European Heart Journal (2013) **34**, 3251–3258
doi:10.1093/eurheartj/eht301

CURRENT OPINION

Stabilization of atherosclerotic plaques: an update

Seppo Ylä-Herttuala[1]*, Jacob Fog Bentzon[2], Mat Daemen[3], Erling Falk[2], Hector M. Garcia-Garcia[4], Joerg Herrmann[5], Imo Hoefer[6], Suvi Jauhiainen[7], J. Wouter Jukema[8], Rob Krams[9], Brenda R. Kwak[10], Nikolaus Marx[11], Marek Naruszewicz[12], Andrew Newby[13], Gerard Pasterkamp[6], Patrick W.J.C. Serruys[4], Johannes Waltenberger[14], Christian Weber[15], and Lale Tokgözoglu[16], ESC Working Group of Atherosclerosis and Vascular Biology

[1]A.I. Virtanen Institute, University of Eastern Finland, FI-70211 Kuopio, Finland; [2]Aarhus University Hospital, Aarhus, Denmark; [3]Academic Medical Center, Amsterdam, The Netherlands; [4]Erasmus University, Rotterdam, The Netherlands; [5]Mayo Clinic, Rochester, MN, USA; [6]University Medical Center Utrecht, Utrecht, The Netherlands; [7]University of Eastern Finland, Kuopio, Finland; [8]Leiden University Medical Center, Leiden, The Netherlands; [9]Imperial College, London, UK; [10]University of Geneva, Geneva, Switzerland; [11]University Hospital Aachen, Aachen, Germany; [12]Medical University of Warsaw, Warsaw, Poland; [13]Bristol Heart Institute, Bristol, UK; [14]University Hospital Münster, Münster, Germany; [15]Ludwig-Maximilians-University, Munich, Germany; and [16]Hacettepe University, Ankara, Turkey

Received 1 December 2011; revised 19 June 2013; accepted 19 July 2013; online publish-ahead-of-print 21 August 2013

Vulnerable plaques

The majority of coronary thrombi (~75%) is caused by *plaque rupture*.[1,2] Prototype of the rupture-prone plaque contains a large, soft, lipid-rich necrotic core with a thin and inflamed fibrous cap, so-called thin-cap fibroatheroma (TCFA) (*Figure 1*).[3,4] Other common features include expansive remodelling, large plaque size, plaque haemorrhage, neovascularization, adventitial inflammation, and 'spotty' calcifications.[4] Thin-cap fibroatheroma caps are usually <65 μm thick.[4] *Figure 2* summarizes factors contributing to the formation of vulnerable plaques. No distinct morphological features have been identified for the erosion-prone plaques, but they are usually rarely associated with expansive remodelling, scarcely calcified, and contain only limited inflammation.[2,5]

Inflammatory cells, cytokines, chemokines, and growth factors

Vulnerable plaques contain monocytes, macrophages, and T-cells. Of the T-cells, CD4+ T-helper (Th) cells are the most prominent.[6] T-cells can differentiate into a Th1 phenotype, which secretes and responds to IFN-γ or a Th2 phenotype, which secretes and responds to IL-4, IL-10, and IL-13 (*Figure 3*). T-cells promote the vulnerability of plaques through their effects on macrophages. Similarly, there are two main plaque macrophage phenotypes: pro-inflammatory M1 macrophages (IFN-γ-induced) and anti-inflammatory or regulatory M2 macrophages (IL-4/IL-13-induced).[7]

Cytokines and chemokines important for regulating inflammatory and immune responses are listed in Supplementary material online, *Table S1*.[7–11] The concept that Th1-related pro-inflammatory cytokines drive progression whereas Th2- and regulatory T-cell-related cytokines exert anti-atherogenic effects provides a useful theoretical framework (*Figure 3*). For an unstable phenotype, IFN-γ, IL-12, and IL-18 seem to be important factors. CCR5 drives Th1-type pro-inflammatory responses and contributes to plaque formation.[12] Important players for plaque destabilization are macrophage migration inhibitory factor (MIF)[13] and monocyte chemotactic protein-1.[14] Of the plaque-stabilizing factors, IL-10 and TGF-β are of the greatest significance.[11,15]

Extracellular proteases and platelets

Extracellular proteases correlate with changes associated with plaque vulnerability,[16] such as macrophage ingress and apoptosis, and loss of collagen and elastin.[17,18] Apoptosis of SMCs contributes to weakening of plaques. Knockout models supported a role for matrix metalloproteinases (MMPs)[19] and cathepsins[20] in plaque rupture, although the effects of MMP inhibitors on plaque stability have been mixed. Recent studies with more selective drugs[21] provide new hope that inhibiting proteases or preventing their secretion[19] may lead to plaque stabilization.

Platelets contribute to atherogenesis through secretory functions and as modulators of inflammatory responses. Antiplatelet drugs might, therefore, serve as plaque-stabilizing compounds. However, experimental data on antiplatelet drugs are contradictory.[22–25] Although antiplatelet drugs have proven benefits in the secondary prevention of CVD, their direct role in plaque stabilization remains unclear.

The opinions expressed in this article are not necessarily those of the Editors of the *European Heart Journal* or of the European Society of Cardiology.

* Corresponding author. Tel: +358 40 3552075, Email: seppo.ylaherttuala@uef.fi

Endothelial dysfunction, wall stress, and shear stress

Impairment in endothelium-dependent vasodilatation is the clinical hallmark of endothelial dysfunction.[26] In atherosclerosis, there is coexistence of segments with normal vasodilatory and abnormal vasoconstrictive responses to acetylcholine. In virtual histology (VH)-intravascular ultrasound (IVUS), segments with endothelial dysfunction have larger plaques and necrotic core areas.[27] Under sympathetic activity, dysfunctional endothelium will respond with paradoxical vasoconstriction. The release from platelets of peptides, in particular serotonin and thrombin, leads to further vasoconstriction and perpetuation of the situation.[28–31]

Shear stress plays a key role during initiation of atherosclerosis.[32,33] Recent studies indicate that it also predicts location of advanced lesions.[34] Repeated measurements indicate that low shear stress is predictive of not only plaque location, but also of plaque growth.[35,36] Role of wall stress in plaque rupture has been increasingly recognized, since it seems to predict plaque rupture better than shear stress.[37] The levels of these forces inducing rupture are in the order of ~150 kPa or ~1100 mmHg, which have been shown to occur at the shoulder regions.[37] In the PREDICTION trial, large plaque burden and low local endothelial shear stress provided independent and additive prediction to identify plaques that develop progressive enlargement and lumen narrowing.[38]

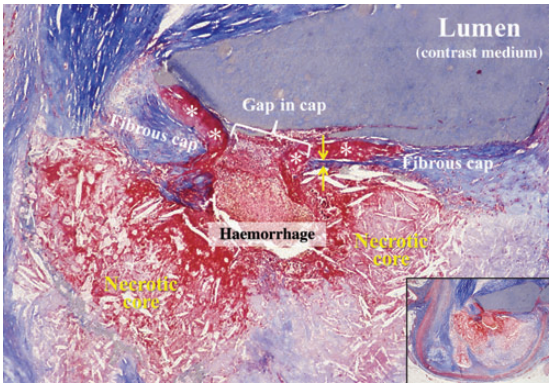


Figure 1 Cross-sectioned coronary artery showing a ruptured thin-cap fibroatheroma. The fibrous cap is very thin near the rupture site (between arrows) and a non-obstructive mural thrombus (asterisks) is bordering the gap in the disrupted cap. A haemorrhage has penetrated from the lumen through the gap into the lipid-rich necrotic core in which the characteristic cholesterol clefts are clearly seen. The lumen contains contrast medium injected postmortem. Overview in inset. Trichrome, staining collagen blue, and thrombus and haemorrhage red.

Angiogenesis

Microvessels increase with plaque progression, are abundant in vulnerable plaques,[39] and can contribute to plaque inflammation.[40] Fragile microvessels allow extravasation of lipoproteins and red blood cells,[41] which contribute to plaque lipids. Whether haemorrhage from neovessels triggers plaque rupture (or vice versa) remains to be demonstrated. Mechanisms regulating plaque angiogenesis involve hypoxia-inducible factor and growth factors, such as VEGFs, PlGF, PDGFs, and FGFs.[42] However, the net effect of all these regulators remains unclear. While VEGF is expressed in atherosclerotic lesions,[43] patients receiving anti-VEGF antibodies for cancer show increased CVD complications. This finding is compatible with vasculoprotective effect of VEGF, and transient treatment of mice with VEGF has not increased atherosclerosis.[44] Whether therapeutic manipulation of angiogenesis can stabilize plaques remains to be investigated.[45]

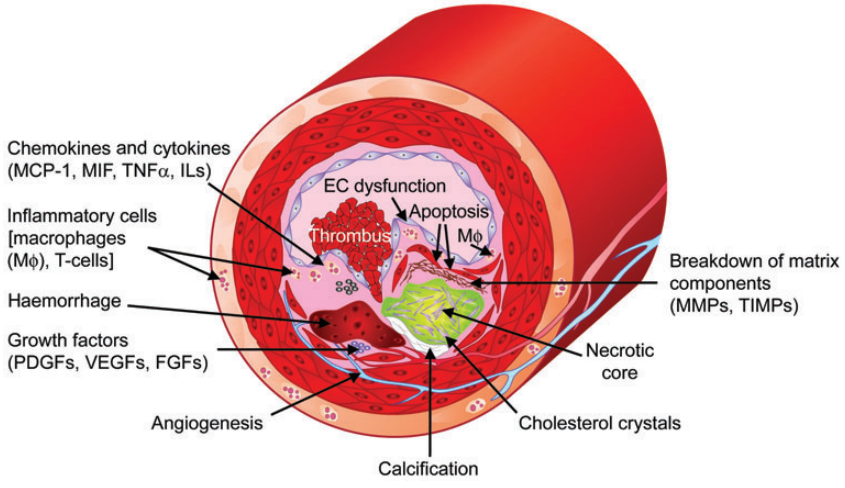


Figure 2 Factors contributing to the formation of vulnerable plaques. MCP-1, monocyte chemotactic protein-1; MIF, migration inhibitory factor; TNFα, tumour necrosis factor-α; ILs, interleukins; MMPs, matrix metalloproteinases; TIMPs, tissue inhibitors of metalloproteinases; PDGFs, platelet-derived growth factors; VEGFs, vascular endothelial growth factors; FGFs, fibroblast growth factors; Mϕ, macrophages.

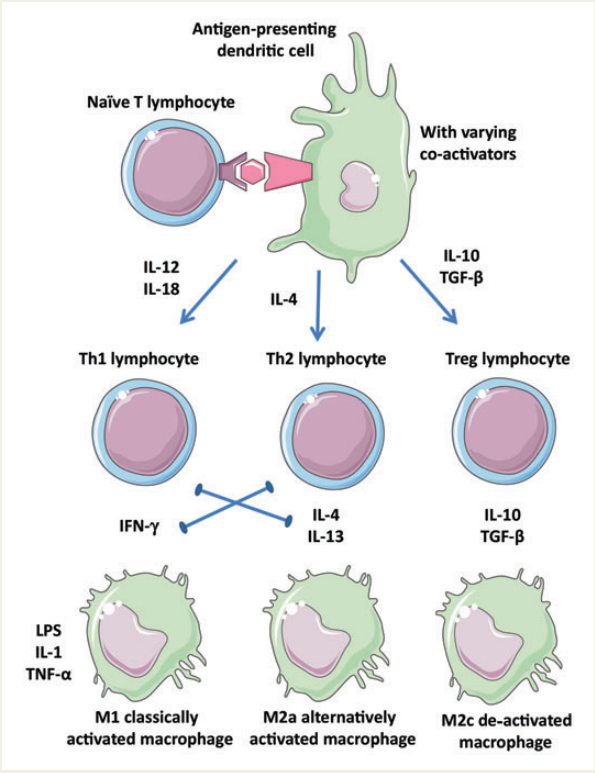


Figure 3 Diverse leucocyte populations in atherosclerotic plaques. Depending on the context of antigen presentation including the cytokine environment, naïve T-cells and macrophages may adopt several phenotypes that are more or less inflammatory. Polarization of the environment is promoted by the positive and negative interactions indicated. Th1, Th2, Treg: T-cell subtypes; M1, M2a, M2c: macrophage subtypes.

Progenitor cells

Clinical studies show correlations of endothelial progenitor cells (EPCs) with atherogenesis,[46] suggesting that EPCs may provide protection against atherosclerosis. Recent data, however, question these findings: putative EPCs measured in the clinics have generated mostly inflammatory cells rather than endothelial cells.[47] Also, mouse studies tracking endothelial origin in atherogenesis have found rare, if any, contributions from the blood.[48]

Smoking

Smoking is a major CVD risk factor causing endothelial damages, disturbances in coagulation, and inflammation.[49] Stopping smoking is beneficial for plaque stabilization.

Biomarkers, genetic testing, and imaging in the detection of unstable plaques

Biomarkers and genetic testing

Single nucleotide polymorphism and GWAS studies have identified approximately 160 genetic loci that are associated with CVD, MI, and restenosis.[50,51] However, there are no data to pinpoint specific genetic signatures to the vulnerable plaque. Although a genetic test to identify patients who carry vulnerable plaques is the ultimate goal, this seems currently unlikely. It seems clear that part of the gene–environment interactions are regulated by epigenetics.[52] As chromatin alterations are reversible, epigenetic modifications are amendable to pharmacological interventions, which may provide new treatments for CVD.

Detection of unstable plaques

Plaque burden correlates well with calcification, but is not an indicator of stability. Computerised tomography shows that lesion area in ruptured plaques is larger than in stable lesions.[53] Using IVUS, it was found that patients with acute MI had larger plaque area compared with patients with unstable or stable angina. VH-IVUS allows classification of lesions as fibrous, fibrocalcific, fibroatheroma, and TCFAs.[54] The definition of IVUS-derived TCFA is a lesion with plaque burden $\geq$40% and confluent necrotic core $\geq$10% in direct contact with lumen. VH-IVUS identified the following characteristics as predictors of clinical events[5]: TCFA, plaque burden $\geq$70%, and minimum lumen area $\leq$4 mm^2. However, even combining these characteristics resulted in only 18% event rate during 3 years, which illustrates current limitations of imaging techniques.

Optical coherence tomography (OCT) gives a spatial resolution of $\leq$20 μm allowing more accurate assessment of cap thickness (*Figure 4*).[55] Optical coherence tomography has potential to assess plaque macrophage content. In non-flow-limiting coronary lesions, high-risk plaque characteristics (such as thin fibrous cap, large lipid pools, and microchannels) were associated with plaque progression.[56] NIR spectroscopy is another technique designed to identify lipid-containing plaques.[57] Emerging imaging techniques utilize MRI markers homing to rupture-prone plaques and markers of macrophage metabolic activity.[58] Developing such techniques remains a challenge for the future.[59]

Current treatments and future perspectives of plaque stabilization

Statin therapy

Patients receiving pravastatin 3 months before carotid endarterectomy showed significantly less inflammation and a higher collagen content in carotid plaques, suggesting plaque stabilization.[60] The ATROCAP study randomized two-step bilateral carotid endatherectomy patients to atorvastatin or placebo for 4–6 months after the first procedure. Plaques from treated patients showed a trend towards fewer inflammatory cells, whereas no change was observed in controls.[61] Results are consistent with pleiotropic, anti-inflammatory effects of statins, which may contribute to the stabilization of plaques.[62] Recent experimental finding of plaque stabilization with ezetimide, which lacks pleiotropic effects, lends support to the lipid-lowering therapy *per se*.[63] However, it is not yet possible to discern the contribution of each mechanism to clinical results.

The German Atorvastatin Study demonstrated that hyperechogenicity of plaques significantly increased after 12 months compared with non-statin-based lipid lowering.[64] In the ASTEROID[65] and SATURN studies,[66] aggressive lipid lowering regressed atheroma volume in IVUS. Data from several prospective IVUS trials confirmed

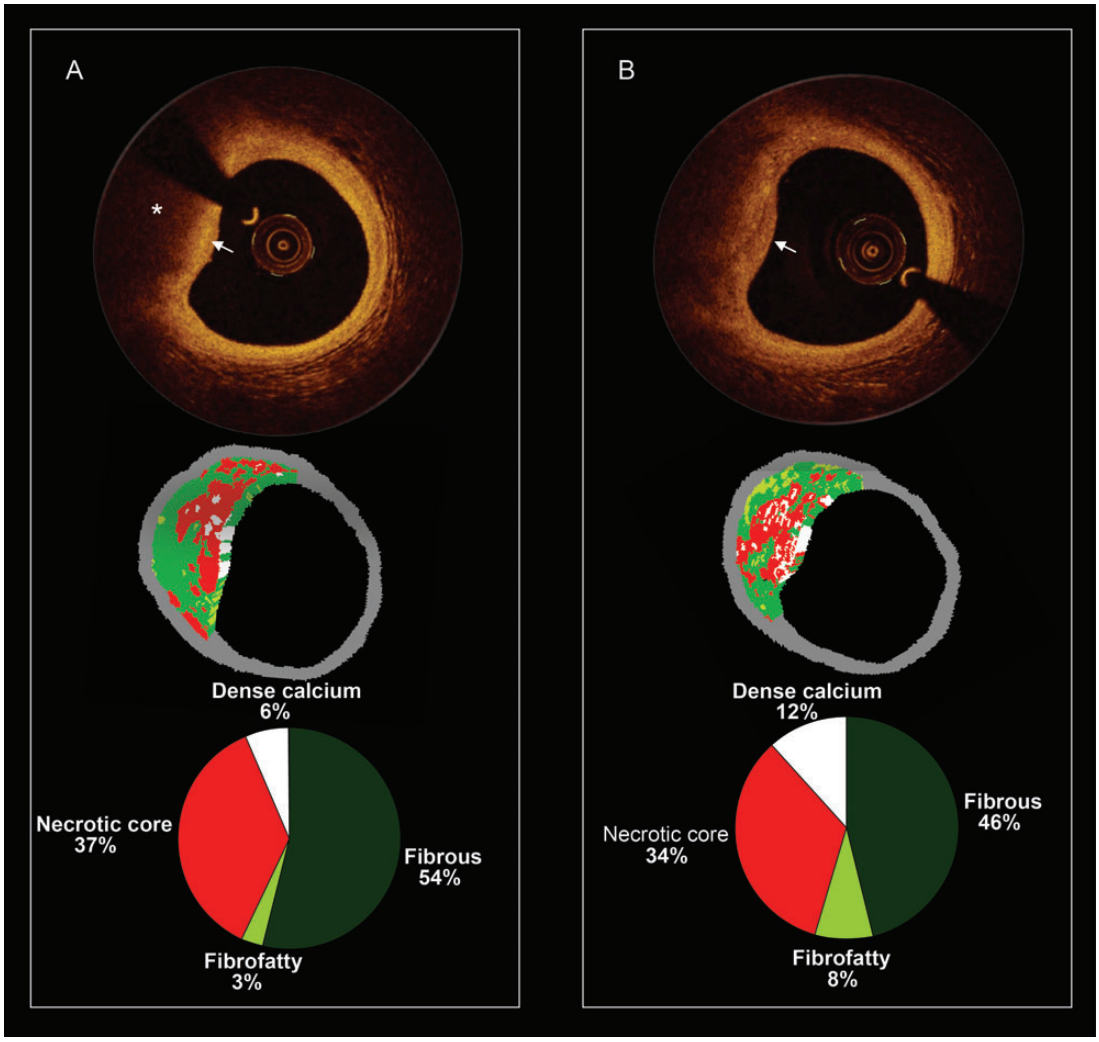


Figure 4 Serial and corresponding virtual histology and optical coherence tomography. (*A*) The baseline optical coherence tomography frame (top), the corresponding virtual histology frame (mid), and the quantification of the virtual histology tissue types (bottom). The optical coherence tomography frame shows from 8 to 12 o'clock a fibroatheroma which is composed of a fibrous cap (white arrow) and a necrotic core (asterisk). The corresponding virtual histology frames show also a fibroatheroma (necrotic core-rich plaque in red colour). In (*B*), the patient was reimaged at 1 year and some plaque changes have been observed. In the optical coherence tomography frame, the fibrous cap became thinner (please note that at baseline, the signal rich area overlying the necrotic core was wider).

significant atheroma regression after LDL reduction[67] and the PROVE-IT trial showed lower CVD endpoints after 24 months under intense lipid lowering in ACS patients.[68] In addition, the JUPITER study in healthy subjects with LDL <3.4 mmol/L and hs-C-reactive protein above 2 mg/L showed that 20 mg of rosuvastatin significantly reduced major CVD events in this low-risk group.[69]

Antiplatelet and antihypertensive therapies

Aspirin is effective for CVD secondary prevention, and a major reduction in CVD events was found in the CURE trial, where clopidogrel was added to aspirin in ACS patients.[70] However, these agents mostly reduce complications of plaque rupture and may not be plaque-stabilizing agents *per se*. Whether new platelet inhibitors ticagrelor and prasugrel and platelet thrombin receptor inhibitor vorapaxar have plaque-stabilizing properties remains unknown, although recent meta-analyses have suggested the same benefits in patients with recent ACS.[71]

Four recent IVUS trials have shown that β-blockers slow the progression of CVD.[72] Endothelial function can be improved by renin–angiotensin inhibitors, and HOPE[73] and ONTARGET[74] trials have shown a larger reduction in CVD events that could be predicted from the reduction in blood pressure, supporting plaque-stabilizing effects.

Other anti-atherosclerotic therapies

HDL-raising therapies

ApoA1-Milano and other HDL-like apoA1 complexes have been shown to regress atherosclerosis possibly via several HDL-related

protective mechanisms like reverse cholesterol transport, anti-oxidative activity, endothelial vasoprotection, and reduction of platelet activation.[75] HDL also inhibits coagulation cascade. Cholesterol ester transfer protein (CETP) is a plasma protein that catalyses exchange of cholesteryl esters and triglycerides between lipoproteins. Reduction in CETP activity is associated with cholesterol reduction in VLDL and LDL and enrichment of HDL. However, the ILLUMINATE trial with a CETP inhibitor torcetrapib failed due to toxicity.[76] New trials with novel CETP inhibitors such as anacetrapib (Supplementary material online, *Table S2*) are underway, but dal-OUTCOMES trial assessing dalcetrapib has been stopped due to the lack of efficacy.[77] Thus, these recent trials and a large Mendelian randomization study[78] question the usefulness of HDL-raising therapies, if no simultaneous beneficial changes can be achieved in VLDL or LDL levels.

Niacin/nicotinic acid

With interest in HDL-raising therapies, niacin has been recently re-investigated. Two trials in statin-treated patients with low HDL have shown that modified-release nicotinic acid significantly reduced carotid atherosclerosis,[79] and that the use of slow-release niacin significantly reduced carotid intima-media thickness in comparison with statin.[80] However, AIM-HIGH and HPS-2-THRIVE trials failed to show any added benefits (Supplementary material online, *Table S2*), which raises doubts about the usefulness of this approach.

Phospholipase inhibitors

Another approach to reduce plaque inflammation is to inhibit lipoprotein-associated phospholipase A_2, which has prevented increase in necrotic core when compared with placebo.[81] Two major trials testing this approach are now ongoing (STABILITY and SOLID-TIMI 52 trials).

New approaches

Antagonists against pro-atherogenic chemokine receptor CCR5 and its ligand CCL5 have been developed.[82] Migration inhibitory factor is involved in atheroprogression and its inhibition with biologicals or small molecules may be useful for plaque stabilization.[13]

PCSK9 is involved in hypercholesterolaemia by favouring degradation of LDL receptor.[83] Some natural PCSK9 mutations increase its function and cause hypercholesterolaemia, whereas loss-of-function mutations cause hypocholesterolaemia. Therefore, PCSK9 is an attractive target for lowering plasma LDL with potential plaque-stabilizing features. The ODYSSEY OUTCOMES trial is now testing the efficacy of PCSK9 inhibitor in CVD (Supplementary material online, *Table S2*).

siRNAs against apoB100 have been used to reduce LDL levels.[84] Whether this technology will be useful in the prevention of plaque ruptures remains unknown. Innate and adaptive immunity regulates pro-atherogenic inflammation. Immunization of hyperlipidaemic animals with LDL preparations or apoB100 fragments reduces atherosclerosis, suggesting that vaccination may become a potential strategy for the prevention of CVD.[85,86]

Key points (adapted from Ylä-Herttuala *et al.*[1])

- *Vulnerable plaques* are prone to rupture and thrombosis. Two types of vulnerable plaques are rupture-prone and erosion-prone. Prototype of the rupture-prone plaque contains large and soft lipid-rich necrotic core covered by thin and inflamed fibrous cap.
- *Thin-cap fibroatheroma*: If the fibrous cap is thin, the plaque is called TCFA. Thin fibrous caps are usually heavily inflamed.
- *Plaque stabilization* can be achieved by increasing thickness of fibrous cap, reducing inflammation in the fibrous cap, and reducing size of atheromatous core. Plaques may be stabilized against thrombosis independent of changes in plaque size and luminal obstruction.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Acknowledgements

The invaluable help of Ms Marja Poikolainen in preparing the manuscript is greatly acknowledged.

Funding

This study was supported by ESC Working Group of Atherosclerosis and Vascular Biology.

Conflict of interest: I.H. has received research grants from NWO, CTMM, BMM, and TI Pharma. J.W.J. has received grants from Astellas, Astra-Zeneca, Biotronik, Boston Scientific, Daiichi Sankyo, Lilly, Genzyme, Medtronic, MSD, Pfizer, Orbus Neich, Novartis, Roche, Servier, Sanofi-Aventis, the Netherlands Heart Foundation, the Interuniversity Cardiology Institute of the Netherlands, and the European Community Framework FP7 Programme. R.K. has received grants from the Netherlands and British Heart Foundations, the CTMM, the BBSRC and EPSRC, the FP7 Programme, and Johnson & Johnson. B.R.K. has received grants from the Swiss National Science Foundation, Fondation Leenaards, and the Fondation Prevot. N.M. has received research grants from Boehringer Ingelheim, GSK, MSD, and Takeda. A.N. has received grants from the British Heart Foundation and the UK National Institute for Health Research. He is also consultant for PlaqueTec. G.P. is a co-founder of Cavadis. C.W. is a shareholder of Carolus Therapeutics, Inc. S.Y.-H has received grants from the Academy of Finland, the Finnish Heart Foundation, and EU FP7 programme grants CliniGene, Baculogenes, BIOMAGSCAR, and BAMI.

References

1. Ylä-Herttuala S, Bentzon J, Daemen M, Falk E, Garcia-Garcia H, Herrmann J, Hoefer I, Jukema W, Krams R, Kwak B, Marx N, Naruszewicz M, Newby A, Pasterkamp G, Serruys P, Waltenberger J, Weber C, Tokgözoglu L. Opinion paper, European Society of Cardiology, Working Group of Atherosclerosis and Vascular Biology: stabilisation of atherosclerotic plaques. *Thromb Haemost* 2011;**106**:1–19.
2. Schaar JA, Muller JE, Falk E, Virmani R, Fuster V, Serruys PW, Colombo A, Stefanadis C, Ward Casscells S, Moreno PR, Maseri A, van der Steen AF. Terminology for high-risk and vulnerable coronary artery plaques. Report of a meeting on the vulnerable plaque, June 17 and 18, 2003, Santorini, Greece. *Eur Heart J* 2004;**25**:1077–1082.
3. Falk E, Shah PK, Fuster V. Coronary plaque disruption. *Circulation* 1995;**92**:657–671.

4. Kolodgie FD, Burke AP, Farb A, Gold HK, Yuan J, Narula J, Finn AV, Virmani R. The thin-cap fibroatheroma: a type of vulnerable plaque: the major precursor lesion to acute coronary syndromes. *Curr Opin Cardiol* 2001;**16**:285–292.
5. Stone GW, Maehara A, Lansky AJ, de Bruyne B, Cristea E, Mintz GS, Mehran R, McPherson J, Farhat N, Marso SP, Parise H, Templin B, White R, Zhang Z, Serruys PW. A prospective natural-history study of coronary atherosclerosis. *N Engl J Med* 2011;**364**:226–235.
6. Hansson GK, Hermansson A. The immune system in atherosclerosis. *Nat Immunol* 2011;**12**:204–212.
7. Martinez FO, Helming L, Gordon S. Alternative activation of macrophages: an immunologic functional perspective. *Annu Rev Immunol* 2008;**27**:451–483.
8. Kleemann R, Zadelaar S, Kooistra T. Cytokines and atherosclerosis: a comprehensive review of studies in mice. *Cardiovasc Res* 2008;**79**:360–376.
9. Zernecke A, Weber C. Chemokines in the vascular inflammatory response of atherosclerosis. *Cardiovasc Res* 2010;**86**:192–201.
10. Ait-Oufella H, Taleb S, Mallat Z, Tedgui A. Recent advances on the role of cytokines in atherosclerosis. *Arterioscler Thromb Vasc Biol* 2011;**31**:969–979.
11. Tedgui A, Mallat Z. Cytokines in atherosclerosis: pathogenic and regulatory pathways. *Physiol Rev* 2006;**86**:515–581.
12. Potteaux S, Combadière C, Esposito B, Lecureuil C, Ait-Oufella H, Merval R, Ardouin P, Tedgui A, Mallat Z. Role of bone marrow-derived CC-chemokine receptor 5 in the development of atherosclerosis of low-density lipoprotein receptor knockout mice. *Arterioscler Thromb Vasc Biol* 2006;**26**:1858–1863.
13. Zernecke A, Bernhagen J, Weber C. Macrophage migration inhibitory factor in cardiovascular disease. *Circulation* 2008;**117**:1594–1602.
14. Ylä-Herttuala S, Lipton BA, Rosenfeld ME, Särkioja T, Yoshimura T, Leonard EJ, Witztum JL, Steinberg D. Expression of monocyte chemoattractant protein 1 in macrophage-rich areas of human and rabbit atherosclerotic lesions. *Proc Natl Acad Sci USA* 1991;**88**:5252–5256.
15. Potteaux S, Esposito B, van Oostrom O, Brun V, Ardouin P, Groux H, Tedgui A, Mallat Z. Leukocyte-derived interleukin 10 is required for protection against atherosclerosis in low-density lipoprotein receptor knockout mice. *Arterioscler Thromb Vasc Biol* 2004;**24**:1474–1478.
16. Dollery CM, Libby P. Atherosclerosis and proteinase activation. *Cardiovasc Res* 2006;**69**:625–635.
17. Sluijter JP, de Kleijn DP, Pasterkamp G. Vascular remodeling and protease inhibition—bench to bedside. *Cardiovasc Res* 2006;**69**:595–603.
18. Sluijter JPG, Pulskens WPC, Schoneveld AH, Velema E, Strijder CF, Moll F, de Vries JP, Verheijen J, Hanemaaijer R, de Kleijn DP, Pasterkamp G. Matrix metalloproteinase 2 is associated with stable and matrix metalloproteinases 8 and 9 with vulnerable carotid atherosclerotic lesions: a study in human endarterectomy specimen pointing to a role for different extracellular matrix metalloproteinase inducer glycosylation forms. *Stroke* 2006;**37**:235–239.
19. Newby AC, George SJ, Ismail Y, Johnson JL, Sala-Newby GB, Thomas AC. Vulnerable atherosclerotic plaque metalloproteinases and foam cell phenotypes. *Thromb Haemost* 2009;**101**:1006–1011.
20. Lutgens SP, Cleutjens KB, Daemen MJ, Heeneman S. Cathepsin cysteine proteases in cardiovascular disease. *FASEB J* 2007;**21**:3029–3041.
21. Johnson JL, Devel L, Czarny B, George SJ, Jackson CL, Rogakos V, Beau F, Yiotakis A, Newby AC, Dive V. A selective matrix metalloproteinase-12 inhibitor retards atherosclerotic plaque development in apolipoprotein e-knockout mice. *Arterioscler Thromb Vasc Biol* 2011;**31**:528–535.
22. Liu H, Jiang D, Zhang S, Ou B. Aspirin inhibits fractalkine expression in atherosclerotic plaques and reduces atherosclerosis in ApoE gene knockout mice. *Cardiovasc Drugs Ther* 2010;**24**:17–24.
23. Afek A, Kogan E, Maysel-Auslender S, Mor A, Regev E, Rubinstein A, Keren G, George J. Clopidogrel attenuates atheroma formation and induces a stable plaque phenotype in apolipoprotein E knockout mice. *Microvasc Res* 2009;**77**:364–369.
24. Schulz C, Konrad I, Sauer S, Orschiedt L, Koellnberger M, Lorenz R, Walter U, Massberg S. Effect of chronic treatment with acetylsalicylic acid and clopidogrel on atheroprogression and atherothrombosis in ApoE-deficient mice in vivo. *Thromb Haemost* 2008;**99**:190–195.
25. Yamamoto Y, Yamashita T, Kitagawa F, Sakamoto K, Giddings JC, Yamamoto J. The effect of the long term aspirin administration on the progress of atherosclerosis in apoE-/- LDLR-/- double knockout mouse. *Thromb Res* 2010;**125**:246–252.
26. Herrmann J, Lerman A. The endothelium: dysfunction and beyond. *J Nucl Cardiol* 2001;**8**:197–206.
27. Lavi S, Bae JH, Rihal CS, Prasad A, Barsness GW, Lennon RJ, Holmes DR Jr, Lerman A. Segmental coronary endothelial dysfunction in patients with minimal atherosclerosis is associated with necrotic core plaques. *Heart* 2009;**95**:1525–1530.
28. Willerson JT, Golino P, Eidt J, Campbell WB, Buja LM. Specific platelet mediators and unstable coronary artery lesions. Experimental evidence and potential clinical implications. *Circulation* 1989;**80**:198–205.
29. Golino P, Piscione F, Willerson JT, Cappelli-Bigazzi M, Focaccio A, Villari B, Indolfi C, Russolillo E, Condorelli M, Chiariello M. Divergent effects of serotonin on coronary-artery dimensions and blood flow in patients with coronary atherosclerosis and control patients. *N Engl J Med* 1991;**324**:641–648.
30. Weyrich AS, Solis GA, Li KS, Tulenko TN, Santamore WP. Platelet amplification of vasospasm. *Am J Physiol* 1992;**263**:H349–H358.
31. Kaul S, Padgett RC, Heistad DD. Role of platelets and leukocytes in modulation of vascular tone. *Ann NY Acad Sci* 1994;**714**:122–135.
32. Davies PF, Polacek DC, Shi C, Helmke BP. The convergence of haemodynamics, genomics, and endothelial structure in studies of the focal origin of atherosclerosis. *Biorheology* 2002;**39**:299–306.
33. Wentzel JJ, Whelan DM, van der Giessen WJ, van Beusekom HMM, Andhyiswara I, Serruys PW, Slager CJ, Krams R. Coronary stent implantation changes 3-D vessel geometry and 3-D shear stress distribution. *J Biomech* 2000;**33**:1287–1295.
34. Krams R, Wentzel JJ, Oomen JA, Vinke R, Schuurbiers JC, de Feyter PJ, Serruys PW, Slager CJ. Evaluation of endothelial shear stress and 3D geometry as factors determining the development of atherosclerosis and remodeling in human coronary arteries in vivo. Combining 3D reconstruction from angiography and IVUS (ANGUS) with computational fluid dynamics. *Arterioscler Thromb Vasc Biol* 1997;**17**:2061–2065.
35. Samady H, Eshtehardi P, McDaniel MC, Suo J, Dhawan SS, Maynard C, Timmins LH, Quyyumi AA, Giddens DP. Coronary artery wall shear stress is associated with progression and transformation of atherosclerotic plaque and arterial remodeling in patients with coronary artery disease. *Circulation* 2011;**124**:779–788.
36. Chatzizisis YS, Giannoglou GD. Shear stress and inflammation: are we getting closer to the prediction of vulnerable plaque? *Expert Rev Cardiovasc Ther* 2010;**8**:1351–1353.
37. Teng Z, Canton G, Yuan C, Ferguson M, Yang C, Huang X, Zheng J, Woodard PK, Tang D. 3D critical plaque wall stress is a better predictor of carotid plaque rupture sites than flow shear stress: an in vivo MRI-based 3D FSI study. *J Biomech Eng* 2010;**132**:031007.
38. Stone PH, Saito S, Takahashi S, Makita Y, Nakamura S, Kawasaki T, Takahashi A, Katsuki T, Nakamura S, Namiki A, Hirohata A, Matsumura T, Yamazaki S, Yokoi H, Tanaka S, Otsuji S, Yoshimachi F, Honye J, Harwood D, Reitman M, Coskun AU, Papafaklis MI, Feldman CL. Prediction of progression of coronary artery disease and clinical outcomes using vascular profiling of endothelial shear stress and arterial plaque characteristics: the PREDICTION Study. *Circulation* 2012;**126**:172–181.
39. Virmani R, Kolodgie FD, Burke AP, Finn AV, Gold HK, Tulenko TN, Wrenn SP, Narula J. Atherosclerotic plaque progression and vulnerability to rupture: angiogenesis as a source of intraplaque hemorrhage. *Arterioscler Thromb Vasc Biol* 2005;**25**:2054–2061.
40. Eriksson EE. Intravital microscopy on atherosclerosis in apolipoprotein E-deficient mice establishes microvessels as major entry pathways for leukocytes to advanced lesions. *Circulation* 2011;**124**:2129–2138.
41. Sluimer JC, Gasc JM, van Wanroij JL, Kisters N, Groeneweg M, Sollewijn Gelpke MD, Cleutjens JP, van den Akker LH, Corvol P, Wouters BG, Daemen MJ, Bijnens AP. Hypoxia, hypoxia-inducible transcription factor, and macrophages in human atherosclerotic plaques are correlated with intraplaque angiogenesis. *J Am Coll Cardiol* 2008;**51**:1258–1265.
42. Herrmann J, Lerman LO, Mukhopadhyay D, Napoli C, Lerman A. Angiogenesis in atherogenesis. *Arterioscler Thromb Vasc Biol* 2006;**26**:1948–1957.
43. Rutanen J, Leppänen P, Tuomisto T, Rissanen TT, Hiltunen MO, Vajanto I, Niemi M, Häkkinen T, Karkola K, Stacker SA, Achen MG, Alitalo K, Ylä-Herttuala S. Vascular endothelial growth factor expression in human atherosclerotic lesions. *Cardiovasc Res* 2003;**59**:971–979.
44. Leppänen P, Koota S, Kholova I, Koponen J, Fieber C, Eriksson U, Alitalo K, Ylä-Herttuala S. Gene transfers of VEGF-A, VEGF-B, VEGF-C and VEGF-D have no effects on atherosclerosis in hypercholesterolemic low-density lipoprotein-receptor/apolipoprotein B48-deficient mice. *Circulation* 2005;**112**:1347–1352.
45. Moulton KS, Heller E, Konerding MA, Flynn E, Palinski W, Folkman J. Angiogenesis inhibitors endostatin or TNP-470 reduce intimal neovascularization and plaque growth in apolipoprotein E-deficient mice. *Circulation* 1999;**99**:1726–1732.
46. Werner N, Kosiol S, Schiegl T, Ahlers P, Walenta K, Link A, Böhm M, Nickenig G. Circulating endothelial progenitor cells and cardiovascular outcomes. *N Engl J Med* 2005;**353**:999–1007.
47. Timmermans F, Plum J, Yoder MC, Ingram DA, Vandekerckhovea B, Case J. Endothelial progenitor cells: identity defined? *J Cell Mol Med* 2009;**13**:87–102.
48. Hagensen MK, Shim J, Thim T, Falk E, Bentzon JF. Circulating endothelial progenitor cells do not contribute to plaque endothelium in murine atherosclerosis. *Circulation* 2010;**121**:898–905.
49. Teo KK, Ounpuu S, Hawken S, Pandey MR, Valentin V, Hunt D, Diaz R, Rashed W, Freeman R, Jiang L, Zhang X, Yusuf S; INTERHEART Study Investigators. Tobacco

use and risk of myocardial infarction in 52 countries in the INTERHEART study: a case-control study. *Lancet* 2006;**368**:647–658.
50. Wang TJ, Gona P, Larson MG, Tofler GH, Levy D, Newton-Cheh C, Jacques PF, Rifai N, Selhub J, Robins SJ, Benjamin EJ, D'Agostino RB, Vasan RS. Multiple biomarkers for the prediction of first major cardiovascular events and death. *N Engl J Med* 2006;**355**:2631–2639.
51. Roy H, Bhardwaj S, Ylä-Herttuala S. Molecular genetics of atherosclerosis. *Hum Genet* 2009;**125**:467–491.
52. Turunen MP, Aavik E, Ylä-Herttuala S. Epigenetics and atherosclerosis. *Biochim Biophys Acta* 2009;**1790**:886–891.
53. Hoffmann U, Moselewski F, Nieman K, Jang IK, Ferencik M, Rahman AM, Cury RC, Abbara S, Joneidi-Jafari H, Achenbach S, Brady TJ. Noninvasive assessment of plaque morphology and composition in culprit and stable lesions in acute coronary syndrome and stable lesions in stable angina by multidetector computed tomography. *J Am Coll Cardiol* 2006;**47**:1655–1662.
54. Garcia-Garcia HM, Mintz GS, Lerman A, Vince DG, Margolis MP, van Es GA, Morel MA, Nair A, Virmani R, Burke AP, Stone GW, Serruys PW. Tissue characterisation using intravascular radiofrequency data analysis: recommendations for acquisition, analysis, interpretation and reporting. *EuroIntervention* 2009;**5**:177–189.
55. Kubo T, Imanishi T, Takarada S, Kuroi A, Ueno S, Yamano T, Tanimoto T, Matsuo Y, Masho T, Kitabata H, Tsuda K, Tomobuchi Y, Akasaka T. Assessment of culprit lesion morphology in acute myocardial infarction: ability of optical coherence tomography compared with intravascular ultrasound and coronary angioscopy. *J Am Coll Cardiol* 2007;**50**:933–939.
56. Uemura S, Ishigami K, Soeda T, Okayama S, Sung JH, Nakagawa H, Somekawa S, Takeda Y, Kawata H, Horii M, Saito Y. Thin-cap fibroatheroma and microchannel findings in optical coherence tomography correlate with subsequent progression of coronary atheromatous plaques. *Eur Heart J* 2012;**33**:78–85.
57. Brugaletta S, Garcia-Garcia HM, Serruys PW, de Boer S, Ligthart J, Gomez-Lara J, Witberg K, Diletti R, Wykrzykowska J, van Geuns RJ, Schultz C, Regar E, Duckers HJ, van Mieghem N, de Jaegere P, Madden SP, Muller JE, van der Steen AF, van der Giessen WJ, Boersma E. NIRS and IVUS for characterization of atherosclerosis in patients undergoing coronary angiography. *JACC Cardiovasc Imaging* 2011;**4**:647–655.
58. Lamare F, Hinz R, Gaemperli O, Pugliese F, Mason JC, Spinks T, Camici PG, Rimoldi OE. Detection and quantification of large-vessel inflammation with 11c-(r)-pk11195 pet/ct. *J Nucl Med* 2011;**52**:33–39.
59. Wu JC, Ylä-Herttuala S. Human gene therapy and imaging: cardiology. *Eur J Nucl Med Mol Imaging* 2005;**32**:S346–S357.
60. Crisby M, Nordin-Fredriksson G, Shah PK, Yano J, Zhu J, Nilsson J. Pravastatin treatment increases collagen content and decreases lipid content, inflammation, metalloproteinases, and cell death in human carotid plaques: implications for plaque stabilization. *Circulation* 2001;**103**:926–933.
61. Cortellaro M, Cofrancesco E, Arbustini E, Rossi F, Negri A, Tremoli E, Gabrielli L, Camera M. Atorvastatin and thrombogenicity of the carotid atherosclerotic plaque: the ATROCAP study. *Thromb Haemost* 2002;**88**:41–47.
62. Tuomisto TT, Lumivuori H, Kansanen E, Häkkinen SK, Turunen MP, van Thienen JV, Horrevoets AJ, Levonen AL, Ylä-Herttuala S. Simvastatin has an anti-inflammatory effect on macrophages via upregulation of an atheroprotective transcription factor, Kruppel-like factor 2. *Cardiovasc Res* 2008;**78**:175–184.
63. Patel R, Janoudi A, Vedre A, Aziz K, Tamhane U, Rubinstein J, Abela OG, Berger K, Abela GS. Plaque rupture and thrombosis are reduced by lowering cholesterol levels and crystallization with ezetimibe and are correlated with fluorodeoxyglucose positron emission tomography. *Arterioscler Thromb Vasc Biol* 2011;**31**:2007–2014.
64. Schartl M, Bocksch W, Koschyk DH, Voelker W, Karsch KR, Kreuzer J, Hausmann D, Beckmann S, Gross M. Use of intravascular ultrasound to compare effects of different strategies of lipid-lowering therapy on plaque volume and composition in patients with coronary artery disease. *Circulation* 2001;**104**:387–392.
65. Nissen SE, Nicholls SJ, Sipahi I, Libby P, Raichlen JS, Ballantyne CM, Davignon J, Erbel R, Fruchart JC, Tardif JC, Schoenhagen P, Crowe T, Cain V, Wolski K, Goormastic M, Tuzcu EM; ASTEROID Investigators. Effect of very high-intensity statin therapy on regression of coronary atherosclerosis: the ASTEROID trial. *JAMA* 2006;**295**:1556–1565.
66. Nicholls SJ, Borgman M, Nissen SE, Raichlen JS, Ballantyne C, Barter P, Chapman MJ, Erbel R, Libby P. Impact of statins on progression of atherosclerosis: rationale and design of SATURN (Study of Coronary Atheroma by InTravascular Ultrasound: effect of Rosuvastatin versus AtorvastatiN). *Curr Med Res Opin* 2011;**27**:1119–1129.
67. Nicholls SJ, Tuzcu EM, Sipahi I, Grasso AW, Schoenhagen P, Hu T, Wolski K, Crowe T, Desai MY, Hazen SL, Kapadia SR, Nissen SE. Statins, high-density lipoprotein cholesterol, and regression of coronary atherosclerosis. *JAMA* 2007;**297**:499–508.
68. Cannon CP, Braunwald E, McCabe CH, Rader DJ, Rouleau JL, Belder R, Joyal SV, Hill KA, Pfeffer MA, Skene AM. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med* 2004;**350**:1495–1504.
69. Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto AM Jr, Kastelein JJ, Koenig W, Libby P, Lorenzatti AJ, MacFadyen JG, Nordestgaard BG, Shepherd J, Willerson JT, Glynn RJ; JUPITER Study Group. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med* 2008;**359**:2195–2207.
70. Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK; Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med* 2001;**345**:494–502.
71. Oldgren J, Wallentin L, Alexander JH, James S, Jönelid B, Steg G, Sundström J. New oral angicoagulants in addition to single or dual antiplatelet therapy after an acute coronary syndrome: a systematic review and meta-analysis. *Eur Heart J* 2013;**34**:1670–1680.
72. Sipahi I, Tuzcu EM, Wolski KE, Nicholls SJ, Schoenhagen P, Hu B, Balog C, Shishehbor M, Magyar WA, Crowe TD, Kapadia S, Nissen SE. Beta-blockers and progression of coronary atherosclerosis: pooled analysis of 4 intravascular ultrasonography trials. *Ann Intern Med* 2007;**147**:10–18.
73. Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. *N Engl J Med* 2000;**342**:145–153.
74. Yusuf S, Teo KK, Pogue J, Dyal L, Copland I, Schumacher H, Dagenais G, Sleight P, Anderson C; ONTARGET Investigators. Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med* 2008;**358**:1547–1559.
75. Shah PK, Yano J, Reyes O, Chyu KY, Kaul S, Bisgaier CL, Drake S, Cercek B. High-dose recombinant apolipoprotein A-I(milano) mobilizes tissue cholesterol and rapidly reduces plaque lipid and macrophage content in apolipoprotein e-deficient mice. Potential implications for acute plaque stabilization. *Circulation* 2001;**103**:3047–3050.
76. Barter PJ, Caulfield M, Eriksson M, Grundy SM, Kastelein JJP, Komajda M, Lopez-Sendon J, Mosca L, Tardif J-C, Waters DD, Shear CL, Revkin JH, Buhr KA, Fisher MR, Tall AR, Brewer B; for the ILLUMINATE Investigators. Effect of torcetrapib in patients at high risk for coronary events. *N Engl J Med* 2007;**357**:2109–2122.
77. Schwartz GG, Olsson AG, Abt M, Ballantyne CM, Barter PJ, Brumm J, Chaitman BR, Holme IM, Kallend D, Leiter LA, Leitersdorf E, McMurray JJV, Mundi H, Nicholls SJ, Shah PK, Tardif J-C, Wright RS; for the dal-OUTCOMES Investigators. Effects of dalcetrapib in patients with a recent acute coronary syndrome. *N Engl J Med* 2012;**367**:2089–2099.
78. Voight BF, Peloso GM, Orho-Melander M, Frikke-Schmidt R, Barbalic M, Jensen MK, Hindy G, Hólm H, Ding EL, Johnson T, Schunkert H, Samani NJ, Clarke R, Hopewell JC, Thompson JF, Li M, Thorleifsson G, Newton-Cheh C, Musunuru K, Pirruccello JP, Saleheen D, Chen L, Stewart A, Schillert A, Thorsteinsdottir U, Thorgeirsson G, Anand S, Engert JC, Morgan T, Spertus J, Stoll M, Berger K, Martinelli N, Girelli D, McKeown PP, Patterson CC, Epstein SE, Devaney J, Burnett MS, Mooser V, Ripatti S, Surakka I, Nieminen MS, Sinisalo J, Lokki ML, Perola M, Havulinna A, de Faire U, Gigante B, Ingelsson E, Zeller T, Wild P, de Bakker PI, Klungel OH, Maitland-van der Zee AH, Peters BJ, de Boer A, Grobbee DE, Kamphuisen PW, Deneer VH, Elbers CC, Onland-Moret NC, Hofker MH, Wijmenga C, Verschuren WM, Boer JM, van der Schouw YT, Rasheed A, Frossard P, Demissie S, Willer C, Do R, Ordovas JM, Abecasis GR, Boehnke M, Mohlke KL, Daly MJ, Guiducci C, Burtt NP, Surti A, Gonzalez E, Purcell S, Gabriel S, Marrugat J, Peden J, Erdmann J, Diemert P, Willenborg C, König IR, Fischer M, Hengstenberg C, Ziegler A, Buysschaert I, Lambrechts D, Van de Werf F, Fox KA, El Mokhtari NE, Rubin D, Schrezenmeir J, Schreiber S, Schäfer A, Danesh J, Blankenberg S, Roberts R, McPherson R, Watkins H, Hall AS, Overvad K, Rimm E, Boerwinkle E, Tybjaerg-Hansen A, Cupples LA, Reilly MP, Melander O, Mannucci PM, Ardissino D, Siscovick D, Elosua R, Stefansson K, O'Donnell CJ, Salomaa V, Rader DJ, Peltonen L, Schwartz SM, Altshuler D, Kathiresan S. Plasma HDL cholesterol and risk of myocardial infarction: a mendelian randomisation study. *Lancet* 2012;**380**:572–580.
79. Lee JM, Robson MD, Yu LM, Shirodaria CC, Cunnington C, Kylintireas I, Digby JE, Bannister T, Handa A, Wiesmann F, Durrington PN, Channon KM, Neubauer S, Choudhury RP. Effects of high-dose modified-release nicotinic acid on atherosclerosis and vascular function: a randomized, placebo-controlled, magnetic resonance imaging study. *J Am Coll Cardiol* 2009;**54**:1787–1794.
80. Taylor AJ, Villines TC, Stanek EJ, Devine PJ, Griffen L, Miller M, Weissman NJ, Turco M. Extended-release niacin or ezetimibe and carotid intima-media thickness. *N Engl J Med* 2009;**361**:2113–2122.
81. Serruys PW, Garcia-Garcia HM, Buszman P, Erne P, Verheye S, Aschermann M, Duckers H, Bleie O, Dudek D, Bøtker HE, von Birgelen C, D'Amico D, Hutchinson T,

Zambanini A, Mastik F, van Es GA, van der Steen AF, Vince DG, Ganz P, Hamm CW, Wijns W, Zalewski A; Integrated Biomarker and Imaging Study-2 Investigators. Effects of the direct lipoprotein-associated phospholipase A(2) inhibitor darapladib on human coronary atherosclerotic plaque. *Circulation* 2008;**118**:1172–1182.
82. Koenen RR, Weber C. Therapeutic targeting of chemokine interactions in atherosclerosis. *Nat Rev Drug Discov* 2009;**9**:141–153.
83. Tibolla G, Norata GD, Artali R, Meneghetti F, Catapano AL. Proprotein convertase subtilisin/kexin type 9 (PCSK9): from structure-function relation to therapeutic inhibition. *Nutr Metab Cardiovasc Dis* 2011;**21**:835–843.
84. Akdim F, Tribble DL, Flaim JAD, Yu R, Su J, Geary RS, Baker BF, Fuhr R, Wedel MK, Kastelein JJP. Efficacy of apolipoprotein B synthesis inhibition in subjects with mild-to-moderate hyperlipidaemia. *Eur Heart J* 2011;**32**:2650–2659.
85. Binder CJ, Chang M-K, Shaw PX, Miller YI, Hartvigsen K, Dewan A, Witztum JL. Innate and acquired immunity in atherogenesis. *Nat Med* 2002;**8**:1218–1226.
86. Ahmed T, Karalis I, Jukema JW. Emerging drugs for coronary artery disease. From past achievements and current needs to clinical promises. *Expert Opin Emerg Drugs* 2011;**16**:203–233.

CARDIOVASCULAR FLASHLIGHT

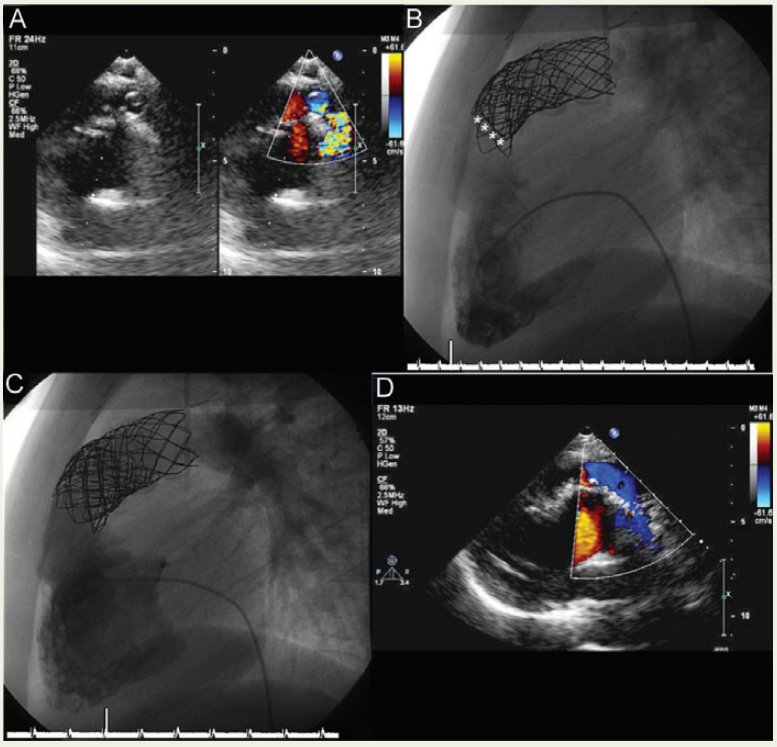
doi:10.1093/eurheartj/eht025
Online publish-ahead-of-print 1 February 2013

Accidental stent fracture due to chest trauma after percutaneous Melody valve implantation

Sven Hormann, Walter Knirsch*, and Oliver Kretschmar

Division of Cardiology, University Children's Hospital Zurich, Steinwiesstrasse 75, Zurich 8032, Switzerland

* Corresponding author. Tel: +41 44 2667617, Fax: +41 44 2667981, Email: walter.knirsch@kispi.uzh.ch



A 12-year-old boy was treated with percutaneous Melody valve implantation (Medtronic, Inc., USA) due to a severe right ventricular (RV) to pulminary artery (PA) homograft stenosis. Two years later, while playing at a swimming pool, the boy received a powerful and unexpected hit to his back by a rubber tyre. He immediately complained about severe back and chest pain, general weakness, nausea, and one episode of syncope during exertion. Doppler echocardiography revealed a new severe pulmonary (Melody) valve stenosis with a narrowed lumen and a free floating structure inside (*Panel A*). Cardiac catheterization revealed severe RV-PA obstruction (peak-to-peak-gradient 40 mmHg). This was caused by fractures of anterior and proximal stent struts of the Melody valve just behind sternal boarder ("coup contre-coup" mechanism) leading to dynamic narrowing of the stent lumen by protruding like an additional valve into the vessel lumen during systole (*Panel B*, asterisks; Supplementary material online, *Video loop S1*). Melody valve integrity itself was not affected. Therefore, implantation of a second Melody valve inside the old valve ("valve-in-valve") was carried out. After intervention, Melody valve position and function were excellent (*Panel C*; Supplementary material online, *Video loop S2*). On echo, at discharge 3 days later, Melody valve showed a laminar flow pattern (*Panel D*).

Coup contre-coup mechanism due to accidental chest trauma may cause strut fractures of the valved stent due its anatomic nearness to sternal border. In this situation, a percutaneous valve-in-valve procedure has to be considered. This can be performed safely and avoids cardiopulmonary bypass surgery.

Supplementary material is available at *European Heart Journal* online.