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YEAR IN CARDIOLOGY SERIES

The Year in Atherothrombosis

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A recent workshop sponsored by the European Commission identified atherothrombosis as among the top current priorities for translational research in cardiovascular disease (1). In the present review, we summarize significant advances during the past year in this field. Major journals in cardiology and internal medicine published in English were carefully searched, selecting relevant studies in 4 categories: epidemiology, mechanisms of disease, early detection and risk stratification, and prevention and treatment.

Epidemiology

Recent improvements in survival related to coronary heart disease (CHD) can be partly explained by reductions in risk factors in the population. Despite overall positive trends, particularly in dyslipidemia and smoking, a comparison of 4 NHANES (National Health and Nutrition Examination Surveys) indicated that in the past decade, the prevalence of low risk factor burden has decreased, with increases in blood pressure levels and obesity (2). Risk profile and the incidence of myocardial infarction may have particularly worsened among middle-aged women (3). Type 2 diabetes increased not only in the industrialized world but also in developing countries (4). Similar discouraging results came from the EUROASPIRE (European Action on Secondary Prevention Through Intervention to Reduce Events) survey in 8 European countries (5). Despite improvements in lipid control, no significant changes in blood pressure levels or smoking were obtained, and increases in obesity and diabetes were seen in patients with established CHD (Fig. 1).

Several studies addressed the importance of cardiovascular risk factors at an early age. A prospective study in 20 European countries predicted a doubling of incident cases of type 1 diabetes in children before 2020 (6). Dyslipidemia during adolescence, particularly in combination with obesity, was associated with future subclinical atherosclerosis as determined by the carotid intima-media thickness (CIMT) (7). In 10-year-old children, tobacco exposure was correlated with low-grade inflammation and altered lipid metabolism (8). Moreover, fetal exposure to parental smoking leads to higher CIMT during youth (9).

Mechanisms of Disease

The progression of atherosclerosis from early development to plaque rupture was viewed as the failure of 3 main defense mechanisms (endothelial progenitor cells, plaque neovascularization, and reverse cholesterol transport) to counteract continuous aggression to the vessel wall, and the promotion of these mechanisms was proposed as an approach to preserve vascular health (10). The second defense mechanism received special attention in 2009. Plaque neovascularization constitutes a response to tissue hypoxia and cholesterol deposition in the vessel wall. A potential regulatory effect on angiogenesis of the atheroprotective adipokine adiponectin was described (11). A detailed electron microscopy study revealed that coronary neovessels contain endothelial cells of abnormal morphology, aberrant gap junctions, and leukocyte adherence (12). This leads to increased permeability that precipitates intraplaque hemorrhage, with deleterious effects of extracorpuscular hemoglobin (10). On a protective basis, haptoglobin counteracts the redox activity of hemoglobin, and the haptoglobin genotype 2-2 was shown to be the major determinant of the amount of redox active iron in the plaque (13). The presence of intraplaque bleeding also promotes macrophage recruitment and activation, which in turn causes a release of proteinases and favors plaque rupture. A novel atheroprotective hemorrhage-associated macrophage population was described, defined by high levels of scavenger receptor CD163 and high iron content, and promoted by interleukin 10 (14). Analysis of human coronary endarterectomy samples showed enhanced expression of CD163 and interleukin 10 in plaques from patients with acute coronary syndromes (15). Heme oxygenase-1 is an intracellular enzyme that degrades free heme into ferrous iron, which is rapidly sequestered by ferritin. Heme oxygenase-1 gene expression was found to be increased in human plaques from patients with diabetes (16). On a different topic, the presence of cholesterol crystals was strongly associated with plaque rupture, thrombus, symptoms, and plaque size and was proposed as a mechanical contributor to plaque disruption (17).

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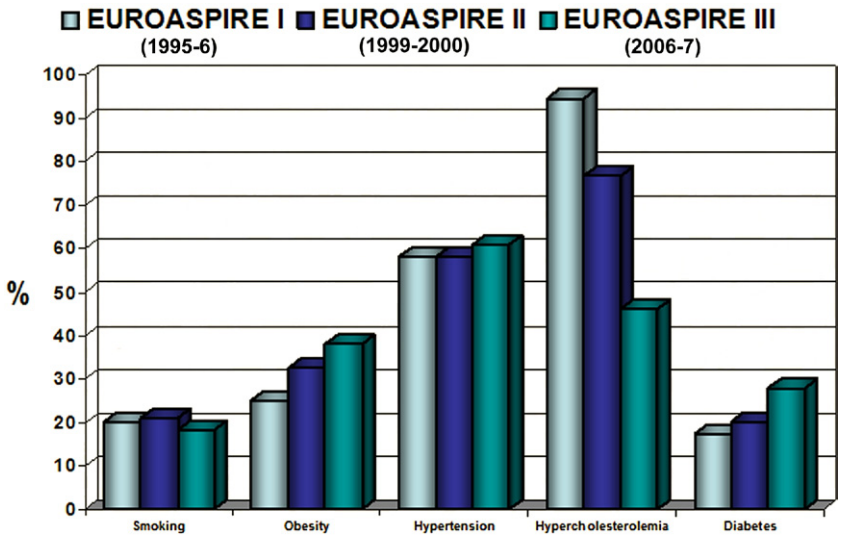

Figure 1 European Trends in Risk Factor Control

The 12-year trends in risk factor control in Europe in patients with established coronary heart disease.
EUROASPIRE = European Action on Secondary Prevention Through Intervention to Reduce Events. Data from Kotseva et al. (5).

Early Detection and Risk Stratification

Conventional risk factors. Long-term follow-up of the Framingham Offspring cohort (18) allowed the derivation of 30-year risk equations for hard and overall cardiovascular events that provide substantial additional information in comparison with 10-year estimates (Fig. 2). A unified definition for the metabolic syndrome (Table 1) was also proposed in an attempt to avoid previous discrepancies (19).

The optimal lipid fraction for proper risk stratification continued to be discussed. The apolipoprotein B/apolipoprotein A-I ratio outperformed standard lipid measurements in predicting cardiovascular mortality in 7,594 adults from NHANES III, although it was not better than apolipoprotein B alone (20). Conversely, conventional cholesterol measurements were as predictive of mortality as apolipoprotein concentrations in 5,096 patients with CHD (21). A U-shaped relationship between body mass index and total and cardiovascular mortality was reported in a combined analysis of studies including almost 900,000 participants (22). In addition, data from a large prospective cohort indicated additive value of indexes of overall adiposity (such as waist circumference or the waist/hip ratio) to body mass index in predicting survival (23). Regarding the impact of pollution, one investigation of >9 million elderly subjects demonstrated an association between short-term exposure to ambient carbon monoxide and risk for cardiovascular disease

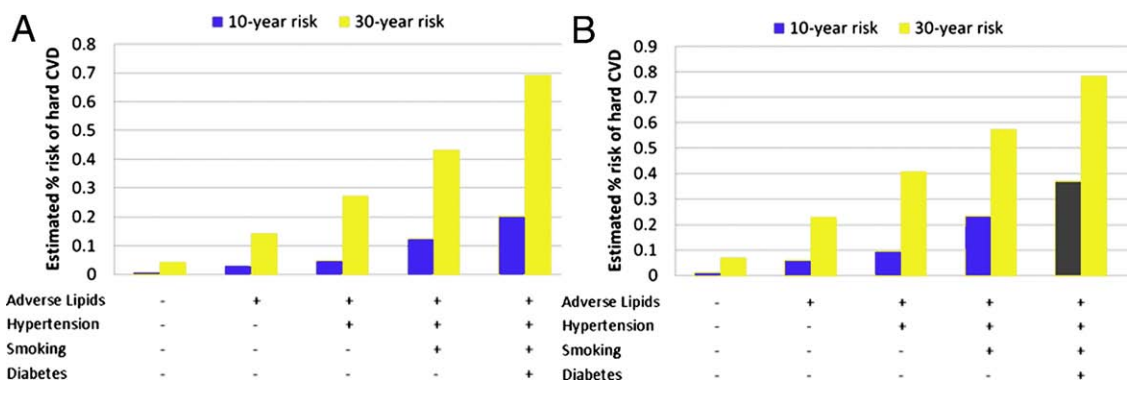

Figure 2 Short- Versus Long-Term Cardiovascular Risk

Ten- versus 30-year risk of hard cardiovascular disease events in a 45-year-old woman **(A)** and man **(B)** with different risk factors profiles. Modified, with permission, from Pencina et al. (18).

Table 1 Unified Definition of the Metabolic Syndrome

Marker	Cut Points
Elevated waist circumference	Population- and country-specific definitions
Elevated triglycerides (or drug therapy for it)	≥150 mg/dl
Reduced HDL cholesterol (or drug therapy for it)	<40 mg/dl in men; <50 mg/dl in women
Elevated blood pressure (or drug therapy for it)	Systolic ≥130 mm Hg and/or diastolic ≥85 mm Hg
Elevated fasting glucose (or drug therapy for it)	≥100 mg/dl

Modified from Alberti et al. (19).
HDL = high-density lipoprotein.

hospitalization, even at very low levels well below current regulatory standards (24).

Functional biomarkers. Functional markers of subclinical disease showed additive predictive value over conventional risk factors. Endothelial dysfunction as determined by abnormal flow-mediated vasodilation was associated with 5-year incident cardiovascular events in apparently healthy participants in the MESA (Multi-Ethnic Study of Atherosclerosis). It led to a net reclassification improvement (the proportion of patients whose risk is correctly reclassified) of 29% compared with the Framingham risk score (25). Not only the presence but also the progression of peripheral arterial disease (defined as a decline in the ankle-brachial index >0.15 over 5 years) was independently associated with increased cardiovascular risk (26).

Serum biomarkers. The use of novel biomarkers for prognostic stratification in apparently healthy subjects was reported to increase net reclassification improvement, particularly if restricted to the intermediate-risk subjects (27). Beyond their implications for patient management (see the following discussion), the roles of inflammation in atherogenesis and risk assessment continued to be a matter of debate. It was shown in animal models that inflammation causes impairment in reverse cholesterol transport (28). In addition, a study demonstrated that human circulating C-reactive protein (CRP) can be dissociated by activated platelets into a proinflammatory form that deposits in atherosclerotic plaques (29). However, large genomewide association studies continued to argue against a relevant causal role of CRP in CHD (30). The potential role of CRP in guiding therapy was addressed in the JUPITER (Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin) study (see the following discussion). Data from the Dallas Heart Study identified independent associations of endothelial cell–selective adhesion molecule and burden of atherosclerosis that were not observed for other adhesion molecules (31). In addition, statin-associated decrease in peripheral monocyte count was proposed as a novel marker of coronary atherosclerotic regression (32).

A meta-analysis of 36 prospective studies confirmed significant although modest independent associations between lipoprotein(a) and incident myocardial infarction and stroke (33). Besides its known prothrombotic effects, another potential deleterious role of this biomarker may be as a carrier of proinflammatory oxidized low-density lipoprotein (LDL) cholesterol (34). The possible influence of altered calcium-phosphate metabolism in cardiovascular risk was addressed in different studies. Low vitamin D levels, which may lead to secondary hyperparathyroidism, were found in approximately 75% of U.S. adults with cardiovascular disease (35). A potential mechanism for these findings was described: vitamin D inhibited macrophage transformation into foam cells in patients with diabetes (36). High concentrations of parathyroid hormone were related to cardiovascular mortality in elderly men beyond vitamin D levels or other markers of mineral metabolism (37). Similarly, elevated levels of alkaline phosphatase, perhaps acting as a mediator of vascular calcification, were independently associated with death both in patients with previous myocardial infarctions and in the general population (38).

Genetic markers. The field of genetics was particularly active in 2009. Variants of the *ABCB1* and *CYP2C19* alleles, involved in the absorption and metabolic activation of clopidogrel, respectively, were independently associated with a higher risk for 1-year mortality, nonfatal myocardial infarction, or stroke in >2,200 infarct survivors receiving this therapy (39). In contrast, similar genetic variants of cytochrome P450 activity did not affect drug action or event rates in persons treated with prasugrel (40). A study involving 11,550 patients and 11,205 controls confirmed the link between the *9p21.3* locus and CHD risk and replicated associations of 3 other loci also identified in prior studies (41). The *9p21.3* region was shown to contain an enhancer that regulates the expression of genes involved in cellular proliferation, providing a possible mechanistic link for increased atherosclerosis in carriers of the risk allele (42). However, the addition of knowledge of *9p21.3* carrier status to >22,000 white participants in the Women's Health Study did not provide additive prognostic value to conventional risk stratification (43). Finally, genome-wide association studies combining data from 4 prospective population-based cohorts identified mildly increased risk for atherothrombotic stroke in carriers of chromosome *12p13* variants (44).

Invasive imaging. Pooled data from 7 intravascular ultrasound (IVUS) studies in patients with established CHD revealed that both very low LDL cholesterol (≤70 mg/dl) and low systolic blood pressure (≤120 mm Hg) are associated with slower progression of coronary atherosclerosis (45). A large registry of almost 1,000 patients who underwent IVUS and virtual histology reported larger necrotic cores in association with age, diabetes mellitus, hypertension, and low high-density lipoprotein (HDL) cholesterol (46). The presence of multiple plaques with features of vulnerability in nontarget vessels as detected with coronary IVUS may have prognostic implications, according to a study in 183 patients with CHD (47). These findings are also relevant in view of the significant estimated prevalence of high-risk, nonstenotic coronary plaques in >50% of

middle-age, apparently healthy subjects (48). Similar potential prognostic value for the use of IVUS with virtual histology was reported in the PROSPECT (Providing Regional Observations to Study Predictors of Events in the Coronary Tree) trial. A thin fibrous cap, a minimum lumen $\leq$4.0 mm^2, and a plaque burden $\geq$70% were predictors of the 3-year lesion-related incidence of events (49).

Studies using optical coherence tomography additionally provided important insights into the physiopathology of CHD. It was suggested that thin fibrous caps can rupture both at rest and with exercise, whereas some thick fibrous cap lesions may also rupture in relation to exertion (50). Moreover, an inverse correlation was described between fibrous cap thickness and plasma levels of inflammatory markers, including CRP, interleukin-18, tumor necrosis factor-alpha, and peripheral white blood cell counts (51). Finally, a catheter-based near-infrared spectroscopy system was validated for detection of coronary lipid-rich plaques in vivo (Fig. 3) (52).

Noninvasive imaging. Data from a large randomized trial of antihypertensive therapy replicated the independent association of CIMT with cardiovascular prognosis; however, the investigators questioned the value of using it as an end point in the evaluation of atheroprotective therapy, as CIMT changes were not predictive of outcomes (53). In vivo contrast enhancement of human carotid plaques evaluated with ultrasound was used to study the degree of neovascularization. The incidence of enhancement and the ratio of plaque to luminal enhancement were more pronounced in patients with symptomatic cerebrovascular disease (54). Reinforcing the importance of long-term cardiovascular risk, a study measuring CIMT and coronary artery calcium (CAC) in subjects with low 10-year risk by the National Cholesterol Education Program Adult Treatment Panel III demonstrated a higher atherosclerotic burden and faster progression in those with high lifetime risk (55).

A report from the MESA study indicated that absolute CAC scores predict CHD better than age-, gender-, or ethnicity-adjusted percentiles (56). A study including over 44,000 asymptomatic subjects confirmed the excellent prognosis associated with absent CAC, with a 10-year mortality of 1%, whereas minimal CAC (Agatston score: 1 to 10) doubles the risk (57). This year there was more evidence of the utility of noninvasive plaque imaging with contrast-enhanced computed tomography (CT). A registry of 432 patients identified noncalcified coronary plaque as a predictor of outcomes with incremental value over the calcium score (58). In an important investigation including >1,000 subjects undergoing coronary CT angiography, the presence of 2 features of plaque vulnerability (positive remodeling and low attenuation suggestive of a lipid-rich core) (Fig. 4) were strongly associated with same-site development of acute coronary syndromes during the next 2 years (hazard

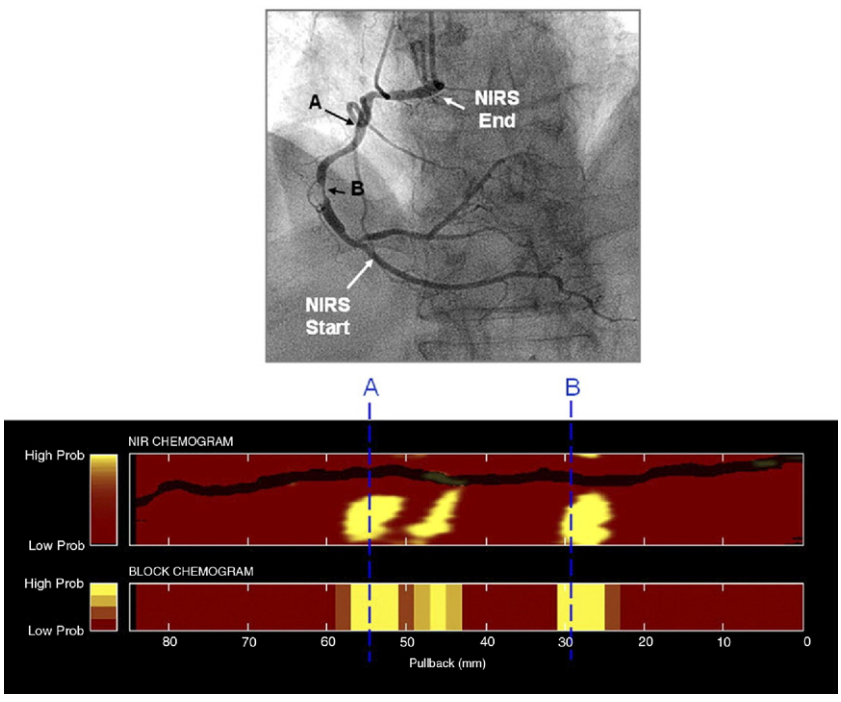

Figure 3 Near-Infrared Spectroscopy

(Top) Invasive angiogram of the right coronary artery of a patient with unstable angina, showing a complex culprit lesion in the mid segment **(B)**. **(Bottom)** Corresponding near-infrared spectroscopy (NIRS) scan revealing prominent lipid content at the level of the culprit stenosis **(B)** and another lipid-rich area in an "angiographically normal" proximal segment **(A)**. Prob = probability. Reproduced, with permission, from Waxman et al. (52).

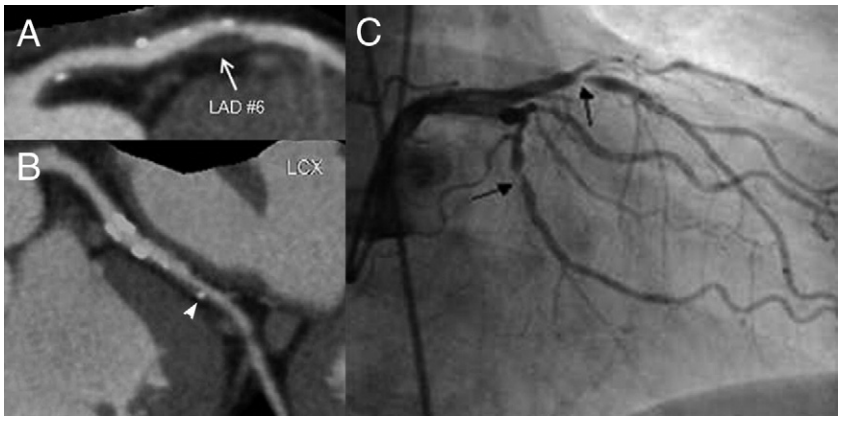

Figure 4 **Coronary CT Angiogram of Noncalcified Plaques**

Contrast-enhanced computed tomography (CT) angiogram of the left anterior descending coronary artery (LAD) **(A)** and left circumflex coronary artery (LCX) **(B)**. There is a large noncalcified plaque with low attenuation and marked positive remodeling in the proximal LAD **(white arrow)** and a significant stenosis in the LCX **(white arrowhead)**. The patient presented 6 months later with an acute coronary syndrome. An invasive angiogram **(C)** identified the culprit lesion at the level of the proximal LAD plaque **(upper black arrow)** and confirmed the LCX lesion **(lower black arrow)**. Modified, with permission, from Motoyama et al. (59).

ratio: 22.8; $p < 0.001$) (59). The feasibility of studying serial changes in plaque burden with CT was also reported in an experimental atherosclerosis model (60). Combining CT and positron emission tomography, vascular calcification and inflammation were shown to rarely coexist (Fig. 5), supporting the notion that calcification represents a healing response in atherosclerosis. Moreover, inflammation was correlated directly to serum matrix metalloproteinase levels and inversely to adiponectin concentrations (61).

A magnetic resonance imaging (MRI) study in asymptomatic men with moderate carotid stenosis indicated that intraplaque hemorrhage predicted cerebrovascular events within 2 years (62). Intraplaque hemorrhage and a large lipid core were also independently associated with thin

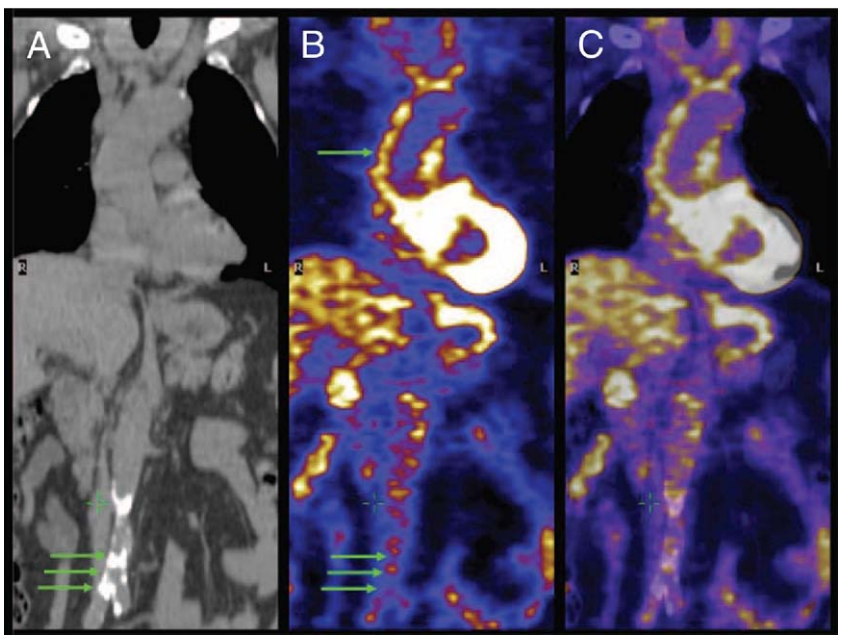

Figure 5 **Imaging of Vascular Inflammation**

Computed tomography **(A)**, positron emission tomography **(B)**, and fused images from both techniques **(C)** depicting the aorta of a patient with systemic atherosclerosis. Computed tomography demonstrates absent calcification in the ascending aorta and significant calcium in the infrarenal abdominal segment **(A) (green arrows)**. However, there is marked inflammation in the ascending aorta **(B) (green arrow)** and little in the abdominal portion **(B) (green arrows)**. Reproduced, with permission, from Rudd et al. (61).

and/or ruptured fibrous caps (63). A substudy of the MESA demonstrated the feasibility of quantifying coronary wall remodeling in asymptomatic subjects with MRI (64). Moreover, the plaque characterization capabilities of MRI were also explored in the coronary tree (65).

Molecular imaging. Ultrasmall superparamagnetic iron oxide particles, an MRI contrast agent that is taken up by macrophages, were used to successfully track reductions in human carotid inflammation with high-dose statin therapy (66). Similar findings were reported for matrix metalloproteinase activity in an experimental model of atherosclerosis with a technetium-99m–labeled tracer (67). The change in MRI signal intensity associated with plaque uptake of gadofluorine M in a rabbit model of atherosclerosis was significantly higher in advanced plaques compared with early atheroma and was correlated with the degree of neovascularization and inflammation (68). Gadolinium-loaded lipid-based nanoparticles targeted to the macrophage scavenger receptor were shown to improve the detection of inflammation in human carotid artery specimens (69). Another aspect of inflammation, the expression of endothelial vascular cell adhesion molecule-1, was evaluated using a radiolabeled tracer and positron emission tomography (70). Some studies explored the potential of molecular techniques not only for diagnosis but also for the delivery of therapy. Glycoprotein IIb/IIIa–targeted microbubbles coupled with high-mechanical index ultrasound led to improvements in both coronary patency and microvascular perfusion in a porcine model of myocardial infarction (71). In addition, external guidance of magnetically labeled endothelial progenitor cells enhanced their delivery to sites of experimental arterial injury (72).

The role of different invasive and noninvasive modalities in the evaluation of plaque characteristics (Fig. 6) was elegantly reviewed elsewhere (73).

Prevention and Treatment

The long-term benefits of lifestyle choices were revisited in almost 75,000 women followed for 20 years: greater adherence to the Mediterranean diet was independently associated with lower CHD and stroke incidence (74). According to a meta-analysis of 11 trials, banning public smoking is associated with a 17% reduction of myocardial infarction incidence, an effect greater for the young and nonsmokers (75). The importance of primary prevention was reinforced by a registry showing that the 3-year incidence of vascular death, myocardial infarction, or stroke is 12% for patients with established atherothrombotic disease and 6% for patients with ≥3 risk factors (76). These data were derived from a population with a relatively high use of modern secondary prevention therapies; however, a study from the U.S. found that only 30% to 60% of patients with CHD receive appropriate treatment (77). The pharmacodynamic effects of a once-daily polypill containing aspirin (100 mg), simvastatin (20 mg), thiazide (12.5 mg), atenolol (50 mg), and ramipril (5 mg) were tested in a multicenter primary prevention study performed in India. After 12 weeks of active therapy, the polypill was as effective as the individual components in decreasing blood pressure and slowing heart rate, with slightly less (although still substantial) lipid-lowering and platelet inhibitor effects. The investigators estimated that the reductions in risk factors observed would potentially decrease incident CHD by 62% and stroke by 48% (78).

The importance of intensive medical therapy was emphasized in subanalyses of the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial. In stable CHD, it proved as beneficial as revascularization in elderly patients (79) or in those with high-risk features (80), although at the expense of high crossover rates in the medical therapy arm. The BARI 2D

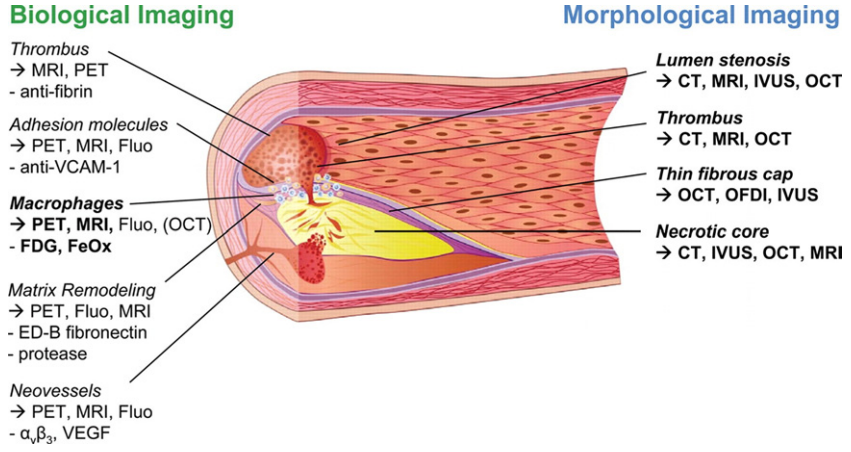

Figure 6 Techniques for Plaque Imaging

Techniques for plaque imaging. Reproduced, with permission, from Matter et al. (73). CT = computed tomography; ED-B = extradomain B; FDG = fluorodeoxyglucose; FeOx = iron oxide; Fluo = fluorescence imaging; IVUS = intravascular ultrasound; MRI = magnetic resonance imaging; OCT = optical coherence tomography; OFDI = optical frequency domain imaging; PET = positron emission tomography; VCAM = vascular cell adhesion molecule; VEGF = vascular endothelial growth factor.

(Bypass Angioplasty Revascularization Investigation 2 Diabetes) trial randomized 2,368 patients with type 2 diabetes and proven obstructive CHD to intensive medical therapy with or without early revascularization (81). The revascularization strategy (percutaneous or surgical) was chosen by the treating physician as the most appropriate. Therefore, and not surprisingly, patients referred for surgery had more extensive disease than those referred for percutaneous intervention. Overall, there were no differences in 5-year survival rates between the medical therapy group and the revascularization group (87.8% vs. 88.3%, respectively; p = 0.97). Similar results were found for the incidence of a composite end point of death, myocardial infarction, or stroke (24.1% and 22.8%, respectively; p = 0.70), although 42% of patients initially treated medically required revascularization on follow-up. In those patients in whom surgical intervention was considered most appropriate, revascularization reduced the risk for subsequent nonfatal events in comparison with medical therapy (Fig. 7). These findings resemble those previously reported in the context of surgical versus percutaneous revascularization in the SYNTAX (Synergy Between PCI With Taxus and Cardiac Surgery) trial (82).

Dyslipidemia. LDL cholesterol continues to be the first therapeutic target in atherothrombotic disease, and data

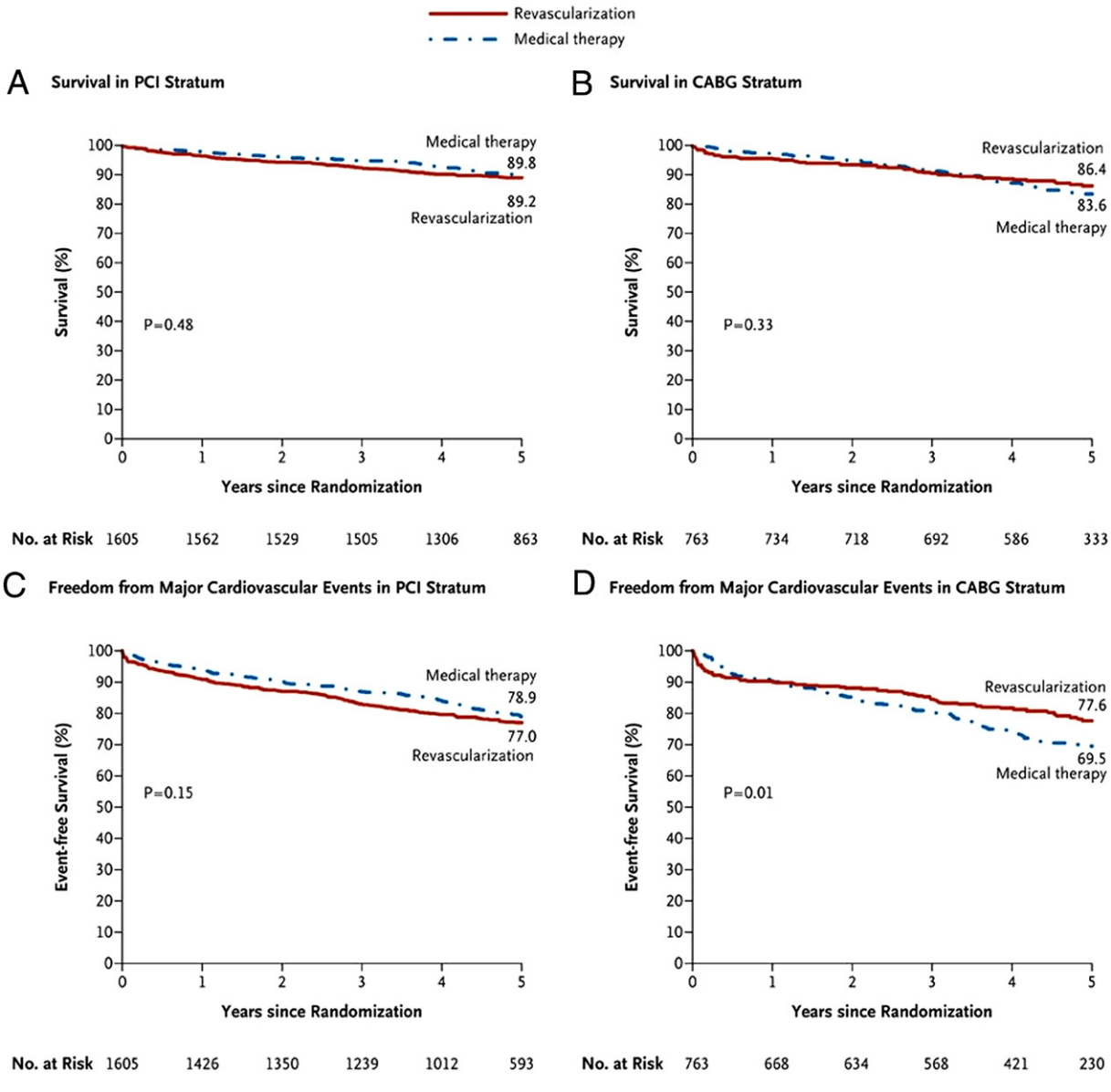

Figure 7 **Summary Results of the BARI 2D Trial**

Rates of survival **(A, B)** and freedom from major cardiovascular events (defined as death, myocardial infarction, or stroke) **(C, D)** for patients treated medically or with revascularization in the BARI (Bypass Angioplasty Revascularization Investigation 2 Diabetes) trial. Reproduced, with permission, from Frye et al. (81). CABG = coronary artery bypass grafting; PCI = percutaneous coronary intervention.

from >20,000 male subjects demonstrated that the largest cardiovascular benefits derive from most pronounced reductions in LDL levels, regardless of age (83). In addition, further support for the National Cholesterol Education Program Adult Treatment Panel III recommendation to use non-HDL cholesterol as a secondary goal for treatment came from a meta-analysis of 30 trials (84). The potential of HDL as an additional therapeutic target was highlighted in the Framingham Offspring study. Long-term follow-up demonstrated that increases in HDL cholesterol with lipid-lowering therapy were independently associated with improved cardiovascular outcomes (85). This was further supported by 16-year follow-up data from the BIP (Bezafibrate Infarction Prevention) trial, which demonstrated significant reductions in mortality for patients with CHD who achieved the largest increases in HDL concentrations (86). Modified-release nicotinic acid therapy for 12 months caused a regression of carotid and aortic atherosclerosis by MRI in statin-treated patients with low HDL cholesterol (87). In another randomized trial in patients with CHD or CHD equivalent, extended-released niacin also caused a small (although statistically significant) CIMT regression (88). Moreover, reconstituted HDL infusion demonstrated antithrombotic effects by attenuating platelet hyperreactivity in subjects with type 2 diabetes (89).

CRP may constitute a nonlipid target to guide statin therapy. Data from the JUPITER trial indicated that clinical benefit derived from rosuvastatin 20 mg/day versus placebo in apparently healthy subjects was highest in patients in whom both LDL cholesterol and CRP levels were reduced by therapy. Regardless of the LDL concentration lowering reached, benefit was higher across decreasing strata of achieved CRP levels (Fig. 8) (90). On the basis of the prevalence of low LDL but high CRP levels, it was estimated that in the U.S., approximately 6.5 million adults would be candidates for statin therapy (91) and that on the basis of CRP alone, the percentage of elderly patients requiring statins would increase from 35% to 68% (92). Pleiotropic effects of statin therapy were also addressed in JUPITER, where the risk for venous thromboembolic events was halved in those receiving rosuvastatin (93).

Additionally, previous observational evidence regarding the potential benefits of statin therapy in patients with chronic kidney disease was not replicated in a large, multicenter trial that randomized 2,776 patients on hemodialysis, with and without known cardiovascular disease, to rosuvastatin 10 mg/day or placebo. After a mean follow-up of 3.8 years and despite significant reductions in LDL cholesterol and CRP levels, statins were not associated with different rates of cardiovascular morbidity or mortality (94).

Hypertension. A multicenter trial performed in Italy including >1,100 patients without diabetes proposed a target systolic blood pressure of <130 mm Hg in this population because of a significant reduction in the rate of left ventricular hypertrophy and a combined cardiovascular end point at 2 years in comparison with the standard target of <140 mm Hg (95). The ACCOMPLISH (Avoiding Cardiovascular Events Through Combination Therapy in Patients Living With Systolic Hypertension) trial randomized 11,506 patients with hypertension and high cardiovascular risk (defined as diabetes, renal failure, or prior cardiovascular disease) to benazepril plus either amlodipine or hydrochlorothiazide. The average blood pressures achieved were 131.6/73.3 and 132.5/74.4 mm Hg, respectively ($p < 0.001$). The study was stopped prematurely after 3 years because of marked reductions (hazard ratio: 0.80; $p < 0.001$) in the primary end point of cardiovascular death plus a combination of cardiovascular events in the arm receiving the calcium-channel blocker (96). Conversely, a reanalysis of data from the ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial) supported the use of thiazide diuretics as the first-line therapy for treating hypertension because of favorable effects on

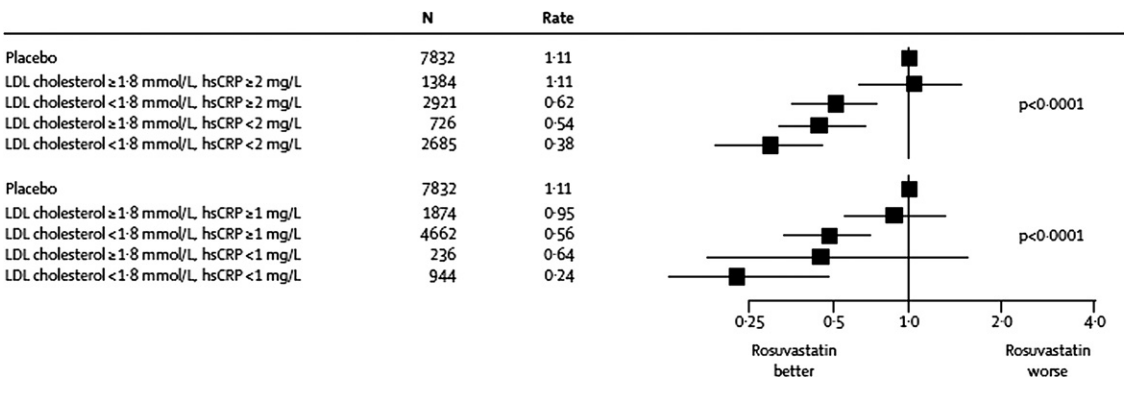

Figure 8 Cardiovascular Risk and hsCRP and LDL Levels

Multivariate-adjusted hazard ratios for incident cardiovascular events (expressed per 100 person-years) according to achieved concentrations of low-density lipoprotein (LDL) cholesterol and high-sensitivity C-reactive protein (hsCRP) in the JUPITER (Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin) study. Reproduced, with permission, from Ridker et al. (90).

cardiovascular outcomes, particularly in reducing heart failure, in comparison with other antihypertensive classes (97).

Diabetes. Patients with diabetes in the Framingham Heart Study experienced decreases in all-cause and cardiovascular mortality during the past 50 years, although they remain at higher risk than patients without diabetes (98). These reductions appear to be largely dependent on aggressive treatment of conventional risk factors (99), whereas the role of intensive glycemic control in the risk for macrovascular complications has remained controversial.

The VADT (Veterans Affairs Diabetes Trial) randomized 1,791 patients with poorly controlled type 2 diabetes to standard or intensive glucose-lowering therapy. After a median follow-up period of 5.6 years, the study failed to show benefits of intensive therapy for any macrovascular outcome (100). In contrast, long-term (20-year) follow-up of a smaller study demonstrated lower risk for CHD in patients with diabetes with decreasing levels of glycosylated hemoglobin (101). Moreover, a meta-analysis of 5 prospective randomized trials including >33,000 participants identified associations of intensive glucose-lowering regimens (overall glycosylated hemoglobin level: 6.6% vs. 7.5%) with a 15% reduction in CHD events (Fig. 9) but no significant changes in stroke or overall mortality (102). In a joint position statement, the American Diabetes Association, the American Heart Association, and the American College of Cardiology continued to endorse the current target of glycosylated hemoglobin <7%, as there is clear evidence that it leads to reductions in microvascular complications. Such a target may also lead to decreased macrovascular disease, perhaps later in life (a IIb recommendation). More aggressive therapy may be beneficial in patient subgroups (such as those with shorter duration of diabetes or no known cardiovascular disease) but detrimental in others (i.e., those with long-term diabetes, advanced cardiovascular disease, or histories of severe hypoglycemia) (103). Regarding specific therapies, the BARI 2D trial did not find different cardiovascular outcomes with insulin provision versus insulin sensitization (81).

Antithrombotic therapy. A meta-analysis of the use of aspirin for primary (6 trials, 95,000 subjects) or secondary (16 trials, 17,000 subjects) cardiovascular prevention reported associations of conventional risk factors with the probability of adverse events and questioned its widespread use in patients without previous cardiovascular disease, even with moderate baseline risk (104). Another meta-analysis raised similar doubts about aspirin use for secondary prevention in patients with established peripheral arterial disease (105). A prospective study including >500 patients with noncardioembolic ischemic stroke and no significant carotid stenoses evaluated the pathogenic role of aortic arch atherosclerosis. Large and complex aortic plaques (present in almost 20% of the patients) independently doubled the 2-year incidence of recurrent stroke or death, without differences between patients treated with either warfarin or aspirin (106). Finally, in patients with acute coronary syndromes, the PLATO (Platelet Inhibition and Patient Outcomes) study tested the effects of dual-antiplatelet therapy with aspirin and ticagrelor, a novel short-acting adenosine diphosphate receptor antagonist that, as opposed to clopidogrel, does not require metabolic conversion and has more potent inhibitory properties. The study randomized >18,000 patients with acute coronary syndromes (with and without ST-segment elevation) to aspirin plus either clopidogrel or ticagrelor for 12 months. Ticagrelor significantly reduced cardiovascular outcomes during follow-up (Fig. 10), without overall increases in major bleeding, although there was an increase in non-procedure-related hemorrhage (107). Two recent randomized trials tested the clinical utility of another short-acting, reversible adenosine diphosphate receptor antagonist, cangrelor. Both studies showed that cangrelor was not superior to the established use of clopidogrel in reducing periprocedural events in patients

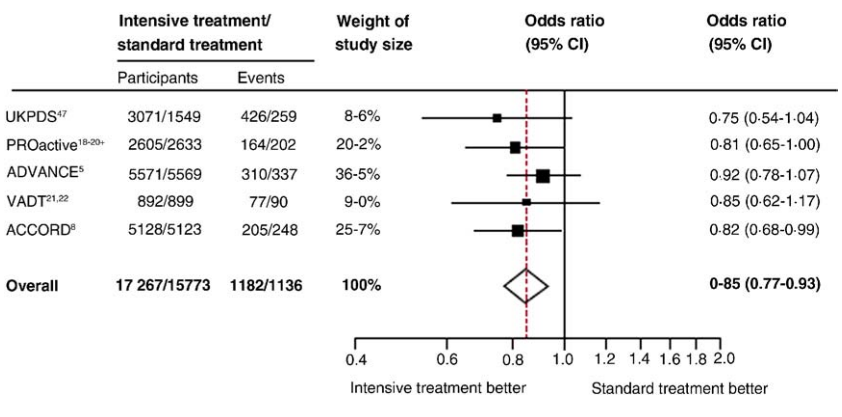

Figure 9 **Intensive Versus Standard Glucose-Lowering Therapy in Diabetes**

Meta-analysis of the probability of coronary heart disease events with intensive versus standard glucose-lowering therapy in 5 trials. Reproduced, with permission, from Ray et al. (102). ACCORD = Action to Control Cardiovascular Risk in Diabetes; ADVANCE = Action in Diabetes and Vascular Disease: Preterax and Diamicron-MR Controlled Evaluation; CI = confidence interval; PROactive = Prospective Pioglitazone Clinical Trial in Macrovascular Events; UKPDS = United Kingdom Prospective Diabetes Study; VADT = Veterans Affairs Diabetes Trial.

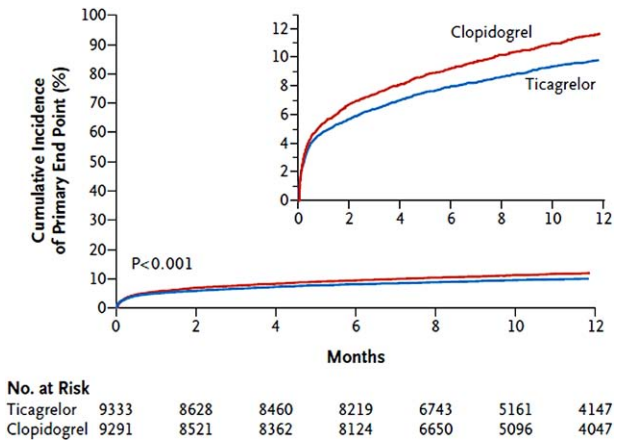

Figure 10 **Ticagrelor in Acute Coronary Syndromes**

Cumulative survival free from death from vascular causes, myocardial infarction, or stroke in the PLATO (Platelet Inhibition and Patient Outcomes) trial. Reproduced, with permission, from Wallentin et al. (107).

undergoing percutaneous coronary interventions (108,109). Finally, although not specifically tested in atherothrombotic disease, oral direct thrombin inhibitors represent a novel promising approach to antithrombotic therapy (110).

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