

1 **Intravascular imaging assessment of pharmacotherapies targeting atherosclerosis:**
2 **advantages and limitations in predicting their prognostic implications**

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4 Vincenzo Tufaro^{a,b,c}, MD; Patrick W Serruys^d, MD, PhD; Lorenz Räber^e, MD, PhD;
5 Martin R Bennett^f, MD, PhD; Ryo Torii^g, PhD; Sophie Z Gu^f, MB ChB, MRCP;
6 Yoshinobu Onuma^h, MD, PhD; Anthony Mathur^{a,b}, MD, PhD; Andreas Baumbach^{a,b,i}, MD, PhD;
7 Christos Bourantas^{a,b,j*}, MD, PhD

8 ^a Department of Cardiology, Barts Heart Centre, Barts Health NHS Trust, London, UK

9 ^b Centre for Cardiovascular Medicine and Devices, William Harvey Research Institute, Queen Mary
10 University of London, UK

11 ^c Department of Biomedical Sciences, Humanitas University, Pieve Emanuele-Milan, Italy.

12 ^d National Heart and Lung Institute, Imperial College London, London, UK

13 ^e Department of Cardiology, Bern University Hospital, University of Bern, Switzerland

14 ^f Division of Cardiovascular Medicine, University of Cambridge, Cambridge, UK

15 ^g Department of Mechanical Engineering, University College London, London, UK

16 ^h Department of Cardiology, National University of Ireland, Galway, Ireland

17 ⁱ Yale University School of Medicine, New Haven, Connecticut, US

18 ^j Institute of Cardiovascular Sciences, University College London, London, UK

19 **Short title:** coronary plaque changes and cardiovascular outcome.

20 ***Address for correspondence**

21 Christos Bourantas, MD, PhD

22 Consultant Cardiologist, Barts Heart Centre,

23 Barts Heart Centre, West Smithfield, London EC1A 7BE

24 E-mail: cbourantas@gmail.com

25 Phone: +44 20 7377 7000, Fax: +44 20 7791 9670

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Abstract

Intravascular imaging has been often used over the recent years to examine the efficacy of emerging therapies targeting plaque evolution. Serial intravascular ultrasound, optical coherence tomography, or near infrared spectroscopy-intravascular ultrasound studies have allowed us to evaluate the effects of different therapies on plaque burden and morphology, providing unique mechanistic insights about the mode of action of these treatments. Plaque burden reduction, a decrease in necrotic core component or macrophages accumulation – that have been associated with inflammation - and an increase in fibrous cap thickness over fibroatheromas have been used as surrogate endpoints to assess the value of several drugs in inhibiting plaque evolution and improving clinical outcomes.

However, some reports have demonstrated weak associations between the effects of novel treatments on coronary atheroma and composition and their prognostic implications. This review examines the value of invasive imaging in assessing pharmacotherapies targeting atherosclerosis. It summarizes the findings of serial intravascular imaging studies assessing the effects of different drugs on atheroma burden and morphology and compares them with the results of large-scale trials evaluating their impact on clinical outcome. Furthermore, it highlights the limited efficacy of established intravascular imaging surrogate endpoints in predicting the prognostic value of these pharmacotherapies and introduces alternative imaging endpoints based on multimodality/hybrid intravascular imaging that may enable more accurate assessment of the athero-protective and prognostic effects of emerging therapies.

Keywords: lipid-lowering drugs; coronary atherosclerosis; intravascular ultrasound; optical coherence tomography; near infrared spectroscopy.

1 **Introduction**

2 Coronary artery disease (CAD) is the most common cause of death in the developed world, is associated
3 with increased morbidity and has devastating economic consequences in Europe and US. Therefore, an
4 effort has been made to understand the pathophysiological mechanisms that regulate plaque progression
5 and develop effective therapies that will inhibit atherosclerosis evolution, improve quality of life, and
6 prolong life expectancy in patients who suffer from CAD.¹

7 Intravascular imaging, which enables detailed assessment of plaque pathology albeit with some
8 limitations (Figure 1), has been used to examine the effect of these therapies on plaque burden (PB) and
9 provided unique insights into the effects of these drugs on plaque morphology.²⁻⁴ In contrast to outcome
10 trials that require large numbers of patients to prove prognostic benefit, intravascular imaging studies use
11 imaging-based surrogate endpoints such as changes in percent atheroma volume (PAV) or composition to
12 evaluate their efficacy on plaque progression using a smaller number of patients and at a lower cost.⁵
13 Imaging-based studies have been performed to investigate the mechanisms of action of emerging
14 therapies and provide proof of their athero-protective effect that would justify the conduction of large
15 outcome studies, or to complement ongoing outcome studies with mechanistical insights on *in-vivo*
16 modes of action. Nevertheless, some reports demonstrated only a weak association between changes in
17 PB or its characteristics and clinical outcomes, questioning the value of imaging-based endpoints in
18 assessing the efficacy of novel treatments (Supplementary Figure 1).

19 The aim of this review is to present the findings of intravascular imaging studies evaluating the efficacy
20 of different drugs, summarize the results of clinical trials that tested their prognostic value, and discuss
21 the advantages and limitations of invasive imaging endpoints in predicting the potency of these therapies
22 in reducing cardiovascular event rates.

23 **The rationale behind intravascular imaging for assessing the efficacy of novel therapies targeting** 24 **atherosclerosis**

25 The use of intravascular imaging-based surrogate endpoints to examine the value of novel
26 pharmacotherapies in improving outcomes relies on the premise that specific plaque characteristics,

1 which can be assessed by intravascular imaging, are associated with a risk of subsequent major adverse
2 cardiovascular events (MACE).

3 Cumulative data have shown that PB and its changes provide useful prognostic information and
4 identification of patients at risk of future events. A metaanalysis including 4137 patients recruited in 6
5 clinical trials showed that baseline PAV and its change at 18-24 months follow-up were independent
6 predictors of MACE.⁶

7 The above findings were also confirmed in prospective studies reporting patient-level results. In the
8 European Collaborative Project on Inflammation and Vascular Wall Remodeling in Atherosclerosis-
9 Intravascular Ultrasound (ATHEROREMO-IVUS) study that included 581 patients undergoing single
10 vessel virtual histology (VH)-intravascular ultrasound (IVUS), patients with PB $\geq 70\%$ and a thin-cap
11 fibroatheroma (TCFA) phenotype were at high-risk of developing MACE.⁷ The prognostic value of
12 plaque morphology was also shown in the ATHEROREMO-near infrared spectroscopy (NIRS)⁸, the
13 Lipid Rich Plaque (LRP)⁹ and the Providing Regional Observations to Study Predictors of Events in the
14 Coronary Tree (PROSPECT) II¹⁰ studies which demonstrated that increased lipid component detected by
15 NIRS was associated with worse prognosis on a patient-level analysis (Figure 2).

16 Prospective large-scale studies which investigated clinical endpoints on a lesion-level analysis also
17 provided relevant data on the value of intravascular imaging in identifying vulnerable plaques. The
18 PROSPECT¹¹, the VH-IVUS in Vulnerable Atherosclerosis (VIVA)¹², the Prediction of Progression of
19 Coronary Artery Disease and Clinical Outcome Using Vascular Profiling of Shear Stress and Wall
20 Morphology (PREDICTION)¹³ and the PROSPECT II¹⁰ have underscored the prognostic implications of
21 PB and composition and highlighted the efficacy of intravascular imaging in detecting plaques that were
22 prone to progress and cause events. In addition, the Relationship Between OCT Coronary Plaque
23 Morphology and Clinical Outcome (CLIMA)¹⁴ was the first study demonstrating that the thickness of
24 fibrous cap over lipid-rich plaques and vascular inflammation indicated by the presence of macrophages
25 on optical coherence tomography (OCT) imaging were independent predictors of MACE (Figure 2).

1 Based on the findings of the above studies and the evidence from histology reports showing that culprit
2 lesions have a specific phenotype¹⁵⁻¹⁷, it has been hypothesized that a decrease in PB, necrotic core and
3 vascular inflammation as well as an increase in fibrous cap thickness (FCT) over lipid rich-plaques
4 indicate plaque passivation and thus these variables can be used as surrogate endpoints to predict the
5 efficacy of emerging therapies targeting atherosclerosis in reducing cardiovascular events.⁵

6 **Efficacy of drug therapies in modifying plaque size and composition and improving outcomes**

7 In this section we focused our attention on pharmacotherapies, introduced to inhibit plaque evolution, that
8 have been tested in intravascular imaging-based studies (Supplementary Table 1 and 2) and/or outcome
9 trials (Supplementary Table 3) in secondary prevention of CAD.

10 *Statins*

11 Statins target hepatocytes and are selective, competitive inhibitors of hydroxymethylglutaryl-CoA (HMG-
12 CoA) reductase, a key regulator of cholesterol biosynthesis (Supplementary Figure 2). The reduction in
13 intracellular cholesterol production causes upregulation of hepatic low-density lipoprotein (LDL)
14 receptors which decreases levels of circulating LDL as well as oxidized LDL within the arterial intima
15 thwarting the inflammatory cascade that promotes monocyte recruitment and foam cell formation, the
16 initial and key step in atherogenesis. Furthermore, statins also have cholesterol-independent
17 cardiovascular protective effects that include reduction of oxidative stress and platelet aggregation,
18 vascular tone improvement (increase nitric oxide synthesis and reduce smooth muscle cell activation and
19 proliferation), plaque stabilization (promote macrocalcification and increase FCT), as well as systemic
20 and local anti-inflammatory effects [i.e., they reduce C-reactive protein (CRP), Tumor Necrosis Factor
21 (TNF) alpha, Interleukin (IL)-1beta and leukocytes endothelial adhesion].¹⁸

22 The prognostic implications of statin therapy are well established and seem to be associated with the
23 reduction in LDL-C induced by these drugs (Supplementary Figure 3). A meta-analysis including 21
24 statin trials and more than 129000 patients showed that at every 1.0mmol/l reduction in LDL-C there is a
25 22% reduction in cardiovascular events and a 10% reduction in all-cause mortality.¹⁹ In addition,

1 numerous intravascular imaging studies have attempted to provide mechanistic insights and examine the
2 effects of statin therapy on plaque morphology and burden.

3 Rosuvastatin

4 The ASTEROID (A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived
5 Coronary Atheroma Burden)²⁰, a single arm observational study, and the SATURN (Study of Coronary
6 Atheroma by Intravascular Ultrasound: Effect of Rosuvastatin Versus Atorvastatin)²¹, an appropriately
7 powered randomized control trial, showed that treatment with rosuvastatin 40 mg daily led to a marginal
8 but statistical significant reduction in PAV (-0.98%, $p<0.001$ and -1.22%, $p<0.001$, respectively) on
9 IVUS imaging at 2-year follow-up. An exploratory sub-analysis of the SATURN – including 71 patients
10 undergoing serial VH-IVUS – demonstrated no changes in the lipid and fibrotic tissue components but an
11 increase in the calcific and a reduction in the fibrofatty tissue burden at follow-up.²²

12 The IBIS-4 (The fourth Integrated Biomarker and Imaging Study)⁴ confirmed that rosuvastatin 40 mg
13 reduces PAV by -0.9% ($p=0.007$) in patients with ST elevation myocardial infarction (STEMI), while
14 VH-IVUS analysis showed an increase in the calcific burden and a reduction of the fibrotic tissue
15 component but no change in the plaque phenotype at follow-up. The OCT-sub-study of IBIS 4
16 demonstrated that this drug regimen may promote plaque stabilization increasing FCT over lipid-rich
17 plaques by +24.4 μm ($p=0.008$) and reducing macrophages accumulation at 13 months follow-up
18 (Supplementary Table 2).³ An advantage of the IBIS-4 study is the fact that it studied the entire coronary
19 tree including the culprit and non-culprit vessels with both VH-IVUS and OCT at two time points to
20 identify changes in plaque morphology; however, its main limitation is the lack of a control group that
21 would allow us to test the superiority of this regimen over low dose statin therapy.

22 Conversely, the IBIS-3 (The third Integrated Biomarker and Imaging Study)²³ showed that rosuvastatin
23 40 mg did not change the necrotic core volume at 6 or 12-month follow-up (Supplementary Table 2). This
24 was an observational single arm study that aimed to recruit 300 patients but managed to enrol 241
25 patients. From these patients, 164 had evaluable serial VH-IVUS imaging, while 103 matched baseline
26 and follow-up NIRS. The study was underpowered for the primary endpoint that was the change in the

1 necrotic core volume at follow-up assessed by VH-IVUS. The secondary endpoint of the study was the
2 change in the lipid core burden index (LCBI) of the studied segment assessed by NIRS, and the authors
3 found no difference in the LCBI at follow-up; however, for this endpoint there was no power calculation.
4 For the above reasons, the IBIS-3 findings should be interpreted with caution.

5 Multimodality IVUS and NIRS imaging was also used in the YELLOW (Reduction in Yellow Plaque by
6 Aggressive Lipid LOWering Therapy) study²⁴ to evaluate the short-term implications (6-8 weeks follow-
7 up) of rosuvastatin 40mg in flow-limiting lesions. Patients treated with this regimen exhibited a higher
8 reduction in maxLCBI_{4mm} compared to the control group, but there were no changes in PB at follow-up
9 (Supplementary Table 1). The small number of recruited patients, differences in plaque composition
10 between groups and need for NIRS and IVUS co-registration at two time points raised concerns about the
11 validity of the reported results. Furthermore, these findings were not confirmed in the YELLOW II
12 study²⁵ which had a similar design and demonstrated no difference in the maxLCBI_{4mm} between baseline
13 and follow-up. However, in the YELLOW II also serial OCT was used showing a significant increase in
14 minimum FCT and decrease in the incidence of TCFA (Supplementary Table 2), but it was an exploratory
15 analysis because the study was not powered for these endpoints.

16 Finally, the STABLE (Statin and Atheroma Vulnerability Evaluation) study²⁶ which randomized patients
17 with non-flow-limiting disease to high or moderate-dose of rosuvastatin showed similar reduction in both
18 groups in the percent necrotic core volume and in the incidence of VH-IVUS-defined TCFA at 1-year
19 follow-up (Supplementary Table 1). However, the study included only 225 patients with serial
20 intravascular imaging instead of 276 and, thus, it was underpowered for the primary endpoint – that was
21 the change in VH-defined percent compositional volume within the target segment from baseline to
22 follow-up – and for the secondary endpoint – defined as the change in percent compositional volume at
23 follow-up between the two treatment groups.

24 Studies investigating the prognostic implications of rosuvastatin in secondary prevention of CAD are
25 limited and were performed only in patients with chronic heart failure. Two randomised studies^{27, 28}
26 including patients suffering from ischemic or non-ischemic heart failure failed to demonstrate a

1 prognostic benefit of rosuvastatin in this cohort (Supplementary Table 3); however, a patient-level
2 metanalysis²⁹ of these two studies demonstrated that treatment with rosuvastatin is associated with a lower
3 incidence of myocardial infarction (MI) in patients suffering from ischaemic heart disease (HR 0.81, 95%
4 CI 0.66-0.99, $p < 0.05$); therefore it is expected that rosuvastatin will be equally effective as the other
5 statins in preventing MACE in patients with CAD.

6 Atorvastatin

7 Several studies have underscored the beneficial effects of intensive or moderate-dose atorvastatin therapy
8 on plaque burden. In the REVERSAL (Reversal of Atherosclerosis with Aggressive Lipid Lowering)
9 study³⁰ atorvastatin 80mg daily inhibited disease progression, whereas there was plaque progression on
10 IVUS in the pravastatin group at 18-month follow-up (Total Atheroma Volume, TAV: -0.4 vs +2.7%,
11 $p=0.02$). Conversely, there was no difference in PAV changes between the rosuvastatin and atorvastatin
12 group in the SATURN²¹ where atorvastatin 80 mg daily reduced PAV by -0.99% ($p < 0.001$) at follow-up.

13 Small randomized studies demonstrated that even low dose atorvastatin may have beneficial effects on
14 atheroma burden assessed by IVUS in patients with acute coronary syndrome (ACS)³¹ and in those with
15 mild coronary atherosclerotic lesions (Supplementary Table 1).³²

16 The Effect of Atorvastatin Therapy on Fibrous Cap Thickness in Coronary Atherosclerotic Plaque as
17 Assessed by Optical Coherence Tomography (EASY-FIT) was the only prospective and properly
18 powered study that compared the implications of two atorvastatin doses (20mg vs 5mg daily) on FCT.
19 This study showed that the higher atorvastatin dose significantly increased FCT at 12-month follow-up
20 leading to plaque stabilization (69% vs 17%, $p < 0.001$).³³

21 The prognostic value of atorvastatin therapy in patients with CAD was first tested in the PROVE IT-
22 TIMI22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial
23 Infarction 22) trial³⁴ that randomised 4,162 patients who suffered an ACS to atorvastatin 80mg or
24 pravastatin 40mg and described a lower MACE rate in the atorvastatin arm (22.4% vs 26.3%, $p=0.005$) at
25 2-year follow-up. In patients with stable CAD, the TNT (Treating to New Targets) trial³⁵ demonstrated
26 that 80mg/day of atorvastatin was more effective than 10mg/day in reducing the risk of death from CAD,

1 non-fatal MI, resuscitation after cardiac arrest or stroke over a median follow-up of 4.9 years
2 (Supplementary Table 3).

3 Pravastatin and Pitavastatin

4 The effects of Pravastatin and Pitavastatin on PB and composition have been extensively studied.

5 In the REVERSAL trial³⁰, treatment with Pravastatin 40mg was associated with an increase in TAV at
6 follow-up as previously documented. The JAPAN-ACS (Japan Assessment of Pitavastatin and
7 Atorvastatin in Acute Coronary Syndrome) study demonstrated that treatment with Pitavastatin 4mg/day
8 was associated with a significant reduction in PAV in the treated culprit vessel at 8-12 month follow-up
9 with no significant differences compared to a low-dose atorvastatin regimen.³¹ The TRUTH³⁶ (treatment
10 with statin on atheroma regression evaluated by IVUS with VH) was a small prospective study that
11 randomized Japanese patients to Pitavastatin or Pravastatin and showed that both statin regimens
12 modified plaque composition by reducing the fibrofatty and increasing the calcified plaque component
13 assessed by VH-IVUS at 8-month follow-up.

14 The CARE (Cholesterol and Recurrent Events) trial examined the prognostic value of pravastatin in
15 secondary prevention and showed that pravastatin 40mg/day was more effective than placebo in reducing
16 fatal and non-fatal coronary events (24% relative risk reduction, 95% CI: 9-36%; p=0.003) in patients
17 with ACS who had normal cholesterol.³⁷ Similarly, the LIPID study (Long-term Intervention with
18 Pravastatin in Ischaemic Disease) showed that pravastatin reduced cardiovascular events and all-cause
19 mortality compared to placebo in patients who had a previous ACS (Supplementary Table 3).³⁸
20 Pitavastatin does not have an indication in secondary prevention, but it is approved for the treatment of
21 primary hyperlipidaemia.

22 ***Ezetimibe plus statin***

23 Ezetimibe is a lipid-lowering drug that targets the Niemann–Pick C1–like 1 protein and localizes in the
24 brush border of the small intestinal enterocytes reducing the uptake of cholesterol into the enterocytes
25 (Supplementary Figure 2) and its overall delivery to the liver, thereby promoting the synthesis of LDL
26 receptors with a subsequent reduction of serum LDL-C. Apart from this systemic effect recent studies

1 suggest that ezetimibe also inhibits macrophages migration by decreasing VCAM-1, MCP-1 and TNF- α
2 levels and reduces ROS levels that are instigators of plaque progression.³⁹

3 When added to statins, ezetimibe reduces LDL-C levels by -22.3% compared to placebo⁴⁰; therefore,
4 ezetimibe is recommended as an add-on therapy in patients who do not reach the LDL-C goal with the
5 maximum tolerated dose of statin.⁴¹

6 The PRECISE-IVUS (Plaque Regression With Cholesterol Absorption Inhibitor or Synthesis Inhibitor
7 Evaluated by Intravascular Ultrasound) is the largest study investigating effect of ezetimibe on plaque
8 burden; it randomized 246 patients to atorvastatin 10mg plus ezetimibe 10mg daily or atorvastatin alone
9 and demonstrated a greater PAV regression (-1.4% vs -0.3%, $p=0.001$) in the dual-therapy group.⁴² A
10 recently published meta-analysis pooling data from the PRECISE-IVUS study and 5 smaller studies
11 comprising 583 patients in total confirmed that the combination of ezetimibe and statin therapy was more
12 effective than statin monotherapy in reducing atheroma volume.⁴³ Small scale studies examining the role
13 of combined ezetimibe and statin therapy on plaque composition have consistently demonstrated that the
14 addition of ezetimibe has no significant effect on the changes on plaque characteristics at follow-up
15 (Supplementary Table 1).

16 The clinical benefit of combining ezetimibe and a statin was shown for the first time in the IMPROVE-IT
17 (Improved Reduction of Outcomes: Vytorin Efficacy International Trial)⁴⁴, which randomized 18,144
18 patients admitted with ACS to simvastatin 40mg plus ezetimibe 10mg once a day or simvastatin 40mg
19 monotherapy. A 6.4% relative risk reduction in dual-therapy group was noted for the composite endpoint
20 of cardiovascular death, nonfatal MI, unstable angina requiring rehospitalization, coronary
21 revascularization or nonfatal stroke at 7 years follow-up (32.7% vs 34.7%, $p=0.016$). A similar trend was
22 also reported in the HIJ-PROPER trial (Heart Institute of Japan Proper level of lipid lowering with
23 Pitavastatin and Ezetimibe in acute coRonary syndrome) that included 1,734 patients with ACS and
24 dyslipidaemia who were randomized to dual therapy with ezetimibe 10mg and pitavastatin 2mg daily or
25 pitavastatin monotherapy; however, the difference in the event rate between groups was not statically
26 significant as the study was underpowered for the primary end-point (Supplementary Table 3).⁴⁵

1 *Proprotein convertase subtilisin-kexin type 9 inhibitors*

2 Proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors prevents degradation of LDL receptors
3 which in turn increase their number on the surface of hepatocytes and promote LDL clearance
4 (Supplementary Figure 2); these drugs can reduce LDL-C by 45-60% if used alone or in combination with
5 a statin.^{46, 47} PCSK9 inhibitors may also have pleiotropic effects as it appears that PCSK9 is expressed by
6 various cell types involved in atherosclerosis and it affects endothelial function, promotes smooth muscle
7 cell migration, and exerts paracrine function on macrophages in the intima increasing the expression of
8 pro-inflammatory cytokines and modifying the uptake of oxidized LDL.⁴⁸

9 The GLAGOV (Global Assessment of Plaque reGression with a PCSK9 antiBody as Measured by
10 intraVascular Ultrasound) trial² was the first that examined the effect of PCSK9 inhibitors on PB. The
11 included patients were randomised to evolocumab plus high or moderate intensity statin or statin
12 monotherapy and had serial IVUS imaging in a single vessel with non-significant stenosis at baseline and
13 at 76-week follow-up. In this study, the PAV decreased by -0.95% ($p < 0.001$) in the combined therapy
14 group, while it remained unchanged in the statin monotherapy arm. A pre-specified sub-study of
15 GLAGOV⁴⁹ which included patients who had concomitant VH-IVUS imaging showed no differences in
16 changes in plaque composition between groups (Supplementary Table 1).

17 Conversely, the ODYSSEY-J IVUS (Evaluation of Effect of Alirocumab on Coronary Atheroma Volume
18 in Japanese Patients Hospitalized for Acute Coronary Syndrome With Hypercholesterolemia) trial failed
19 to demonstrate any difference in the changes in PAV or TAV between patients treated with alirocumab
20 and a statin (rosuvastatin ≥ 5 mg/day or atorvastatin ≥ 10 mg/day) and those receiving statin monotherapy at
21 36 week follow-up.⁵⁰ However, this study had significant limitations: power calculation assumed a large
22 % change difference in the normalized TAV between the two groups that led to recruitment of a small
23 number of patients; IVUS imaging was performed in both culprit and non-culprit vessels where it is likely
24 the TAV to be different and thus introduce bias; ezetimibe was added in the control group in 40% of the
25 patients during the follow-up period.

1 A recent randomized study⁵¹ including only 48 patients showed a reduction in the lipid index and
2 macrophages grade and an increase in the FCT assessed by OCT in patients treated with alirocumab
3 compared to those receiving statin, whereas an observational report⁵² of 53 patients showed a reduction in
4 the maxLCBI_{4mm} on NIRS-IVUS imaging in patients treated with PCSK9 inhibitors compared to those
5 being on statin monotherapy. However, in the former study no power calculation was performed, while
6 the latter included two different PCSK9 inhibitors and was not a randomised study. Therefore, both
7 reports should be regarded as exploratory analyses and their findings require confirmation in the two large
8 appropriately powered randomised control studies that are currently ongoing. The Imaging of Coronary
9 Plaques in Subjects Treated With Evolocumab (HUYGENS; NCT03570697)⁵³ trial aims to assess the
10 effect of treatment with evolocumab on FCT in 164 patients admitted with an non-ST elevation
11 myocardial infarction, while the Vascular Effects of Alirocumab in Acute MI-Patients (PACMAN-AMI;
12 NCT03067844)⁵⁴ study utilises serial NIRS-IVUS and OCT imaging in 300 patients with acute MI to
13 assess the effect of alirocumab on plaque volume, lipid burden and FCT.

14 Large outcomes trials reported that PCSK9 inhibitors combined with a statin therapy decrease the risk of
15 MACE. In the FOURIER (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects
16 with Elevated Risk) trial, evolocumab reduced rate of MI (3.4% vs 4.6%, p<0.001) and coronary
17 revascularization (5.5% vs 7%, p<0.001) compared to placebo in statin-treated patients at a median
18 follow-up of 2.2 years, without reducing cardiovascular mortality.⁵⁵ Similarly, the ODYSSEY
19 OUTCOMES (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During
20 Treatment With Alirocumab) trial that included patients with an ACS showed that the addition of
21 aliorumab to high-dose statin therapy reduced the incidence of recurrent cardiovascular events at 2.8
22 years of follow-up (Supplementary Table 3).⁵⁶

23 *Drugs increasing high-density lipoprotein cholesterol*

24 High-density lipoprotein (HDL) mimetics

25 HDL cholesterols have been a target for drug development because of their anti-atherogenic properties.
26 Several HDL mimetic drugs have been developed by combining peptides and proteins with varying

1 structures, all of which bind lipids found in HDL. Infusion of reconstituted HDL directly increases the
2 number of functional HDL particles in the circulation and thus cholesterol efflux capacity,⁵⁷ in other
3 words it promotes the extraction of cholesterol from donor cells located in peripheral tissues – such as
4 macrophages – and its transportation to the liver (Supplementary Figure 2).

5 HDL mimetic agents have attracted attention after animal studies highlighting their athero-protective
6 effects.^{58, 59} Over the last 20 years three different HDL mimetics (ETC-126, now called MDCO-216,
7 CER-001 and CSL-111) have been evaluated in randomized control trials which enrolled patients with
8 history of ACS and used invasive imaging surrogate endpoints to assess their value in inhibiting plaque
9 progression. Apart from the first study that showed that 5-week ETC-216 infusion reduces PB on IVUS
10 imaging⁶⁰, all the other trials demonstrated a neutral effect of the HDL mimetics on PB (Supplementary
11 Table 1).⁶¹⁻⁶⁴ A possible explanation of this paradox is the small number of patients included in the first
12 report that did not allow us to draw safe conclusion and the fact that the patients recruited in recent
13 studies received contemporary treatment for atherosclerotic disease and had normal HDL-cholesterol
14 levels which is likely to potentially limit their effect on plaque pathobiology. Whether infusion of HDL
15 mimetics is effective in the context of strongly reduced HDL-cholesterol levels and impaired cholesterol
16 efflux capacity remains unknown.

17 There is no current evidence on the role of HDL mimetics in preventing cardiovascular events. The
18 efficacy and safety of CSL-112 in patients after an ACS is currently under investigation in the ApoA-I
19 Event Reducing in Ischemic Syndromes II (AEGIS II, NCT03473223) trial.⁶⁵

20 Cholesterylester transfer protein (CETP) inhibitors

21 CETP is a hydrophobic glycoprotein that is synthesized mainly in the liver and regulates the exchange of
22 lipids between different lipoprotein particles. This process leads to a net mass transfer of cholesterol
23 esters and triglycerides from non-atherogenic HDLs to ApoB100-containing lipoproteins such as very
24 low-density lipoproteins (VLDLs) and LDLs that are proatherogenic (Supplementary Figure 2). Inhibition
25 of this pathway eventually increases the content of cholesterol in HDL particles and the formation of
26 larger HDL particles that are catabolized slower than the normal HDL.⁶⁶

1 The role of these agents in modifying plaque size has been evaluated in the Investigation of Lipid Level
2 Management Using Coronary Ultrasound to Assess Reduction of Atherosclerosis by CETP Inhibition and
3 HDL Elevation (ILLUSTRATE) trial⁶⁷ which randomized patients with evidence of mild to moderate
4 CAD to atorvastatin alone and atorvastatin in addition to torcetrapib 60mg daily and showed no
5 differences in PAV changes between the two groups after 24 months (Supplementary Table 1).
6 Interestingly, The Investigation of Lipid Level Management to Understand Its Impact in Atherosclerotic
7 Events (ILLUMINATE) trial⁶⁸ demonstrated that torcetrapib in association with atorvastatin significantly
8 increased the risk of MACE and all-cause mortality compared to atorvastatin in patients with history of
9 type 2 diabetes mellitus or previous cardiovascular disease. Conversely, anacetrapib – another CETP
10 inhibitor – demonstrated promising results in reducing MACE⁶⁹, while evacetrapib had a neutral effect on
11 MACE⁷⁰ when compared to placebo in patients with cardiovascular disease (Supplementary Table 3). A
12 possible explanation of the prognostic benefit of anacetrapib is the fact that, in contrast to the other CETP
13 inhibitors, this medication not only enhances reverse LDL transport, but also reduces apolipoprotein b
14 levels. On the other hand, evacetrapib and torcetrapib increase apoA1 in HDL subspecies containing
15 apoC3 and other HDL subspecies associated with increased risk of CAD; these mechanisms may explain
16 their lack of clinical benefits although they raise HDL.⁷¹

17 **Anti-inflammatory drugs**

18 Apart from lipid lowering drugs that have an established role in reducing MACE in patients with CAD,
19 recent evidence indicates that aggressive inhibition of inflammation may also improve prognosis in this
20 population.⁷² Several anti-inflammatory drugs have been introduced to inhibit vascular inflammation; the
21 lipoprotein-associated phospholipase A2 (Lp-PLA2) inhibitor Darapladib was the first drug that has been
22 evaluated in both intravascular imaging and large-scale outcome trials.

23 Darapladib

24 Darapladib is a direct inhibitor of the Lp-PLA2 which is a calcium-independent enzyme secreted by the
25 inflammatory cells (including monocyte-derived macrophages, T cells and mast cells), circulates in
26 plasma in its active form and it is primarily bound to LDL-cholesterol. Lp-PLA2 is involved in the

1 metabolism of oxidized-LDL (Supplementary Figure 2) generating potent proinflammatory mediators that
2 contribute to plaque development, progression, and destabilization by promoting foam cell formation,
3 endothelial dysfunction and apoptosis.⁷³⁻⁷⁵ Histological data⁷⁶ showed that the concentration of Lp-PLA2
4 protein is increased in TCFAs compared to smaller and more stable plaques, and there is evidence that
5 raised Lp-PLA2 plasma levels are associated with coronary events.⁷⁷

6 In the Integrated Biomarker and Imaging Study-2 (IBIS-2), 12-month therapy with darapladib had no
7 effect on TAV but it appeared to inhibit necrotic core progression, resulting in a significant difference in
8 the changes of the necrotic core volume between patients treated with darapladip and the control group at
9 follow-up (Supplementary Table 1).⁷⁸ Of note, IBIS-2 study was not powered to assess for changes in
10 TAV and composition which were secondary end-points of the study but to examine the effect of
11 darapladib on plaque deformability estimated by palpography, a modality that later was proven unreliable
12 in assessing plaque vulnerability.⁷⁹

13 The effects of darapladip on clinical outcomes were examined in the STABILITY (Stabilization of
14 Atherosclerotic Plaque by Initiation of Darapladib Therapy) trial which included 15,828 patients with
15 stable CAD randomized to darapladib or placebo who were followed up for 3.7 years.⁸⁰ Darapladib did
16 not reduce the primary composite endpoint of cardiovascular death, myocardial infarction, or stroke, but
17 decreased the rate of major and total coronary events. Similarly, the SOLID-TIMI 52 (Stabilization of
18 Plaque Using Darapladib-Thrombolysis in Myocardial Infarction 52) trial that included 13,026 patients
19 admitted with ACS showed no prognostic benefit of darapladib at 3-year follow-up (Supplementary Table
20 3).⁸¹

21 Methotrexate

22 Methotrexate is a chemotherapy agent and immune-system suppressant that inhibits the enzyme
23 dihydrofolate reductase that is essential for nucleotide synthesis. There is evidence that patients with
24 chronic inflammatory diseases such as rheumatoid or psoriatic arthritis treated with low-dose
25 methotrexate had fewer cardiovascular events than patients who received other therapies or placebo.^{82, 83}

26 Methotrexate appears to suppress YAP (yes-associated protein 1) activation that leads to a reduction in

1 the levels of inflammatory factors (e.g. IL-6, connective tissue growth factor) and adhesion molecules;
2 and through this mechanism it may inhibit atherosclerotic disease progression.⁸⁴

3 The National Institutes of Health–sponsored CIRT (Cardiovascular Inflammation Reduction Trial) that
4 included 4,786 patients who had stable atherosclerosis with diabetes mellitus or metabolic syndrome
5 reported that low-dose methotrexate did not reduce MACE (Supplementary Table 3).⁸⁵ A possible
6 explanation of this finding is the fact that low-dose methotrexate also failed to reduce the plasma levels of
7 IL-1 β , IL-6, or CRP.

8 Canakinumab

9 Canakinumab is a recombinant human monoclonal antibody that has anti-inflammatory effects by
10 selectively inhibiting IL-1 β receptor binding. IL-1 β is released following activation of the NLRP3
11 inflammasome and plays a central role in the systemic inflammatory response by increasing the
12 production of IL-6 by various cell types and driving its signalling pathway.⁸⁶ IL-6 mediates the acute
13 phase response by stimulating the liver to produce proteins for host defences, but also promotes
14 thrombosis and inhibits fibrinolysis. IL-1 β has also direct pro-atherogenic effects as it increases the
15 expression of leukocyte adhesion molecules and thrombogenic mediators and promotes smooth muscle
16 cells proliferation and endothelial cells activation.^{87, 88}

17 The CANTOS (Canakinumab Anti-Inflammatory Thrombosis Outcome Study)⁸⁹ demonstrated that in
18 patients with previous MI and evidence of ongoing sub-clinical inflammation – defined by a high-
19 sensitivity CRP ≥ 2 mg/L – inhibition of IL-1 β with canakinumab at a dose of 150mg every 3 months was
20 associated with a 15% reduction in MACE regardless of lipid-level lowering (Supplementary Table 3). A
21 subsequent analysis of the CANTOS trial found that random allocation to canakinumab compared to
22 placebo reduced the total number of serious cardiovascular events during a median of 3.7 years of follow-
23 up irrespective of the administered dose.⁹⁰ However, this drug did not have any effect on the all-cause
24 mortality compared to placebo due to a higher rate of fatal infections.⁸⁹

25

26

1 Colchicine

2 Colchicine is a unique anti-inflammatory agent with broad cellular effects. It is avidly taken up by
3 leucocytes, and binding to microtubules and interfering with their function affecting the expression of
4 cytokines and interleukins, and the ability of neutrophils to marginate, ingress, aggregate, express
5 superoxide, release neutrophil extracellular traps, and interact with platelets.⁹¹

6 In a serial angiography and IVUS study, Deftereos *et al.* demonstrated that colchicine was associated with
7 a lower incidence of binary restenosis due to a reduction in the normalised neointima volume in diabetic
8 patients treated with bare metal stents.⁹² However, there is lack of evidence on the effect of colchicine in
9 preventing coronary plaque evolution in native segments.

10 So far, four independent randomized controlled trials have evaluated the effect of colchicine in patients
11 with acute and chronic coronary syndromes (Supplementary Table 3). The Low-Dose Colchicine
12 (LoDoCo) study⁹³, which included patients with stable CAD, demonstrated a reduction in the incidence of
13 cardiovascular events in patients treated with colchicine, however this was an open-label trial involving
14 only 532 patients. The Low-Dose Colchicine 2 (LoDoCo2)⁹⁴ - a randomized, controlled, double-blind,
15 event-driven trial - enrolled 5522 patients who were randomized to placebo or colchicine 0.5mg once
16 daily and demonstrated that colchicine prevents cardiovascular events. Similarly, the Colchicine
17 Cardiovascular Outcomes Trial (COLCOT)⁹⁵ showed a reduction in the incidence of MACE by -23% in
18 patients with ACS at 2-year follow-up. Nevertheless, in contrast to the LoDoCo and COLCOT trials, the
19 Australian Colchicine in Patients with Acute Coronary Syndrome (COPS)⁹⁶ trial demonstrated that
20 colchicine did not reduce cardiovascular events at 1-year follow-up and there was a trend towards a
21 higher rate of all-cause mortality in the colchicine group compared to placebo; however, this study was
22 underpowered to assess the effect of colchicine on clinical outcome. A recent metanalysis⁹⁷ including
23 11,816 patients with CAD showed that colchicine reduced MACE rate as well as the risk of MI, stroke
24 and coronary revascularization compared to placebo, with no significant differences in all-cause mortality
25 or cardiovascular death between the two groups.

1 The above studies were important to highlight the value of colchicine in secondary prevention but also
2 had significant limitations. None of them used clinical or biological markers of inflammation for the
3 selection of participants, cholesterol levels or blood pressure at enrolment were not reported and they
4 recruited predominantly male patients. In the coming years, the CLEAR SYNERGY and the
5 COLCARDIO trial (ACTRN12616000400460) will provide additional evidence on the efficacy and long-
6 term safety of colchicine in patients with ACS.

7 **Other therapies**

8 Antihypertensive agents

9 Several antihypertensive agents, in particular angiotensin-converting enzyme (ACE) inhibitors and
10 calcium channel blockers, have been tested in intravascular imaging-based studies to investigate their role
11 in inhibiting plaque progression. The rationale behind their potential benefits in inhibiting atherosclerosis
12 might be explained by the pleiotropic effects of these drugs in addition to blood pressure reduction. For
13 instance, ACE inhibitors downregulate the pro-atherogenic effects induced by angiotensin-II that
14 increases oxidative stress, expression of inflammatory cytokines and adhesion molecules modulating
15 endothelial function as well as cellular migration and proliferation.⁹⁸ Calcium channel blockers may affect
16 smooth muscle cells proliferation and migration, increase lipid resistance to oxidative stress, and improve
17 endothelial function by inhibiting apoptosis and modulating nitric oxide expression.⁹⁹

18 The Comparison of Amlodipine vs Enalapril to Limit Occurrences of Thrombosis (CAMELOT) study
19 showed that neither amlodipine nor enalapril reduced PAV after 2 years of treatment.¹⁰⁰ In the
20 PERindopril's Prospective Effect on Coronary aTherosclerosis by Angiography and IntraVascular
21 Ultrasound Evaluation (PERSPECTIVE) study,¹⁰¹ no difference was noted between perindopril and
22 placebo in the changes in plaque area at 3-year follow-up. Similar findings were reported by the Effect of
23 Nifedipine on Coronary Endothelial Function and Plaque Formation in Patients With Coronary Artery
24 Disease (ENCORE II) study where nifedipine did not reduce PAV compared to placebo during a follow-
25 up of 18-24 months (Supplementary Table 1).¹⁰² It has to be stressed, however, that IVUS-based

1 endpoints were not the primary outcomes of these studies and thus none of them was powered to detect
2 differences in PB.

3 In line with the intravascular imaging studies, calcium channel blockers do not seem to improve outcomes
4 in patients with CAD. In the PREVENT (Prospective Randomized Evaluation of the Vascular Effects of
5 Norvasc Trial) study amlodipine 5-10mg did not reduce MACE over a 3-year follow-up period, despite
6 reducing hospital admissions for unstable angina and coronary revascularization.¹⁰³ Similarly, the
7 ACTION (A Coronary disease Trial Investigating Outcome with Nifedipine) study showed no prognostic
8 benefit of treatment with nifedipine in patients with stable CAD.¹⁰⁴ Conversely, the HOPE (Heart
9 Outcomes Prevention Evaluation)¹⁰⁵ and the EUROPA (EUropean Trial on Reduction of Cardiac Events
10 with Perindopril in stable CAD)¹⁰⁶ trials which evaluated the prognostic benefit of treatment with ramipril
11 and perindopril, respectively, showed that both drugs improve outcomes in patients with established
12 CAD. On the other hand, in the Prevention of Events with Angiotensin-Converting Enzyme inhibition
13 (PEACE) trial, trandolapril did not improve prognosis in patients with stable CAD and preserved left
14 ventricular systolic function (Supplementary Table 3).¹⁰⁷ This paradox can be explained by the fact that
15 the ACE inhibitors are not equally effective against cardiovascular disease; perindopril may be superior to
16 trandolapril in this setting as it has a beneficial effect on endothelial function.^{108, 109}

17 Antidiabetic drugs

18 The implications of oral glucose-lowering agents on PB have been investigated in IVUS-base studies. In
19 the Pioglitazone Effect on Regression of Intravascular Sonographic Coronary Obstruction Prospective
20 Evaluation (PERISCOPE) study¹¹⁰, pioglitazone was superior to glimepiride in inhibiting plaque
21 progression (PAV: -0.16% vs +0.73%, p=0.02), whereas the Assessment on the Prevention of Progression
22 by Rosiglitazone on Atherosclerosis in Diabetes Patients With Cardiovascular History (APPROACH)
23 study¹¹¹ showed no difference between the effect of rosiglitazone and glipizide on PAV (Supplementary
24 Table 1).

25 A meta-analysis showed that pioglitazone reduces the risk of MACE, stroke and MI in patients with a
26 previous history of cardiovascular disease, but it also increases the risk of heart failure.¹¹² In contrast, in a

1 sub-analysis of the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial
2 rosiglitazone did not affect MACE in patients with type 2 diabetes mellitus and established CAD.¹¹³
3 Similarly, the Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) study showed that
4 sitagliptin was not associated with a higher risk of MACE and hospitalization for heart failure when
5 added to usual care in patients with type 2 diabetes mellitus and cardiovascular disease (Supplementary
6 Table 3).¹¹⁴

7 **Discussion**

8 From the above studies, it is apparent that the pharmacotherapies which have been associated with a
9 prognostic benefit in large-scale outcome trials have a minimal but consistent effect among appropriately
10 powered intravascular imaging studies on PB, while there is limited data about their implications on
11 plaque composition. Studies assessing the effects of emerging therapies on necrotic core component, FCT
12 and macrophages accumulation have included small numbers of patients or have not been powered for
13 these endpoints; therefore, further research is needed towards this direction to fully explore the potential
14 of these intravascular imaging-based surrogate endpoints in predicting the prognostic value of novel
15 therapies.

16 Although there is a consistency between intravascular imaging and outcome studies – i.e., drugs that
17 reduce PB are associated with prognostic benefit – it seems that the changes in PB are disproportionately
18 lower than the reduction of events reported in clinical studies. This could be due to differences in
19 inclusion criteria between studies, but also to the fact that an increased PB does not necessarily indicate a
20 high-risk lesion. In the PROSPECT study¹¹, PB $\geq 70\%$ was the strongest predictor of MACE but it had a
21 low positive predictive value for events of only 9.5% in a lesion-level analysis.

22 Plaque features such as lipid burden, FTC over lipid tissue and macrophages accumulation have been
23 associated with plaque vulnerability and future events. For instance, in the PROSPECT II study¹⁰ PB and
24 composition assessed by NIRS-IVUS provided complementary information and these variables were
25 independent predictors of MACE. Similar were the findings of the CLIMA study¹⁴ where patients with

1 lesions characterized by small lumen area, increased lipid component, a thin fibrous cap over the lipid
2 tissue and macrophages infiltration were at higher risk of suffering future events.

3 It is likely that pharmacotherapies targeting coronary plaque evolution may change not only PB but also
4 its composition and reduce vascular inflammation leading to plaque passivation.

5 Multimodality-hybrid imaging for more accurate assessment of the changes in plaque phenotype

6 Over the recent years there has been a shift towards the use of multimodality imaging to better assess
7 vessel wall response to treatment with novel therapies.^{3, 4, 25, 115} However, this approach has also
8 significant limitations. Firstly, all the existing intravascular imaging modalities have limited efficacy in
9 assessing some high-risk plaque features, such as its composition, the presence of macrophages, FCT,
10 cholesterol crystals and neo-vessels (Figure 1). Secondly the co-registration of the imaging data acquired
11 by two different catheters is a challenging and tedious process that is prone to errors. Advances in hybrid
12 intravascular imaging and the design of catheters with multiple imaging probes for simultaneous data
13 acquisition are expected to overcome this limitation enabling complete and comprehensive assessment of
14 plaque composition and biology.¹¹⁵

15 Thirdly, without prospective evidence from large-scale multimodality intravascular imaging studies, there
16 are no established scores that combine different plaque features to allow more accurate quantification of
17 plaque stability. Fourthly, some of the current intravascular imaging studies focus on the changes in PB
18 and composition in the entire studied segment. This approach averages changes in PB in disease-free and
19 atherosclerotic sub-segments, whereas drug effects may be more intense; therefore, this approach is likely
20 to underestimate drug effects on plaque stabilization.^{4, 24} Future studies focusing on the changes at lesion-
21 level will allow more representative assessment of therapies on plaque vulnerability and will reduce the
22 cost of studies as they will require recruitment of a smaller number of patients to meet their primary
23 endpoints since high-risk patients have multiple plaques in the coronary tree.^{11, 116}

24 Implications of pharmacotherapies on local hemodynamic forces

25 Cumulative data have highlighted the role of endothelial shear stress in vulnerable plaque formation and
26 destabilisation showing that low shear stress promotes the formation of high-risk plaques, whereas high

1 shear stress appears to activate mechano-transduction pathways that lead to their destabilisation.^{117, 118} The
2 PREDICTION¹³ and ad hoc analyses of the PROSPECT study^{119, 120} have recently shown that shear
3 stress may be an independent predictor of plaque vulnerability and has a higher accuracy than IVUS or
4 VH-IVUS-derived variables in predicting MACE. Similarly, plaque axial and longitudinal stress also
5 provide useful prognostic information to identify lesions at risk (Figure 3).^{120, 121} Minor changes in PB and
6 composition noted in intravascular imaging studies may have a detrimental effect on shear stress
7 distribution. In the IBIS 4 study,⁴ high dose rosuvastatin therapy did not change lumen area at follow-up
8 in “segment-level analysis”, but increased lumen area in the 10mm most diseased segment by 2.5%. This
9 change is expected to affect shear stress distribution and reduce mean shear stress in this segment by
10 approximately 3.6% if there is no change in coronary flow. Likewise, a minor decrease in PB,
11 remodelling index and a necrotic core burden and especially an increase in the FCT may increase the
12 minimum stress required to cause fibrous cap destabilisation and plaque rupture.¹²² It is essential therefore
13 to focus on lesion level analysis, use multimodality imaging to thoroughly and meticulously assess the
14 effects of novel athero-protective medications on plaque morphology and examine their implications on
15 its physiology that determines plaque evolution and vulnerability.¹²³

16 Pleiotropic effects of drugs targeting atherosclerosis

17 In addition to plaque anatomy and pathophysiology, atherosclerotic evolution also depends on systemic
18 factors such as blood viscosity, platelet activity, fibrinogen levels, and the interplay between coagulation
19 and fibrinolytic system which regulate thrombus formation.^{124, 125} These pathways determine the clinical
20 consequences of plaque rupture as well as the effects of plaque erosion or the eruption of a calcific nodule
21 that constitute common causes of acute coronary events.¹⁶ Some of the tested pharmacotherapies have
22 pleiotropic effects affecting plaque evolution and also endothelial function, platelet reactivity and
23 vascular inflammation. For instance, statins not only increase the number of intimal smooth muscle cells
24 and the expression of type I procollagen, but also decrease the proliferation and activation of
25 macrophages as well as tissue factor expression in animal models.^{126, 127} Similarly, experimental studies
26 have shown that anti-PCKS9 antibodies reduce macrophages infiltration within aortic plaques and

1 increase the endothelial progenitor and circulating angiogenic cells.¹²⁸ These changes may play a key role
2 in promoting plaque healing following plaque rupture and thus reducing the risk of ACS.¹²⁹ Finally, lipid-
3 lowering drugs by reducing cholesterol levels seem also to induce collagen synthesis which is important
4 not only for the passivation of high-risk lesions but also for the healing of ruptured or eroded plaques.^{3, 130,}
5 ¹³¹ It is apparent that intravascular imaging studies cannot assess all these pleiotropic effects of novel
6 therapies on plaque biology and their prognostic implications. Therefore, outcome studies should be
7 always considered as the ultimate test for examining the potency of novel drugs.

8 **Conclusions**

9 The changes in PB which has been the traditional intravascular imaging endpoint for assessing the
10 efficacy of pharmacotherapies targeting atherosclerosis have a consistent but limited efficacy in
11 predicting their prognostic benefit. While this may reflect the pleiotropic effects of some of these drugs, it
12 also indicates that PB alone does not accurately reflect plaque vulnerability. Future studies evaluating the
13 effects of novel drugs on plaque characteristics are expected to utilize serial multimodality/hybrid
14 imaging to assess more accurately plaque morphology and incorporate physiological endpoints such as
15 shear stress and plaque stress.

16 These studies are anticipated to enrich our understanding, provide mechanistic insights about the effect of
17 drugs on atherosclerotic evolution, and fully explore the potential of intravascular imaging in predicting
18 their effect on clinical outcomes.

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26 **Conflict of Interest**

27 Nothing to disclose.

28

1 **References**

- 2 1. Hegele RA, Tsimikas S. Lipid-Lowering Agents. *Circ Res* 2019;**124**:386-404.
- 3 2. Nicholls SJ, Puri R, Anderson T, Ballantyne CM, Cho L, Kastelein JJ, Koenig W, Somaratne R,
4 Kassahun H, Yang J, Wasserman SM, Scott R, Ungi I, Podolec J, Ophuis AO, Cornel JH, Borgman
5 M, Brennan DM, Nissen SE. Effect of Evolocumab on Progression of Coronary Disease in Statin-
6 Treated Patients: The GLAGOV Randomized Clinical Trial. *JAMA* 2016;**316**:2373-2384.
- 7 3. Raber L, Koskinas KC, Yamaji K, Taniwaki M, Roffi M, Holmvang L, Garcia Garcia HM, Zanchin T,
8 Maldonado R, Moschovitis A, Pedrazzini G, Zaugg S, Dijkstra J, Matter CM, Serruys PW, Luscher
9 TF, Kelbaek H, Karagiannis A, Radu MD, Windecker S. Changes in Coronary Plaque Composition
10 in Patients With Acute Myocardial Infarction Treated With High-Intensity Statin Therapy (IBIS-4):
11 A Serial Optical Coherence Tomography Study. *JACC Cardiovasc Imaging* 2019;**12**:1518-1528.
- 12 4. Raber L, Taniwaki M, Zaugg S, Kelbaek H, Roffi M, Holmvang L, Noble S, Pedrazzini G,
13 Moschovitis A, Luscher TF, Matter CM, Serruys PW, Juni P, Garcia-Garcia HM, Windecker S,
14 Investigators IT. Effect of high-intensity statin therapy on atherosclerosis in non-infarct-related
15 coronary arteries (IBIS-4): a serial intravascular ultrasonography study. *Eur Heart J* 2015;**36**:490-
16 500.
- 17 5. Bose D, von Birgelen C, Erbel R. Intravascular ultrasound for the evaluation of therapies
18 targeting coronary atherosclerosis. *J Am Coll Cardiol* 2007;**49**:925-932.
- 19 6. Nicholls SJ, Hsu A, Wolski K, Hu B, Bayturan O, Lavoie A, Uno K, Tuzcu EM, Nissen SE.
20 Intravascular ultrasound-derived measures of coronary atherosclerotic plaque burden and
21 clinical outcome. *J Am Coll Cardiol* 2010;**55**:2399-2407.
- 22 7. Cheng JM, Garcia-Garcia HM, de Boer SP, Kardys I, Heo JH, Akkerhuis KM, Oemrawsingh RM, van
23 Domburg RT, Ligthart J, Witberg KT, Regar E, Serruys PW, van Geuns RJ, Boersma E. In vivo
24 detection of high-risk coronary plaques by radiofrequency intravascular ultrasound and
25 cardiovascular outcome: results of the ATHEROREMO-IVUS study. *Eur Heart J* 2014;**35**:639-647.
- 26 8. Oemrawsingh RM, Cheng JM, Garcia-Garcia HM, van Geuns RJ, de Boer SP, Simsek C, Kardys I,
27 Lenzen MJ, van Domburg RT, Regar E, Serruys PW, Akkerhuis KM, Boersma E, Investigators A-N.
28 Near-infrared spectroscopy predicts cardiovascular outcome in patients with coronary artery
29 disease. *J Am Coll Cardiol* 2014;**64**:2510-2518.
- 30 9. Waksman R, Di Mario C, Torguson R, Ali ZA, Singh V, Skinner WH, Artis AK, Cate TT, Powers E,
31 Kim C, Regar E, Wong SC, Lewis S, Wykrzykowska J, Dube S, Kazziha S, van der Ent M, Shah P,
32 Craig PE, Zou Q, Kolm P, Brewer HB, Garcia-Garcia HM, Investigators LRP. Identification of
33 patients and plaques vulnerable to future coronary events with near-infrared spectroscopy
34 intravascular ultrasound imaging: a prospective, cohort study. *Lancet* 2019;**394**:1629-1637.
- 35 10. Erlinge D, Maehara A, Ben-Yehuda O, Botker HE, Maeng M, Kjoller-Hansen L, Engstrom T,
36 Matsumura M, Crowley A, Dressler O, Mintz GS, Frobert O, Persson J, Wiseth R, Larsen AI,
37 Okkels Jensen L, Nordrehaug JE, Bleie O, Omerovic E, Held C, James SK, Ali ZA, Muller JE, Stone
38 GW, Investigators PI. Identification of vulnerable plaques and patients by intracoronary near-
39 infrared spectroscopy and ultrasound (PROSPECT II): a prospective natural history study. *Lancet*
40 2021;**397**:985-995.
- 41 11. Stone GW, Maehara A, Lansky AJ, de Bruyne B, Cristea E, Mintz GS, Mehran R, McPherson J,
42 Farhat N, Marso SP, Parise H, Templin B, White R, Zhang Z, Serruys PW, Investigators P. A
43 prospective natural-history study of coronary atherosclerosis. *N Engl J Med* 2011;**364**:226-235.
- 44 12. Calvert PA, Obaid DR, O'Sullivan M, Shapiro LM, McNab D, Densem CG, Schofield PM, Braganza
45 D, Clarke SC, Ray KK, West NE, Bennett MR. Association between IVUS findings and adverse
46 outcomes in patients with coronary artery disease: the VIVA (VH-IVUS in Vulnerable
47 Atherosclerosis) Study. *JACC Cardiovasc Imaging* 2011;**4**:894-901.

- 1 13. Stone PH, Saito S, Takahashi S, Makita Y, Nakamura S, Kawasaki T, Takahashi A, Katsuki T,
2 Nakamura S, Namiki A, Hirohata A, Matsumura T, Yamazaki S, Yokoi H, Tanaka S, Otsuji S,
3 Yoshimachi F, Honye J, Harwood D, Reitman M, Coskun AU, Papafaklis MI, Feldman CL,
4 Investigators P. Prediction of progression of coronary artery disease and clinical outcomes using
5 vascular profiling of endothelial shear stress and arterial plaque characteristics: the PREDICTION
6 Study. *Circulation* 2012;**126**:172-181.
- 7 14. Prati F, Romagnoli E, Gatto L, La Manna A, Burzotta F, Ozaki Y, Marco V, Boi A, Fineschi M,
8 Fabbiochi F, Taglieri N, Niccoli G, Trani C, Versaci F, Calligaris G, Ruscica G, Di Giorgio A, Vergallo
9 R, Albertucci M, Biondi-Zoccai G, Tamburino C, Crea F, Alfonso F, Arbustini E. Relationship
10 between coronary plaque morphology of the left anterior descending artery and 12 months
11 clinical outcome: the CLIMA study. *Eur Heart J* 2020;**41**:383-391.
- 12 15. Abela GS, Aziz K, Vedre A, Pathak DR, Talbott JD, Dejong J. Effect of cholesterol crystals on
13 plaques and intima in arteries of patients with acute coronary and cerebrovascular syndromes.
14 *Am J Cardiol* 2009;**103**:959-968.
- 15 16. Burke AP, Farb A, Malcom GT, Liang YH, Smialek J, Virmani R. Coronary risk factors and plaque
16 morphology in men with coronary disease who died suddenly. *N Engl J Med* 1997;**336**:1276-
17 1282.
- 18 17. Naghavi M, Libby P, Falk E, Casscells SW, Litovsky S, Rumberger J, Badimon JJ, Stefanadis C,
19 Moreno P, Pasterkamp G, Fayad Z, Stone PH, Waxman S, Raggi P, Madjid M, Zarrabi A, Burke A,
20 Yuan C, Fitzgerald PJ, Siscovick DS, de Korte CL, Aikawa M, Juhani Airaksinen KE, Assmann G,
21 Becker CR, Chesebro JH, Farb A, Galis ZS, Jackson C, Jang IK, Koenig W, Lodder RA, March K,
22 Demirovic J, Navab M, Priori SG, Rekhter MD, Bahr R, Grundy SM, Mehran R, Colombo A,
23 Boerwinkle E, Ballantyne C, Insull W, Jr., Schwartz RS, Vogel R, Serruys PW, Hansson GK, Faxon
24 DP, Kaul S, Drexler H, Greenland P, Muller JE, Virmani R, Ridker PM, Zipes DP, Shah PK, Willerson
25 JT. From vulnerable plaque to vulnerable patient: a call for new definitions and risk assessment
26 strategies: Part I. *Circulation* 2003;**108**:1664-1672.
- 27 18. Almeida SO, Budoff M. Effect of statins on atherosclerotic plaque. *Trends Cardiovasc Med*
28 2019;**29**:451-455.
- 29 19. Cholesterol Treatment Trialists C, Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, Bhalu
30 N, Peto R, Barnes EH, Keech A, Simes J, Collins R. Efficacy and safety of more intensive lowering
31 of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials.
32 *Lancet* 2010;**376**:1670-1681.
- 33 20. Nissen SE, Nicholls SJ, Sipahi I, Libby P, Raichlen JS, Ballantyne CM, Davignon J, Erbel R, Fruchart
34 JC, Tardif JC, Schoenhagen P, Crowe T, Cain V, Wolski K, Goormastic M, Tuzcu EM, Investigators
35 A. Effect of very high-intensity statin therapy on regression of coronary atherosclerosis: the
36 ASTEROID trial. *JAMA* 2006;**295**:1556-1565.
- 37 21. Nicholls SJ, Ballantyne CM, Barter PJ, Chapman MJ, Erbel RM, Libby P, Raichlen JS, Uno K,
38 Borgman M, Wolski K, Nissen SE. Effect of two intensive statin regimens on progression of
39 coronary disease. *N Engl J Med* 2011;**365**:2078-2087.
- 40 22. Puri R, Libby P, Nissen SE, Wolski K, Ballantyne CM, Barter PJ, Chapman MJ, Erbel R, Raichlen JS,
41 Uno K, Kataoka Y, Tuzcu EM, Nicholls SJ. Long-term effects of maximally intensive statin therapy
42 on changes in coronary atheroma composition: insights from SATURN. *Eur Heart J Cardiovasc*
43 *Imaging* 2014;**15**:380-388.
- 44 23. Oemrawsingh RM, Garcia-Garcia HM, van Geuns RJ, Lenzen MJ, Simsek C, de Boer SP, Van
45 Mieghem NM, Regar E, de Jaegere PP, Akkerhuis KM, Ligthart JM, Zijlstra F, Serruys PW,
46 Boersma E. Integrated Biomarker and Imaging Study 3 (IBIS-3) to assess the ability of
47 rosuvastatin to decrease necrotic core in coronary arteries. *EuroIntervention* 2016;**12**:734-739.

- 1 24. Kini AS, Baber U, Kovacic JC, Limaye A, Ali ZA, Sweeny J, Maehara A, Mehran R, Dangas G, Mintz
2 GS, Fuster V, Narula J, Sharma SK, Moreno PR. Changes in plaque lipid content after short-term
3 intensive versus standard statin therapy: the YELLOW trial (reduction in yellow plaque by
4 aggressive lipid-lowering therapy). *J Am Coll Cardiol* 2013;**62**:21-29.
- 5 25. Kini AS, Vengrenyuk Y, Shameer K, Maehara A, Purushothaman M, Yoshimura T, Matsumura M,
6 Aquino M, Haider N, Johnson KW, Readhead B, Kidd BA, Feig JE, Krishnan P, Sweeny J, Milind M,
7 Moreno P, Mehran R, Kovacic JC, Baber U, Dudley JT, Narula J, Sharma S. Intracoronary Imaging,
8 Cholesterol Efflux, and Transcriptomes After Intensive Statin Treatment: The YELLOW II Study. *J
9 Am Coll Cardiol* 2017;**69**:628-640.
- 10 26. Park SJ, Kang SJ, Ahn JM, Chang M, Yun SC, Roh JH, Lee PH, Park HW, Yoon SH, Park DW, Lee SW,
11 Kim YH, Lee CW, Mintz GS, Han KH, Park SW. Effect of Statin Treatment on Modifying Plaque
12 Composition: A Double-Blind, Randomized Study. *J Am Coll Cardiol* 2016;**67**:1772-1783.
- 13 27. Kjekshus J, Apetrei E, Barrios V, Bohm M, Cleland JG, Cornel JH, Dunselman P, Fonseca C,
14 Goudev A, Grande P, Gullestad L, Hjalmarson A, Hradec J, Janosi A, Kamensky G, Komajda M,
15 Korewicki J, Kuusi T, Mach F, Mareev V, McMurray JJ, Ranjith N, Schaufelberger M, Vanhaecke J,
16 van Veldhuisen DJ, Waagstein F, Wedel H, Wikstrand J, Group C. Rosuvastatin in older patients
17 with systolic heart failure. *N Engl J Med* 2007;**357**:2248-2261.
- 18 28. Tavazzi L, Maggioni AP, Marchioli R, Barlera S, Franzosi MG, Latini R, Lucci D, Nicolosi GL, Porcu
19 M, Tognoni G, Gissi HFI. Effect of rosuvastatin in patients with chronic heart failure (the GISSI-HF
20 trial): a randomised, double-blind, placebo-controlled trial. *Lancet* 2008;**372**:1231-1239.
- 21 29. Feinstein MJ, Jhund P, Kang J, Ning H, Maggioni A, Wikstrand J, Kjekshus J, Tavazzi L, McMurray
22 J, Lloyd-Jones DM. Do statins reduce the risk of myocardial infarction in patients with heart
23 failure? A pooled individual-level reanalysis of CORONA and GISSI-HF. *Eur J Heart Fail*
24 2015;**17**:434-441.
- 25 30. Nissen SE, Tuzcu EM, Schoenhagen P, Brown BG, Ganz P, Vogel RA, Crowe T, Howard G, Cooper
26 CJ, Brodie B, Grines CL, DeMaria AN, Investigators R. Effect of intensive compared with
27 moderate lipid-lowering therapy on progression of coronary atherosclerosis: a randomized
28 controlled trial. *JAMA* 2004;**291**:1071-1080.
- 29 31. Hiro T, Kimura T, Morimoto T, Miyauchi K, Nakagawa Y, Yamagishi M, Ozaki Y, Kimura K, Saito S,
30 Yamaguchi T, Daida H, Matsuzaki M, Investigators J-A. Effect of intensive statin therapy on
31 regression of coronary atherosclerosis in patients with acute coronary syndrome: a multicenter
32 randomized trial evaluated by volumetric intravascular ultrasound using pitavastatin versus
33 atorvastatin (JAPAN-ACS [Japan assessment of pitavastatin and atorvastatin in acute coronary
34 syndrome] study). *J Am Coll Cardiol* 2009;**54**:293-302.
- 35 32. Lee CW, Kang SJ, Ahn JM, Song HG, Lee JY, Kim WJ, Park DW, Lee SW, Kim YH, Park SW, Park SJ.
36 Comparison of effects of atorvastatin (20 mg) versus rosuvastatin (10 mg) therapy on mild
37 coronary atherosclerotic plaques (from the ARTMAP trial). *Am J Cardiol* 2012;**109**:1700-1704.
- 38 33. Komukai K, Kubo T, Kitabata H, Matsuo Y, Ozaki Y, Takarada S, Okumoto Y, Shiono Y, Orii M,
39 Shimamura K, Ueno S, Yamano T, Tanimoto T, Ino Y, Yamaguchi T, Kumiko H, Tanaka A, Imanishi
40 T, Akagi H, Akasaka T. Effect of atorvastatin therapy on fibrous cap thickness in coronary
41 atherosclerotic plaque as assessed by optical coherence tomography: the EASY-FIT study. *J Am
42 Coll Cardiol* 2014;**64**:2207-2217.
- 43 34. Cannon CP, Braunwald E, McCabe CH, Rader DJ, Rouleau JL, Belder R, Joyal SV, Hill KA, Pfeffer
44 MA, Skene AM, Pravastatin or Atorvastatin E, Infection Therapy-Thrombolysis in Myocardial
45 Infarction I. Intensive versus moderate lipid lowering with statins after acute coronary
46 syndromes. *N Engl J Med* 2004;**350**:1495-1504.

- 1 35. LaRosa JC, Grundy SM, Waters DD, Shear C, Barter P, Fruchart JC, Gotto AM, Greten H, Kastelein
2 JJ, Shepherd J, Wenger NK, Treating to New Targets I. Intensive lipid lowering with atorvastatin
3 in patients with stable coronary disease. *N Engl J Med* 2005;**352**:1425-1435.
- 4 36. Nozue T, Yamamoto S, Tohyama S, Umezawa S, Kunishima T, Sato A, Miyake S, Takeyama Y,
5 Morino Y, Yamauchi T, Muramatsu T, Hibi K, Sozu T, Terashima M, Michishita I. Statin treatment
6 for coronary artery plaque composition based on intravascular ultrasound radiofrequency data
7 analysis. *Am Heart J* 2012;**163**:191-199 e191.
- 8 37. Sacks FM, Pfeffer MA, Moye LA, Rouleau JL, Rutherford JD, Cole TG, Brown L, Warnica JW,
9 Arnold JM, Wun CC, Davis BR, Braunwald E. The effect of pravastatin on coronary events after
10 myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent
11 Events Trial investigators. *N Engl J Med* 1996;**335**:1001-1009.
- 12 38. Long-Term Intervention with Pravastatin in Ischaemic Disease Study G. Prevention of
13 cardiovascular events and death with pravastatin in patients with coronary heart disease and a
14 broad range of initial cholesterol levels. *N Engl J Med* 1998;**339**:1349-1357.
- 15 39. Niedzielski M, Broncel M, Gorzelak-Pabis P, Wozniak E. New possible pharmacological targets for
16 statins and ezetimibe. *Biomed Pharmacother* 2020;**129**:110388.
- 17 40. Sudhop T, Lutjohann D, Kodal A, Igel M, Tribble DL, Shah S, Perevozskaya I, von Bergmann K.
18 Inhibition of intestinal cholesterol absorption by ezetimibe in humans. *Circulation*
19 **2002**;**106**:1943-1948.
- 20 41. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, Chapman MJ, De Backer GG,
21 Delgado V, Ference BA, Graham IM, Halliday A, Landmesser U, Mihaylova B, Pedersen TR,
22 Riccardi G, Richter DJ, Sabatine MS, Taskinen MR, Tokgozoglul L, Wiklund O, Group ESCSD. 2019
23 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce
24 cardiovascular risk. *Eur Heart J* 2020;**41**:111-188.
- 25 42. Tsujita K, Sugiyama S, Sumida H, Shimomura H, Yamashita T, Yamanaga K, Komura N, Sakamoto
26 K, Oka H, Nakao K, Nakamura S, Ishihara M, Matsui K, Sakaino N, Nakamura N, Yamamoto N,
27 Koide S, Matsumura T, Fujimoto K, Tsunoda R, Morikami Y, Matsuyama K, Oshima S, Kaikita K,
28 Hokimoto S, Ogawa H, Investigators P-I. Impact of Dual Lipid-Lowering Strategy With Ezetimibe
29 and Atorvastatin on Coronary Plaque Regression in Patients With Percutaneous Coronary
30 Intervention: The Multicenter Randomized Controlled PRECISE-IVUS Trial. *J Am Coll Cardiol*
31 **2015**;**66**:495-507.
- 32 43. Mirzaee S, Thein PM, Nagic J, Nerlekar N, Nasis A, Brown AJ. The effect of combined ezetimibe
33 and statin therapy versus statin therapy alone on coronary plaque volume assessed by
34 intravascular ultrasound: A systematic review and meta-analysis. *Journal of clinical lipidology*
35 **2018**;**12**:1133-1140.e1115.
- 36 44. Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, Darius H, Lewis BS,
37 Ophuis TO, Jukema JW, De Ferrari GM, Ruzyllo W, De Lucca P, Im K, Bohula EA, Reist C, Wiviott
38 SD, Tershakovec AM, Musliner TA, Braunwald E, Califf RM, Investigators I-I. Ezetimibe Added to
39 Statin Therapy after Acute Coronary Syndromes. *N Engl J Med* 2015;**372**:2387-2397.
- 40 45. Hagiwara N, Kawada-Watanabe E, Koyanagi R, Arashi H, Yamaguchi J, Nakao K, Tobaru T, Tanaka
41 H, Oka T, Endoh Y, Saito K, Uchida T, Matsui K, Ogawa H. Low-density lipoprotein cholesterol
42 targeting with pitavastatin + ezetimibe for patients with acute coronary syndrome and
43 dyslipidaemia: the HIJ-PROPER study, a prospective, open-label, randomized trial. *Eur Heart J*
44 **2017**;**38**:2264-2276.
- 45 46. Robinson JG, Farnier M, Krempf M, Bergeron J, Luc G, Averna M, Stroes ES, Langslet G, Raal FJ, El
46 Shahawy M, Koren MJ, Lepor NE, Lorenzato C, Pordy R, Chaudhari U, Kastelein JJ, Investigators
47 OLT. Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. *N Engl J Med*
48 **2015**;**372**:1489-1499.

- 1 47. Sabatine MS, Giugliano RP, Wiviott SD, Raal FJ, Blom DJ, Robinson J, Ballantyne CM, Somaratne
2 R, Legg J, Wasserman SM, Scott R, Koren MJ, Stein EA, Open-Label Study of Long-Term
3 Evaluation against LDLCI. Efficacy and safety of evolocumab in reducing lipids and cardiovascular
4 events. *N Engl J Med* 2015;**372**:1500-1509.
- 5 48. Ragusa R, Basta G, Neglia D, De Caterina R, Del Turco S, Caselli C. PCSK9 and atherosclerosis:
6 Looking beyond LDL regulation. *Eur J Clin Invest* 2021;**51**:e13459.
- 7 49. Nicholls SJ, Puri R, Anderson T, Ballantyne CM, Cho L, Kastelein JJP, Koenig W, Somaratne R,
8 Kassahun H, Yang J, Wasserman SM, Honda S, Shishikura D, Scherer DJ, Borgman M, Brennan
9 DM, Wolski K, Nissen SE. Effect of Evolocumab on Coronary Plaque Composition. *J Am Coll
10 Cardiol* 2018;**72**:2012-2021.
- 11 50. Ako J, Hibi K, Tsujita K, Hiro T, Morino Y, Kozuma K, Shinke T, Otake H, Uno K, Louie MJ, Takagi Y,
12 Miyauchi K. Effect of Alirocumab on Coronary Atheroma Volume in Japanese Patients With
13 Acute Coronary Syndrome- The ODYSSEY J-IVUS Trial. *Circ J* 2019;**83**:2025-2033.
- 14 51. Sugizaki Y, Otake H, Kawamori H, Toba T, Nagano Y, Tsukiyama Y, Yanaka KI, Yamamoto H,
15 Nagasawa A, Onishi H, Takeshige R, Nakano S, Matsuoka Y, Tanimura K, Takahashi Y, Fukuyama
16 Y, Shinke T, Ishida T, Hirata KI. Adding Alirocumab to Rosuvastatin Helps Reduce the
17 Vulnerability of Thin-Cap Fibroatheroma: An ALTAIR Trial Report. *JACC Cardiovasc Imaging*
18 2020;**13**:1452-1454.
- 19 52. Ota H, Omori H, Kawasaki M, Hirakawa A, Matsuo H. Clinical impact of PCSK9 inhibitor on
20 stabilization and regression of lipid-rich coronary plaques: a near-infrared spectroscopy study.
21 *Eur Heart J Cardiovasc Imaging* 2021.
- 22 53. Nicholls SJ, Nissen SE, Prati F, Windecker S, Kataoka Y, Puri R, Hucko T, Kassahun H, Liao J,
23 Somaratne R, Butters J, Di Giovanni G, Jones S, Psaltis PJ. Assessing the impact of PCSK9
24 inhibition on coronary plaque phenotype with optical coherence tomography: rationale and
25 design of the randomized, placebo-controlled HUYGENS study. *Cardiovasc Diagn Ther*
26 2021;**11**:120-129.
- 27 54. Zanchin C, Koskinas KC, Ueki Y, Losdat S, Haner JD, Bar S, Otsuka T, Inderkum A, Jensen MRJ,
28 Lonborg J, Fahrni G, Ondracek AS, Daemen J, van Geuns RJ, Iglesias JF, Matter CM, Spirk D, Juni
29 P, Mach F, Heg D, Engstrom T, Lang I, Windecker S, Raber L. Effects of the PCSK9 antibody
30 alirocumab on coronary atherosclerosis in patients with acute myocardial infarction: a serial,
31 multivessel, intravascular ultrasound, near-infrared spectroscopy and optical coherence
32 tomography imaging study-Rationale and design of the PACMAN-AMI trial. *Am Heart J*
33 2021;**238**:33-44.
- 34 55. Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, Kuder JF, Wang H,
35 Liu T, Wasserman SM, Sever PS, Pedersen TR, Committee FS, Investigators. Evolocumab and
36 Clinical Outcomes in Patients with Cardiovascular Disease. *N Engl J Med* 2017;**376**:1713-1722.
- 37 56. Schwartz GG, Steg PG, Szarek M, Bhatt DL, Bittner VA, Diaz R, Edelberg JM, Goodman SG,
38 Hanotin C, Harrington RA, Jukema JW, Lecorps G, Mahaffey KW, Moryusef A, Pordy R, Quintero
39 K, Roe MT, Sasiela WJ, Tamby JF, Tricoci P, White HD, Zeiher AM, Committees OO, Investigators.
40 Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome. *N Engl J Med*
41 2018;**379**:2097-2107.
- 42 57. Tardy C, Goffinet M, Boubekeur N, Ackermann R, Sy G, Bluteau A, Cholez G, Keyserling C,
43 Lalwani N, Paolini JF, Dasseux JL, Barbaras R, Baron R. CER-001, a HDL-mimetic, stimulates the
44 reverse lipid transport and atherosclerosis regression in high cholesterol diet-fed LDL-receptor
45 deficient mice. *Atherosclerosis* 2014;**232**:110-118.
- 46 58. Badimon JJ, Badimon L, Galvez A, Dische R, Fuster V. High density lipoprotein plasma fractions
47 inhibit aortic fatty streaks in cholesterol-fed rabbits. *Lab Invest* 1989;**60**:455-461.

- 1 59. Nicholls SJ, Cutri B, Worthley SG, Kee P, Rye KA, Bao S, Barter PJ. Impact of short-term
2 administration of high-density lipoproteins and atorvastatin on atherosclerosis in rabbits.
3 *Arterioscler Thromb Vasc Biol* 2005;**25**:2416-2421.
- 4 60. Nissen SE, Tsunoda T, Tuzcu EM, Schoenhagen P, Cooper CJ, Yasin M, Eaton GM, Lauer MA,
5 Sheldon WS, Grines CL, Halpern S, Crowe T, Blankenship JC, Kerensky R. Effect of recombinant
6 ApoA-I Milano on coronary atherosclerosis in patients with acute coronary syndromes: a
7 randomized controlled trial. *JAMA* 2003;**290**:2292-2300.
- 8 61. Nicholls SJ, Andrews J, Kastelein JJP, Merkely B, Nissen SE, Ray KK, Schwartz GG, Worthley SG,
9 Keyserling C, Dasseux JL, Griffith L, Kim SW, Janssan A, Di Giovanni G, Pisaniello AD, Scherer DJ,
10 Psaltis PJ, Butters J. Effect of Serial Infusions of CER-001, a Pre-beta High-Density Lipoprotein
11 Mimetic, on Coronary Atherosclerosis in Patients Following Acute Coronary Syndromes in the
12 CER-001 Atherosclerosis Regression Acute Coronary Syndrome Trial: A Randomized Clinical Trial.
13 *JAMA Cardiol* 2018;**3**:815-822.
- 14 62. Nicholls SJ, Puri R, Ballantyne CM, Jukema JW, Kastelein JJP, Koenig W, Wright RS, Kallend D,
15 Wijngaard P, Borgman M, Wolski K, Nissen SE. Effect of Infusion of High-Density Lipoprotein
16 Mimetic Containing Recombinant Apolipoprotein A-I Milano on Coronary Disease in Patients
17 With an Acute Coronary Syndrome in the MILANO-PILOT Trial: A Randomized Clinical Trial. *JAMA*
18 *Cardiol* 2018;**3**:806-814.
- 19 63. Tardif JC, Ballantyne CM, Barter P, Dasseux JL, Fayad ZA, Guertin MC, Kastelein JJ, Keyserling C,
20 Klepp H, Koenig W, L'Allier PL, Lesperance J, Luscher TF, Paolini JF, Tawakol A, Waters DD, Can
21 HDLISQARI. Effects of the high-density lipoprotein mimetic agent CER-001 on coronary
22 atherosclerosis in patients with acute coronary syndromes: a randomized trial. *Eur Heart J*
23 2014;**35**:3277-3286.
- 24 64. Tardif JC, Gregoire J, L'Allier PL, Ibrahim R, Lesperance J, Heinonen TM, Kouz S, Berry C, Bassier R,
25 Lavoie MA, Guertin MC, Rodes-Cabau J, Effect of r HDLoA-S, Efficacy I. Effects of reconstituted
26 high-density lipoprotein infusions on coronary atherosclerosis: a randomized controlled trial.
27 *JAMA* 2007;**297**:1675-1682.
- 28 65. Gibson CM, Kastelein JJP, Phillips AT, Aylward PE, Yee MK, Tendera M, Nicholls SJ, Pocock S,
29 Goodman SG, Alexander JH, Lincoff AM, Bode C, Duffy D, Heise M, Berman G, Mears SJ, Tricoci
30 P, Deckelbaum LI, Steg PG, Ridker P, Mehran R. Rationale and design of ApoA-I Event Reducing
31 in Ischemic Syndromes II (AEGIS-II): A phase 3, multicenter, double-blind, randomized, placebo-
32 controlled, parallel-group study to investigate the efficacy and safety of CSL112 in subjects after
33 acute myocardial infarction. *Am Heart J* 2021;**231**:121-127.
- 34 66. Armitage J, Holmes MV, Preiss D. Cholesteryl Ester Transfer Protein Inhibition for Preventing
35 Cardiovascular Events: JACC Review Topic of the Week. *J Am Coll Cardiol* 2019;**73**:477-487.
- 36 67. Nissen SE, Tardif JC, Nicholls SJ, Revkin JH, Shear CL, Duggan WT, Ruzyllo W, Bachinsky WB,
37 Lasala GP, Tuzcu EM, Investigators I. Effect of torcetrapib on the progression of coronary
38 atherosclerosis. *N Engl J Med* 2007;**356**:1304-1316.
- 39 68. Barter PJ, Caulfield M, Eriksson M, Grundy SM, Kastelein JJ, Komajda M, Lopez-Sendon J, Mosca
40 L, Tardif JC, Waters DD, Shear CL, Revkin JH, Buhr KA, Fisher MR, Tall AR, Brewer B, Investigators
41 I. Effects of torcetrapib in patients at high risk for coronary events. *N Engl J Med* 2007;**357**:2109-
42 2122.
- 43 69. Group HTRC, Bowman L, Hopewell JC, Chen F, Wallendszus K, Stevens W, Collins R, Wiviott SD,
44 Cannon CP, Braunwald E, Sammons E, Landray MJ. Effects of Anacetrapib in Patients with
45 Atherosclerotic Vascular Disease. *N Engl J Med* 2017;**377**:1217-1227.
- 46 70. Lincoff AM, Nicholls SJ, Riesmeyer JS, Barter PJ, Brewer HB, Fox KAA, Gibson CM, Granger C,
47 Menon V, Montalescot G, Rader D, Tall AR, McErlean E, Wolski K, Ruotolo G, Vangerow B,
48 Weerakkody G, Goodman SG, Conde D, McGuire DK, Nicolau JC, Leiva-Pons JL, Pesant Y, Li W,

- 1 Kandath D, Kouz S, Tahirkheli N, Mason D, Nissen SE, Investigators A. Evacetrapib and
 2 Cardiovascular Outcomes in High-Risk Vascular Disease. *N Engl J Med* 2017;**376**:1933-1942.
- 3 71. Furtado JD, Ruotolo G, Nicholls SJ, Dullea R, Carvajal-Gonzalez S, Sacks FM. Pharmacological
 4 Inhibition of CETP (Cholesteryl Ester Transfer Protein) Increases HDL (High-Density Lipoprotein)
 5 That Contains ApoC3 and Other HDL Subspecies Associated With Higher Risk of Coronary Heart
 6 Disease. *Arterioscler Thromb Vasc Biol* 2021:ATVBHA121317181.
- 7 72. Lawler PR, Bhatt DL, Godoy LC, Luscher TF, Bonow RO, Verma S, Ridker PM. Targeting
 8 cardiovascular inflammation: next steps in clinical translation. *Eur Heart J* 2021;**42**:113-131.
- 9 73. Mohler ER, 3rd, Ballantyne CM, Davidson MH, Hanefeld M, Ruilope LM, Johnson JL, Zalewski A,
 10 Darapladib I. The effect of darapladib on plasma lipoprotein-associated phospholipase A2
 11 activity and cardiovascular biomarkers in patients with stable coronary heart disease or
 12 coronary heart disease risk equivalent: the results of a multicenter, randomized, double-blind,
 13 placebo-controlled study. *J Am Coll Cardiol* 2008;**51**:1632-1641.
- 14 74. Mallat Z, Lambeau G, Tedgui A. Lipoprotein-associated and secreted phospholipases A(2) in
 15 cardiovascular disease: roles as biological effectors and biomarkers. *Circulation* 2010;**122**:2183-
 16 2200.
- 17 75. Rosenson RS, Stafforini DM. Modulation of oxidative stress, inflammation, and atherosclerosis
 18 by lipoprotein-associated phospholipase A2. *J Lipid Res* 2012;**53**:1767-1782.
- 19 76. Kolodgie FD, Burke AP, Skorija KS, Ladich E, Kutys R, Makuria AT, Virmani R. Lipoprotein-
 20 associated phospholipase A2 protein expression in the natural progression of human coronary
 21 atherosclerosis. *Arterioscler Thromb Vasc Biol* 2006;**26**:2523-2529.
- 22 77. Lp PLASC, Thompson A, Gao P, Orfei L, Watson S, Di Angelantonio E, Kaptoge S, Ballantyne C,
 23 Cannon CP, Criqui M, Cushman M, Hofman A, Packard C, Thompson SG, Collins R, Danesh J.
 24 Lipoprotein-associated phospholipase A(2) and risk of coronary disease, stroke, and mortality:
 25 collaborative analysis of 32 prospective studies. *Lancet* 2010;**375**:1536-1544.
- 26 78. Serruys PW, Garcia-Garcia HM, Buszman P, Erne P, Verheye S, Aschermann M, Duckers H, Bleie
 27 O, Dudek D, Botker HE, von Birgelen C, D'Amico D, Hutchinson T, Zambanini A, Mastik F, van Es
 28 GA, van der Steen AF, Vince DG, Ganz P, Hamm CW, Wijns W, Zalewski A, Integrated B, Imaging
 29 Study I. Effects of the direct lipoprotein-associated phospholipase A(2) inhibitor darapladib on
 30 human coronary atherosclerotic plaque. *Circulation* 2008;**118**:1172-1182.
- 31 79. Brugaletta S, Garcia-Garcia HM, Serruys PW, Maehara A, Farooq V, Mintz GS, de Bruyne B,
 32 Marso SP, Verheye S, Dudek D, Hamm CW, Farhat N, Schiele F, McPherson J, Lerman A, Moreno
 33 PR, Wennerblom B, Fahy M, Templin B, Morel MA, van Es GA, Stone GW. Relationship between
 34 palpography and virtual histology in patients with acute coronary syndromes. *JACC Cardiovasc*
 35 *Imaging* 2012;**5**:S19-27.
- 36 80. Investigators S, White HD, Held C, Stewart R, Tarka E, Brown R, Davies RY, Budaj A, Harrington
 37 RA, Steg PG, Ardissino D, Armstrong PW, Avezum A, Aylward PE, Bryce A, Chen H, Chen MF,
 38 Corbalan R, Dalby AJ, Danchin N, De Winter RJ, Denchev S, Diaz R, Elisaf M, Flather MD, Goudev
 39 AR, Granger CB, Grinfeld L, Hochman JS, Husted S, Kim HS, Koenig W, Linhart A, Lonn E, Lopez-
 40 Sendon J, Manolis AJ, Mohler ER, 3rd, Nicolau JC, Pais P, Parkhomenko A, Pedersen TR, Pella D,
 41 Ramos-Corrales MA, Ruda M, Sereg M, Siddique S, Sinnaeve P, Smith P, Sritara P, Swart HP, Sy
 42 RG, Teramoto T, Tse HF, Watson D, Weaver WD, Weiss R, Viigimaa M, Vinereanu D, Zhu J,
 43 Cannon CP, Wallentin L. Darapladib for preventing ischemic events in stable coronary heart
 44 disease. *N Engl J Med* 2014;**370**:1702-1711.
- 45 81. O'Donoghue ML, Braunwald E, White HD, Lukas MA, Tarka E, Steg PG, Hochman JS, Bode C,
 46 Maggioni AP, Im K, Shannon JB, Davies RY, Murphy SA, Crugnale SE, Wiviott SD, Bonaca MP,
 47 Watson DF, Weaver WD, Serruys PW, Cannon CP, Investigators S-T, Steen DL. Effect of

- 1 darapladib on major coronary events after an acute coronary syndrome: the SOLID-TIMI 52
 2 randomized clinical trial. *JAMA* 2014;**312**:1006-1015.
- 3 82. Westlake SL, Colebatch AN, Baird J, Kiely P, Quinn M, Choy E, Ostor AJ, Edwards CJ. The effect of
 4 methotrexate on cardiovascular disease in patients with rheumatoid arthritis: a systematic
 5 literature review. *Rheumatology (Oxford)* 2010;**49**:295-307.
- 6 83. Micha R, Imamura F, Wyler von Ballmoos M, Solomon DH, Hernan MA, Ridker PM, Mozaffarian
 7 D. Systematic review and meta-analysis of methotrexate use and risk of cardiovascular disease.
 8 *Am J Cardiol* 2011;**108**:1362-1370.
- 9 84. Liu D, Lv H, Liu Q, Sun Y, Hou S, Zhang L, Yang M, Han B, Wang G, Wang X, Du W, Nie H, Zhang R,
 10 Huang X, Hou J, Yu B. Atheroprotective effects of methotrexate via the inhibition of YAP/TAZ
 11 under disturbed flow. *J Transl Med* 2019;**17**:378.
- 12 85. Ridker PM, Everett BM, Pradhan A, MacFadyen JG, Solomon DH, Zaharris E, Mam V, Hasan A,
 13 Rosenberg Y, Iturriaga E, Gupta M, Tsigoulis M, Verma S, Clearfield M, Libby P, Goldhaber SZ,
 14 Seagle R, Ofori C, Saklayen M, Butman S, Singh N, Le May M, Bertrand O, Johnston J, Paynter NP,
 15 Glynn RJ, Investigators C. Low-Dose Methotrexate for the Prevention of Atherosclerotic Events.
 16 *N Engl J Med* 2019;**380**:752-762.
- 17 86. Swanson KV, Deng M, Ting JP. The NLRP3 inflammasome: molecular activation and regulation to
 18 therapeutics. *Nat Rev Immunol* 2019;**19**:477-489.
- 19 87. Libby P. Interleukin-1 Beta as a Target for Atherosclerosis Therapy: Biological Basis of CANTOS
 20 and Beyond. *J Am Coll Cardiol* 2017;**70**:2278-2289.
- 21 88. Ridker PM, Rane M. Interleukin-6 Signaling and Anti-Interleukin-6 Therapeutics in Cardiovascular
 22 Disease. *Circ Res* 2021;**128**:1728-1746.
- 23 89. Ridker PM, Everett BM, Thuren T, MacFadyen JG, Chang WH, Ballantyne C, Fonseca F, Nicolau J,
 24 Koenig W, Anker SD, Kastelein JJP, Cornel JH, Pais P, Pella D, Genest J, Cifkova R, Lorenzatti A,
 25 Forster T, Kobalava Z, Vida-Simiti L, Flather M, Shimokawa H, Ogawa H, Dellborg M, Rossi PRF,
 26 Troquay RPT, Libby P, Glynn RJ, Group CT. Antiinflammatory Therapy with Canakinumab for
 27 Atherosclerotic Disease. *N Engl J Med* 2017;**377**:1119-1131.
- 28 90. Everett BM, MacFadyen JG, Thuren T, Libby P, Glynn RJ, Ridker PM. Inhibition of Interleukin-
 29 1beta and Reduction in Atherothrombotic Cardiovascular Events in the CANTOS Trial. *J Am Coll*
 30 *Cardiol* 2020;**76**:1660-1670.
- 31 91. Imazio M, Nidorf M. Colchicine and the heart. *Eur Heart J* 2021;**42**:2745-2760.
- 32 92. Deftereos S, Giannopoulos G, Raisakis K, Kossyvakis C, Kaoukis A, Panagopoulou V, Driva M,
 33 Hahalis G, Pyrgakis V, Alexopoulos D, Manolis AS, Stefanadis C, Cleman MW. Colchicine
 34 treatment for the prevention of bare-metal stent restenosis in diabetic patients. *J Am Coll*
 35 *Cardiol* 2013;**61**:1679-1685.
- 36 93. Nidorf SM, Eikelboom JW, Budgeon CA, Thompson PL. Low-dose colchicine for secondary
 37 prevention of cardiovascular disease. *J Am Coll Cardiol* 2013;**61**:404-410.
- 38 94. Nidorf SM, Fiolet ATL, Mosterd A, Eikelboom JW, Schut A, Opstal TSJ, The SHK, Xu XF, Ireland
 39 MA, Lenderink T, Latchem D, Hoogslag P, Jerzewski A, Nierop P, Whelan A, Hendriks R, Swart H,
 40 Schaap J, Kuijper AFM, van Hessen MWJ, Saklani P, Tan I, Thompson AG, Morton A, Judkins C,
 41 Bax WA, Dirksen M, Alings M, Hankey GJ, Budgeon CA, Tijssen JGP, Cornel JH, Thompson PL,
 42 LoDoCo2 Trial I. Colchicine in Patients with Chronic Coronary Disease. *N Engl J Med*
 43 2020;**383**:1838-1847.
- 44 95. Tardif JC, Kouz S, Waters DD, Bertrand OF, Diaz R, Maggioni AP, Pinto FJ, Ibrahim R, Gamra H,
 45 Kiwan GS, Berry C, Lopez-Sendon J, Ostadal P, Koenig W, Angoulvant D, Gregoire JC, Lavoie MA,
 46 Dube MP, Rhoads D, Provencher M, Blondeau L, Orfanos A, L'Allier PL, Guertin MC, Roubille F.
 47 Efficacy and Safety of Low-Dose Colchicine after Myocardial Infarction. *N Engl J Med*
 48 2019;**381**:2497-2505.

- 1 96. Tong DC, Quinn S, Nasis A, Hiew C, Roberts-Thomson P, Adams H, Sriamaweswaran R, Htun NM,
2 Wilson W, Stub D, van Gaal W, Howes L, Collins N, Yong A, Bhindi R, Whitbourn R, Lee A, Hengel
3 C, Asress K, Freeman M, Amerena J, Wilson A, Layland J. Colchicine in Patients With Acute
4 Coronary Syndrome: The Australian COPS Randomized Clinical Trial. *Circulation* 2020;**142**:1890-
5 1900.
- 6 97. Fiolet ATL, Opstal TSJ, Mosterd A, Eikelboom JW, Jolly SS, Keech AC, Kelly P, Tong DC, Layland J,
7 Nidorf SM, Thompson PL, Budgeon C, Tijssen JGP, Cornel JH. Efficacy and safety of low-dose
8 colchicine in patients with coronary disease: a systematic review and meta-analysis of
9 randomized trials. *Eur Heart J* 2021;**42**:2765-2775.
- 10 98. Silva GM, Franca-Falcao MS, Calzerra NTM, Luz MS, Gadelha DDA, Balarini CM, Queiroz TM. Role
11 of Renin-Angiotensin System Components in Atherosclerosis: Focus on Ang-II, ACE2, and Ang-1-
12 7. *Front Physiol* 2020;**11**:1067.
- 13 99. Mason RP. Mechanisms of plaque stabilization for the dihydropyridine calcium channel blocker
14 amlodipine: review of the evidence. *Atherosclerosis* 2002;**165**:191-199.
- 15 100. Nissen SE, Tuzcu EM, Libby P, Thompson PD, Ghali M, Garza D, Berman L, Shi H, Buebendorf E,
16 Topol EJ, Investigators C. Effect of antihypertensive agents on cardiovascular events in patients
17 with coronary disease and normal blood pressure: the CAMELOT study: a randomized controlled
18 trial. *JAMA* 2004;**292**:2217-2225.
- 19 101. Rodriguez-Granillo GA, Vos J, Bruining N, Garcia-Garcia HM, de Winter S, Ligthart JM, Deckers
20 JW, Bertrand M, Simoons ML, Ferrari R, Fox KM, Remme W, De Feyter PJ, Investigators of the ES.
21 Long-term effect of perindopril on coronary atherosclerosis progression (from the perindopril's
22 prospective effect on coronary atherosclerosis by angiography and intravascular ultrasound
23 evaluation [PERSPECTIVE] study). *Am J Cardiol* 2007;**100**:159-163.
- 24 102. Luscher TF, Pieper M, Tendera M, Vrolix M, Rutsch W, van den Branden F, Gil R, Bischoff KO,
25 Haude M, Fischer D, Meinertz T, Munzel T. A randomized placebo-controlled study on the effect
26 of nifedipine on coronary endothelial function and plaque formation in patients with coronary
27 artery disease: the ENCORE II study. *Eur Heart J* 2009;**30**:1590-1597.
- 28 103. Pitt B, Byington RP, Furberg CD, Hunninghake DB, Mancini GB, Miller ME, Riley W. Effect of
29 amlodipine on the progression of atherosclerosis and the occurrence of clinical events. PREVENT
30 Investigators. *Circulation* 2000;**102**:1503-1510.
- 31 104. Poole-Wilson PA, Lubsen J, Kirwan BA, van Dalen FJ, Wagener G, Danchin N, Just H, Fox KA,
32 Pocock SJ, Clayton TC, Motro M, Parker JD, Bourassa MG, Dart AM, Hildebrandt P, Hjalmarsen A,
33 Kragten JA, Molhoek GP, Otterstad JE, Seabra-Gomes R, Soler-Soler J, Weber S, Coronary disease
34 Trial Investigating Outcome with Nifedipine gastrointestinal therapeutic system i. Effect of long-
35 acting nifedipine on mortality and cardiovascular morbidity in patients with stable angina
36 requiring treatment (ACTION trial): randomised controlled trial. *Lancet* 2004;**364**:849-857.
- 37 105. Heart Outcomes Prevention Evaluation Study I, Yusuf S, Sleight P, Pogue J, Bosch J, Davies R,
38 Dagenais G. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular
39 events in high-risk patients. *N Engl J Med* 2000;**342**:145-153.
- 40 106. Fox KM, Investigators EUtOrocewPiscAd. Efficacy of perindopril in reduction of cardiovascular
41 events among patients with stable coronary artery disease: randomised, double-blind, placebo-
42 controlled, multicentre trial (the EUROPA study). *Lancet* 2003;**362**:782-788.
- 43 107. Braunwald E, Domanski MJ, Fowler SE, Geller NL, Gersh BJ, Hsia J, Pfeffer MA, Rice MM,
44 Rosenberg YD, Rouleau JL, Investigators PT. Angiotensin-converting-enzyme inhibition in stable
45 coronary artery disease. *N Engl J Med* 2004;**351**:2058-2068.
- 46 108. Bots ML, Remme WJ, Luscher TF, Fox KM, Bertrand M, Ferrari R, Simoons ML, Grobbee DE,
47 Investigators E-P. ACE inhibition and endothelial function: main findings of PERFECT, a sub-study
48 of the EUROPA trial. *Cardiovasc Drugs Ther* 2007;**21**:269-279.

- 1 109. Ceconi C, Fox KM, Remme WJ, Simoons ML, Bertrand M, Parrinello G, Kluft C, Blann A, Cokkinos
2 D, Ferrari R, Investigators E, Investigators P, the Statistical C. ACE inhibition with perindopril and
3 endothelial function. Results of a substudy of the EUROPA study: PERTINENT. *Cardiovasc Res*
4 2007;**73**:237-246.
- 5 110. Nissen SE, Nicholls SJ, Wolski K, Nesto R, Kupfer S, Perez A, Jure H, De Laroche R, Staniloae
6 CS, Mavromatis K, Saw J, Hu B, Lincoff AM, Tuzcu EM, Investigators P. Comparison of
7 pioglitazone vs glimepiride on progression of coronary atherosclerosis in patients with type 2
8 diabetes: the PERISCOPE randomized controlled trial. *JAMA* 2008;**299**:1561-1573.
- 9 111. Gerstein HC, Ratner RE, Cannon CP, Serruys PW, Garcia-Garcia HM, van Es GA, Kolatkar NS,
10 Kravitz BG, Miller DM, Huang C, Fitzgerald PJ, Nesto RW, Group AS. Effect of rosiglitazone on
11 progression of coronary atherosclerosis in patients with type 2 diabetes mellitus and coronary
12 artery disease: the assessment on the prevention of progression by rosiglitazone on
13 atherosclerosis in diabetes patients with cardiovascular history trial. *Circulation* 2010;**121**:1176-
14 1187.
- 15 112. de Jong M, van der Worp HB, van der Graaf Y, Visseren FLJ, Westerink J. Pioglitazone and the
16 secondary prevention of cardiovascular disease. A meta-analysis of randomized-controlled trials.
17 *Cardiovasc Diabetol* 2017;**16**:134.
- 18 113. Bach RG, Brooks MM, Lombardero M, Genuth S, Donner TW, Garber A, Kennedy L, Monrad ES,
19 Pop-Busui R, Kelsey SF, Frye RL, Investigators BD. Rosiglitazone and outcomes for patients with
20 diabetes mellitus and coronary artery disease in the Bypass Angioplasty Revascularization
21 Investigation 2 Diabetes (BARI 2D) trial. *Circulation* 2013;**128**:785-794.
- 22 114. Green JB, Bethel MA, Armstrong PW, Buse JB, Engel SS, Garg J, Josse R, Kaufman KD, Koglin J,
23 Korn S, Lachin JM, McGuire DK, Pencina MJ, Standl E, Stein PP, Suryawanshi S, Van de Werf F,
24 Peterson ED, Holman RR, Group TS. Effect of Sitagliptin on Cardiovascular Outcomes in Type 2
25 Diabetes. *N Engl J Med* 2015;**373**:232-242.
- 26 115. Bourantas CV, Jaffer FA, Gijzen FJ, van Soest G, Madden SP, Courtney BK, Fard AM, Tenekecioglu
27 E, Zeng Y, van der Steen AFW, Emelianov S, Muller J, Stone PH, Marcu L, Tearney GJ, Serruys PW.
28 Hybrid intravascular imaging: recent advances, technical considerations, and current
29 applications in the study of plaque pathophysiology. *Eur Heart J* 2017;**38**:400-412.
- 30 116. Garcia-Garcia HM, Gomez-Lara J, Gonzalo N, Garg S, Shin ES, Goedhart D, Serruys PW. A
31 comparison of the distribution of necrotic core in bifurcation and non-bifurcation coronary
32 lesions: an in vivo assessment using intravascular ultrasound radiofrequency data analysis.
33 *EuroIntervention* 2010;**6**:321-327.
- 34 117. Gijzen F, Katagiri Y, Barlis P, Bourantas C, Collet C, Coskun U, Daemen J, Dijkstra J, Edelman E,
35 Evans P, van der Heiden K, Hose R, Koo BK, Krams R, Marsden A, Migliavacca F, Onuma Y, Ooi A,
36 Poon E, Samady H, Stone P, Takahashi K, Tang D, Thondapu V, Tenekecioglu E, Timmins L, Torii
37 R, Wentzel J, Serruys P. Expert recommendations on the assessment of wall shear stress in
38 human coronary arteries: existing methodologies, technical considerations, and clinical
39 applications. *Eur Heart J* 2019;**40**:3421-3433.
- 40 118. Thondapu V, Bourantas CV, Foin N, Jang IK, Serruys PW, Barlis P. Biomechanical stress in
41 coronary atherosclerosis: emerging insights from computational modelling. *Eur Heart J*
42 2017;**38**:81-92.
- 43 119. Stone PH, Maehara A, Coskun AU, Maynard CC, Zaromytidou M, Siasos G, Andreou I, Fotiadis D,
44 Stefanou K, Papafaklis M, Michalis L, Lansky AJ, Mintz GS, Serruys PW, Feldman CL, Stone GW.
45 Role of Low Endothelial Shear Stress and Plaque Characteristics in the Prediction of Nonculprit
46 Major Adverse Cardiac Events: The PROSPECT Study. *JACC Cardiovasc Imaging* 2018;**11**:462-471.

- 1 120. Costopoulos C, Maehara A, Huang Y, Brown AJ, Gillard JH, Teng Z, Stone GW, Bennett MR.
 2 Heterogeneity of Plaque Structural Stress Is Increased in Plaques Leading to MACE: Insights
 3 From the PROSPECT Study. *JACC Cardiovasc Imaging* 2020;**13**:1206-1218.
- 4 121. Brown AJ, Teng Z, Calvert PA, Rajani NK, Hennessy O, Nerlekar N, Obaid DR, Costopoulos C,
 5 Huang Y, Hoole SP, Goddard M, West NE, Gillard JH, Bennett MR. Plaque Structural Stress
 6 Estimations Improve Prediction of Future Major Adverse Cardiovascular Events After
 7 Intracoronary Imaging. *Circ Cardiovasc Imaging* 2016;**9**.
- 8 122. Doradla P, Otsuka K, Nadkarni A, Villiger M, Karanasos A, Zandvoort L, Dijkstra J, Zijlstra F, Soest
 9 GV, Daemen J, Regar E, Bouma BE, Nadkarni SK. Biomechanical Stress Profiling of Coronary
 10 Atherosclerosis: Identifying a Multifactorial Metric to Evaluate Plaque Rupture Risk. *JACC*
 11 *Cardiovasc Imaging* 2020;**13**:804-816.
- 12 123. Costopoulos C, Huang Y, Brown AJ, Calvert PA, Hoole SP, West NEJ, Gillard JH, Teng Z, Bennett
 13 MR. Plaque Rupture in Coronary Atherosclerosis Is Associated With Increased Plaque Structural
 14 Stress. *JACC Cardiovasc Imaging* 2017;**10**:1472-1483.
- 15 124. Okafor ON, Gorog DA. Endogenous Fibrinolysis: An Important Mediator of Thrombus Formation
 16 and Cardiovascular Risk. *J Am Coll Cardiol* 2015;**65**:1683-1699.
- 17 125. Lordan R, Tsoupras A, Zabetakis I. Platelet activation and prothrombotic mediators at the nexus
 18 of inflammation and atherosclerosis: Potential role of antiplatelet agents. *Blood Rev*
 19 2020:100694.
- 20 126. Aikawa M, Rabkin E, Sugiyama S, Voglic SJ, Fukumoto Y, Furukawa Y, Shiomi M, Schoen FJ, Libby
 21 P. An HMG-CoA reductase inhibitor, cerivastatin, suppresses growth of macrophages expressing
 22 matrix metalloproteinases and tissue factor in vivo and in vitro. *Circulation* 2001;**103**:276-283.
- 23 127. Fukumoto Y, Libby P, Rabkin E, Hill CC, Enomoto M, Hirouchi Y, Shiomi M, Aikawa M. Statins
 24 alter smooth muscle cell accumulation and collagen content in established atheroma of
 25 watanabe heritable hyperlipidemic rabbits. *Circulation* 2001;**103**:993-999.
- 26 128. Schuster S, Rubil S, Endres M, Princen HMG, Boeckel JN, Winter K, Werner C, Laufs U. Anti-
 27 PCSK9 antibodies inhibit pro-atherogenic mechanisms in APOE*3Leiden.CETP mice. *Sci Rep*
 28 2019;**9**:11079.
- 29 129. Vergallo R, Crea F. Atherosclerotic Plaque Healing. *N Engl J Med* 2020;**383**:846-857.
- 30 130. Hougaard M, Hansen HS, Thayssen P, Maehara A, Antonsen L, Junker A, Mintz GS, Jensen LO.
 31 Influence of Ezetimibe on Plaque Morphology in Patients with ST Elevation Myocardial Infarction
 32 Assessed by Optical Coherence Tomography: An OCTIVUS Sub-Study. *Cardiovasc Revasc Med*
 33 2020;**21**:1417-1424.
- 34 131. Yano H, Horinaka S, Ishimitsu T. Effect of evolocumab therapy on coronary fibrous cap thickness
 35 assessed by optical coherence tomography in patients with acute coronary syndrome. *J Cardiol*
 36 2020;**75**:289-295.

37

1 **Figure legends**

2 **Figure 1.** Advantages and limitations of the clinically available intravascular imaging modalities for
 3 assessing vessel wall pathology. The table at the bottom of the figure provides a quantification of the
 4 efficacy of each modality in detecting different tissue types using histology as reference standard. The
 5 symbol (-) indicates that the modality is unable to detect the specific characteristic. Conversely, the
 6 symbols (+), (++) , (+++) indicate weak, moderate, and excellent ability of the modality to detect a plaque
 7 characteristic, respectively.

8 **Figure footnote:** IVUS, intravascular ultrasound; NIRS, near infrared spectroscopy; OCT, optical
 9 coherence tomography; RF, radiofrequency.

10 *White arrows* indicate neo-vessels, cholesterol crystal, erupted calcified nodule, thin fibrous cap and
 11 macrophages infiltration on cross-sectional OCT images. *Asterisks* indicate calcific tissue on IVUS (upper
 12 panel) and OCT (lower panel) and evidence of intraluminal thrombus on OCT. A *red arc* defines lipid
 13 necrotic core on NIRS-IVUS image. The superimposed light blue colour indicates plaque burden and
 14 positive remodelling on IVUS, while the ivory colour defines fibrous tissue on OCT image.

15 **Figure 2.** Design and outcome of studies assessing the efficacy of intravascular imaging in predicting
 16 events.

17 **Figure footnote:** ACS, acute coronary syndrome; AS, area stenosis; CFD, computational fluid dynamics;
 18 DS, diameter stenosis; FCT, fibrous cap thickness; IB, integrated backscatter; IVUS, intravascular
 19 ultrasound; LCBI, lipid core burden index; maxLCBI_{4mm}, maximum LCBI in 4mm segment; MI,
 20 myocardial infarction; MLA, minimum lumen area; NIRS, near-infrared spectroscopy; NPV, negative
 21 predictive value; OCT, optical coherence tomography; PAV, percent atheroma volume; PB, plaque
 22 burden; PCI, percutaneous coronary intervention; PPV, positive predictive value; RI, remodelling index;
 23 TCFA, thin cap fibroatheroma; UA, unstable angina; VH, virtual histology; WSS, wall shear stress.

24 **Figure 3.** Case examples highlighting the prognostic value of the local hemodynamic forces in predicting
 25 events. Panel (A) illustrates the angiographic image of a lesion located in the mid left circumflex that
 26 caused an event at 13-month follow-up (D). VH-IVUS imaging showed a moderate lesion with a

1 minimum lumen area of 2.94mm^2 (indicated with a white circle on angiography, the corresponding VH-
2 IVUS cross section is shown in the white inset), a plaque burden of 70.5% and a thin-cap fibroatheroma
3 phenotype. Blood flow simulation analysis demonstrated high wall shear stress (WSS) at the throat of the
4 lesion with the maximum predominant WSS estimated at 6.94Pa (B), while plaque structural stress (PSS)
5 analysis showed also increased plaque stress (C) estimated at 123kPa (maximum PSS location on
6 coronary angiography is indicated with a light blue circle, the corresponding VH-IVUS cross section is
7 shown in the light blue inset). Panel (E) portrays the angiographic image of a moderate lesion located in
8 the right coronary artery that remained quiescent at 13-month follow-up (H). VH-IVUS imaging showed
9 a plaque with a thin-cap fibroatheroma phenotype, minimum lumen area of 3.75mm^2 (its location in
10 coronary angiography is shown with a white circle and the VH-IVUS image in the white inset) and
11 similar plaque burden (78.6%) compared to the previous lesion. However, in this occasion the maximum
12 predominant WSS was normal (3.73 Pa, panel F), while PSS (the location in angiography is shown with a
13 white arrow and the corresponding VH-IVUS frame in the light blue inset) was lower (71 kPa, panel G)
14 suggesting an athero-protective hemodynamic environment that inhibited atherosclerotic disease
15 progression.

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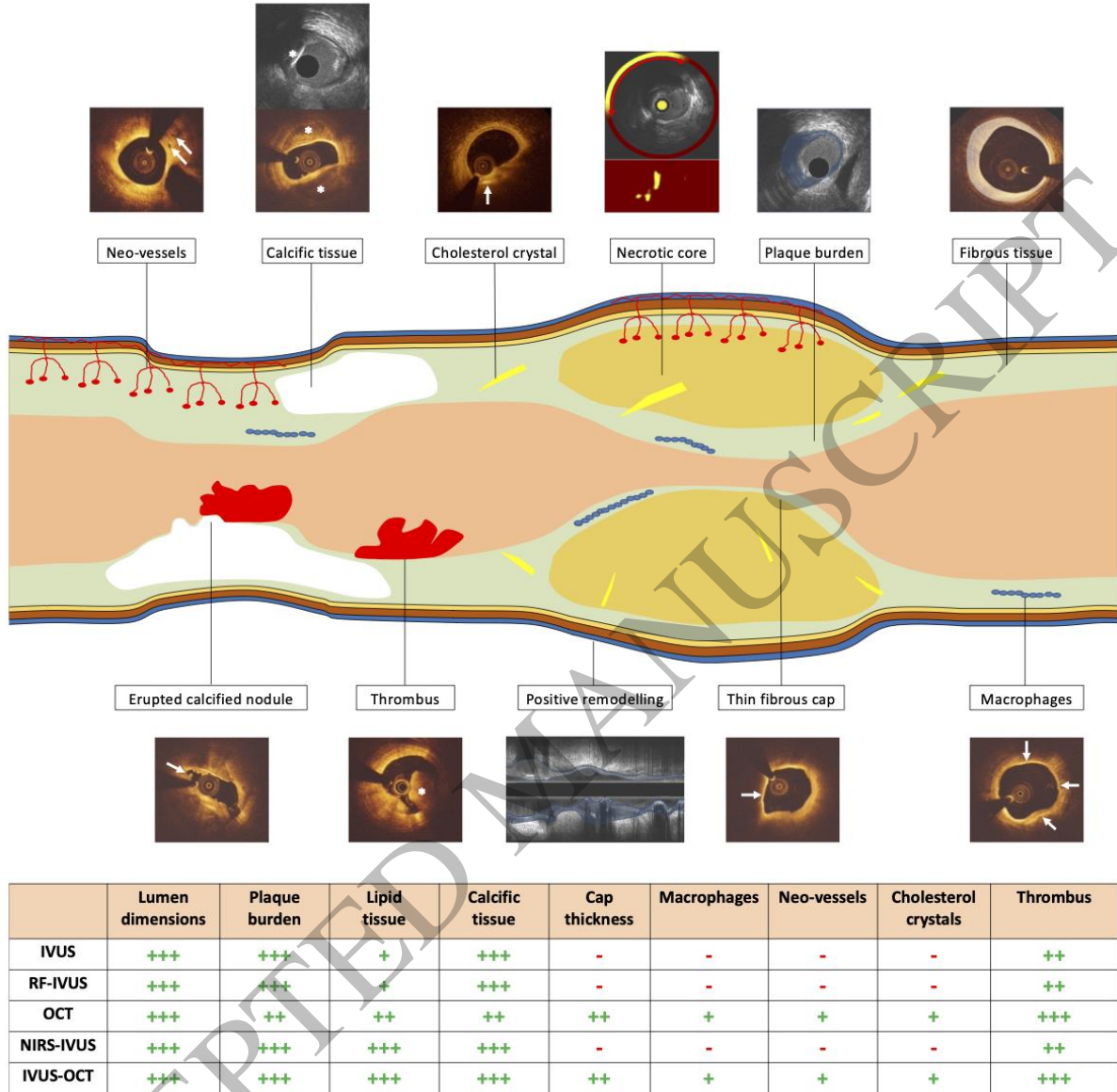


Figure 1
315x310 mm (x DPI)

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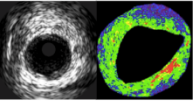
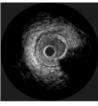
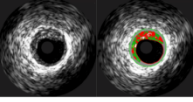
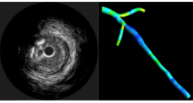

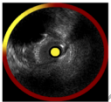
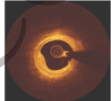
Imaging modality	Study	Number of patients	Follow-up (years)	Clinical endpoints	Event predictors	PPV	NPV
 IB-IVUS	Sano et al	140	1	ACS (patient-level analysis)	Fibrous area $\leq 25\%$ Lipid area $\geq 65\%$ RI ≥ 1.25 Eccentricity rate ≥ 0.65 PB $\geq 58\%$	-	-
 IVUS	Nicholls et al	4137	1.8	All-cause death, MI and revascularization (patient-level analysis)	Baseline PAV Change in PAV	-	-
 VH-IVUS	PROSPECT	697	3.4	Cardiac death or arrest, MI, rehospitalization due to UA or progressive angina (lesion-level analysis)	PB $\geq 70\%$ MLA $\leq 4 \text{ mm}^2$ TCFA phenotype	18.2%	98.1%
	VIVA	170	1.7	Death, MI, unplanned revascularization (lesion-level analysis)	PB $> 70\%$ TCFA phenotype RI	-	-
	ATHEROREMO-IVUS	581	1	All-cause death, ACS, or unplanned revascularization (patient-level analysis)	PB $> 70\%$ TCFA phenotype	20.5%	93.9%
 IVUS, CFD	PREDICTION	506	1	PCI due to ACS or worsening stable angina, or disease progression on angiography (lesion-level analysis)	PB $\geq 58\%$ WSS $< 1 \text{ Pa}$	41%	92%
 NIRS	ATHEROREMO-NIRS	203	1	All-cause death, nonfatal ACS, stroke, and unplanned revascularization in a native vessel (patient-level analysis)	LCBI ≥ 43	16.7%	96%
 NIRS-IVUS	LRP	1563	2	Cardiac death or arrest, ACS, revascularization, rehospitalization for angina and $> 20\%$ DS progression on angiography (patient-level* and lesion-level [§] analysis)	maxLCBI _{4mm} ≥ 400	3%* 13% [§]	99%* 94% [§]
	PROSPECT II	898	3.7	Cardiac death, MI, unstable angina or progressive angina either requiring revascularization or with rapid lesion progression (lesion-level analysis)	maxLCBI _{4mm} ≥ 324.7 PB $\geq 70\%$	-	-
 OCT	Xing et al	1474	2	Cardiac death, MI, and ischemia-driven revascularization (lesion-level analysis)	Lipid length $> 5.9 \text{ mm}$ Maximal lipid arc $> 192.8^\circ$ AS $> 68.5\%$	-	-
	CLIMA	1003	1	Cardiac death and/or target-segment MI (lesion-level analysis)	MLA $< 3.5 \text{ mm}^2$ FCT $< 75 \mu\text{m}$ Lipid arc $> 180^\circ$ Macrophages	18.8%	97%

Figure 2
447x559 mm (x DPI)

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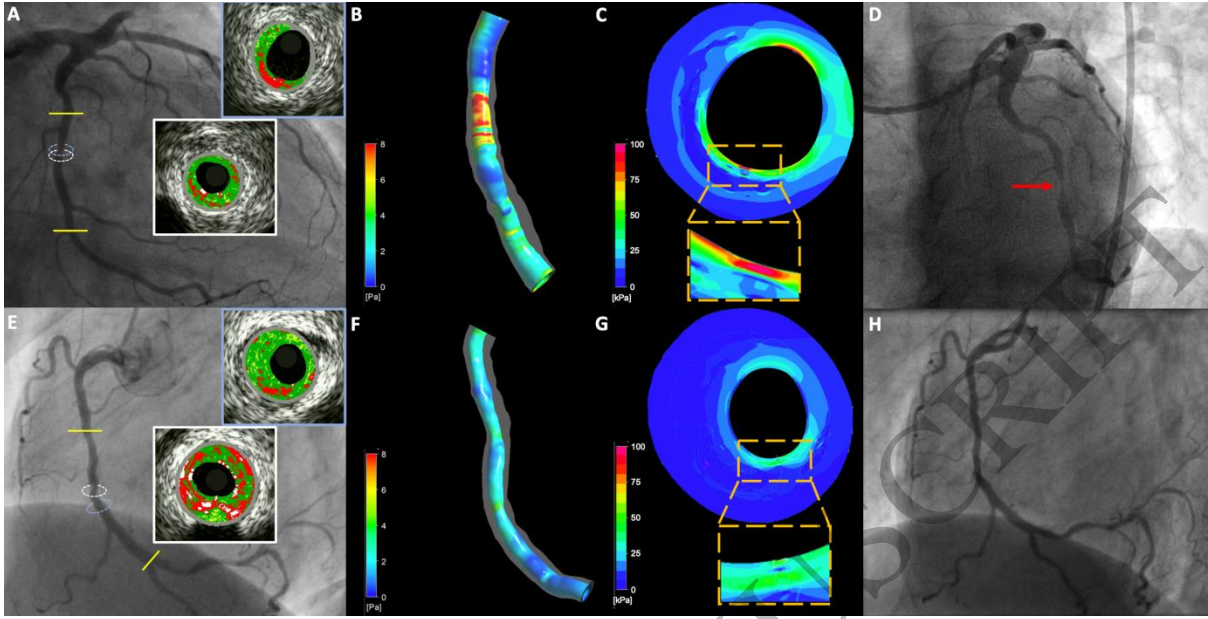


Figure 3
458x234 mm (x DPI)

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ACCEPTED MANUSCRIPT