WHAT HAVE WE LEARNED ABOUT LIPIDS AND CARDIOVASCULAR RISK FROM PCSK9 INHIBITOR OUTCOMES TRIALS?

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ABBREVIATIONS:

ACC	American College of Cardiology
ACS	Acute Coronary Syndromes
AHA	American Heart Association
ASCVD	Atherosclerotic cardiovascular disease
CANTOS	Canakinumab Antiinflammatory Thrombosis Outcome Study
EBBINGHAUS	Evaluating PCSK9 Binding Antibody Influence on Cognitive Health in High Cardiovascular Risk Subjects
FH	Familial hypercholesterolaemia
FOURIER	Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk
LDL-C	Low-density lipoprotein cholesterol
Lp(a)	Lipoprotein(a)
ODYSSEY Outcomes	Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab
PCSK9:	Proprotein convertase subtilisin/kexin type 9
SAMS	Statin-associated muscle symptoms
siRNA	Small interfering ribonucleic acid

1. Introduction

The role of proprotein convertase subtilisin/kexin type 9 (PCSK9) in the regulation of the LDL-receptor and plasma cholesterol was identified in 2003[1]. This seminal discovery led to the rapid exploitation of PCSK9 as a drug target. Fifteen years later, investigators have completed two large outcomes trials of monoclonal antibody inhibitors of PCSK9 (PCSK9Is). Evolocumab was evaluated in The Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER)[2], and alirocumab was tested in the Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab (ODYSSEY Outcomes)[3] trials (**Table 1**). Treatment of patients with these agents has been remarkably successful in achieving lower plasma concentrations of LDL-C than had ever previously been attainable with lipid lowering therapy. Therefore, in addition to the 'headline' event-rate reduction results of these trials, which will certainly inform clinical practice, scrutiny of the trial data can yield more general information about lipid-lowering therapy. This commentary will briefly discuss what we have learned from outcome trials of evolocumab and alirocumab, and what the future holds for these agents.

2. What have we learned from PCSK9I outcomes trials, and how has practice changed?

The addition of alirocumab and evolocumab to lipid-lowering therapy with statins (with or without ezetimbe), has enabled the effective management of patient groups for whom achievement and maintenance of lipid-targets were previously extremely difficult. In particular the very large reductions in LDL-C elicited by PCSK9 inhibitors has been used to manage patients with familial hypercholesterolaemia (FH). Using these agents, it has been possible to meet LDL-targets for most of this population, and additionally for some of them (even for 93%) it is now possible to entirely replace LDL-C apheresis (or to reduce the frequency of procedures) using PCSK9 inhibitor therapy. In several European countries, FH patients are the

only group for whom reimbursement for PCSK9 inhibitors is allowed (**Figure 1**). The availability of an effective therapeutic approach to FH has in fact led to a revival in interest in this condition[4] in many countries in which knowledge of this condition (and other genetically based lipid disorders) was very poor. Hopefully this will lead to redoubled efforts to identify undiagnosed FH patients.

Statin intolerance, in particular statin-associated muscle symptoms (SAMS) is an important cause of statin non-adherence, discontinuation and suboptimal lipid management [5,6]. Inhibitors of PCSK9 have also prompted discussion on the definition of statin intolerance and its effective diagnosis[7]. Additionally these agents have shown promise in the effective management of plasma lipid concentrations in statin intolerant patients, for whom there was previously no effective therapy[5-7]. The GAUSS-3 trial found that in patients with confirmed statin-intolerance, evolocumab was associated with a 53% reduction in LDL-C at 24 weeks. Muscle symptoms were reported in only 21% of evolocumab-treated patients[8]. Similarly, in the ODYSSEY-alternative trial, alirocumab reduced mean LDL-C by 45% at 24 weeks[9]. In both cases PCSK9 inhibition was superior to ezetimibe. The demonstration of the concept of effective lipid-lowering in statin intolerant patients has led to trials investigating alternative lipid-lowering therapies such as bempedoic acid and to look for the other alternative therapies that might reduce LDL-C in patients with high cardiovascular (CV) risk[10,11].

The extremely low plasma concentrations of LDL-C achieved by treatment with PCSK9 inhibitors has renewed focus on residual (i.e. non-LDL-C–mediated) risk for cardiovascular disease (CVD). This is timely in light of the recent demonstrations of the importance of inflammatory risk factors for cardiovascular disease in the Canakinumab Antiinflammatory Thrombosis Outcome Study (CANTOS)[12] and Reasons for Geographic and Racial Differences in Stroke (REGARDS) study[13]. Additionally, the importance of lipoprotein(a) (Lp(a)) in mediating CV risk has received renewed attention. It is worth mentioning that purely on the basis of data with PCSK9 inhibitors, physicians in many countries worldwide have started

(re)measuring Lp(a). This highly atherogenic and pro-thrombotic lipoprotein is resistant to many lipid-lowering therapies[14], but appears to be effectively reduced by PCSK9 inhibitors[15].

Importantly, FOURIER[2] and ODYSSEY-Outcomes[3] have demonstrated conclusively that additional lipid-lowering therapy can be very beneficial in reducing cardiac outcomes in patients already taking optimal statin therapy. Previously, the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) had demonstrated a reduction of a composite endpoint when ezetimibe was added to statin therapy[16], however ODYSSEY-Outcomes additionally demonstrated an important reduction in all-cause mortality with alirocumab [3]

Furthermore, ODYSSEY-Outcomes[3] and FOURIER[2] have added further evidence to support the '*lower is better for longer'* paradigm with respect to LDL-C. In alirocumab-treated patients mean LDL-C levels at 4 months, 12 months, and 48 months were 0.98 mmol/l (38 mg/dl), 1.1 mmol/l (42 mg/dl), and 1.4 mmol/l (53 mg/dl), respectively with the composite primary outcome (death from coronary heart disease, nonfatal myocardial infarction, fatal or nonfatal ischemic stroke, or unstable angina requiring hospitalization) reduced by 15% (95%Cl: 0.78-0.93) (with absolute risk reduction [aRR] 2% - number needed to treat [NNT]: 50][3] . Patients treated with evolocumab achieved mean LDL-C of 2.4 mmol/l (30 mg/dl) and this was associated with a 15% reduction (95%Cl: 0.79-0.92; aRR=2%, NNT=50) in the primary outcome (a composite of cardiovascular death, myocardial infarction, stroke, hospitalisation for unstable angina or coronary revascularisation)[2]. A secondary analysis of the data revealed that the benefits persisted at LDL-C levels <0.5 mmol/L (20 mg/dL)[17]. Importantly, these benefits do not appear to be associated with excessive adverse effects and reassuringly, the rigorously conducted Evaluating PCSK9 Binding Antibody Influence on Cognitive Health in High Cardiovascular Risk Subjects (EBBINGHAUS) study found no evidence of cognitive impairment over a median of 19 months of evolocumab therapy[18].

How should PCSKIs be used in high-risk patients?

The high acquisition cost of PCSK9 inhibitors, and the fact that high-risk individuals have been included in clinical trials has led to a discussion about the most appropriate method to stratify risk in the secondary prevention of CVD. Risk stratification is essential in order to select the patients who are most likely to benefit from treatments, and consequently to improve the cost-effectiveness of these medicines in measures such as Quality Adjusted Life Years (QALYs) and other techniques used economic evaluations of medicines. Based on the previous analyses PCSK9 inhibitor therapy should be considered in all high-risk patient groups where the number needed to treat (NNT) is less than 30[19]. Using the available data and sub-analyses of PCSK9 trials such patient groups have been identified by the *International Lipid Expert Panel* (ILEP)[20] (**Table 2**), however further development of risk stratification algorithms would be extremely beneficial in deciding whether to initiate therapy with statin monotherapy, or to use combination therapy with statins and ezetimibe or a PCSK9 inhibitor from the outset. A risk stratification tool has previously been developed to assist therapeutic decision-making with respect to the initiation of the thrombin receptor antagonist vorapaxar in patients with ischemic heart disease[21]. A similar scheme for decision making with respect to PCSK9 inhibitors would likely include clinical details in addition to baseline lipid levels[19] and coronary artery calcium scores[22,23] to enable optimal decision making with respect to initial treatment. Based on these analyses we should consider changes in risk stratification for secondary prevention patients and introducing the group of *extremely high risk* patients to finally give clear answers as to which patients should be treated with the highest statin doses (80 mg atorvastatin and 40 mg rosuvastatin instead of the recommended ranges of 40-80 and 20-40 mg for atorvastatin and rosuvastatin, respectively), which patients should initiate treatment with combination therapy, and which ones might benefit the most from new therapies[20]. Furthermore, recently published findings and ongoing studies may potentially expand the scope of PCSK9I therapy to include

new patient groups including pregnancy, primary prevention and comorbidities such as chronic kidney disease, and diabetes [20,24].

What does the future hold for PCSK9 inhibitors?

Recently published data from ODYSSEY-Outcomes[3] and FOURIER[2] suggests that evolocumab and alirocumab are extremely effective in lowering atherogenic lipoproteins, and consequently in preventing major adverse CV events. Availability of PCSK9 inhibitors to patients is determined by local policies on reimbursement. Such policies vary widely between countries, with no availability still in some countries, or with the reimbursement only for limited group of patients with FH in others (**Figure 1**). Cost-benefit analyses are likely to move in favour of PCSK9 inhibitors because of recent price reductions in these agents. In October 2018, Amgen announced that it was lowering the price of Repatha® (evolocumab) by, by approximately 60% from $14,000 to $5850 a year. This followed an announcement in May 2018 that Regeneron and Sanofi, the manufacturers of Praluent® (alirocumab) would reduce the price of this agent for a large number of patients. Physician familiarity with, and use of PCSK9Is is likely to increase following the publication of the recent American College of Cardiology and American Heart Association (ACC/AHA) Guideline on the Management of Blood Cholesterol. The guideline makes a class IIa recommendation for patients with multiple CV risk factors following acute coronary syndromes (ACS); but surprisingly a class IIb recommendation for patients with FH [25].

With excellent clinical trial results and improving affordability, PCSK9-inibitors are likely to be a rational choice of lipid-lowering therapy in an increasing number of very high and extremely high-risk patients. In parallel with the rapid clinical developments, PCSK9 has continued to be remarkably fruitful field of study for basic scientists. As an alternative to monoclonal antibody inhibitors to PCSK9, the ORION series of clinical trials have demonstrated safety and lipid-lowering efficacy of inclisiran, a small interfering RNA (siRNA)

which targets the messenger RNA for PCSK9[26]. Recent preclinical studies have shown promising results for an anti-PCSK9 antisense oligonucleotide, which reduces serum PCSK9 in a rat model [27].

The remarkably rapid progress from the identification of PCSK9 as a drug target to the development, clinical evaluation and regulatory approval of multiple PCSK9Is is almost unique in modern medicine. This success is clearly due to close collaboration between basic scientists and clinical researchers in high-quality translational research projects. It is hoped that continued collaborative research will lead to more cost-effective therapies so that the remarkable benefits of PCSK9 inhibition can be extended to as many patients as possible.

Declaration of Interest:

Maciej Banach: speakers bureau: Abbott/Mylan, Abbott Vascular, Actavis, Akcea, Amgen, Biofarm, KRKA, MSD, Sanofi-Aventis, Servier and Valeant; consultant to Abbott Vascular, Akcea, Amgen, Daichii Sankyo, Esperion, Lilly, MSD, Polfarmex, Resverlogix, Sanofi-Aventis; Grants from Sanofi and Valeant; *Peter Penson* owns four shares in AstraZeneca PLC and has received speaker's fees from Amgen Inc.

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Figure 1. The information on reimbursement of PCSK9 inhibitors in Europe (status as of 1st Nov. 2018).

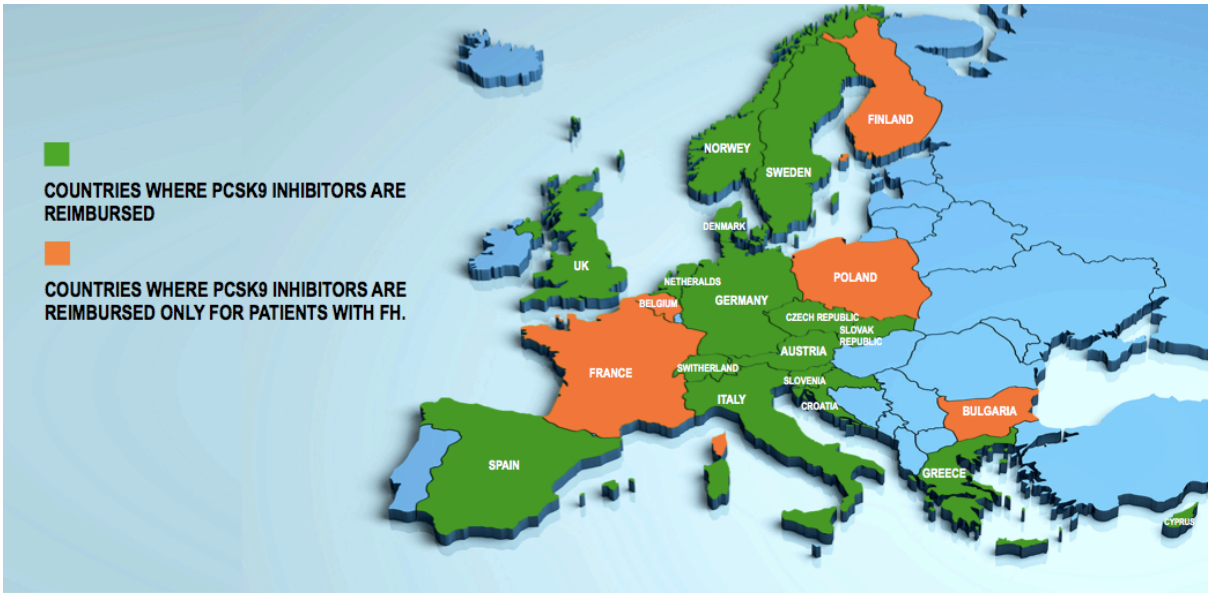

Table 1: Comparison of FOURIER and ODYSSEY-Outcomes trials

	FOURIER[2]	**ODYSSEY-Outcomes**[3]
Characteristics of study and participants		
Publication year	2017	2018
Trial design	Randomised double-blind placebo-controlled trial	Randomised double-blind placebo-controlled trial
Drug regiments	Evolocumab subcutaneously either 140mg every 2 weeks or 420mg monthly	Alirocumab (dose adjusted to meet LDL-C target of 25 to 50 mg/dl)
Mean follow-up	2.2 years	2.8 years
Number of participants	27,564	18.924
Mean age of participants	62.5 ± 9.1 (evolocumab) 62.5 ± 8.9 (placebo)	58.5 ± 9.3 (alirocumab) 58.6 ± 9.4 (placebo)
% of male participants	75.4% evolocumab 75.5% placebo	74.7 (alirocumab) 74.9 (placebo)
Main inclusion criteria	Age >40 <85 Clinically relevant ASCVD Additional 'high risk' characteristics Fasting LDL-C ≥ 70mg/dl or non-HDL-C ≥ 100mg/dl on optimal therapy	Age >40 Hospitalized with ACS 1-12 months before randomization LDL-C ≥ 70 mg/dl Non HDL-C ≥ 100mg/dl or apolipoprotein B ≥ 80 mg/dl.
Background therapy	High intensity statin (69.3%) Moderate intensity statin (30.4%) Low intensity/ no data (0.03%) Ezetimibe (5.3%)	High intensity atorvastatin/rosuvastatin (88.9%) Low/ moderate intensity atorvastatin/rosuvastatin (8.5%) Other statin (0.25%) No Statin (2.4%)

		Ezetimibe (2.9%)
Endpoints and Results		
Primary endpoint and hazard ratio	Composite of cardiovascular death, myocardial infarction, stroke, hospitalisation for unstable angina or coronary revascularisation. HR (95%CI) v placebo 0.85 (0.79-0.92)	Composite of death from coronary heart disease, nonfatal myocardial infarction, fatal or nonfatal ischemic stroke, or unstable angina requiring hospitalization. HR (95%CI) v placebo 0.85 (0.78-0.93)

Table 2: Selected groups of patients that might benefit most from the use of PCSK9 inhibitors based on the most recent data summarized by the International Lipid Expert Panel (ILEP)[20].

Patient group	**Background therapy**	**Biomarkers**	**NNT**
Patients with early ACS (up to 1-12 months)	Optimal treatment	Persistent LDL≥100 mg/dl	29
Patient with fresh ACS (up to 1-12 months)	Optimal treatment	Persistent LDL≥70 mg/dl + diabetes mellitus and/or baseline Lp(a)> 60 mg/dl	30
Patients with very high cardiovascular risk (after ACS)	Optimal treatment	Persistent LDL≥70 mg/dl + diabetes and/or baseline CRP> 3 mg/dl	<30
Patient in the group of very high cardiovascular risk (after ACS) on	Optimal treatment	Persistent LDL≥70 mg/dl + with concomitant PAD	29
Patients with very high cardiovascular risk (after ACS)	Optimal treatment	Persistent LDL≥70 mg/dl + ≥2 previous ACS and initially with diabetes / Lp(a)>60 mg/dl / CRP> 3 mg/l	<30
Patients with very high cardiovascular risk (after ACS)	Optimal treatment	Persistent LDL≥70 mg/dl + with multivessel disease	29