No effect of PCSK9 inhibitor alirocumab on the incidence of diabetes in a pooled analysis from 10 ODYSSEY Phase 3 studies

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Aims	Statins have modest adverse effects on glycaemic control. Alirocumab, a proprotein convertase subtilisin/kexin type 9 inhibitor, lowers low-density lipoprotein cholesterol. This study assessed the effects of alirocumab on new-onset diabetes and pre-diabetes incidence in individuals without diabetes at baseline.
Methods and results	Pooled analysis of 10 ODYSSEY Phase 3 trials ($n = 4974$) of 24–104 weeks duration. Six trials ($n = 4211$) were ≥ 52 weeks in length. Most patients received background maximally tolerated statin. Alirocumab effect on the rate of diabetes-related treatment-emergent adverse events (TEAEs), and/or fasting plasma glucose (FPG) and glycated haemoglobin A_{1C} (HbA$_{1C}$) was measured at baseline and every 12–24 weeks. Transition to diabetes analysis combined TEAE and FPG/HbA$_{1C}$ laboratory data. At baseline, 30.7% of individuals had diabetes and were excluded from the current analysis. The remaining 3448 individuals without diabetes had pre-diabetes (39.6%) or were normoglycaemic (29.7%). The hazard ratio (HR; 95% confidence interval) for diabetes-related TEAEs in alirocumab was 0.64 (0.36–1.14) vs. placebo and 0.55 (0.22–1.41) vs. ezetimibe. The HR associated for transition from pre-diabetes to new-onset diabetes for alirocumab was 0.90 (0.63–1.29) vs. placebo and 1.10 (0.57–2.12) vs. ezetimibe. Mean change in FPG/HbA$_{1C}$ over time showed no difference between treatment groups in patients without diabetes.
Conclusions	There was no evidence of an effect of alirocumab on transition to new-onset diabetes in 3448 individuals without diabetes at baseline with a follow-up period of 6–18 months, compared to either placebo or ezetimibe. Longer follow-up with larger number of individuals is needed to conclusively rule out an effect.
Keywords	Glycaemia • Diabetes • PCSK9 inhibitor • Low-density lipoprotein cholesterol • HbA$_{1C}$ • Fasting plasma glucose

Introduction

Recent evidence suggests that statin therapy increases the rate of transition to diabetes.[1–5] In those receiving rosuvastatin 20 mg in the JUPITER (Justification for Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) study,[3,4] there was a 28% excess risk of diabetes (hazard ratio [HR] 1.28, 95% confidence interval [CI] 1.07–1.54, $P = 0.01$) compared with placebo. The excess risk of diabetes occurred only in those with one or more risk factors for developing diabetes; no increase in diabetes was

observed in those individuals without a major diabetes risk factor (HR 0.99, 95% CI 0.45–2.21, P = 0.99).[4] Since the initial JUPITER report, several meta-analyses reported a small increase in the risk of statin-associated diabetes.[1,5] Although most reports conclude that the cardiovascular (CV) and mortality benefits from statin therapy outweigh the diabetes hazard, the US Food and Drug Administration (FDA) implemented safety label changes stating increase in glycated haemoglobin A_{1C} (HbA_{1C}) and fasting plasma glucose (FPG) levels with statin use.[6] Meanwhile, the exact mechanism of the statin-associated glycaemic effect is not understood raising the question of whether such an effect will pertain for other low-density lipoprotein cholesterol (LDL-C) lowering drugs.[7–10]

Alirocumab is a fully human proprotein convertase subtilisin/kexin type 9 (PCSK9) monoclonal antibody that lowers LDL-C levels by increasing the number of low-density lipoprotein receptors (LDLRs).[11] Alirocumab reduces LDL-C by up to 61% as monotherapy or in addition to statins, with or without other lipid-lowering therapy (LLT) in Phase 3 studies and is now approved by the FDA and European Medicines Agency (EMA) for use in hypercholesterolemia patients who require additional lowering of LDL-C in adjunct to diet and maximally tolerated statin therapy[12–18] In the US, alirocumab is indicated additionally in patients with clinical atherosclerotic CV disease, while the EMA has approved the use of alirocumab in patients with dyslipidaemia. Given that statin therapy for LDL-C reduction has been shown to affect glycaemic control, it is important to assess effects of alirocumab on the development of new-onset diabetes with regard to its safety profile as well as to yield mechanistic insight on statin-induced diabetes.

Methods

Study design

The pooled analysis included 10 main ODYSSEY Phase 3 randomized, double-blind, controlled trials (*n* = 4974) with subcutaneous alirocumab dosing every 2 weeks (Q2W) (24–102 weeks' duration). Patients were randomized to alirocumab, or to either placebo (LONG TERM [NCT01507831], FH I [NCT01623115], FH II [NCT01709500], HIGH FH [NCT01617655], COMBO I [NCT01644175]) or to ezetimibe (COMBO II [NCT01644188], MONO [NCT01644474], OPTIONS I [NCT01730040], OPTIONS II [NCT01730053], ALTERNATIVE [NCT01709513]) as comparators (Supplementary material online, *Table S1*). LONG TERM and HIGH FH utilized 150 mg Q2W from the outset (*Figure 1*) and the other studies used alirocumab 75 mg Q2W with uptitration to 150 mg Q2W at Week 12 if LDL-C goals were not achieved at Week 8 depending on CV risk. Treatment allocation was in addition to maximally tolerated statin therapy in ODYSSEY LONG TERM, FH I, FH II, COMBO I, COMBO II, and HIGH FH; in addition to commonly used statin doses which could be up-titrated in the OPTIONS I and II studies; and there was no background statin in the MONO and ALTERNATIVE studies. Intensity of statin doses across the pooled studies is provided in *Figure 1*.

Patients

All patients provided written informed consent and were aged ≥18 years. The MONO study included only patients with moderate CV risk, based on European guidelines.[19,20] The ALTERNATIVE study included statin intolerant patients with moderate, high, or very high CV risk and the remaining studies were in those at high or very high CV risk (*Figure 1*; Supplementary material online, *Table S1*). Inclusion criteria

for baseline LDL-C were ≥1.8 mmol/L for those who had experienced prior CV events or ≥2.6 mmol/L for those who had experienced no prior experience of CV events with the exception of the HIGH FH and LONG TERM study in which LDL-C had to be ≥4.14 mmol/L and ≥1.8 mmol/L, respectively, for all individuals (Supplementary material online, *Table S1*) at baseline.

Categorization of individuals into diabetes, pre-diabetes, or normoglycaemia

Individuals were categorized as having diabetes, pre-diabetes, or being normoglycaemic at baseline and follow-up. Four sources of data were used: medical history data at baseline; treatment-emergent adverse events (TEAEs); HbA_{1C}, measured once during baseline and then measured at Week 12, 24, 52, and 78; and FPG measured twice during the baseline phase and at Week 12, 24, 36, 52, 64, and 78. The term pre-diabetes (as per American Diabetes Association [ADA], guidelines)[21] was used instead of impaired glucose tolerance since evaluation of individuals for diabetes and pre-diabetes status was performed using FPG/HbA_{1C} measurements and not oral glucose tolerance test measurements.

For the main analyses, diabetes at baseline was considered present if a Custom Medical Dictionary for Regulatory Activities (MedDRA) Query (CMQ) of the medical history reported 'diabetes'. We considered this a more specific definition than additionally including the baseline phase FPG (≥7.0 mmol/L) or a single HbA_{1C} (≥6.5%) measure to define baseline diabetes but we also report sensitivity analyses using these laboratory measurements. As per the ADA 2015 *Standards of Care*, two different tests above diagnostic threshold (such as HbA_{1C} ≥6.5% and FPG ≥7.0 mmol/L) confirms diagnosis of diabetes.[22] The latter increased the number of patients with diabetes at baseline from 1526 to 1636 (+7%: Supplementary material online, *Table S2*). Pre-diabetes was defined as those assigned CMQ code 'pre-diabetes' recorded in the medical history OR baseline HbA_{1C} ≥5.7%, OR two values of FPG (at screening and randomization) ≥5.6 mmol/L.

Definition of transition to diabetes or to pre-diabetes during follow-up

Figure 1 details the definition but, in brief, transition to new-onset diabetes during follow-up in individuals without diabetes at baseline was explored in two ways. The first analysis was of TEAEs based on the CMQ 'diabetes mellitus or diabetic complications' which included MedRA terms that refer to 'high glucose or glycaemia'. New anti-diabetes drug use was requested to be reported in TEAEs. Second, in order to maximize the sensitivity for detecting transition to diabetes, additional analyses were conducted for transition to diabetes based on two consecutive values of FPG ≥7.0 mmol/L or two values of HbA_{1C} ≥6.5% at least 2 months apart consistent with diabetes or a CMQ code for 'diabetes' but excluding MedRA terms that refer to 'high glucose or glycaemia' (*Figure 1*). Thirty-eight patients reported new diabetes drug use; all were captured as transition to diabetes or pre-diabetes except three: two patients belonging to alirocumab and one to the placebo group.

In the absence of transition to diabetes, transition to pre-diabetes during follow-up in individuals with baseline normoglycaemia was defined as having a TEAE report with CMQ code 'pre-diabetes' or two consecutive values of FPG ≥5.6 mmol/L or two values of HbA_{1C} ≥5.7% at least 2 months apart. Regression to normoglycaemia among those with pre-diabetes at baseline was also quantified.

Additional sensitivity analysis of transition to new-onset diabetes during follow-up

To account for HbA_{1C}/FPG variability, a sensitivity analysis was performed in which FPG and HbA_{1C} were further required to have
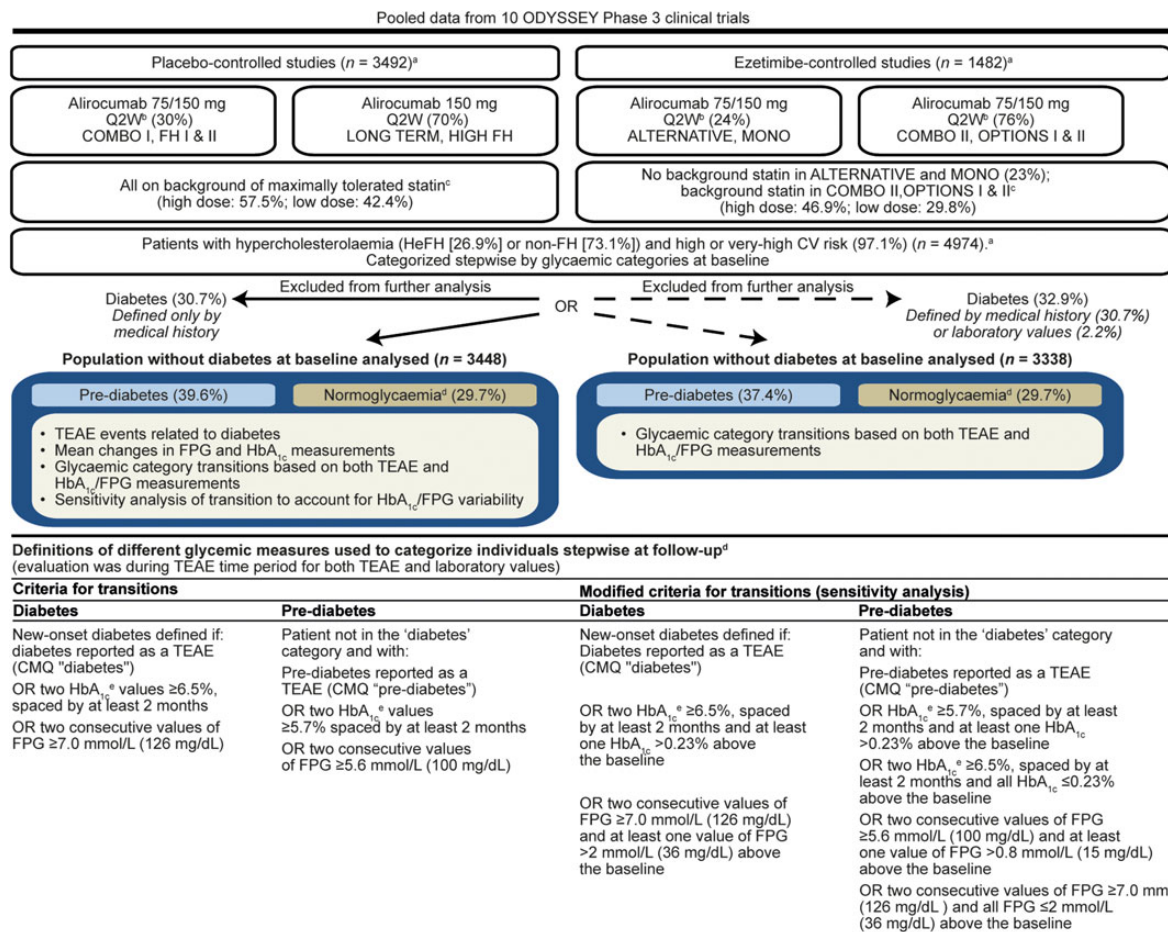
Figure 1 Schematic of population characteristics and study design. [a]*n* values represent number of individuals in the safety analysis. [b]Dose adjustment to 150 mg Q2W at Week 12 if LDL-C was not at goal by Week 8. [c]Background statin was maximally tolerated dose in COMBO II, atorvastatin 20−40 mg in OPTIONS I, and rosuvastatin 10−20 mg in OPTIONS II and no statin in MONO and ALTERNATIVE. In addition, patients were allowed to receive other LLT (except for ezetimibe in ezetimibe-controlled studies). Maximally tolerated statin was defined as high-dose statin (atorvastatin 40−80 mg, rosuvastatin 10−20 mg, or simvastatin 80 mg daily), or lower doses with an investigator-documented reason, e.g. intolerance. [d]An individual not in diabetes or pre-diabetes category as defined above was considered normoglycaemic. Categorization of individuals at both baseline and follow-up was performed stepwise. [e]HbA$_{1C}$ was measured once during baseline. CMQ, Custom MedDRA Query; CV, cardiovascular; FH, familial hypercholesterolaemia; FPG, fasting plasma glucose; HbA$_{1C}$, glycated haemoglobin A$_{1C}$; HeFH, heterozygous familial hypercholesterolemia; LLT, lipid-lowering therapy; Q2W, every 2 weeks; TEAE, treatment-emergent adverse event.

increased by a specified amount from baseline (*Figure 1*; Supplementary material online, Methods). *Post hoc* we considered whether analyses allowing two consecutive diagnostic values, one of FPG and one of HbA$_{1C}$ to qualify as diabetes were warranted. However, this would have increased the number of transitions very little; five individuals in the placebo-controlled pool (two in placebo, three in alirocumab) and one patient in the ezetimibe-controlled pool (one in alirocumab) and so was not reported further.

Statistical methods

The safety population was defined as all randomized individuals who received at least one full or partial dose of study drug. Data were pooled into four groups: alirocumab and placebo from the placebo-controlled trials; and alirocumab and ezetimibe from the ezetimibe-controlled trials. The evaluation period was from the first dose of study treatment up to the last injection plus 70 days (termed the TEAE period). Follow-up time was up to transition to diabetes or, if diabetes did not occur, on transition to pre-diabetes or else at the end of the TEAE period. Occurrence of events of interest was summarized using incidence rate, event rate per 100 patient-years, with 95% CI. The mid-*P* method was used to determine these CIs due to the discrete distribution of the endpoint and the low number of events.[23] The HR was calculated using a Cox proportional hazards model stratified on the study in order to compare treatment groups. Effects on HbA$_{1C}$ and FPG measurements are presented using descriptive statistics and graphs during the treatment period, i.e. up to 21 days after the last injection. These data focus on the placebo-controlled rather than ezetimibe-controlled studies as these had the longer follow-up (median exposure of 78 weeks vs. 24−38 weeks in the placebo-controlled vs. the ezetimibe-controlled studies, respectively). These analyses were not right-censored for new diabetes drugs initiation. SAS version 9.2 was used for the statistical analyses.

Results

Baseline categorization of individuals related to their glycaemic status

The prevalence of diabetes, pre-diabetes, and normoglycaemia was comparable between treatment groups in both placebo-controlled and ezetimibe-controlled pools (*Table 1*). Overall, across the studies, 30.7% had diabetes, 39.6% had pre-diabetes, and 29.7% were normoglycaemic. Demographic and baseline characteristics of individuals without diabetes at baseline for the randomized populations of the 10 studies were similar within the pooled treatment groups (Supplementary material online, *Table S3*). Median duration of alirocumab exposure of individuals without diabetes at baseline in the placebo-controlled pool was ~78 weeks. In the ezetimibe-controlled pool, median duration of exposure to study drug ranged from 24 to 38 weeks (Supplementary material online, *Table S4*). Overall, in individuals without diabetes at baseline, 63% received alirocumab 150 mg Q2W (mostly derived from LONG TERM where individuals were treated with a fixed dose of 150 mg Q2W) and 37% were treated with alirocumab 75 mg Q2W. Cumulative exposure for alirocumab vs. placebo was 2128.7 and 1078.2 patient-years, respectively; for alirocumab vs. ezetimibe, it was 474.6 and 292 patient-years, respectively (Supplementary material online, *Table S4*) among this subset of patients without diabetes at baseline. There was no difference between the treatment arms in the dosage category or frequency of background statin usage during the TEAE period (Supplementary material online, *Figure S1*).

Transition to diabetes based on treatment-emergent adverse event data alone

The transition to diabetes based solely on the TEAE terms among those without diabetes at baseline is shown in *Table 2*. Overall, there were 66 such transitions across the studies. There was no increase in the incidence of diabetes, thus defined, in the alirocumab group compared with controls with HR (95% CI) = 0.64 (0.36−1.14) in the placebo-controlled pool and 0.55 (0.22−1.41) in the ezetimibe-controlled pool. The combined estimate across the two pools was HR = 0.62 (0.38−1.00).

Changes in mean fasting plasma glucose and HbA$_{1C}$ measurements during follow-up by treatment allocation

Mean HbA$_{1C}$ (*Figure 2A*) and FPG (*Figure 2B*) change from baseline measures between different treatment groups compared with placebo control showed no meaningful difference in individuals without diabetes at baseline. As shown in *Figure 2*, both HbA$_{1C}$ and FPG varied slightly in both alirocumab and placebo groups over the course of the studies. These variations seen in mean HbA$_{1C}$ and FPG change from baseline were of similar magnitude in both the alirocumab and placebo groups (0.04% and 0.05% for HbA$_{1C}$ and −0.02 mmol/dL and −0.02 mmol/dL for FPG at the Week 78 visit, in alirocumab and placebo group, respectively). Minor variations in biochemical parameters can occur during trials and emphasize the need for appropriate comparator groups. Such individuals in the placebo-controlled pool were on background maximally tolerated statin therapy (*Figure 1*). As shown in Supplementary material online, *Figure S2*, there is no evidence of any significant adverse effect of alirocumab compared with ezetimibe in the very small number of participants not on background statins, in the ezetimibe-controlled studies. Due to the small sample size, the power to detect effects from these data is very limited.

Transition to diabetes based on combined treatment-emergent adverse event and fasting plasma glucose/HbA$_{1C}$ laboratory data

Transition to new-onset diabetes and pre-diabetes using both the TEAE data and the FPG and HbA$_{1C}$ data are shown in *Table 3* and further detailed in Supplementary material online, *Table S5*. Among

Table I Glycaemic categories at baseline in the pool of 10 Phase 3 studies

n (%)	Placebo-controlled pool		Ezetimibe-controlled pool	
	Placebo (*n* = 1174)	Alirocumab (*n* = 2318)	Ezetimibe (*n* = 618)	Alirocumab (*n* = 864)
Diabetes *as per medical history* (excluded from further analysis)[a]	356 (30.3)	698 (30.1)	190 (30.7)	282 (32.6)
Pre-diabetes[b]	453 (38.6)	903 (39.0)	254 (41.1)	359 (41.6)
As per medical history	28 (2.4)	52 (2.2)	20 (3.2)	33 (3.8)
As per laboratory data only	425 (36.2)	851 (36.7)	234 (37.9)	326 (37.7)
As per HbA$_{1C}$ only	214 (18.2)	452 (19.5)	118 (19.1)	138 (16.0)
As per FPG only	64 (5.5)	141 (6.1)	47 (7.6)	57 (6.6)
Normoglycaemia[c]	365 (31.1)	717 (30.9)	174 (28.2)	223 (25.8)

[a]Diabetes at baseline is defined as those assigned CMQ code 'diabetes' recorded in the medical history.
[b]Pre-diabetes defined as those assigned CMQ code 'pre-diabetes' recorded in the medical history OR baseline HbA$_{1C}$ ≥5.7%, OR two values of FPG (at screening and randomization) ≥5.6 mmol/L. HbA$_{1C}$ was measured once during baseline.
[c]An individual not in diabetes or pre-diabetes category as defined above was considered normoglycaemic. Categorization of individuals at baseline was performed stepwise.
CMQ, Custom MedDRA Query; FPG, fasting plasma glucose; HbA$_{1C}$, glycated haemoglobin A$_{1C}$.

Table 2 Transition to diabetes based on treatment-emergent adverse event data alone by treatment group

	Placebo-controlled pool		Ezetimibe-controlled pool	
	Placebo (n = 818)	Alirocumab (n = 1620)	Ezetimibe (n = 428)	Alirocumab (n = 582)
Incident diabetes mellitus or diabetic complications TEAE				
n (%,95% mid-P CI)	21 (2.6, 1.6−3.8)	27 (1.7, 1.1−2.4)	9 (2.1, 1.0−3.8)	9 (1.5, 0.8−2.8)
Number of patients with an event per 100 patient-year[a] (95% CI)	1.8 (1.1−2.8)	1.2 (0.8−1.7)	2.8 (1.3−5.4)	1.8 (0.8−3.4)
HR vs. control (95% CI)[b]	0.64 (0.36−1.14)		0.55 (0.22−1.41)	
Diabetes mellitus or diabetic complications TEAE, n (%)				
Diabetes mellitus or diabetic complications (CMQ)	21 (2.6)	27 (1.7)	9 (2.1)	9 (1.5)
Type 2 diabetes mellitus	13 (1.6)	21 (1.3)	2 (0.5)	5 (0.9)
Diabetes mellitus	4 (0.5)	4 (0.2)	2 (0.5)	2 (0.3)
Diabetic neuropathy	0	1 (<0.1)	0	0
Diabetic retinopathy	0	1 (<0.1)	0	0
Glucose tolerance decreased	0	1 (<0.1)	0	0
Blood glucose increased	1 (0.1)	0	3 (0.7)	1 (0.2)
Hyperglycaemia	3 (0.4)	0	2 (0.5)	1 (0.2)

MedDRA 17.1. The selection of preferred terms (PTs) is based on the CMQ 'diabetes mellitus or diabetic complications'.
n (%) = number and percentage of individuals with at least one event. Table sorted by decreasing incidence of PT in the alirocumab group of placebo-controlled pool. Individuals without diabetes at baseline defined as those not assigned CMQ code 'diabetes' recorded in medical history.
[a]Calculated as number of individuals with an event divided by total patient years.
[b]Calculated using a Cox model stratified on the study.
CI, confidence interval; CMQ, Custom Medical Query; HR, hazards ratio; MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event.

those with pre-diabetes at baseline, the majority remained in this category during follow-up. Overall, 8.7% of these individuals transitioned to new-onset diabetes and most progressions were based on laboratory parameters rather than clinical TEAE reports (Supplementary material online, Table S5). The HR (95% CI) for transition associated with alirocumab was not significant in either placebo (0.90 [0.63−1.29]) or ezetimibe (1.10 [0.57−2.12]) controlled pools (Table 3). Among those with pre-diabetes at baseline, regression to normoglycaemia was common but there was no difference between alirocumab and control groups on this regression.

Among those categorized normoglycaemic at baseline, there were no transitions to diabetes or pre-diabetes based on TEAEs and just three transitions to new-onset diabetes all based on FPG measurements (Supplementary material online, Table S5). Transition to pre-diabetes based on lab parameters was common across all treatment groups - about one-third of all individuals in the placebo-controlled pool and about one-quarter in the ezetimibe-controlled pool (Supplementary material online, Table S5). The HR (95% CI) for transition associated with alirocumab was not significant for either the placebo (1.20 [0.96−1.49]) or ezetimibe (0.88 [0.59−1.32]) controlled pools (Table 3).

The sensitivity analysis, assessing the variability of HbA$_{1C}$/FPG, did not alter the conclusions. Similar and non-significant HRs for transition to new-onset diabetes or pre-diabetes in both treatment groups was observed as for the main analyses (Supplementary material online, Table S6).

A further sensitivity analysis of the transition to new-onset diabetes further excluding those with baseline diabetes based also on laboratory baseline parameters rather than medical history alone did not alter the conclusions (Supplementary material online, Table S7). When analyses were restricted to the LONG TERM study in which the higher fixed dose of alirocumab 150 mg Q2W was used, the conclusions were unchanged. Our analysis includes all those who received at least one dose of drug. Discontinuation rates were low and were balanced between the treatment arms. In the placebo pool, the treatment discontinuation rate at 24 weeks was 7.7% in both the alirocumab- and placebo-treated groups. In the ezetimibe pool, the treatment discontinuation rate is 13.5% in the alirocumab-treated group and 15.7% in the ezetimibe-treated group.

Regarding general safety across the ODYSSEY Phase 3 programme in all 10 studies including individuals with and without diabetes, the percentage of individuals who experienced at least one TEAE, at least one treatment-emergent serious adverse event, and any TEAE leading to permanent treatment discontinuation was similar between the alirocumab and control groups. Injection-site reactions, influenza, and pruritus occurred more frequently in individuals receiving alirocumab than control. These events were transient and mild in intensity and did not necessitate treatment discontinuation.

Discussion

In this pooled analysis of 10 Phase 3 studies from the ODYSSEY programme, we found no evidence that alirocumab affects the incidence of new-onset diabetes in 3448 individuals without diabetes at baseline with a follow-up period of 6−18 months. Our study comprises all the available data to-date on transition to diabetes in the ODYSSEY programme for the PCSK9 inhibitor alirocumab. Further
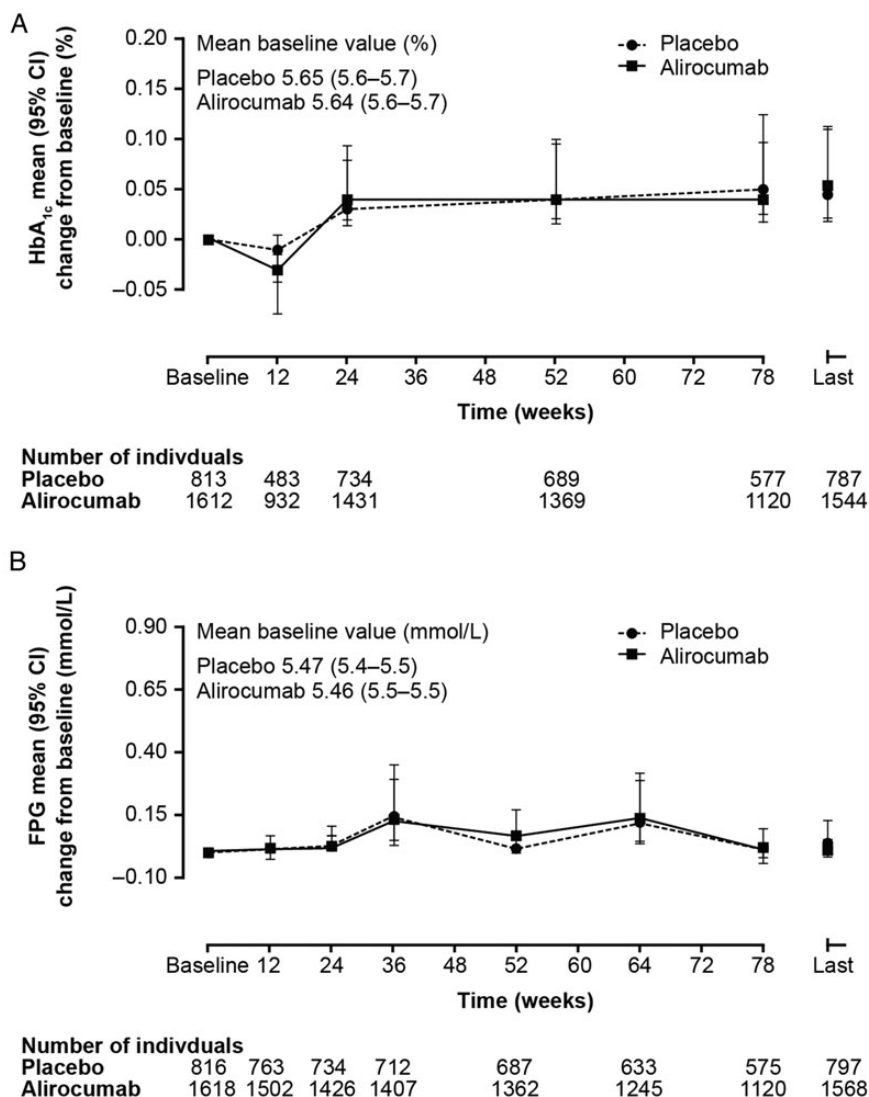
Figure 2 HbA$_{1C}$ (%) and fasting plasma glucose (mmol/L) trajectories (change from baseline) in those without diabetes at baseline: alirocumab vs. placebo. Placebo-controlled studies: Phase 3 (LONG TERM, FH I, FH II, HIGH FH, COMBO I). At Week 12, HbA$_{1C}$ was measured only in the LONG TERM. The last on-treatment value is defined as the last value collected up to 21 days after the last double-blind IMP injection. Patients who had that parameter assessed at baseline and/or at follow-up are included. Individuals without diabetes at baseline defined as those not assigned CMQ code 'diabetes' recorded in medical history. CMQ, Custom MedDRA Query; FPG, fasting plasma glucose; HbA$_{1C}$, glycated haemoglobin A$_{1C}$; IMP, Investigational Medicinal Product; CI, confidence interval.

data and longer follow-up are needed to conclusively rule out any effect. However, so far there was no evidence of an effect of alirocumab on transition to diabetes based on TEAEs related to diabetes and diabetic complications (*Table 2*), or on a composite measure combining TEAEs with threshold values for HbA$_{1C}$ or FPG (*Table 3*). Neither was there evidence of any effect on transition from normoglycaemia to pre-diabetes. Transitions in both directions between the normoglycaemic and pre-diabetes states were common. The percent of those patients transiting to pre-diabetes from normoglycaemia and the percent of patients regressing from pre-diabetes to normoglycaemia were both higher for alirocumab than control-treated pools but with no significant effects in either direction being

found. In contrast, a 9% increased risk for new-onset diabetes (odds ratio [OR] 1.09; 95% CI 1.02–1.17) was associated with statin use in a meta-analyses with 91 140 participants followed for an average of 4 years.[5] In a subsequent analysis of five statin trials (*n* = 32 752) with a weighted mean (standard deviation [SD]) follow-up of 4.9 (1.9) years, intensive-statin therapy was associated with an increased risk of new-onset diabetes compared with moderate-statin therapy (OR 1.12, 95% CI 1.04–1.22).[1] In the JUPITER trial where a similar 50% reduction in LDL-C to that reported in the placebo-controlled studies here was seen, the HR for physician-reported diabetes was 1.25 overall. While our CI for the equivalent diabetes incidence TEAEs are wide, they do exclude this estimate.

Table 3 Transition between glycaemic categories based on the treatment-emergent adverse event or laboratory data by treatment group[a]

	Placebo-controlled pool		Ezetimibe-controlled pool	
	Placebo (n = 818)	Alirocumab (n = 1620)	Ezetimibe (n = 428)	Alirocumab (n = 582)
Pre-diabetes at baseline, n/N1 (%)				
Developed diabetes[a]	47/453 (10.4)	84/903 (9.3)	14/254 (5.5)	26/359 (7.2)
Remained with pre-diabetes[a]	342/453 (75.5)	663/903 (73.4)	162/254 (63.8)	237/359 (66.0)
Regressed to normoglycaemia	64/453 (14.1)	156/903 (17.3)	78/254 (30.7)	96/359 (26.7)
Analysis of transition from baseline pre-diabetes to new-onset diabetes (by TEAE or laboratory measurements)				
n (%,95% mid-P CI)	47 (10.4, 7.8−13.4)	84 (9.3, 7.5−11.3)	14 (5.5, 3.2−8.9)	26 (7.2, 4.9−10.3)
Number of patients with an event/100 patient-year[b] (95% CI)	7.7 (5.6−10.2)	6.9 (5.5−8.5)	7.2 (3.9−12.1)	8.4 (5.5−12.3)
HR vs. control (95% CI)[c]	0.90 (0.63−1.29)		1.10 (0.57−2.12)	
Normoglycaemic at baseline, n/N1 (%)				
Developed diabetes[a]	1/365 (0.3)	1/717 (0.1)	0/174	1/223 (0.4)
Developed pre-diabetes[a]	115/365 (31.5)	261/717 (36.4)	42/174 (24.1)	59/223 (26.5)
Remained normoglycaemic	249/365 (68.2)	455/717 (63.5)	132/174 (75.9)	163/223 (73.1)
Analysis of transition from baseline normoglycaemic to pre-diabetes (by TEAE or laboratory measurements)				
n (%,95% mid-P CI)	115 (31.5, 26.9−36.4)	261 (36.4, 32.9−40.0)	42 (24.1, 18.2−30.9)	59 (26.5, 21.0−32.5)
Number of patients with an event/100 patient-year[b] 95% CI	28.8 (23.8−34.6)	35.1 (31.0−39.7)	45.2 (32.6−61.1)	42.9 (32.6−55.3)
HR vs. control (95% CI)[c]	1.20 (0.96−1.49)		0.88 (0.59−1.32)	

The number (n) represents the subset of the total number of individuals who met the criterion at least once during the TEAE period. The denominator (N1) for each parameter within a treatment group is the number of individuals who had that parameter assessed at follow-up (not missing) during the TEAE period, by baseline glycaemic category. Diabetes at baseline is defined using medical history. Pre-diabetes and diabetes at follow-up are defined using specific TEAE terms reported, raw values in HbA$_{1C}$, and FPG (Figure 1). MedDRA terms for high glucose or glycaemia were not included here since FPG and HbA$_{1C}$ are being directly queried.
[a]Breakdown of the basis of transition classification by TEAE or laboratory values in Supplementary material online, Table S5.
[b]Calculated as number of individuals with an event divided by total patient years.
[c]Calculated using a Cox model stratified on the study.
CI, confidence interval; FPG, fasting plasma glucose; HbA$_{1C}$, glycated haemoglobin A$_{1C}$; HR, hazards ratio; MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment emergent adverse event.

Few of the previous studies on statins analyzing the risk of new-onset diabetes have measured HbA$_{1C}$ or FPG serially during the treatment period. We found no meaningful difference in effect of alirocumab vs. comparator on changes in FPG or HbA$_{1C}$ when serially measured in these studies of up to 78 weeks follow-up. In contrast, a small but significant difference in HbA$_{1C}$ values was previously reported in a comparatively larger rosuvastatin trial of >15 000 individuals at 24 months exposure.[3,4] In the Collaborative Atorvastatin in Diabetes (CARDS) trial, among individuals with diabetes at baseline, atorvastatin 10 mg daily increased HbA$_{1C}$ by only 0.14% (95% CI 0.08−0.21) (1.5 mmol/mol [95% CI 0.8−2.3]) an effect that was seen within the first year of exposure in 2739 participants.[24]

An important aspect of our analysis is that the majority of people were already on background statin therapy. Around 54% of the individuals in our pooled analysis (n = 4974) were receiving high-dose background statin therapy, namely atorvastatin 40−80 mg, rosuvastatin 20−40 mg, or simvastatin 80 mg daily. There were too few persons in the trial programme not on any statin to examine incidence of diabetes in this group separately (n = 289 in the ezetimibe-controlled studies from MONO and ALTERNATIVE).

The exact molecular mechanism by which statins impact glycaemic control is not understood.[10] The most recent meta-analysis of 129 170 trial participants observed the effect of statin on the incidence of diabetes and reported an association with modestly increased body weight but, unlike effects on glycaemia, was dose independent.[7] In that same study, a Mendelian randomization performed with common variants of the *3-hydroxy-methylglutaryl coenzyme A reductase (HMGCR)* gene indicated the association of certain single nucleotide polymorphisms of *HMGCR* gene with type 2 diabetes, consistent with the glycaemic effects of statins resulting from the downstream effects of HMGCR inhibition itself rather than an off-target effect.[7] A 6-year observational cohort study in 8749 participants reported decreases in insulin sensitivity and insulin secretion associated in statin users.[9] Others have postulated a lipotoxic effect on the pancreatic β-cell due to increased accumulation of cholesterol in the β-cell. Consistent with this, the prevalence of type 2 diabetes was reduced in the presence of *LDLR* mutations in HeFH individuals suggesting a causal relationship between LDLR-mediated transmembrane cholesterol transport and type 2 diabetes and inverse associations were found between type 2 diabetes incidence and LDL-C

levels in the Framingham Heart Study.[25,26] Given the uncertainty regarding the underlying mechanism, an important question is whether the increased risk of new-onset diabetes is an inevitable consequence of LDL-C lowering with any drug class. A recent analysis of 18 144 individuals on background statin therapy in the IMPROVE-IT (IMProved Reduction of Outcomes: Vytorin Efficacy International Trial) programme, associated ezetimibe with a net 24% reduction in LDL-C vs. placebo but found no difference in the new-onset of diabetes between groups.[27] While this suggests that a glycaemic effect is not inevitable with LDL-C lowering, the question remains whether more powerful LDL-C lowering agents, or those that increase LDL receptor levels as statins and PCSK9 inhibitors do, will lead to a worsening of glycaemia.

Accordingly, our data on the alirocumab trials to date are important in suggesting that PCSK9 inhibition may not lead to hyperglycaemia. For evolocumab, another drug in the PCSK9 inhibitor class, Blom *et al.* reported no significant effects on glycaemia in a smaller dataset of 901 participants in the DESCARTES (Durable Effect of PCSK9 Antibody CompARed wiTh placEbo Study) trial followed for 52 weeks[28] and Henry *et al.* reported no effect on glycaemia in 1104 participants over 52 weeks in the OSLER trial.[29] A recent random-effects meta-analysis of randomized clinical trials comparing the efficacy of evolocumab, placebo, and ezetimibe[30] also found no evidence of evolocumab effect on glycaemic measures.[30] Other sources of data on the effect of PCSK9 inhibition on glycaemia have been inconclusive. In a recent Mendelian randomization analysis, Bonnefond *et al.* reported that the R46L loss-of-function variant in the *PCSK9* gene was associated with a −0.393 mmol/L lower LDL-C but was not associated with any altered markers of glucose homeostasis or type 2 diabetes risk.[31] Another study reported a difference of 10% vs. 6% in the combined frequency of pre-diabetes and diabetes between carriers and non-carriers of the *PCSK9* InsLeu loss-of-function variant ($P = 0.04$).[32] Studies conducted in *PCSK9*-null mice investigating the role of the protein on glycaemic control have also thus far yielded contradictory results.[33,34]

In summary, pooled analysis from the Phase 3 ODYSSEY trial programme for the PCSK9 inhibitor alirocumab shows no evidence of an effect on diabetes incidence at this point despite the very substantial 40−60% LDL-C lowering achieved.[12−18] As effects of statin on glycaemic control were not suggested until data from larger outcomes studies were available, longer follow-up with a larger number of individuals will be important to determine definitively the effect of PCSK9 inhibitors on the development of diabetes. The ongoing ODYSSEY OUTCOMES trial, randomizing ∼18 000 individuals for 2−5 years follow-up capturing diabetes events, serial HbA$_{1C}$, and FPG measurements, will provide further data to establish whether alirocumab has any effect on glycaemic measures.

Authors' contributions

L.M. performed statistical analysis. All authors were involved in data analysis and interpretation. H.G., J.R., L.L., and B.C. were involved in data acquisition. H.C., H.G., J.R., M.B.D., and R.P were involved in the conception and design of the research. H.C., M.B.D., and L.M. were involved in drafting the manuscript. All authors made critical revision of the manuscript for key intellectual content.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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