 \)
PCSK9i associated with higher HbA1c by 0.032% (0.011 - 0.050) - weighted mean difference
PCSK9i associated with higher fasting plasma glucose by 1.88 mg/dL (0.91 to 2.68) - weighted mean difference
What about PCSK9 inhibitors and the risk of incident type 2 diabetes?
PCSK9i did not increase the risk of incident type 2 diabetes [mean follow-up 1.5 year]
Change in LDL-C (per 10 mg/dL) -2.35% (95% CI -4.41 to -0.29%)  p-value=0.029*
Duration of treatment (per month)  $+0.51\%$ (95\% CI 0.06 to 0.95\%)  \hspace{1cm} p$-value=0.026$^*$
Limitations

- Study-level nature
- Rarity of the clinical outcome
- Relatively short-term follow-up
- Lack of information on the concomitant use and up or down-titration of antidiabetic medications
Conclusions

- At short-term, PCSK9i therapy favors a small, but significant increase in plasma glycaemia and HbA1c.
- The effect on type 2 diabetes risk is only apparent among individuals who achieved very low levels of LDL-C after treatment.