An estimation of the consequences of reinforcing the 2016 and 2019 ESC/EAS guidelines on current lipid-lowering treatment in patients with type 2 diabetes in tertiary care – a SwissDiab study

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Abstract

Background

In 2019, the ESC/EAS updated the 2016 guidelines for the management of dyslipidaemias recommending more stringent LDL-cholesterol (LDL-C) targets in diabetes mellitus type 2 (DM2). Based on a real-world patient population, this study aimed to determine the feasibility and cost of attaining guideline-recommended LDL-C targets, and assess cardiovascular benefit.

Methods

The Swiss Diabetes Registry is a multicentre longitudinal observational study of outpatients in tertiary diabetes care. Patients with DM2 and a visit 01.01.2018 – 31.08.2019 that failed the 2016 LDL-C target were identified. The theoretical intensification of current lipid-lowering medication needed to reach the 2016 and 2019 LDL-C target was determined and the cost thereof extrapolated. The expected number of MACE prevented by treatment intensification was estimated.

Results

294 patients (74.8%) failed the 2016 LDL-C target. The percentage of patients that theoretically achieved the 2016 and 2019 target with the indicated treatment modifications were: high-intensity statin, 21.4% and 13.3%; ezetimibe, 46.6% and 27.9%; PCSK9 inhibitor (PCSK9i), 30.6% and 53.7%; ezetimibe and PCSK9i, 1.0% and 3.1%, whereas one (0.3%) and five patients (1.7%) failed to reach target, respectively. Achieving the 2016 versus 2019 target would reduce the estimated 4-year MACE from 24.9 to 18.6 versus 17.4 events, at an additional annual cost of medication of 2,140 CHF versus 3,681 CHF per patient, respectively.

Conclusions

For 68% of the patients, intensifying statin treatment and/or adding ezetimibe would be sufficient to reach the 2016 target, whereas 57% would require cost-intensive PCSK9i therapy to reach the 2019 target, with limited additional medium-term cardiovascular benefit.

Word count abstract: 250

Lay summary

Based on 294 patients with type 2 diabetes and elevated LDL-cholesterol, this study looked at how much patients' lipid-lowering medication would need to be intensified for them to be able to reach the old and the new, lower treatment target for LDL-cholesterol that was introduced in 2019, along with the cost and feasibility, and estimated cardiovascular benefits of doing so.

- The majority of patients would reach the old LDL-cholesterol target by optimizing therapy with statin and ezetimibe, with a clear expected cardiovascular benefit. It would however be difficult for the majority of patients to reach the new, lower LDL-cholesterol target, as this would require treatment with a PCSK9 inhibitor. This expensive treatment would not be reimbursed for the majority of patients that would need them. The additional expected cardiovascular benefit was also less clear.
- Tools that help physicians to weigh the additional reduction in cardiovascular risk that the patient might benefit from by reaching the new rather than the old LDL-cholesterol target against known benefits of targeting other important risk factors (e.g. smoking, physical inactivity, overweight and obesity) would help guide efficient cardiovascular risk management, and identify patients that would most benefit from PCSK9 inhibitor therapy.

Key words

Diabetes mellitus type 2, LDL-cholesterol, treatment target, ESC/EAS guideline, statin, ezetimibe, PCSK9 inhibitor

Background

Atherosclerotic cardiovascular disease (ASCVD) is the major cause of death and disability in patients with diabetes. Beside glycaemic control, low-density lipoprotein cholesterol (LDL-C) level is an important modifiable risk factor for the development of ASCVD [1, 2]. Guidelines for the management of dyslipidaemias by the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS) specify strict LDL-C targets in patients with diabetes mellitus type 2 (DM2). An update of the 2016 ESC/EAS guidelines was released in August 2019 [3, 4], which was also adopted in the 2019 ESC guidelines on diabetes, pre-diabetes and cardiovascular diseases developed in collaboration with the European Association for the Study of Diabetes [1]. In light of several clinical trials having clearly demonstrated the effectiveness of intensified lipid-lowering medication for the prevention of cardiovascular disease in patients with DM2 [5-7], with cardiovascular risk reduction being evident down to LDL-C levels <1 mmol/L [8], the recommended targets in DM2 were lowered from <1.8 mmol/L to <1.4 mmol/L in patients at very high risk of ASCVD, and from <2.6 mmol/L to <1.8 mmol/L in patients at high risk of ASCVD [3, 4]. In addition to the absolute target, ≥50% reduction of the LDL-C level before lipid-lowering medication was initiated should be obtained in patients at high or very high risk for ASCVD (**Table 1**).

Table 1. The 2016 and 2019 ESC/EAS guidelines on LDL-cholesterol in patients with type 2 diabetes mellitus.

ASCVD risk category	**LDL-cholesterol target**	
	2016 ESC/EAS guideline	**2019** ESC/EAS guideline
Very high risk	<1.8 mmol/L or ≥50% reduction if the baseline level is 1.8-3.5 mmol/L	<1.4 mmol/L and ≥50% reduction from baseline
High risk	<2.6 mmol/L or ≥50% reduction if the baseline level is 2.6-5.2 mmol/L	<1.8 mmol/L and ≥50% reduction from baseline
Moderate risk	<3 mmol/L	<2.6 mmol/L

ASCVD, atherosclerotic cardiovascular disease; EAS, European Atherosclerosis Society; ESC, European Society of Cardiology; LDL, low-density lipoprotein.

In Switzerland, prevention of ASCVD in daily clinical practice is based on the recommendations by the ESC/EAS. The national guidelines established by the lipid and atherosclerosis working group of the Swiss Society of Cardiology were updated in 2020, adopting the more stringent LDL-C targets by the ESC/EAS [9]. While the evidence for lowering LDL-C levels for prevention of ASCVD is clear, studies have repeatedly highlighted the difficulty and lack of LDL-C target attainment in daily clinical care. Among 22,063 patients on statin therapy in primary or secondary care in 2008/2009 across 11 European countries and Canada, 48% did not reach the LDL-C target [10]. In the most recent EUROASPIRE survey conducted in 27 European countries in 2016-17, 71.0% of patients hospitalized for a coronary event had an LDL-C level ≥1.8 mmol/L six to 24 months later [11]. A retrospective cross-sectional analysis based on electronic medical records from 540 general practitioners in Switzerland showed that the proportion of patients treated between September 2016 and August 2019 that reached the LDL-C target at the latest available visit dropped from 31.1% to 16.5% when implementing the 2019 ESC/EAS treatment recommendations [12]. Based on a recent study from Sweden, only 17% of more than 25,000 patients in the SWEDEHEART study reached the 2019 ESC/EAS LDL-C target despite close to 90% being treated with high-intensity statins [13]. The results of these studies indicate that a significant proportion of patients at risk of ASCVD would need intensified lipid-lowering combination therapy to reach the 2016 LDL-C target, implying that an even more aggressive combination therapy would be needed to reach the more stringent 2019 target.

High-intensity statins consistently lower LDL-C levels by 50%, but long-term adherence is poor and statin-associated muscle symptoms lead to discontinuation of treatment in up to 20% of users [1, 10, 14, 15]. Therefore, in addition to reinforcement of statin therapy, combination treatment with ezetimibe and/or proprotein convertase subtilisin/kexin type 9 inhibitor (PCSK9i) in addition to statins is likely required in

an increasing proportion of patients at high risk of ASCVD to reach recommended treatment targets. Since ezetimibe provides a rather modest ~24% reduction in LDL-C levels, a considerable number of patients may need the addition of PCSK9i, which is known to lower LDL-C levels by 60% on top of statins [1]. These compounds are generally well tolerated, but despite recent major price cuts the cost-effectiveness of PCSK9i therapy has been questioned and access continues to be limited by health authorities in many countries [16-18]. At the time of the analysis, the use of PCSK9i in Switzerland was restricted to patients with DM2 and prevalent ASCVD with LDL-C >2.6 mmol/L despite maximally tolerated statin therapy [19].

The practical implications of enforcing the 2019 ESC/EAS LDL-C targets in daily clinical care of outpatients with DM2 treated in tertiary diabetes care, a patient population usually at high or very high ASCVD risk, remain unclear. The aim of the current study was to provide an estimation of the extent of additional lipid-lowering medication that patients with elevated LDL-C based on the 2016 ESC/EAS targets would theoretically need, the cost thereof, and expected cardiovascular benefits in terms of major adverse cardiovascular events (MACE) prevented, when enforcing the new rather than the old LDL-C treatment targets in patients with DM2 currently enrolled in the Swiss Diabetes Registry (SwissDiab).

Materials and methods

Study population

SwissDiab is an ongoing multicentre longitudinal observation study of outpatients with diabetes mellitus in tertiary care. The objectives include assessment of diabetes care and management, prevalence and incidence of diabetes-related complications, and quality of life of the patients. The overall aim is to provide feedback on the state of daily clinical practice to help ensure that best clinical care is provided [20]. Eligible for participation are patients ≥18 years of age regardless of diabetes type (gestational diabetes excluded), duration, or treatment. Exclusion criteria include a life expectancy <1 year due to severe comorbidity or inability to comply with the study protocol. Patients are enrolled at the tertiary

diabetes care centres at the Cantonal Hospital of St. Gallen, Bern University Hospital (Inselspital), Zürich University Hospital, and since 2020 at the Geneva University Hospital. The coordinating centre is the Division of Endocrinology and Diabetes at the Cantonal Hospital of St. Gallen. Patients enrolled in SwissDiab attend a standardized annual health examination. Data on medical history, diabetes-related complications, cardiovascular risk factors, and medication are collected. Patients also answer questionnaires related to satisfaction with diabetes treatment and quality of life. Written informed consent was provided by all SwissDiab participants and the study protocol was approved by the local cantonal ethics committees (BASEC-Nr. PB_2016-01449).

Study design

Patients with DM2 and a SwissDiab study visit between the 1st of January 2018 and 31st August 2019 were included, i.e. 18 months prior to the release of the 2019 ESC/EAS guidelines. If a patient had more than one visit during this time period the most recent was used, unless missing data justified the use of the previous visit. The ASCVD risk and LDL-C target was determined for each patient in accordance with the 2016 and 2019 ESC/EAS guideline, respectively [3, 4] (**Table 1**). The patients that did not reach the 2016 ESC/EAS LDL-C target were eligible for the current analysis.

Baseline and current LDL-C levels

Blood was drawn following an overnight fast and plasma LDL-C was measured according to routine methods at the laboratory medicine at each centre (**Supplementary Table 1**). The LDL-C level prior to statin initiation (hereafter referred to as baseline LDL-C), was retrieved retrospectively from the medical records. Baseline LDL-C was defined as the most recent available LDL-C level within three years prior to initiation of lipid-lowering medication. If a baseline LDL-C level could not be retrieved retrospectively, it was extrapolated based on the average LDL-C-lowering effect of the current lipid-lowering medication; assuming 25%, 35%, and 50% reduction for low-, medium-, and high-intensity statins, respectively, 6% for fibrates, 24% for ezetimibe, and 60% for PCSK9i [1].

Additional lipid-lowering medication needed to reach LDL-C target

The theoretical intensification of the current lipid-lowering medication needed for each patient to reach the 2016 and 2019 ESC/EAS LDL-C target was estimated by first ensuring that all patients were treated with high-intensity statin. For statin naïve patients high-intensity statin was added, whereas statin was up-titrated for patients on a sub-maximal intensity. This was done assuming an average LDL-C-lowering effect of 25%, 35%, and 50% for low-, medium-, and high-intensity statins, i.e. an additional 25% and 15% reduction of LDL-C was assumed when going from low- to high-intensity and medium- to high-intensity statin, respectively. The LDL-C-lowering effect of ezetimibe (24% reduction), PCSK9i (60% reduction), and ezetimibe + PCSK9i was then added in a stepwise manner until the resulting LDL-C level were in agreement with the 2016 and 2019 target, respectively.

The annual cost of the additional lipid-lowering medication needed to reach the respective LDL-C target was determined based on the average cost of each drug class (generic alternatives only) in accordance with the list prices provided by the Swiss Federal Office of Public Health [19], accessed in February 2021. Drug prices in Switzerland are ascertained according to the therapeutic efficacy with respect to drugs for the same indication, and are referenced to the prices in other European health systems.

Eligibility for reimbursement for PCSK9i therapy

The proportion of patients that would need the addition of a PCSK9i to reach the LDL-C target that would be eligible for reimbursement was determined based on the regulations of the Swiss Federal Office of Public Health. Eligible for reimbursement at the time of the analysis are patients with DM2 with established ASCVD and an LDL-C >2.6 mmol/L despite maximal tolerated statin therapy [19].

Estimation of cardiovascular benefits

Number of MACE prevented

The expected number of MACE among the SwissDiab patients over a 4-year period was extrapolated based on the reported incidence of MACE in the placebo arm of the DECLARE-TIMI 58 study, a cardiovascular outcome trial of dapagliflozin in patients with DM2 that exhibit similar clinical characteristics as the SwissDiab participants [21]. Rather than using the overall incidence rate observed in the placebo arm, the individual rates reported for participants with established ASCVD and multiple risk factors, respectively, were used. This was done to account for the slightly different patient characteristics, including a lower prevalence of established ASCVD, among the SwissDiab patients (**Supplementary Table 2-3**). Based on the average mmol/L reduction in LDL-C obtained in the SwissDiab patients as a result of the intensified lipid-lowering treatment, and assuming 1 mmol/L reduction in LDL-C corresponding to a 21% risk reduction in MACE over four years [22, 23], the expected number of MACE prevented over a 4-year period was estimated (**Supplementary information**).

Statistical analysis

Descriptive statistics are presented as medians with interquartile ranges (IQR) for continuous variables, and frequencies and proportions (%) for dichotomous variables unless otherwise indicated. The software SAS V.9.4 (SAS Institute, Cary, NC) was used for the analyses.

Results

Overall, 404 patients with DM2 had a study visit between the 1st of January 2018 and 31st of August 2019 (enrolled at the Division of Diabetes, Endocrinology, Nutritional Medicine, and Metabolism, Inselspital Bern, University Hospital, Bern; the Division of Endocrinology and Diabetes, Cantonal Hospital of St.Gallen; and the Division of Endocrinology, Diabetology and Clinical Nutrition, Zürich University

Hospital). LDL-C was missing in eight patients (2.0%) and an additional three (0.7%) lacked information needed to determine cardiovascular risk, leaving 393 patients (97.3%) with data available for evaluation of LDL-cholesterol target attainment (**Figure 1**). Seventy-four patients (18.8%) were not on statin therapy. Of the 319 patients (81.2%) on statin, baseline LDL-C could be retrieved retrospectively from the medical records for 183 patients (57.4%) and were extrapolated for the remaining 136 patients (42.6%).

Of the 393 patients with data available, 294 (74.8%) did not reach the 2016 ESC/EAS LDL-C target and were included in the analysis, of which 18 (6.1%) were at high ASCVD risk and 276 (93.9%) at very high ASCVD risk. Lipid-lowering medication was prescribed to 235 patients (79.9%). Of these, 234 patients (99.6%) were on statin therapy of which seven (3.0%) were also treated with fibrate, 18 (7.7%) with ezetimibe, and one (0.4%) with PCSK9i. One patient was on ezetimibe mono-therapy. Clinical characteristics of the patients included in the analysis are presented in **Table 2**.

Additional lipid-lowering medication needed to reach LDL-C target

The following intensifications of the current lipid-lowering medication were theoretically required for the patients to reach the 2016 and 2019 LDL-C target; prescribing high-intensity statin, 21.4% and 13.3% of the patients; adding ezetimibe, 46.6% and 27.9% of the patients; adding PCSK9i, 30.6% and 53.7% of the patients; adding ezetimibe and PCSK9i, 1.0% and 3.1% of the patients, respectively (**Figure 2**). One patient was already on statin, ezetimibe and PCSK9i without reaching the 2016 target and no further intensifications could be made. For five additional patients, the LDL-C level could theoretically not be lowered enough to reach the 2019 target.

As detailed in **Table 3**, the total annual cost for the additional medication needed for patients to reach the 2016 and 2019 LDL-C target was 627,139 CHF and 1,078,415 CHF, respectively, averaging 2,140 CHF and 3,681 CHF/patient (including patients that despite treatment intensification did not reach the LDL-C

target). One patient was already prescribed a statin, ezetimibe and a PCSK9i and was therefore excluded from the cost analysis.

Table 3. Estimated annual cost of intensifications needed to current lipid-lowering medication to reach recommended LDL-cholesterol targets.

	2016 LDL-C target [1]		**2019 LDL-C target [1]**	
Required drug intensification	n (%)	Annual cost (CHF)	n (%)	Annual cost (CHF)
High-intensity statin[2]	63 (21.5)	15 107	39 (13.3)	10 001
Statin[2] + ezetimibe	83 (28.3)	35 891	66 (22.5)	31 754
Ezetimibe	54 (18.4)	20 999	16 (5.5)	6 222
Statin[2] + PCSK9i	34 (11.6)	203 587	75 (25.6)	449 709
PCSK9i	56 (19.1)	332 572	85 (29.0)[3]	504 797
Ezetimibe + PCSK9i	3 (1.0)	18 983	12 (4.1)[4]	75 932
Total cost (CHF)		627 139		1 078 415

Data are n (%) unless otherwise specified. LDL-C, low-density lipoprotein cholesterol; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor [1] One patient was already prescribed statin, ezetimibe, and PCSK9i and was excluded from the cost analysis [2] High-intensity statin added to statin naïve patients or up-titrated for patients already on lower dose therapy [3] Of which two patients were not able to reach LDL-C target. [4] Of which three patients were not able to reach LDL-C target.

As shown in **Table 4**, 93 patients (31.6%) would need the addition of PCSK9i to reach the 2016 LDL-C target (including patients that despite treatment intensification would not reach the LDL-C target). Of these, 24 (25.8%) would be eligible for treatment based on the current regulation of the Swiss Federal Office of Public Health. Of the 172 patients (58.5%) that would need PCSK9i to reach the 2019 LDL-C target 26 (15.1%) would be eligible for treatment.

Table 4. Clinical characteristics of patients that require addition of PCSK9i to reach LDL-cholesterol targets.

Characteristics	2016 LDL-C target N_{tot}=93	2019 LDL-C target N_{tot}=172
Eligible for PCSK9i	24 (25.8)	26 (15.1)
LDL-C >2.6 mmol/L	64 (68.8)	74 (43.0)
CVD[1]	35 (37.6)	64 (37.2)
BMI ≥30 kg/m^2	59 (63.4)	108 (62.8)
Statin treatment	89 (95.7)	161 (93.6)
Low-intensity	1 (1.1)	2 (1.2)
Moderate-intensity	29 (32.6)	62 (38.5)
High-intensity	59 (66.3)	97 (60.3)
Ezetimibe	12 (12.9)	17 (9.9)

Data are frequency (%). BMI, body mass index; CVD, cardiovascular disease; LDL-C, low-density lipoprotein cholesterol; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor [1] In accordance with the 2016 and 2019 ESC/EAS definition, respectively.

Estimated cardiovascular benefits

MACE prevented

In the placebo arm of the DECLARE-TIMI 58 study, 15.3% of the participants with established ASCVD suffered a MACE within the median follow-up time of 4.2 years [21]. The corresponding number in the group without established ASCVD but with multiple risk factors was 5.2%. Among the 294 SwissDiab patients in the current study, 95 (32.3%) had established ASCVD, 139 (47.3%) had multiple risk factors and 60 (20.4%) did not fall into either category based on the definitions in the DECLARE-TIMI 58 study (**Supplementary Table 2 and 3**). Based on the 2016 ESC/EAS guidelines, 83% of the patients in the latter group were categorized as being at very high risk of ASCVD and the remaining 17% at high risk of ASCVD. For the sake of the analysis these 60 patients were thus included in the group with multiple risk factors.

Based on the stratified rates reported in the DECLARE-TIMI 58 study, 24.9 MACE were expected to occur among the SwissDiab patients over four years. The additional lipid-lowering medication needed for

patients to reach the 2016 LDL-C target resulted in an average LDL-C reduction of 1.2±0.8 mmol/L. Assuming that 1 mmol/L reduction in LDL-C levels reduces the 4-year risk of MACE by 21% [22, 23], this would translate to a 25.2% risk reduction among the SwissDiab patients. Intensifying lipid-lowering medication to ensure patients reach the 2016 LDL-C target would thus theoretically prevent 6.3 MACE among the 294 SwissDiab patients over four years, equivalent to 5.4 events prevented per 1000 patient years. Similarly, an average LDL-C reduction of 1.4±0.8 mmol/L was required for patients to reach the 2019 LDL-C target, which would theoretically prevent 7.5 MACE, equivalent to 6.4 events prevented per 1000 patient years. Enforcing the 2019 rather than the 2016 LDL-C target would thus prevent 1.2 additional MACE over a 4-year period in our SwissDiab study population of 294 patients, or 1.0 event per 1000 patient years (more details available in **Supplementary information**).

If instead assuming that no MACE would occur over four years among the 60 SwissDiab patients with neither established ASCVD nor multiple risk factors based on the DECLARE TIMI-58 definition, the number of expected MACE would reduce from 24.9 to 21.8, with 1.1 instead of 1.2 additional MACE expected to be prevented by enforcing the 2019 rather than the 2016 LDL-C target (**Supplementary information**).

The 4-year cost of the additional lipid-lowering medication needed for patients to reach the 2016 and 2019 LDL-C target was 2,508,557 CHF and 4,313,661 CHF, respectively (**Supplementary Table 4**).

Discussion

The estimations in the current study indicate that for 68% of the patients the addition of high-intensity statin and/or ezetimibe would be sufficient to reach the 2016 ESC/EAS LDL-C target, whereas 57% would need PCSK9i therapy to reach the more stringent 2019 LDL-C target. One patient was already on statin, ezetimibe, and PCSK9i without achieving LDL-C target, and for five patients LDL-C could not be lowered enough to reach the 2019 target. The annual cost of the additional medication needed to try to ensure

that the 293 patients reached the 2016 and 2019 ESC/EAS LDL-C target was estimated to 627,139 CHF and 1,078,415 CHF, respectively, averaging 2,140 CHF and 3,681 CHF per patient. Of the patients that theoretically would need a PCSK9i to reach the 2016 and 2019 LDL-C target, 26% and 15% would be eligible for reimbursement based on the current regulation of the Swiss Federal Office of Public Health, respectively. Theoretically intensifying the lipid-lowering medication to ensure patients reach the 2016 and 2019 LDL-C target was estimated to prevent 6.3 and 7.5 MACE over a 4-year period, respectively. Enforcing the 2019 instead of the 2016 LDL-C target over a 4-year period would cost an additional 1,805,104 CHF and would be expected to prevent 1.2 additional MACE.

In the current study, 294 out of 393 (74.8%) SwissDiab patients with DM2 did not meet the 2016 ESC/EAS LDL-C targets despite 81% being prescribed lipid-lowering medication. These results are in line with multiple studies showing the difficulty and lack of LDL-C target attainment in primary and secondary care [10-13, 24]. Among the 294 SwissDiab patients, 93 (32%) would need a PCSK9i to reach the 2016 ESC/EAS LDL-C target. A simulation study published in 2017 based on 105,269 adults with ASCVD identified in the US claims database found that 14.0-20.9% of patients would need a PCSK9i on top of oral lipid-lowering therapy to reach an LDL-C level of 1.8 mmol/L, the recommended target by the American College of Cardiology and the American Heart Association at the time [25]. The estimated number of SwissDiab patients that would need a PCSK9i to reach LDL-C target increased from 93 (32%) to 172 patients (59%) when enforcing the 2019 instead of the 2016 target. A similar increase in the proportion of patients that theoretically would require PCSK9i to reach the updated ESC/EAS LDL-C target was shown in another patient population at very high cardiovascular risk; using an analytical approach similar to the current study on 2,023 patients hospitalized for acute coronary syndromes in Switzerland between 2009 and 2014, 2.7% of the patients were estimated to need a PCSK9i to reach the recommended 2016 LDL-C target one year post-event [26]. In a recently published update of the analysis

among 2,521 patients (hospitalized between 2009 and 2017), 51% would need a PCSK9i to reach the 2019 LDL-C target one year post-event [27].

In Switzerland, the eligibility of reimbursement for PCSK9i therapy is restricted by the Swiss Federal Office of Public Health. During the time of the analysis, PCSK9i therapy in primary prevention is reimbursed for patients with DM2 and familial hypercholesterinaemia and an LDL-C >4.5 mmol/L. In secondary prevention reimbursement is approved for patients with DM2 and established ASCVD and LDL-C >2.6 mmol/L despite maximally tolerated statin dose. The current regulations would render 26% and 15% of the SwissDiab patients that would need PCSK9i therapy to reach the 2016 and 2019 LDL-C target eligible for treatment, respectively. These results highlight an apparent discordance between established best clinical practice recommendations and the treatment covered by health insurance. Strictly enforcing the current LDL-C treatment recommendations would leave a substantial amount of patients having to pay the annual treatment cost with PCSK9i, close to 6,000 CHF, out of pocket (69 out of 93 and 146 out of 172 patients with respect to the 2016 and 2019 LDL-C target, respectively).

Based on the current estimations, enforcing the 2016 ESC/EAS LDL-C target would prevent 6.3 MACE over a 4-year period at an additional cost of lipid-lowering medication of 2,508,557 CHF. Intensifying lipid-lowering medication for patients to reach the 2019 LDL-C target would cost an additional 1,805,104 CHF and would prevent 1.2 additional MACE. Despite the limitations and crude estimations of expected cardiovascular benefits, the results raise the question to what extent patients can be more appropriately stratified to reflect cardiovascular benefit from PCSK9i therapy. Although patients at very high or high ASCVD risk are treated as homogenous groups in the ESC/EAS guidelines, they show a range of estimated cardiovascular risk based on other metrics. The importance of taking into consideration all existing risk factors when assessing the cardiovascular risk of patients, and inversely, potential interventions for risk reduction has been illustrated in a large Swedish cohort study. Elevated HbA1c, LDL-C, and blood pressure, current smoking and presence of albuminuria were determined in 271,174 patients with DM2

and 1,355,870 matched controls. The risk of death, MI, or stroke among patients with DM2 without any risk factors were found to be similar to that observed among non-diabetic matched controls. The risk of adverse events increased with increasing number of risk factors present [28]. In light of this, and with limited health resources available, the high cost of PCSK9i therapy should be weighed against other potential interventions with proven cardiovascular risk reduction such as smoking cessation counselling (over 20% of the SwissDiab patients at very high ASCVD risk were active smokers) and weight reduction (60% of the SwissDiab patients at very high risk of ASCVD were obese). General clinical guidelines should always be considered in the context of patient-specific characteristics. But the current results illustrate the degree of uncertainty that the current guidelines present for individual physicians and health care systems on where resources are best served.

An important limitation of the study is that it is based on a set of theoretical assumptions. First, the analysis does not take into consideration that high-intensity statin treatment might not be possible in all patients due to statin intolerance, and the effect on LDL-C levels by up-titrating low- and medium-intensity statin might be overestimated. This has likely overestimated the magnitude of LDL-C reduction that could be obtained by maximizing statin therapy, which in turn would underestimate the magnitude of additional intensifications needed to the current lipid-lowering medication to ensure patients reach the 2016 and 2019 LDL-C targets, respectively. The same is probably true for the estimated lipid-lowering effect of combination therapies. Second, in 43% of the patients for which a baseline LDL-C could not be retrieved from the medical records the baseline LDL-C was extrapolated based on the average known effect of the current lipid-lowering medication that the patient received. Comparing the extrapolated baseline LDL-C value for the 57% of patients for which a baseline LDL-C could be retrieved from the medical records, the median (IQR) difference was 0 (-0.8, 0.9) mmol/L. A similar proportion of under- and over-estimation of the relative LDL-C target can thus be assumed for the patients where an extrapolated baseline LDL-C was used. Although this could influence the magnitude by which the individual patient's

lipid-lowering medication would need to be intensified to reach target, the effect on the overall results is likely limited. Third, we did not consider the newest developments in lipid-lowering pharmacotherapy. Bempedoic acid, like statins, targets the cholesterol biosynthesis pathway but specifically in the liver, and is thus not associated with the relatively common muscles-related side effects that often leads to statin discontinuation. Bempedoic acid has been shown to reduce LDL-C on top of maximally tolerated statin therapy with 14-18% [29, 30]. In addition, a 38% reduction in LDL-C was observed in patients with ASCVD or multiple cardiovascular risk factors treated with bempedoic acid in combination with ezetimibe on top of maximally tolerated statin therapy [31]. Bempedoic acid, available at a relatively low price, is thus likely to play an important role to improve cardiovascular risk prevention in patients with statin-intolerance, and patients for which PCSK9i is not obtainable. In the current study, 54.8% and 65.9% of the patients that needed the addition of PCSK9i to reach the 2016 and 2019 target, respectively, required >38% reduction to reach target (data not shown). Inclisiran is a long-acting, small interfering RNA that, similar to PCSK9i, targets hepatic PCSK9 production to ultimately increase the uptake of circulating LDL-C via the LDL-receptors. Inclisiran has been shown to reduce LDL-C levels by approximately 50%, with the added benefit of only two dose per year being required [32, 33]. The price in Switzerland falls within the same price range as PCSK9i. A further limitation is the cross-sectional nature of the study. While our estimations are based on one LDL-C measurement, which might not accurately reflect the general lipid profile of the patients, physicians should take into consideration the long-term lipid profile of the patient when making decisions about appropriate lipid-lowering therapy. The current study might thus have slightly overestimated the required intensifications needed to the current lipid-lowering treatment. In addition, the analysis assumes full patient adherence to treatment and any deviations would influence treatment costs and reduce expected cardiovascular benefits accordingly.

The expected number of MACE among the SwissDiab patients are based on the incidence reported in the placebo arm of the DECLARE-TIMI 58 study, a large clinical trial of patients with DM2 with ASCVD or very high risk of ASCVD [21]. SwissDiab patients had similar mean age and BMI as the DECLARE-TIMI 58 patients but with slightly longer median disease duration, better glycaemic control, a larger proportion of patients on insulin, and a lower prevalence of established ASCVD in accordance with the definition in the DECLARE-TIMI 58 study (Supplementary Table 3). It is thus likely that the estimated number of MACE among the SwissDiab patients over a 4-year period are an overestimation, and the cardiovascular benefits in terms of MACE prevented by enforcing the respective LDL-C target are, at least in the short term, likely to be overestimated. Although the current analysis is limited in its scope, the results illustrate the need for properly designed cost-effectiveness analysis with respect to implementation of the current LDL-C treatment recommendations in patients with DM2.

A recent study comparing basic clinical characteristics of 358 patients with DM2 enrolled in SwissDiab and 474 non-participating patients at one of the tertiary diabetes centres showed that SwissDiab participants tend to have slightly better controlled diabetes and related cardiovascular risk factors. Lipid-lowering medication was more common among SwissDiab participants compared to non-participating patients and the median (IQR) LDL-C was significantly lower (2.4 (1.9, 3.0) mmol/L vs 2.6 (1.9-3.3) mmol/L, respectively; *P*-value=0.03) [34]. These results indicate that the LDL-C levels in the general patient population in tertiary care is likely higher than observed in the current study and the extent to which current lipid-lowering medication in general would need to be intensified in this patient population is likely underestimated. SwissDiab is furthermore an observational study of outpatients with diabetes in tertiary care and as such the results are not generalizable to the overall diabetes population in Switzerland or other countries.

Conclusion

Adding statin and/or ezetimibe would be sufficient for the majority of the SwissDiab patients to reach the 2016 ESC/EAS LDL-C target. However, roughly three in five patients would need the addition of PCSK9i to reach the more stringent 2019 LDL-C target, at significantly increased treatment costs and limited expected medium-term cardiovascular benefit. The results highlight the need to better define the appropriate role of the LDL-C targets and PCSK9i in diabetes care and management, and the patients most likely to benefit.

List of abbreviations

ASCVD	Atherosclerotic cardiovascular disease
BASEC	Business administration system for ethics committees
BMI	Body mass index
CHF	Swiss francs
DECLARE-TIMI	Dapagliflozin Effect on CardiovascuLAR Events
DM2	Diabetes mellitus type 2
EAS	European Atherosclerosis Society
ESC	European Society of Cardiology
HbA1c	Glycated haemoglobin A1c
IQR	Interquartile range
LDL-C	Low-density lipoprotein cholesterol
MACE	Major adverse cardiovascular events
MI	Myocardial infarction
PCSK9	Proprotein convertase subtilisin/kexin type 9
PCSK9i	Proprotein convertase subtilisin/kexin type 9 inhibitor
SAS	Statistical Analysis System
SWEDEHEART	Swedish Web System for Enhancement of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies
SwissDiab	Swiss Diabetes Registry

Declarations

Ethics approval and consent to participate

Written informed consent was provided by all SwissDiab participants and the study protocol was approved by the regional cantonal ethics committees (Bern, Ostschweiz, und Zürich), BASEC-Nr. PB_2016-01449).

Consent for publication

Not applicable

Availability of data and materials

The dataset analysed during the current study is not publicly available as this is not approved by the participants within the framework of the informed consent, and because of possible identification of patients by individuals or organisations with access to overlapping data sets.

Competing interests

HS has received honoraria for attending an Advisory Board Meeting for AstraZeneca. RL has received honoraria for talks and attended invited Advisory Board Meetings for Abbott, AstraZeneca, Bayer, Boehringer Ingelheim, Daiichi Sankyo, Novo Nordisk, Merck Sharp & Dohme, and Sanofi. SB has received honoraria for talks and attended invited Advisory Board Meetings for Amgen, Bayer, Daichii-Sankyo, Novartis, NovoNordisk, and Sanofi. All other authors declare that they have no competing interests.

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Authors' contribution

MB and SB conceptualized the research question, FR, HS, MB, and SB contributed to the analytical plan, HS, MB, ML, and RL provided data, FR performed the statistical analysis, FR and HS interpreted the results and drafted the manuscript. All authors critically appraised the paper.

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Information about additional files:

Filename: Singeisen_Additional File

File format: DOC

Title of data: An estimation of the consequences of reinforcing the 2016 and the 2019 ESC/EAS guidelines on current lipid-lowering treatment in patients with type 2 diabetes in tertiary care – Supplementary material

1 Description of data: Supplementary information and data (indexed on the first page)

References

1. Cosentino F, Grant PJ, Aboyans V, et al. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. *Eur Heart J*. 2020;**41**(2):255-323.
2. Howard BV, Robbins DC, Sievers ML, et al. LDL cholesterol as a strong predictor of coronary heart disease in diabetic individuals with insulin resistance and low LDL: The Strong Heart Study. *Arterioscler Thromb Vasc Biol*. 2000;**20**(3):830-5.
3. Catapano AL, Graham I, De Backer G, et al. 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias. *Eur Heart J*. 2016;**37**(39):2999-3058.
4. Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J*. 2020;**41**(1):111-88.
5. Cholesterol Treatment Trialists C, Fulcher J, O'Connell R, et al. Efficacy and safety of LDL-lowering therapy among men and women: meta-analysis of individual data from 174,000 participants in 27 randomised trials. *Lancet*. 2015;**385**(9976):1397-405.
6. Giugliano RP, Cannon CP, Blazing MA, et al. Benefit of Adding Ezetimibe to Statin Therapy on Cardiovascular Outcomes and Safety in Patients With Versus Without Diabetes Mellitus: Results From IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial). *Circulation*. 2018;**137**(15):1571-82.
7. Sabatine MS, Leiter LA, Wiviott SD, et al. Cardiovascular safety and efficacy of the PCSK9 inhibitor evolocumab in patients with and without diabetes and the effect of evolocumab on glycaemia and risk of new-onset diabetes: a prespecified analysis of the FOURIER randomised controlled trial. *Lancet Diabetes Endocrinol*. 2017;**5**(12):941-50.
8. Giugliano RP, Pedersen TR, Park JG, et al. Clinical efficacy and safety of achieving very low LDL-cholesterol concentrations with the PCSK9 inhibitor evolocumab: a prespecified secondary analysis of the FOURIER trial. *Lancet*. 2017;**390**(10106):1962-71.
9. Riesen WF, Kaiser W, Gallino A, et al. Neue ESC/EAS-Dyslipidämie-Guidelines. *Swiss Medical Forum*. 2020;**20**(0910):140-48.
10. Gitt AK, Drexel H, Feely J, et al. Persistent lipid abnormalities in statin-treated patients and predictors of LDL-cholesterol goal achievement in clinical practice in Europe and Canada. *Eur J Prev Cardiol*. 2012;**19**(2):221-30.
11. De Backer G, Jankowski P, Kotseva K, et al. Management of dyslipidaemia in patients with coronary heart disease: Results from the ESC-EORP EUROASPIRE V survey in 27 countries. *Atherosclerosis*. 2019;**285**:135-46.

12. Meier R, Rachamin Y, Rosemann T, et al. The Impact of the 2019 European Guideline for Cardiovascular Risk Management: A Cross-Sectional Study in General Practice. *J Clin Med*. 2020;**9**(7):2140.
13. Allahyari A, Jernberg T, Hagstrom E, et al. Application of the 2019 ESC/EAS dyslipidaemia guidelines to nationwide data of patients with a recent myocardial infarction: a simulation study. *Eur Heart J*. 2020;**41**(40):3900-09.
14. Josan K, Majumdar SR, McAlister FA. The efficacy and safety of intensive statin therapy: a meta-analysis of randomized trials. *CMAJ*. 2008;**178**(5):576-84.
15. Law M, Rudnicka AR. Statin safety: a systematic review. *Am J Cardiol*. 2006;**97**(8A):52C-60C.
16. Arrieta A, Hong JC, Khera R, et al. Updated Cost-effectiveness Assessments of PCSK9 Inhibitors From the Perspectives of the Health System and Private Payers: Insights Derived From the FOURIER Trial. *JAMA Cardiol*. 2017;**2**(12):1369-74.
17. Kazi DS, Penko J, Coxson PG, et al. Cost-Effectiveness of Alirocumab: A Just-in-Time Analysis Based on the ODYSSEY Outcomes Trial. *Ann Intern Med*. 2019;**170**(4):221-29.
18. Kazi DS, Penko J, Coxson PG, et al. Updated Cost-effectiveness Analysis of PCSK9 Inhibitors Based on the Results of the FOURIER Trial. *JAMA*. 2017;**318**(8):748-50.
19. Swiss Federal Office of Public Health. Spezialitätenliste Schweiz . http://www.spezialitätenliste.ch. [accessed February-March 2021]
20. Schimke KE, Renstrom F, Meier S, et al. Compliance with guidelines for disease management in diabetes: results from the SwissDiab Registry. *BMJ Open Diabetes Res Care*. 2018;**6**(1):e000454.
21. Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med*. 2019;**380**(4):347-57.
22. Cholesterol Treatment Trialists (CTT) Collaboration. Efficacy and safety of statin therapy in older people: a meta-analysis of individual participant data from 28 randomised controlled trials. *Lancet*. 2019;**393**(10170):407-15.
23. Cholesterol Treatment Trialists (CTT) Collaboration. Kearney PM, Blackwell L, et al. Efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: a meta-analysis. *Lancet*. 2008;**371**(9607):117-25.
24. Halcox JP, Tubach F, Lopez-Garcia E, et al. Low rates of both lipid-lowering therapy use and achievement of low-density lipoprotein cholesterol targets in individuals at high-risk for cardiovascular disease across Europe. *PLoS One*. 2015;**10**(2):e0115270.
25. Cannon CP, Khan I, Klimchak AC, et al. Simulation of Lipid-Lowering Therapy Intensification in a Population With Atherosclerotic Cardiovascular Disease. *JAMA Cardiol*. 2017;**2**(9):959-66.

26. Gencer B, Koskinas KC, Raber L, et al. Eligibility for PCSK9 Inhibitors According to American College of Cardiology (ACC) and European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) Guidelines After Acute Coronary Syndromes. *J Am Heart Assoc*. 2017;**6**(11).
27. Koskinas KC, Gencer B, Nanchen D, et al. Eligibility for PCSK9 inhibitors based on the 2019 ESC/EAS and 2018 ACC/AHA guidelines. *Eur J Prev Cardiol*. 2021;**28**(1):59-65.
28. Rawshani A, Rawshani A, Franzen S, et al. Risk Factors, Mortality, and Cardiovascular Outcomes in Patients with Type 2 Diabetes. *N Engl J Med*. 2018;**379**(7):633-44.
29. Goldberg AC, Leiter LA, Stroes ESG, et al. Effect of Bempedoic Acid vs Placebo Added to Maximally Tolerated Statins on Low-Density Lipoprotein Cholesterol in Patients at High Risk for Cardiovascular Disease: The CLEAR Wisdom Randomized Clinical Trial. *JAMA*. 2019;**322**(18):1780-88.
30. Ray KK, Bays HE, Catapano AL, et al. Safety and Efficacy of Bempedoic Acid to Reduce LDL Cholesterol. *N Engl J Med*. 2019;**380**(11):1022-32.
31. Ballantyne CM, Laufs U, Ray KK, et al. Bempedoic acid plus ezetimibe fixed-dose combination in patients with hypercholesterolemia and high CVD risk treated with maximally tolerated statin therapy. *Eur J Prev Cardiol*. 2020;**27**(6):593-603.
32. Leiter LA, Teoh H, Kallend D, et al. Inclisiran Lowers LDL-C and PCSK9 Irrespective of Diabetes Status: The ORION-1 Randomized Clinical Trial. *Diabetes Care*. 2019;**42**(1):173-76.
33. Ray KK, Wright RS, Kallend D, et al. Two Phase 3 Trials of Inclisiran in Patients with Elevated LDL Cholesterol. *N Engl J Med*. 2020;**382**(16):1507-19.
34. Eichmuller T, Renstrom F, Schimke K, et al. Representativeness of the Swiss Diabetes Registry - a single centre analysis. *Swiss Med Wkly*. 2021;**151**:w20525.

Table 2. Characteristics of the 294 patients with type 2 diabetes mellitus included in the analysis.

Characteristics	n	median (IQR), or %
Females	81	27.6
Age, yrs	294	65.5 (58.6-71.4)
Age at diagnosis, yrs	293	51.0 (44.0-56.0)
Years since diagnosis, yrs	293	13.0 (8.0-20.0)
Higher education [1,2]	101	34.6
BMI, kg/m^2	294	31.2 (28.1-35.0)
BMI ≥30 kg/m^2	174	59.2
Waist circumference, cm	274	109.0 (98.3-117.0)
Systolic BP, mmHg	290	132.5 (122.0-144.0)
Diastolic BP, mmHg	290	79.0 (73.0-84.0)
Smoking status		
Current smoker	60	20.4
Former smoker	110	37.4
Never smoker	124	42.2
HbA1c, %	289	7.1 (6.5-7.9)
HbA1c, mmol/mol	289	54 (48-63)
Lipid levels, mmol/L		
Triglycerides	291	1.8 (1.3-2.6)
Total cholesterol	291	4.0 (3.5-4.8)
HDL-cholesterol	293	1.0 (0.9-1.2)
LDL-cholesterol	294	2.3 (2.0-2.9)
Baseline LDL-cholesterol [3,4]	294	3.5 (2.8-4.4)
Extrapolated baseline LDL-C	294	3.8 (2.9-4.6)
Dyslipidaemia [5,2]	209	71.6
eGFR, ml/min/1.73m^2 [6]	293	78.3 (58.7-93.8)
Diabetes-related complications		
Severe CKD [7,8]	8	2.7
Nephropathy [8,9]	124	42.3
Neuropathy [10]	149	50.7
Retinopathy [11]	51	17.4
CVD, 2016 ESC definition [12]	93	31.6
CVD, 2019 ESC definition [13]	96	32.7
Myocardial infarction	29	9.9
Stroke	15	5.1
Lipid-lowering therapy	236	80.0
Statin	234	79.6
Low intensity	7	3.0
Medium intensity	114	48.7
High intensity	113	48.3
Fibrate	7	2.4
Ezetimibe	19	6.5
PCSK9 inhibitor	1	0.3
Anti-hypertensive therapy [8]	230	78.5
Non-insulin ADs [8,14]	248	84.6
Insulin therapy [8]	187	63.8
Insulin + non-insulin ADs [8]	150	51.2

Data are median (IQR), or percent, unless otherwise specified. ACR, albumin-creatinine ratio; ADs, antidiabetic drugs; BMI, body mass index; BP, blood pressure; eGFR; estimated glomerular filtration rate; ESC, European Society of Cardiology; HbA1c, glycated haemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; OAD,

oral antidiabetic treatment; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor. [1] College or University degree [2] Information missing in two patients [3] LDL-cholesterol within three years prior to initiation of lipid-lowering medication [4] Extrapolated in 157 patients [5] Triglyceride ≥1.7 mmol/L and/or HDL-cholesterol <1.3 mmol/L in women; <1.0 mmol/L in men [6] Based on the CKD EPI equation [7] eGFR <30 ml/min/1.73m^2 [8] Information missing in one patient [9] Micro- or macro-albuminuria or albumin creatinine ratio >3 mg/mmol [10] Polyneuropathy, pallaesthesia MT I <5 on at least one foot or monofilament ≤3 on at least one foot. [11] Non-proliferative or proliferative retinopathy [12] Prevalence of prior MI, percutaneous transluminal coronary angioplasty (PTCA), coronary artery bypass grafting (CABG), stroke and/or current PAD by the 2016 ESC/EAS definition [13] CVD by the 2016 ESC definition + stable angina (CCS>0) [14] Including metformin, sulfonylurea, glinid, α-glukosidas inhibitor, dipeptidyl peptidase 4 inhibitor, glucagon-like peptide-1 receptor agonist, and sodium-glucose co-transporter 2 inhibitor.

Figure legends

Figure 1. Participant flowchart. Flowchart showing the exclusions applied when identifying the patients enrolled in the SwissDiab study that were eligible for analysis.

Figure 2. Theoretical intensifications of lipid-lowering medication needed to reach the 2016 and 2019 LDL-cholesterol targets. Pie charts showing the theoretical intensifications of current lipid-lowering medication needed for 294 patients with type 2 diabetes to reach the 2016 and 2019 ESC/EAS LDL-C target, respectively. DM2, diabetes mellitus type 2; EAS, European Atherosclerosis Society; ESC, European Society of Cardiology; LDL-C, Low-density lipoprotein cholesterol

Figure 1

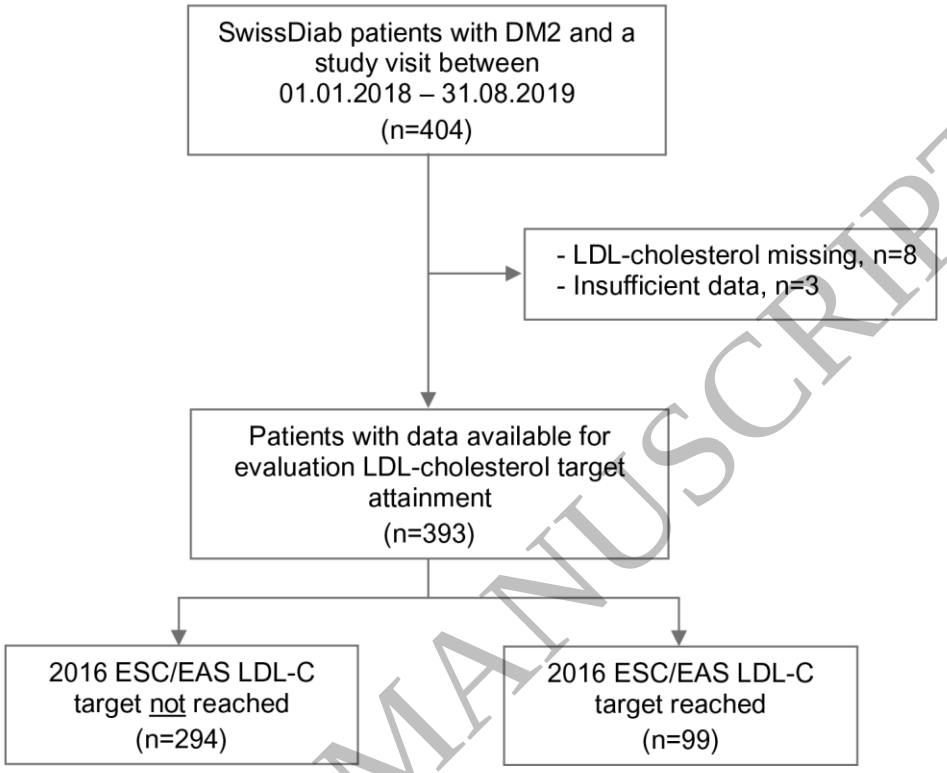

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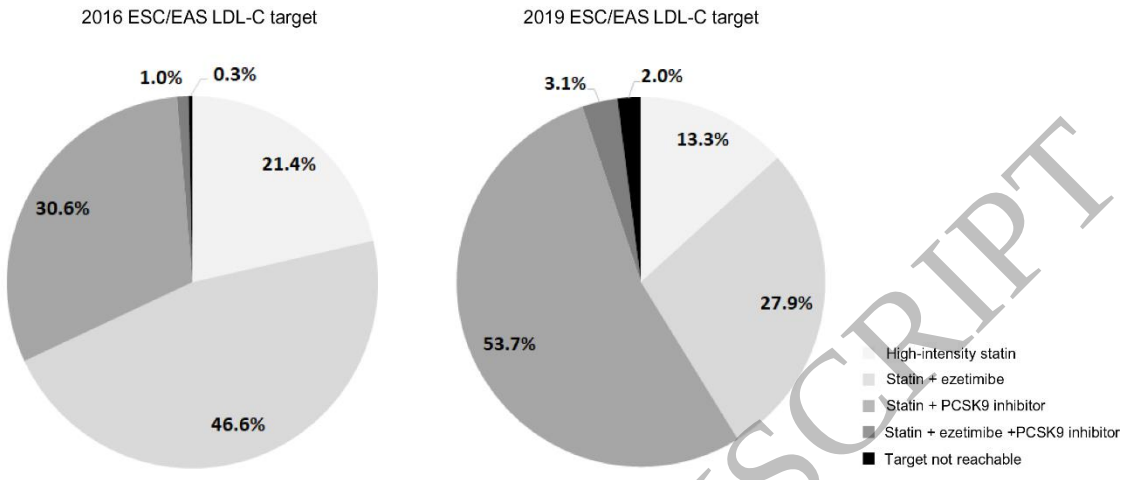
Figure 2



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