This review summarizes important advances that took place during the last year in the field of atherothrombotic disease. Papers were selected based on relevance, novelty, and scientific quality. Because of space limitations, when several publications reported similar findings, a representative study was included. The paper is divided into 4 distinct sections: epidemiology, mechanisms of disease, early detection and risk stratification, and prevention and treatment. The main highlights of this review are summarized in Table 1.

Epidemiology

A study from Canada confirmed that improved risk factor profiles account for approximately 50% of recent reductions in coronary heart disease (CHD) age-adjusted mortality (1). According to the National Health and Nutrition Examination Surveys (NHANES), blood pressure control in the last decade has improved to approximately 50% of the U.S. population with known hypertension (2). Similarly, data from NHANES expanding over 30 years reported improvements in total and low-density lipoprotein (LDL) cholesterol concentrations in U.S. adults (3). It was nonetheless estimated that approximately one-half of the patients receiving statins could benefit from therapies targeting other lipid abnormalities, particularly low high-density lipoprotein (HDL) cholesterol concentration (4). Unfortunately, in the past 30 years, the prevalence of obesity doubled, accompanied by increases in triglyceride levels (3). Moreover, assuming maintenance of current trends, it was estimated that average U.S. life expectancy decline will be offset by mean reductions in 1 year due to growing obesity (5). The importance of obesity during childhood and adolescence was highlighted in a report that linked its presence to the development of adult metabolic syndrome, type 2 diabetes mellitus, and subclinical atherosclerosis (6). On a positive note, the increasing obesity rate appears slower during the past decade for adults (7) and particularly for children (8).

Data from the multinational REACH (Reduction of Atherothrombosis for Continued Health Registry) reported the contemporary 4-year rates of major cardiovascular events among patients with high risk for or established atherothrombosis (Fig. 1). Independent predictors of events were polyvascular disease (hazard ratio [HR]: 1.99), an ischemic event in the previous year (HR: 1.71), and the presence of diabetes (HR: 1.44; p < 0.001 for all) (9). Although these and other risk factors are consistent throughout different world regions, the same registry identified a direct relationship between educational level and atherothrombotic events in low- to middle-income countries, the opposite of that observed in high-income regions (10). This finding may reflect higher access to a westernized lifestyle with higher education in developing countries, leading to an impaired risk factor profile. The Institute of Medicine released recommendations to address the “epidemic” of cardiovascular disease in the developing world and promote cardiovascular health worldwide (11).

Mechanisms of Disease

The role of mechanical forces on atherogenesis was revisited in 2010. Computational fluid dynamics evaluated with coronary intravascular ultrasound (IVUS) in experimental atherosclerosis or carotid magnetic resonance imaging in patients provided further evidence of the role of reduced shear stress not only in plaque formation but also in its progression (12,13). Conversely, high wall stress at the shoulder of abdominal aneurysms in humans was found to predict more rapid expansion (14).

Regarding inflammation and atherogenesis, monocytes and T-lymphocytes are known to be important in plaque development. Experimental and clinical studies suggested an additional contribution of neutrophils to early lesion formation and plaque vulnerability (15,16). Both systemic and intraplaque markers of inflammation were associated with symptomatic stroke and features of plaque vulnerability (17). In addition, associations were described between periodontitis, low-grade inflammation, and cardiovascular events (18). Moreover, addressing the interplay between obesity, inflammation, and vascular disease, a provoking hypothesis came from a smaller study involving 71 obese subjects that proposed obstructive sleep apnea, rather than...
obesity, as the main determinant of vascular inflammation and endothelial dysfunction (19).

Further evidence of the role of plaque neovascularization in the development of intraplaque hemorrhage came from an autopsy study that demonstrated correlations between vessel density and concentrations of intraplaque iron and erythrocyte fragments. Neovessel density was higher in nonstenotic segments and stenotic noncalcified plaques than in normal segments or calcified lesions (Fig. 2) (20). Moreover, the presence of extensive plaque neovascularization and, particularly, intraplaque hemorrhage in carotid endarterectomy specimens were associated with respective multiajusted hazard ratios of 2.2 (95% confidence interval [CI]: 1.2 to 3.8) and 1.5 (95% CI: 1.1 to 2.2) of subsequent cardiovascular events such as death, stroke, or myocardial infarction after a mean follow-up of 2.3 years (21), probably reflecting increased vulnerability not only locally but also systemically.

Finally, investigations addressed the differences between eroded and ruptured symptomatic plaques. In a series of 111 sudden cardiac death victims, plaque ruptures occurred in regions with higher plaque burden and inflammation, whereas erosions were associated with lower degrees of stenosis and more advanced thrombus healing, possibly leading to poor outcome through distal microembolization (22). Additionally, systemic and local intrathrombus levels of myeloperoxidase were proposed as important players in thrombus formation associated with erosion rather than rupture (23).

### Early Detection and Risk Stratification

**Conventional risk factors.** The strengths and limitations of novel biomarkers for risk stratification in comparison...
with traditional risk factors was reviewed elsewhere (24,25).
Nonetheless, quantification of conventional risk factors
remains the mainstay of cardiovascular risk stratification and
the only class I indication in the setting of primary preven-
tion according to recent guidelines (26). As previously
shown for CHD, the INTERSTROKE study indicated
that 10 potentially modifiable factors account for most of
the risk of stroke worldwide (27). Growing evidence links
cardiovascular risk factors and vascular atherosclerosis not
only with stroke but also with loss of cognitive function
(28,29), expanding the clinical significance of this disease.
For those who achieve low LDL cholesterol levels, the
prognostic significance of other lipid fractions such as
HDL cholesterol may be more relevant to patients with
established CHD (30) than in the context of primary
prevention (31). An important study challenged the
notion that maintaining usual blood pressure within
targets is the optimal approach for hypertension manage-
ment, and demonstrated an independent role of systolic
blood pressure variability and instability in the prediction
of stroke and coronary events (Fig. 3)(32). According to
a large meta-analysis of >100 studies involving almost
700,000 subjects without previous disease, diabetes ap-
proximately doubles cardiovascular events independent of
other risk factors, whereas impaired fasting glucose in-
creases risk only modestly (33). The REACH registry
reported lower rates of major cardiovascular events for
diabetic patients with risk factors than for nondiabetic
patients with established atherothrombotic disease, ques-
tioning the concept that diabetes mellitus should be
considered a CHD equivalent (9). Conversely, a history
of prior stroke seems to reflect a risk level (≥20% in 10
years) comparable to that of prior CHD (34).
Regarding clustering of risk factors, obesity and the
metabolic syndrome are often associated. A study involving
1,758 middle-aged men followed up for a median of 30
years demonstrated that each predicts incident cardiovascu-
lar disease in the absence of the other (35). A meta-analysis
of >950,000 patients found an approximately twofold
increase in cardiovascular events associated with the pres-
ence of the metabolic syndrome (36). The metabolic syn-
drome was also a predictor of myocardial infarction across
the world, although not beyond its individual components
(37). Comparable findings were reported in a meta-
analysis of 7 IVUS trials regarding the effects of the
metabolic syndrome on progression of coronary athero-
sclerosis (38).
Functional biomarkers. In 6,647 participants enrolled in
MESA (Multi-Ethnic Study of Atherosclerosis), the ankle-
brachial index was predictive of incident CHD, stroke, or
other atherosclerotic cardiovascular death independent of
traditional risk factors, serum biomarkers, electrocardio-
graphic abnormalities, the carotid intima-media thickness
(CIMT), and the coronary calcium score (39). In 2,232
participants of the Framingham Heart Study followed up
for a median of 7.8 years, arterial stiffness as reflected by
aortic pulse wave velocity was also associated with incident
major cardiovascular events after adjusting for standard risk
factors, including systolic blood pressure or history of
hypertension (40).
Serum biomarkers. The presence of diabetes is typically
diagnosed from abnormal fasting glucose levels, whereas
glycated hemoglobin is used to monitor glucose control after diagnosis. Nonetheless, data from >11,000 black and white participants in the ARIC (Atherosclerosis Risk In Communities) study without known diabetes indicated that glycated hemoglobin was a better predictor of death, CHD, and stroke, particularly for concentrations >6%, than was fasting glucose (41). The use and significance of C-reactive protein (CRP) for risk stratification continued to be a subject of intense debate during 2010. Data from the Copenhagen City Heart Study suggested there is no casual role of CRP in increased risk of mortality, but that it rather represents a marker of underlying cardiovascular or noncardiovascular disease (42). A large meta-analysis of 54 prospective studies including >160,000 participants without evidence of cardiovascular disease reported continuous log-linear associations between CRP and multiple vascular and nonvascular outcomes. After adjusting for sex and conventional risk factors, a 3-fold higher CRP concentration resulted in increases in CHD, ischemic stroke, and vascular death ranging from 27% to 55% (43). Data from the ARIC

Figure 3 Blood Pressure Variability and Outcome

The figure shows the hazard ratios for stroke (left column) and coronary events (right column) according to deciles (red diamonds) of SD of systolic blood pressure (SBP) (upper row) or of variation independent of mean (VIM) SBP (lower row) in patients with an average SBP less than the median value for the trial population (<142.8 mm Hg). Note the impaired outcome with increasing blood pressure variability despite (near) normal average SBP. Reproduced, with permission, from Rothwell et al. (32). CI = confidence interval.
study substantiated the presence of higher cardiovascular risk when LDL cholesterol levels are low (<130 mg/dl) and CRP is elevated (≥2.0 mg/l) during a mean follow-up of 6.9 years, in comparison with the limited 1.9-year follow-up in JUPITER (Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin), which was stopped early (44). An additional high-risk subgroup may be that of persons with high HDL cholesterol but elevated CRP (45).

A large meta-analysis of 40 prospective studies including >87,000 participants confirmed independent associations between serum levels of brain natriuretic peptides and incident cardiovascular disease (>10,000 events) in a variety of scenarios, including the general population, persons with risk factors, and patients with known stable vascular disease. These associations persisted after adjusting for conventional risk factors, renal function, left ventricular ejection fraction, or CRP, although improvements in risk discrimination were, overall, modest (46). The significance of subclinical myocardial necrosis as demonstrated with high-sensitivity troponin assays was also addressed in several investigations. In 3,679 patients with stable CHD and preserved left ventricular function, plasma levels of troponin T well below the limits of detection of standard assays showed a strong, graded, and independent association with incident cardiovascular death (Fig. 4) and heart failure, but not myocardial infarction (47). Similarly, baseline or newly elevated levels of high-sensitivity troponin T were predictive of cardiovascular death and heart failure in 4,221 elderly subjects followed up for >11 years (48).

Importantly, with respect to multimarker approaches, another study evaluated 30 serum biomarkers in >10,000 participants without established cardiovascular disease. No single biomarker consistently improved 10-year risk stratification above and beyond conventional risk factors, although the authors proposed a composite “score” combining brain natriuretic peptide, CRP, and sensitive troponin I (49). Other novel biomarkers in cardiovascular disease were reviewed elsewhere (50).

**Genetic markers.** The year 2010 witnessed a myriad of studies addressing genetic variants associated with cardiovascular disease and, particularly, with response to therapy. Recent reviews have addressed genetic markers in atherothrombosis in detail for the interested reader (51). Several investigations addressed the potential of scores based on allele carrier status or gene expression profiles to estimate the likelihood of either incident cardiovascular events or presence of obstructive CHD. These scores provided additive (although modest) information to conventional clinical stratification in some studies (52,53) but not all (54). One of the variants most consistently associated with CHD involves the 9p21 gene, which was linked to increased coronary atheroma burden both at early and late disease stages (55). Conversely, reduced leukocyte telomere length (a marker of cellular aging) was associated with advanced (but not early) disease in 800 subjects observed prospectively for 8 years (56).

In the field of pharmacogenetics, studies in 2010 extended prior evidence of an association of CYP2C19 and ABCB1 loss-of-function variants with increased subsequent events in patients treated with clopidogrel but not prasugrel, maybe because of faster metabolic activation of the latter (57). However, the clinical impact of these variants seems more relevant in patients with an acute coronary syndrome.
undergoing stenting, and their significance in other patient subgroups remains uncertain (58). Conversely, the PLATO (Platelet Inhibition and Patient Outcomes) study identified no interactions between these genetic variants and treatment effect of ticagrelor, an antiplatelet drug that does not require metabolic activation (59).

**Intravascular ultrasound.** Pooled data from 6 clinical trials that used serial IVUS in >4,000 patients demonstrated that baseline burden of coronary atherosclerosis as well as accelerated progression were independently associated with major cardiovascular events (particularly revascularization) during follow-up (60). Plaque progression was shown to occur in >20% of patients who achieve LDL cholesterol levels ≤70 mg/dl. Baseline percent atheroma volume, diabetes mellitus, increments in systolic blood pressure, inability to raise HDL cholesterol, and smaller reductions in apolipoprotein B levels were all associated with progression in this setting (61). Another study of serial IVUS demonstrated the highly dynamic nature of coronary atherosclerosis: during a 12-month interval, in symptomatic patients receiving conventional medical therapies, as much as 75% of nonculprit thin-cap fibroatheroma present at baseline transformed into a more stable lesion type, whereas new thin-cap fibroatheroma developed (62). These findings could be of relevance regarding risk stratification based on plaque features from a single time point, or on lesion-targeted therapeutic strategies.

**Noninvasive imaging.** Regarding imaging of subclinical atherosclerosis with carotid ultrasound, data from the ARIC study confirmed that adding the presence/absence of carotid plaque to the quantification of CIMT improves prediction of incident CHD (63). In experimental atherosclerosis, contrast-enhanced ultrasonography was validated for the noninvasive detection of plaque neovascularization (64). In a cross-sectional study of patients with stroke or transient ischemic attack imaged within 48 h of symptom onset, the presence of ipsilateral type-VI carotid plaque as determined by magnetic resonance imaging (characterized by large necrotic cores, cap rupture, thrombus, or intraplaque hemorrhage) showed the strongest association with symptoms after adjusting for the Framingham risk score, with an odds ratio of 11.7 (95% CI: 5.3 to 25.6; p < 0.0001) (65).

Several studies addressed the ability of coronary calcium scoring for reclassification of risk category in asymptomatic persons. The largest included 5,878 nondiabetic MESA study participants followed up for a median of 5.8 years, in whom addition of the calcium score to conventional stratification improved coronary risk classification in 25% of the subjects, particularly those in the intermediate category (Fig. 5)(66). The prognostic value of coronary computed tomography angiography was also revisited. Coronary computed tomography was an independent predictor of cardiac death and myocardial infarction in >2,000 mostly symptomatic patients followed up for 16 ± 8 months. Beyond disease severity and left ventricular ejection fraction, a score of plaque burden provided incremental prognostic informa-
tion for the prediction of all-cause mortality and nonfatal myocardial infarction (67).

**Molecular imaging.** The evaluation of vascular inflammation with $^{18}$fluorodeoxyglucose positron emission tomography was the central topic of several investigations. A study of carotid positron emission tomography demonstrated increased inflammatory activity in patients with impaired fasting glucose, and even higher in the presence of overt diabetes. Moreover, tracer uptake progressed across Framingham risk categories (68). In a different in vivo investigation, carotid inflammatory activity in symptomatic patients was associated with higher frequency of ipsilateral brain microemboli (69). Using a different tracer that binds benzodiazepine receptors expressed in activated macrophages, positron emission tomography could detect arterial wall inflammation in patients with vasculitis (70). Moving into experimental models of disease, magnetic resonance imaging allowed for the detection of intravascular thrombi with the use of a contrast agent targeted to activated platelets (71). Spectral computed tomography, a technique that enables differentiation of various contrast agents in a single scan based on their X-ray attenuation properties, demonstrated potential for simultaneous depiction of arterial inflammation (using a gold-HDL–based contrast agent taken up by macrophages), intraluminal contrast, and calcification (72). Another investigation demonstrated the feasibility of nonviral delivery, with the use of ultrasound microbubbles, of gene therapy aimed at inhibiting expression of intercellular adhesion molecule-1 in injured murine arteries, resulting in successful suppression of neointimal formation (73).

**Prevention and Treatment**

The importance of prevention through lifestyle choices cannot be overemphasized. Interventions at the societal level could have enormous impact on public health. In the context of high blood pressure, the most prevalent risk factor, an intervention to reduce dietary salt consumption by 3 g/day (approximately by 30% to 50% of the usual intake) was predicted to reduce cardiovascular events at least as effectively as other interventions targeting, for example, tobacco or obesity (Table 2) (74). Smoking cessation was associated with 1-year improvements in endothelial function despite weight gain (75). A study examining different diets reported that weight loss maintained for a 2-year period can induce regression of carotid atherosclerosis, probably through associated reductions in blood pressure (76). However, dietary supplements of omega-3 fatty acids failed to reduce subsequent cardiovascular events among myocardial infarction survivors in large randomized trials (77).

**Dyslipidemia and statin therapy.** Statins continue to be the mainstay of medical therapy for atherothrombosis. A meta-analysis of nearly 170,000 participants supported intensive statin therapy by confirming that protection from myocardial infarction and ischemic stroke is directly proportional to the absolute LDL level reductions, with no evidence of a threshold below which these benefits are lost (78). Statin benefits seem to come at the expense of a small risk (odds ratio: 1.09; 95% CI: 1.02 to 1.17) of increased incidence of diabetes according to another meta-analysis of 13 controlled trials (79). In the setting of primary prevention and regarding the use of an approach like that of the JUPITER study in the community, it was reported that statin initiation at lower risk without CRP testing would be more cost effective than measuring CRP levels, assuming that statins provide benefit in the absence of increased CRP (80). In the presence of moderate kidney disease, rosuvastatin therapy still improves outcomes, according to a secondary analysis of the JUPITER trial (81). In line with these findings, but in contrast with prior randomized studies that failed to demonstrate benefit of statin therapy on dialysis patients, interesting results came from SHARP (Study of Heart And Renal Protection). The SHARP trial evaluated the combination of simvastatin and ezetimibe in 9,500 adults with moderate to severe chronic kidney disease (one-third were on dialysis). After a median follow-up of 4.9 years, patients randomly assigned to the drug combination experienced a 17% reduction in major atherothrombotic events compared with the placebo group ($p = 0.0021$) (82). These findings question the prior failure of simvastatin/ezetimibe to reduce surrogates of cardiovascular disease such as the CIMT.

High-density lipoprotein cholesterol as a therapeutic target was revisited in 2010. A meta-analysis of 18 placebo-controlled trials and >45,000 participants reported that fibrates are associated with a 10% relative risk reduction of major cardiovascular events, driven mainly by a 13% reduc-

<table>
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<th>Table 2: Projected Annual Reductions of Cardiovascular Events for Various Population Interventions</th>
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<td><strong>Intervention</strong></td>
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<td>Salt reduction (3 g/day)–low-high estimates</td>
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<td>Smoking cessation (by 50%)</td>
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Values are percent reduction.

CHD = coronary heart disease; MI = myocardial infarction.
tion in coronary events (83). Extended-release niacin was shown to increase not only HDL concentrations but also its endothelial-protective properties in diabetic patients (84).

Two large prospective cohorts reported associations between reduced cholesterol ester transfer protein (CETP) levels or activity with impaired cardiovascular outcomes, challenging the concept of CETP inhibition as a cardioprotective pharmacologic approach (85,86). Although this notion might be supported by the previous failure of torcetrapib, which caused increases in both blood pressure and mortality, the novel CETP inhibitor anacetrapib was tested in 1,623 patients with known CHD or high cardiovascular risk receiving statins. In comparison with placebo, anacetrapib lowered LDL cholesterol by 39.8%, lipoprotein(a) by 36.4%, and increased HDL cholesterol by 138.1%, without increases in blood pressure, aldosterone levels, or identifiable adverse events during 18 months (87). It remains to be proven if these favorable lipid changes translate into improved outcomes. In a feasibility study, infusing autologous delipidated HDL after an acute coronary syndrome was shown to markedly increase concentrations of pre-B-like HDL, resulting in nonsignificant reductions in coronary atheroma volume (88).

**Diabetes mellitus.** Because of the higher baseline cardiovascular risk associated with diabetes, it has been largely hypothesized that tighter metabolic control could improve outcomes in this setting. However, prior studies failed to clearly demonstrate reductions in macrovascular events with intensive glucose-lowering approaches, maybe because of higher incidence of hypoglycemia (89). In addition, the risks associated with intensive glucose lowering seem to be especially relevant in patients with more advanced disease as reflected by higher hemoglobin A1c concentrations (Fig. 6) (90). Several investigations published last year did not support the use of more intensive lipid or antihypertensive therapy either. A substudy of the ACCORD (Action to Control Cardiovascular Risk in Diabetes) study randomly assigned 5,518 patients with type 2 diabetes with and without cardiovascular disease to simvastatin plus either placebo or fenofibrate. After an average of 4.7 years of follow-up and despite significant increases in HDL and reductions in triglycerides levels, no benefit was observed in terms of major cardiovascular events (HR: 0.95, 95% CI: 0.79 to 1.08; p = 0.32) or any of the secondary outcomes (91). Another substudy of the same trial enrolling 4,733 patients with the same follow-up compared intensive antihypertensive therapy to a target systolic pressure <120 mm Hg versus the standard of <140 mm Hg. Despite an average systolic blood pressure of 119.3 mm Hg in the intensive arm (vs. 133.5 mm Hg in the standard arm), there were no significant reductions in major events (Fig. 7). The rates of stroke were reduced in the intensive-therapy arm, although at the cost of an increase in serious side effects (92). Similar lack of benefit was reported in a secondary analysis according to blood pressure achieved in another large trial: among 6,400 diabetic patients, those who reached a systolic pressure <130 mm Hg did not experience improved outcomes and, in fact, an increase in all-cause mortality was noted (93). These findings may reflect different susceptibility of various organs to lower perfusion pressure in the setting of diabetic arteriopathy (94). Regarding the optimal antihypertensive agent in diabetes, data from the ACCOMPLISH (Avoiding Cardiovascular Events Through Combination Therapy in Patients Living With Systolic Hypertension) study supported the addition of a calcium-channel blocker (amlodipine) as opposed to a diuretic (hydrochlorothiazide) to an angiotensin-converting enzyme inhibitor because of reduced cardiovascular events (95). Conversely, the use of valsartan versus placebo in patients with impaired glucose tolerance and established cardiovascular disease or cardiovascular risk factors for a median of 5 years reduced the incidence of diabetes but not cardiovascular events in the NAVIGATOR (Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research) study (96).

The controversy regarding cardiovascular safety of common oral glucose-lowering agents, specifically thiazolidinediones, continued in 2010. As a result, the American Heart Association and American College of Cardiology Foundation issued a Scientific Advisory recommending that these drugs should not be expected to reduce cardiovascular disease, that they should be avoided for patients in functional class III/IV as they increase the risk of heart failure, and that there are insufficient data to support the choice of pioglitazone over rosiglitazone (97). Nonetheless, in a nationwide evaluation of 227,571 elderly Medicare beneficiaries, rosiglitazone increased the risk of stroke, heart failure, and all-cause mortality, but not myocardial infarction, in comparison with pioglitazone, although this was a retrospective analysis (98). In the setting of impaired glucose tolerance, the short-acting insulin secretagogue natameteglinide was also tested in the NAVIGATOR study, leading to no reductions in either incident diabetes or cardiovascular events in comparison with placebo (99).

**Drug therapy for weight loss.** After the withdrawal from the market of cannabinoid-1 receptor-blocker rimonabant because of safety concerns, new agents for weight loss were tested in 2010. The norepinephrine and serotonin reuptake inhibitor sibutramine was associated with higher rates of nonfatal cardiovascular events but not mortality among high-risk obese patients, particularly those with known cardiovascular disease (100). More promising results were reported with the daily use of the serotonin 2C-receptor agonist lorcaserin. In comparison with placebo, it led to maintained although modest reductions in weight with improvements in cardiovascular risk factors and good safety profile over 2 years (101).

**Antithrombotic therapy.** The role of aspirin for primary prevention continued to be a matter of debate. In particular, there are certain clinical scenarios with intrinsically higher cardiovascular risk where the use of aspirin was evaluated. In the context of diabetes, a joint statement of the American
Heart Association, American College of Cardiology, and American Diabetes Association recommended considering low-dose aspirin (75 to 165 mg/day) for diabetic patients with an estimated 10-year cardiovascular risk >10% (102). In patients with peripheral artery disease, the Aspirin for Asymptomatic Atherosclerosis trial randomly allocated 3,350 asymptomatic participants with low ankle-brachial index (≤0.95) to receive placebo or aspirin 100 mg once daily. After a mean follow-up of 8.2 years, there was no significant reduction in cardiovascular events but a trend for increased bleeding (103). Conversely, a post-hoc analysis of a large trial of hypertensive patients mostly free from cardiovascular disease showed that, in the presence of chronic kidney disease, low-dose aspirin (75 mg daily) provided a significant net beneficial effect that appeared more pronounced for those with more severe reductions in glomerular filtration rate (104).

Regarding thienopyridines, concern exists of a potential interaction between clopidogrel and protease pump inhibitors, which also inhibit the cytochrome P450 isoenzyme CYP2C19. This was addressed in a trial that randomly assigned 3,761 patients to dual antiaggregation therapy with aspirin and clopidogrel plus either omeprazole or placebo. Omeprazol reduced gastrointestinal bleeding by at least 70%, without evidence of increased cardiovascular events. These results should be interpreted with caution in view of the limited follow-up (median 108 days) (105). Data from TRITON–TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel–Thrombolysis In Myocardial Infarction 38) suggested that a strategy using prasugrel in lieu of clopidogrel for up to 15 months (particularly in the Asymptomatic Atherosclerosis trial randomly allocated 3,350 asymptomatic participants with low ankle-brachial index (≤0.95) to receive placebo or aspirin 100 mg once daily. After a mean follow-up of 8.2 years, there was no significant reduction in cardiovascular events but a trend for increased bleeding (103). Conversely, a post-hoc analysis of a large trial of hypertensive patients mostly free from cardiovascular disease showed that, in the presence of chronic kidney disease, low-dose aspirin (75 mg daily) provided a significant net beneficial effect that appeared more pronounced for those with more severe reductions in glomerular filtration rate (104).

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first month) may be cost effective for patients with an acute coronary syndrome undergoing percutaneous coronary intervention (106). Also in this group of patients, a subanalysis of the PLATO study reinforced the clinical superiority of ticagrelor with a reduction in the combination of cardiovascular death, myocardial infarction, or stroke (HR: 0.84, 95% CI: 0.75 to 0.94; \( p = 0.0025 \)) without increases in bleeding complications (107). In addition, studies showed that ticagrelor provides greater and more consistent platelet inhibition than clopidogrel, and once approved for clinical use, it might be considered as an alternative for clopidogrel nonresponders (108,109).

**Stable CHD.** Several studies addressed different therapeutic strategies for patients with stable multivessel CHD and confirmed that, in general, surgery outperforms percutaneous revascularization in more complex disease (i.e., higher SYNTAX [The SYNergy between PCI with TAXUS and Cardiac Surgery] score) and when subsequent revascularization is included as an outcome. In the 10-year follow-up report of MASS II (Second Medical, Angioplasty, or Surgery Study), which enrolled patients with stable angina, multivessel disease, and preserved ventricular function who were good candidates for all 3 therapies, surgical revascularization reduced the incidence of combined mortality, infarction, or refractory angina requiring revascularization in comparison with percutaneous intervention (HR: 0.53, 95% CI: 0.39 to 0.72; \( p < 0.001 \)) or medical therapy (HR: 0.43, 95% CI: 0.32 to 0.58; \( p < 0.001 \)) (110). In diabetic patients treated with aggressive medical therapy in the BARI 2D (Bypass Angioplasty Revascularization Investigation 2 Diabetes) trial, prompt revascularization provided increased protection against myocardial infarction (particularly if combined with insulin-sensitizing therapy) only when surgery was deemed the optimal revascularization approach, typically in patients with more extensive disease. Five-year outcomes were similar for medical therapy or percutaneous revascularization in patients with less complex disease (111). Moreover, in this patient subset, a strategy of intensive medical therapy followed by delayed revascularization if clinically indicated was found to be cost effective (112). In addition, the previously reported benefits in mortality and myocardial infarction of percutaneous revascularization guided by fractional flow reserve as opposed to angiographic lesion severity were extended up to 2 years in a report from the FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) study (113).

**Peripheral atherothrombosis.** Several relevant studies compared outcomes after surgical versus percutaneous intervention in peripheral arterial disease. The multicenter CREST (Carotid Revascularization Endarterectomy vs. Stenting Trial) randomly allocated 2,502 patients with symptomatic or asymptomatic carotid stenosis amenable for both surgical and percutaneous repair to undergo carotid endarterectomy or stenting, and observed them for a median of 2.5 years (114). There was no significant difference in long-term outcome as evaluated by the combination of periprocedural stroke, myocardial infarction, or death, or long-term stroke (HR with stenting: 1.11; 95% CI: 0.81 to 1.51; \( p = 0.51 \)). Endarterectomy was associated with more periprocedural myocardial infarction and stenting with more periprocedural strokes (reported to have a stronger impact on quality of life). However, short-term follow-up data from the ICSS (International Carotid Stenting Study) indicated increased incidence of stroke, death, or procedural myocardial infarction with stenting (HR: 1.69, 95% CI: 1.16 to 2.45; \( p = 0.006 \)) and supported surgery as the current therapy of choice (115). Similarly, a meta-analysis of 3 different trials concluded that endarterectomy is associated with better outcomes than stenting, particularly for patients >70 years of age (116).

Regarding the treatment of abdominal aortic aneurysms, endovascular repair (stenting) has been associated with decreased perioperative mortality in comparison with surgery. The EVAR (Endovascular Aneurysm Repair) trial presented long-term (median 6 years) follow-up data on 1,252 patients with aneurysms \( \geq 5.5 \) cm in diameter and a mean age of 74 years who were randomly assigned to either stenting or surgical repair. The initial 6-month benefits of stenting were lost subsequently, with no differences in overall mortality at 2 years or in aneurysm-related death at 6 years. In addition, stenting was associated with higher costs (117). Among patients ineligible for surgical repair, aneurysm-related mortality, but not overall survival, was reduced with stenting versus medical therapy, again at the expense of increased costs (118).

**REFERENCES**


Key Words: atherosclerosis • imaging • risk factors • thrombosis • vasculature.