



Universiteit
Leiden
The Netherlands

Effect of alirocumab on major adverse cardiovascular events according to renal function in patients with a recent acute coronary syndrome: prespecified analysis from the ODYSSEY OUTCOMES randomized clinical trial

Tunon, J.; Steg, P.G.; Bhatt, D.L.; Bittner, V.A.; Diaz, R.; Goodman, S.G.; ... ; ODYSSEY OUTCOMES Investigators

Citation

Tunon, J., Steg, P. G., Bhatt, D. L., Bittner, V. A., Diaz, R., Goodman, S. G., ... Schwartz, G. G. (2020). Effect of alirocumab on major adverse cardiovascular events according to renal function in patients with a recent acute coronary syndrome: prespecified analysis from the ODYSSEY OUTCOMES randomized clinical trial. *European Heart Journal*, 41(42), 4114-4123. doi:10.1093/eurheartj/ehaa498



Version: Publisher's Version

License: [Creative Commons CC BY-NC 4.0 license](#)

Downloaded from: <https://hdl.handle.net/1887/3232709>

Note: To cite this publication please use the final published version (if applicable).

Effect of alirocumab on major adverse cardiovascular events according to renal function in patients with a recent acute coronary syndrome: prespecified analysis from the ODYSSEY OUTCOMES randomized clinical trial

José Tuñón^{1*}, Philippe Gabriel Steg^{2,3}, Deepak L. Bhatt ⁴, Vera A. Bittner ⁵, Rafael Díaz⁶, Shaun G. Goodman ^{7,8}, J. Wouter Jukema⁹, Yong-Un Kim ¹⁰, Qian H. Li¹¹, Christian Mueller ¹², Alexander Parkhomenko¹³, Robert Pordy ¹¹, Piyamitr Sritara¹⁴, Michael Szarek ¹⁵, Harvey D. White ¹⁶, Andreas M. Zeiher¹⁷, and Gregory G. Schwartz¹⁸; for the ODYSSEY OUTCOMES Investigators[†]

¹Division of Cardiology, Fundación Jiménez Díaz, Autónoma University, and CIBER CV, Avenida Reyes Católicos 2, 28040 Madrid, Spain; ²Department of Cardiology, Université de Paris, Assistance Publique-Hôpitaux de Paris, Hôpital Bichat, Université de Paris, FACT (French Alliance for Cardiovascular Trials), INSERM U1148, Paris, France; ³National Heart and Lung Institute, Imperial College, Royal Brompton Hospital, London, UK; ⁴Department of Medicine, Brigham and Women's Hospital, Boston, MA, USA; ⁵Division of Cardiovascular Disease, University of Alabama at Birmingham, Birmingham, AL, USA; ⁶Cardiology Department, Estudios Clínicos Latinoamérica, Instituto Cardiovascular de Rosario, Rosario, Argentina; Canadian VIGOUR Centre, University of Alberta, Edmonton, AB, Canada; ⁸Division of Cardiology, St. Michael's Hospital, University of Toronto, Toronto, ON, Canada; ⁹Department of Cardiology, Leiden University Medical Center, Leiden, the Netherlands; ¹⁰R & D clinical Development, Sanofi, Paris, France; ¹¹Clinical Sciences-Cardiovascular & Metabolism Therapeutics, Regeneron Pharmaceuticals, Tarrytown, NY, USA; ¹²Cardiovascular Research Institute Basel (CRIB) and Department of Cardiology, University Hospital Basel, University of Basel, Switzerland; ¹³Institute of Cardiology, Kyiv, Ukraine; ¹⁴Department of Medicine, Ramathibodi Hospital, Bangkok, Thailand; ¹⁵State University of New York, Downstate School of Public Health, Brooklyn, NY, USA; ¹⁶Green Lane Cardiovascular Services Auckland City Hospital, Auckland, New Zealand; ¹⁷Department of Medicine III, Goethe University, Frankfurt am Main, Germany; and ¹⁸Division of Cardiology, University of Colorado School of Medicine, Aurora, CO, USA

Received 30 January 2020; revised 18 April 2020; editorial decision 27 May 2020; accepted 29 May 2020; online publish-ahead-of-print 21 August 2020

See page 4124 for the editorial comment on this article (doi: 10.1093/eurheartj/ehaa550)

Aims

Statins reduce cardiovascular risk in patients with acute coronary syndrome (ACS) and normal-to-moderately impaired renal function. It is not known whether proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors provide similar benefit across a range of renal function. We determined whether effects of the PCSK9 inhibitor alirocumab to reduce cardiovascular events and death after ACS are influenced by renal function.

Methods and results

ODYSSEY OUTCOMES compared alirocumab with placebo in patients with recent ACS and dyslipidaemia despite intensive statin treatment. Estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m² was exclusionary. In 18 918 patients, baseline eGFR was 82.8 ± 17.6 mL/min/1.73 m², and low-density lipoprotein cholesterol (LDL-C) was 92 ± 31 mg/dL. At 36 months, alirocumab decreased LDL-C by 48.5% vs. placebo but did not affect eGFR (P = 0.65). Overall, alirocumab reduced risk of the primary outcome (coronary heart disease death, non-fatal myocardial infarction, ischaemic stroke, or unstable angina requiring hospitalization) with fewer deaths. There was no interaction

* Corresponding author. Tel: +34-915504800, Email: jtonon@fd.es

[†] A complete list of the ODYSSEY OUTCOMES investigators is provided in the [Supplementary material online](#).

© The Author(s) 2020. Published by Oxford University Press on behalf of the European Society of Cardiology.

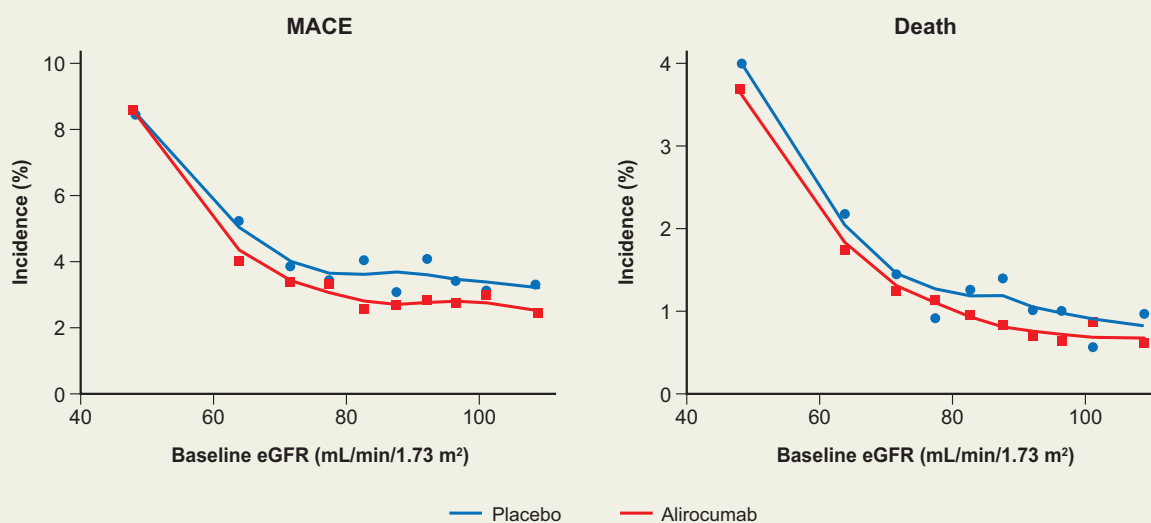
This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/4.0/>), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com

between continuous eGFR and treatment on the primary outcome or death ($P=0.14$ and 0.59 , respectively). Alirocumab reduced primary outcomes in patients with eGFR ≥ 90 mL/min/1.73 m² ($n=7470$; hazard ratio 0.784, 95% confidence interval 0.670–0.919; $P=0.003$) and 60 to <90 ($n=9326$; 0.833, 0.731–0.949; $P=0.006$), but not in those with eGFR <60 ($n=2122$; 0.974, 0.805–1.178; $P=0.784$). Adverse events other than local injection-site reactions were similar in both groups across all categories of eGFR.

Conclusions

In patients with recent ACS, alirocumab was associated with fewer cardiovascular events and deaths across the range of renal function studied, with larger relative risk reductions in those with eGFR >60 mL/min/1.73 m².

Graphical Abstract



Keywords

PCSK9 inhibition • Acute coronary syndrome • Low-density lipoprotein cholesterol • Chronic kidney disease • Glomerular filtration rate • Major adverse cardiovascular events

Introduction

Patients with chronic kidney disease (CKD) are at high risk for major adverse cardiovascular events (MACE).^{1–3} Several factors may account for this high risk. First, CKD is associated with other established risk factors, including age, hypertension, and diabetes. Second, lipoprotein abnormalities frequently accompany CKD, including increased triglycerides, decreased high-density lipoproteins, and an excess of small, dense low-density lipoprotein particles.² Third, CKD is associated with elevated inflammatory biomarkers,⁴ abnormal platelet function,⁵ and extensive vascular calcifications.⁶

Statins decrease the incidence of cardiovascular events in patients with moderate-to-severe CKD,⁷ but not in those on dialysis.^{8,9} Although some guidelines suggest the use of moderate-dose statins

in patients with moderate-to-severe CKD,¹⁰ the recent US guidelines on the management of blood cholesterol consider CKD stages 3 or 4 to be one of the 'very high risk' conditions that warrant the use of high-intensity or maximum-tolerated statin treatment for secondary prevention, and the addition of ezetimibe or an inhibitor of proprotein convertase subtilisin-kexin type 9 (PCSK9) if low-density lipoprotein cholesterol (LDL-C) remains above 70 mg/dL.³ Similarly, recent European guidelines indicate that a goal of treatment in patients with moderate-to-severe CKD is to 'achieve the largest possible absolute reduction in LDL-C safely'.¹¹

The PCSK9 inhibitors alirocumab¹² and evolocumab¹³ decrease the incidence of cardiovascular events in patients with acute coronary syndromes (ACS) and chronic atherosclerotic cardiovascular disease, respectively. Alirocumab reduces LDL-C levels without

significant safety concerns in patients with CKD.¹⁴ Likewise, evolocumab therapy was associated with reduced MACE in patients with CKD and chronic atherosclerosis treated with statins.¹⁵

Patients with CKD and ACS are at particularly high risk for recurrent MACE. The efficacy and safety of PCSK9 inhibition in such patients has not previously been investigated. In this prespecified analysis of the ODYSSEY OUTCOMES trial, we examined whether the reduction of MACE with alirocumab, added to intensive or maximum-tolerated statin therapy after ACS, depends upon the level of estimated glomerular filtration rate (eGFR).

Methods

Trial design

The design¹⁶ and primary efficacy and safety results¹² of the ODYSSEY OUTCOMES trial (clinicaltrials.gov: NCT01663402) have been published. Ethics committee approval was obtained at all participating centres. All participants provided written informed consent. The trial was a randomized, double-blind, placebo-controlled comparison of alirocumab or placebo in 18 924 patients with an ACS (myocardial infarction or unstable angina) 1–12 months before randomization. Qualifying patients had persistent dyslipidaemia [LDL-C \geq 70 mg/dL (1.81 mmol/L), non-high-density lipoprotein cholesterol (non-HDL-C) \geq 100 mg/dL (2.59 mmol/L), or apolipoprotein B \geq 80 mg/dL (0.0016 mmol/L)] despite treatment with atorvastatin 40–80 mg daily, rosuvastatin 20–40 mg daily, or the maximum-tolerated dose of one of these statins (including no statin in case of documented intolerance). An eGFR of $<$ 30 mL/min/1.73 m² at the screening visit for the study was an exclusion criterion. At the randomization visit, baseline laboratory studies were obtained, and participants were randomly assigned (1:1) to receive alirocumab 75 mg or matching placebo subcutaneously every 2 weeks. A treat-to-target design aimed to achieve an LDL-C level of 25–50 mg/dL among alirocumab-treated patients. Alirocumab 75 mg was blindly up-titrated to 150 mg if the LDL-C level was $>$ 50 mg/dL. If LDL-C was $<$ 15 mg/dL on two consecutive measurements on the 75 mg dose of alirocumab, placebo was blindly substituted for the rest of the trial. Participants and physicians were blinded to the treatment allocation. To protect the blind, all treatment kit boxes had the same look and feel and were labelled with a double-blind label. Details on randomization procedures are included in [Supplementary material online](#).

The primary outcome was a composite of MACE, including death due to coronary heart disease, non-fatal myocardial infarction, ischaemic stroke, or unstable angina requiring hospitalization. Death from any cause was a secondary outcome. All outcomes were blindly adjudicated.

In this prespecified analysis, we investigated whether the effect of alirocumab on MACE and death varied across the range of baseline renal function, gauged by eGFR calculated using the Chronic Kidney Disease Epidemiology Collaboration equation.¹⁷ We also analysed the incidence of adverse effects as a function of eGFR, and looked for potential effects of alirocumab on eGFR.

Statistical analysis

Details on the sample size calculation are included in the [Supplementary material online](#). The comparisons of baseline differences among eGFR subgroups were tested using the χ^2 test for categorical variables and analysis of variance for continuous variables, except for triglycerides and lipoprotein(a), which were tested using median regression due to their skewed distributions. Efficacy analyses were performed on an intention-to-treat basis. Incidence rates per 100 patient-years for MACE and all

cause death were estimated by treatment groups in each decile of baseline eGFR, and smoothed curves were fit to estimations based on each eGFR decile subgroup using local regression. Interactions between study treatment and baseline eGFR for MACE and death were tested using proportional hazard models, using either eGFR subgroups or a continuous value of eGFR. Differences in eGFR at Month 36 between treatment groups were assessed using the Student's *t*-test. Differences between treatment groups in the proportion of adverse events were evaluated using the χ^2 test. This test was also used to compare treatment differences in the percentages of patients whose eGFR at the end of treatment was reduced by 30%, 40%, or 50% from baseline. Statistical significance was set at $P < 0.05$ (two-sided) without multiplicity adjustment. Analyses were performed in SAS version 9.4.

Results

A total of 18 924 patients underwent randomization at 1315 sites in 57 countries ([Supplementary material online, Table S1](#)). Of these, 9462 were assigned to alirocumab and 9462 to placebo ([Figure 1](#)). Outside of China, patients were randomized between November 2012 and November 2015. In China, 613 patients were randomized between May 2016 and February 2017. In this analysis, 6 of the patients (4 in the placebo group and 2 in the alirocumab group) were excluded because their baseline serum creatinine values were not available, leaving 18 918 patients for the analysis (9460 in the alirocumab group and 9458 in the placebo group). Median follow-up was 2.8 (interquartile range 2.3–3.4) years.

In the aggregate trial cohort, baseline eGFR was 82.8 ± 17.6 mL/min/1.73 m². There were 7470 (39.5%) patients with eGFR \geq 90 [98.6 (94.3, 103.5)] mL/min/1.73 m², 9326 (49.3%) with eGFR 60 to $<$ 90 [77.8 (70.6, 84.2)] mL/min/1.73 m², and 2122 (11.2%) with eGFR $<$ 60 [51.4 (44.2, 56.1)] mL/min/1.73 m². While eGFR $<$ 30 mL/min/1.73 m² was a screening exclusion criterion, 69 patients (0.4%) had eGFR $<$ 30 mL/min/1.73 m² at randomization and were included in the analysis. [Supplementary material online, Table S2](#) shows the distribution of the population according to eGFR range and study treatment. Of patients receiving alirocumab, 7.8% were switched to placebo, primarily due to two consecutive LDL-C values $<$ 15 mg/dL (0.39 mmol/L) in the subgroups with eGFR $<$ 60 and 60 to $<$ 90 mL/min/1.73 m², and 7.6% in the subgroup with eGFR \geq 90 mL/min/1.73 m².

Baseline characteristics of the population across eGFR subgroups are shown in [Supplementary material online, Table S3](#). Overall, patients with lower eGFR were older; more likely to have a history of hypertension, diabetes, myocardial infarction, coronary revascularization, stroke, peripheral artery disease, and heart failure; and had higher levels of triglycerides and lipoprotein(a). In addition, patients with lower eGFR were less likely to receive intensive statin treatment and dual antiplatelet therapy but were more likely to receive inhibitors of the renin–angiotensin system and oral anticoagulants.

At baseline, mean LDL-C was 92 ± 31 mg/dL in both treatment groups. Alirocumab decreased LDL-C by 62.2% and 48.5% vs. placebo at 4 and 36 months, respectively. The effect of alirocumab on LDL-C was consistent across eGFR subgroups at 4 months: the LDL-C values of patients on alirocumab were 40 ± 30 mg/dL in the eGFR $<$ 60 mL/min/1.73 m² subgroup, 38 ± 30 mg/dL in the 60 to $<$ 90 mL/min/1.73 m² subgroup, and 38 ± 28 mg/dL in the \geq 90 mL/min/1.73 m² subgroup. At 36 months, these values were 52 ± 36 , 56 ± 40 , and

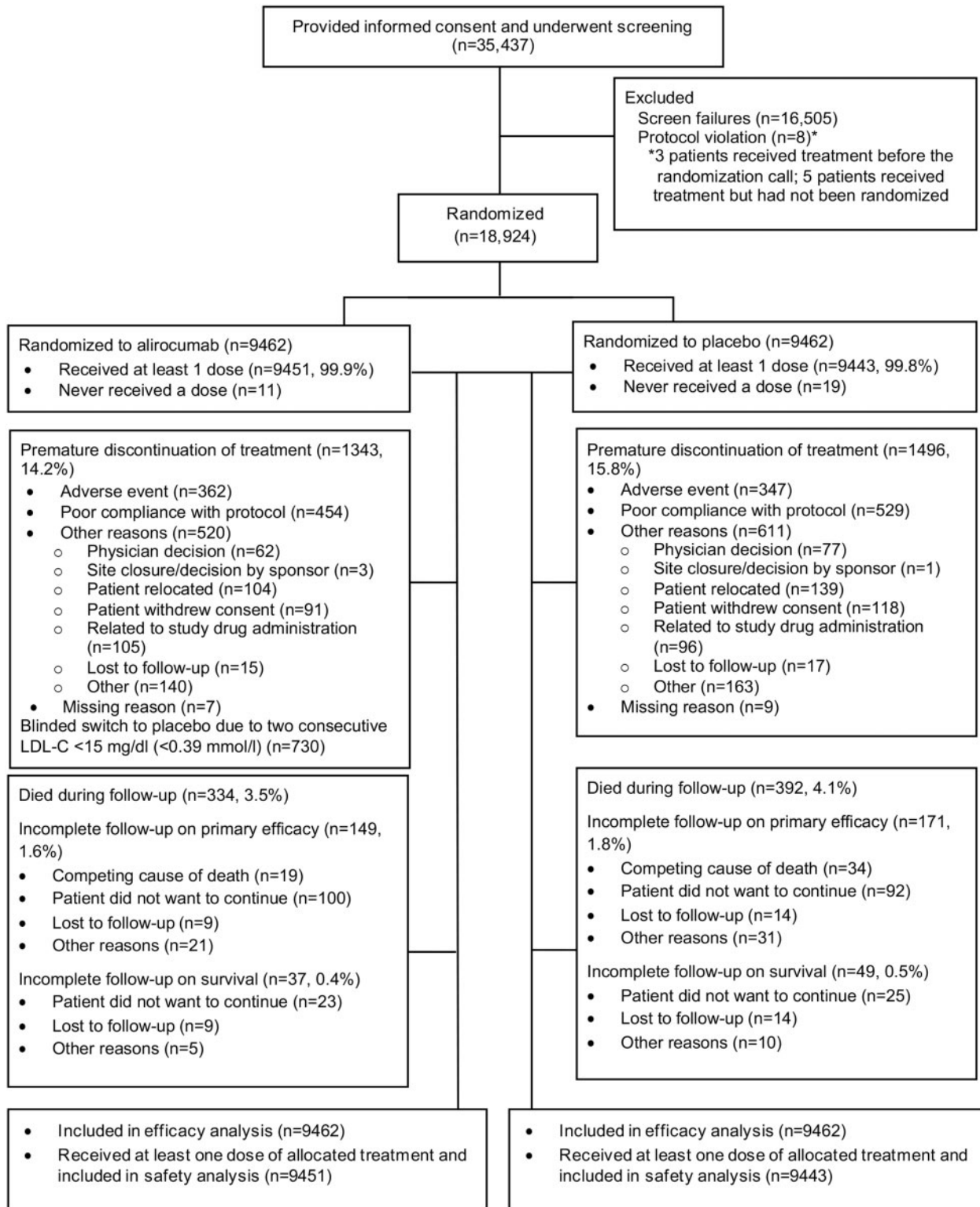


Figure 1 Consort diagram. *The most common reasons for screen failures during the run-in period were related to lipid criteria (34.1% of patients) or withdrawal of patient consent (6.1% of patients). From Schwartz *et al.*¹² Copyright © (2018) Massachusetts Medical Society. Reprinted with permission.

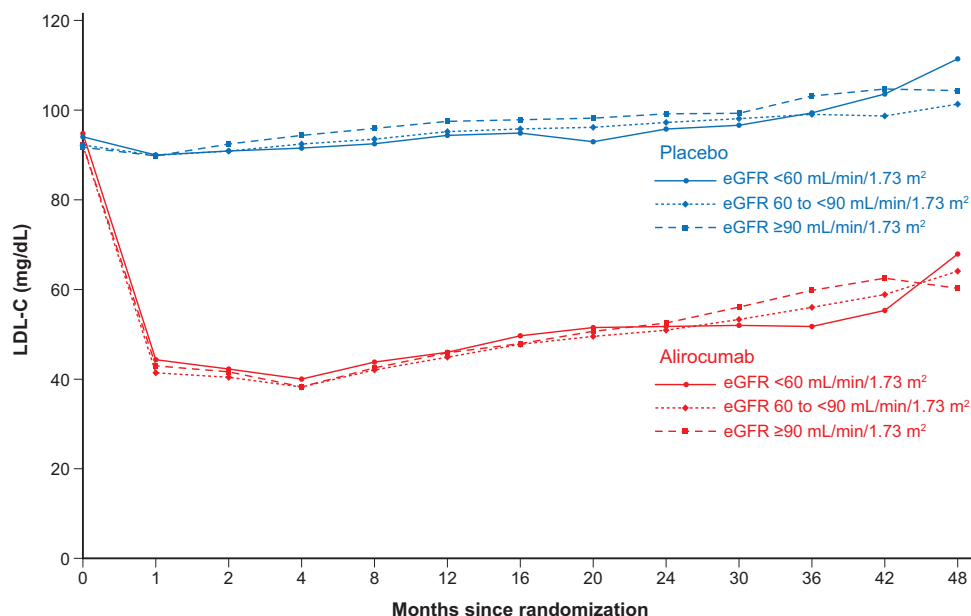
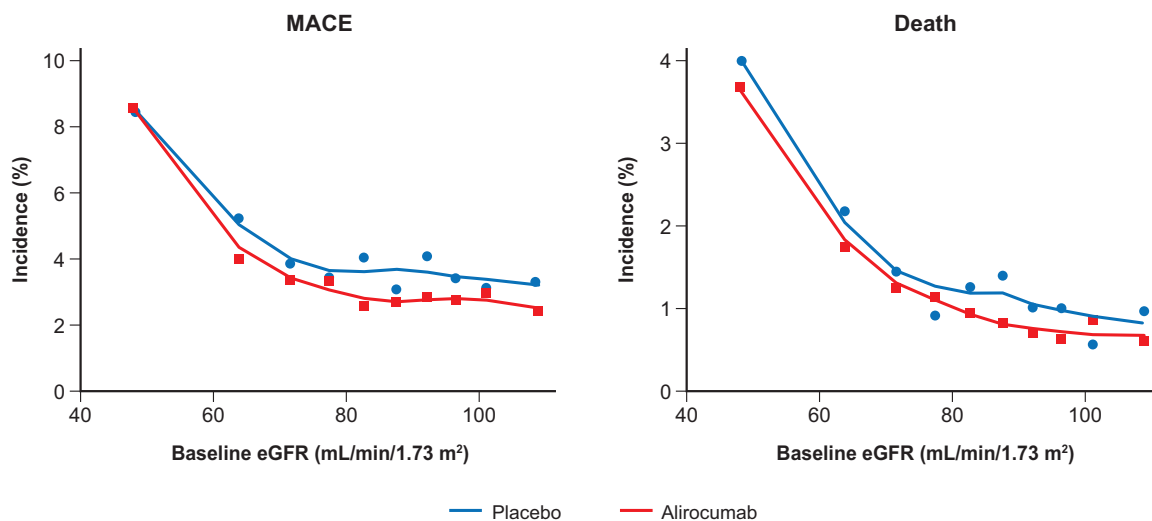


Figure 2 Low-density lipoprotein cholesterol values achieved over time according to treatment in each estimated glomerular filtration rate category (intention-to-treat). eGFR, estimated glomerular filtration rate; LDL-C, low-density lipoprotein cholesterol.



Take home figure Incidence of major adverse cardiovascular event and death per 100 patient-years at risk according to estimated glomerular filtration rate as a continuous variable. There was no significant interaction between the use of alirocumab and the estimated glomerular filtration rate for major adverse cardiovascular event ($P = 0.14$) or all-cause death ($P = 0.59$). eGFR, estimated glomerular filtration rate; MACE, major adverse cardiovascular event.

60 ± 42 mg/dL, respectively (Figure 2 and Supplementary material online, Table S4). Supplementary material online, Figures S1–S4 show the effect of alirocumab on apolipoprotein B, triglycerides, HDL-C, and non-HDL-C, respectively, across the three categories of eGFR. Alirocumab decreased apolipoprotein B and non-HDL-C and increased HDL-C homogeneously across eGFR categories. At

baseline, triglyceride levels were higher in patients with eGFR <60 mL/min/1.73 m² than in the other two subgroups and the decrease in triglycerides with alirocumab was greatest in that eGFR category.

Overall, alirocumab reduced incident MACE [9.5% vs. 11.1%; hazard ratio (HR) 0.85, 95% confidence interval (CI) 0.78–0.93] and was

Table 1 Effect of alirocumab on the incidence of MACE and death in different subgroups according to eGFR

eGFR subgroup	n	Incidence per 100 patient-years at risk			Hazard ratio (95% CI)	P	P _{interaction}
		Alirocumab	Placebo	ARR			
MACE							0.21
eGFR (mL/min/1.73 m ²)							
<60	2122	7.9	8.1	0.2	0.97 (0.81–1.18)	0.78	
60 to <90	9326	3.2	3.9	0.7	0.83 (0.73–0.95)	0.006	
≥90	7470	2.7	3.5	0.8	0.78 (0.67–0.92)	0.0026	
All-cause death							0.83
eGFR (mL/min/1.73 m ²)							
<60	2122	3.4	3.8	0.4	0.90 (0.69–1.18)	0.46	
60 to <90	9326	1.2	1.4	0.2	0.82 (0.66–1.01)	0.07	
≥90	7470	0.7	0.9	0.2	0.81 (0.60–1.10)	0.18	

ARR, absolute risk reduction; CI, confidence interval; eGFR, estimated glomerular filtration rate; MACE, major adverse cardiovascular event.

associated with fewer deaths (3.5% vs. 4.1%; HR 0.85, 95% CI 0.73–0.98). The incidences of MACE and death over the range of baseline eGFR are presented in the alirocumab and placebo groups in the *Take home figure*. The annualized incidence rates for MACE and death increased progressively as eGFR decreased, beginning at eGFR values <80 mL/min/1.73 m². Patients receiving alirocumab had fewer MACE and deaths than those on placebo across all values of eGFR. There were no significant interactions of assigned treatment (alirocumab or placebo) and eGFR on the incidence rates for MACE and death ($P = 0.14$ and $P = 0.59$, respectively).

When the population was divided in subgroups according to CKD stage, alirocumab was associated with a significant reduction in the incidence of MACE in patients with eGFR ≥90 mL/min/1.73 m² and between 60 and <90 mL/min/1.73 m² (Table 1), but not in patients with eGFR <60 mL/min/1.73 m². In all three subgroups, there were numerically fewer deaths in patients receiving alirocumab, without statistical significance in any individual category. The interaction P -value between eGFR and alirocumab was 0.21 for MACE and 0.83 for death.

When the population was divided into quintiles according to eGFR, patients on alirocumab had a lower incidence of MACE in all the quintiles (Supplementary material online, Figure S5A). Similar findings were observed for the incidence of death, with the exception of quintile 2, where it was similar in both groups (Supplementary material online, Figure S5B).

At baseline, eGFR was 82.7 ± 17.7 mL/min/1.73 m² in the alirocumab group and 82.9 ± 17.6 mL/min/1.73 m² in the placebo group. Alirocumab had no effect on eGFR over the duration of the trial; for example, at 36 months, these values were 83.9 ± 18.0 and 84.1 ± 17.6 mL/min/1.73 m², respectively ($P = 0.65$) (Supplementary material online, Figure S6). The percentages of patients having a decrease in eGFR from baseline of at least 30% [1.8% ($n = 170$) vs. 2.1% ($n = 202$); $P = 0.09$], 40% [0.8% ($n = 78$) vs. 0.9% ($n = 87$); $P = 0.48$], or 50% [0.3% ($n = 30$) vs. 0.4% ($n = 34$); $P = 0.62$, for alirocumab and placebo, respectively] were similar in both treatment groups.

In the overall trial population and in each category of baseline eGFR, compared with patients on placebo, patients in the alirocumab group had a higher incidence of local injection-site reactions, without

any excess of all treatment-emergent adverse events, serious adverse events, adverse events leading to death, rhabdomyolysis, or increases in liver enzymes or creatine kinase (Table 2).

Discussion

This is the first analysis of the effects of a PCSK9 inhibitor on clinical outcomes according to renal function in post-ACS patients. In this prespecified analysis, we found that alirocumab had a consistent effect on plasma LDL-C and on the incidence of MACE across the range of baseline renal function of patients in the study. Subgroup analysis showed a significant decrease in the incidence of MACE among patients with eGFR 60 to <90 or >90 mL/min/1.73 m². The decrease was not significant in patients with eGFR <60 mL/min/1.73 m². There was no excess of any adverse event other than local injection-site reactions with alirocumab compared with placebo in any category of eGFR. Alirocumab or placebo treatment did not influence the level of eGFR at 36 months after randomization.

Patients with CKD are at high risk of developing cardiovascular events.^{1–3} Statins with or without ezetimibe decrease cardiovascular risk in patients with moderate-to-severe CKD.^{7,18,21} However, part of the benefit of statins in this setting may be counterbalanced by an increased risk of adverse events.¹⁸ Furthermore, this benefit seems to decrease as eGFR declines, with little or no benefit in patients on dialysis.^{8,9,19} Given this background, it cannot be assumed that the balance of efficacy and safety with a lipid-lowering drug in a broad population applies similarly to patients with CKD.

Proprotein convertase subtilisin-kexin type 9 inhibitors are powerful lipid-lowering drugs, decreasing LDL-C, apolipoprotein B, triglycerides, and lipoprotein(a), without evidence to date of any serious safety concerns.^{13,20} A subanalysis of the FOURIER (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Patients With Elevated Risk) trial in patients with chronic atherosclerotic cardiovascular disease demonstrated that evolocumab reduced the incidence of cardiovascular events across CKD subgroups.¹⁵ Here, we present the first evidence of the effects of a PCSK9 inhibitor according to renal function in patients 1–12 months post-ACS.

Table 2 Incidence of TEAEs according to baseline eGFR category

	Alirocumab	Placebo	P value
All patients	(n=9460)	(n=9458)	
Any TEAE, n (%)	7164 (75.7)	7278 (77.0)	0.0481
Any serious TEAE, n (%)	2201 (23.3)	2350 (24.8)	0.011
TEAE leading to death, n (%)	181 (1.9)	222 (2.3)	0.0388
TEAE leading to discontinuation, n (%)	343 (3.6)	324 (3.4)	0.456
Local injection-site reaction, n (%)	360 (3.8)	203 (2.1)	<0.0001
AST >3 times ULN, n (%)	169 (1.8)	161 (1.7)	0.658
ALT >3 times ULN, n (%)	218 (2.3)	219 (2.3)	0.960
Creatine kinase >10 times ULN, n (%)	49 (0.5)	47 (0.5)	0.839
Rhabdomyolysis, n (%)	22 (0.2)	17 (0.2)	0.423
Baseline eGFR <60 mL/min/1.73 m ²	(n=1077)	(n=1045)	
Any TEAE, n (%)	863 (80.1)	852 (81.5)	0.413
Any serious TEAE, n (%)	353 (32.8)	366 (35.0)	0.274
TEAE leading to death, n (%)	48 (4.5)	65 (6.2)	0.071
TEAE leading to discontinuation, n (%)	56 (5.2)	53 (5.1)	0.894
Local injection-site reaction, n (%)	28 (2.6)	16 (1.5)	0.084
AST >3 times ULN, n (%)	23 (2.1)	19 (1.8)	0.560
ALT >3 times ULN, n (%)	34 (3.2)	22 (2.1)	0.131
Creatine kinase >10 times ULN, n (%)	6 (0.6)	8 (0.8)	0.553
Rhabdomyolysis, n (%)	3 (0.3)	2 (0.2)	0.679
Baseline eGFR ≥60 to <90 mL/min/1.73 m ²	(n=4669)	(n=4657)	
Any TEAE, n (%)	3565 (76.4)	3591 (77.1)	0.388
Any serious TEAE, n (%)	1085 (23.2)	1179 (25.3)	0.019
TEAE leading to death, n (%)	92 (2.0)	93 (2.0)	0.927
TEAE leading to discontinuation, n (%)	167 (3.6)	168 (3.6)	0.937
Local injection-site reaction, n (%)	177 (3.8)	106 (2.3)	<0.0001
AST >3 times ULN, n (%)	85 (1.8)	81 (1.7)	0.767
ALT >3 times ULN, n (%)	108 (2.3)	103 (2.2)	0.742
Creatine kinase >10 times ULN, n (%)	24 (0.5)	23 (0.5)	0.891
Rhabdomyolysis, n (%)	11 (0.2)	8 (0.2)	0.494
Baseline eGFR ≥90 mL/min/1.73 m ²	(n=3714)	(n=3756)	
Any TEAE, n (%)	2736 (73.7)	2835 (75.5)	0.072
Any serious TEAE, n (%)	763 (20.5)	805 (21.4)	0.346
TEAE leading to death, n (%)	41 (1.1)	64 (1.7)	0.028
TEAE leading to discontinuation, n (%)	120 (3.2)	103 (2.7)	0.215
Local injection-site reaction, n (%)	155 (4.2)	81 (2.2)	<0.0001
AST >3 times ULN, n (%)	61 (1.6)	61 (1.6)	0.950
ALT >3 times ULN, n (%)	76 (2.0)	94 (2.5)	0.186
Creatine kinase >10 times ULN, n (%)	19 (0.5)	16 (0.4)	0.588
Rhabdomyolysis, n (%)	8 (0.2)	7 (0.2)	0.779

ALT, alanine aminotransferase; AST, aspartate aminotransferase; eGFR, estimated glomerular filtration rate; TEAE, treatment-emergent adverse event; ULN, upper limit of normal.

Overall in the ODYSSEY OUTCOMES trial, treatment with alirocumab decreased the incidence of MACE and was associated with fewer total deaths.¹² Of the patients in the trial, 60% had an eGFR <90 mL/min/1.73 m², reflecting at least mild CKD, and 10.9% (n = 2053) had an eGFR of 30 to <60 mL/min/1.73 m², indicating moderate CKD. The low number of patients in the latter category limited power to determine an effect of alirocumab on MACE or death. The FOURIER trial was larger than ODYSSEY OUTCOMES, included more than twice the number of patients with eGFR

<60 mL/min/1.73 m² (n = 4443), and had a different primary MACE endpoint of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization. Notwithstanding these differences, the qualitative findings in both trials are similar. In both, there was no difference in treatment effects of PCSK9 inhibition on LDL-C, apolipoprotein B, non-HDL-C or HDL-C across categories of eGFR, and a larger absolute decrease in triglycerides in patients with eGFR <60 mL/min/1.73 m². In both trials, the point estimate of the treatment HR for the primary Endpoint was

numerically lowest in patients with baseline eGFR ≥ 90 mL/min/1.73 m² and numerically highest in patients with baseline eGFR < 60 mL/min/1.73 m², but with no significant interaction across categories of baseline eGFR. Similarly, the Cholesterol Treatment Trialists collaboration¹⁹ has reported a trend towards smaller reduction in the risk of MACE per mmol/L decrease in LDL-C as eGFR declines.

Although there is no complete explanation for this finding, reasons may include differences in the pathophysiology of atherosclerosis in patients with CKD, manifest by enhanced inflammation and complex lipid abnormalities such as excessive LDL-C oxidation and high-density lipoprotein cholesterol dysfunction.^{1,21} Furthermore, non-atherosclerotic comorbidities present in CKD may influence outcomes without modification by lipid-lowering therapies.

Compared to patients with better renal function, patients with lower eGFR were older and had a higher prevalence of cardiovascular risk factors, atherosclerosis, and heart failure, which are associated with greater absolute risk of MACE and death. However, unlike characteristics such as diabetes, polyvascular disease, or prior coronary artery bypass surgery that were associated with both greater risk of MACE and greater MACE reduction with alirocumab in this trial,^{22–24} we did not find evidence for greater absolute reduction of MACE or death with alirocumab among patients with lower eGFR at baseline.

Alirocumab did not affect the eGFR values, suggesting that the drug does not directly affect renal function, and corroborating findings by Toth *et al.*¹⁴ in an analysis of 4629 hypercholesterolaemic patients treated with alirocumab or placebo up to 104 weeks. Likewise, the FOURIER study, which included 27 564 patients with a median follow-up of 2.2 years, demonstrated no difference in renal function between the evolocumab and placebo groups.¹⁵ Moreover, eGFR did not appear to influence the safety and tolerability of alirocumab. In each category of baseline eGFR, the only adverse event with greater incidence in the alirocumab group was local injection-site reactions.

Limitations

Estimated glomerular filtration rate < 30 mL/min/1.73 m² was an exclusion criterion, as is common in cardiovascular outcomes trials. Thus, the potential benefits and risks of alirocumab treatment in patients with severe CKD, or in those receiving dialysis treatment, were not determined. The proportion of patients with eGFR < 60 mL/min/1.73 m² was relatively modest (11.2%; $n = 2122$), limiting power to detect an effect of alirocumab on MACE in this population. In contrast, there were many patients with eGFR between 60 and < 90 mL/min/1.73 m² (Stage 2 CKD). Previous analyses²⁵ as well as the present data indicate that these patients have an elevated risk of MACE and death compared to those with preserved renal function, and thus comprise an important group to assess the efficacy of PCSK9 inhibition. Finally, the effect of alirocumab on eGFR must be interpreted with caution given a relatively short follow-up, limiting the ability to detect a potential influence on CKD progression.

Conclusions

In patients with recent ACS, alirocumab treatment was associated with a reduction in MACE and fewer deaths, independent of baseline eGFR, across a broad range above 30 mL/min/1.73 m². This reduction

did not achieve statistical significance in the subgroup of patients with eGFR < 60 mL/min/1.73 m². Other than local injection-site reactions, no differences in the rates of adverse events were apparent between treatment groups across the range of eGFR values studied.

Supplementary material

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

Acknowledgements

We thank the patients, study coordinators, and investigators who participated in this trial. Sophie K. Rushton-Smith (MedLink Healthcare Communications, London) provided editorial assistance in the preparation of the manuscript (limited to editing for style and referencing, as well as figure and table editing) and was funded by Sanofi, Paris, France.

Funding

The trial was funded by Sanofi and Regeneron Pharmaceuticals, Inc.

Conflict of interest: J.T. reports personal fees from Sanofi, Amgen, and Diasorin Iberia. P.G.S. reports grants and nonfinancial support (cochair of the ODYSSEY OUTCOMES trial; as such, he received no personal fees, but his institution has received funding for the time he has devoted to trial coordination, and he has received support for travel related to trial meetings) from Sanofi; research grants and personal fees from Bayer (Steering Committee MARINER, grant for epidemiological study), Merck (speaker fees, grant for epidemiological studies), Sanofi (cochair of the ODYSSEY OUTCOMES trial; cochair of the SCORED trial; consulting, speaking), Servier (Chair of the CLARIFY registry; grant for epidemiological research), and Amarin (executive steering committee for the REDUCE-IT trial [Disease Reduction of Cardiovascular Events With Icosapent Ethyl–Intervention Trial]; consulting); and personal fees from Amgen, Bristol-Myers Squibb, Boehringer Ingelheim, Pfizer, Novartis, Regeneron Pharmaceuticals, Lilly, and AstraZeneca. P.G.S. also has a European application number/patent number, issued on 26 October 2016 (no. 15712241.7), for a method for reducing cardiovascular risk. D.L.B. reports advisory board fees from Cardax, Cereno Scientific, Elsevier Practice Update Cardiology, Medscape Cardiology, PhaseBio, Regado Biosciences; Board of Directors membership for Boston VA Research Institute, Society of Cardiovascular Patient Care, TobeSoft; position of Chair for the American Heart Association Quality Oversight Committee; membership of Data Monitoring Committees for the Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute, for the PORTICO trial, funded by St. Jude Medical, now Abbott), Cleveland Clinic (including for the ExCEED trial, funded by Edwards), Duke Clinical Research Institute, Mayo Clinic, Mount Sinai School of Medicine (for the ENVISAGE trial, funded by Daiichi Sankyo), Population Health Research Institute; honoraria from the American College of Cardiology (Senior Associate Editor, Clinical Trials and News, ACC.org; Vice-Chair, ACC Accreditation Committee), Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute; RE-DUAL PCI clinical trial steering committee funded by Boehringer Ingelheim; AEGIS-II executive committee funded by CSL Behring), Belvoir Publications (Editor in Chief, Harvard Heart Letter), Duke Clinical Research Institute (clinical trial steering committees, including for the PRONOUNCE trial, funded by Ferring Pharmaceuticals), HMP Global (Editor in Chief, Journal of Invasive Cardiology), Journal of the American College of Cardiology (Guest Editor; Associate Editor), Medtelligence/ReachMD (CME steering committees), Population Health Research

Institute (for the COMPASS operations committee, publications committee, steering committee, and USA national co-leader, funded by Bayer), Slack Publications (Chief Medical Editor, Cardiology Today's Intervention), Society of Cardiovascular Patient Care (Secretary/Treasurer), WebMD (CME steering committees); other relationships with Clinical Cardiology (Deputy Editor), NCDR-ACTION Registry Steering Committee (Chair), VA CART Research and Publications Committee (Chair); research funding from Abbott, Afimmune, Amarin, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Chiesi, CSL Behring, Eisai, Ethicon, Ferring Pharmaceuticals, Forest Laboratories, Fractyl, Idorsia, Ironwood, Ischaemix, Lilly, Medtronic, PhaseBio, Pfizer, PLx Pharma, Regeneron, Roche, Sanofi Aventis, Synaptic, The Medicines Company; royalties from Elsevier (Editor, Cardiovascular Intervention: A Companion to Braunwald's Heart Disease); position as a site co-investigator for Biotronik, Boston Scientific, CSI, St. Jude Medical (now Abbott), Svelte; position as a trustee for the American College of Cardiology; and unfunded research for FlowCo, Merck, Novo Nordisk, and Takeda. V.A.B. reports grant support from Sanofi, AstraZeneca, DalCor, Esperion, Bayer, The Medicines Company, and Amgen, all paid direct to her institution; and personal fees from Sanofi. R.D. reports research grants from Sanofi, DalCor Pharmaceuticals, Population Health Research Institute, Duke Clinical Research Institute, the TIMI group, Amgen, Cirius, Montreal Health Innovations Coordinating Center, and Lepetit; and personal fees, as a member of the Executive Steering Committee, from Amgen and Cirius. S.G.G. reports research grants from Daiichi-Sankyo, Luitpold Pharmaceuticals, Merck, Novartis, Servier, Regeneron Pharmaceuticals, Inc., Sanofi, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, CSL Behring, Eli Lilly, Pfizer, and Tenax Therapeutics; honoraria from Bristol-Myers Squibb, Eli Lilly, Esperion, Fenix Group International, Ferring Pharmaceuticals, Merck, Novartis, Pfizer, Servier, Regeneron Pharmaceuticals, Inc., Sanofi, Amgen, AstraZeneca, Bayer, and Boehringer Ingelheim; and serving as a consultant or on advisory boards (or both) for AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, HLS Therapeutics, Pfizer, Servier, Tenax Therapeutics, Sanofi, Amgen, and Bayer. J.W.J. reports research grants from the Netherlands Heart Foundation, the Interuniversity Cardiology Institute of the Netherlands, and the European Commission Seventh Framework Programme; and research support from Amgen, Astellas, AstraZeneca, Daiichi-Sankyo, Lilly, Merck-Schering-Plough, Pfizer, Roche, and Sanofi. Y.-U.K. is an employee of and holds shares in Sanofi. Q.H.L. is an employee of Regeneron Pharmaceuticals, Inc. C.M. reports research grants from Sanofi, and speaker/consulting honoraria from Amgen and Sanofi. A.L. reports receiving grants and personal fees from Pfizer, Bayer, Janssen, Sanofi, and Amgen. R.P. is an employee of Regeneron Pharmaceuticals, Inc. P.S. reports nothing to disclose. M.S. reports serving as a consultant or on advisory boards (or both) for CiVi, Resverlogix, Baxter, Esperion, and Regeneron Pharmaceuticals, Inc. H.D.W. reports receiving grant support paid to the institution and fees for serving on a steering committee for the ODYSSEY OUTCOMES trial (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab) from Sanofi-Aventis and Regeneron Pharmaceuticals, for the ACCELERATE study (A Study of Evacetrapib in High-Risk Vascular Disease) from Eli Lilly, for the STRENGTH trial (Outcomes Study to Assess Statin Residual Risk Reduction With EpaNova in High CV Risk Patients With Hypertriglyceridaemia) from Omthera Pharmaceuticals, for the SPIRE trial (The Evaluation of Bococizumab [PF-04950615; RN 316] in Reducing the Occurrence of Major Cardiovascular Events in High Risk Subjects) from Pfizer USA, for the HEART-FID study (Randomized Placebo-Controlled Trial of FCM as Treatment for Heart Failure With Iron Deficiency) from American Regent; for the CAMELLIA-TIMI study (A Study to Evaluate the Effect of Long-term Treatment With BELVIQ [Lorcaserin HC] on the Incidence of

Major Adverse Cardiovascular Events and Conversion to Type 2 Diabetes Mellitus in Obese and Overweight Subjects With Cardiovascular Disease or Multiple Cardiovascular Risk Factors) from Eisai Inc., for the dal-GenE study (Effect of Dalcetrapib vs. Placebo on CV Risk in a Genetically Defined Population With a Recent ACS) from DalCor Pharma UK Inc., for the AEGIS-II study from CSL Behring, for the SCORED trial (Effect of Sotagliflozin on Cardiovascular and Renal Events in Patients With Type 2 Diabetes and Moderate Renal Impairment Who Are at Cardiovascular Risk) and the SOLOIST-WHF trial (Effect of Sotagliflozin on Cardiovascular Events in Patients With Type 2 Diabetes Post Worsening Heart Failure) from Sanofi-Aventis Australia Pty Ltd, and for the CLEAR Outcomes Study (Evaluation of Major Cardiovascular Events in Patients With, or at High Risk for, Cardiovascular Disease Who Are Statin Intolerant Treated With Bempedoic Acid [ETC-1002] or Placebo) from Esperion Therapeutics Inc. Dr White was on the Advisory Boards for Acetelion, Sirtex and Genentech, Inc. (an affiliate of F. Hoffmann-La Roche Ltd, 'Roche'; Lytics Post-PCI Advisory Board at European Society of Cardiology), and received lecture fees from AstraZeneca. Dr A.M.Z. reports receiving fees for serving on a steering committee for the ODYSSEY OUTCOMES trial from Sanofi, and advisory board and speaker fees from Sanofi, Amgen, Boehringer Ingelheim, Bayer, Novartis, Pfizer, AstraZeneca, and Vifor. G.G.S. reports research grants to the University of Colorado from Resverlogix, Sanofi, The Medicines Company, and Roche; and is coinventor of pending US patent 62/806,313 ('Methods for Reducing Cardiovascular Risk') assigned in full to the University of Colorado.

References

1. Gansevoort RT, Correa-Rotter R, Hemmelgarn BR, Jafar TH, Heerspink HJ, Mann JF, Matsushita K, Wen CP. Chronic kidney disease and cardiovascular risk: epidemiology, mechanisms, and prevention. *Lancet* 2013;**382**:339–352.
2. Catapano AL, Graham I, De Backer G, Wiklund O, Chapman MJ, Drexel H, Hoes AW, Jennings CS, Landmesser U, Pedersen TR, Reiner Z, Riccardi G, Taskiran MR, Tokgozoglul L, Verschuren WMM, Vlachopoulos C, Wood DA, Zamorano JL, Cooney MT; ESC Scientific Document Group. 2016 ESC/EAS guidelines for the management of dyslipidaemias. *Eur Heart J* 2016;**37**:2999–3058.
3. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, Braun LT, de Ferranti S, Faiella-Tommasino J, Forman DE, Goldberg R, Heidenreich PA, Hlatky MA, Jones DW, Lloyd-Jones D, Lopez-Pajares N, Ndumele CE, Orringer CE, Peralta CA, Saseen JJ, Smith SC Jr, Sperling L, Virani SS, Yeboah J. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APHA/ASPC/NLA/PCNA Guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation* 2019;**139**:e1082–e1143.
4. Swaminathan S, Shah SV. Novel inflammatory mechanisms of accelerated atherosclerosis in kidney disease. *Kidney Int* 2011;**80**:453–463.
5. Weigert AL, Schafer AI. Uremic bleeding: pathogenesis and therapy. *Am J Med Sci* 1998;**316**:94–104.
6. McCullough PA, Agrawal V, Danielewicz E, Abela GS. Accelerated atherosclerotic calcification and Monckeberg's sclerosis: a continuum of advanced vascular pathology in chronic kidney disease. *Clin J Am Soc Nephrol* 2008;**3**:1585–1598.
7. Barylski M, Nikfar S, Mikhailidis DP, Toth PP, Salari P, Ray KK, Pencina MJ, Rizzo M, Rysz J, Abdollahi M, Nicholls SJ, Banach M; Lipid, Blood Pressure Meta-Analysis Collaboration Group. Statins decrease all-cause mortality only in CKD patients not requiring dialysis therapy—a meta-analysis of 11 randomized controlled trials involving 21,295 participants. *Pharmacol Res* 2013;**72**:35–44.
8. Wanner C, Krane V, Marz W, Olschewski M, Mann JF, Ruf G, Ritz E; German Diabetes and Dialysis Study Investigators. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. *N Engl J Med* 2005;**353**:238–248.
9. Fellstrom BC, Jardine AG, Schmieder RE, Holdaas H, Bannister K, Beutler J, Chae DW, Chevaile A, Cobbe SM, Gronhagen-Riska C, De Lima JJ, Lins R, Mayer G, McMahon AW, Parving HH, Remuzzi G, Samuelsson O, Sonkodi S, Sci D, Suleymanlar G, Tsakiris D, Tesar V, Todorov V, Wiecek A, Wuthrich RP, Gottlow M, Johnsson E, Zannad F; AURORA Study Group. Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. *N Engl J Med* 2009;**360**:1395–1407.
10. Tonelli M, Wanner C; Kidney Disease: Improving Global Outcomes Lipid Guideline Development Work Group Members. Lipid management in chronic

- kidney disease: synopsis of the Kidney Disease: improving Global Outcomes 2013 clinical practice guideline. *Ann Intern Med* 2014;**160**:182–189.
11. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, Chapman MJ, De Backer GG, Delgado V, Ference BA, Graham IM, Halliday A, Landmesser U, Mihaylova B, Pedersen TR, Riccardi G, Richter DJ, Sabatine MS, Taskinen MR, Tokgozoglu L, Wiklund O, Group E. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J* 2019;doi: 10.1093/eurheartj/ehz455.
 12. Schwartz GG, Steg PG, Szarek M, Bhatt DL, Bittner VA, Diaz R, Edelberg JM, Goodman SG, Hanotin C, Harrington RA, Jukema JW, Lecorps G, Mahaffey KW, Moryusef A, Pordy R, Quintero K, Roe MT, Sasiela WJ, Tamby JF, Tricoci P, White HD, Zeiher AM; ODYSSEY OUTCOMES Committees Investigators. Alirocumab and cardiovascular outcomes after acute coronary syndrome. *N Engl J Med* 2018;**379**:2097–2107.
 13. Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, Kuder JF, Wang H, Liu T, Wasserman SM, Sever PS, Pedersen TR; Fourier Steering Committee Investigators. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N Engl J Med* 2017;**376**:1713–1722.
 14. Toth PP, Dwyer JP, Cannon CP, Colhoun HM, Rader DJ, Upadhyay A, Louie MJ, Koren A, Letierce A, Mandel J, Banach M. Efficacy and safety of lipid lowering by alirocumab in chronic kidney disease. *Kidney Int* 2018;**93**:1397–1408.
 15. Charytan DM, Sabatine MS, Pedersen TR, Im K, Park J-G, Pineda AL, Wasserman SM, Deedwania P, Olsson AG, Sever PS, Keech AC, Giugliano RP. Efficacy and safety of evolocumab in chronic kidney disease in the FOURIER trial. *J Am Coll Cardiol* 2019;**73**:2961–2970.
 16. Schwartz GG, Bessac L, Berdan LG, Bhatt DL, Bittner V, Diaz R, Goodman SG, Hanotin C, Harrington RA, Jukema JW, Mahaffey KW, Moryusef A, Pordy R, Roe MT, Rorick T, Sasiela WJ, Shirodaria C, Szarek M, Tamby JF, Tricoci P, White H, Zeiher A, Steg PG. Effect of alirocumab, a monoclonal antibody to PCSK9, on long-term cardiovascular outcomes following acute coronary syndromes: rationale and design of the ODYSSEY outcomes trial. *Am Heart J* 2014;**168**:682–689.
 17. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J; CKD EPI. A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009;**150**:604–612.
 18. Palmer SC, Navaneethan SD, Craig JC, Johnson DW, Perkovic V, Hegbrant J, Strippoli GF. HMG CoA reductase inhibitors (statins) for people with chronic kidney disease not requiring dialysis. *Cochrane Database Syst Rev* 2014;CD007784. doi: 10.1002/14651858.CD007784.pub2.
 19. Cholesterol Treatment Trialists' (CTT) Collaboration. Impact of renal function on the effects of LDL cholesterol lowering with statin-based regimens: a meta-analysis of individual participant data from 28 randomised trials. *Lancet Diabetes Endocrinol* 2016;**4**:829–839.
 20. Robinson JG, Farnier M, Krempf M, Bergeron J, Luc G, Averna M, Stroes ES, Langslet G, Raal FJ, El Shahawy M, Koren MJ, Lepor NE, Lorenzato C, Pordy R, Chaudhari U, Kastelein JJ, Odyssey L, Term I. Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. *N Engl J Med* 2015;**372**:1489–1499.
 21. Bakris G. Lipid disorders in uremia and dialysis. *Contrib Nephrol* 2012;**178**:100–105.
 22. Ray KK, Colhoun HM, Szarek M, Baccara-Dinet M, Bhatt DL, Bittner VA, Budaj AJ, Diaz R, Goodman SG, Hanotin C, Harrington RA, Jukema JW, Loizeau V, Lopes RD, Moryusef A, Murin J, Pordy R, Ristic AD, Roe MT, Tuñón J, White HD, Zeiher AM, Schwartz GG, Steg PG, Schwartz GG, Steg PG, Bhatt DL, Bittner VA, Diaz R, Goodman SG, Harrington RA, Jukema JW, Szarek M, White HD, Zeiher AM, Tricoci P, Roe MT, Mahaffey KW, Edelberg JM, Hanotin C, Lecorps G, Moryusef A, Pordy R, Sasiela WJ, Tamby J-F, Aylward PE, Drexel H, Sinnaeve P, Dilic M, Lopes RD, Gotcheva NN, Prieto J-C, Yong H, López-Jaramillo P, Pećin I, Reiner Z, Ostadal P, Viigimaa M, Nieminen MS, Chumburidze V, Marx N, Danchin N, Liberopoulos E, Montenegro Valdovinos PC, Tse H-F, Kiss RG, Xavier D, Zahger D, Valgimigli M, Kimura T, Kim HS, Kim S-H, Erglis A, Laucevicius A, Kedev S, Yusoff K, Ramos López GA, Alings M, Halvorsen S, Correa Flores RM, Budaj A, Morais J, Dorobantu M, Karpov Y, Ristic AD, Chua T, Murin J, Fras Z, Dalby AJ, Tuñón J, de Silva HA, Hagström E, Landmesser U, Chiang C-E, Sritara P, Guneri S, Parkhomenko A, Ray KK, Moriarty PM, Vogel R, Chaitman B, Kelsey SF, Olsson AG, Rouleau J-L, Simoons ML, Alexander K, Meloni C, Rosenson R, Sijbrands EJJ, Tricoci P, Alexander JH, Armaganjian L, Bagai A, Bahit MC, Brennan JM, Clifton S, DeVore AD, Deloatch S, Dickey S, Dombrowski K, Ducrocq G, Eapen Z, Endsey P, Eppinger A, Harrison RW, Hess CN, Hlatky MA, Jordan JD, Knowles JW, Kolls BJ, Kong DF, Leonardi S, Lillis L, Maron DJ, Marcus J, Mathews R, Mehta RH, Mentz RJ, Moreira HG, Patel CB, Bernardes-Pereira S, Perkins L, Povsic TJ, Puymirat E, Schuyler Jones W, Shah BR, Sherwood MW, Stringfellow K, Sujavanich D, Toma M, Trotter C, Van Diepen S, Wilson MD, Yan AT, Schiavi LB, Garrido M, Alvarisqueta AF, Sassone SA, Bordonava AP, Alves De Lima AE, Schmidberg JM, Duronto EA, Caruso OC, Novaretto LP, Hominal MA, Montaña OR, Caccavo A, Gomez Vilamajo OA, Lenzetti AJ, Cartasegna LR, Paterlini G, Mackinnon JJ, Caimo GD, Amuchastegui M, Salomone O, Codutti OR, Jure HO, Bono JO, Hrabar AD, Vallejos JA, Ahuad Guerrero RA, Novoa F, Patocchi CA, Zaidman CJ, Giuliano ME, Dran RD, Vico ML, Carnero GS, Guzman PN, Medrano Allende JC, Garcia Brasca DF, Bustamante Labarta MH, Nani S, Blumberg ED, Colombo HR, Liberman A, Fuentealba V, Lucardi HL, Waisman GD, Berli MA, Garcia Duran RO, Cestari HG, Luquez HA, Giordano JA, Saavedra SS, Zapata G, Costamagna O, Llois S, Waites JH, Collins N, Soward A, Hii CL, Shaw J, Arstall MA, Horowitz J, Ninio D, Rogers JF, Colquhoun D, Oqueli Flores RE, Roberts-Thomson P, Raffel O, Lehman SJ, Aroney C, Coverdale SG, Garrahy PJ, Starmer G, Sader M, Carroll PA, Dick R, Zweiker R, Hoppe U, Huber K, Berger R, Delle-Karth G, Frey B, Weidinger F, Faes D, Hermans K, Pirenne B, Leone A, Hoffer E, Vrolix MCM, De Wolf L, Wollaert B, Castadot M, Dujardin K, Beauloye C, Vervoort G, Striekwold H, Convens C, Roosen J, Barbato E, Claeys M, Cools F, Terzic I, Barakovic F, Midzic Z, Pojskic B, Fazlibegovic E, Kulić M, Durak-Nalbantac A, Vulić D, Muslibegovic A, Goronja B, Reis G, Sousa L, Nicolau JC, Giorgeto FE, Silva RP, Nigro Maia L, Rech R, Rossi PR, Cerqueira MJA, Duda N, Kalil R, Kormann A, Abrantes JAM, Pimentel Filho P, Soggia AP, de Santos MO, Neuenschwander F, Bodanese LC, Michalaros YL, Eliaschewitz FG, Vidotti MH, Leaes PE, Botelho RV, Kaiser S, Manenti ERF, Precoma DB, Moura Jorge JC, de B Silva PG, Silveira JA, Saporito W, Marin-Neto JA, Feitosa GS, Ritt LEF, de Souza JA, Costa F, Souza WK, Reis HJ, Machado L, Ayoub JCA, Todorov GV, Nikolov FP, Velcheva ES, Tzekova ML, Benov HO, Petranov SL, Tumbevs HS, Shehova-Yankova NS, Markov DT, Raev DH, Mollov MN, Kichukov KN, Ilieva-Pandeva KA, Ivanova R, Gospodinov M, Mincheva P, Lazov PV, Dimov BI, Senaratne M, Stone J, Kornder J, Pearce S, Dion D, Savard D, Pesant Y, Pandey A, Robinson S, Gosselin G, Vizel S, Hoag G; ODYSSEY OUTCOMES Committee Investigators. Effects of alirocumab on cardiovascular and metabolic outcomes after acute coronary syndrome in patients with or without diabetes: a prespecified analysis of the ODYSSEY OUTCOMES randomised controlled trial. *Lancet Diabetes Endocrinol* 2019;**7**:618–628.
 23. Jukema JW, Szarek M, Zijlstra LE, de Silva HA, Bhatt DL, Bittner VA, Diaz R, Edelberg JM, Goodman SG, Hanotin C, Harrington RA, Karpov Y, Moryusef A, Pordy R, Prieto JC, Roe MT, White HD, Zeiher AM, Schwartz GG, Steg PG; ODYSSEY OUTCOMES Committees Investigators. Alirocumab in patients with polyvascular disease and recent acute coronary syndrome: ODYSSEY OUTCOMES trial. *J Am Coll Cardiol* 2019;**74**:1167–1176.
 24. Goodman SG, Aylward PE, Szarek M, Chumburidze V, Bhatt DL, Bittner VA, Diaz R, Edelberg JM, Hanotin C, Harrington RA, Jukema JW, Kedev S, Letierce A, Moryusef A, Pordy RR, Lopez GA, Roe MT, Viigimaa M, White HD, Zeiher AM, Steg PG, Schwartz GG. Odyssey Outcomes Committees Investigators. Effects of alirocumab on cardiovascular events after coronary bypass surgery. *J Am Coll Cardiol* 2019;**74**:1177–1186.
 25. Chronic Kidney Disease Prognosis Consortium, Matsushita K, van der Velde M, Astor BC, Woodward M, Levey AS, de Jong PE, Coresh J, Gansevoort RT. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. *Lancet* 2010;**375**:2073–2081.