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To cite this version:
Antoine Rimbert, Sarra Smati, Wieneke Dijk, Cedric Le May, Bertrand Cariou. Genetic Inhibition of PCSK9 and Liver Function. JAMA Cardiology, 2020, 10.1001/jamacardio.2020.5341 . hal-03100949

HAL Id: hal-03100949
https://nantes-universite.hal.science/hal-03100949
Submitted on 11 Apr 2022

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Genetic Inhibition of PCSK9 and Liver Function

Inhibition of proprotein convertase subtilisin/kexin type 9 (PCSK9) with anti-PCSK9 monoclonal antibodies (alirocumab and evolocumab) or with small-interfering RNAs (inclisiran) lowers plasma low-density lipoprotein cholesterol (LDL-C) levels, a major risk factor for the development of atherosclerotic cardiovascular disease (ASCVD).\(^1\),\(^2\) So far, the pharmacologic inhibition of PCSK9 presents with a favorable safety profile, but longer-term safety remains to be proven. Studies in preclinical models and in humans have suggested a potential link between PCSK9 deficiency and the risk of nonalcoholic fatty liver disease (NAFLD),\(^3\),\(^4\) a spectrum of progressive liver diseases ranging from simple steatosis to fibrosis that can lead to cirrhosis and hepatocellular carcinoma. Notably, it has been shown that PCSK9 knockout mice are more prone to develop severe hepatic steatosis and fibrosis when receiving a high-fat diet.\(^3\)

This study aims to study the associations of the lifelong genetic inhibition of PCSK9 with plasma liver enzymes and NAFLD by using the loss-of-function variant PCSK9-p.Arg46Leu as a genetic instrument. For comparison, we used 2 variants in PNPLA3 and TM6SF2, known to be involved in the pathogenesis of NAFLD.\(^5\)

**Methods**

**Approval.** Both the UK Biobank and the Electronic Medical Record and Genomics (eMERGE) cohort have obtained regulatory approvals, and all participants provided written informed consent. Because the data were publicly available, we did not obtain specific approval for this study.

**UK-Biobank Data Sets.** Genetic associations with biologic traits (plasma circulating liver enzymes) in the UK-Biobank cohort were extracted from the second-round results (released August 1, 2018) by the Nealelab (see description in http://www.nealelab.is/uk-biobank/). These data were obtained from 361194 participants (19474 women and 167020 men) of the UK-Biobank cohort (https://www.ukbiobank.ac.uk).

**The eMERGE Cohort.** Genetic association with risk of NAFLD was assessed by using summary data from the study published by Namjou et al\(^5\) in 2019 that studied 9677 individuals (1106 cases and 8571 controls) from the eMERGE cohort (https://emerge-network.org).

**Results**

Using data from the UK-Biobank, we show that the variant PCSK9-p.Arg46Leu is not associated with higher levels in circulating liver enzymes (alanine aminotransferase [ALT], mean [SD] \(β, 0.071 [0.123] \) U/L; \(P = .57\), aspartate aminotransferase [AST], mean [SD] \(β, 0.045 [0.095] \) U/L; \(P = .63\), \(γ\)-glutamyltransferase (GGT) (mean [SD] \(β, 0.22 [0.12] \) U/L; \(P = .10\)).

![Figure. Association of PCSK9-p.Arg46Leu With Plasma Liver Enzymes and Nonalcoholic Fatty Liver Disease (NAFLD)](https://example.com/figure.png)

**A.** Markers of liver function (plasma ALT, AST, and GGT) as a function of PNPLA3-p.Ile148Met (blue), TM6SF2-p.Glu167Lys (orange), and PCSK9-p.Arg46Leu variants (dark blue) in more than 300000 individuals from UK-Biobank as \(β\) coefficients per alternative allele compared with noncarriers (horizontal bars show standard error). **B.** Odds ratio for NAFLD as a function of PNPLA3-p.Ile148Met (blue), TM6SF2-p.Glu167Lys (orange), and PCSK9-p.Arg46Leu variants (dark blue) compared with noncarriers from the eMERGE study (1106 cases vs 8571 controls). The effects are shown as odds ratio per alternative allele. Horizontal bars depict maximum and minimum values.
In contrast, we confirm that the genetic variants PNPLA3-p.Ile148Met and TM6SF2-p.Glu167Lys, which have been robustly linked to NAFLD, are significantly associated with higher ALT and AST levels in the same cohort (Figure, A). Of note, statistical associations of PNPLA3 and TM6SF2 variants are weaker for GGT plasma levels (mean [SD] β, −0.004 [0.379] U/L; P = .99, in more than 340,000 individuals [Figure, A]).

We further demonstrate that PCSK9-p.Arg46Leu is not associated with NAFLD in the eMERGE cohort (P = .61; odds ratio, 0.89; 95% CI, 0.55-1.42), whereas PNPLA3-p.Ile148Met and TM6SF2-p.Glu167Lys are indeed associated with an increased risk for NAFLD (PNPLA3-p.Ile148Met, P = 1.7 × 10−20; odds ratio, 1.79; 95% CI, 1.58-2.02; and TM6SF2-p.Glu167Lys, P = .04; odds ratio, 1.24; 95% CI, 1.01-1.52).

Discussion | In contrast to data published in 2017 and 2019,3,4 this study clearly demonstrates that the genetic inhibition of PCSK9 in humans is not associated with an increased risk of NAFLD in 2 large cohorts. These findings are consistent with the safety data of randomized clinical trials with anti-PCSK9 monoclonal antibodies and inclisiran, which have found no significant changes in liver enzymes.1,2

Hepatic adverse effects have been major concerns of other intracellullar lipid-lowering therapies, such as mipomersen and lomitapide, which reduce LDL-C by blocking the hepatic secretion of apolipoprotein B (ApoB) and very low-density lipoproteins. In contrast, PCSK9 inhibitors and statins reduce LDL-C by affecting the LDL receptor pathway. In accordance with a neutral effect of PCSK9 inhibition on liver function, statins do not worsen NAFLD and even might exert a beneficial effect on NAFLD progression to NASH.6 These data suggest that lipid-lowering drugs targeting ApoB secretion present a risk for NAFLD development but that molecules targeting ApoB catalolism do not. As such, the data presented here are reassuring for the hepatic safety of long-term intracellular PCSK9 inhibition and support the potential use of PCSK9 inhibitors in patients with NAFLD who are at increased risk of ASCVD.

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Accepted for Publication: August 27, 2020.

Published Online: November 4, 2020. doi:10.1001/jamacardio.2020.5341

Author Contributions: Dr Cariou had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Rimbert, Smati, Le May, Cariou.

Acquisition, analysis, or interpretation of data: Rimbert, Dijk.

Drafting of the manuscript: Rimbert, Dijk, Cariou.

Critical revision of the manuscript for important intellectual content: Rimbert, Smati, Dijk, Le May.

Statistical analysis: Rimbert.

Obtained funding: Le May, Cariou.

Administrative, technical, or material support: Cariou.

Supervision: Le May, Cariou.

Conflict of Interest Disclosures: Dr Cariou reported grants, personal fees, and nonfinancial support from Amgen and Sanofi; grants from Pfizer; grants and personal fees from Regeneron; personal fees and nonfinancial support from Merck (MSD); and personal fees from Akcea outside the submitted work. No other disclosures were reported.

Funding/Sponsor: Dr Rimbert is supported by a postdoctoral fellowship grant from the Institut de France-Fondation Lefoulou-Delalande. This work was supported by the French national research project CHOPIN (Cholesterol Personalized Innovation) funded by the Agence Nationale de la Recherche (ANR-16-RHUS-0007) and coordinated by the CHU of Nantes.

Role of the Funder/Sponsor: The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Additional Contributions: We thank all participants of these different cohorts and authors that made genetic and genomic data available. We thank Bahram Namjou, MD, Center for Autoimmune Genomics and Etiology (CAGE), Cincinnati Children’s Hospital Medical Center, Cincinnati, Ohio, who kindly shared genetic data from his association study.5 No compensation was received from a funding source for these contributions. We acknowledge the use of data from UK-biobank cohort (https://www.ukbiobank.ac.uk) and from eMERGE cohort (https://emerge-network.org).


