The ESC congress 2018, held this year in Munich, Germany, is the largest cardiology congress in the world. It has a world-renowned faculty, and a global reputation for providing delegates with both the latest late-breaking clinical trial data and in-depth educational sessions. This year the ESC congress brought together almost 33,000 delegates from 150 countries, who had the opportunity to attend a vast array of presentations covering 400 different cardiology topics – over 5 days, 4500 abstract presentations were given in 500 expert sessions.
The first Amgen-sponsored symposium at the ESC congress 2018 comprised an interactive set of presentations and patient cases for HCPs. The faculty painted a thought-provoking and educational picture of real-life management of patients with ASCVD.

Ulrich Laufs  
Universitätsklinikum Leipzig, Germany  
Robert Giugliano  
Harvard Medical School, USA  
Gaetano De Ferrari  
University of Pavia, Italy  
Naveed Sattar  
University of Glasgow, UK

The criticality of elevated LDL-C  
Ulrich Laufs

Professor Laufs began the symposium by highlighting the central role that LDL-C plays in endothelial dysfunction and atherogenesis. He indicated that the risk reductions for CHD associated with a 50% reduction in LDL-C have the potential to be very large; for example, a 50% reduction in LDL-C for a patient with a baseline LDL-C of 252 mg/dL equates to a 92% relative reduction in lifetime risk for CHD.

Despite the huge potential benefits associated with reducing LDL-C, many patients are still not at the target LDL-C level of 70 mg/dL. Professor Laufs stressed that the current level of LDL-C target attainment is poor, and much needs to be done to improve the situation. He emphasised this point by highlighting data from a survey of 41,540 patients with ASCVD, which indicated that 66.5–81.0% of patients on statins were not at LDL-C goal.

When statins are not enough  
Robert Giugliano

Dr Giugliano assessed the case for reducing LDL-C further than with statins alone by using add-on non-statin therapies. He began his case by highlighting the incremental benefit that ezetimibe can bring to patients when used in addition to statin therapy. In the IMPROVE-IT study, the 7-year RRR in CV events in patients receiving ezetimibe in addition to statin therapy versus those who did not was 6.4% (P=0.016). Dr Giugliano pointed out that despite modest benefits, IMPROVE-IT teaches the valuable lesson that in terms of LDL-C, even lower is even better.

Dr Giugliano then moved on to discuss still further LDL-C reductions with Repatha®, which provides the possibility of reducing LDL-C levels much further than has historically been feasible. Dr Giugliano discussed the safety and efficacy of very low LDL-C levels and illustrated his points with data from the FOURIER trial. Focusing on the subset of FOURIER patients that had relatively low LDL-C to start with (<70 mg/dL at baseline), Dr Giugliano highlighted that in this subgroup, the patients appeared to still derive benefit with a numerical reduction of the key secondary endpoint of CV death, MI or stroke of 30% (HR 0.70; 95% CI 0.48–1.01, P=0.44 for interaction), delivering the key message that LDL-C lowering can benefit patients, even if they already have LDL-C below target levels.

Further to this, after 30 months the median achieved LDL-C level in this subset of patients was very low: just 19 mg/dL. Importantly, when patients in the FOURIER trial were stratified by baseline LDL-C, safety events were found to be equivalent across all five quintiles, including this lowest quintile. This indicates that there are no additional safety risks in these patients, who have very low LDL-C.

Given these FOURIER efficacy and safety data, Dr Giugliano concluded that in terms of LDL-C, lower is better, but lowest is best.

Treating cardiovascular patients at risk: cases in action  
Ulrich Laufs, Gaetano De Ferrari, Naveed Sattar

Three interactive patient cases illustrating where PCSK9 inhibitors could make a real difference to patients were presented by Professors Laufs, De Ferrari and Sattar.

Professor Laufs began by presenting the case of a patient with multiple morbidities. This patient suffered with severe PAD and type 2 diabetes, and had experienced a stroke. After the stroke, the patient’s LDL-C was also elevated at 121 mg/dL despite receiving rosuvastatin 40 mg and ezetimibe 10 mg.

Professor Laufs used data from the FOURIER trial to indicate the benefit of Repatha® in patients with such morbidities, focusing on patients with PAD. Patients with PAD can greatly benefit from treatment with Repatha®: in FOURIER, 3642 patients had PAD, and in this cohort the RRR in the key secondary endpoint after 30 months of Repatha® treatment was 27% (P=0.0040).

The situation for patients with diabetes was discussed in more detail by Professor Sattar. He presented the case of a patient with diabetes and a prior MI who had elevated cholesterol and HbA1c. Such patients are at increased risk of mortality: this patient may suffer from 16 years of life lost compared with a corresponding person without diabetes and a prior MI.
Professor Sattar stressed the importance of not just treating the ‘diabetes’ in such patients, but also LDL-C. He concluded that in this case, since the patient was only able to take a very low dose of a statin and ezetimibe due to statin-associated side effects, they were therefore in a position to benefit from additional LDL-C lowering from a PCSK9 inhibitor.

Professor De Ferrari concluded the patient cases with the case of a patient with hyperlipidaemia who had suffered two prior MIs. Despite the patient having an LDL-C close to target on a statin and ezetimibe, Professor De Ferrari argued the case for providing this patient with a PCSK9 inhibitor.

Professor De Ferrari reinforced his points with a sub-analysis of the FOURIER trial demonstrating that Repatha® has a greater actual benefit in patients with ≥2 prior MIs versus those with 1 prior MI (RRR of the key secondary endpoint 21% [P=0.006] versus 16% [P=0.008] (P=0.57 for interaction). He also highlighted data from FOURIER that show Repatha® has a greater actual benefit in patients when used within 2 years of an MI, compared to >2 years after an MI. After putting forward this evidence he concluded by asking the audience: “If the patient wants more protection, what else can you offer?”

Experts-on-the-Spot session

An Experts-on-the-Spot session followed the symposium on Monday 27 August 2018. In this, Professor Laufs, Dr Giugliano and Professor De Ferrari continued the theme of the symposium by discussing the following key questions:

- Why is it so critical to control LDL-C?
- Why are LDL-C targets not achieved?
- Which patients are suitable for treatment with a PCSK9 inhibitor?

The faculty discussed their thoughts on each of the three key questions and concluded:

- For physiological parameters such as blood pressure, there is a U-shaped association between benefits and level of parameter, and benefits do not keep increasing as the parameter approaches zero. LDL-C in this sense is more like a toxin in that the lower the level, the better. We can aggressively treat LDL-C to reduce risk without worrying about additional safety implications.

- Patients are not achieving LDL-C targets because they are not receiving high enough doses of statin. Education in the safety of statins and low levels of LDL-C should improve this situation. In addition, in many high-risk patients, statins alone are not enough to reach target LDL-C levels but use of add-on therapies such as ezetimibe and PCSK9 inhibitors are currently underutilised.

- Patients who should be targeted with PCSK9 inhibitors are those at highest risk of CV events, because they stand to benefit the most. These include patients with multiple MIs, or established ASCVD with diabetes or metabolic syndrome.
Introduction

Ulf Landmesser
Berlin Institute of Health, Germany

Kausik Ray
Imperial College London, UK

Christie Ballantyne
Baylor College of Medicine, USA

Improving secondary prevention in atherosclerotic disease ‘When less LDL-C is more’

Tuesday 28 August 2018, Messe München, Munich, Germany

The second Amgen-sponsored symposium at the ESC congress 2018 provided a thought-provoking session in which HCPs were invited to consider the current state of management of patients with ASCVD. The session included a didactic presentation on when to consider using a PCSK9 inhibitor.

In his introduction, Professor Landmesser outlined the many different areas of treatment that should be considered in the management of coronary disease, namely:

- Control of lifestyle factors
- Lipid targeting
- Blood pressure lowering
- Anti-thrombotic therapy
- Anti-diabetic therapy
- Anti-inflammatory therapy
- Microbiome-targeted therapy

The scene was then set for the following presentations; Professor Landmesser reminded the audience of the crucial role LDL-C plays in coronary disease, and how lower LDL-C is clearly correlated with lower risk of coronary disease. He closed his introduction by reminding the audience that most of us already have coronary atherosclerosis, and that the development of atherosclerotic disease begins early in life.

What approach to CV risk management in 2018?

Kausik Ray

Professor Ray introduced the concept that CV risk is multifactorial, and strongly recommended that effective management of CVD should involve a ‘global approach’—i.e. all of a patient’s CV risk factors should be managed as a whole.

However, Professor Ray noted that there is a caveat to reducing risk factors, as for many there is a balance between risk and benefit. This he illustrated with the example of the COMPASS trial; low-dose rivaroxaban and aspirin combined was more beneficial in terms of prevention of CV events than high-dose rivaroxaban alone, but this was counterbalanced by the increased risk of bleeding. Similarly, in CANTOS, CV outcomes benefits associated with higher doses of canakinumab are counterbalanced by the increased incidence of infections. In this sense LDL-C is an unusual risk factor in that data suggest that there appears to be no lower limit to the benefits of lowering LDL-C so far, and safety events do not increase as LDL-C levels are reduced.

Returning to CANTOS, Professor Ray used the concept of ‘global risk reduction’ to point out that patients with elevated hsCRP can have their overall CV risk reduced by using Repatha®. He showed data from a substudy of FOURIER which showed that Repatha® has an increasing benefit in CV outcomes with increasing baseline hsCRP, despite not having any effect on hsCRP itself. The benefit is derived instead from reduction in LDL-C, and from this he concluded: by focusing on one risk factor we become too narrow, and we need to start assessing patient’s risk as a whole.

The presentation concluded with a key voting question to the audience: What do you consider to be the lowest LDL-C level that is safe? To which 64% of the audience responded that they would feel comfortable going below 25 mg/dL.

Where PCSK9 inhibitors can make a difference

Christie Ballantyne

The unmet need in patients with ASCVD was the starting point for the presentation from Dr Ballantyne. As shown by the EUROASPIRE V survey, only 29% of patients are reaching the LDL-C target of 70 mg/dL, and data from
the Pinnacle registry show that although many patients are prescribed statins, high-dose statin prescription is very variable between practices.\(^2\) Although increased prescription of high-dose statins would help more patients achieve their LDL-C targets, EUROASPIRE V also shows that only 36% of patients on high-intensity lipid-lowering therapy achieve their target of LDL-C <70 mg/dL, and, therefore, there is great unmet need in lowering LDL-C levels further in patients at risk of CV events.

Dr Ballantyne followed this with a review of the evidence in support of additional non-statin therapies in the treatment of patients with ASCVD. From a meta-analysis of statin trials\(^2\) and from GLAGOV,\(^2\) atherosclerosis is regressed regardless of whether a statin or non-statin lipid-lowering therapy is used; a huge amount of outcomes data demonstrate that non-statin therapies added on top of statin therapy give additional CV outcomes benefits. To date, there are six major trials (including >120,000 patients) in support of this additional benefit.\(^6,7,24-26\)

Data from FOURIER suggest there does not seem to be a lower limit for LDL-C in terms of CV outcomes benefits and safety.\(^27\) Dr Ballantyne remarked that this is useful not only in managing the global risk of patients, but in discussions with patients themselves when consulting on add-on therapies. According to Dr Ballantyne, patients are often reluctant to start an additional therapy if it has common side effects, especially if those side effects are severe or challenging to manage.

Dr Ballantyne pointed out that physicians are not only worried about primary CV events in their patients, but all events, and highlighted that Repatha\(^\circledR\) is valuable in preventing further CV events. In FOURIER, for every 1000 patients treated with Repatha\(^\circledR\) for 3 years, 52 primary endpoint events are avoided, of which 22 are first events.\(^28\)

In terms of the urgency to treat patients to prevent further events, Dr Ballantyne focused on the FOURIER MI sub-group analysis. Patients with an MI represent a high-risk group, and data from FOURIER show Repatha\(^\circledR\) has a greater actual risk reduction in patients with prior MI if used within 2 years of the event, compared with after 2 years.\(^1\) Dr Ballantyne asked the audience for their opinion on when to initiate PCSK9 inhibitor therapy in patients with an MI, to which 91% responded that they would do so within 3 months of the event.

The presentation concluded with Dr Ballantyne addressing the question of which patients have the potential to benefit the most from additional PCSK9 inhibitor therapy. He concluded that these patients were: those with high burden of atherosclerosis and those with aggressively progressive atherosclerosis, and that in these patients there is a wealth of evidence that lower LDL-C is better for CV outcomes.

The satellite symposium was followed later in the day by an Experts-on-the-Spot session in which Professor Ray, Dr Ballantyne and Professor Landmesser dived into the themes of the symposium in more detail. They addressed the following key questions:

- What are the unmet needs in the management of high-risk CV patients?
- How can CV risk be reduced effectively??
- How safe are aggressive reductions in LDL-C together with sustained very low LDL-C?

The faculty summarised the above in the following key points:

- Physicians already know instinctively which of their patients are at highest risk of CV events, these are patients with high burden of atheroma, or with aggressive atherosclerosis. The sub-analyses from FOURIER indicating very high-risk patients that stand to gain the most benefit from receiving Repatha\(^\circledR\) all fall into one of these categories.
- Physicians need to view the global CV risk of their patients and critically appraise risk as they would critically appraise an ECG. A better appreciation of risk factors and the overall risk of each patient as a whole will lead to better management of CV risk in patients with ASCVD.
- Evidence from FOURIER shows there is no difference in safety if LDL-C is lowered with Repatha\(^\circledR\) to very low levels (<19 mg/dL), even when compared with patients that only achieved LDL-C levels ≥100 mg/dL.

Abstract spotlight

Please find below a selection of abstracts from the ESC Congress 2018, chosen for you because of your interest in the latest Repatha\(^\circledR\) data. The congress abstracts and other content (presentation slides and posters) are available online. Click here if you wish to read the abstracts in full or find out more about the latest developments in lipid management.
FOURIER – Efficacy of PCSK9 inhibition with evolocumab in patients with metabolic syndrome
Prakash Deedwania

This sub-analysis of patients from the FOURIER study investigated the safety and efficacy of Repatha® in patients with metabolic syndrome at baseline, compared with those without metabolic syndrome. Based on the NCEP III criteria, 16,361 (60%) of the 27,342 total subjects enrolled in FOURIER had metabolic disease at baseline. These patients had a 20% higher risk of experiencing a CV event compared with those without metabolic syndrome (HR 1.22 for the key secondary endpoint, P=0.005).

Repatha® significantly reduced the chances of patients with metabolic disease experiencing a CV event with respect to placebo (see Figure 1), and the ARR was higher for patients with metabolic syndrome versus those without. There was also no increase in new-onset diabetes in the patients with metabolic syndrome who received Repatha®, versus those who received placebo (12.3% versus 11.2%, respectively [P=NS]).

These data show increased benefit of Repatha® in this higher risk patient population, i.e. in patients with metabolic syndrome versus those without.

**Figure 1.** Effect of Repatha® on the primary* and key secondary† endpoint of FOURIER in patients with and without metabolic disease at baseline

![Graph showing the effect of Repatha® on primary and key secondary endpoints](graph.png)

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Patient and caregiver productivity loss and indirect costs associated with cardiovascular events in Europe
Kornelia Kotseva

This poster presented a cross-sectional study which aimed to estimate the productivity loss and indirect costs associated with an ACS or stroke in the first year post-event. The analysis encompassed 7 European countries and involved 196 patients with ACS (86% MI) and 198 with stroke (99% ischaemic). The mean age of patients was 53 years and 82% were male.

**Productivity loss in the first year following an ASC or stroke was found to be substantial,** and was mainly driven by absenteeism associated with the index event (hospitalisation and sick days), followed by requirement of assistance from a caregiver (see Figure 2). For ACS, patient and caregiver loss added up to 70 days in the year, and for stroke, 68 days were lost.

**Figure 2.** Patient and caregiver productivity loss drivers for ACS and stroke; mean work days lost in the year
Benefit of LDL-C lowering with evolocumab on cardiovascular outcomes by age and sex: an analysis of the FOURIER trial

Peter Sever

Professor Sever presented a prespecified analysis of the efficacy and safety of Repatha® in the FOURIER trial by patient age and sex. The need for this analysis was driven by evidence suggesting the benefits of lipid lowering with statins may attenuate in the elderly, and by concerns raised over the undertreatment of women compared with men.

Repatha® gave similar reductions in LDL-C regardless of patient age and sex, and there were only very small differences in the efficacy of Repatha® when the different age quartiles and sexes were analysed (see Figure 3). Professor Sever stressed that these differences were likely due to differences in the baseline characteristics of the patients rather than their age or sex.

Irrespective of the age or sex of the patients, there were also no significant differences in the safety profile of Repatha®. Repatha® therefore confers CV outcomes benefits for patients irrespective of their age or sex.

**Figure 3.** Efficacy of Repatha® stratified by age and sex: HRs for the key secondary point

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<th>P interaction</th>
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<tr>
<th>Sex</th>
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<tr>
<td>Male</td>
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**Abbreviations**

- ACS = acute coronary syndrome; ASCVD = atherosclerotic cardiovascular disease; ARR = absolute risk reduction; CHD = coronary heart disease; CI = confidence interval; CV = cardiovascular; ECG = echocardiogram; HCP = healthcare professional; HR = hazard ratio; hsCRP = high-sensitivity C-reactive protein; LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction; NCEP = National Cholesterol Education Program; PAD = peripheral arterial disease; PCSK9 = proprotein convertase subtilisin/kexin type 9; RRR = relative risk reduction; UA = unstable angina.

**References**

1. About ESC congress website. Available at: https://www.escardio.org/Congresses-%26-Events/ESC-Congress/About-the-congress Accessed September 2018

**Expert opinion**

For expert opinion from the ESC congress 2018, follow the link by clicking on the image below.
Repatha® (evolocumab) Brief Prescribing Information

Please refer to the Summary of Product Characteristics (SmPC) before prescribing Repatha. **Pharmaceutical Form:** Pre-filled pen (SureClick®) and pre-filled syringe containing 140 mg of evolocumab in 1 mL solution for injection. Automated mini-doser cartridge containing 420 mg of evolocumab in 3.5 mL solution for injection (120 mg/mL). **Indication:** Hypercholesterolaemia and mixed dyslipidaemia: Repatha is indicated in adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet: in combination with a statin or statin with other lipid lowering therapies in patients unable to reach LDL C goals with the maximum tolerated dose of a statin or; alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated. Homozygous familial hypercholesterolaemia: Repatha is indicated in adults and adolescents aged 12 years and over with homozygous familial hypercholesterolaemia in combination with other lipid-lowering therapies. Established atherosclerotic cardiovascular disease: Repatha is indicated in adults with established atherosclerotic cardiovascular disease (myocardial infarction, stroke or peripheral arterial disease) to reduce cardiovascular risk by lowering LDL-C levels, as an adjunct to correction of other risk factors: in combination with the maximum tolerated dose of a statin with or without other lipid-lowering therapies or; alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated. **Dosage and Administration:** Repatha is for subcutaneous injection into the abdomen, thigh or upper arm region. Repatha is intended for patient self-administration after proper training. Prior to initiating Repatha, secondary causes of hyperlipidaemia or mixed dyslipidaemia (e.g., nephrotic syndrome, hypothyroidism) should be excluded. **Primary hypercholesterolaemia and mixed dyslipidaemia in adults:** The recommended dose of Repatha is either 140 mg every two weeks or 420 mg once monthly; both doses are clinically equivalent. The safety and efficacy of Repatha in children aged less than 18 years has not been established. **Homozygous familial hypercholesterolaemia in adults and adolescents aged 12 years and over:** The initial recommended dose is 420 mg once monthly. After 12 weeks of treatment, dose frequency can be up titrated to 420 mg once every 2 weeks if a clinically meaningful response is not achieved. Patients on apheresis may initiate treatment with 420 mg every two weeks to correspond with their apheresis schedule. The safety and efficacy of Repatha in children aged less than 12 years has not been established. **Established atherosclerotic cardiovascular disease in adults:** The recommended dose of Repatha is either 140 mg every two weeks or 420 mg once monthly; both doses are clinically equivalent. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients. **Special Warnings and Precautions:** Renal impairment: There is limited experience with Repatha in patients with severe renal impairment (defined as eGFR < 30 mL/min/1.73 m2). Repatha should be used with caution in patients with severe renal impairment. Hepatic impairment: In patients with moderate hepatic impairment, a reduction in total evolocumab exposure was observed that may lead to a reduced effect on LDL C reduction. Therefore, close monitoring may be warranted in these patients. Patients with severe hepatic impairment (Child-Pugh C) have not been studied. Repatha should be used with caution in patients with severe hepatic impairment. Dry natural rubber: The needle cover of the glass pre-filled pen (SureClick®) and pre-filled syringe is made from dry natural rubber (a derivative of latex), which may cause allergic reactions. **Interactions:** No formal drug-drug interaction studies have been conducted for Repatha. **Fertility, pregnancy and lactation:** There are no or limited amount of data from the use of Repatha in pregnant women. It is unknown whether evolocumab is excreted in human milk. A risk to breastfed newborns/infants cannot be excluded. No data on the effect of evolocumab on human fertility are available. **Undesirable Effects:** The following common (≥ 1/100 to < 1/10) adverse reactions have been reported in pivotal, controlled clinical studies: influenza, nasopharyngitis, upper respiratory tract infection, rash, nausea, back pain, arthralgia, injection site reactions. Please consult the SmPC for a full description of undesirable effects. **Pharmaceutical Precautions:** Store in a refrigerator (2°C – 8°C). Do not freeze. Keep the pre-filled pen (SureClick®), pre-filled syringe, automated mini-doser and cartridge in the original carton in order to protect from moisture and/or light. If removed from the refrigerator, Repatha may be stored at room temperature (up to 25°C) in the original carton and must be used within 1 month. **Legal Category:** POM. **Marketing Authorisation Numbers:** Repatha 140 mg solution for injection in pre-filled syringe: EU/1/15/1016/001 (1 pre-filled syringe); Repatha 140 mg solution for injection in pre-filled pen: EU/1/15/1016/002 (1 pre-filled pen); EU/1/15/1016/003 (2 pre-filled pens); EU/1/15/1016/004 (3 pre-filled pens); EU/1/15/1016/005 (6 (3x2) pre-filled pens (multipack)); Repatha 420 mg solution for injection in cartridge: EU/1/15/1016/006 (1 cartridge with co-packed automated mini-doser); EU/1/15/1016/007 (3 (3x1) cartridges with co-packed automated mini-doses (multipack)). Not all pack sizes may be marketed.

**Marketing Authorisation Holder:** Amgen Europe B.V., Minervum 7061, 4817 ZK Breda, The Netherlands. **Date of PI preparation:** July 2018 (Ref: EUHQ-P-145-0618-065958.)

▼This medicinal product is subject to additional monitoring. Adverse events should be reported. Reporting forms and information can be found at [http://www.ema.europa.eu/docs/en_GB/document_library/Template_or_form/2013/03/WC500139752.doc](http://www.ema.europa.eu/docs/en_GB/document_library/Template_or_form/2013/03/WC500139752.doc)

EUHQ-P-145-0818-067124
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Date of preparation: September 2018

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