Why do we fail to achieve Glagovian atheroregression in lipid-lowering trials?

Keywords: atheroregression • bioresorbable scaffolds • coronary computed tomography angiography • Glagov phenomenon • intravascular ultrasound • lipid-lowering drugs • nanomedicine • optical coherence tomography • plaque burden • total atheroma volume

Reduction of total atheroma volume provides cardiology with a hope to reverse atherosclerosis in hands of the modern-day lipid-lowering medications

Prevention of atherosclerosis and treatment of its complications remain a clinical challenge [1]. Some recent clinical trials demonstrated [1–10] moderate atheroprotective effect of the different lipid-lowering medications. There are some achievements as well as methodological flaws, which require our attention in order to optimize the research tools for imaging and treatment in interventional cardiology with the final goal to reverse Glagov atherogenesis. HMGCoA (3-hydroxy-3-methyl-glutaril-CoA reductase, or HMGCR) reductase inhibitors have an outstanding track record of lowering cholesterol and improving outcomes. Clinical trials such as MIRACL (The Myocardial Ischemia Reduction with Acute Cholesterol Lowering Trial, 2001) [1], REVERSAL (The Reversal of Atherosclerosis with Lipitor, 2004) [1], PROVE IT (The Pravastatin or Atorvastatin Evaluation and Infection Therapy, 2004) [2,3], ESTABLISH (Early Statin Treatment in Patients with Acute Coronary Syndrome, 2004) [4], ASTEROID (A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden, 2006) [5], JAPAN-ACS (Japan Assessment of Pitavastatin and Atorvastatin in Acute Coronary Syndrome, 2007) [7], JUPITER (The Justification for the Use of Statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin, 2008) [6–9], SATURN (the Study of Coronary Atheroma by Intravascular Ultrasound: Effect of Rosuvastatin versus Atorvastatin, 2011) [10], and IBIS-4 (Integrated Biomarkers and Imaging Study-4) [11] have demonstrated (Table 1) that lowering LDL levels through intensive statin therapy can slow progression, or even partially reduce the total atheroma volume (TAV; up to 13.14 mm³) in coronary arteries with minimal difference in outcomes between hydrophilic and lipophilic statins. However, in these trials statin therapy was associated with only a 30% relative reduction in major cardiovascular events [1–10]. By the way of comparison, in a pilot trial recombinant ApoA-I Milano demonstrated a 14.1 mm³ reduction in total atheroma volume with unproven effect on clinical outcomes [12]. Necrotic core and calcification may limit the maximal benefit that risk factor modification and systemic drug therapy may achieve [1–10,12–21]. The most recent ZEUS (eZEtimibe Ultrasound Study, 2014) trial [14] with ezetimibe revealed a 8.2 mm³ atheroregression promising new era in the lipid-lowering management of the vulnerable patients. Some methodological flaws such as absence of the unified guidelines for imaging of coronaries, wrong interpretation of the vessel contours and adventitia, incorrect validation of plaque burden, and dramatically low percent atheroma volume at the baseline (at least below a 40% Glagovian threshold of the plaque burden) significantly impair results of the lipid-lowering trials and underestimate clinical potential of these medications.
Table 1. Glagov atheroregression in the trials with the drug treatment and implantation of coronary devices.

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<td></td>
<td>Mean plaque volume (TAV)</td>
<td>Mean absolute change in plaque volume (TAV)*</td>
</tr>
<tr>
<td>REVERSAL, 2004 [1]</td>
<td>RCT double-blind</td>
<td>Atorvastatin 80 mg (vs pravastatin 40 mg)</td>
<td>253 (vs 249)</td>
<td>18 months</td>
<td>184.4 mm³</td>
<td>-0.9 mm³ (median)</td>
</tr>
<tr>
<td>CAMELOT, 2004 [2]</td>
<td>RCT placebo-controlled</td>
<td>Amlodipine 10 mg (vs enalapril 20 mg and placebo)</td>
<td>663 (vs 673 and 655)</td>
<td>24 months</td>
<td>NA</td>
<td>39.9%</td>
</tr>
<tr>
<td>A-Plus, 2004 [3]</td>
<td>RCT double-blind placebo-controlled</td>
<td>Avasimibe 750 mg</td>
<td>117</td>
<td>24 months</td>
<td>202.3 mm³</td>
<td>45.3%</td>
</tr>
<tr>
<td>ESTABLISH, 2004 [4]</td>
<td>RCT</td>
<td>Atorvastatin 20 mg daily</td>
<td>24</td>
<td>6 months</td>
<td>69.6 mm³</td>
<td>29.9%</td>
</tr>
<tr>
<td>ASTEROID, 2006 [5]</td>
<td>Prospective open-label blinded end points</td>
<td>Rosuvastatin 40 mg daily</td>
<td>349</td>
<td>24 months</td>
<td>212.2 mm³</td>
<td>39.6%</td>
</tr>
<tr>
<td>ACTIVATE, 2006 [6]</td>
<td>RCT placebo-controlled</td>
<td>Pactimibe 100 mg daily (ACAT inhibitor)</td>
<td>554</td>
<td>18 months</td>
<td>198.1 mm³</td>
<td>39.8%</td>
</tr>
<tr>
<td>PERISCOPE, 2008 [6]</td>
<td>RCT double-blind</td>
<td>Pioglitazone 15 to 45 mg (vs glimepiride 1 to 4 mg)</td>
<td>543</td>
<td>18 months</td>
<td>NA</td>
<td>40.6%</td>
</tr>
<tr>
<td>ILLUSTRATE, 2008 [6]</td>
<td>RCT</td>
<td>Torcetrapib/atorvastatin</td>
<td>910</td>
<td>24 months</td>
<td>NA</td>
<td>37.0%</td>
</tr>
<tr>
<td>STRADIVARIUS, 2008 [6]</td>
<td>RCT placebo-controlled</td>
<td>Rimonabant (anti-obesity drug)</td>
<td>839</td>
<td>20 months</td>
<td>191.7 mm³</td>
<td>37.5%</td>
</tr>
<tr>
<td>JAPAN-ACS, 2009 [7]</td>
<td>RCT open-label parallel</td>
<td>Atorvastatin 20 mg daily (vs pitavastatin 4 mg daily)</td>
<td>252</td>
<td>12 months</td>
<td>63.9 mm³</td>
<td>50.5%</td>
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*p-value < 0.05 for all comparisons. *Information is provided by the web-service of the US NIH ClinicalTrials.Gov. TAV and PAV calculated by analysis of IVUS.

ACAT: The enzyme acyl-CoA : cholesterol acyltransferase; BVS: Biodegradable vascular scaffold; IVUS: Intravascular ultrasound; LpPLA2: Lipoprotein-associated phospholipase A2; MICS: Minimally invasive cardiac surgery; NA: Non-available or Not applicable; NS: Non-significant changes of variables (p-value > 0.05); PAV: Percent atheroma volume; PCSK9: Proprotein convertase subtilisin kexin 9; PPTT: Plasmonic photothermal therapy; RCT: Randomized controlled trial; TAV: Total atheroma volume (mm³).
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<td></td>
<td>Mean plaque volume (TAV)</td>
<td>Mean plaque burden (PAV)</td>
</tr>
<tr>
<td>COSMOS, 2009 [8]</td>
<td>Open-label observational</td>
<td>Rosuvastatin 2.5 mg daily with titration up to 20 mg daily</td>
<td>214</td>
<td>15 months</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>TOGETHAR, 2010 [9]</td>
<td>Open-label observational</td>
<td>Pitavastatin 2 mg daily</td>
<td>90</td>
<td>12 months</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>SATURN, 2011 [10]</td>
<td>RCT double-blind</td>
<td>Rosuvastatin 40 mg daily (vs atorvastatin 80 mg)</td>
<td>520 (vs 519)</td>
<td>24 months</td>
<td>144.1 mm³</td>
<td>36.7%</td>
</tr>
<tr>
<td>IBIS-4, 2015 [11]</td>
<td>Prospective cohort study</td>
<td>Rosuvastatin 40 mg daily</td>
<td>103</td>
<td>13 months</td>
<td>258.3 mm³</td>
<td>43.9%</td>
</tr>
<tr>
<td>Lipid-lowering medications</td>
<td></td>
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<tr>
<td>ApoAl-Milano, 2003 [11]</td>
<td>RCT double-blind placebo-controlled</td>
<td>Combined ETC-216 15 mg/kg and 45 mg/kg (five weekly infusions)</td>
<td>36</td>
<td>5 weeks</td>
<td>268.4 mm³</td>
<td>38.96%</td>
</tr>
<tr>
<td>IBIS-2, 2008 [12]</td>
<td>RCT double-blind placebo-controlled</td>
<td>Darapladib 160 mg daily orally (LpPLA2 inhibitor)</td>
<td>175</td>
<td>12 months</td>
<td>327 mm³</td>
<td>40.7%</td>
</tr>
<tr>
<td>ZEUS, 2014 [13]</td>
<td>Prospective study</td>
<td>Ezetimibe 10 mg/day + atorvastatin 20 mg/day vs atorvastatin 20 mg/day</td>
<td>50 (vs 45)</td>
<td>6 months</td>
<td>75.1 mm³ (vs 77.5 mm³)</td>
<td>47.5% (vs 46.7%)</td>
</tr>
<tr>
<td>PRECISE-IVUS, 2014*</td>
<td>RCT open-label</td>
<td>Ezetimibe 10 mg/dl + Atorvastatin vs atorvastatin</td>
<td>245</td>
<td>12 months</td>
<td>NA</td>
<td>NA</td>
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<th>Mean relative change in plaque volume (TAV)*</th>
<th>Mean change in plaque burden (PAV)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>OUH-OCTIVUS, 2014*</td>
<td>RCT double-blind placebo-controlled</td>
<td>Ezetimibe 10 mg/dl + 80 mg Atorvastatin vs 80 mg Atorvastatin</td>
<td>87</td>
<td>12 months</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>GLAGOV (Phase III), 2016*</td>
<td>RCT double-blind placebo-controlled</td>
<td>Evolocumab/AMG 145 (PCSK9 MAb)</td>
<td>970</td>
<td>20 months</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Animal studies of mTOR inhibitors, 2002–2013 [14]</td>
<td>NA</td>
<td>Rapamycin 0.01–8 mg/kg/day (mTOR inhibitor)</td>
<td>NA</td>
<td>1–3 months</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>-0.4–85%</td>
</tr>
<tr>
<td><strong>Coronary devices</strong></td>
<td></td>
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</tr>
<tr>
<td>ABSORB A, 2009 [16]</td>
<td>Prospective open-label study</td>
<td>Implantation of the bioresorbable scaffold Absorb BVS (Abbott Vascular, CA, USA)</td>
<td>29</td>
<td>6-24 months</td>
<td>116.9 mm³ (6 months post-procedure)</td>
<td>62.3%</td>
<td>-13.38 mm³ (median)</td>
<td>-15.6% (from 6 months)</td>
<td>-6.9%</td>
</tr>
<tr>
<td>PLASMONICS, 2008 [17]</td>
<td>Bench study, Yukatan swines on western diet</td>
<td>MICS implantation onto coronary artery of the bioengineered patch bearing gold nanoparticles with further intravascular transcatheter PPTT by near-infrared laser</td>
<td>101</td>
<td>12 months</td>
<td>179.6 mm³</td>
<td>60.9%</td>
<td>-79.4 mm³ (mean)</td>
<td>-44.2%</td>
<td>-29.8%</td>
</tr>
<tr>
<td>NANOM-FIM, 2012 [18]</td>
<td>Prospective observational study</td>
<td>The same as above in PLASMONICS study</td>
<td>60</td>
<td>12 months</td>
<td>178.4 mm³</td>
<td>68.5%</td>
<td>-60.3 mm³</td>
<td>-33.8%</td>
<td>-30.7%</td>
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TAV and PAV calculated by analysis of IVUS.

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Figure 1. Comparative analysis of methodology for the plaque burden’s calculation between the first representation of the positive remodeling with morphology by Seymour Glagov (1987), and the assessment of the vascular enlargement and atheroregression with intravascular ultrasound by Steven Nissen (2003). (A) Glagov, in autopsy study of 136 hearts [22], concluded that coronary arteries (see left panel with a cross section and corresponding contour of the left main coronary artery, magnification x 7.4) enlarge in relation to plaque area and functionally important lumen stenosis may be delayed until the lesion occupies 40% of the internal elastic lamina area. The lumen area did not decrease in relation to the percentage of stenosis (lesion area/internal elastic membrane area x 100) for values between zero and 40% (r = -0.73, p-value < 0.001). The artery initially enlarges (see right bottom panel) in association with plaque accumulation to maintain an adequate, if not normal, lumen area. Early stages of lesion development may be associated with overcompensation. At more than 40% stenosis, however, the plaque area continues to increase to involve the entire circumference of the vessel, and the artery no longer enlarges at a rate sufficient to prevent narrowing of the lumen. Figure adapted from [22]. (B) In case of Nissen’s group [12], the PAV was calculated as shown at the left formula, where EEM area is the cross-sectional area of the external elastic membrane, and lumenarea is the cross-sectional area of the lumen. The change in PAV was calculated as the PAV at 12 months minus the PAV at baseline. The TAV was calculated as shown at the right formula. The top left panel illustrates the appearance of a single cross-section at baseline intravascular ultrasound examination, while the top right panel shows the same cross-section after 24 months of treatment. The bottom two panels illustrate the same cross-sections, but with measurements superimposed. Atheroma area was reduced from 10.16 to 5.81 mm². Figure adapted from [5].

EEM: External elastic membrane; IEM: Internal elastic membrane; Le: Lesion; Lu: Lumen; PAV: Percent atheroma volume; TAV: Total atheroma volume.

The Glagov atheroregression below a 40% threshold of plaque burden as the ultimate goal of atheroprotective strategy

New generations of devices may help fulfill the ultimate goal of atheroregression below the Glagov threshold by reversing atherogenesis, slowing aging and triggering repair of diseased arteries. The Glagov’s observation [22] in 1987 (see Figure 1) suggests that vascular remodeling maintains the artery lumen dimensions as long as the plaque burden (PB) threshold of 40% is not surpassed, representing the limit where the growth of the plaque can no longer be accommodated by external elastic membrane (EEM) expansion. This process of EEM enlargement in accommodating the plaque and maintaining the lumen dimensions is referred to as the Glagov phenomenon, which is a cornerstone concept in atheroprotective strategies. Although Glagov phenomenon was originally described only for the case of arterial remodeling in response to growth of atherosclerotic
Invasive intravascular imaging

- Intravascular ultrasound (IVUS)
- Virtual histology IVUS (VH-IVUS)
- Optical coherence tomography (OCT)
- Histology

Noninvasive imaging

- Computed tomography angiography (CTA)

**A**

- Two contours of EEM
- Contour of Lumen
- Two contours of EEM

**B**

0 HU 19.0 mm²
50 HU 13.0 mm²
70 HU 12.0 mm²

**C**

**D**
Figure 2. Comparative detection of the vessel contours by intravascular ultrasound, optical coherence tomography, histology and computed tomography angiography. Detection of the contours for lumen, EEM and adventitia by IVUS (resolution 70–150 μm), VH-IVUS (virtual histology), OCT (resolution 10–20 μm) in histology and by the CTA (resolution 350–500 μm) from the left to the right in the random human coronary frames of the different patients demonstrated in panel (A). In some recent trials EEM interpreted as an adventitia, but this is totally misguided understanding. Adventitia by the strict definition is a layer which consists mainly of connective tissue fibers, vasa vasorum and nervi vasorum. The tunica adventitia blends with the connective tissue surrounding the vessel. The definition of the outer limit of the tunica adventitia is therefore somewhat arbitrary. As opposed to adventitia, EEM is a dense relatively thick elastic lamina that might be very simply distinguished with two contours from both media and adventitia. Unfortunately, technical limitations of both OCT and CTA make unreliable to assess EEM in all cases. Regretfully, OCT does not allow us to distinguish adventitia either, but CTA comprises such a potential to delineate outer border of adventitia and it means to calculate the total vessel volume. Coronary CTA images with the automated plaque quantification showed at the right panel with the HU-based density map [25] with the thresholds of 0 to 50 HU (dark green), 50 to 70 HU (light green) and >70 HU (light brown) which was overlayered on the transverse cross-section of coronary artery. The use of a 50-HU threshold for vessel area determination by CTA leads to its significant overestimation, whereas 70-HU threshold is close to that of EEM on IVUS. CTA may accurately delineate the coronary adventitial border by using a 0-HU threshold. The respective borders are manually delineated in all panels. The right panel adapted from [25], (B) depicts experience of the Mintz’s group [25] with the delineation of adventitia. The respective borders of the vessel (outer border of adventitia) are manually delineated at the left image of coronary CTA. IVUS images showed at the right pictures: the presumably adventitial border is delineated on the basis of careful examination of both transverse and longitudinal artery cross-sections as the additional bright acoustic echo directly adhering to the external edge of EEM. Panel (C) and (D) demonstrate how IVUS (C) and VH-IVUS (D) are truly accurate to distinguish the outer border of adventitia. The brightness of the picture is able to significantly impact results of the calculation (at least 25.5% deviation between opposite modes of brightness) as it is shown on four modes of the same frame with the increasing brightness from 20 to 80 units (from the left to the right). Red contours delineate lumen and EEM, but the yellow one shows the probable outer border of adventitia. In case of VH-IVUS (D), the EEM might be perfectly appreciated as the gray line you see at the upper panel with the conventional composition of the fibroatheroma including red necrotic core and white depositions of calcium. At the bottom panel you see approach with another color scheme when we have a chance to distinguish adventitia as the white tissue in case if the lumen border will be delineated by the EEM, and the EEM border will be drawn by the outer border of adventitia. In that case VH-IVUS is able to calculate the volume of adventitia in very accurate fashion, but further studies are required in order to match colorful findings of VH-IVUS and histology for the correct interpretation of the tissues. CTA: Computed tomography angiography; EEM: External elastic membrane; GW: Guidewire; HU: Hounsfield unit; IVUS: Intravascular ultrasound; OCT: Optical coherence tomography.

plaque burden?  

Definitely, there is a gap between both Glagov’s and Nissen’s approach to assess the dimensions of the vessel wall and it means to correctly clarify what is a threshold of the artery wall enlargement (Figure 1). Glagov could calculate the genuine size of the lesion at his morphologic samples between EEM and internal elastic membrane, nothing to talk about thickness of adventitia. The intravascular ultrasound (IVUS) with approach of the Nissen’s group [5] granted us with a tool to detect and measure lesion in alive patient but with another resolution and accuracy strictly between visible EEM and lumen, which means we are able to assess so called plaque-media size only. Neither IVUS or optical coherence tomography (OCT) nor computed tomography angiography (CTA) allow us to comprehensively distinguish all the artery layers (Figure 2). Moreover, the unified approach for the CoreLab three-head expert analysis is required.

The modern trials commit a sin by the excessively free interpretation of the vessel contours, which is able to significantly impact results (at least 13.1% deviation by the data of NANOM-FIM trial [19] in case of the EEM wrong detection, p < 0.05) [26]. The plaque-media volume must be calculated strictly between internal contour of EEM and lumen. Both EEM and adventitia are mostly invisible in OCT images, meanwhile, CTA delineates just the approximate outer border of adventitia, which let us to judge total vessel volume (TVV) only (Figure 2). The current modern-day IVUS approach to define TVV [17] is essentially incorrect because it comprises exclusively the external contour of EEM, but not adventitia. The correct definition of adventitia must be formulated [26] for interventional cardiology. Regretfully, we failed to propose a methodology how to measure adventitia and particularly its external contour by both IVUS and histology. The adventitia is essentially a layer without clear outer border if compared with the dense two-circuit EEM, which is sometimes wrongly interpreted as an adventitia by interventionists. Moreover the
Figure 3. Glagovian remodeling after implantation of stents and bioresorbable scaffolds. Panel shows the general concept of the Glagov phenomenon (frames I–IV), and of the BRS-mediated reversal (frames V–VII) within the remodeling concept of Pasterkamp [27]. After BRS implantation, an artery undergoes the remodeling process with lumen enlargement, vessel wall thinning (plaque-media reduction) and pseudo-atheroregression (with OCT-visible ‘golden tube’), which can be regarded as a kind of vascular reparative therapy. At 24 months, most struts of BVS 1.0 ABSORB (Abbott Vascular, CA, USA) are no longer detectable. In contrast to BRS, a metal cage (usually sirolimus-DES or BMS; see frames V, VIII, XI) provokes chronic irritation of tissue with progressive neoatherosclerosis, or can prevent neoatherosclerosis (DES; see frames V, VIII, IX, X) with OCT-detectable coronary evaginations – defined as outward bulges in the luminal contour between struts (sirolimus-DES; see frame IX) fixed to the struts, limiting further artery wall expansion. ESS adjusts to artery remodeling and transient scaffolding.

BMS: Bare metal stent; BRS: Bioresorbable scaffold; DES: Drug-eluting stent; ESS: Endothelial shear stress; OCT: Optical coherence tomography.

Risk factors

Glagov phenomenon

I II III IV

Lumen enlargement

BRS
‘Golden tubes’
phenomenon

V VI VII

VIII IX X

Sirolimus-DES
Phenomenon of evaginations

XI XII

BMS with permanent
alien body in artery
Neoatherosclerosis

Everolimus-DES
No neoatherosclerosis

Figure 3. Glagovian remodeling after implantation of stents and bioresorbable scaffolds. Panel shows the general concept of the Glagov phenomenon (frames I–IV), and of the BRS-mediated reversal (frames V–VII) within the remodeling concept of Pasterkamp [27]. After BRS implantation, an artery undergoes the remodeling process with lumen enlargement, vessel wall thinning (plaque-media reduction) and pseudo-atheroregression (with OCT-visible ‘golden tube’), which can be regarded as a kind of vascular reparative therapy. At 24 months, most struts of BVS 1.0 ABSORB (Abbott Vascular, CA, USA) are no longer detectable. In contrast to BRS, a metal cage (usually sirolimus-DES or BMS; see frames V, VIII, XI) provokes chronic irritation of tissue with progressive neoatherosclerosis, or can prevent neoatherosclerosis (DES; see frames V, VIII, IX, X) with OCT-detectable coronary evaginations – defined as outward bulges in the luminal contour between struts (sirolimus-DES; see frame IX) fixed to the struts, limiting further artery wall expansion. ESS adjusts to artery remodeling and transient scaffolding.

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Size of adventitia substantially varies in the different stage lesions, but there are no studies with the special focus on adventitia remodeling [27] within the concept of the natural history of atherogenesis which means CTA-related TVV is not that informative to track progress of atherosclerosis. The experience of the Mintz’s group [25] is perfect in sense of the methodology to match IVUS and CTA images (Figure 2), but the accuracy of IVUS remains debatable especially in sense of the quest for the optimal approach to calculate the volume of adventitia. Further studies matching IVUS, virtual histology-IVUS and histology are able to upgrade our understanding of both how to delineate the vessel contours and what is the natural history of artery remodeling. Regrettfully, there is no way to assess the true PB by 64- or 128-slice CTA due to absence of the tools to verify EEM for today. In case of the quantitative coronary angiography (QCA) we can judge PB only obliquely by the percent of stenosis minding the fact that narrowing of the lumen becomes possible only in case if PB stays above 40%. These factors can partly explain why we do not see the genuine Glagov atheroregression in case of the modern-day lipid-lowering trials.
**Transient scaffolding of coronaries & nanotechnologies promise new revolution in theranostics of atherosclerosis**

To date, the biodegradable scaffold Absorb BVS (Abbott Vascular, CA, USA) is the first coronary device which has shown phenomena such as late lumen enlargement (without pathological remodeling) and Glagovian wall thinning with at least 12% reduction of PB [16,17] (see Table 1 & Figure 3). Biodegradable scaffold may represent a new era in cardiovascular medicine, since interventions will address not only the obstructive component of atherosclerotic disease, but also the biologic and functional properties of the vessel. In fact, Absorb BVS in combination with other state-of-the-art approaches has a potential to pave the way for a new era of atheroregression and so-called by the team of Serruys PW [13,16–17], vascular reparative therapy. For today, the extensive experience in over 100 thousand patients demonstrates such advantages of BRS as reduction of late events (ABSORB EXTEND, 2014), restored vessel function (ABSORB cohort B trial, 2014), reduced revascularization rates (ABSORB II, 2014), plaque regression (a multi-imaging modality study in 2014 documented a biphasic change of the total plaque area shows a biphasic change with an increase between the first and second year and a plaque reduction between the second and third-year follow-up) [28], and lumen gain (ABSORB cohort B trial, 2011, 2013). Definitely, BRS performs well in STEMI patients if compared with DES, but thrombosis raises concerns. Running ABSORB III and IV trials aim to prove superiority of BRS [16,29].

At present, although atheroregression below the Glagovian threshold has not been yet achieved, developments in nanotechnologies may ultimately realize this goal. A single multifunctional gold nanoparticle-based platform (‘mix-and-match’ with suitably selected components for each individual application) incorporating multiple receptor targeting, multimodality imaging (ex vivo and in vivo) and multiple therapeutic entities (molecular target therapy, atheroregression and thrombolysis) in a close interaction with near-infrared laser technologies may provide the ultimate ‘magic gold bullet’ for interventional vascular medicine [20,21].

Plasmonics, and particularly plasmonic photothermal therapy is a novel and promising approach that can be combined with metal nanoparticles. When nanoparticles are irradiated with a near-infrared laser, they absorb energy, which is quickly transferred through the nonradiative relaxation into heat which leads to irreparable damage of tissue. Systematic experimental (2001–2010) [18] and human (2007–2010) [19] studies over the last 15 years have demonstrated the main pros and cons of plasmonic photothermal therapy with the different delivery approaches. In bench tests (PLASMONICS study) [18], the mean PB reduction achieved 79.4 mm³ with the use of mini-invasive surgery-based implantation of bioengineered patches on the artery with fixation to the myocardium. The NANOM-FIM trial [19] showed truly unprecedented 60.3 mm³ plaque volume reduction at 12 months in 60 patients using similar nanotechnology (see Table 1). The concept of this approach was validated by another group [21], but these results require further investigation and need to be confirmed in larger studies.

**What we expect from the small lesions in the lipid-lowering trials?**

The findings of NANOM-FIM trial [19] and historical results of statin studies are not entirely comparable due to significant difference between populations and baseline parameters such as TAV, TVV and PB at the compensated vessels without signs of the true positive or negative remodeling. In most statin trials (Figure 4), the baseline PB was below 40% which means already beyond Glagov threshold. These lesions cannot be interpreted as fibroatheromas, and, moreover, PROSPECT study [24] affirmed a 70% PB as the independent predictor of the major cardiac adverse events in non-culprit lesions, which means we cannot expect any major outcomes in those trials either. In that case here is a question what we try to achieve in such young and most probably clinically silent lesions. On the one hand, plaques at those trials could be characterized as relatively small and early-stage lesions that a priori makes them more sensitive to the intensive drug therapy in comparison with the late-stage and advanced fibroatheromas with pronounced inorganic component. On the other hand, these tiny lesions depreciate the atheroprotective potential of the drug agent or device due to low initial vessel volume, which means the clinical value of the approach could be merely underestimated.

**Total atheroma volume or percent atheroma volume: what variable is more favorable to judge atheroregression?**

Moreover, the TAV remains a kind of the ‘gold standard’ to assess real absolute alterations in the atheromatous lesions being meanwhile essentially less informative if compared with the percent atheroma volume (PAV). The PAV is the only parameter to describe changes in the vessel geometry from the Glagov phenomenon point of view because it mathematically reflects patterns between both vessel and lumen size. In case of TAV we ignore sometimes the size of the artery wall and natural history of the vessel remodeling which means our achievements might be misinterpreted. The best example of such misguidance is two Chinese meta-analyses with a focus on...
Changes of plaque burden (PAV) from baseline to follow-up, %

Asteroid (Δ 0.98%, 24 MO, P < 0.05)
Pre-clinical studies of Absorb BVS (Δ 12.7%, 24 MO, P < 0.05)
Saturn (Δ 1.3%, 24 MO, P < 0.05)
APOAI-milano (Δ 1.36%, 5 week, P < 0.05)
Japan-ACS (Δ 6.3%, 12 MO, P < 0.05)
Zeus (Δ 12.5%, 6 MO, P < 0.05)

Glagov threshold
Fibroatheroma
Thin-cap fibroatheroma
Plaque rupture
Progressive plaques (Pathologic intimal thickening, fibroatheroma)

IVUS predictor of non-culprit lesion-related major adverse cardiac events (PB > 70%, p < 0.001)
the effects of the statin therapy on regression of coronary atherosclerosis using IVUS. The group of Gao WQ [32] reported meta-analysis of 20 trials with 5910 patients, and concluded that intensive lowering LDL-cholesterol (LDL-C) (rosuvastatin mean 33 mg daily and atorvastatin mean 60 mg daily) therapy with a >17-month duration could lead to the regression of the lesions (TAV -0.162 mm³, p = 0.0001; -0.101 mm³, p = 0.016; respectively). Moreover, LDL-C level should be reduced by >40% or to a target level of <78 mg/dl. Another analysis (17 trials, 2171 patients) of Tian J [33] documented that statin therapy (especially that involving a high dose and long duration and achieving <100 mg/dl LDL-C level) can significantly decrease TAV (-5.3 mm³; 95% CI: -3.3 mm³ to -7.2 mm³; p < 0.001). Unfortunately, in both cases dynamics of more informative parameter – a PB (PAV) – was not taken into account. Furthermore, one of the first CTA trials of statins [34] documented a 47.7 mm³ TAV regression of the noncalcified plaques. Regrettfully, authors technically measured not even TAV, but TVV with adventitia. In that case we cannot judge atheroregression just because the remodeling of adventitia substantially affects results. There in the automated quantified lesions with a low (>30%) Hounsfield unit threshold neither lumen size nor PAV were provided, which makes this trial overestimated and pointless.

How to optimize the strategy to examine atheroprotective agents?

In fact, in order to optimize our results we are obliged to pay more attention to the different imaging modalities and proceed with the IVUS or a 70 Hounsfield unit CTA assessment of PB at any trial, which has an objective to estimate Glagovian atheroregression. Potentially, neither vessel size or TAV nor narrowing of the lumen per se is of intrinsic importance. The only point there is the PB with a threshold of 40% (PAV above 40% at the baseline, and below 40% at the follow-up) as the ultimate criterion of the clinically valuable lesion we are able to examine in order to judge the real atheroregression. We know that all the trials with the baseline PAV above 40% demonstrated higher atheroregressive potential (for instance, ASTEROID [8] vs JAPAN-ACS [7] with the baseline PAV of 39.6 vs 50.5% and further reduction of PB up to 0.98 vs 6.3% respectively, p < 0.05) due to most probably activated Glagovian mechanisms of the artery remodeling and higher sensitivity to any intrinsic or extrinsic factors. Further comprehensive analysis is required in order to validate the genuine threshold of the artery enlargement between a 20 and 55% PAV when positive correlation between lumen area and PB get replaced by the negative correlation with the progressive narrowing of the lumen. Furthermore, the correlation between initial PAV in intact coronaries and degree of atheroregression as well as clinical outcomes at the follow-up must be clarified either.

Future perspective

Two aggressive statin therapy trials SATURN and IBIS-4 demonstrated very controversial results with atheroregression up to 1.22% [35], reduction of fibrous tissue and certain amount of intramural lipids, but with very slight effect on necrotic core accelerating calcium deposition whereas the fact that numerous studies of the cholesterol lowering strategies have failed to document a mortality benefit, and, so, the benefits of statins may have been overstated [36,37] which require further validation. So, the adoption of transient scaffolding with bioresorbable platforms and progress of nanomedicine in hands of the harmonized imaging have become the most compelling breakthroughs of theranostics in interventional cardiology, offering potential solutions in the imaging, targeting and treatment of atherosclerosis with the ultimate goal to achieve atheroregression below 40% Glagov threshold.

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Executive summary

- Reduction of total atheroma volume provides cardiology with a hope to reverse atherosclerosis in hands of the modern-day lipid-lowering medications;
- ASTEROID and SATURN trials demonstrated the potential of statins which reduce the total atheroma volume up to 6.38 mm³ in coronary arteries and 30% decrease in outcomes;
- Recombinant ApoA-I Milano demonstrated a 14.1 mm³ reduction in total atheroma volume with unproven effect on clinical outcomes;
- ZEUS trial with ezetimibe revealed an 8.2 mm³ atheroregression.
- The plaque burden with a Glagovian threshold of 40% (PAV [percent atheroma volume] above 40% at the baseline, and below 40% at the follow-up) is the ultimate criterion of the clinically valuable lesion we are able to examine in order to judge the genuine Glagovian atheroregression.
- Some methodological flaws of the modern-day interventional imaging approaches including improper interpretation of the vessel contours, misunderstanding of such parameters as total atheroma volume and PAV, absence of the unified CoreLab expert methodology for assessment of both intravascular and noninvasive coronary imaging significantly impact results and further progress in this field;
- There is a difference in methodology how to assess plaque burden between histology of Glagov and IVUS-imaging of Nissen;
- Neither intravascular intravascular ultrasound (IVUS) or optical coherence tomography nor noninvasive computed tomography angiography allow us to comprehensively distinguish all the artery layers;
- External elastic membrane and adventitia could be quantitatively assessed by IVUS only;
- Some new medications as well as progress in the development of the bioresorbable scaffolds and nanomedicine promise to revolutionize the cardiovascular biomedicine with the main goal to achieve Glagovian atheroregression below 40% threshold of the PB:
- The bioresorbable scaffold Absorb BVS (Abbott Vascular, CA, USA) is the first coronary device which has shown phenomena such as late lumen enlargement and wall thinning with at least 12% reduction of plaque burden;
- NANOM-FIM trial of plasmonic photothermal therapy with silica-gold nanoparticles showed truly unprecedented 60.3 mm³ plaque volume reduction.
- The modern-day statin trials were conducted in patients with relatively small lesions when PAV never exceeded 40% and without proper methodology, which means that the revealed phenomenon of atheroregression is essentially the pseudo reduction of the atheroma volume.
- The PAV or plaque burden is the only parameter to describe changes in the vessel geometry from the Glagov phenomenon point of view because it mathematically reflects patterns between both vessel and lumen size.
- IVUS with assessment of plaque burden remains the golden standard to evaluate atheroregressive patterns of medications or medical devices in clinical trials:
- Trials with the baseline PAV above 40% demonstrated higher potential of the plaque burden reduction;
- Further comprehensive analysis is required in order to validate the genuine threshold of the artery enlargement between a 20 and 55% PAV when positive correlation between lumen area and PB gets replaced by the negative correlation with the progressive narrowing of the lumen.

References

Papers of special note have been highlighted as: • of interest; •• of considerable interest.


• Represents original results of the ASTEROID trial with...
comprehensive description of intravascular intravascular ultrasound methodology.


** Being essentially very successful statin trial with a 6.3% reduction of plaque burden.


• Represents original results of the SATURN trial.


• Provides with the first description of the intravascular ultrasound methodology to measure plaque burden from the Nissen and Nicholls group.


• First ezetimibe study with significant plaque burden reduction.


• This is the only ABSORB study which demonstrated plaque burden reduction.


• Represents the first animal study of the plasmonic photothermal therapy of atherosclerosis.


• Provides with the first original results of NANOM-FIM trial.


• Observes plasmonic photothermal therapy of atherosclerosis through the prism of the Glagovian atheroregression.


• Discovers the feasibility study of the plasmonic photothermal therapy of atherosclerosis (by design of NANOM-FIM trial) when combined with photoacoustics.


• The first description of the Glagovian phenomenon.


• The first evidence-based description of the methodology for computed tomography angiography assessment of plaque burden.


28 Serruys PW, Onuma Y, Muramatsu T et al. Dynamics of vessel wall changes following the implantation of the absorb everolimus-eluting bioresorbable vascular scaffold: a multi-imaging modality study at 6, 12, 24 and 36 months. EuroIntervention 9(11), 1271–1284 (2014).


- The pivotal morphological description of the atheroprogression.


