

New Approaches in Atherothrombosis

Summaries of Ten Seminal Papers

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Prevention of cardiovascular events and death
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Inflammation, atherosclerosis, and coronary artery disease

G. K. Hansson

N Engl J Med. 2005;352:1685-1695

For every clinical cardiologist and cardiovascular researcher, Dr Göran Hansson's review article on inflammation, atherosclerosis, and coronary artery disease should be compulsory reading. In his paper, Hansson covers both the basic science aspects of atherosclerosis as well as the clinical scenario of acute coronary syndromes and therapeutic options, all with just the right amount of detail to please both basic researchers and clinicians.

In the first section, the author delineates the main features of atherosclerotic lesion development. The principles of atherosclerotic lesion formation, propagation and, finally, plaque rupture are explained and beautifully illustrated by histological sections as well as colorful drawings. Since mice do not spontaneously develop atherosclerosis, he explains how animal models have proven helpful for studying atherogenesis and how genetic models such as the apolipoprotein E (apoE) or the low-density lipoprotein (LDL) receptor knockout mouse are used to mimic disease progression in humans. By cross-breeding these mice with knockout animals deficient in certain immunoregulatory genes, it became possible to study specific aspects of the inflammatory mechanisms of atherogenesis. Hansson further explains how these animal models, as well as *in vitro* and *ex vivo* human studies, have helped elucidating the different steps of plaque propagation, including endothelial cell activation, macrophage infiltration, foam cell formation, and T-cell activation—all of which through production and secretion of a wealth of mediators contribute to the pronounced proinflammatory environment of the atherosclerotic plaque. Finally, the author explains how anti-inflammatory mediators such as interleukin-10 and transforming growth factor- β act as protective elements in atherogenesis.

The second section is devoted to the clinical scenario of acute coronary syndromes. Hansson elegantly elucidates the mechanisms of atherosclerotic plaque rupture and the inflammatory events involved (especially the effects of matrix metalloproteinases and cysteine proteases), which inhibit the formation of a stable cap and instead lead to plaque destabilization. In the event of plaque rupture, the

prothrombotic content of the atherosclerotic plaque (including phospholipids, tissue factor (see below), and platelet-adhesive matrix molecules) is directly exposed to the blood stream, leading to activation of coagulation and, eventually, thrombotic vessel occlusion. This event is mirrored in the systemic circulation by elevated levels of acute phase proteins such as C-reactive protein (CRP), CD40 ligand, fibrinogen, and interleukins, which have therefore been proposed as markers for the risk of coronary artery disease. However, the author is careful to avoid ascribing a causative role to any single one of these mediators as several inflammatory markers with distinct biological properties contribute to the increased risk of coronary artery disease.

The final section discusses the treatments available to counter these events, in particular those that prevent and treat atherosclerotic diseases by taking into account the inflammatory nature of atherosclerosis. Among the most widely used drugs, β -hydroxy- β -methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) have been most extensively studied. These drugs appear to directly interfere with plaque progression, mainly due to their pleiotropic anti-inflammatory effects. Other experimental, potential therapeutic approaches such as immunization or the use of immunosuppressive drugs are equally being discussed. Last but not least, this very well written and comprehensive review lists 112 very useful references for further in depth reading.

2005

2005 is named the World Year of Physics in recognition of the 100th anniversary of the publication of Einstein's four landmark papers; English playwright and poet Harold Pinter wins the Nobel prize for literature; and Ellen MacArthur breaks the world record for a solo circumnavigation when she completes the 27 000-mile journey in 71 days, 14 hours, 18 minutes, and 33 seconds



Reduced endothelial nitric oxide synthase expression and production in human atherosclerosis

B. S. Oemar, M. R. Tschudi, N. Godoy, V. Brovkovich, T. Malinski, T. F. Lüscher

Circulation. 1998;97:2494-2498

Nitric oxide (NO) plays a pivotal role in vascular tone regulation and hemostasis. It relaxes vascular smooth muscle cells, inhibits platelet activation, and modulates migration and proliferation of smooth muscle cells. It was already known before the publication of this paper from animal models that the endothelial NO pathway is importantly involved in atherosclerosis; however, little was known about this in humans. In their manuscript, Oemar and colleagues provided the first evidence that NO release as well as endothelial NO synthase (eNOS) expression is severely reduced in human atherosclerotic vessels.

The authors compared carotid arteries from 10 patients to internal mammary arteries (IMA) from 10 age-matched control subjects. The internal mammary artery was chosen as the "control" vessel as it is known to rarely be affected by atherosclerosis. The presence or absence of atherosclerotic lesions was confirmed histologically.

In order to study NO release, isolated vessel segments were cut longitudinally and placed in an organ chamber. After stimulation with 10 $\mu\text{mol/L}$ calcium ionophore, NO release was measured by means of a NO microsensor placed on the endothelial surface of the vessel. The authors observed a rapid release of NO in atherosclerosis-free IMA segments in response to the ionophore. In contrast, both the initial peak of NO release as well as maximal NO concentrations were significantly reduced in atherosclerotic arteries. Great care was taken to handle the specimens as gently as possible (since damage to the endothelial layer can greatly impede its function and hence its capacity to release NO); this included skilled preparation of the vessel *in situ*, careful handling of the vessel *ex vivo* and immediate analysis (<30 minutes after explantation) of NO release.

The second section of the manuscript looks at immunohistochemical analyses. When normal arterial segments were labeled with a monoclonal antibody for eNOS, the authors found high levels of eNOS expression in luminal endothelial cells, whereas it was undetectable in luminal

endothelial cells of carotid segments with advanced atherosclerosis. Since failure to stain may always represent a technical artifact of immunohistochemistry (rather than a true phenomenon) the authors convincingly demonstrate that this is not the case in their study, since the vasa vasorum of atherosclerotic vessels on the same slides strongly stained for eNOS.

An important point of discussion was the obvious contradiction of the authors' results with previous animal data where rabbit models of atherosclerosis displayed increased eNOS protein and mRNA levels in the atherosclerotic aorta. The authors discuss this issue on several levels. On the one hand, atherosclerosis develops over decades in humans, whereas it only takes months in rabbits; as a consequence, vascular lesions of hypercholesterolemic rabbits mimic human plaques only in part, and thus the entire animal model may not fully resemble the situation encountered in humans. From a more fundamental standpoint, the difference between animal and human data encountered in this specific work once more exemplified a well-known dilemma in translational research: while some *in vitro* and *in vivo* animal results translate well into the situation in humans, others are lost in translation. Here, Oemar and colleagues have contributed in a significant way to the current understanding of endothelial dysfunction in atherosclerotic vascular disease in humans.

1998

The Chicago Bulls win their 6th NBA title, marking the end of Michael Jordan's career as a Bull;
Nepalese police intercept a shipment of 272 human skulls in Kathmandu; and a high-speed train crashes into a concrete pillar of a road overpass in Northern Germany causing 98 deaths

A comparison of balloon-expandable-stent implantation with balloon angioplasty in patients with coronary artery disease

P. W. Serruys, P. de Jaegere, F. Kiemeneij, C. Macaya, W. Rutsch, G. Heyndrickx, H. Emanuelsson, J. Marco, V. Legrand, P. Materne, et al; Benestent Study Group

N Engl J Med. 1994;331:489-495

In patients with stable coronary artery disease, percutaneous interventions are most frequently performed in the case of 1- and 2-vessel disease, while patients with main stem or 3-vessel disease usually undergo surgery. In the early days, the main mid- to long-term limitation of balloon angioplasty was the development of coronary restenosis, with rates ranging up to 50% of cases.

In their landmark study, Patrick Serruys and the Benestent Study Group investigated the long-term effectiveness of balloon-expandable stent implantation to hold coronary vessels open after dilation in an end-point driven, randomized clinical trial. A total of 520 patients with stable angina and 1-vessel coronary artery disease were randomized to either standard balloon angioplasty or angioplasty plus stent implantation. The primary clinical end points were death (from any cause), the need for coronary artery bypass surgery (involving the previously treated segment), the occurrence of cerebrovascular accident or myocardial infarction, or a repeat percutaneous transluminal coronary angioplasty (PTCA)—either immediately at the time of intervention or during the following 7 months. After 7 months, a primary clinical end point was reached by 30% of patients treated with angioplasty alone, compared with 20% of patients treated with stent implantation, corresponding to a relative risk reduction of 32%. The benefit of stent implantation was most striking with respect to the reduction in the need of an elective second revascularization, which was reduced by 42%, compared with angioplasty alone. The primary angiographic end point was set to be the minimal lumen diameter at the 7 months follow-up angiography (or earlier, if needed). After stent implantation, the minimal lumen diameter was 1.82 mm (± 0.64 mm) vs 1.73 (± 0.55 mm), which, however, fell short of reaching statistical significance ($P=0.09$). Restenosis (defined as $>50\%$ stenosis) was 22% after stenting vs 32% after balloon angioplasty ($P=0.02$).

In contrast, the rate of bleeding and vascular complications was higher after stent implantation (13.5%) vs balloon angioplasty alone (3.1%), corresponding to an increased

relative risk of 4.34-fold. This, however, did not come as a surprise, and may in fact be explained by the common practice at the time to put patients on warfarin for 3 months after stent implantation (in the absence of potent, dual antiplatelet therapy as is now standard). The authors argue against the possibility that oral anticoagulation per se was also responsible for the observed clinical benefits of stent implantation, as a number of earlier clinical studies collectively failed to observe an effect of oral anticoagulation on the development of restenosis.

In the same issue of the *New England Journal of Medicine*, David Fishmann and the Stent Restenosis Study Investigators reported similar results in their study of 410 patients with coronary artery disease. Together with others, these two studies paved the way for the widespread use of coronary artery stents in the treatment of coronary artery disease. Eventually, stenting in more complex vessels (eg, small vessels, bypass vessels) as well as in the setting of highly prothrombotic situations such as acute myocardial infarction, became established. However, several limitations of this technique remained, and while restenosis continued to be a concern (although not to the same degree than after PTCA alone), the widespread use of coronary artery stents also gave rise to the “iatrogenic disease” of stent thrombosis, which to this very day remains one of the most dreaded complications of interventional cardiology.

1994

The Russian army leaves Estonia;
Wollemia nobilis, a living fossil and the sole remaining species in the genus *Wollemia* is discovered by bushwalker David Noble 150 km northwest of Sydney; and Woodstock '94 begins in Saugerties, NY, to mark the 25th anniversary of the original Woodstock festival



Site of intimal rupture or erosion of thrombosed coronary atherosclerotic plaques is characterized by an inflammatory process irrespective of the dominant plaque morphology

A. C. van der Wal, A. E. Becker, C. M. van der Loos, P. K. Das

Circulation. 1994;89:36-44

By the beginning of the 1990s, evidence had emerged that the risk of atherosclerotic plaque rupture and coronary thrombosis was related to the composition of the atherosclerotic plaque. Furthermore, the inflammatory nature of atherogenesis was increasingly appreciated. The significance of these pathological and inflammatory changes for the progression and fate of the atherosclerotic plaque, however, was not entirely clear. Allard van der Wal and colleagues report in this paper on the sites of plaque rupture in 20 patients who had died of acute myocardial infarction. Their aim was to find out whether rupture-borne plaques shared certain characteristics with respect to their morphology and/or composition, and what role the inflammatory process played in plaque rupture and thrombosis.

To do so, the authors identified on autopsy the thrombosed coronary arteries responsible for the recent transmural myocardial infarctions. The hearts were embedded, serially sliced, and examined by histochemistry and immunohistochemistry. The latter included sophisticated stainings for IA4 (for smooth muscle actin), HAM56 (for macrophages and some endothelial cells), CR3/43 (for MHC class II molecules on macrophages, endothelium and activated T cells, and a subpopulation of smooth muscle cells), LCA (for CD45 present on all lymphocytes), and UCHL-1 (for CD45RO present on memory T cells and a subpopulation of macrophages), including the necessary negative controls to exclude nonspecific antibody binding.

The results are presented based on a wealth of very instructive and high-quality histological sections. Overall, a large lipid core of the coronary atherosclerotic plaques underlying a recent luminal thrombus was found in 17 out of 20 cases. In 10 cases, virtually no fibrous cap was detected, while 7 had a prominent fibrous cap.

In 12 of the plaques, the fibrous cap was entirely ruptured, and the fissure extended into the lipid core with evidence of recent intraplaque hemorrhage and (in some cases) extrusion of the lipids core. In these cases, the plaque was extremely attenuated and immunohistochemical staining

showed an impressive macrophage predominance with only comparatively few lymphocytes. In 4 cases, a thick and well-developed fibrous cap with smooth muscle cell predominance was observed. Interestingly, no rupture occurred in the areas in which smooth muscle cells predominated. In contrast, a small area of tightly packed macrophages (again with some T lymphocytes) could be observed at the rupture site of all of these plaques.

Fibrous cap rupture was absent in 8 of the 20 cases examined; instead, these plaques "only" showed evidence of intimal erosions with damage to the endothelium and superficial intimal layers. Overall, these cases displayed a heterogeneous composition; yet, in all instances, a mixture of macrophages and T lymphocytes was detected at the site of the lesion.

In summary, the authors inevitably came to the conclusion that, whatever the underlying atherosclerotic plaque morphology (deep plaque rupture vs endothelial erosions), a pronounced inflammatory reaction consisting of large numbers of macrophages and T cells, combined with the absence of smooth muscle cells, is invariably present at the site of plaque rupture. Van der Wal and colleagues' work hence contributed in a major way to the perception that the inflammatory component of the plaque is of pivotal importance with respect to its potential to rupture and cause subsequent thrombotic vessel occlusion.

1994

The grunge rock band Nirvana plays its last show in Munich, Germany; Rwandan President Juvénal Habyarimana and Burundi President Cyprien Ntaryamira die when a missile shoots down their jet near Kigali, Rwanda; and former United States President Richard Nixon dies in New York City

Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation

S. Yusuf, F. Zhao, S. R. Mehta, S. Chrolavicius, G. Tognoni, K. Fox; Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators

New Engl J Med. 2001;345:494-502

Atherosclerotic plaque rupture with subsequent thrombus formation is the anatomical and pathophysiological correlate of acute coronary syndromes. It was long known that inhibition of platelet aggregation with aspirin reduces the risk of death from cardiovascular events (including new myocardial infarctions) in patients with known coronary artery disease. Furthermore, combining aspirin with a thienopyridine like clopidogrel for a short period of time had been proven beneficial after percutaneous transluminal coronary angioplasty (PTCA) with stenting due to the complementary mechanisms of platelet inhibition (ie, blockade of the ADP P2Y₁₂ receptor by clopidogrel and inhibition of cyclooxygenase by aspirin).

In the landmark CURE (Clopidogrel in Unstable Angina to prevent Recurrent Events) study, Salim Yusuf and colleagues investigated the efficacy and safety of clopidogrel in addition to aspirin in patients with acute coronary syndrome without ST-segment elevation. Over 12 000 patients presenting within 24 hours after symptom onset were randomly assigned to receive clopidogrel or placebo in addition to aspirin, for 3 to 12 months.

The composite end point of death from cardiovascular causes, nonfatal myocardial infarction, or stroke (ie, the first primary outcome) was observed in 9.3% and 11.4% of patients in the clopidogrel and the placebo group, respectively, corresponding to a relative risk reduction of 20%. The second primary outcome (ie, death from cardiovascular causes, nonfatal myocardial infarction, stroke, or refractory ischemia) was reduced by 14%, occurring in 16.5% and 18.8% of patients in the clopidogrel and the placebo group, respectively. In the analyses of the different components of the primary outcome measures, the most impressive risk reduction occurred in the incidence of myocardial infarction, which was reduced by 33% with the use of clopidogrel (from 6.7% to 5.2%).

Interestingly, the benefit of clopidogrel in terms of death from cardiovascular causes, nonfatal myocardial infarction, stroke, or refractory or severe ischemia was most pro-

nounced within the first 24 hours, resulting in a decrease in these events by 34%. This difference was maintained over time, as also within the first 30 days (relative risk reduction 21%), and between 30 days and the end of the study (relative risk reduction, 18%), the reduction in events remained significant and clinically relevant. Moreover, the benefits of clopidogrel were observed over the entire range of patients both at low, medium, and high risk of cardiovascular events. On the downside, the authors noted an increase in major bleeding after application of clopidogrel (3.7% vs 2.7%, relative increased risk 28%), while life-threatening bleeding or hemorrhagic strokes were similar.

In summary, a clear benefit of adding clopidogrel to aspirin was observed for the prevention of atherothrombotic complications in patients with acute coronary syndromes without ST-segment changes. By showing that, CURE changed the way in which patients with non-ST-segment-elevation myocardial infarction (NSTEMI) were treated, and over the following years, dual antiplatelet therapy with aspirin and clopidogrel was to acquire an ever increasingly important role in the treatment of patients with coronary artery disease. Subsequent to CURE, its benefit was observed in patients undergoing revascularization (studied in the PCI [Percutaneous Coronary Intervention]-CURE subgroup analysis as well as in the CREDO [Clopidogrel for the Reduction of Events During Observation] trial). Recently, dual antiplatelet inhibition has been shown to be of great benefit (if not indispensable) in patients after drug-eluting stent implantation, especially as a result of the potentially increased risk of stent thrombosis with these stents.

2001

R&B singer Aaliyah dies when her plane crashes in the Bahamas; the Japanese cities of Urawa, Omiya, and Yono merge to form the city of Saitama; and Mohammad Khatami becomes President of Iran, promising to enact reforms in his second term



Pathology of drug-eluting stents in humans: delayed healing and late thrombotic risk

M. Joner, A. V. Finn, A. Farb, E. K. Mont, F. D. Kolodgie, E. Ladich, R. Kutys, K. Skorija, H. K. Gold, R. Virmani

J Am Coll Cardiol. 2006;48:193-202

The timing of this seminal article on the pathology of drug-eluting stents (DES) in humans, by Joner and colleagues, could probably not have been any better. After the initial enthusiasm of almost abolished restenosis with the use of this novel type of stent, clues were slowly but surely emerging from long-term follow up of randomized clinical trials and large-scale registries pointing to a potentially increased risk for stent thrombosis in DES compared with bare-metal stents (BMS). In their article, the authors provide a possible pathological basis for this observation.

Joner and colleagues examined 40 consecutive autopsy cases with evidence of one or more DES implantation. A total of 23 of these stents had been implanted >30 days previously and were compared with 25 controls matched for age, gender, case duration, and artery of implantation, who had a BMS implanted for >30 days. The stented arteries were processed and stained by histochemistry. Cases with histologic evidence of a thrombus in the stented artery were defined as late stent thrombosis (LST).

As expected, the analyzed BMS had significantly more in-stent restenosis (32.1% vs 20.2%) and neointimal growth compared with DES. However, LST was detected in 14 of the 23 DES cases (61%) vs only 2/25 (8%) matched BMS cases. The authors present one of the potential explanations for this phenomenon: the percentage of endothelial coverage was considerably higher in BMS (89.8%) compared with DES (55.8%), and delayed arterial healing turned out to be the "cardinal risk factor" in all 14 patients with LST in DES. Further pathologic risk factors for LST in DES were chronic vessel wall inflammation, stenting along major side branches using the crush technique and/or stenting over major branch points, malapposition or incomplete stent apposition, in-stent restenosis with superimposed thrombosis, and strut penetration of the necrotic plaque core. In contrast, the 2 BMS cases with LST appeared to have occurred secondary to restenosis. The authors accompany these bare numbers with impressive cross-sectional images of stented coronary artery segments. Moreover, discontinuation of antiplatelet therapy

appeared as a clinical risk factor (as had been suggested in several previous clinical observations) with only 7/14 patients (50%) still on dual antiplatelet therapy at the time of stent thrombosis.

The authors then seek to determine whether there is a difference in the type of vessel wall reactivity to rapamycin-eluting stents as compared with paclitaxel-eluting stents. They found that 60 days after implantation, the rapamycin-eluting Cypher stent was associated with a greater inflammatory reaction of the vessel wall (including eosinophils and giant cells), while paclitaxel-eluting Taxus stents showed greater fibrin deposition; BMS did not show fibrin deposition at that time point, but a significantly greater neointimal area with considerably less inflammation. However, these comparisons, especially the ones between the 2 types of DES, were limited due to the small overall number of stents examined.

This article by Joner and colleagues is in line with previous publications from Virmani's laboratory emphasizing the key hypothesis in the pathogenesis of DES thrombosis, ie, delayed endothelial healing. Their work has inspired both clinicians and researchers in their effort for optimal patient treatment and the development of the next generation of coronary stents.

2006

The Nathula Pass between India and China, closed during the Sino-Indian War, reopens for trade after 44 years; Italy defeats France 5-3 on penalties to win the 2006 football World Cup; and American cyclist Floyd Landis wins the Tour de France; however, tour officials soon announce that he has failed a doping test

Tissue factor in cardiovascular diseases: molecular mechanisms and clinical implications

J. Steffel, T. F. Lüscher, F. C. Tanner

Circulation. 2006;113:722-731

Tissue factor (TF) is the key initiator of coagulation and as such plays a pivotal role in thrombus formation and, consequently, in atherosclerotic-based vascular diseases like acute coronary syndromes. In this review—published in *Circulation's* “Basic Science For Clinicians” series—the authors comprehensively cover the spectrum of TF biology: its molecular regulation, its role in clinical scenarios such as acute coronary syndrome, and the potential for directed therapeutic interventions.

The molecular regulation of TF is complex and has been the subject of intense research. TF is constitutively expressed in subendothelial cells of the vessel wall (such as vascular smooth muscle cells and fibroblasts), and allows rapid initiation of coagulation when vessel damage occurs. In contrast, cells that come into contact with the flowing blood under physiological conditions, ie, endothelial cells and monocytes, only express TF in very scarce amounts, if at all. However, TF expression and activity can be induced in these cells as well in response to numerous (mostly inflammatory) stimuli such as tumor necrosis factor α (TNF- α), thrombin, endotoxin, and histamine. In the first section of their paper, the authors delineate the molecular mechanisms involved in TF induction, particularly in endothelial cells and monocytes, and summarize recent advances in terms of signal transduction, transcription, and posttranscriptional modification such as surface TF “encryption” and TF microparticle release.

In the second section, the authors discuss the role of TF in cardiovascular diseases. Interestingly, TF expression and/or activity has been observed to be increased in patients with cardiovascular risk factors such as hypertension, diabetes mellitus, dyslipidemia, and smoking. Consequently, therapeutic interventions based on angiotensin-converting enzyme (ACE) inhibitors, angiotensin II type I receptor blockade, insulin treatment, and statins reduce TF levels in vitro and in vivo. Of note, TF not only serves as the main initiating event in the coagulation cascade, but also stimulates vascular smooth muscle cell migration and proliferation, and may thus directly promote atherogenesis and resteno-

sis. However, while the concept of a direct effect of cardiovascular risk factors on TF levels seems appealing, it cannot be excluded that the increase in TF levels in these situations occurs because of TF release from already established plaques. Indeed, due to the pronounced inflammatory nature of atherosclerosis, the atherosclerotic plaque represents an enormous reservoir of TF, arising both from massively increased expression of TF by surrounding cells as well as from the TF-containing particles amassed in the necrotic plaque core. Consequently, rupture of an atherosclerotic plaque (as occurs in acute coronary syndromes) releases this highly procoagulant content into the blood stream, resulting in the immediate initiation of coagulation, thrombus formation, and, eventually thrombotic vessel occlusion.

The need for (and the clinical benefit of) potent antiplatelet therapy can intuitively be derived from this scenario. Other, more upstream and more TF-specific therapeutic interventions are discussed in the last section of the manuscript, including (i) direct inhibition of TF induction at the signal transduction and transcriptional level; (ii) anti-TF antibodies; (iii) inactivated factor VIIa, recombinant tissue factor pathway inhibitor (TFPI); and (iv) recombinant nematode anticoagulant protein c2 (rNAPc2). However, while platelet inhibition both in acute coronary syndromes and after stent implantation has long been part of routine clinical practice, TF-directed antithrombotic strategies are still at the experimental level. This review is rounded off by four detailed figures that summarize the essential aspects of TF biology.

2006

The Pittsburgh Steelers defeat the Seattle Seahawks 21-10 to win Super Bowl XL; the 1 billionth song is purchased from the Apple iTunes Store; and 1800 people die when a mudslide occurs on Leyte Island in the Philippines



A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization

M.C. Morice, P. W. Serruys, J. E. Sousa, J. Fajadet, E. Ban Hayashi, M. Perin, A. Colombo, G. Schuler, P. Barragan, G. Guagliumi, et al; RAVEL Study Group

N Engl J Med. 2002;346:1773-1780

Coronary remodeling and, in turn, restenosis rates were significantly reduced with the introduction of balloon-expandable stents as compared with angioplasty alone (see above). As the absolute risk of restenosis still remained in the range of 20%, however, novel concepts were needed to further reduce it. Rapamycin, a macrocyclic lactone, had long been used as an immunosuppressant after organ transplantation; in addition to its potent immunosuppressive properties, however, it also quite effectively inhibits vascular smooth muscle cell migration and proliferation, the cellular mechanisms mainly responsible for restenosis, through interference with cell cycle regulators.

Marie-Claude Morice and her colleagues from the RAVEL (Randomized Study with the Sirolimus-Coated Bx Velocity Balloon-Expandable Stent in the Treatment of Patients with de Novo Native Coronary Artery Lesions) Study Group were among the first to examine the efficacy of a rapamycin-eluting stent compared with a standard, uncoated bare-metal stent (BMS) in 238 patients with angina pectoris in a randomized, double-blind, multicenter trial.

The primary angiographic end point was in-stent late luminal loss (ie, the difference between the minimal luminal diameter immediately vs 6 months after the procedure); secondary end points included the percentage of in-stent stenosis and the rate of restenosis (ie, luminal narrowing of >50%). The results were astonishing: after 6 months, the mean in-stent late loss was -0.01 mm in the drug-eluting stent (DES) group vs 0.80 mm in the BMS group; the percentage stenosis was 14.7% vs 36.7% of patients in the DES vs BMS groups, respectively; and $\geq 50\%$ stenosis was observed 0% vs 26.6% of patients after DES vs BMS, respectively. Consequently, on intravascular ultrasound evaluation, segments stented with DES demonstrated significantly less neointimal hyperplasia (2 mm³ vs 37 mm³).

The primary clinical end point of the study was a composite of major cardiac events (MACE), including death, myocardial infarction (MI), coronary artery bypass surgery (CABG), and target lesion or target vessel revascularization 30 days,

6 months, and 12 months after the index procedure. There was no difference in the incidence of death, MI, or CABG. However, target lesion revascularization was performed in none of the DES recipients, but in 27% of recipients of BMS. Overall, the MACE rate was 5.8% vs 28.8% in the DES- vs BMS-stented group, a difference that could entirely be attributed to the reduced need for revascularization of the target vessel in the DES group.

After publication of these results, the enthusiasm was enormous, leading to the authors' opening statement of their discussion section that implantation of a rapamycin-coated stent "resulted in virtual elimination of in-stent hyperplasia." As such, RAVEL (as well as the following series of similar studies) prepared the ground for the unparalleled success of DES in interventional cardiology. However, several limitations, which were mostly only appreciated long after presentation of these data, were nonetheless inherent in this landmark study, including the conceivably simple type of patients and lesions included in the study, the rather short period of follow-up (6 months), and the overall small number of patients. Hence, it was impossible to infer the risk of more rare (but potentially serious-to-life-threatening) complications, such as stent thrombosis, based on these findings. Only later, after the availability of long-term data from both randomized trials and large-scale registries, did the drawbacks of DES, including the potentially increased risk of stent thrombosis, slowly become apparent—and have remained a topic of intense debate without a definite conclusion yet.

2002

The planetoid Quaoar is discovered orbiting the Sun in the Kuiper belt; Serena Williams defeats her sister Venus Williams in straight sets to win the 2002 French Open tennis title; and the Igandu train disaster in the Dodoma Region of Tanzania kills 281 people in the worst rail accident in African history

Inflammatory markers at the site of ruptured plaque in acute myocardial infarction: locally increased interleukin-6 and serum amyloid A but decreased C-reactive protein

W. Maier, L. A. Altwegg, R. Corti, S. Gay, M. Hersberger, F. E. Maly, MD; G. Sütsch, M. Roffi, M. Neidhart, F. R. Eberli, et al.

Circulation. 2005;111:1355-1361

More than 10 years after Van der Wal and colleagues' work, Maier and colleagues studied the nature of the inflammatory microenvironment after coronary plaque rupture in vivo. To do so, the authors examined blood samples and thrombus material directly from the site of coronary occlusion in 42 patients with acute myocardial infarction (AMI) scheduled to undergo acute percutaneous coronary intervention (PCI).

The methodology of specimen sampling was key for this purpose and therefore deserves special attention. To sample blood and thrombus material directly from the culprit lesion (and, hence, from the "scene of the crime" of AMI), they used the PercSurge GuardWire temporary occlusion and aspiration system. A distal protection balloon was inflated for distal occlusion of the culprit vessel. An aspiration catheter was then inserted, and blood and thrombus were aspirated from the "closed" compartment between the thrombotic vessel occlusion (proximal) and the occlusion device (distal). The samples obtained through this procedure hence contained blood directly from the surrounding microenvironment of plaque rupture. These values were compared with those from blood of the aortic root (representing "systemic" levels); hence, every patient served as his/her own control.

Analysis of blood levels for inflammatory markers yielded interesting and in part unexpected findings. A 76% and 10% increase in "local" intracoronary levels of interleukin 6 (IL-6) and serum amyloid A (SAA), respectively, was observed versus the "systemic" samples from the aortic root. In contrast (and in a way unexpectedly), high sensitivity C-reactive protein (CRP) was not increased locally, rather even decreased (by 16%) as compared with aortic levels. Lipoprotein (a) Lp(a) concentrations were similar in both sites. Interestingly, systemic as well as local levels of high sensitivity CRP, IL-6, and SAA were higher in patients who had symptoms prior to the AMI (so-called "heralded" AMI) than in "unheralded" AMI. In the thrombus material aspirated from the site of plaque rupture, large amounts of CD68-positive monocytes as well as of IL-6 (colocalized with macrophages) were immuno-

histochemically evidenced. In addition, all stains exhibited strong immunoreactivity to SAA both in the thrombus and in the cytoplasm of white blood cells. In contrast, CRP was detected in 10 of 17 thrombi in some white blood cells (but not outside the cells), which the authors interpreted as being indicative of possible phagocytosis of CRP.

This observation of increased local levels of IL-6 and SAA at the site of coronary plaque rupture added to the growing evidence of important local dynamics of the inflammatory processes involved in plaque rupture and AMI. The increase in local SAA blood levels and the presence of SAA in the thrombus material was unexpected, as SAA (like CRP) is an acute phase protein thought to be mainly produced in the liver. However, the findings reported in this paper strongly suggest that SAA is equally produced at the site of coronary occlusion, either by white blood cells within the thrombus or by cells of the atherosclerotic vessel wall. Furthermore, this paper refueled the debate over CRP as a marker of inflammation vs an active mediator of disease. According to the authors, locally decreased levels with respect to systemic levels suggest that the first is true, and not the latter, and that local production is low. Alternatively, the authors point out, the presence of CRP within white blood cells could point to local uptake and catabolism of the protein as the main reason for its locally decreased levels.

2005

The Tulip Revolution in Kyrgyzstan climaxes with the overthrow of president Askar Akayev; the People's Republic of China ratifies an anti-secession law, to prevent Taiwan from declaring independence; and Wales beats Ireland 32-20 to win their first Grand Slam title since 1978 in Rugby Union's Six Nations tournament



Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels

Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group

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In this seminal study, the Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group investigated the effect of cholesterol-lowering therapy on mortality from coronary heart disease and overall mortality. By the time the study was undertaken (it was initiated in 1989), a strong epidemiological association had been established between plasma cholesterol levels and the risk of coronary artery disease. While the risk of coronary events could be reduced by statin therapy, its effect on coronary heart disease and overall mortality remained unclear at the time.

In their double-blind trial, the LIPID investigators randomized over 9000 patients with a history of myocardial infarction or hospitalization for unstable angina and cholesterol levels of 155-271 mg/dL, to either pravastatin (40 mg/d) or placebo. Patients were followed over a mean period of 6.1 years, and the primary outcome of mortality from coronary disease was examined.

The authors found that the primary study end point was reached in 6.4% of patients in the pravastatin vs 8.3% of patients in the control group, corresponding to a relative risk reduction of 24%. Moreover, overall mortality was reduced from 14.1% to 11.0% in the placebo vs pravastatin group, respectively, resulting in a relative risk reduction of 22%. Interestingly, death from trauma, suicide, or any cancer was also lower in the pravastatin group; this, however, did not reach statistical significance. Nevertheless, these findings were important insofar as they underlined that the higher incidence of breast cancer in women on pravastatin observed in the previous Cholesterol And Recurrent Events (CARE) trial had probably occurred by chance. On the safety side, the rate of adverse or serious adverse events ultimately attributed to the study medication was similar in both groups; in the same way, elevation of liver transaminases or creatinine kinase levels occurred to a similar degree in both groups.

One of the most important findings of the LIPID study was that the observed beneficial effects on cardiovascular and all-cause mortality were—in contrast to the Scandinavian

Simvastatin Survival Study (4S), CARE, and West Of Scotland COronary Prevention Study (WOSCOPS) trials, which were at that time already published—observed in patients with average cholesterol levels, which are “representative of those seen in current practice,” as opposed to those with elevated levels that had already been studied. The authors further elaborate that their findings also extend the evidence of benefit to patients who were not specifically included in 4S and CARE, eg, those with unstable angina.

The authors conclude with the statement that, given their results, “cholesterol-lowering therapy should now be considered for virtually all patients presenting with coronary heart disease”—a paradigm that would soon thereafter be instituted into daily clinical practice and appears common sense to cardiologists today. At the time, however, this statement was of great importance, as several studies had just revealed that in the USA and the UK, only 30% and 10%, respectively, of patients who had survived a myocardial infarction were prescribed lipid-lowering drugs. Moreover, the results of the LIPID study can be viewed as one of the major advances toward recognizing the benefit of statins independently of cholesterol levels, and as such as the precursor to further groundbreaking studies like PROVE-IT (Pravastatin or Atorvastatin Evaluation and Infection Therapy) or Treating to New Targets (TNT).

1998

The European Court of Human Rights is instituted; Tony Blair becomes the first British Prime Minister to address the Dáil Éireann, the Republic of Ireland’s parliament; and Galina Starovoitova, a leading Russian lawmaker and potential presidential candidate, is shot dead in St Petersburg