DISEASE REGISTRY REPORT

Compound(s): Not applicable

Hypercholesterolemia Diagnosis, Treatment Patterns and Target Achievement in Clinical Practice in Germany in Patients with Familial Hypercholesterolemia

Registry number: DIREGL07803

Registry name: HYDRA-FH

Registry initiation date [date first patient in (FPI)]: 20-FEB-2017

Registry completion date [last patient completed/last patient out (LPO)]: 18-JUN-2020

Registry design: National, multicenter, non-interventional study with focus on therapeutic approaches; prospective longitudinal study: disease registry with follow-ups at 12 and 24 months**.**

Report date: 18-MAY-2021

This registry was performed in compliance with the guidelines for Good Epidemiology Practice. This report has been prepared based on the publication 'Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) – Guidelines for reporting observational studies – Ann Intern Med. 2007'.

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SYNOPSIS

Title of the registry:	Hypercholesterolemia Diagnosis, Treatment Patterns and Target Achievement in Clinical Practice in Germany in Patients with Familial Hypercholesterolemia: HYDRA-FH DIREGL07803
Design:	National, multicenter, non-interventional Prospective longitudinal study: disease registry with follow-ups at 12 and 24 months
Objectives:	**Primary objective**: Documentation of lipid target values in patients with definite familial hypercholesterolemia in clinical practice in Germany. **Secondary objectives:** 1. The documentation of lipid profiles and lipid-lowering therapy in clinical practice in Germany 2. The validation of the applicability of the current guidelines for the treatment of dyslipidemia in secondary prevention in clinical practice in Germany. 3. The documentation of drug utilization pattern in secondary prevention in clinical practice in Germany. 4. The documentation of cardiovascular and cerebrovascular events over a follow-up period of 2 years.
Participants as of 30-	**Countries:** Germany **Number of planned sites**: 100 **Number of planned patients**: 500 **Site Settings:** Sites that routinely treat patients with definite familial hypercholesterolemia in Germany in order to represent the clinical care routine of this patient group as realistically as possible. A list of participating sites is provided in section 1.8. **Patient eligibility criteria:** - ≥ 18 years of age and capable of giving informed consent - Diagnosis of definite familial hypercholesterolemia - Written informed consent - No concurrent participation in a clinical trial Apart from concurrent participation in a clinical trial, no explicit exclusion criteria were provided to avoid systematic bias in the inclusion of suitable patients and to present the clinical treatment routine without restrictions.
Scientific committee	Dr Anselm Gitt, Ludwigshafen (Chair) Prof Dr Klaus Parhofer, München Prof Dr Ulrich Laufs, Homburg Prof Dr Winfried März, Mannheim Prof Dr Nikolaus Marx, Aachen
Publications (reference):	To date, publications and abstracts resulting from the registry were not prepared. Statement about initiatives for any local communication in participating countries/regions: Not applicable.
Introduction - Background/rationale:	Familial hyperlipidemia is usually insufficiently diagnosed in clinical routine, although it is a highly prevalent genetic dyslipidemia (1:200), which is a significant risk factor for early CAD. The ESC and EAS guidelines [1] place particular emphasis on the use of the MedPed and WHO criteria for the clinical

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	diagnosis of heterogeneous familial hyperlipidemia to identify patients at high risk of subsequent cardiovascular disease and requiring lipid-lowering therapy. Considering the widely documented deficit in the achievement of the target values of current lipid-lowering therapies and the still stricter target values of the international guidelines for the treatment of dyslipidemia, an expansion of the therapy options is urgently needed. To obtain an insight into the current treatment situation of patients with FH, the multicenter HYDRA-FH registry study was initiated to document the clinical characteristics of patients with definite familial hypercholesterolemia in everyday clinical practice in Germany. In addition, the lipid profiles, lipid-lowering therapy, and lipid target achievement in the course of treatment were documented over a period of 2 years.
Methodology:	**(a) Site and patient selection:** Site selection: Sites were selected that routinely treated patients with definite familial hypercholesterolemia in Germany in order to represent the clinical care routine of this patient group as realistically as possible. Patient selection: The inclusion criteria were limited to the presence of definite (diagnosed) familial hypercholesterolemia in adult patients (≥ 18 years) and the written informed consent of the patient. Apart from concurrent participation in a clinical trial, no explicit exclusion criteria were provided to avoid systematic bias in the inclusion of suitable patients and to present the clinical treatment routine without restrictions. To avoid systematic bias, suitable patients were included consecutively in the study sites. The study design should reflect the treatment situation of these patients under real conditions as closely as possible. Within the framework of this non-interventional observational study, all therapies that were approved for the treatment of this patient group could be applied. Treatment was solely at the discretion of the treating physician; the study did not provide explicit treatment guidelines. **(b) Data collection:** Data was collected electronically via eCRF. **(c) Safety data collection:** Since the study was designed as a disease registry, treatment with individual drugs was not investigated. Only adverse drug reactions (ADRs) were therefore collected. Adverse drug reactions were documented by the site investigator on an adverse drug reaction form (=ISI form) and then sent to the external service provider (IHF GmbH) within one working day. IHF GmbH transferred the contents of the adverse drug reaction form (ISI form/source document) in English within one working day to a separate ISI form, which was then sent within one working day together with any source document to the pharmacovigilance department at Sanofi. This procedure also applied to ADRs discovered at the time of an audit by IHF GmbH or during a telephone call to the site. All ADRs that were presumed to be related to drugs from Sanofi-Aventis Deutschland GmbH, Winthrop Arzneimittel GmbH, Zentiva Pharma GmbH or Genzyme GmbH were forwarded to Sanofi and entered into the Sanofi pharmacovigilance database. Cases subject to reporting were reported to the authorities by Sanofi (see Appendix II). **(d) Data management, review, validation:** All data management processes are described in detail in the Data Management Plan (see Appendix III, section 3.5). **(e) Statistical considerations:** Due to the observational design of the registry, all collected parameters were evaluated descriptively. Analysis sets: The statistical analyses include the data of all patients included in the study (i.e. all patients who have met the inclusion criteria and have given written consent to participate). If a patient cancels the study participation prematurely, their data are included in the analyses documented before the discontinuation of participation. The **Baseline Analysis Set (BAS**) consists of all patients who meet all inclusion criteria according to

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	the observation plan, have at least one further documented entry in the first documentation section of the eCRF and whose Baseline CRF is signed. The BAS is used to analyses the data collected in the context of the initial documentation (interim analysis of baseline data). The BAS was used to evaluate the baseline data. The **Full-Analysis Set (FAS**) consists of all patients of the BAS with documented lipid parameter LDL-C and lipid-lowering therapy at the time of the index event, 12 month follow-up and 24 month follow-up and both follow-up CRFs signed. The FAS was used to evaluate the longitudinal data. The above described analysis sets were extended post-hoc (based on the data obtained in the study; goal: to include a larger proportion of patients in the final analyses): The **Extended Baseline Analysis Set (EBAS)** consists of all patients who meet all inclusion criteria according to the observation plan. The EBAS was used to evaluate the baseline data. The **Extended Analysis Set (EAS)** consists of all patients of the EBAS with documented LDL-C values at the time of the index event and at 12-months follow-up. The acceptable time window for follow-ups was extended to ± 4 months (in contrast to ± 3 months in the FAS). The EAS was used to evaluate the longitudinal data. Variables and evaluation criteria: All variables documented in the eCRF were evaluated in a descriptive report. Key variables were - Lipid target achievement as measured by the reduction of LDL cholesterol over time (baseline to 12-M FU to 24-M-FU); absolute and relative reduction of LDL cholesterol at 12 and 24 months following baseline (defined as (i) LDL < 70mg/dl and (ii) LDL < 70mg/dl or 50% reduction in LDL according to baseline LDL value). - Changes in other relevant lipid values over time; absolute and relative change of total cholesterol, HDL cholesterol, and triglycerides at 12 and 24 months following baseline. - Non-drug lipid lowering therapy in clinical routine (life style and nutrition); percentage of patients with non-drug lipid-lowering therapy over time (baseline, 12-M-FU, 24-M-FU) - Lipid-lowering pharmacotherapy in clinical routine; percentage of patients with lipid-lowering pharmacotherapy over time (baseline, 12-M-FU, 24-M-FU) - Drug utilization patterns in secondary prevention; percentage of patients with pharmacotherapy over time (baseline, 12-M-FU, 24-M-FU) - Cardiovascular and cerebrovascular events over time; percentage of patients with complications at baseline; percentage of patients with non-fatal events since baseline (12-M-FU, 24-M-FU) The following groupings were chosen: - Sex (male, female) - Age (18-65 years, >65 years) Data analyses: Categorical variables were presented as absolute and relative frequencies. Continuous variables were presented as absolute number n, mean, standard deviation, median, 1st and 3rd quartile, 1st and 99th percentile. No formal statistical tests were performed. The following graphical analyses were provided: - Distributions of lipid values are analyzed via histograms and kernel density curves (pre-post comparison, if necessary group comparisons) - Lipid lowering medication (single and combination therapies) are analyzed over time. graphically analyzed using bar charts (stacked) All statistical analyses as well as data handling processes (i.e. categorizations, calculation of derived variables, laboratory parameters, or pre-post differences etc.) are described in detail in the Statistical Analysis Plan (see Appendix III, section 3.2). No imputations were made to replace missing data. All available data was displayed. For time-to-event analyses, the patient data was censored on the basis of their last known follow-up on the right (i.e. in

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	the case of premature drop-out, the last existing value was used).
Registry period:	This report includes patient data reported to the HYDRA-FH Registry as of cutoff 30-NOV-2020.
RESULTS – Part I	The following result are based on the analysis sets BAS and FAS (as defined in section Methodology).

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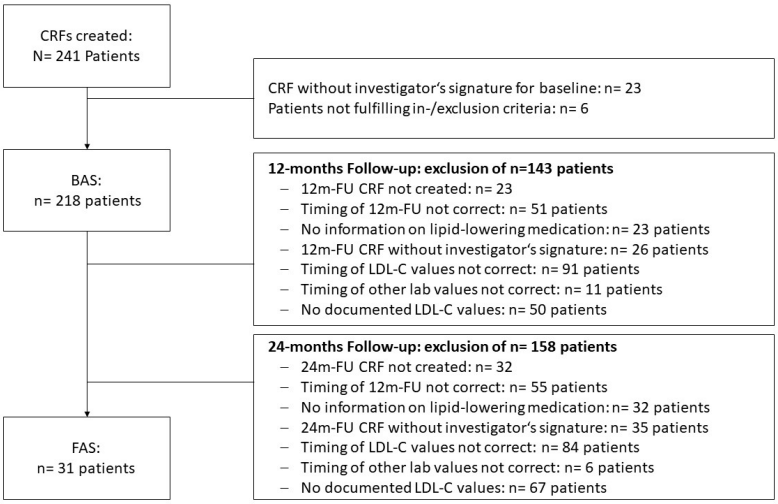
Participants (actual):	**(a) Overall participation status:** The registry was conducted in Germany. 35 sites participated in the registry. 218 patients were included in the baseline analyses. 31 patients were included in the full analysis set (FAS) to evaluate the longitudinal data. **(b) Participation per period of the registry:** The following flow chart illustrates the number of patients at each stage of the registry, including the number of patients lost to follow-up and the amount of missing data for the variables of interest (i.e. lipid profiles):  Of 218 patients in baseline, complete follow-up data (for both 12- and 24-months follow-up concurrently) were available in 31 patients. Overall, 187 patients were excluded from the longitudinal analyses: - 29 patients with incomplete data for 12-months follow-up - 44 patients with incomplete data for 24-months follow-up - 114 patients with incomplete data for both 12- and 24-months follow-up
Participant characteristics and primary analyses:	**(a) Descriptive data** <u>Characteristics of registry physicians</u>**:** Type of sites were as follows (see BAS tables CTR-1 to -5 in Appendix II): - Hospital, n= 2; - Joint practice, n= 8 - Single practice, n= 16 - Medical care center, n= 1; - No information provided, n= 8 <u>Characteristics of registry patients</u>**:** The Baseline Analysis Set (BAS) consisted of 218 documented patients. Duration of enrolment was on average 143.6 days (SD: 118.9 days). On average, 6.2 patients (SD: 6.2; MD: 3) were enrolled per study site. The following table shows the demographic and clinical characteristics of the registry patients at

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baseline (BAS):

Characteristics	N= 218
Sex – *no. of participants (%)*	
Male	129 (59.2)
Female	89 (40.8)
Mean age *(SD) - yr*	60.9 (13.7)
Cardiovascular History – *no. of participants (%)*	
Coronary heart disease,	119 (54.6)
PCI	73 (33.5)
Acute coronary syndrome	42 (19.3)
Aortocoronary bypass	29 (13.3)
Stroke	12 (5.5)
TIA	3 (1.4)
Comorbidities and Risk Factors – *no. of participants (%)*	
Arterial hypertension	162 (74.3)
Diabetes mellitus	91 (41.7)
Heart failure	50 (22.9)
Heart valve disease	34 (15.6)
Depression	29 (13.3)
Renal insufficiency	24 (11.0)
Stable angina pectoris	22 (10.1)
Peripheral arterial occlusive disease	17 (7.8)
Atrial fibrillation	12 (5.5)
COPD	12 (5.5)
Carcinoma	9 (4.1)
Device implantation	5 (2.3)
Deep vein thrombosis	2 (0.9)
Pulmonary embolism	1 (0.5)
Phenotypic Findings – *no. of participants (%)*	
Xanthelasma	45 (20.6)
Xanthomas	25 (11.5)
Arcus cornealis	20 (9.2)
Functional mutation in LDLR, apoB or PCSK9 gene	19 (8.7)
Age at initial diagnosis, *mean (SD)*	46.4 (10.5)
Family History – *no. of participants (%)*	
Family history of elevated cholesterol levels	136 (62.4)
Family history of CHD	120 (55.1)
Family history of MI	107 (49.1)
Family history of cerebral/vascular disease	51 (23.4)
Family history of tendon xanthomas	19 (8.7)
Family history of arcus cornealis	8 (3.7)
Lipid Apheresis Therapy – *no. of participants (%)*	11 (5.1)
Body-mass Index, *mean (SD)*	28.4 (4.5)

More details on patient characteristics at baseline (incl. stratification by sex [male, female] and age [18-65 years, >65 years] are given in Appendix II (BAS; tables E1, E2, B1 – B17).

Follow-up duration (i.e. time from baseline to follow-up in days):
With regard to the Baseline Analysis Set (taking into account all patients regardless of completeness of follow-up data; n= 218 patients) time to follow-up was on average 367.7 days (SD: 217.8) for the 12-months follow-up and 749.9 days (SD: 45.5) for the 24-months follow-up.

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A complete descriptive report of follow-up data for this population is given in Appendix II (12-months follow-up: tables 1FU1 – 1FU9, BAS; 24-months follow-up: tables 2FU1 – 2FU9, BAS).

(b) Primary analyses: Lipid Target Achievement
The Full Analysis Set (FAS) consisted of 31 patients with complete (LDL) data on both 12-months and 24-months follow-up.

Follow-up duration (i.e. time from baseline to follow-up in days):
With regard to the Full Analysis Set (taking into account all patients with complete data on LDL cholesterol and correct timing for both follow-ups; n= 31) time to follow-up was on average 380.2 days (SD: 13.6) for the 12-months follow-up and 758.8 days (SD: 28.2) for the 24-months follow-up.

A complete descriptive report of follow-up data for this population is given in Appendix II (12-months follow-up: tables 1FU1 – 1FU9, FAS; 24-months follow-up: tables 2FU1 – 2FU9, FAS).

Distribution of LDL cholesterol values (mg(dl)**:**
The following table shows mean LDL cholesterol values at baseline, 12-months follow-up and 24-months follow-up (FAS):

	Mean	Standard deviation	Median	1st Quartile	3rd Quartile	N
LDL-Cholesterol [mg/dl]	114.2	42.5	103	87	149	31
LDL-Cholesterol @12MFU	99.8	39.1	94	84	102	31
LDL-Cholesterol @24MFU	100.2	43.5	89	81	111	31

More details on LDL cholesterol values (incl. stratification by sex [male, female] and age [18-65 years, >65 years] are given in Appendix II (FAS; tables CHOL-1 – CHOL-3).

The following figure illustrates the distribution of LDL cholesterol values (mg/dl) at baseline, 12-months and 24-months follow-up (FAS):

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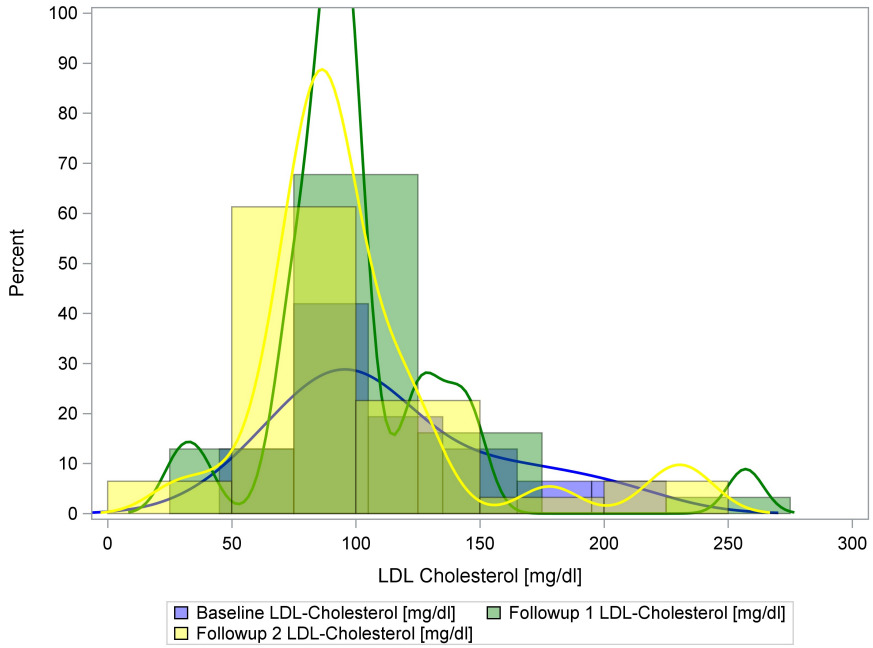

Target achievement of LDL cholesterol values (mg/dl):
Data were analysed according to lipid target achievement as measured by the reduction of LDL cholesterol over time (baseline to 12-M FU to 24-M-FU); absolute and relative reduction of LDL cholesterol at 12 and 24 months following baseline (FAS).

Target ranges were set as follows (see also SAP, section 7.2; Appendix III, section 3.2):

- Within target range: < 70mg/dl
- Above target range: ≥ 70 mg/dl

Within target range (LDL <70 mg/dl) were

- At 12-months follow-up: n= 2 patients (6.4%)
- At 24-months follow-up: n= 3 patients (9.7%)

Above target range (LDL ≥ 70 mg/dl) were

- At 12-months follow-up: n= 29 patients (93.6%)
- At 24-months follow-up: n= 28 patients (90.3%)

According to guidelines applicable at the time of data collection (see References [1]), target achievement was defined as LDL< 70mg/dl or 50% of reduction in LDL (see also SAP, section 6.1.1; Appendix III, section 3.2).

Within this target range (LDL< 70mg/dl or 50% of reduction in LDL) were:

- At 12-months follow-up: n= 2 patients (6.4%; 95% CI: -0.03, 0.16)
- At 24-months follow-up: n= 4 patients (12.9%; 95% CI: 0.00, 0.25)

Above this target range (LDL< 70mg/dl or 50% of reduction in LDL) were:

- At 12-months follow-up: n= 29 patients (93.6%)

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- At 24-months follow-up: n= 27 patients (87.1%)

More details on LDL-C target achievement (target ranges of LDL cholesterol at baseline and follow-up; incl. stratification by sex [male, female] and age [18-65 years, >65 years] are given in Appendix II (FAS; tables PZ-5 to PZ-10).

The following table shows lipid target achievement (LDL cholesterol; absolute and relative difference from baseline) in registry patients with complete data (FAS):

	Mean	Standard deviation	Median	1st Quartile	3rd Quartile	N
Absolute difference (Baseline -> FU 12-15 Month) LDL-C [mg/dl]	-14.4	30.9	-6	-21	-2	31
Relative difference (Baseline -> FU 12-15 Month) LDL-C [%]	-9.3	23.1	-5	-20	-2	31
Absolute difference (Baseline -> FU 24-27 Month) LDL-C [mg/dl]	-14.0	42.5	-10	-25	4	31
Relative difference (Baseline -> FU 24-27 Month) LDL-C [%]	-7.9	31.2	-10	-23	4	31

The 95% confidence interval for the mean relative difference from baseline to 12-months follow-up was -17.8, -0.9 (p= 0.03201).
The 95% confidence interval for the mean relative difference from baseline to 24-months follow-up was -19.3, -3.6 (p= 0.17126).

The following figure illustrates the distribution of LDL cholesterol values (mg/dl; absolute and relative difference from baseline) 12-months and 24-months follow-up; in registry patients with complete data (FAS):

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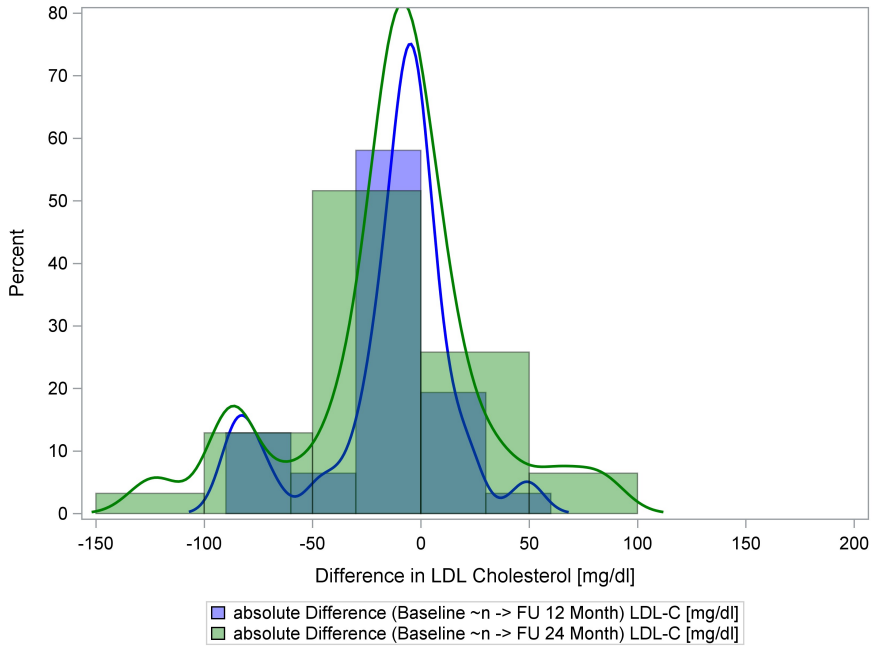

More details on LDL-C target achievement (LDL cholesterol; absolute and relative difference from baseline; incl. stratification by sex [male, female] and age [18-65 years, >65 years] are given in Appendix II (FAS; tables PZ1 – PZ4).

More details on LDL-cholesterol values (latest data available) at baseline and follow-up (incl. stratification by sex [male, female] and age [18-65 years, >65 years] are given in Appendix II (baseline: FAS; tables B13-5 – B13-10; 12-months follow-up: FAS; tables 1FU7-13 – 1FU13-16; 24-months follow-up: FAS, tables 2FU7-15 – 2FU7-18).

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Other analyses:

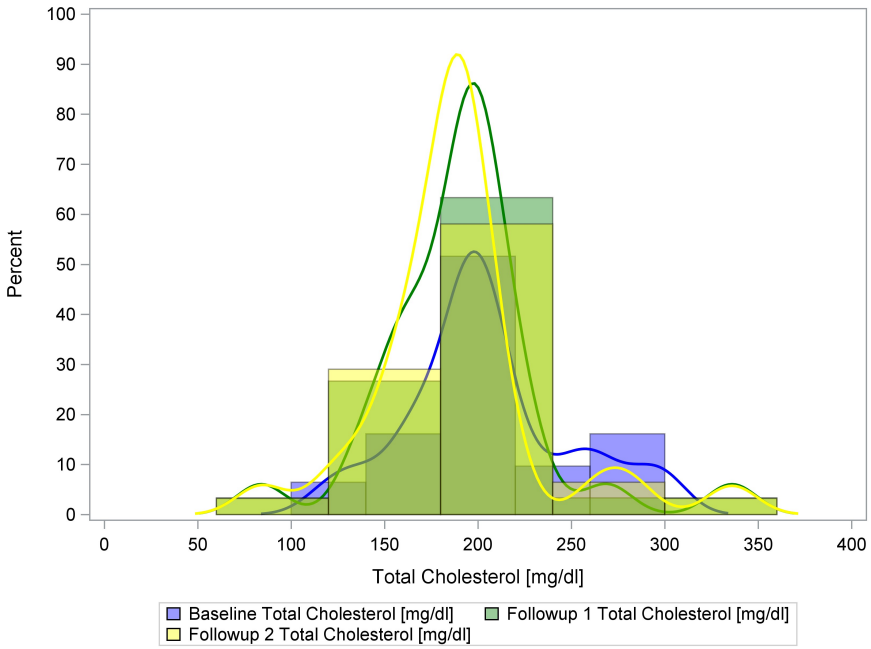
(1) Progression of other relevant lipid parameters

The Full Analysis Set (FAS) consisted of 31 patients with complete data (regarding LDL data) on both 12-months and 24-months follow-up.

Data were analysed according to changes in other relevant lipid values over time; absolute and relative change of total cholesterol, HDL cholesterol, and triglycerides at 12 and 24 months following baseline.

Total cholesterol

The following figure illustrates the distribution of total cholesterol values (mg/dl) at baseline, 12-months and 24-months follow-up (FAS):



The following table shows lipid target achievement (total cholesterol; absolute and relative difference from baseline) in registry patients with complete data (FAS):

	Mean	Standard deviation	Median	1st Quartile	3rd Quartile	N
Absolute difference (Baseline -> FU 12-15 Month) total cholesterol [mg/dl]	-15.2	34.5	-5	-25	3	30
Relative difference (Baseline -> FU 12-15 Month) total cholesterol [%]	-6.4	15.0	-3	-12	2	30
Absolute difference (Baseline -> FU 24-27 Month) total cholesterol [mg/dl]	-16.0	46.0	-9	-28	4	31
Relative difference (Baseline -> FU 24-27 Month) total cholesterol [%]	-6.0	19.7	-5	-14	2	31

More details on total cholesterol target achievement (total cholesterol; absolute and relative difference from baseline; incl. stratification by sex [male, female] and age [18-65 years, >65 years] are given in Appendix II (FAS; tables SZ1 – SZ4).

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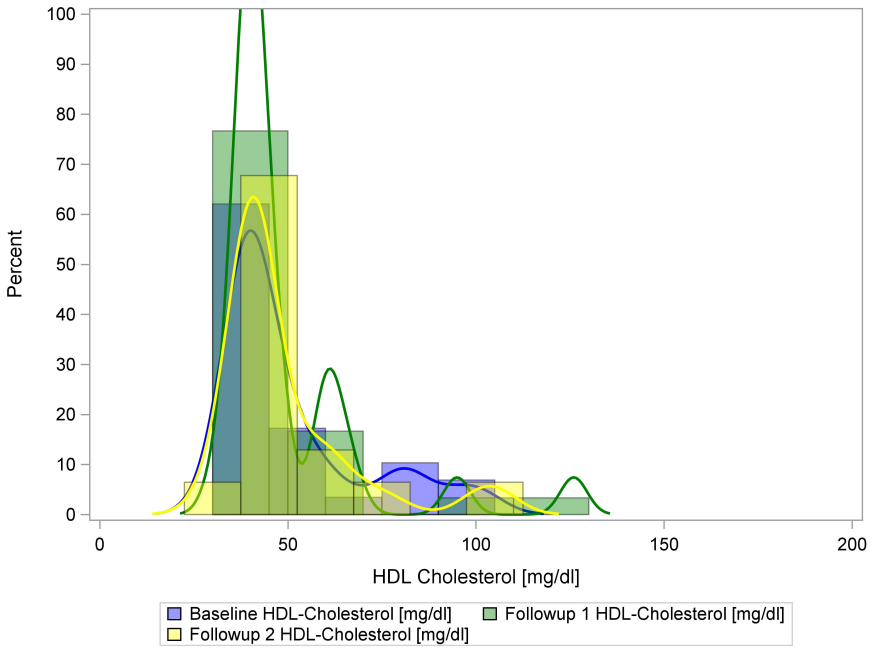
More details on total cholesterol values (latest data available) at baseline and follow-up (incl. stratification by sex [male, female] and age [18-65 years, >65 years] are given in Appendix II (baseline: FAS; tables B13-1 – B13-4; 12-months follow-up: FAS; tables 1FU7-1 – 1FU7-4; 24-months follow-up: FAS, tables 2FU7-3 – 2FU7-6).

HDL cholesterol

The following figure illustrates the distribution of HDL cholesterol values (mg/dl) at baseline, 12-months and 24-months follow-up (FAS):



The following table shows lipid target achievement (HDL cholesterol; absolute and relative difference from baseline) in registry patients with complete data (FAS):

	Mean	Standard deviation	Median	1st Quartile	3rd Quartile	N
Absolute difference (Baseline -> FU 12-15 Month) HDL-C [mg/dl]	-0.6	8.0	0	-3	1	28
Relative difference (Baseline -> FU 12-15 Month) HDL-C [%]	-1.1	10.3	0	-6	3	28
Absolute difference (Baseline -> FU 24-27 Month) HDL-C [mg/dl]	-1.1	8.2	0	-1	1	29
Relative difference (Baseline -> FU 24-27 Month) HDL-C [%]	-0.9	11.0	0	-2	3	29

More details on HDL cholesterol target achievement (HDL cholesterol; absolute and relative difference from baseline; incl. stratification by sex [male, female] and age [18-65 years, >65 years] are given in Appendix II (FAS; tables SZ5 – SZ8).

More details on HDL cholesterol values (latest data available) at baseline and follow-up (incl.

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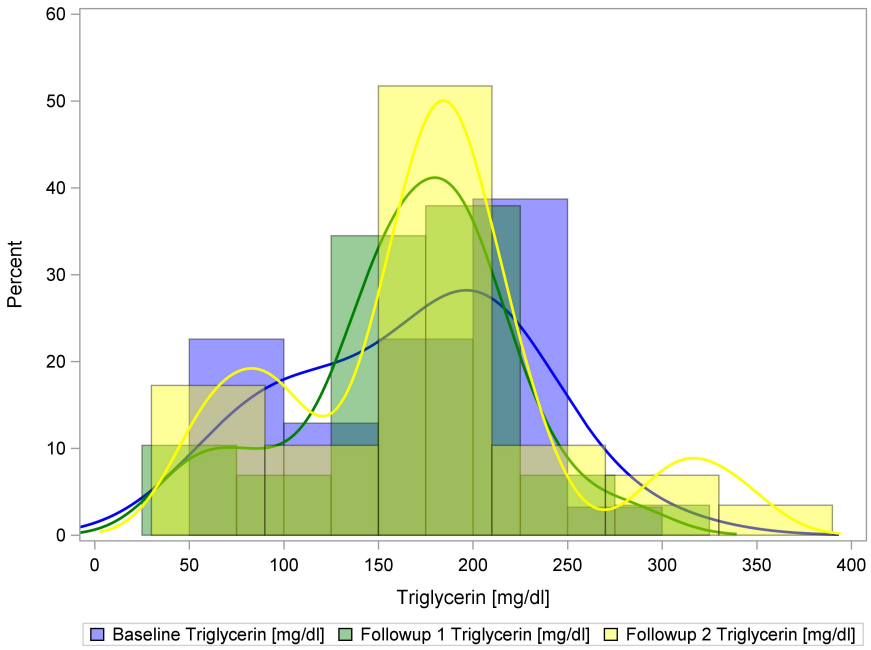
stratification by sex [male, female] and age [18-65 years, >65 years] are given in Appendix II (baseline: FAS; tables B13-11 – B13-14; 12-months follow-up: FAS; tables 1FU7-9 – 1FU7-12; 24-months follow-up: FAS, tables 2FU7-11 – 2FU7-14).

Triglycerides

The following figure illustrates the distribution of triglycerides values (mg/dl) at baseline, 12-months and 24-months follow-up (FAS):



The following table shows lipid target achievement (triglycerides; absolute and relative difference from baseline) in registry patients with complete data (FAS):

	Mean	Standard deviation	Median	1st Quartile	3rd Quartile	N
Absolute difference (Baseline -> FU 12-15 Month) Triglycerides [mg/dl]	-6.5	43.2	-9	-15	4	29
Relative difference (Baseline -> FU 12-15 Month) Triglycerides [%]	2.9	40.1	-5	-7	2	29
Absolute difference (Baseline -> FU 24-27 Month) Triglycerides [mg/dl]	2.6	59.8	-9	-20	5	29
Relative difference (Baseline -> FU 24-27 Month) Triglycerides [%]	7.8	48.7	-6	-11	3	29

More details on triclycerides target achievement (triglcerides; absolute and relative difference from baseline; incl. stratification by sex [male, female] and age [18-65 years, >65 years] are given in Appendix II (FAS; tables SZ9 – SZ12).

More details on triclycerides values (latest data available) at baseline and follow-up (incl. stratification by sex [male, female] and age [18-65 years, >65 years] are given in Appendix II (baseline: FAS; tables

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B13-19 – B13-22; 12-months follow-up: FAS; tables 1FU7-25 – 1FU7-28; 24-months follow-up: FAS, tables 2FU7-27 – 2FU7-30).

(2) Evaluation of lipid-lowering therapy in clinical routine
The Full Analysis Set (FAS) consisted of 31 patients with complete data on both 12-months and 24-months follow-up.

(2a) Pharmacotherapy
The following table shows the proportions of patients with lipid-lowering pharmacotherapy over time: baseline to 12-months follow-up to 24-months follow-up (FAS).

Pharmacotherapy (type)	Baseline		12-months Follow-up		24-months Follow-up	
	N	%	N	%	N	%
P2Y12 antagonist						
No	27	87.10%	31	100.00%	29	93.55%
Yes	4	12.90%	0	0	2	6.45%
Other platelet aggregation inhibitor						
No	8	25.81%	8	25.81%	9	29.03%
Yes	23	74.19%	23	74.19%	22	70.97%
Vitamin-K antagonist						
No	30	96.77%	30	96.77%	30	96.77%
Yes	1	3.23%	1	3.23%	1	3.23%
Direct Oral Anticoagulant (DOA)						
No	31	100.00%	30	96.77%	31	100.00%
Yes	0	0	1	3.23%	0	0
Beta blocker						
No	20	64.52%	18	58.06%	18	58.06%
Yes	11	35.48%	13	41.94%	13	41.94%
Angiotensin II receptor blocker						
No	22	70.97%	20	64.52%	18	58.06%
Yes	9	29.03%	11	35.48%	13	41.94%
ACE inhibitor						
No	18	58.06%	19	61.29%	21	67.74%
Yes	13	41.94%	12	38.71%	10	32.26%
Diuretic						
No	26	83.87%	27	87.10%	27	87.10%
Yes	5	16.13%	27	87.10%	4	12.90%
If channel inhibitor						
No	29	93.55%	30	96.77%	30	96.77%
Yes	2	6.45%	1	3.23%	1	3.23%
Calcium channel blocker						
No	17	54.84%	17	54.84%	16	51.61%
Yes	14	45.16%	14	45.16%	15	48.39%
Oral Antidiabetic						
No	20	64.52%	21	67.74%	21	67.74%
Yes	11	35.48%	10	32.26%	10	32.26%
GLP-1 receptor agonist						
No	28	90.32%	28	90.32%	27	87.10%
Yes	3	9.68%	3	9.68%	4	12.90%
Insulin						
No	26	83.87%	27	87.10%	27	87.10%

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Yes	5	16.13%	4	12.90%	4	12.90%
Renin inhibitor						
No	31	100.00%	31	100.00%	31	100.00%
Muscarinic receptor blocker						
No	31	100.00%	31	100.00%	31	100.00%
Antianginous Drug						
No	29	93.55%	29	93.55%	29	93.55%
Yes	2	6.45%	2	6.45%	2	6.45%
Fibrates						
No	31	100.00%	31	100.00%	31	100.00%
Cholesterol resorption inhibitor						
No	13	41.94%	16	51.61%	15	48.39%
Yes	18	58.06%	15	48.39%	16	51.61%
PCSK-9 inhibitor						
No	23	74.19%	22	70.97%	21	67.74%
Yes	8	25.81%	9	29.03%	10	32.26%
Statin						
No	5	16.13%	4	12.90%	5	16.13%
Yes	26	83.87%	27	87.10%	26	83.87%
Other lipid-lowering therapy						
No	28	90.32%	29	93.55%	29	93.55%
Yes	3	9.68%	2	6.45%	2	6.45%
None						
No	30	96.77%	31	100.00%	31	100.00%
Yes	1	3.23%	31	100.00%	0	0

The following figure illustrates the distribution of lipid lowering medication at inclusion, baseline, 12-months and 24-months follow-up (FAS):

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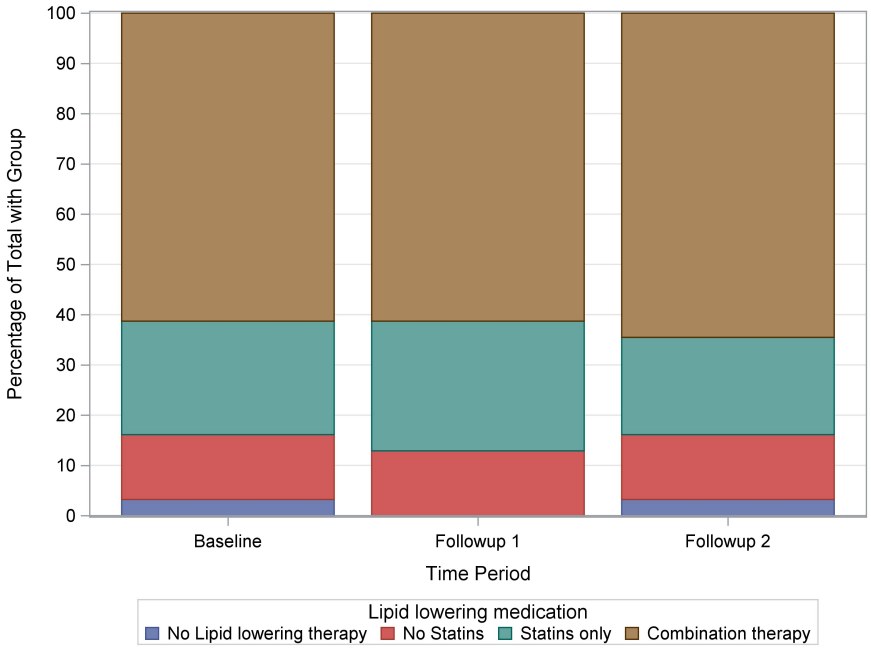

More details on lipid-lowering pharmacotherapy (incl. stratification by sex [male, female] and age [18-65 years, >65 years] are given in Appendix II (FAS, tables B17-1 – B17-14; FAS, tables 1FU9-1 – 1FU9-14 and 2FU9-1 – 2FU9-14).

(2b) Non-drug lipid lowering therapy

The following table shows the proportions of patients with non-drug lipid-lowering therapy (lifestyle and diet) over time: baseline to 12-months follow-up to 24-months follow-up (FAS).

	Baseline		12-months Follow-up		24-months Follow-up	
	N	%	N	%	N	%
Physical exercise						
None	7	22.58%	5	16.13%	5	16.13%
1x per week	18	58.06%	16	51.61%	19	61.29%
2-3x per week	6	19.35%	9	29.03%	7	22.58%
>3x per week	0	0	1	3.23%	0	0
Fruit and vegetable consumption						
≥3x per week	15	48.39%	15	48.39%	16	51.61%
<3x per week	16	51.61%	16	51.61%	14	45.16%
None	0	0	0	0	1	3.23%
Fish consumption						
≥2x per week	4	12.90%	7	22.58%	9	29.03%
<2x per week	22	70.97%	18	58.06%	15	48.39%
None	5	16.13%	6	19.35%	7	22.58%
Alcohol consumption (amount of alcoholic beverages)						
≥2x per day	1	3.23%	0	0	0	0
<2x per day	19	61.29%	17	54.84%	16	51.61%

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None	11	35.48%	13	41.94%	14	45.16%
Smoking status						
Non-smoker	10	32.26%	12	38.71%	13	41.94%
Current smoker	4	12.90%	4	12.90%	2	6.45%
Ex-smoker	17	54.84%	15	48.39%	16	51.61%

More details on non-drug lipid-lowering therapy (incl. stratification by sex [male, female] and age [18-65 years, >65 years] are given in Appendix II (FAS, tables B9-1 – B9-17; FAS, tables 1FU8-1 – 1FU8-18 and 2FU8-1 – 2FU8-18).

(3) Drug utilization pattern in secondary prevention
The Full Analysis Set (FAS) consisted of 31 patients with complete data on both 12-monts and 24-months follow-up.

The following table shows the proportions of patients with (any) pharmacotherapy over time (baseline visit [first digit], 12-months follow-up [second digit], 24-months follow-up [third digit]; 0= no medication; 1= medication intake; FAS).

Pharmacotherapy (type)	N	%
None		
0 0 0	30	96.77%
1 0 0	1	3.23%
Beta blocker		
0 0 0	15	48.39%
0 0 1	1	3.23%
0 1 0	2	6.45%
0 1 1	2	6.45%
1 0 0	1	3.23%
1 0 1	1	3.23%
1 1 1	9	29.03%
Other platelet aggregation inhibitor		
0 0 0	6	19.35%
0 1 1	2	6.45%
1 0 0	1	3.23%
1 0 1	1	3.23%
1 1 0	2	6.45%
1 1 1	19	61.29%
Oral Antidiabetic		
0 0 0	20	64.52%
1 0 0	1	3.23%
1 1 1	10	32.26%
Insulin		
0 0 0	26	83.87%
1 0 0	1	3.23%
1 1 1	4	12.90%
Renin inhibitor		
0 0 0	31	100.00%
Muscarinic receptor blocker		
0 0 0	31	100.00%
Angiotensin II receptor blocker		
0 0 0	28	90.32%

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0 1 0	1	3.23%
1 0 1	1	3.23%
1 1 1	1	3.23%
Fibrates		
0 0 0	31	100.00%
Cholesterol resorption inhibitor		
0 0 0	12	38.71%
0 1 1	1	3.23%
1 0 0	3	9.68%
1 0 1	1	3.23%
1 1 1	14	45.16%
PCSK-9-Inhibitor		
0 0 0	21	67.74%
0 1 1	2	6.45%
1 0 1	1	3.23%
1 1 1	7	22.58%
Statins		
0 0 0	3	9.68%
0 1 1	2	6.45%
1 0 0	1	3.23%
1 1 0	1	3.23%
1 1 1	24	77.42%
GLP-1 receptor agonist		
0 0 0	27	87.10%
0 0 1	1	3.23%
1 1 1	3	9.68%
P2Y12 antagonist		
0 0 0	25	80.65%
0 0 1	2	6.45%
1 0 0	4	12.90%
Vitamin-K antagonist		
0 0 0	30	96.77%
1 1 1	1	3.23%
Direct Oral Anticoagulant (DOA)		
0 0 0	30	96.77%
0 1 0	1	3.23%
Angiotensin II receptor blocker		
0 0 0	17	54.84%
0 0 1	2	6.45%
0 1 1	3	9.68%
1 0 0	1	3.23%
1 1 1	8	25.81%
ACE inhibitor		
0 0 0	17	54.84%
0 1 0	1	3.23%
1 0 0	2	6.45%
1 1 0	1	3.23%
1 1 1	10	32.26%
Diuretic		
0 0 0	24	77.42%
0 0 1	1	3.23%
0 1 1	1	3.23%
1 0 0	2	6.45%

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1 1 0	1	3.23%
1 1 1	2	6.45%
If channel inhibitor		
0 0 0	29	93.55%
1 0 0	1	3.23%
1 1 1	1	3.23%
Other lipid-lowering therapy		
0 0 0	26	83.87%
0 1 0	1	3.23%
0 1 1	1	3.23%
1 0 0	2	6.45%
1 0 1	1	3.23%
Calcium channel blocker		
0 0 0	15	48.39%
0 0 1	1	3.23%
0 1 1	1	3.23%
1 0 0	1	3.23%
1 1 1	13	41.94%

(4) Cardiovascular and cerebrovascular events within the follow-up period of two years
With regard to the Baseline Analysis Set (taking into account all patients regardless of completeness of follow-up data; n= 218 patients) the following non-fatal events since baseline were documented:

Non-fatal events since baseline were documented in 14 patients (6.42%) at 12-months follow-up since baseline and in 24 patients (11.01%) at 24-months follow-up since baseline.

Event type, n (%)	12-months follow-up (since baseline) n= 218	24-months follow-up (since baseline) n=218
Myocardial infarction	2 (0.92) 95% CI: -0.00, 0.02	2 (0.92) 95% CI: -0.00, 0.02
Cardiac Catheter Examination without PCI	2 (0.92) 95% CI: -0.00, 0.02	5 (2.29) 95% CI: 0.00, 0.04
Balloon dilatation (PCI)	4 (1.83) 95% CI: 0.00, 0.04	6 (2.75) 95% CI: 0.01, 0.05
Bypass surgery	0	1 (0.5) 95% CI: -0.00, 0.01
Stroke	0	0
TIA	0	0
Hospitalisation due to event	6 (2.75)	10 (4.59)
Hospitalisation due to event; *mean duration*	4.8 days (SD: 4.1)	4.5 days (SD: 4.0)
Rehabilitation	0	1 (0.5) 95% CI: -0.00, 0.01
Other inpatient stay	9 (4.13) 95% CI: 0.01, 0.07	14 (6.42) 95% CI: 0.03, 0.10
Other inpatient stay, *mean duration*	11.2 days (SD: 7.7)	18.5 days (SD: 30.1)

More details on non-fatal events (incl. stratification by sex [male, female] and age [18-65 years, >65 years] are given in Appendix II (BAS, 12-months follow-up: tables 1FU2-1 – 1FU2-14; 24-months follow-up: tables 2FU2-1 – 2FU2-14).

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With regard to the Full Analysis Set (taking into account all patients with complete data on LDL cholesterol and correct timing for both follow-ups; n= 31) the following non-fatal events were documented:

Non-fatal events since baseline were documented in 1 patient (3.23%) at both 12-months and 24-months follow-up since baseline.

Event type, n (%)	12-months follow-up (since baseline) n=31	24-months follow-up (since baseline) n=31
Myocardial infarction	0	0
Cardiac Catheter Examination without PCI	0	0
Balloon dilatation (PCI)	1 (3.23) 95% CI: -0.03, 0.10	1 (3.23) 95% CI: -0.03, 0.10
Bypass surgery	0	0
Stroke	0	0
TIA	0	0
Hospitalisation due to event	0	0
Rehabilitation	0	0
Other inpatient stay	0	0

More details on non-fatal events (incl. stratification by sex [male, female] and age [18-65 years, >65 years] are given in Appendix II (FAS, 12-months follow-up: tables 1FU2-1 – 1FU2-14; 24-months follow-up: tables 2FU2-1 – 2FU2-14).

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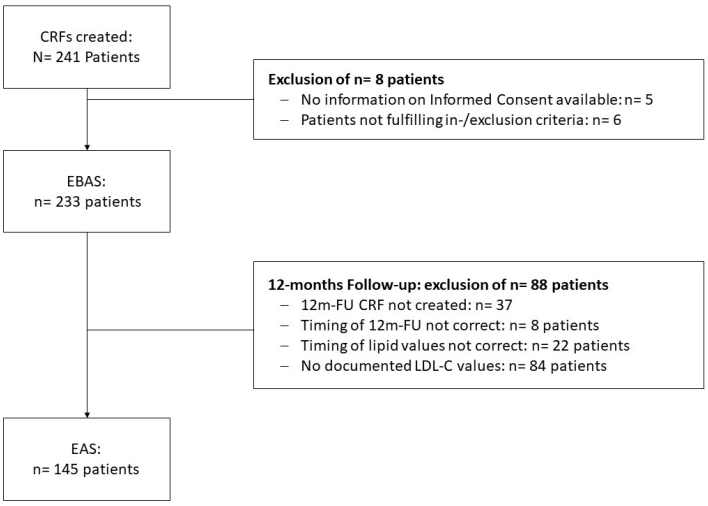
RESULTS **Part II**	The following result are based on the analysis sets EBAS and EAS (as defined in section Methodology).
Participants (actual):	**(a) Overall participation status:** The registry was conducted in Germany. 35 sites participated in the registry. 233 patients were included in the baseline analyses. 145 patients were included in the extended analysis set (EAS) to evaluate the longitudinal data. **(b) Participation per period of the registry:** The following flow chart illustrates the number of patients at each stage of the registry, including the number of patients lost to follow-up and the amount of missing data for the variables of interest (i.e. lipid profiles):  Of 233 patients in baseline, complete follow-up data for the 12-months follow-up were available in 145 patients. Overall, 88 patients were excluded from the longitudinal analyses.
Participant characteristics and primary analyses:	**(a) Descriptive data** Characteristics of registry physicians: Type of sites were as follows (see EBAS tables CTR-1 to CTR-5 in Appendix II): - Hospital, n= 2; - Joint practice, n= 8 - Single practice, n= 16 - Medical care center, n= 1; - No information provided, n= 8 **Characteristics of registry patients:** The Extended Baseline Analysis Set (EBAS) consisted of 233 documented patients. Duration of enrolment was on average 143.6 days (SD: 118.9 days). On average, 6.9 patients (SD: 5.9; MD: 4) were enrolled per study site. The following table shows the demographic and clinical characteristics of the registry patients at baseline (EBAS):

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Characteristics[#]	N= 233
Sex – *no. of participants (%)*	
Male	137 (58.8)
Female	96 (41.2)
Mean age *(SD) - yr*	61.1 (14.0)
Cardiovascular History – *no. of participants (%)*	
Coronary heart disease,	126 (54.1)
PCI	78 (33.5)
Acute coronary syndrome	46 (19.7)
Aortocoronary bypass	30 (12.9)
Stroke	12 (5.2)
TIA	3 (1.3)
Comorbidities and Risk Factors – *no. of participants (%)*	
Arterial hypertension	168 (72.1)
Diabetes mellitus	95 (40.8)
Heart failure	52 (22.3)
Heart valve disease	37 (15.9)
Depression	32 (13.7)
Renal insufficiency	24 (10.3)
Stable angina pectoris	22 (9.4)
Peripheral arterial occlusive disease	17 (7.3)
Atrial fibrillation	12 (5.2)
COPD	12 (5.2)
Carcinoma	11 (4.7)
Device implantation	5 (2.1)
Deep vein thrombosis	2 (0.9)
Pulmonary embolism	1 (0.4)
Phenotypic Findings – *no. of participants (%)*	
Xanthelasma	48 (20.6)
Xanthomas	28 (12.0)
Arcus cornealis	20 (8.6)
Functional mutation in LDLR, apoB or PCSK9 gene	21 (9.0)
Age at initial diagnosis, *mean (SD), based on n=20 documented data*	46.4 (10.5)
Family History – *no. of participants (%)*	
Family history of elevated cholesterol levels	147 (63.1)
Family history of CHD	131 (56.2)
Family history of MI	113 (48.5)
Family history of cerebral/vascular disease	59 (25.3)
Family history of tendon xanthomas	25 (10.7)
Family history of arcus cornealis	14 (6.1)
Lipid Apheresis Therapy – *no. of participants (%)*	11 (4.7)
Body-mass Index, *mean (SD)*	28.5 (4.50)

[#] Percentages are given for the total population of n=233, including missing values

More details on patient characteristics at baseline (incl. stratification by sex [male, female] and age [18-65 years, >65 years] are given in Appendix II EBAS; tables E1, E2, B1 – B17).

Follow-up duration (i.e. time from baseline to follow-up in days):
With regard to the Extended Baseline Analysis Set (taking into account all patients regardless of completeness of follow-up data; n= 233 patients) time to follow-up was on average 365.5 days (SD: 219.3) for the 12-months follow-up and 750.2 days (SD: 45.5) for the 24-months follow-up.

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A complete descriptive report of follow-up data for this population is given in Appendix II (12-months follow-up: tables 1FU1 – 1FU9, EBAS; 24-months follow-up: tables 2FU1 – 2FU9, EBAS).

(b) Primary analyses: Lipid Target Achievement
The Extended Analysis Set (EAS) consisted of 145 patients with complete (LDL) data on the 12-months follow-up.

Follow-up duration (i.e. time from baseline to follow-up in days):
With regard to the Full Analysis Set (taking into account all patients with complete data on LDL cholesterol and correct timing for the 12-months follow-ups; n= 145) time to follow-up was on average 378.7 days (SD: 28.2) for the 12-months follow-up and 749.3 days (SD: 35.2) for the 24-months follow-up.

A complete descriptive report of follow-up data for this population is given in Appendix II (12-months follow-up: tables 1FU1 – 1FU9, EAS; 24-months follow-up: tables 2FU1 – 2FU9, EAS).

Distribution of LDL cholesterol values (mg(dl):
The following table shows mean LDL cholesterol values at baseline, 12-months follow-up and 24-months follow-up (EAS):

	Mean	Standard deviation	Median	1st Quartile	3rd Quartile	N
LDL-Cholesterol [mg/dl]	139.0	60.7	128	89	194	145
LDL-Cholesterol @12MFU	114.2	52.0	99	78	144	145
LDL-Cholesterol @24MFU	107.9	53.0	91	72	130	101

More details on LDL cholesterol values (incl. stratification by sex [male, female] and age [18-65 years, >65 years] are given in Appendix II (EAS; tables CHOL-1 – CHOL-3).

The following figure illustrates the distribution of LDL cholesterol values (mg/dl) at baseline, 12-months and 24-months follow-up (EAS):

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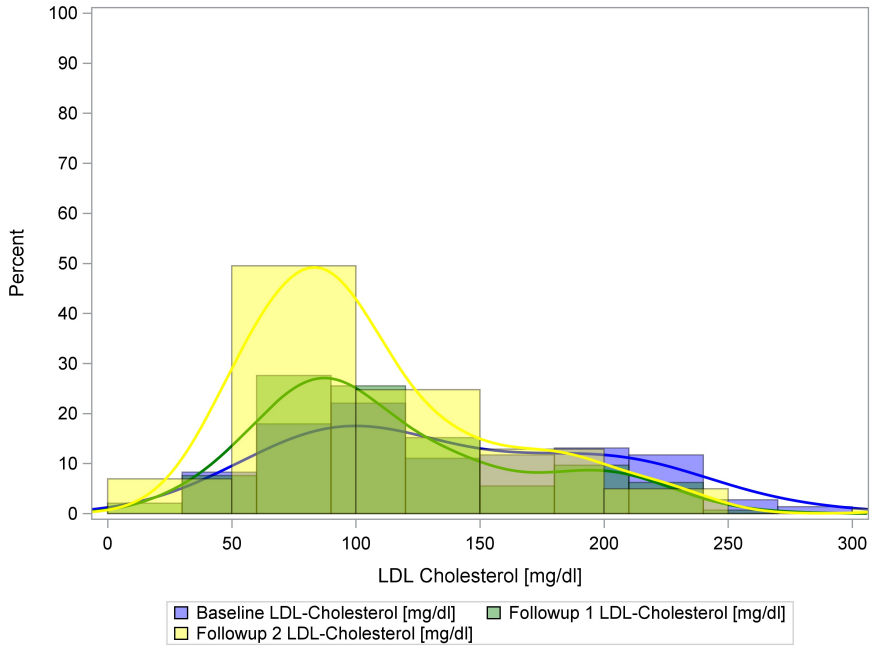

Target achievement of LDL cholesterol values (mg/dl):
Data were analysed according to lipid target achievement as measured by the reduction of LDL cholesterol over time (baseline to 12-M FU to 24-M-FU); absolute and relative reduction of LDL cholesterol at 12 and 24 months following baseline (EAS).

Target ranges were set as follows (see also SAP, section 7.2; Appendix III, section 3.2):

- Within target range: < 70mg/dl
- Above target range: ≥ 70 mg/dl

Within target range (LDL <70 mg/dl) were

- At 12-months follow-up: n= 25 patients (17.2%)
- At 24-months follow-up: n= 23 patients (15.9%; n= 44 missing values)

Above target range (LDL ≥ 70 mg/dl) were

- At 12-months follow-up: n= 120 patients (82.8%)
- At 24-months follow-up: n= 78 patients (53.8%; n= 44 missing values)

According to guidelines applicable at the time of data collection (see References [1]), target achievement was defined as LDL< 70mg/dl or 50% of reduction in LDL (see also SAP, section 6.1.1; Appendix III, section 3.2).

Within this target range (LDL< 70mg/dl or 50% of reduction in LDL) were:

- At 12-months follow-up: n= 30 patients (20.7% [30/145]; 95% CI: 0.14, 0.27)
- At 24-months follow-up: n= 26 patients (25.7% [26/101]; 95% CI: 0.17, 0.34)

Above this target range (LDL< 70mg/dl or 50% of reduction in LDL) were:

- At 12-months follow-up: n= 115 patients (79.3%)

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- At 24-months follow-up: n= 75 patients (51.7%; n= 44 missing values)

More details on LDL-C target achievement (target ranges of LDL cholesterol at baseline and follow-up; incl. stratification by sex [male, female] and age [18-65 years, >65 years] are given in Appendix II (EAS; tables PZ-5 to PZ-10).

The following table shows lipid target achievement (LDL cholesterol; absolute and relative difference from baseline) in registry patients with complete data at 12-months follow-up (EAS):

	Mean	Standard deviation	Median	1st Quartile	3rd Quartile	N
Absolute difference (Baseline -> FU 12-16 Month) LDL-C [mg/dl]	-24.7	43.3	-14	-43	1	145
Relative difference (Baseline -> FU 12-16 Month) LDL-C [%]	-12.2	31.0	10	-33	2	145
Absolute difference (Baseline -> FU 24-28 Month) LDL-C [mg/dl]	-20.3	53.2	-10	-45	5	101
Relative difference (Baseline -> FU 24-28 Month) LDL-C [%]	-6.7	51.8	-10	-27	8	101

The 95% confidence interval for the mean relative difference from baseline to 12-months follow-up was -17.3, -7.1 (p< 0.00001).
The 95% confidence interval for the mean relative difference from baseline to 24-months follow-up was -16.9, -3.5 (p= 0.19665).

The following figure illustrates the distribution of LDL cholesterol values (mg/dl; absolute and relative difference from baseline) 12-months and 24-months follow-up; in registry patients with complete data at 12-months follow-up (EAS):

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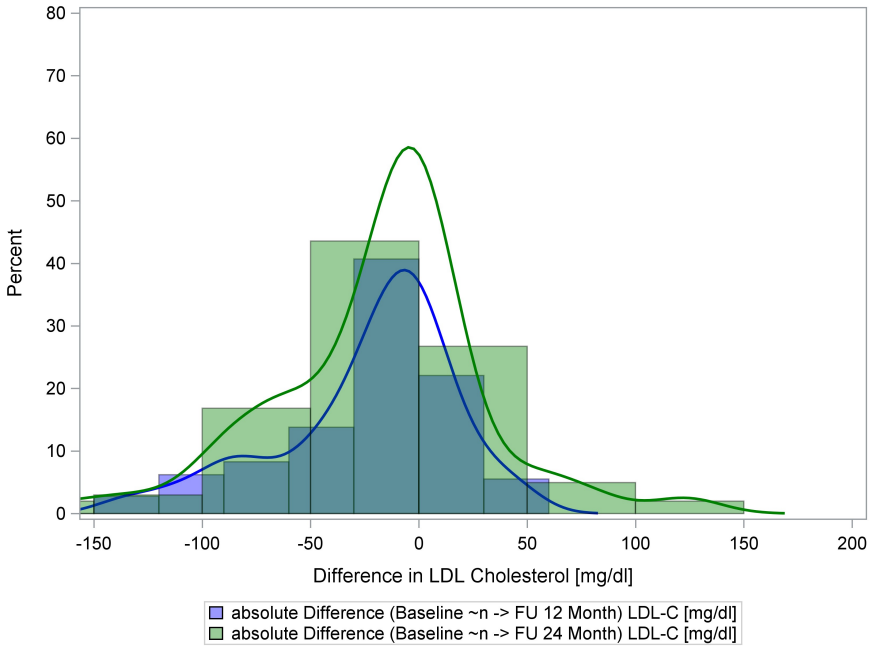

More details on LDL-C target achievement (LDL cholesterol; absolute and relative difference from baseline; incl. stratification by sex [male, female] and age [18-65 years, >65 years] are given in Appendix II (EAS; tables PZ1 – PZ4).

More details on LDL-cholesterol values (latest data available) at baseline and follow-up (incl. stratification by sex [male, female] and age [18-65 years, >65 years] are given in Appendix II (baseline: EAS; tables B13-5 – B13-10; 12-months follow-up: EAS; tables 1FU7-13 – 1FU13-16; 24-months follow-up: EAS, tables 2FU7-15 – 2FU7-18).

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Other analyses:

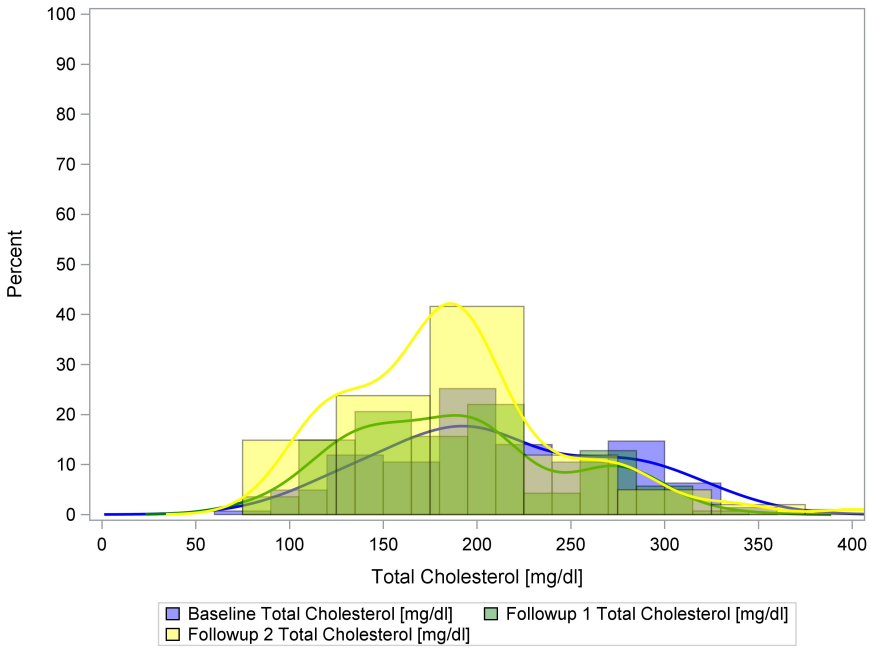
(1) Progression of other relevant lipid parameters

The Extended Analysis Set (EAS) consisted of 145 patients with complete data (regarding LDL-C data) on the 12-months follow-up.

Data were analysed according to changes in other relevant lipid values over time; absolute and relative change of total cholesterol, HDL cholesterol, and triglycerides at 12 and 24 months following baseline.

Total cholesterol

The following figure illustrates the distribution of total cholesterol values (mg/dl) at baseline, 12-months and 24-months follow-up (EAS):



The following table shows lipid target achievement (total cholesterol; absolute and relative difference from baseline) in registry patients with complete data (EAS):

	Mean	Standard deviation	Median	1st Quartile	3rd Quartile	N
Absolute difference (Baseline -> FU 12-16 Month) total cholesterol [mg/dl]	-24.1	43.1	-15	-48	-1	140
Relative difference (Baseline -> FU 12-16 Month) total cholesterol [%]	-9.2	20.3	-6	-23	0	140
Absolute difference (Baseline -> FU 24-28 Month) total cholesterol [mg/dl]	-19.2	52.5	-10	-45	4	101
Relative difference (Baseline -> FU 24-28 Month) total cholesterol [%]	-6.7	24.2	-5	-19	2	101

More details on total cholesterol target achievement (total cholesterol; absolute and relative difference from baseline; incl. stratification by sex [male, female] and age [18-65 years, >65 years] are given in Appendix II (EAS; tables SZ1 – SZ4).

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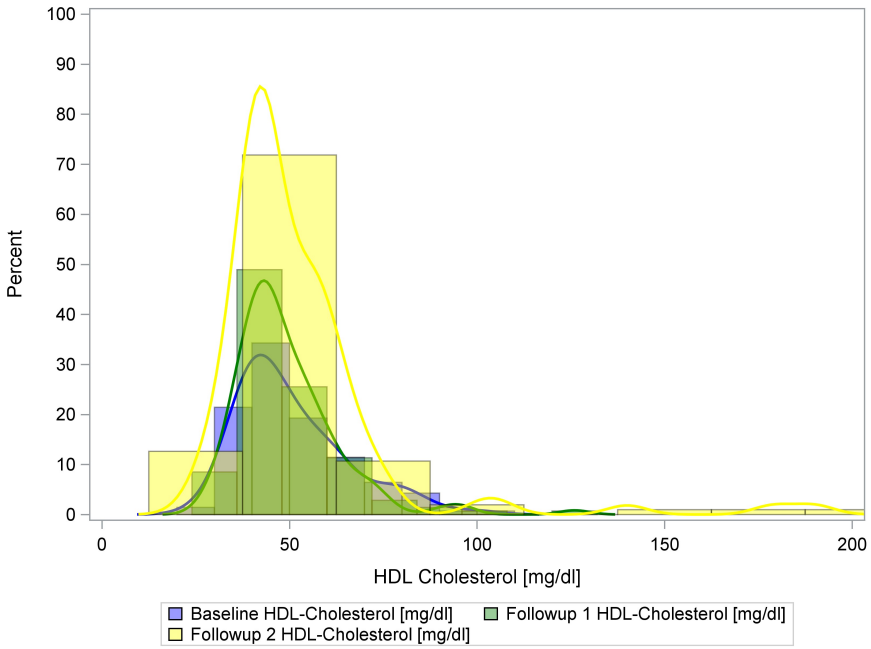
More details on total cholesterol values (latest data available) at baseline and follow-up (incl. stratification by sex [male, female] and age [18-65 years, >65 years] are given in Appendix II (baseline: EAS; tables B13-1 – B13-4; 12-months follow-up: EAS; tables 1FU7-1 – 1FU7-4; 24-months follow-up: EAS, tables 2FU7-3 – 2FU7-6).

HDL cholesterol

The following figure illustrates the distribution of HDL cholesterol values (mg/dl) at baseline, 12-months and 24-months follow-up (EAS):



The following table shows lipid target achievement (HDL cholesterol; absolute and relative difference from baseline) in registry patients with complete data at the 12-months follow-up (EAS):

	Mean	Standard deviation	Median	1st Quartile	3rd Quartile	N
Absolute difference (Baseline -> FU 12-16 Month) HDL-C [mg/dl]	-1.3	8.1	0	-4	2	138
Relative difference (Baseline -> FU 12-16 Month) HDL-C [%]	-1.1	13.9	0	-8	5	138
Absolute difference (Baseline -> FU 24-28 Month) HDL-C [mg/dl]	3.4	22.1	0	-3	4	100
Relative difference (Baseline -> FU 24-28 Month) HDL-C [%]	7.8	41.6	0	-6	8	100

More details on HDL cholesterol target achievement (HDL cholesterol; absolute and relative difference from baseline; incl. stratification by sex [male, female] and age [18-65 years, >65 years] are given in Appendix II (EAS; tables SZ5 – SZ8).

More details on HDL cholesterol values (latest data available) at baseline and follow-up (incl.

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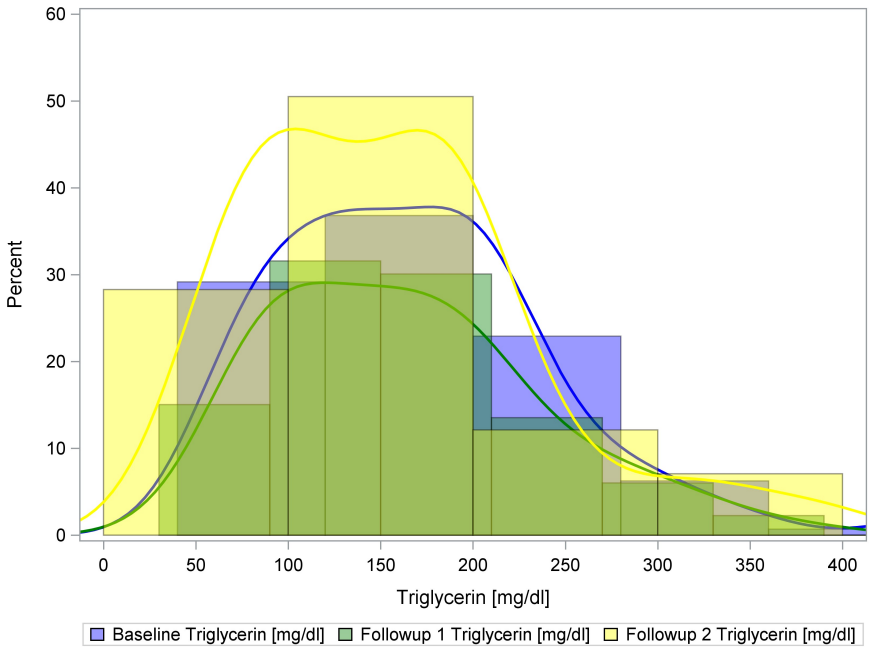
stratification by sex [male, female] and age [18-65 years, >65 years] are given in Appendix II (baseline: EAS; tables B13-11 – B13-14; 12-months follow-up: EAS; tables 1FU7-9 – 1FU7-12; 24-months follow-up: EAS, tables 2FU7-11 – 2FU7-14).

Triglycerides

The following figure illustrates the distribution of triglycerides values (mg/dl) at baseline, 12-months and 24-months follow-up (EAS):



The following table shows lipid target achievement (triglycerides; absolute and relative difference from baseline) in registry patients with complete data at the 12-months follow-up (EAS):

	Mean	Standard deviation	Median	1st Quartile	3rd Quartile	N
Absolute difference (Baseline -> FU 12-16 Month) Triglycerides [mg/dl]	-11.5	81.7	-8	-31	20	132
Relative difference (Baseline -> FU 12-16 Month) Triglycerides [%]	1.8	38.8	-4	-21	19	132
Absolute difference (Baseline -> FU 24-28 Month) Triglycerides [mg/dl]	-13.2	78.5	-9	-34	10	99
Relative difference (Baseline -> FU 24-28 Month) Triglycerides [%]	0.9	57.6	-8	-23	5	99

More details on triclycerides target achievement (triglcerides; absolute and relative difference from baseline; incl. stratification by sex [male, female] and age [18-65 years, >65 years] are given in Appendix II (EAS; tables SZ9 – SZ12).

More details on triclycerides values (latest data available) at baseline and follow-up (incl. stratification by sex [male, female] and age [18-65 years, >65 years] are given in Appendix II (baseline: EAS; tables

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B13-19 – B13-22; 12-months follow-up: EAS; tables 1FU7-25 – 1FU7-28; 24-months follow-up: EAS, tables 2FU7-27 – 2FU7-30).

(2) Evaluation of lipid-lowering therapy in clinical routine
The Extended Analysis Set (EAS) consisted of 145 patients with complete data on the 12-months follow-up.

(2a) Pharmacotherapy
The following table shows the proportions of patients with lipid-lowering pharmacotherapy over time: baseline to 12-months follow-up to 24-months follow-up (EAS).

Pharmacotherapy (type)	Baseline n=145		12-months Follow-up n=145		24-months Follow-up n=124	
	N	%	N	%	N	%
P2Y12 antagonist						
No	138	91.03	138	95.17	116	95.55
Yes	13	8.97	7	4.83	8	6.45
Other platelet aggregation inhibitor						
No	83	57.24	73	50.34	63	50.81
Yes	62	42.76	72	49.66	61	49.19
Vitamin-K antagonist						
No	139	95.86	142	97.93	121	97.58
Yes	6	4.14	3	2.07	3	2.42
Direct Oral Anticoagulant (DOA)						
No	140	96.55	140	96.55	121	97.58
Yes	5	3.45	5	3.45	3	2.42
Beta blocker						
No	108	74.48	92	63.45	71	57.26
Yes	37	25.52	53	36.55	53	42.74
Angiotensin II receptor blocker						
No	99	68.28	98	67.59	83	66.94
Yes	46	31.72	47	32.41	41	33.06
ACE inhibitor						
No	98	67.59	99	68.28	94	75.81
Yes	47	32.41	46	31.72	30	24.19
Diuretic						
No	116	80.00	121	83.45	105	84.68
Yes	29	20.00	24	16.55	19	15.32
If channel inhibitor						
No	136	93.79	142	97.93	121	97.58
Yes	9	6.21	2	2.07	3	2.42
Calcium channel blocker						
No	107	73.79	101	69.66	89	71.77
Yes	38	26.21	44	30.34	35	28.23
Oral Antidiabetic						
No	108	74.48	115	79.31	97	78.23
Yes	37	25.52	30	20.69	27	21.77
GLP-1 receptor agonist						
No	134	92.41	135	93.10	117	94.35
Yes	11	7.59	10	6.90	7	5.65
Insulin						

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No	128	88.28	130	89.66	114	91.94
Yes	17	11.72	15	10.34	10	8.06
Renin inhibitor						
No	143	98.62	144	99.31	124	100
Yes	2	1.38	1	0.69	0	0
Muscarinic receptor blocker						
No	145	100	145	100	124	100
Antianginous Drug						
No	140	96.55	141	97.24	120	96.77
Yes	5	3.45	4	2.76	4	3.23
Fibrates						
No	143	98.62	144	99.31	121	97.58
Yes	2	1.38	1	0.69	3	2.42
Cholesterol resorption inhibitor						
No	90	62.07	94	64.83	75	60.48
Yes	55	37.93	51	35.17	49	39.52
PCSK-9 inhibitor						
No	111	76.55	109	75.17	93	75.00
Yes	34	23.45	36	24.83	31	25.00
Statin						
No	20	13.79	28	19.31	22	17.74
Yes	125	86.21	117	80.69	102	82.26
Other lipid-lowering therapy						
No	131	90.34	131	90.34	112	90.32
Yes	14	9.66	14	9.66	12	9.68
None						
No	145	100	139	95.86	122	98.39
Yes	0	0	6	4.14	2	1.61

The following figure illustrates the distribution of lipid lowering medication at inclusion, baseline, 12-months and 24-months follow-up (EAS):

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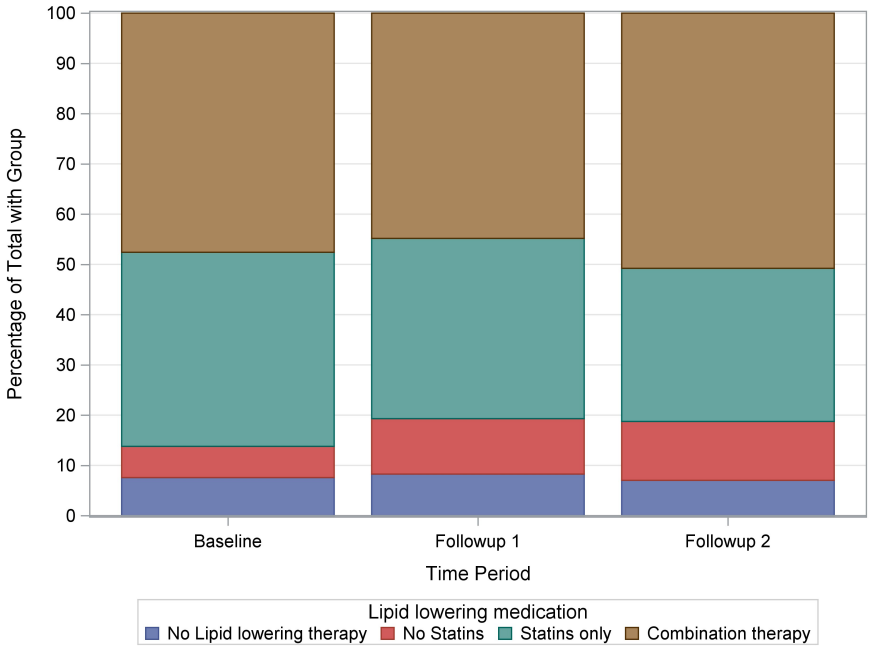

More details on lipid-lowering pharmacotherapy (incl. stratification by sex [male, female] and age [18-65 years, >65 years] are given in Appendix II (EAS, tables B17-1 – B17-14; EAS, tables 1FU9-1 – 1FU9-14 and 2FU9-1 – 2FU9-14).

(2b) Non-drug lipid lowering therapy

The following table shows the proportions of patients with non-drug lipid-lowering therapy (lifestyle and diet) over time: baseline to 12-months follow-up to 24-months follow-up (EAS).

	Baseline		12-months Follow-up		24-months Follow-up	
	N	%	N	%	N	%
Physical exercise						
None	57	39.31	53	36.55	43	34.68
1x per week	55	37.93	47	32.41	46	37.10
2-3x per week	23	15.86	34	23.45	26	20.97
>3x per week	10	6.90	10	6.90	6	4.84
Not possible	0	0	0	0	2	1.61
Fruit and vegetable consumption						
≥3x per week	91	62.76	86	59.31	68	54.84
<3x per week	50	34.48	52	35.86	52	41.94
None	4	2.76	6	4.14	2	1.61
Fish consumption						
≥2x per week	29	20.00	30	20.69	24	19.35
<2x per week	99	68.28	90	62.07	78	62.90
None	17	11.72	25	17.24	21	16.94
Alcohol consumption (amount of alcoholic beverages)						
≥2x per day	15	10.34	15	10.34	14	11.29

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<2x per day	65	44.83	70	48.28	51	41.13
None	65	44.83	59	40.69	57	45.97
Smoking status						
Non-smoker	98	67.59	107	73.79	90	72.58
Current smoker	13	8.97	11	7.59	6	4.84
Ex-smoker	34	23.45	27	18.62	26	20.97

More details on non-drug lipid-lowering therapy (incl. stratification by sex [male, female] and age [18-65 years, >65 years] are given in Appendix II (EAS, tables B9-1 – B9-17; EAS, tables 1FU8-1 – 1FU8-18 and 2FU8-1 – 2FU8-18).

(3) Drug utilization pattern in secondary prevention
The Extended Analysis Set (EAS) consisted of 145 patients with complete data on the 12-months follow-up.

The following table shows the proportions of patients with (any) pharmacotherapy over time (baseline visit [first digit], 12-months follow-up [second digit], 24-months follow-up [third digit]; 0= no medication; 1= medication intake; EAS).

Pharmacotherapy (type)	N	%
None		
0 0 0	157	67.38%
0 0 1	2	0.86%
0 1 0	6	2.58%
0 1 1	1	0.43%
1 0 0	3	1.29%
1 1 0	1	0.43%
1 1 1	3	1.29%
Beta blocker		
0 0 0	89	38.20%
0 0 1	10	4.29%
0 1 0	7	3.00%
0 1 1	17	7.30%
1 0 0	4	1.72%
1 0 1	2	0.86%
1 1 0	3	1.29%
1 1 1	41	17.60%
Other platelet aggregation inhibitor		
0 0 0	76	32.62%
0 0 1	3	1.29%
0 1 0	3	1.29%
0 1 1	16	6.87%
1 0 0	3	1.29%
1 0 1	3	1.29%
1 1 0	14	6.01%

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1 1 1	55	23.61%
Oral Antidiabetic		
0 0 0	128	54.94%
0 0 1	2	0.86%
0 1 0	1	0.43%
0 1 1	1	0.43%
1 0 0	6	2.58%
1 0 1	3	1.29%
1 1 0	2	0.86%
1 1 1	30	12.88%
Insulin		
0 0 0	153	65.67%
1 0 0	2	0.86%
1 0 1	1	0.43%
1 1 0	4	1.72%
1 1 1	13	5.58%
Renin inhibitor		
0 0 0	171	73.39%
0 1 0	1	0.43%
1 0 0	1	0.43%
Muscarinic receptor blocker		
0 0 0	173	74.25%
Angiotensin II receptor blocker		
0 0 0	162	69.53%
0 0 1	2	0.86%
0 1 0	4	1.72%
1 0 0	1	0.43%
1 0 1	1	0.43%
1 1 1	3	1.29%
Fibrates		
0 0 0	165	70.82%
0 0 1	3	1.29%
0 1 0	1	0.43%
1 0 0	1	0.43%
1 1 0	1	0.43%
1 1 1	2	0.86%
Cholesterol resorption inhibitor		
0 0 0	96	41.20%
0 0 1	2	0.86%
0 1 0	1	0.43%
0 1 1	8	3.43%
1 0 0	12	5.15%
1 0 1	7	3.00%

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1 1 0	5	2.15%
1 1 1	42	18.03%
PCSK-9-Inhibitor		
0 0 0	125	53.65%
0 0 1	1	0.43%
0 1 0	1	0.43%
0 1 1	9	3.86%
1 0 0	6	2.58%
1 0 1	1	0.43%
1 1 0	3	1.29%
1 1 1	27	11.59%
Statins		
0 0 0	18	7.73%
0 0 1	3	1.29%
0 1 0	1	0.43%
0 1 1	5	2.15%
1 0 0	10	4.29%
1 0 1	10	4.29%
1 1 0	10	4.29%
1 1 1	116	49.79%
GLP-1 receptor agonist		
0 0 0	162	69.53%
0 0 1	1	0.43%
0 1 0	1	0.43%
1 0 0	2	0.86%
1 1 0	1	0.43%
1 1 1	6	2.58%
P2Y12 antagonist		
0 0 0	151	64.81%
0 0 1	4	1.72%
0 1 0	1	0.43%
0 1 1	1	0.43%
1 0 0	9	3.86%
1 0 1	1	0.43%
1 1 1	6	2.58%
Vitamin-K antagonist		
0 0 0	167	71.67%
1 0 0	3	1.29%
1 1 1	3	1.29%
Direct Oral Anticoagulant (DOA)		
0 0 0	165	70.82%
0 1 0	3	1.29%
1 1 0	1	0.43%

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1 1 1	4	1.72%
Angiotensin II receptor blocker		
0 0 0	105	45.06%
0 0 1	7	3.00%
0 1 0	3	1.29%
0 1 1	7	3.00%
1 0 0	5	2.15%
1 0 1	4	1.72%
1 1 0	8	3.43%
1 1 1	34	14.59%
ACE inhibitor		
0 0 0	110	47.21%
0 0 1	2	0.86%
0 1 0	2	0.86%
0 1 1	3	1.29%
1 0 0	8	3.43%
1 0 1	2	0.86%
1 1 0	10	4.29%
1 1 1	36	15.45%
Diuretic		
0 0 0	124	53.22%
0 0 1	6	2.58%
0 1 0	2	0.86%
0 1 1	3	1.29%
1 0 0	11	4.72%
1 0 1	3	1.29%
1 1 0	4	1.72%
1 1 1	20	8.58%
If channel inhibitor		
0 0 0	163	69.96%
1 0 0	5	2.15%
1 1 1	5	2.15%
Other lipid-lowering therapy		
0 0 0	140	60.09%
0 0 1	3	1.29%
0 1 0	5	2.15%
0 1 1	6	2.58%
1 0 0	6	2.58%
1 0 1	4	1.72%
1 1 0	4	1.72%
1 1 1	5	2.15%
Calcium channel blocker		
0 0 0	120	51.50%

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0 0 1	3	1.29%
0 1 0	2	0.86%
0 1 1	4	1.72%
1 0 0	4	1.72%
1 0 1	3	1.29%
1 1 0	5	2.15%
1 1 1	32	13.73%

(4) Cardiovascular and cerebrovascular events within the follow-up period of two years
With regard to the **Extended Baseline Analysis Set** (taking into account all patients regardless of completeness of follow-up data; n= 233 patients) the following non-fatal events since baseline were documented:

Non-fatal events since baseline were documented in 14 patients (6.0%) at 12-months follow-up since baseline and in 24 patients (10.3%) at 24-months follow-up since baseline.

Event type, n (%)	12-months follow-up (since baseline) n= 233	24-months follow-up (since baseline) n=233
Myocardial infarction	2 (0.86) 95% CI: -0.00, 0.02	2 (0.86) 95% CI: -0.00, 0.02
Cardiac Catheter Examination without PCI	2 (0.86) 95% CI: -0.00, 0.02	5 (2.15) 95% CI: 0.00, 0.04
Balloon dilatation (PCI)	4 (1.72) 95% CI: 0.00, 0.03	6 (2.58) 95% CI: 0.01, 0.05
Bypass surgery	0	0
Stroke	0	0
TIA	0	0
Hospitalisation due to event	6 (2.58)	10 (4.29)
Hospitalisation due to event; *mean duration*	4.8 days (SD: 4.1)	4.5 days (SD: 4.0)
Rehabilitation	0	1 (0.43) 95% CI: -0.00, 0.01
Other inpatient stay	9 (3.86) 95% CI: 0.01, 0.06	14 (6.01) 95% CI: 0.03, 0.09
Other inpatient stay, *mean duration*	11.2 days (SD: 7.7)	18.5 days (SD: 30.1)

More details on non-fatal events (incl. stratification by sex [male, female] and age [18-65 years, >65 years] are given in Appendix II (EBAS, 12-months follow-up: tables 1FU2-1 – 1FU2-14; 24-months follow-up: tables 2FU2-1 – 2FU2-14).

With regard to the **Extended Analysis Set** (taking into account all patients with complete data on LDL cholesterol and correct timing at 12-months follow-up; n= 145) the following non-fatal events were documented:

Non-fatal events since baseline were documented in 7 patients (4.83%) at 12-months follow-up in 16 patients (11.03%) at 24-months follow-up since baseline.

Event type, n (%)	12-months follow-up (since baseline) n=145	24-months follow-up (since baseline) n=145

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Myocardial infarction	2 (1.38) 95% CI: -0.01, 0.03	2 (1.38) 95% CI: -0.01, 0.03
Cardiac Catheter Examination without PCI	0	3 (2.07) 95% CI: -0.01, 0.04
Balloon dilatation (PCI)	3 (2.07) 95% CI: -0.00, 0.04	5 (3.45) 95% CI: 0.00, 0.06
Bypass surgery	0	1 (0.7) 95% CI: -0.01, 0.02
Stroke	0	0
TIA	0	0
Hospitalisation due to event	4 (2.76)	8 (5.52)
Hospitalisation due to event; *mean duration*	4.5 days (SD: 3.7)	4.3 days (SD: 3.7)
Rehabilitation	0	1 (0.69) 95% CI: -0.01, 0.02
Other inpatient stay	3 (2.07) 95% CI: -0.00, 0.04	7 (4.83) 95% CI: 0.01, 0.08
Other inpatient stay, *mean duration*	9.3 days (SD: 8.1)	9.4 days (SD: 7.5)

More details on non-fatal events (incl. stratification by sex [male, female] and age [18-65 years, >65 years] are given in Appendix II (EAS, 12-months follow-up: tables 1FU2-1 – 1FU2-14; 24-months follow-up: tables 2FU2-1 – 2FU2-14).

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Discussions:	**(a) Key results – Part I (Analysis sets BAS / FAS)** In general: The HYDRA-FH registry was conducted in 35 participating sites in Germany. 218 patients were included in the baseline analyses and 31 patients were included in the full analysis set (FAS) to evaluate the longitudinal data. Of 218 patients in baseline, complete follow-up data (for both 12- and 24-months follow-up concurrently; regarding complete information on LDL values at follow-up and correct timing) were available in 31 patients. Overall, 187 patients were excluded from the longitudinal analyses (n= 29 patients with incomplete data for 12-months follow-up; 44 patients with incomplete data for 24-months follow-up; 114 patients with incomplete data for both 12- and 24-months follow-up). The main reasons for exclusion from longitudinal analyses were incorrect timing of LDL value assessment at follow-up and the lack of documented LDL values at follow-up. Duration of enrolment was on average 143.6 days (SD: 118.9 days). On average, 6.2 patients (SD: 6.2; MD: 3) were enrolled per study site. Baseline characteristics: 129 patients (59.2%) were male. The mean age of the patients was 60.9 years. The most common diseases and conditions in cardiovascular history were coronary heart disease (54.6%), PCI (33.5%), acute coronary syndrome (19.3%) and aortocoronary bypass (13.3%). The most common comorbidities in this population were arterial hypertension (74.3%), diabetes mellitus (41.7%), heart failure (22.9%), and heart valve disease (15.6%). The most frequent phenotypic findings in this population were xanthelasma (20.6%) and xanthomas (11.5%). A functional mutation in LDLR, apoB or PCSK9 gene was documented in only 19 patients (8.7%). With regard to the family history, the most frequent diseases and conditions were elevated cholesterol levels (62.4%), coronary heart disease (55.1%), and myocardial infarction (49.1%). LDL target achievement: Among the 31 patients with valid follow-up data, only very few achieved the therapeutic target of LDL < 70 mg/dl or a reduction of at least 50% from baseline (2 patients at 12-months follow-up and 4 patients at 24-months follow-up). Moreover, only a slight decrease in LDL-C could be observed over time (i.e. average reduction in LDL-C over time: -9.3% (SD: 23.1)from baseline to 12-months follow-up and -7.9% (SD: 31.2) from baseline to 24-months follow-up). Non-fatal events since baseline: In the overall population (n= 218), only few non-fatal events since baseline were observed (at 12-months follow-up: non-fatal events in 14 patients [6.42%; type of events: myocardial infarction, 2 (0.9%); balloon dilatation/PCI, 4 (1.8%); other hospitalization, 9 (4.1%)]; at 24-months follow-up: non-fatal events in 24 patients [11.01%; type of events: myocardial infarction, 2 (0.9%); cardiac catheterization without PCI, 5 (2.3%); other hospitalization, 14 (6.4%)]). Hospitalization due to a non-fatal event was observed in 6 patients (2.75%) with a mean duration of 4.8 days (12-months follow-up) and in 10 patients (4.59%) with a mean duration of 4.5 days (24-months follow-up). **(b) Key Results – Part II (Analysis sets EBAS / EAS)** In general: Taking into account less stringent criteria for the analysis sets (see Methodology), the analyzable population could be enlarged considerably: 233 patients were included in the baseline analyses and 145 patients were included in the extended analysis set (EAS) to evaluate the longitudinal data. Of 233 patients in baseline, complete follow-up data (for the 12- follow-up; regarding complete information on LDL values at follow-up and correct timing) were available in 145 patients. Overall, 88 patients were excluded from the longitudinal analyses. The main reasons for exclusion from longitudinal analyses were the fact that follow-ups were not performed by the sites in a considerable amount of patients (n= 37) and the lack of documented LDL values at follow-up.

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	Duration of enrolment was on average 143.6 days (SD: 118.9 days). On average, 6.9 patients (SD: 5.9; MD: 4) were enrolled per study site. Baseline characteristics: 137 patients (58.8%) were male. The mean age of the patients was 61.1 years. The most common diseases and conditions in cardiovascular history were coronary heart disease (54.1%), PCI (33.5%), acute coronary syndrome (19.7%) and aortocoronary bypass (12.9%). The most common comorbidities in this population were arterial hypertension (72.13%), diabetes mellitus (40.8%), heart failure (22.3%), and heart valve disease (15.9%). The most frequent phenotypic findings in this population were xanthelasma (20.6%) and xanthomas (12.0%). A functional mutation in LDLR, apoB or PCSK9 gene was documented in only 19 patients (8.7%). With regard to the family history, the most frequent diseases and conditions were elevated cholesterol levels (63.1%), coronary heart disease (56.2%), and myocardial infarction (48.5%). LDL target achievement: Among the 145 patients with valid follow-up data, only few achieved the therapeutic target of LDL < 70 mg/dl or a reduction of at least 50% from baseline (25 patients at 12-months follow-up and 23 patients at 24-months follow-up). Moreover, only a slight to moderate decrease in LDL-C could be observed over time (i.e. average reduction in LDL-C over time: -12.2% (SD: 31.0) from baseline to 12-months follow-up and -6.7% (SD: 51.8) from baseline to 24-months follow-up). Non-fatal events since baseline: In the overall population (n= 233), only few non-fatal events since baseline were observed (at 12-months follow-up: non-fatal events in 14 patients [6.0%; type of events: myocardial infarction, 2 (0.9%); balloon dilatation/PCI, 4 (1.7%); other hospitalization, 9 (3.9%)] ; at 24-months follow-up: non-fatal events in 24 patients [10.3%); type of events: myocardial infarction, 2 (0.9%); cardiac catheterization without PCI, 5 (2.1%); other hospitalization, 14 (6.0%)]). Hospitalization due to a non-fatal event was observed in 6 patients (2.58%) with a mean duration of 4.8 days (12-months follow-up) and in 10 patients (4.29%) with a mean duration of 4.5 days (24-months follow-up). **(c) Interpretation and generalizability:** There are considerable limitations in the interpretation of the results regarding lipid target achievement due to the fact that only a small proportion of the initially enrolled patients could be included in the analysis of the follow-up data (BAS/FAS: 31 of 218 patients; EBAS/EAS: 145 of 233 patients). The main reasons for exclusion from the longitudinal analyses were with regard to BAS/FAS the incorrect timing of LDL value assessment at follow-up and the lack of documented LDL values at follow-up and with regard to EBAS/EAS the fact that follow-ups were not performed by the sites in a considerable amount of patients (n= 37; 16%) and the lack of documented LDL values at follow-up.

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Conclusions:	Overall, taking into account less stringent criteria for the analysis sets (e.g. expanding the acceptable time window for follow-ups from 3 to 4 months etc.; see section Methodology) the analyzable population could be enlarged considerably, but was still unsatisfactory with roughly 62% of the patients with analyzable follow-up data. The main reasons (i.e. follow-ups not performed and lack of documented LDL values or the incongruous timing of these) are largely owed to the non-interventional design of the study. This mainly affects the availability of the required lipid values (especially LDL as the primary endpoint): it is very likely that this non-interventional design of the study did not sufficiently reflect clinical routine regarding the assessment of lipid parameters. As opposed to an interventional clinical trial, study site visits of the patients to collect a satisfactory proportion of the endpoints could not be performed; thus, it was inevitable to cope with the amount of lipid parameters available within the limits of clinical routine. Lack of representativeness: In general, the study itself was subject to a considerable sample bias due to its observational design. In addition, it is doubtable, whether the observed sample was representative for the target population pf patients with familial hypercholesterolemia (FH), in particular since participation was strictly voluntary and it can, thus, be expected that not every eligible patient finally consented to participate. In this study, only few patients consented to participate (it was planned to include 500 patients, while eventually only n= 218 [BAS] and n= 233 [EBAS] were enrolled at baseline).Moreover, longitudinal data were available for even fewer patients (FAS: n= 31; EAS: n= 145). The lack of representativeness is particularly reflected in the collected data and their corresponding statistical characteristics (i.e. the considerable lengths of the 95% confidence intervals as well as the large standard deviations indicate rather low precision). In addition, mitigating these limitations with quality auditing measures was not entirely promising, since only a very small amount of auditing visits at sites were initially scheduled to be performed (i.e. in 5% of the sites, only).
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