European Atherosclerosis Society
Mässans Gata 18, Box 5243, SE-402 24, Göteborg, Sweden
Tel: +46(0) 31 760 24 27
Email: office@eas-society.org
Web: eas-society.org

Press release #5 New EAS Consensus Panel Statement
EMBARGO until Monday 24 April 11 am CET.

85th Annual Congress of the European Atherosclerosis Society (EAS)
April 23-26th, Prague, Czech Republic

EAS Congress Prague:
New European Atherosclerosis Society Consensus Panel statement: Low-Density Lipoproteins (LDL) cause Cardiovascular Disease

- Published in *The European Heart Journal* today, this EAS Consensus Panel statement shows that the total evidence from genetic studies, epidemiological studies, Mendelian randomization studies, and randomized trials of LDL-lowering therapies, fulfils the criteria for the causality of LDL in atherosclerotic vascular disease (ASCVD).
- The benefit from LDL lowering therapies depends on baseline absolute cardiovascular risk, baseline LDL cholesterol, absolute reduction in LDL cholesterol and duration of exposure to treatment.
- Lowering LDL cholesterol in people at high cardiovascular risk earlier rather than later will result in greater reductions in the risk of cardiovascular events over the lifetime

Complications of atherosclerosis, such as heart attack and stroke, cause nearly half of all deaths in Europe.[1] While LDL cholesterol has long been implicated as a major modifiable cardiovascular risk factor, whether it is simply a biomarker or causal for cardiovascular disease has been the subject of debate. In line with the mission of the European Atherosclerosis Society (EAS) to prevent cardiovascular disease, the EAS Consensus Panel has today announced a new Consensus Statement, published in the *European Heart Journal**, which definitively shows that LDL causes cardiovascular disease, preferably referred to ACSVD. By implication, therefore, targeting LDL cholesterol sooner rather than later will have greater benefit in reducing the lifetime risk of heart attacks and strokes in high risk patients.

According to **Professor M. John Chapman (University of Pierre and Marie Curie, Pitié-Sâlpetrière University Hospital, Paris, France),** a Co-Chair of the EAS Consensus Panel: *'This Consensus Statement sweeps away any doubts about the causal nature of the relationship between LDL and the development of atherosclerotic plaques and cardiovascular disease. The consistency of different types of clinical evidence, including observational and genetic studies, as well as clinical trials shows that LDL is not merely a biomarker but directly causes atherosclerotic cardiovascular disease.'*

Professor Alberico L. Catapano (University of Milan and IRCCS Multimedica, Milan, Italy), a Co-Chair of the EAS Consensus Panel added: *'The evidence presented in this paper fundamentally supports all the guidance given in the EAS consensus papers and in the ESC/EAS guidelines for detection and treatment of dyslipidaemia. LDL is the target for therapy and all approaches aimed at reducing LDL including diet and lifestyle are effective at reducing CVD risk in a manner that is proportional to the extent of LDL reduction.'*

Why do we need this Statement?

Despite accumulated evidence linking LDL and ASCVD, scepticism as to whether LDL causes cardiovascular disease persists. In part this may be due to selection bias, basing conclusions on individual or a small group of studies. To overcome this bias, the EAS Consensus Panel considered the totality of evidence from separate meta-analyses of genetic studies, prospective epidemiologic studies.

European Atherosclerosis Society
Mässans Gata 18, Box 5243, SE-402 24, Göteborg, Sweden
Tel: +46(0) 31 760 24 27
Email: office@eas-society.org
Web: eas-society.org

Cholesterol: is it important and if so, how is it transported?

Cholesterol is a fatty substance that is essential for the normal functioning of the body. Cholesterol is made by virtually every cell, tissue and organ in the body (endogenous), including the brain, and is also obtained from the diet (exogenous). Apolipoprotein (apo) B-containing lipoproteins in the plasma carry cholesterol to any cells or tissues which may need it; LDL account for more than 90% of these apoB-containing lipoproteins.

LDL versus LDL cholesterol: what do they mean?

In clinical practice, it is LDL cholesterol, the cholesterol carried by LDL, rather than the whole LDL particle that is used to assess cardiovascular risk. This is usually calculated rather than measured directly. Most clinical trials have used LDL cholesterol for assessment of therapeutic benefit.

What are the key findings from the evidence reviewed?

- Cumulative LDL burden determines the initiation and progression of ASCVD.
- There is a dose-dependent, log-linear association between absolute LDL cholesterol level and cardiovascular risk.
- This association is independent of other cardiovascular risk factors and consistent across the multiple lines of evidence.
- Evidence accrued from more than 30 randomized trials involving over 200,000 individuals and 30,000 cardiovascular events evaluating treatments specifically designed to lower LDL consistently show that reducing LDL cholesterol reduces the risk of cardiovascular events. This benefit is proportional to the absolute reduction in LDL cholesterol.

Dr Brian Ference (Division of Cardiovascular Medicine, Wayne State University School of Medicine, Detroit, Michigan, USA) lead author of the paper explained the key findings: *'We considered evidence from over 200 studies in more than 2 million people followed for over 20 million person-years and over 150,000 cardiovascular events. There was a remarkably consistent dose-dependent log-linear association between absolute exposure to LDL cholesterol and the risk of cardiovascular events, increasing as exposure to LDL cholesterol increased. These data imply that if we target elevated LDL cholesterol earlier in our high risk patients, there is a greater decrease in the lifetime risk of a cardiovascular event.'*

Professor Henry N. Ginsberg, a Co-Chair of the EAS Consensus Panel (Irving Institute for Clinical and Translational Research at Columbia University Medical Center, New York, USA) added: *'This Consensus Statement, the culmination of several meetings of experts from around the world, provides incontrovertible evidence from a range of human studies and trials that LDL is causal in the development of atherosclerotic cardiovascular disease. LDL-C, as a reasonable marker of LDL particles in most instances, can be used to assess the risk of cardiovascular disease and is a target for therapies.'* –

Are results from recent trials with the PCSK9 inhibitors in line with this evidence?

Proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors reduce LDL cholesterol by more than 50% on top of statin therapy. In FOURIER (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk), treatment with evolocumab on top of statin therapy, lowered LDL cholesterol by 1.4 mmol/L (53.4 mg/dl) to a mean level of 0.78 mmol/L (30 mg/dl) and reduced the composite endpoint of death, heart attack or stroke by 20% over a median of 2.2 years of follow-up.[2] When analysed by each year of treatment, evolocumab had nearly identical effects on the risk of cardiovascular events per mmol/L reduction in LDL cholesterol as that seen with treatment with a statin, as shown by the Cholesterol Treatment Trialists' Collaboration.[3]

European Atherosclerosis Society
Mässans Gata 18, Box 5243, SE-402 24, Göteborg, Sweden
Tel: +46(0) 31 760 24 27
Email: office@eas-society.org
Web: eas-society.org

Added to this, analysis of data from both FOURIER and the SPIRE-2 (Studies of PCSK9 Inhibition and the Reduction of Vascular Events-2) trial with the prematurely-terminated drug, bococizumab, reaffirmed that treatment with PCSK9 inhibitors and statins have nearly identical effects on the risk of cardiovascular events per mmol/L reduction in LDL-C during each year of treatment.[2,4]

Thus, the results of these trials with PCSK9 inhibitors are very much in line with what would be expected with a statin, and confirm without doubt the causal effect of LDL cholesterol on ASCVD.

How will this statement impact on clinical practice?
Unique to this EAS Consensus Panel statement are Tables that indicate the potential clinical benefit derived from lowering plasma LDL cholesterol levels. This is based on the person's baseline cardiovascular risk, baseline LDL cholesterol and the duration of lipid lowering therapy. These Tables provide valuable information to aid clinicians in treatment decisions regarding LDL-lowering therapy.
Furthermore, because the effect of LDL cholesterol on cardiovascular risk is cumulative over time, lowering LDL cholesterol in people at high cardiovascular risk, such as those with inherited high cholesterol (familial hypercholesterolaemia), earlier rather than later, will undoubtedly provide greater reduction in their lifetime risk of an event.

Professor Frederick Raal (University of the Witwatersrand, Johannesburg, South Africa) an author on this paper and lead investigator of the EAS Familial Hypercholesterolaemia Studies Collaboration comments on the implications of reducing lifetime cardiovascular risk: *'As LDL cholesterol levels are elevated from birth in people with familial hypercholesterolemia, early diagnosis and early treatment is essential. It has been remarkable to witness the benefit of LDL-lowering therapy which has allowed these patients with familial hypercholesterolemia, the commonest inherited disease worldwide, to lead longer, healthier lives.'* --

*** Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic and clinical studies. A Consensus Statement from the European Atherosclerosis Society Consensus Panel**
Brian A. Ference, Henry N. Ginsberg, Ian Graham, Kausik K. Ray, Chris J. Packard, Eric Bruckert, Robert A. Hegele, Ronald M. Krauss, Frederick J. Raal, Heribert Schunkert, Gerald F. Watts, Jan Borén, Sergio Fazio, Jay D. Horton, Luis Masana, Stephen J. Nicholls, Børge G. Nordestgaard, Bart van de Sluis, Marja-Riitta Taskinen, Lale Tokgozoglu, Ulf Landmesser, Ulrich Laufs, Olov Wiklund, Jane K. Stock, M. John Chapman, Alberico L. Catapano.

European Heart Journal. doi:10.1093/eurheartj/ehx144.
Available at: https://academic.oup.com/eurheartj/article-lookup/doi/10.1093/eurheartj/ehx1

The EAS Consensus Panel Statement will be discussed on Monday 24th April by:
Dr Brian Ference in the Workshop: Genetics and cardiovascular risk factors, Karel Rokytansky Panorama Hall, 11:00-12:30

Professor John Chapman in the Late Breaking Session, PCSK9 inhibition: the Clinical Benefit, Anitschkow Hall, 13:00-14:30

European Atherosclerosis Society
Mässans Gata 18, Box 5243, SE-402 24, Göteborg, Sweden
Tel: +46(0) 31 760 24 27
Email: office@eas-society.org
Web: eas-society.org

Contact:

EAS Press Officer
Branislav Vohnout, M.D., PhD.
+421 949 824 715
Email:bvohnout@yahoo.com

EAS Administration Executive
Dr. Carmel Hayes
+46768 61 00 51
Email: office@eas-society.org

References

1. European Cardiovascular Disease Statistics 2017 edition. Available at http://www.ehnheart.org/component/downloads/downloads/2452

2. 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 and Investigators. Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease. N Engl J Med 2017; doi: 10.1056/NEJMoa1615664.

3. Collins R, Reith C, Emberson J, Armitage J, Baigent C, Blackwell L, Blumenthal R, Danesh J, Smith GD5, DeMets D, Evans S, Law M, MacMahon S, Martin S, Neal B, Poulter N, Preiss D, Ridker P, Roberts I, Rodgers A, Sandercock P, Schulz K, Sever P, Simes J, Smeeth L, Wald N, Yusuf S, Peto R. Interpretation of the evidence for the efficacy and safety of statin therapy. Lancet 2016 doi: 10.1016/S0140-6736(16)31357-5

4. Ridker PM, Revkin J, Amarenco P, Brunell R, Curto M, Civeira F, Flather M, Glynn R, Gregoire J, Jukema JW, Karpov Y, Kastelein JJ, Koenig W, Lorenzatti , Manga P, Masiukiewicz U, Miller M, Mosterd A, Murin J, Nicolau JC, Nissen S, Ponikowski P, Santos RD, Schwartz PF, Soran H, White H, Wright RS, Vrablik M, Yunis C, Shear CL, Tardif JC; SPIRE Cardiovascular Outcome Investigators. Cardiovascular Efficacy and Safety of Bococizumab in High-Risk Patients. N Engl J Med 2017; doi: 10.1056/NEJMoa1701488

Notes for editors:

Cardiovascular Disease Statistics

- Each year cardiovascular disease (CVD) causes 3.9 million deaths (45% of all deaths) in Europe and over 1.8 million deaths (37% of all deaths) in the European Union (EU).
- In 2015, there were just under 11.3 million new cases of CVD in Europe and 6.1 million new cases of CVD in the EU. More than 85 million people in Europe were living with CVD.
- CVD is responsible for the loss of more than 64 million DALYs in Europe (23% of all DALYs lost) and 26 million DALYs in the EU (19%).
- Overall CVD is estimated to cost the EU economy €210 billion a year.

For further information from 2017 European Cardiovascular Disease statistics:
http://www.ehnheart.org/component/downloads/downloads/2452

European Atherosclerosis Society
Mässans Gata 18, Box 5243, SE-402 24, Göteborg, Sweden
Tel: +46(0) 31 760 24 27
Email: office@eas-society.org
Web: eas-society.org

About the EAS Consensus Panel

The EAS Consensus Panel, comprised of internationally renowned experts in atherosclerosis and cardiovascular disease, was convened in November 2009 to consider the evidence for non-LDL lipids as risk factors for cardiovascular disease. The Panel is co-chaired by Professor John Chapman, France, and Professor Henry N. Ginsberg, USA. EAS Past President Professor Alberico L. Catapano is also a Chair on the latest Panel initiative.

For more information on the publications of the EAS Consensus Panel, refer to

https://www.eas-society.org/?page=consensus_papers