Research Review™
STUDY REVIEW

High-resolution assessment of coronary plaques in a global evolocumab randomised study (HUYGENS)

Making Education Easy 2021

Independent expert commentary provided by Associate Professor John Amerena.

Associate Professor Amerena FRACP, FACC, FCSANZ, trained in Melbourne before spending four years in the United States at the University of Michigan. Over that period of time, he worked in the fields of hypertension and hyperlipidaemia, before returning to Australia where he is now a Cardiologist at Barwon Health. He currently has a joint appointment in the Department of Clinical and Biomedical Sciences at the University of Melbourne and the Department of Epidemiology and Preventive Medicine at Monash University. He is the director of the Geelong Cardiology Research Unit, which is currently involved in many phase II-III clinical trials.

While still actively researching in hypertension, his focus has changed to research in antithrombotic/antiplatelet therapies, particularly in the context of acute coronary syndromes and atrial fibrillation. Heart failure is also a major interest, and he is also the Director of the Heart Failure Programme at Barwon Health. He is well published in these areas, as well as in many other areas of cardiovascular medicine.

Abbreviations used in this review:

ACS = acute coronary syndrome; **ANCOVA =** analysis of covariance; **CAD =** coronary artery disease; **FCT =** fibrous cap thickness; **IVUS =** intravascular ultrasound; **LDL-C =** low-density lipoprotein cholesterol; **NSTE-ACS =** non-ST-elevation acute coronary syndrome; **NSTEMI =** non-ST-elevation myocardial infarction; **OCT =** optical coherence tomography; **PAV =** percent atheroma volume; **PCSK9 =** proprotein convertase subtilisin kexin type 9; **TAV =** total atheroma volume.

This publication presents data from the HUYGENS study, a phase 3, randomised, double-blind, placebo-controlled, global clinical trial which evaluated the impact of evolocumab on fibrous cap thickness (FCT) in patients with non-ST-elevation acute coronary syndrome (NSTE-ACS) who were taking maximally tolerated statin therapy.[1] The outcomes from the study were presented during an oral presentation on 27th August at the virtual European Society of Cardiology Congress, 2021.[2]

Study background

Lowering levels of low-density lipoprotein cholesterol (LDL-C) reduces the risk of negative cardiovascular outcomes in both the primary and secondary prevention setting.[3] As a consequence, treatment guidelines increasingly emphasize the use of intensive statin therapy as preventative treatment for patients at higher risk of cardiovascular disease.[4-6]

Acute coronary syndrome (ACS) events are often the result of vulnerable atherosclerotic plaque ruptures.[7] Vulnerable plaques are commonly composed of a large lipid core with a thin fibrous cap that serves as a wall or barrier around the plaque to keep it intact.[8] Technological advances in arterial wall imaging have enabled the effects of lipid-lowering interventions on atherosclerotic plaque *in vivo* to be determined. Imaging modalities that have been used to demonstrate the impact of statins on atherosclerotic plaque include intravascular ultrasound (IVUS)[9-11] and optical coherence tomography (OCT).[12-15]

OCT is a catheter-based imaging technique, which uses coherent near infrared light to generate images with micrometer spatial resolution from optical backscatter, and it allows detailed imaging of the intimal aspects of the coronary artery wall.[12] OCT enables the visualisation of the fibrous cap and underlying lipid pools with high resolution, permitting their measurement *in vivo*.[16, 17] Serial OCT imaging has been used in clinical studies to demonstrate that statin therapy has a favorable effect on plaque, and results in an increase in fibrous cap thickness (FCT) and a reduction in the size of the lipid pool.[13-15]

The proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitor evolocumab has been associated with incremental low-density lipoprotein cholesterol lowering in statin-treated patients.[18-20] In addition, the Global Assessment of Plaque Regression with a PCSK9 Antibody as Measured by Intravascular Ultrasound (GLAGOV) study investigated the effect of evolocumab on plaque progression in 968 statin-treated patients with angiographic coronary artery disease (CAD).[20] In this multicentre, double-blind, placebo-controlled, clinical trial, patients were randomised to receive evolocumab 420 mg once every month (n=484) or placebo once every month (n=484) via subcutaneous injection for 76 weeks, in addition to statins.[20] During 76 weeks of treatment, evolocumab, compared with placebo, resulted in lower mean time-weighted LDL-C levels (93.0 vs 36.6 mg/dL [2.41 vs 0.95 mmol/L]; p<0.001).[20] The primary efficacy parameter, percent atheroma volume (PAV), as measured by IVUS imaging increased 0.05% with placebo, but decreased 0.95% with evolocumab (p<0.001) from baseline to week 78.[20] The secondary efficacy measure, total atheroma volume (TAV), did not significantly change in patients in the placebo group at week 78 (-0.9 mm^3, p=0.45 vs baseline), but decreased by 5.8 mm^3 in patients treated with evolocumab (p<0.001 vs baseline).[20] More patients treated with evolocumab than patients treated with placebo exhibited plaque regression as indicated by PAV (64.3% vs 47.3%, p<0.001) and TAV (61.5% vs 48.9%; p<0.001).[20]

The GLAGOV study focused on the role of PCSK9 inhibition on atheroma volume,[20] however, it did not characterise the effects of PCSK9 inhibitor on atheroma morphology. To further characterise the effects of PCSK9 inhibition on atherosclerotic plaque, the HUYGENS study (ClinicalTrials.gov: NCT03570697) was undertaken.[1] The HUYGENS sought to identify if morphologic changes, such as an increase in FCT, in atherosclerotic plaques were associated with treatment with evolocumab and maximally tolerated statin therapy in patients presenting with ACS.[1]

Study methods

Design

This phase 3, multicentre, randomised, double-blind, placebo-controlled trial conducted at 27 centres assigned patients in a 1:1 ratio to evolocumab 420 mg or matching placeb administered by subcutaneous injection once every month for 48 weeks (**Figure 1**).[1, 2]

High-resolution assessment of coronary plaques in a global evolocumab randomised study (HUYGENS)

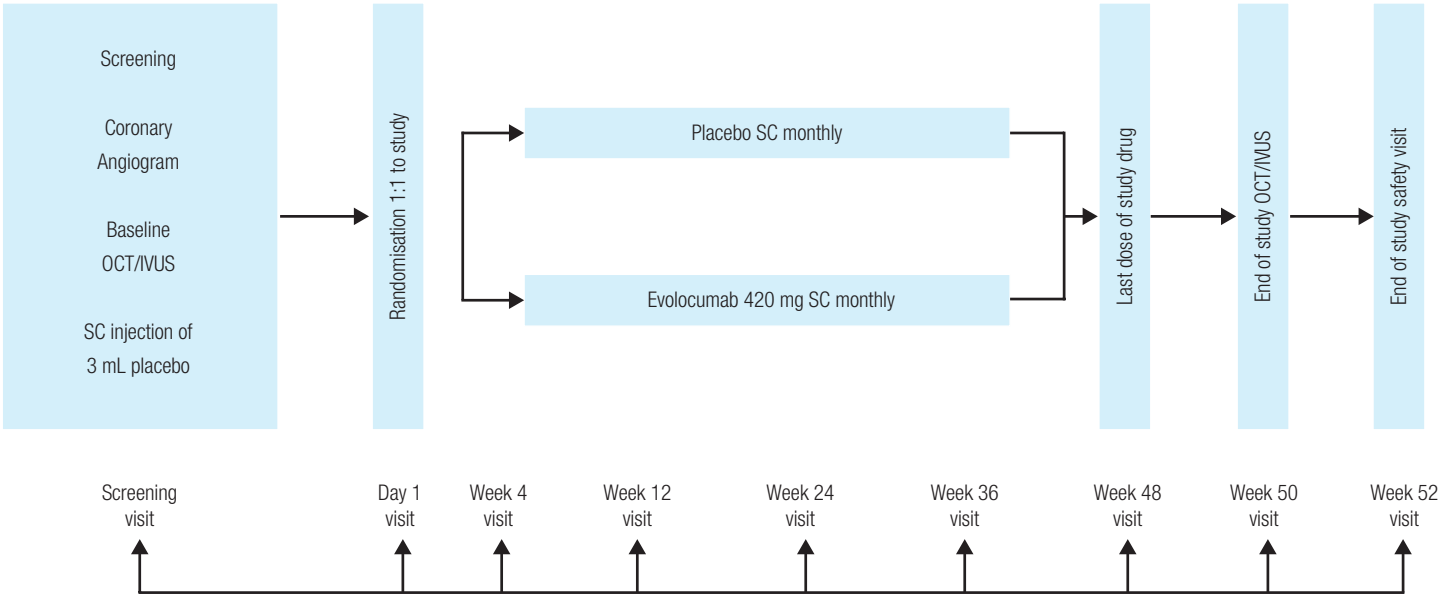

Figure 1. Study design of the HUYGENS trial[1,2]

NSTEMI = non-ST-elevation myocardial infarction; **CAD =** coronary artery disease; **LDL-C =** low-density lipoprotein cholesterol; **FCT =** fibrous cap thickness; **IVUS =** intravascular ultrasound; **OCT =** optical coherence tomography; **SC =** subcutaneous. Adapted from: Nicholls et al. Cardiovasc Diagn Ther. 2021;11(1):120-9.

Patients

Eligible patients had non-ST-elevation myocardial infarction (NSTEMI), angiographic CAD, a qualifying LDL-C level at the time of screening (see **Table 1**), were on maximally tolerated statin therapy, and had an arterial target segment on OCT containing at least one image with a FCT <120 µm and one image with lipid arc >90°. Further details of key inclusion and exclusion criteria for the HUYGENS trial are shown in **Table 1**.[1,2]

Table 1. Key inclusion and exclusion criteria for the HUYGENS trial[1]

Inclusion criteria	Exclusion criteria
➤ Tolerate the placebo run-in injection at the time of screening ➤ Aged ≥18 years at screening ➤ Able to provide written, informed consent ➤ Undergoing clinically indicated coronary angiography during admission due to NSTE-ACS with interventional treatment of culprit plaque ➤ Have a qualifying LDL-C level at the time of screening depending on their use of either: ➢ no statin (LDL-C ≥130 mg/dL [3.36 mmol/L]), ➢ low- or moderate-intensity statin (LDL-C ≥80 mg/dL [2.07 mmol/L]) or ➢ high-intensity statin (LDL-C ≥60 mg/dL [1.55 mmol/L]) ➤ On maximally tolerated statin therapy in accordance with standard of care per local guidelines prior to randomisation ➤ Evidence of: ➢ an angiographic stenosis of ≥20% in addition to the culprit plaque ➢ no left main coronary artery stenosis >50% ➢ a target vessel for imaging which cannot be deemed to be the culprit artery for the index or prior MI, has not undergone or intended to undergo revascularization, and must be accessible by an OCT imaging catheter ➢ an arterial segment containing no stenosis >50%, be at least 40 mm in length, and containing at least one image with a FCT ≤120 µm and one image with a lipid arc >90°	➤ Presence of an ST-elevation MI ➤ Triglyceride levels ≥400 mg/dL (4.52 mmol/L) ➤ Moderate to severe renal dysfunction (eGFR <30 mL/min/1.73m^2) ➤ Malignancy ➤ Statin intolerance ➤ Prior or current use of PCSK9 inhibitors ➤ Women who are pregnant or breastfeeding or intend to become pregnant ➤ Any other condition deemed by the treating physician to impair the ability of the patient to comply with all study-related procedures

eGFR = estimated glomerular filtration rate; **FCT =** fibrous cap thickness; **LDL-C =** low-density lipoprotein-cholesterol; **NSTE-ACS =** non-ST-segment elevation acute coronary syndrome; **MI =** myocardial infarction ; **PCSK9 =** proprotein convertase subtilisin kexin type 9.

Study endpoints

The primary endpoint was the absolute change in minimum FCT in a matched segment of artery as determined by OCT from baseline to week 50.[1]

Secondary efficacy endpoints included the:[1]

- Percent change in minimum FCT,
- Absolute change in the average of the minimum FCT for all images assessed, and
- Absolute change in the maximum lipid arc.

Image acquisition and analysis

Intravascular imaging with OCT and IVUS was performed within the target artery selected for investigation at both baseline and end of study.[1] OCT imaging was acquired by placement of an OCT imaging catheter as distally as possible and withdrawn to the aorta by automatic pullback at a speed of 36 mm/second.[1] For the OCT imaging, cross-sectional images, spaced 0.2 mm apart were selected for analysis. The IVUS imaging was acquired in a similar fashion, using an IVUS imaging catheter at an automatic pullback speed of 0.5 mm/second.[1] For IVUS imaging, cross-sectional images, spaced 0.5 mm apart, were selected for analysis.

Statistical analysis

Primary and secondary endpoints were analysed by analysis of covariance (ANCOVA).[1] Missing values were imputed using the multiple imputation for the primary and secondary endpoints.[1] The non-parametric Quade test was used for the sensitivity analysis on the primary endpoint.[1]

Study results

A total of 161 eligible patients at 27 global centres underwent OCT via motorised pullback at 0.2 mm/sec through >40 mm segment.[2]

A total of 70 placebo recipients and 65 patients treated with evolocumab competed the study.[2]

Patient Characteristics

Key baseline characteristics are shown in **Table 2**.[2]

Table 2. Key demographic and clinical characteristics at baseline[2]

Baseline characteristics	Placebo (n=81)	Evolocumab (n=80)
Mean age, years	60.2	60.0
Male, % pts	67.9	75.0
BMI, kg/m^2	28.0	28.2
Diabetes, % pts	17.3	16.3
Smokers, % pts	59.3	58.3
Prior statin use >4 weeks, % pts	24.4	23.2
Mean LDL cholesterol, mg/dL (mmol/L)	142.1 (3.67)	140.4 (3.63)
Statin use during trial, % pts	96.3	93.8
Statin use intensity, % pts		
High	82.7	78.8
Moderate	13.6	13.8
Low	0	1.3
Optical coherence tomography measures		
Minimum FCT, µm	54.6	56.6
Average minimum FCT, µm	133.6	142.3
Maximum lipid arch,°	224.8	230.2
FCT <65 µm, % pts	71.6	77.5
Lipid-rich plaque*, % pts	91	90

BMI = body mass index; **FCT =** fibrous cap thickness; **LDL =** low-density lipoprotein; **pts =** patients.
*Lipid-rich plaque was defined as three consecutive images containing FCT ≤120 µm and lipid arc >90°.

Efficacy

Primary endpoint: In patients with ACS on optimised statin therapy, evolocumab increased the FCT (measured by OCT) by 42.7 µm (75% increase) compared with an increase of 21.5 µm (39% increase) with placebo (p=0.01).[2]

Secondary endpoints: Evolocumab, compared with placebo, also improved secondary endpoints.[2]

- The percentage change in the minimum FCT was 44.3% with placebo and 81.8% with evolocumab (p=0.04).[2]
- The mean change from baseline in the minimum FCT in placebo recipients was +29.8 µm and +62.3 µm in patients treated with evolocumab (p=0.02).[2]
- The maximum lipid arc decreased by -31.4° in placebo recipients compared with -57.5° in patients treated with evolocumab (p=0.04).[2]

The percentage of patients with an on-treatment minimum FCT <65 µm (an exploratory endpoint) was also significantly fewer with evolocumab than with placebo (12.5% vs 30.2%, p=0.02).[2]

The degree of benefit of evolocumab on the FCT was directly proportional to the intensity of lipid lowering observed.[2]

Safety

Safety and adverse clinical events reported in the study are shown in **Table 3**.[2]

Table 3. Summary of adverse events and safety outcomes[2]

Patients, %	Placebo (n=81)	Evolocumab (n=80)
Deaths	1.2	0
Nonfatal myocardial infarction	3.7	0
Injection site reactions	1.2	0
Myalgia	7.4	6.3
Discontinuation from treatment	12.2	4.9

Expert comment

The outcomes of the HUYGENS study are of great interest. We know that plaque rupture and subsequent ACS are related to plaque instability, which is influenced by both plaque volume and the thickness of the fibrous cap. Previous studies using IVUS have shown that aggressive lipid lowering with statins and PCSK9 inhibitors have been able to show significant reductions in plaque volume, but this technique is unable to examine plaque morphology and the thickness of the protective fibrous cap. The HUYGENS study using OCT showed that lipid lowering with evolocumab in patients with recent ACS undergoing PCI, decreased plaque volume, and increased fibrous cap thickening compared with placebo over 48 weeks in patients with optimal maximally tolerated background therapy, thus potentially increasing the stability of plaques making them less likely to rupture again and cause recurrent ACS. Although not powered for cardiovascular outcomes, the trends were all in the right direction, and the treatment was well tolerated. This change in plaque morphology with aggressive lipid lowering is an important finding as it provides mechanistic support for the "lower is better" approach to managing patients with established ASCVD, and the results of the large outcome studies with lipid-lowering agents.

Study interpretation

The HUGYENS study indicated that evolocumab improved features of plaque stability (increased the minimum FCT and decreased the maximum lipid arc) in patients with ACS treated with maximally tolerated statin therapy.[2] At 12 months after a NSTEMI, 12.5% of patients treated with evolocumab compared with 30.2% of those who received placebo demonstrated evidence of any region with a minimum FCT <65 µm, a feature associated with a high risk of plaque rupture.

The benefits of lipid lowering on plaque burden have been previously demonstrated.[13-15, 20] For example, in the GLAGOV study, treatment with evolocumab in addition to statin therapy resulted in the lowering of lipid levels, as well a reduction in plaque atheroma volume.[20]

Outcomes from the HUGYENS study[2] and GLAGOV study[20] may provide a mechanistic explanation for the reduction in cardiovascular events observed in patients treated with evolocumab and background statin therapy enrolled in the FOURIER study.[21]

The outcomes from the HUGYENS study suggest that evolocumab can favourably modulate plaque phenotype and these changes are likely to contribute to early reductions in cardiovascular risk.[2] The findings from the HUGYENS should further motivate the use of intensive lipid lowering regimens in patients following an ACS.[2]

Take-home messages

- The HUGYENS study indicated that in patients with a NSTEMI receiving maximally tolerated statin therapy, the addition of evolocumab, compared with placebo, for 12 months resulted in greater increases in the minimum FCT and decreases in the maximum lipid arc.
- Significantly fewer patients treated with evolocumab, than placebo, demonstrated evidence of any region with a minimum FCT <65 µm, a feature associated with a high risk of plaque rupture.

Expert's concluding remarks

The FOURIER outcome study enrolled patients with high risk ASCVD, some of whom had a previous ACS,[21] while the ODYSSEY study examined patients up to 12 months after ACS.[23, 24] The studies showed that intensive lipid lowering with evolocumab[21] or alirocumab,[23, 24] respectively, improved outcomes compared with usual therapy. The HUYGENS study started evolocumab in patients soon after ACS and demonstrated significant changes in plaque morphology suggesting that the positive results in the larger outcome trials were probably mediated by the PSCK9 inhibitors producing marked LDL reduction, resulting in plaque passivation and stability by reducing plaque volume and promoting thickening of the protective fibrous cap over the residual plaque.[2] Taken in totality, these studies demonstrate intensive LDL-C reduction with PSCK9 inhibitors in patients after ACS and high risk ASCVD will significantly reduce recurrent CV events, and the HUYGENS study[2] provides mechanistic support for these results. This has been recognised by the PBS as the criteria for reimbursement of PCSK9 inhibitors in patients with non-familial hypercholesterolaemia have been liberalised, so that patients with multivessel CAD, recurrent events, or other high-risk features are now eligible for this therapy.

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