**SUPPLEMENTARY INFORMATION**

**A register-based cohort study on the effectiveness and Safety of anti-PCSK9 treatment in persons with hyperlipidemia**

Authors: Michael Asger Andersen1, Anne Helms Andreasen2, Lia Evi Bang3, Espen Jimenez Solem1, and Tonny Studsgaard Petersen1

1 Department of Clinical Pharmacology, Copenhagen University Hospital - Bispebjerg and Frederiksberg Hospital, Copenhagen, Denmark

2 Center for Clinical Research and Prevention, Copenhagen University Hospital - Bispebjerg and Frederiksberg, Copenhagen, Denmark

3 Department of Cardiology, Copenhagen University Hospital - Rigshospitalet, Copenhagen, Denmark

## Content



## Supplementary Methods

### *WebI*

SAP Web Intelligence (WebI) is a tool that is integrated into the EPIC electronic medical record system. It allows users to create custom reports and analyses of data stored in the EPIC Clarity database. With WebI, users can build queries using a wide range of predefined variables and filters. WebI and can generate reports in a variety of formats including tables, graphs, and maps.

### *Mgcv*

In the present study, we used generalized additive models (GAMs) as implemented in the mgcv package in R to analyze the data. GAMs are a flexible class of regression models that allow for the incorporation of non-linear relationships between the response variable and predictor variables. They are particularly useful for modeling complex, non-linear trends in data and can be seen as an extension of linear regression models. The mgcv package is a popular and widely used tool for fitting GAMs, and it provides a range of options for specifying and estimating model parameters. Overall, the use of GAMs and the mgcv package allowed us to accurately model and analyze the data, leading to insights and conclusions that would not have been possible with traditional linear regression models. To check the model fit of a GAM fitted with the mgcv package, the gam.check() function can be used. This function produces a plot that displays the residuals of the model, as well as a number of diagnostic plots that can be used to assess the model fit. The gam.check() function produces a plot that displays the residuals of the model on the left hand side, and a number of diagnostic plots on the right hand side. The residuals plot shows the residuals of the model as a function of the fitted values. Ideally, the residuals should be randomly distributed around zero, with no discernible pattern. If there is a pattern present in the residuals plot, it may indicate that the model is not adequately fitting the data. In mgcv, most smooths are required to satisfy a sum-to-zero identifiability constraint, which allows for the inclusion of an intercept in the model, especially when the model includes factor parametric terms. This constraint centers the smooth around 0 on the axis. The 0 line represents the average value of the response (or the reference levels for factor parametric terms) on the link scale.

Negative values on the axis indicate that the effect of the covariate causes the response to be below average, while positive values indicate that the response is above average, all while taking into account the other estimated model terms.

*Definitions*

In this study, we used the International Classification of Diseases (ICD) Tenth Revision (ICD-10) codes, the Anatomical Therapeutic Chemical (ATC) codes, and the Nomenclature for Properties and Units (NPU) codes to categorize diagnoses, conditions, medications, and laboratory measurements, respectively. ICD-10 codes are standardized codes used for medical billing and record-keeping purposes. They are used to assign unique codes to every diagnosis, symptom, and procedure recorded in healthcare settings. ATC codes, on the other hand, are a classification system for medications, developed by the World Health Organization (WHO). They are used to classify drugs according to their therapeutic, pharmacological, and chemical characteristics. NPU codes, meanwhile, are used for assigning laboratory measurements. In this study, we used these codes to classify diagnoses and conditions, medications. The use of ICD-10, ATC, and NPU codes allowed us to accurately and consistently record and analyze the data from the laboratory, ensuring the reliability and validity of the results.

**Atherosclerotic cardiovascular disease (ASCVD):**

| Disease | Diagnostic code: | Operation code: |
|---|---|---|
| Coronary heart disease (CHD) | I20, I21, I23, I24 and I25 | KFNA, KFNB, KFNC, KFND, KFNE, KFNH20, KFNF, KFNG00, KFNG02, KFNG05 and KFNG30 |
| Atherosclerotic cerebrovascular disease | I630, I631, I632, I633, I634, I635, I638, I639, I66, I672, G458 and G459 | KAAL10 and KAAL11 |
| Peripheral artery disease (PAD) | I65, I70, I713, I714, I715, I716, I739A, I739C, I741B, I742B, I743B, I744B, I745B, K550H and K551A | KPAF21, KPAK21, KPAF20, KPCE, KPCF, KPCH, KPCN, KPCP, KPDE, KPDF, KPDH, KPDN, KPDP, KPEE, KPEF, KPEH, KPEN, KPEP, KPFE, KPFF, KPFH and KPFN |

**Hypercholesterolemia criteria:**

| Disease: | Diagnostic code: |
|---|---|
| Hypercholesterolemia | E780A, E780C, E780D, E780E, E781, E782, E783, E784 and E785 |

**Familial hypercholesterolemia (FH):**

| Disease | Diagnostic code: |
|---|---|
| FH (non-specific) | E780B |
| Homozygote FH | E780B2 |
| Heterozygote FH | E780B1 |

**Procedures prior to inclusion:**

| Procedure: | Procedure code: | Operation code: |
|---|---|---|

| | | |
|---|---|---|
| Percutaneous coronary intervention (PCI) | None | KFNG and KZFFX01 |
| Coronary artery bypass grafting (CABG) | None | KFNA, KFNB, KFNC, KFND, KFNE, KFNH20 and KFNF |
| Angioplasty and stent placement | None | KPAN, KPAP, KPBN, KPBP, KPCN, KPCP, KPDN, KPDP, KPEN, KPEP, KPFN and KPFP |
| Endarterectomy | None | KPEF, KPAF, KPBF, KPCF and KPDF |
| Thrombectomy | None | KAAL11, KFAB10, KPAE10, KPAE25, KPAE30, KPAE99, KPAU74, KPBE10, KPBE20, KPBE30, KPBE99, KPCE30, KPCE40, KPCE99, KPDE10, KPDE30, KPDU74, KPEE10, KPEE11, KPEE12, KPFE10, KPFE30, KPHE22, KPHE23, KPHE25, KPHE30, KPHE31 and KPHE99 |

**Comorbidities prior to inclusion:**

Cardiovascular comorbidities:

| **Disease:** | **Diagnostic code:** | **Operation code:** | **ATC-code:** |
|---|---|---|---|
| Diabetes (DM) | E10, E11 and N083 | None | A10 |
| Diabetes target organ damage | H360, E103, E113, G590, E104, E114, N083, E102 and E112 | None | None |
| Chronic kidney disease (CKD) | E102, E112, I120, N03, N04, N05, N06, N07, N08, N11, N12, N162, N163, N164, N182, N183, N184, N185, N26 and Q61 | None | None |
| Chronic obstructive pulmonary disease | J43 and J44 | None | None |
| Hypertension | I10, I11, I12, I13 and I15 | None | C07, C08, C09, C03A, C03B, C03C, C03EA, C03EB, C02L, C10BX, C03DA, C03DB, C03E, C02DB, C02DC, C02DD, C02DG, C02A, C02B and |

| | | | |
|---|---|---|---|
| | | | C02C (excluding C02AC02) |
| Heart failure | I099A, I110, I130, I132, I420 and I50 | None | None |
| Cancer, ex. non-melanoma skin cancer | C00, C01, C02, C03, C04, C05, C06, C07, C08, C09, C10, C11, C12, C13, C14, C15, C16, C17, C18, C20, C21, C22, C23, C24, C25, C26, C30, C31, C32, C33, C34, C37, C38, C39, C40, C41, C43, C45, C46, C47, C48, C49, C50, C51, C52, C53, C54, C55, C56, C57, C58, C60, C61, C62, C63, C64, C65, C66, C67, C68, C69, C70, C71, C72, C73, C74, C75, C76, C77, C78, C79, C80, C81, C82, C83, C84, C85, C86, C88, C90, C91, C92, C93, C94, C95 and C96 | None | None |
| Liver disease | K70, K71, K72, K73, K74, K75, K76, K77, B15, B16, B17, B18, B19 and B581 | None | None |
| Rheumatoid arthritis | M05, M060, M069 and M080 | None | None |

**Laboratory values:**

| Biomarker: | Laboratory code: |
|---|---|
| Low-density lipoprotein cholesterol (LDL-C) | NPU01568, NPU10171, AAB00101, AAB00102 and DNK35308 |
| High-density lipoprotein cholesterol (HDL-C) | NPU01567 and NPU10157 |
| Total cholesterol (TC) | NPU18412 and NPU01566 |
| Triglycerides (TGs) | NPU04094 and NPU03620 |
| Lipoprotein a (Lp[a]) | NPU21687, NPU19840 and NPU58475 |
| Apolipoprotein B (Apo-B) | NPU22299 and NPU19697 |

**Cholesterol-lowering drug group classification:**
Contains the ATC-codes used to define the cholesterol-lowering drug groups used in multiple endpoints.

| Drug group: | ATC-code: |
|---|---|
| Statin | C10AA, C10BA01, C10BA02, C10BA03, C10BA04, C10BA05, C10BA06, C10BA07, C10BA08, C10BA09 and C10BX |
| PCSK9i | C10AX13 and C10AX14 |
| Ezetimibe | C10AX09, C10BA02, C10BA05, C10BA06 and C10BA10 |
| Bile acid sequestrants | C10AC01, C10AC02, C10AC03 and C10AC04 |
| Fibrates | C10AB, C10BA03, C10BA04 and C10BA09 |