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Stabilization of vulnerable plaque in the ACS patient: evidence from HUYGENS studies

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The introduction of PCSK9 inhibitors in addition to statin therapy allowed better control of LDL-C plasma levels with a subsequent reduction of cardiovascular events. Human atherosclerosis has been previously considered an irreversible condition; studies firstly based on angiography imaging and secondly with intra-coronary imaging—mainly IVUS based—have demonstrated that lipid-lowering therapy based on statins can stabilize and even reduce atherosclerotic burden of coronary circulation. While plaque stabilization and/or reduction with PCSK9 inhibitors have already been demonstrated in the GLAGOV study, the HUYGENS study showed a positive effect not only on atherosclerotic burden but also on plaque phenotype, with an increased FCT, decrease in maximum lipid arch, and reduction of macrophages infiltration. Further studies need to assess the clinical impact of the reduction of plaques displaying high-risk features with PCSK9 inhibitors.

Introduction

Lipid-lowering therapy plays a pivotal role in reducing the rate of cardiovascular events, both in primary, and secondary prevention. Statin therapy is often the cornerstone of multiple lipid-lowering therapy strategies across the world. The introduction of more potent lipid-lowering therapies such as PCSK9 inhibitors allowed to obtain a greater reduction of LDL-C and have proven to reduce cardiovascular events in addition to statin therapy in patients who had suffered ACS.[1,2] The phenomenon of plaque stabilization and regression has been investigated for more than 3 decades. While statin therapy has proven to stabilize and even reduce the burden of coronary atherosclerosis, the role of the PCSK9 inhibitors in plaque stabilization and regression has been recently investigated by the HUYGENS study.

Early evidence on plaque stabilization and reduction

Human atherosclerosis has been considered an irreversible condition for decades. In the late '80 scientific research tried to break this paradigm and earlier studies have demonstrated the role of statin therapy in the stabilization and reduction of plaque progression with quantitative methods via coronary angiography. In 1993 Blankenhorn et al. in the Monitored Atherosclerosis Regression Study (MARS)[3] enrolled 270 patients between 1985 and 1989 with coronary artery disease defied by the finding of at least two segments involved and at least one segment with a >50% stenosis at coronary angiogram. The patients were then randomized to receive lovastatin 80 mg/d or placebo. A follow-up angiogram was taken 2 years after randomization; a quantitative analysis of stenosis grade was made by a single technician blinded to treatment but not to the temporal order of the angiograms. No statistical difference was recorded when comparing lesions with stenosis less than 50%; conversely, a significant reduction of the grade of the stenosis was associated with lovastatin therapy when confronted with placebo for lesions with stenosis greater than 50% ($-4.1 \pm 11.0\%$ vs. $+0.9 \pm 11.0\%$, $P = 0.005$) at a mean follow-up of 2.2 years.

Plaque vulnerability in light and development of intra-coronary imaging

The later development of intra-coronary imaging techniques allowed a better assessment of atheromatous burden

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and characterization of plaque vulnerability. The prognostic role of plaque high-risk features at IVUS imaging has been assessed in the PROSPECT[4] and PROSPECT II[5] trials and has been associated with increased risk of non-culprit lesion-associated MACE in patients admitted for ACS. These trials did not assess the best treatment for lesions with high-risk features, either with interventional or pharmacological therapy.

The role of statin treatment in reducing high-risk features at IVUS imaging has been assessed in three clinical trials: REVERSAL, ASTEROID, and SATURN trials.

Nissen et al. in the Reversal of Atherosclerosis with Aggressive Lipid Lowering Study (REVERSAL)[6] confronted plaque burden with IVUS in 502 patients with established CAD diagnosed through angiography. The patients were then randomly assigned to receive a moderate vs. intensive statin treatment (pravastatin 40 mg/d, and atorvastatin 80 mg/d respectively). A second angiography with IVUS was taken after 18 months. The percent of atheroma volume (PAV) was defined by the formula: $[\Sigma(EEM_{CSA}-LUMEN_{CSA})/\Sigma EEM_{CSA}]\times 100$. The normalized total atheroma volume (TAV) was defined by the formula: $[\Sigma(EEM_{area}-LUMEN_{area})/\text{no. of images in pullback}]\times$ median no. of images for all patients in the study. The Atorvastatin regimen was associated with greater cholesterol and LDL-C reduction (total cholesterol −34.1% vs. −18.4%, $P=<0.001$; LDL-C −46.3% vs. −25.2% $P=<0.001$) and a decrease in CRP serum levels (−36.4% vs. −5.2%, $P=<0.001$). The Atorvastatin group showed a lower progression of coronary disease, with a significant decrease in both PAV ($0.6\pm5.1\%$ vs. $1.9\pm4.9\%$, $P=0.04$) and TAV (-0.2 ± 31.0 mm^3 vs. 5.1 ± 27.6 mm^3, $P=0.03$).

Nissen et al. evaluated the role of Rosuvastatin in a subsequent prospective study: the study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden (ASTEROID).[7] All patients (N = 507) received high-intensity therapy with rosuvastatin 40 mg/d. Motorized IVUS assessment with PAV calculation was performed at the baseline and after 24 months. Rosuvastatin showed a mean reduction of LDL-C of 53.2 (95% CI: 55.6%-50.9%) and a mean change of PAV (-0.98 ± 3.15 mm^3) with 63.6% of patients showing regression of plaque volume.

Nicholls et al. in the Study of Coronary Atheroma by Intravascular Ultrasound: Effect of Rosuvastatin versus Atorvastatin (SATURN)[8] directly confronted the two high-intensity statins, atorvastatin and rosuvastatin, at maximal dose. In this prospective, randomized, multicenter, double-blind clinical trial, 1039 patients with coronary artery disease underwent serial imaging with IVUS and PAV and TAV assessment. After the baseline imaging, patients were randomized to receive either atorvastatin 80 mg/d or rosuvastatin 40 mg/d for 104 weeks. Rosuvastatin was associated with lower LDL-C plasma levels when confronted with atorvastatin (62.6 ± 1.0 mg/dL vs. 70.2 ± 1.0 mg/dL, $P=<0.001$) and higher levels of HDL-C (50.4 ± 0.5 mg/dL vs. 48.6 ± 0.5 mg/dL, $P=0.01$). A non-significant difference between the two drugs was found regarding the primary efficacy endpoint, the PAV decrease, atorvastatin by −0.99 (95% CI −1.19 to −0.63%) vs. rosuvastatin by −1.22 (95% CI, −1.52 to −0.90%), $P=0.17$. Conversely, normalized TAV decrease was modest but significantly higher in the rosuvastatin group: −6.39 (95% CI, −7.52 to −5.12 mm^3) vs. −4.42 (95% CI −5.98 to −3.26 mm^3), $P=0.01$. Disease regression was observed in approximately 2/3 of the study population.

The role of PCSK9 inhibitors in plaque stabilization and reduction

Nicholls et al. in the Global Assessment of Plaque Regression With a PCSK9 Antibody as Measured by Intravascular Ultrasound trial (GLAGOV)[9] investigated the role of evolocumab in plaque stabilization or reduction. 970 patients with angiographic coronary artery disease were randomized to receive either evolocumab 420 mg/d or placebo and on to statin therapy for 76 weeks. IVUS and IVUS-VH imaging were obtained at baseline and after 78 weeks. The study demonstrated greater LDL-C reduction for evolocumab −56.3 (95% CI: −59.4 to −53.1 mg/dL) vs. 0.2 (95% CI: 2.9 to 3.4 mg/dL), $P=<0.001$); evolocumab performed better in IVUS analysis with significative PAV reduction from baseline (−0.95 (95% CI: −1.33 to −0.58%) vs. 0.05 (95% CI: −0.32% to 0.42%), $P=<0.001$) with 64.3% patient showing regression of PAV. In patients that had undergone VH-IVUS analysis of the virtual histology of the plaques, non-statistical differences were observed between the study groups in plaque composition (changes in calcium, fibrous, fibrofatty, and necrotic volumes).

The road to HUYGENS study

The lack of statistical difference in plaque composition, therefore in the reduction of plaque vulnerability, in the GLAGOV study may be a consequence of the low spatial resolution of IVUS-VH imaging (150 μm); the question considering if an imaging technique with a better spatial resolution (as OCT−15 μm) could identify modifications in plaque composition with PCSK9 inhibitors therapy was left unanswered.

In 2014, Komukai et al. in the EASY-FIT study[10] had already proven that atorvastatin 20 mg/d provided a higher increase in fibrous cap thickness in coronary plaque when compared with its lower dose of atorvastatin 5 mg/d in Asian population with unstable angina, with nominal change at a 12 months follow-up of 73 (95% CI: 28 to 113 μm) vs. 19 (95% CI: −1 to 48 μm), respectively ($P=<0.001$).

Prati et al in the CLIMA study[11] identified OCT high-risk plaque features as predictors of a primary endpoint was a composite of cardiac death and target segment myocardial infarction at a 12-month follow-up; these features include an MLA <3.5 mm^2 (HR: 2.1, 95% CI: 1.1-4.0), an FCT <75 μm (HR: 4.7, 95% CI: 2.4-9.0), a lipid arc circumferential extension >180° (HR: 2.4, 95% CI: 1.2-4.8), and OCT-defined macrophages (HR: 2.7, 95% CI: 1.2-6.1). Even more, the presence of all four risk features in the same plaque was statistically significantly more frequent in patients who experienced the primary endpoint (18.9% vs. 3.0%, HR: 7.54, 95% CI: 3.1%-18.6%; $P=<0.001$). Considering the prognostic role of these high-risk features, the aim of the High-Resolution Assessment of Coronary Plaques in a Global Evolocumab Randomized Study (HUYGENS) was to assess the impact of evolocumab therapy on plaque composition by using *in vivo* serial imaging with OCT.

The HUYGENS study—Study design

The HUYGENS study[12,13] was designed as a multicenter double-blind RCT. It included patients admitted for ACS (NSTEMI) who had undergone PCI of the culprit lesion

and had at least one angiographic lesion in addition to the culprit plaque. The arterial segment should not contain stenosis >50% and be at least 40 mm long; OCT inclusion criteria were at least one image of fibrous cap thickness (FCT) ≤ 120 μm and lipid arc >90°. The patients were randomized to receive evolocumab 420 mg or placebo via subcutaneous injection for 48 weeks. IVUS and OCT imaging was obtained at the baseline angiography and after 50 weeks; for each OCT image were performed measurements of minimum FCT and lipid arch and graded for the presence of macrophage and calcium accumulation. The primary endpoint was to evaluate changes in FCT; the secondary endpoints include the percent change in minimum FCT, the absolute change in the average of the minimum FCT for all images, and the absolute change in the maximum lipid arc.

The HUYGENS study—Results

The study enrolled 161 patients who underwent randomization. Most of the population (80.7%) was receiving a high-intensity statin. The baseline mean LDL-C level was 141.3 ± 33.1 mg/L. As expected, evolocumab therapy was associated with significantly greater LDL-C reduction (absolute change: −114.2 ± 41.7 mg/dL vs. −55.3 ± 47.1 mg/dL, $P = <0.001$). Evolocumab was associated with a greater proportion of patients that reached the treatment threshold of LDL-C: for LDL-C < 70 mg/dL, 93.9% vs. 29.2% ($P < 0.001$); for LDL-C 55 mg/dL 86.4% vs. 20.0% ($P < 0.001$). Regarding the primary endpoint, evolocumab was associated with a significant increase of minimum, fibrous cap thickness +39.0 (95% CI: 20.5–71.0 μm) vs. +22.0 (95% CI: 8.0–36.0 μm), $P = 0.015$. In a non-prespecified analysis, evolocumab maintained its benefits even in FCT <65 μm (decrease from 77.5% to 12.5% vs. 71.6% to 30.2%, $P = 0.001$). A locally weighted polynomial regression showed a linear relationship between an LDL-C reduction and an increase in FCT. All secondary endpoints reached statistical significance; the maximum lipid arc decreased by −31.4° in the placebo group vs. −57.5° in the evolocumab group ($P = 0.04$). The length of the vessel with images containing macrophages was significantly reduced by the evolocumab regimen (−3.17 (95% CI: −4.39 to −1.94 mm) vs. −1.45 (95% CI: −2.66 to −0.24 mm), $P = 0.04$). The analysis of IVUS imaging confirmed the data from the previous GLAGOV study, with a significant reduction of PAV (−2.29 ± 0.47% vs. −0.61 ± 0.46%, $P = 0.009$) and TAV (−19.0 ± 3.7 mm^3 vs. −8.9 ± 3.5 mm^3, $P = 0.04$).

The HUYGENS study—Conclusions

The results of the HUYGENS study promote the early addition of evolocumab on top of high-intensity statin in patients with NSTEMI. A combined lipid-lowering strategy is associated with a reduction of plaque risk features at OCT analysis and a greater reduction of atherosclerotic burden (PAV and TAV) at IVUS analysis.

The HUYGENS study—Study limitations and future perspectives

The study was performed in post-ACS settings; yet further studies need to determine if, in the setting of CCS, evolocumab therapy would have similar effects. The study evaluated only vessels with stenosis <50%; therefore, the impact of evolocumab needs to be evaluated in more stenotic vessels. Although the increased cardiovascular risk (cardiac death and MI) of high-risk plaque features has been reported in the CLIMA trial, the clinical benefit of the evolocumab regimen by reducing these high-risk features needs to be proven.

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Data availability

No new data were generated or analysed in support of this research.

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