



Effective Health Care Program

Technical Brief
Number 3

Vulnerable Atherosclerotic Plaque



Agency for Healthcare Research and Quality
Advancing Excellence in Health Care • www.ahrq.gov

This report is based on research conducted by the Tufts Evidence-based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. 290-02-0022). The findings and conclusions in this document are those of the author(s), who are responsible for its contents; the findings and conclusions do not necessarily represent the views of AHRQ. Therefore, no statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

The information in this report is intended to help health care decisionmakers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

This report may be used, in whole or in part, as the basis for development of clinical practice guidelines and other quality enhancement tools, or as a basis for reimbursement and coverage policies. AHRQ or U.S. Department of Health and Human Services endorsement of such derivative products may not be stated or implied.

Technical Brief

Number 3

Vulnerable Atherosclerotic Plaque

Prepared for:

Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
540 Gaither Road,
Rockville, MD 20850
www.ahrq.gov

Contract No. HHSA-290-02-0022

Prepared by:

Tufts Medical Center Evidence-based Practice Center

Investigators

Alawi A. Alsheikh-Ali, M.D., M.S.¹
Georgios D. Kitsios, M.D., Ph.D.
Ethan M. Balk, MD, M.P.H.
Audrey M. Mahoney, B.F.A.
Joseph Lau, M.D.
Stanley Ip, M.D.

¹Institute for Clinical Research and Health Policy Studies, Tufts Medical Center,
800 Washington Street, Boston, MA 02111.

AHRQ Publication No. 10-EHC-062-EF
August 2010

This document is in the public domain and may be used and reprinted without permission except those copyrighted materials noted, for which further reproduction is prohibited without the specific permission of copyright holders.

No investigators have any affiliations or financial involvement (e.g., employment, consultancies, honoraria, stock options, expert testimony, grants or patents received or pending, or royalties) that conflict with material presented in this report.

Suggested citation: Alsheikh-Ali A, Kitsios GD, Balk E, Mahoney A, Lau J, Ip S. Vulnerable Atherosclerotic Plaque. Technical Brief No. 3 (Prepared by Tufts Evidence-based Practice Center under Contract No. HHS-290-02-0022-EPC II.) AHRQ Publication No. 10-EHC062-EF. Rockville, MD: Agency for Healthcare Research and Quality. August 2010. Available at: www.effectivehealthcare.ahrq.gov/reports/final.cfm.

Preface

The Agency for Healthcare Research and Quality (AHRQ) conducts the Effective Health Care Program as part of its mission to organize knowledge and make it available to inform decisions about health care. As part of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Congress directed AHRQ to conduct and support research on the comparative outcomes, clinical effectiveness, and appropriateness of pharmaceuticals, devices, and health care services to meet the needs of Medicare, Medicaid, and the Children’s Health Insurance Program (CHIP).

AHRQ has an established network of Evidence-based Practice Centers (EPCs) that produce Evidence Reports/Technology Assessments and Comparative Effectiveness Reviews to assist public- and private-sector organizations in their efforts to improve the quality of health care. Technical Briefs are the most recent addition to this body of knowledge.

A Technical Brief provides an overview of key issues related to a clinical intervention or health care service—for example, current indications for the intervention, relevant patient population and subgroups of interest, outcomes measured, and contextual factors that may affect decisions regarding the intervention. Technical Briefs generally focus on interventions for which there are limited published data and too few completed protocol-driven studies to support definitive conclusions. The emphasis, therefore, is on providing an early objective description of the state of science, a potential framework for assessing the applications and implications of the new interventions, a summary of ongoing research, and information on future research needs.

Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an e-mail list to learn about new program products and opportunities for input. Comparative Effectiveness Reviews will be updated regularly, while Technical Briefs will serve to inform new research development efforts.

Carolyn M. Clancy, M.D.
Director
Agency for Healthcare Research and Quality

Jean Slutsky, P.A., M.S.P.H.
Director, Center for Outcomes and Evidence
Agency for Healthcare Research and Quality

Stephanie Chang, M.D., M.P.H.
Director
Evidence-based Practice Center Program
Agency for Healthcare Research and Quality

Elise Berliner, Ph.D.
Task Order Officer
Evidence-based Practice Center Program
Agency for Healthcare Research and Quality

Contents

Introduction.....	1
Methods.....	3
Literature Search Strategy.....	3
Study Eligibility Criteria.....	4
Data Collection.....	4
Results.....	5
Findings from Systematic Literature Overview.....	5
Study Designs.....	5
Characteristics of Primary Studies.....	5
Answers to Key Questions (KQ).....	5
KQ 1. What recent definitions of vulnerable plaque have been proposed? What are the common elements in these definitions?.....	5
KQ 2. What are the histopathological features of a vulnerable plaque?.....	7
KQ 3. Are there any longitudinal natural history studies of vulnerable plaque? If such studies are available, what do they show?.....	7
KQ 4. Has a reference standard for the evaluation of vulnerable plaque been developed?.....	9
KQ 5. How would the diagnosis of vulnerable plaque aid in the disease management (e.g., diagnosis leading to an intervention that decreases the risk of a clinical event)?.....	9
KQ 6a. Using a systematic literature scan approach, describe any specific serum biomarkers that may help predict the presence of features of plaques that are prone to rupture/thrombose.....	11
KQ 6b. Have any of them been cleared by the FDA for this indication?.....	11
KQ 6c. Are there direct comparative studies that examine how these biomarkers differ from those used in the management of patients at risk of developing acute cardiovascular events?.....	11
KQ 7a. Using a systematic literature scan approach, describe the current non-invasive and invasive imaging methods to evaluate features of plaques that are prone to rupture/thrombose.....	12
KQ 7b. Have any of them been cleared by the FDA for this indication?.....	12
KQ 7c. Are there direct comparative studies that examine how these imaging methods differ from those used in the management of patients at risk of developing acute cardiovascular events?.....	13
KQ 8a. Using a systematic literature scan approach, describe the current therapeutic approaches to modify the features of vulnerable plaque.....	13
KQ 8b. Have any of them been cleared by the FDA for this indication?.....	14
KQ 8c. Are there direct comparative studies that examine how these therapeutic approaches differ from those used in the management of patients at risk for developing acute cardiovascular events?.....	14
Discussion.....	15
References.....	73
List of Acronyms/Abbreviations.....	83

Figure

Figure 1. Publication trends for the period 2003-2009	17
---	----

Tables

Table 1. References of primary studies and narrative review articles	18
Table 2. Basic study features of included studies	45
Table 3. Study features of histopathology studies	46
Table 4. Study features of biomarker studies.....	47
Table 5. Grey literature search results for biomarker tests of potential use in the management of patients with vulnerable plaques	49
Table 6. Grey literature search results for imaging devices of potential use in the management of patients with vulnerable plaques.....	55
Table 7. Grey literature search results for therapeutic options of potential use in the management of patients with vulnerable plaques.....	62
Table 8. Study features of imaging studies	64
Table 9. Study features of treatment studies	66
Table 10. ClinicalTrials.gov search results for trials related to vulnerable plaque.....	67

Introduction

Atherosclerosis is a chronic condition with acute cardiovascular manifestations. Most commonly, the acute manifestations of atherosclerosis are triggered by a local arterial occlusion with a thrombus overlying a pre-existing atherosclerotic plaque. Despite landmark advances in the prevention and treatment of cardiovascular disease, it remains the leading cause of morbidity and mortality worldwide, accounting in 2005 for 35% of all deaths in the United States and 30% of all deaths globally.^{1,2} A particular challenge to combating the epidemic of cardiovascular disease is the sudden and often unpredictable nature of its acute manifestations. For many patients with atherosclerosis, the first manifestation is an acute myocardial infarction, sudden cardiac death, or a disabling stroke. This has fueled considerable research aimed at refining existing algorithms for risk stratification and developing new methods to identify subjects before the occurrence of a cardiovascular event so that primary preventive measures can be initiated. Furthermore, among patients who have survived a cardiovascular event, the risk of a subsequent event remains relatively high—approaching 1 in 4 despite aggressive treatment.³ Such recurrence rates highlight the need for novel approaches to secondary prevention of cardiovascular disease and to the treatment of index events.

Over the past two decades, the concept of the “vulnerable plaque” has gained attention as a paradigm to improve risk stratification and potentially lead to newer invasive and non-invasive therapeutic options to prevent and treat atherothrombotic cardiovascular disease. The Effective Health Care Program at the Agency for Healthcare Research & Quality requested a technical brief on the diagnosis and treatment of “vulnerable plaques” of coronary and carotid arteries. Our report is based on a set of key questions designed to explore the concept of “vulnerable plaque” and how this concept could affect the use of existing or developing diagnostic and therapeutic technologies. This report also expands on a technical report on vulnerable plaque that we conducted in 2004.⁴

Methods

The objective of this report is to assess, with a systematic review approach, the volume and type of evidence available on vulnerable plaque. The purpose is to provide a basis for establishing how the research field is evolving and identify topics that may require further research. We created an “evidence map” that describes the tests that have been evaluated, the populations in which they have been evaluated, and the types of studies that have been used. This review is not a detailed technology assessment based on a systematic review of full-text articles. It does not synthesize or evaluate the results of individual clinical studies and does not make clinical recommendations. “Vulnerable plaque” is still an evolving concept and is not an established medical diagnosis. Therefore, any reference to “vulnerable plaque” in this report concerning its natural history, diagnostic methods, and treatments is by necessity inferential. It refers to conditions that might fall under the current concept of vulnerable plaque but not specifically about vulnerable plaque.

Literature Search Strategy

We searched MEDLINE to identify English language publications on vulnerable plaque. Because it is an emerging concept, there are no specific medical subject headings (MeSH terms) available. Therefore, exclusively text words were used. The search terms included vulnerable plaque, unstable plaque, atheromatous plaque, ulcerative plaque, and related words. The search was limited to English language studies conducted in humans. Because we were updating our 2004 technical report and were focusing on the current thinking about the vulnerable plaque concept, we limited the search to the period from 2003 to April 2010. The search results were reviewed independently by four reviewers (AA, EB, GK and SI). All potentially relevant abstracts were re-screened by a cardiologist (AA).

In order to identify the available testing devices, imaging modalities and drugs that would be of interest to vulnerable plaque, a grey literature^a search approach⁵ was used to seek information on the corresponding biomarkers, imaging methods and therapeutic approaches identified by the systematic literature overview. The Google™ website and, specific companies’ websites were searched. For the Google search, topic related keywords were used. Given the non-specific nature of the Google search engine and the lack of a concrete definition of vulnerable plaque, a list of companies known to sponsor clinical trials related to the vulnerable plaque concept⁶ and a list of testing modalities and drugs identified from the systematic literature overview were created.

The products relating to the detection or treatment of plaques were researched within each company site, and relevant information was recorded. Following this, the testing modality keywords were entered into the Google search engine in an effort to identify other producers of related products. Some of the general keywords included: intravascular ultrasound-virtual histology; near-infrared spectroscopy; 320-multidetector computed tomography; angiography; Raman spectroscopy; optical coherence tomography; palpography-elastography; magnetic resonance imaging; and variations of these terms. After inspection, the most relevant and

^aAccording to the Fourth International Conference on Grey Literature in Washington, DC, in October 1999,⁵ grey literature was defined as: “That which is produced on all levels of government, academics, business and industry in print and electronic formats, but which is not controlled by commercial publishers.” Grey literature can include, but is not limited to reports, memoranda, conference proceedings, standards, technical documentation, government documents, and in this case also includes information retrieved from commercial manufacturer and distributor websites.

pertinent information relating to the keywords invariably appeared within the first three to five pages of the Google search results. Thus, search results on these relevant pages were relied upon in order to gather device information.

As the manufacturer and/or company websites varied in their description concerning the FDA regulatory status of the specific tests or drugs, we searched for the relevant information on the FDA website. Specifically, for diagnostic devices and tests, we searched the publicly accessible FDA 510(k) Premarket Notification database for information regarding the FDA clearance status of the products and devices that were identified from our grey literature search using the following method: we searched the 510(k) database⁷ by either product name, or applicant name (or the manufacturer). For drugs, we searched the Drugs@FDA database⁸ by using the active ingredient name. For each test or drug, the following information was recorded: company name; test modality/test name or active ingredient/drug name; FDA indications for use (when available) or indications per company literature; clearance by FDA; and whether or not the test (or drug) has been FDA cleared specifically for “vulnerable plaque.”

Finally, in order to map ongoing research on vulnerable plaque, we performed a systematic search of the Clinicaltrials.gov registry on 02/10/2010 to identify observational and interventional trials on vulnerable plaque. Protocols of retrieved entries were reviewed for use of predictors or outcomes relevant to the concept of vulnerable plaque and those studies were summarized.

Study Eligibility Criteria

We identified abstracts of studies that fit a broad concept of vulnerable plaque. These included studies with the stated or implied aim of examining plaque features thought to be related to the susceptibility of an atherosclerotic plaque to cause a clinical event (e.g., myocardial infarction, angina, stroke, transient ischemic attack). These features included histopathological (i.e., thin-cap fibroatheroma, macrophage infiltration, presence of lipid core or intraplaque hemorrhage) or imaging (i.e., plaque echolucency and density, presence of ulceration or intraplaque hemorrhage and others) findings. We included primary studies or systematic reviews of studies that were conducted in living humans or on carotid or coronary artery tissue removed during procedures on living humans, or autopsy studies. We also collected narrative reviews, commentaries, and editorials on the concept of vulnerable plaque. Studies investigating associations between biomarkers (e.g., C-reactive protein) and clinical outcomes (e.g., acute coronary syndrome or stroke) or exploring the effect of treatment strategies (e.g., statins) on cardiovascular risk without explicit assessment of plaque vulnerability features (i.e., through imaging or histopathology evaluation) are outside the scope of this review and not discussed in this technical brief. Case reports were also excluded.

Data Collection

From eligible primary studies, we extracted the following information from the available abstracts: study design (cross-sectional or longitudinal follow-up, prospective or retrospective collection of data); sample size; population (with or without history of carotid or coronary disease; living patients, tissue samples, or autopsy samples); predictor of interest (imaging characteristics of the plaque, histopathology, biomarkers, others); information on treatments; outcomes (clinical, imaging, or histopathological); and whether the study measured direct impact of a particular diagnostic tool on physician decision making or patient outcomes.

Results

Findings from Systematic Literature Overview

The MEDLINE search yielded 1,466 titles, of which 463 abstracts (both primary and review articles) qualified for inclusion. The references of all included articles are provided in Table 1.

Study Designs

We found that the number of review articles on vulnerable plaque (n=221) published in the last 6 years is almost equal to the number of primary studies (n=242) associated with the concept of vulnerable plaque (Table 2). The large majority of the primary studies (n=216 of 242, 89%) are of cross-sectional design, comparing different potential features of vulnerable plaque (e.g., plaque characteristics on pre-endarterectomy imaging with tissue histology from post-surgical specimen); the remaining 26 studies were longitudinal studies, evaluating the natural history of plaques or the effect of treatment on plaque features thought to be related to the propensity of a plaque to cause a clinical event (e.g., plaque characterization by imaging modalities and subsequent risk of cardiovascular events). Twenty-four of the 26 longitudinal studies used a prospective design.

Since 2003, about 60 articles on vulnerable plaque have been published annually, with a slight increase in the number of publications over time (Figure 1).

Characteristics of Primary Studies

Of the 242 primary studies, 114 (47%) were conducted in patients with coronary artery disease and 130 (54%) in patients with carotid artery disease; five of these studies simultaneously evaluated coronary and carotid artery disease (Table 2). Only 3 studies (1%) were conducted in participants without a history of cardiovascular disease (healthy individuals or individuals with cardiovascular risk factors but no clinical disease). The primary studies enrolled populations falling into three categories: living individuals (number of studies = 143, 59%), tissue samples obtained from living patients during carotid endarterectomy or coronary atherectomy (number of studies = 79, 33%), and autopsy specimens of the coronary or carotid arteries (number of studies = 20, 8%). The predictors of interest (i.e., factors examined for their association with plaque vulnerability) included biomarkers (number of studies = 36, 15%), histopathological findings (number of studies = 60, 25%), imaging features (number of studies = 120, 49%), therapeutic approaches (number of studies = 17, 7%), and combinations of the above or other predictors (number of studies = 9, 4%).

Answers to Key Questions (KQ)

KQ 1. What recent definitions of vulnerable plaque have been proposed? What are the common elements in these definitions?

The term “vulnerable plaque” was first used 20 years ago in the context of studying triggers of acute cardiovascular disease.⁹ It was proposed that acute thrombosis resulting in total arterial occlusion is preceded by the development of the “vulnerable atherosclerotic plaque.”⁹ Plaque vulnerability was defined as the susceptibility of a plaque to rupture, thus causing a

clinical cardiovascular event (e.g., acute myocardial infarction or sudden cardiac death). The introduction of this concept paralleled an increased appreciation of the limitations of imaging arterial lumens and quantifying risk based merely on the severity of arterial stenoses. In several retrospective and prospective serial angiographic studies, the culprit lesion in nearly two-thirds of patients with acute coronary events was shown to have less than 70% (often <50%) diameter narrowing on a coronary angiogram weeks or months before the index event.¹⁰⁻¹³ In addition, the site of myocardial ischemia found during a stress test (an indication of a hemodynamically significant stenosis in the coronary artery supplying that territory) does not accurately predict the site of future myocardial infarction.¹⁴

In retrospective autopsy studies, three histological features were more commonly observed in plaques thought to be responsible for most acute coronary events compared to stable plaques: a larger lipid core (>40% of total lesion area), a thinner fibrous cap (<65 μ), and more inflammatory cells (about 26% macrophage infiltration of fibrous cap compared to 3% in stable plaques).¹⁵⁻¹⁷ Such observations fueled research into invasive and non-invasive imaging tests to detect these histological features, and in so doing identify plaques that presumably are more likely to rupture. Since its introduction, the term “vulnerable plaque” has been used interchangeably in reference to the concept of propensity to result in an acute cardiovascular event or to denote a plaque with the histological hallmarks of culprit lesions from autopsy studies. A more inclusive definition was proposed in 2003 to include not only susceptibility to rupture, but more broadly susceptibility to thrombose or rapidly progress to a culprit lesion.¹⁸ This broadening of the definition was based on observations that plaque rupture, while common in culprit lesions, is not universal. Nearly one-third of such lesions exhibit erosion or nodular calcification without rupture of the fibrous cap.¹⁹

On the basis of retrospective studies of culprit plaques (i.e., plaques that have caused an acute event), several criteria were proposed by investigators in the field to define a vulnerable plaque (i.e., a plaque that has not yet caused an acute event, but is at high risk of doing so). The major criteria for vulnerable plaque included: active inflammation; a thin cap (<100 μ) with a large lipid core (>40% of the plaque’s total volume); endothelial denudation with superficial platelet aggregation; fissured/injured cap (which may indicate a recent rupture); and severe stenosis which would render the plaque more prone to shear stress or may be a marker of other less stenotic but vulnerable plaques.¹⁸ According to this proposal, the presence of at least one of these major criteria may indicate a higher risk of plaque complication. Minor criteria for plaque vulnerability included: the presence of superficial calcified nodules; yellow color which may indicate a larger lipid core; intraplaque hemorrhage; endothelial dysfunction (impaired endothelial vasodilator function); and expansive (positive) remodeling, which refers to compensatory outward enlargement of the vessel wall without luminal compromise.¹⁸ Notably, though, the predictive utility of these criteria has not been prospectively validated. Furthermore, in the absence of a major criterion, how (or whether) the minor criteria can be combined in a risk score to define plaque vulnerability has not been addressed. In addition to the local features characterizing plaque vulnerability, there is evidence that systemic factors may play a role in plaque instability, including the presence of a systemic inflammatory state.¹⁸ This provides the rationale to studying serum biomarkers that may identify patients with high-risk lesions (“vulnerable blood”), which along with “vulnerable myocardium” forms the triad of vulnerability that defines the “vulnerable patient.”¹⁸

KQ 2. What are the histopathological features of a vulnerable plaque?

As mentioned above, common histopathological features of a vulnerable plaque include a thin fibrous cap, a large lipid core and, and more inflammatory cells. Sixty studies evaluated histopathological findings as predictors and all were cross-sectional in design (Table 3).

Twenty-eight studies (47%) evaluated coronary artery samples, derived from living individuals during coronary atherectomy (n=19, 68%) or from autopsy specimens (n=9, 32%). Among the evaluated histopathological features of vulnerability, macrophage infiltration of the plaque was the most commonly examined, but only in 4 studies. The majority of the studies (n=20, 71%) did not assess the commonly reported histopathological features of vulnerability (a thin fibrous cap, a large lipid core and, and more inflammatory cells),²⁰ but focused on examining the tissue expression of molecules or cells proposed to be involved in the pathophysiological processes of the disease. The most commonly investigated locally expressed molecules were C-reactive protein (CRP), matrix metalloproteinases (MMPs), and lipoprotein-associated phospholipase A₂ (Lp-PLA₂). Histopathology was compared to clinical outcomes in 19 studies (68%); most commonly acute coronary syndrome (ACS) (n=17); eight studies compared the tested histopathological features to other reference histopathological features (cap thickness or combination of features).

Thirty-two studies (53%) evaluated carotid artery samples, almost exclusively taken from living individuals (n=31), given the easier availability of carotid artery samples following carotid endarterectomy, compared to coronary tree samples. Macrophage infiltration was the most commonly evaluated hallmark feature of vulnerability but only in 3 studies; most of the studies evaluated the tissue expression of molecules or cells proposed to be involved in the pathophysiological processes of the disease (n=203, 72%). The most commonly examined molecules were MMPs and vascular endothelial growth factor (VEGF). Histopathology was compared to clinical outcomes in 18 studies (56%), most commonly symptomatic carotid disease (n=14); the remaining 14 studies compared the tested histopathological features to other reference histopathological features (cap thickness or combination of features).

KQ 3. Are there any longitudinal natural history studies of vulnerable plaque? If such studies are available, what do they show?

As there is no standard definition for vulnerable plaque, there are no natural history studies for this proposed concept. The 2004 technical report⁴ found several studies that investigated natural history of plaque features that could be indicative of “vulnerability” or instability. Since that report, we have identified 12 additional studies that examined the longitudinal history of these plaque features. Five studies investigated plaque features of coronary arteries and 7 studies of carotid arteries.

Coronary Artery Disease

Motoyama et al.²¹ analyzed computed tomography (CT) angiographic findings in 1059 patients examined for suspected or known coronary artery disease and followed the patients for 27 (±10) months for the development of ACS. The atherosclerotic coronary lesions were analyzed for the presence of 2 features of vulnerability: positive remodeling (defined as >10% greater diameter at the plaque site compared to the reference segment) and low attenuation plaques (defined as non-calcified plaque with <30HU density). ACS developed in 10 of the 45

(22%) patients that showed plaques with both vulnerability features, compared to 4 of the 820 (0.5%) patients that showed plaques without these features. None of the 167 patients with normal angiograms developed ACS. The presence of 1 or 2-feature positive plaques was the only significant independent predictor of ACS (hazard ratio: 22.8, 95% confidence interval: 6.9-75.2). Only 75 of the 1059 (7%) patients screened had at least one vulnerability feature.²¹

Kim et al.²² performed a 3-vessel intravascular ultrasound (IVUS) prospective study in 183 patients undergoing a single stent implantation. Non-target lesions were characterized and vulnerable plaque was defined as presence of rupture, lipid core, dissection or thrombus. The patients were followed for 50 (\pm 20) months for the occurrence of ACS or death. The event-free rate was significantly lower in patients with vulnerable plaques ($p=0.04$), and the multiplicity of vulnerable plaques in non-target vessels was the only independent predictor of events (hazard ratio: 2.2, 95% confidence interval: 1.4-3.4).²²

Lee et al.²³ followed 229 patients with acute myocardial infarction treated with primary angioplasty. Twenty-seven patients with 35 non-culprit complex plaques had simultaneous review of their baseline and 6-month follow-up angiograms: 29 plaques remained complex, 1 was totally occluded, and 4 regressed. The study also found that long-term (not defined) cardiac events after discharge were more likely in patients with multiple complex plaques than in patients with single complex plaques.²³

Ohtani et al.²⁴ followed 552 patients with coronary artery disease. The study found that patients with 2 or more and 5 or more yellow plaques at baseline (by angioscopy) had 2.2- and 3.8-fold higher acute coronary event rates than those with 1 or less yellow plaque at 57 months follow-up (9.0% and 15.6%, respectively, vs. 4.1%; $p<0.02$). The number of yellow plaques was an independent predictor of acute coronary events.²⁴

Bayturan et al.²⁵ utilized IVUS to examine attenuated plaques (hypoechoic plaques with deep ultrasonic attenuation) in nonculprit coronary lesions in 159 patients from the ASTEROID trial. Attenuated plaques were found in 17 of 159 patients and there were no significant differences in clinical presentation and cardiovascular risk factors between patients with and without attenuation. During follow-up, these plaques remained stable, and no events occurred in the patients with attenuated plaques.²⁵

Carotid Artery Disease

Reiter et al.²⁶ followed 574 patients with asymptomatic carotid disease and carotid plaques at the level of the bifurcation with a diameter reduction of at least 30%. The patients had a baseline ultrasound and a second ultrasound 6-9 months later. The study found that increasing echolucency (thought to be indicative of lipid core) of carotid artery plaques over a 6-9 months period was predictive of a first major adverse cardiovascular event, which included all-cause mortality, myocardial infarction, stroke, percutaneous coronary intervention, coronary artery bypass grafting, peripheral percutaneous angioplasty, peripheral vascular surgery, or amputation owing to critical limb ischemia.²⁶

Hashimoto et al.²⁷ performed analyses of plaque echogenicity by B-mode ultrasonography in 250 patients with asymptomatic carotid artery disease. The authors estimated the percent area of each tissue component for each examined plaque, by comparing gray-scale median pixel intensities on B-mode images with carotid endarterectomy specimens. Plaques in the top tertile for the percent area of lipid-like echogenicity and in the lowest tertile for calcification showed an association with future stroke, even after adjustment for the severity of

carotid stenosis (hazard ratio 4.4 for lipid-like and 0.24 for calcification-like component, both $p < 0.05$).²⁷

Brajovic et al.²⁸ followed up a group of 72 patients with asymptomatic carotid stenoses for a 3-year period in order to examine the correlation between plaque morphology in ultrasonography (degree and plaque quality) and local hemodynamic plaque characteristics with onset of new neurological events and deaths. Significant correlations with new neurological events and deaths were found for plaque stenosis $\geq 70\%$, plaque ulceration and mixed plaque morphology (all $p < 0.0001$).²⁸

Takaya et al.²⁹ performed a baseline carotid artery imaging with magnetic resonance imaging (MRI) in 154 patients with asymptomatic disease and followed them for 38 months for the occurrence of cerebrovascular events (stroke, transient ischemic attack or amaurosis fugax). Twelve events occurred ipsilateral to the index artery. In univariate analyses, presence of thin fibrous cap, intraplaque hemorrhage and larger maximum percent lipid-rich/necrotic core volume were associated with subsequent events.³⁰ In a nested case-control sample from the same population,³¹ 14 patients with intraplaque hemorrhage and 15 controls with comparably sized plaque without hemorrhage underwent serial carotid MRI examinations. Over an 18-month period, patients with intraplaque hemorrhage at baseline had significantly higher percent change in wall volume and lipid-rich necrotic core volume, and were significantly more likely to have new plaque hemorrhages.³¹ In a subset of the same population without detectable plaque surface disruption at baseline,³² the percent lipid-rich/necrotic core volume was associated with new-surface disruption during a 3-year follow-up. In a similar, small-scale study by Altaf et al.,³³ the presence of intraplaque hemorrhage in MRI predicted the short-term risk for recurrent cerebrovascular symptoms in patients scheduled for carotid endarterectomy.

KQ 4. Has a reference standard for the evaluation of vulnerable plaque been developed?

No reference standard has been developed for the evaluation of vulnerable plaque. Since its introduction, the term “vulnerable plaque” has been used interchangeably in reference to the concept of propensity to result in an acute cardiovascular event or to denote a plaque with the histological hallmarks of culprit lesions from autopsy studies. A more inclusive definition was proposed in 2003 to include not only susceptibility to rupture, but more broadly susceptibility to thrombose or rapidly progress to a culprit lesion.¹⁸ This broadening of the definition was based on observations that plaque rupture, while common in culprit lesions, is not universal, with nearly one-third of such lesions exhibiting erosion or nodular calcification without rupture of the fibrous cap.¹⁹

KQ 5. How would the diagnosis of vulnerable plaque aid in disease management (e.g., diagnosis leading to an intervention that decreases the risk of a clinical event)?

If vulnerable plaques can be detected accurately, and effective therapeutic interventions initiated before cardiovascular events occur, all in a cost-effective manner, then many (perhaps the majority) of cardiovascular events can, in theory, be prevented. However, for this potential promise to be realized, substantial challenges need to be addressed. These challenges are both conceptual and methodological.

Conceptually, the diagnosis of a “vulnerable plaque” is by definition a probabilistic entity (i.e., it does not denote the occurrence of an event at present, but rather a higher risk of such occurrence in the future relative to a non-vulnerable or less vulnerable plaque). As such, before it

is widely adopted by clinicians, plaque vulnerability (once validated) should be able to provide incremental predictive value on top of currently available methods of risk stratification, which may be less expensive and less invasive than the methods proposed to detect vulnerable plaques. Moreover, the complex implications of such a probabilistic diagnosis are exemplified in the observation that not all plaques that rupture (the basis for the classic definition of the term) actually result in a clinical cardiovascular event. Some plaques would rupture and then quiesce and heal without causing a myocardial infarction or stroke (so called silent plaque rupture).^{34,35} Conversely, not all acute cardiovascular events are the result of plaque rupture, since non-ruptured plaques have been implicated as culprit lesions nearly one-third of the time in autopsy series.¹⁹ To the extent that plaque vulnerability is defined based on features that predict rupture, the observations that not all ruptures result in clinical events, and that not all clinical events are the result of rupture, would limit the sensitivity and specificity of the vulnerable plaque as a predictor of a future event.

A major potential utility of the vulnerable plaque paradigm is to identify apparently healthy subjects (or people with apparently stable plaques) who are at risk for future events. To date, however, almost everything we know about what constitutes a vulnerable plaque is based on studies in patients who have already suffered an event. In our systematic overview of the literature, only 3 of the 242 primary studies were conducted in patients without a known history of cardiovascular disease. In addition, the vast majority of studies were cross-sectional including all histopathological and biomarker studies, and 89% of imaging studies, and most had relatively small sample sizes. The 24 prospective studies identified in the literature had small sample sizes (median 64 patients, IQR 35-186), with a median follow-up duration of 15 months (IQR 6-36). Therefore, large, prospective studies including patients without prior cardiovascular events over relatively long durations of follow-up are required to validate retrospective and cross-sectional studies. Such prospective studies would also have to identify the “individual” vulnerable plaque that develops into a culprit lesion. In the present literature overview, none of the 10 prospective imaging studies^{21-28,36,37} that followed patients for clinical outcomes documented that the “vulnerable” plaque was the one responsible for the clinical event during follow-up. This may be challenging since plaques within a given patient may progress largely independently.³⁸ This adds to the complexity of predicting events from plaque imaging, and suggests local effects (e.g., physical forces) in addition to any systemic effects influencing plaque progression.

Once it is prospectively validated that certain plaque features are independently predictive of a future cardiovascular event, demonstrating the incremental utility of such a concept will be required. In applying the concept in individuals who are not considered high-risk by current criteria (typical of a primary prevention population), the positive predictive value of “plaque vulnerability” will be constrained by the prevalence or pretest probability of cardiovascular disease in the screened population.

Finally, once the incremental predictive utility of detecting a vulnerable plaque is established, it will have to be demonstrated that certain treatments (novel or currently in use) in patients who would otherwise not have been candidates will indeed improve outcomes. For example, would a statin reduce the risk of a future cardiovascular event in a patient who does not meet current treatment indications, but is found to have a “vulnerable plaque” on imaging? Would screening for such patients followed by selective treatment be more cost-effective than unselective treatment without screening? Such questions will need to be answered before the “vulnerable plaque” paradigm could be routinely considered in the prevention and treatment of cardiovascular disease. While such questions are more relevant to the application of the

vulnerable plaque concept in a primary prevention setting, the utility of the concept in a secondary prevention population will still depend on demonstrating incremental predictive value for further risk stratification and selective use of cost-effective therapies.

KQ 6a. Using a systematic literature scan approach, describe any specific serum biomarkers that may help predict the presence of features of plaques that are prone to rupture/thrombose.

Biomarkers were used as predictors by 36 studies (15%), all of which were cross-sectional in design (Table 4). All studies involved measurement of blood or serum biomarkers in living patients. Coronary artery disease was studied in 19 articles (53%), with a median number of 89 subjects enrolled per study (IQR 49-172). The studies investigated 14 biochemical markers in association with vulnerable coronary plaque. The most commonly investigated markers were CRP (n=6) and MMPs (n=2). Biomarkers were most commonly compared to imaging findings of plaques (n=15, 79%). Carotid artery disease was evaluated in 15 biomarker studies (42%), with a median number of 88 subjects enrolled per study (IQR 62-164). Among the 20 biomarkers investigated, CRP (n=4), MMPs (n=2) and pregnancy-associated plasma protein A (PAPP-A, n=2) were the most commonly examined. Biomarkers were compared to clinical outcomes (27%), histopathology features (40%), and imaging findings (33%). One study³⁹ enrolled apparently healthy individuals and compared the Apolipoprotein (Apo) B/ApoA1 ratio to carotid plaque echolucency (as an imaging feature of plaque vulnerability), whereas another study⁴⁰ in elderly individuals examined the association between carotid plaque echolucency and insulin-like growth factors concentrations.

All studies that evaluated the association between biomarkers and vulnerability features of plaques (assessed by imaging or histopathology) and also with clinical outcomes were cross-sectional in design. Even though the specific results in the individual studies were not reviewed in this report, the available literature cannot provide information on the predictive value of biomarkers for future events caused by vulnerable plaques.

KQ 6b. Have any of them been cleared by the FDA for this indication?

From the grey literature search, a list of major companies associated with specific testing modalities and drugs identified from the systematic literature overview were created. They were: Boston Scientific, Inc.; Guidant, Inc. (now acquired by Boston Scientific, Inc.); Volcano, Inc.; Goodman Co.; Fukuda Denshi Inc; GlaxoSmithKline, Inc.; Bristol Myers Squibb; Medical Imaging, Inc.; InfraReDx, Inc.; and Cordis, Inc. The biomarker testing devices, the imaging modalities and the drugs identified are presented in Tables 5, 6, and 7, respectively.

None of the biomarkers commonly examined for the detection of features deemed important in the concept of vulnerable plaque (CRP, MMP-9, PAPP-A) has been cleared by the FDA for the specific indication of identifying “vulnerable plaque” (Table 5).

KQ 6c. Are there direct comparative studies that examine how these biomarkers differ from those used in the management of patients at risk of developing acute cardiovascular events?

There are no direct comparative studies available.

KQ 7a. Using a systematic literature scan approach, describe the current non-invasive and invasive imaging methods to evaluate features of plaques that are prone to rupture/thrombose.

A total of 120 studies (50% of 242 primary studies) used imaging characteristics as predictors of plaque vulnerability; 52 studies (43%) evaluated coronary artery disease and 68 studies (57%) examined carotid artery disease.

Among the coronary artery disease studies, 45 studies were cross-sectional (87%), 6 were prospective (12%), and 1 was retrospective in design (2%) (Table 8). The median number of subjects enrolled was 58 (IQR 30-140). Eleven different imaging modalities were examined; IVUS (33%) and multi-detector computed tomography (MDCT, 25%) were the most commonly used. Most studies evaluated single features of vulnerable plaque (62%); the remaining examined combinations of features. Yellow color on coronary angiography and fibrous cap thickness were the most commonly examined features. Imaging characteristics were compared to clinical outcomes in 37% of studies, histopathological features in 25%, and other imaging outcomes in 37%. Six prospective studies (12%) used an imaging modality for characterization of plaques at baseline and followed up patients for the occurrence of a cardiovascular event (ACS or a composite cardiovascular endpoint). Sample sizes of included cohorts of patients were small (median 183, IQR 27-552) and the median duration of follow-up was 24 months (IQR 18-38). None of these prospective studies was designed to measure the direct impact of imaging modalities on physician's decision making or patient outcomes.

Of the 68 studies that focused on carotid artery disease, 62 studies were cross-sectional (91%), 5 were prospective (7%) and 1 was retrospective (2%). The median number of subjects enrolled was 39 (IQR 18-92). Thirteen different imaging modalities were examined; magnetic resonance imaging (MRI, 46%) and carotid ultrasound (24%) were the most commonly used. Most studies evaluated single features of vulnerable plaque (82%); the remaining examined combinations of features. Plaque echolucency on ultrasound examination, presence of intraplaque hemorrhage and ulceration-complexity of the lesion were the most commonly examined features. Imaging characteristics were compared to clinical outcomes in 26% of studies, histopathological features in 46%, and other imaging outcomes in 13%. Five prospective studies (7%) used an imaging modality for characterization of plaques at baseline; 4 of them followed up patients for the occurrence of a cardiovascular event (symptomatic carotid disease or composite cardiovascular endpoint) and 1 study examined the longitudinal changes of vulnerability features using serial MRI examinations. None of these prospective studies was designed to measure the direct impact of imaging modalities on physician's decision making or patient outcomes.

KQ 7b. Have any of them been cleared by the FDA for this indication?

Based on the grey literature search, none of the imaging methods has been cleared by the FDA for the specific indication of "vulnerable plaque" (Table 6). Regarding the detection of individual features deemed important in the concept of vulnerable plaque, the Infraredx NIR Imaging System (InfraReDx) has been cleared by the FDA for the detection of lipid-core containing plaques.

KQ 7c. Are there direct comparative studies that examine how these imaging methods differ from those used in the management of patients at risk of developing acute cardiovascular events?

There are no direct comparative studies available.

KQ 8a. Using a systematic literature scan approach, describe the current therapeutic approaches to modify the features of vulnerable plaque.

As there is no standard definition for vulnerable plaque, there are no therapeutic approaches specifically developed and tested for the treatment of vulnerable plaque per se. Based on the current concept of the vulnerable plaque, several treatment strategies have been evaluated for their effect on plaque features suspected to confer vulnerability (as determined by imaging or histopathological studies) and the associated reduction in risk of future cardiovascular events. The 2004 technical report⁴ described the proposed treatments for vulnerable plaque along with the conceptual basis for these strategies, and summarized the results of four studies reporting treatments (fish oil, statin, antioxidant, and antibiotic) related to potential therapeutic mechanisms of vulnerable plaque. Since that report, we have identified 17 additional studies⁴¹⁻⁵⁶ that examined interventions evaluated for modifying potential features of vulnerability in atherosclerotic plaques (Table 9). All included primary studies investigated systemic interventions: statins;^{45-50,52,54,55,57-59} multiple risk factor intervention (advice on smoking cessation and optimal lipid levels and metabolic control in diabetics);⁴³ omega-3 and omega-6 polyunsaturated fatty acids;⁴² peroxisome proliferator-activated receptor-gamma (PPAR-g) agonists;^{44,53} and an oral lipoprotein-associated phospholipase A₂ inhibitor (darapladib).⁴¹ Although the premise of focal treatment of vulnerable plaques has been discussed in review articles on the concept,⁶⁰ no primary studies investigating focal approaches were identified by our literature search (apart from case reports, e.g.,⁶¹ which were excluded from further review).

Five studies^{41,45,52,54,55} examined patients with coronary artery disease and 12^{42-44,46-51,53,56,57} studied patients with carotid artery disease (in 3^{47,48,53} of these 12 studies, patients were already diagnosed with coronary artery disease as well). Prospective design was used in 13 (76%) and cross-sectional design was used in 4 (24%) studies. Surrogate imaging or histopathological outcomes were used by 14 (82%) (most commonly plaque echolucency on carotid artery ultrasound) and 3 (18%) studies examined clinical outcomes (symptomatic carotid disease or composite cardiovascular endpoint); of those 3, only 1 study was prospective.⁴³ The median number of subjects enrolled was 63 patients (IQR 48-97).

Coronary Artery Disease

Four studies examined the potential effect of statins on vulnerability features of coronary artery plaques and reported positive findings: statins were associated with loss of yellow color of plaques in angiography^{45,54} increased fibrous-cap thickness as assessed by optical coherence tomography (OCT)⁵⁵ and decrease in histopathological indices of vulnerability (atheromatous necrotic core, fibrous tissue, macrophage infiltration, neoangiogenesis and hemorrhage).⁵² In the randomized study of darapladib,⁴¹ no significant differences were found between groups for the primary endpoint of plaque deformability, although darapladib prevented necrotic core expansion (one of the IVUS-based secondary endpoints).⁴¹

Carotid Artery Disease

Statins were examined by 8 studies, which reported that statin treatment improved echogenicity of the plaques^{47-49,57} or that statin treatment was associated with improvement in other particular plaque characteristics: decrease in inflammatory activation (^{99m}Tc labeled IL-2 uptake);⁴⁶ lower macrophage infiltration and expression of MMP-9;⁵⁰ reduced intraplaque angiogenesis;⁶² and reduced ultrasmall superparamagnetic iron oxide-enhanced MRI signal intensity (surrogate marker of plaque inflammation).⁶³ In the remaining studies: for the risk factors intervention, the beneficial effect was confined to the subgroup of patients with echolucent plaques at baseline;⁴³ for the fish and sunflower oil intervention, fewer macrophages within the plaque and fewer plaques with thin fibrous caps were observed in the fish oil compared to sunflower or control oil group.⁴² We identified two studies of PPAR-g agonists: rosiglitazone was associated with improved histopathology (reduction in inflammatory cells, greater collagen content)⁴⁴ and pioglitazone with improved imaging (increased echogenicity)⁵³ markers of plaque vulnerability; while the effect of PPAR-g agonists on clinical outcomes was not examined by our review, the apparent beneficial effects of PPAR-g agonists on such surrogate markers of plaque vulnerability are not supported by large-scale evidence on clinical cardiovascular outcomes with this class of drugs.^{64,65}

KQ 8b. Have any of them been cleared by the FDA for this indication?

From the grey literature search, we noted that of the therapeutic approaches most commonly evaluated (atorvastatin, pravastatin) or specifically developed (darapladib, vProtect™ Luminal Shield) for treatment of features deemed important in the concept of vulnerable plaque, none has been cleared by the FDA for the specific indication of vulnerable plaque (Table 7).

KQ 8c. Are there direct comparative studies that examine how these therapeutic approaches differ from those used in the management of patients at risk of developing acute cardiovascular events?

There are no direct comparative studies available.

Findings from Search in ClinicalTrials.gov Registry

A total of 29 active (completed or ongoing) trials on vulnerable plaque were identified from the ClinicalTrials.gov registry search. Of those, 16 studies are interventional and 13 observational. Most studies (69%) focus on coronary artery disease and a variety of interventions or predictors of outcomes are examined (including imaging modalities, drugs and invasive coronary interventions). A brief description of the registered trial protocols is provided in Table 10.

Discussion

In the 2004 technical report,⁴ the identified proposed criteria for defining vulnerable plaque included active inflammation, thin cap with large lipid core, endothelial denudation with superficial platelet aggregation, fissured plaque, and stenosis >90%. The treatments identified that were potentially therapeutic for vulnerable plaques were fish oil, statin, antioxidant, and antibiotic treatment. That report further noted that since there was no standard definition for vulnerable plaque, there were no natural history studies for this proposed concept. In 2010, despite many additional publications, there is still no standard definition for vulnerable plaque; and therefore, no available natural history studies for this proposed concept. However, additional natural history studies of individual plaque features deemed important in the concept of vulnerable plaque have been identified.

The vulnerable plaque concept has gained considerable attention in the literature during the last few years, since, if validated, this concept could offer promise in combating cardiovascular disease. If vulnerable plaques can be detected prospectively and accurately, and effective therapeutic interventions initiated before cardiovascular events occur, all in a cost-effective manner, then many (perhaps the majority of) cardiovascular events can be prevented. However, for this potential promise to be realized, substantial challenges need to be addressed. These challenges are both conceptual and methodological.

Conceptually, the presence of a “vulnerable plaque” is by definition a probabilistic entity (i.e., it does not denote the occurrence of an event at present, but rather a higher risk of such occurrence in the future relative to a non-vulnerable or less vulnerable plaque). As such, before it is widely adopted by clinicians, plaque vulnerability (once validated) should be able to provide incremental predictive value on top of currently available methods of risk stratification, which may be less expensive and less invasive than the methods proposed to detect vulnerable plaques. Moreover, the complex implications of such a probabilistic diagnosis are exemplified in the observation that not all plaques that rupture (the basis for the classic definition of the term) actually result in a clinical cardiovascular event. Some plaques would rupture and then quiesce and heal without causing a myocardial infarction or stroke (so called silent plaque rupture).^{34,35} Conversely, not all acute cardiovascular events are the result of plaque rupture, since non-ruptured plaques have been implicated as culprit lesions nearly one-third of the time in autopsy series.¹⁹ To the extent that plaque vulnerability is defined based on features that predict rupture, the observations that not all ruptures result in clinical events, and that not all clinical events are the result of rupture, would limit the sensitivity and specificity of the vulnerable plaque as a predictor of a future event. The value of the available literature is further limited by the use of imaging characteristics that have not been validated as reliable surrogates for histological markers of plaque vulnerability (e.g. echolucency, plaque deformability). Furthermore, whether features of plaque vulnerability are interchangeable among vascular beds is uncertain.⁶⁶ In other words, would a high risk marker validated in coronary artery disease be relevant in studying plaque vulnerability in carotid/cerebral arteries? Understanding such distinctions is relevant to the broad application of the vulnerable plaque concept in predicting and preventing cardiovascular events.

A major potential utility of the vulnerable plaque paradigm is to identify apparently healthy subjects (or people with apparently stable plaques) who are at risk for future events. To date, however, almost everything we know about what constitutes a vulnerable plaque is based on studies in patients who have already suffered an event. In our systematic overview of the

literature, only 3 of the 242 primary studies were conducted in patients without a known history of cardiovascular disease. In addition, the vast majority of studies were cross-sectional including all histopathological and biomarker studies, and 89% of imaging studies, and were mostly done with relatively small sample sizes. The 24 prospective studies identified in the literature had small sample sizes (median 64 patients, IQR 35-186), with a median duration of follow-up of 15 months (IQR 6-36). Therefore, large, prospective studies including patients without prior cardiovascular events over relatively long durations of follow-up are required to validate what we know from retrospective and cross-sectional studies. Such prospective studies would also have to identify the “individual” vulnerable plaque that develops into a culprit lesion. In the present literature overview, none of the 10 prospective imaging studies that followed patients for clinical outcomes documented that the “vulnerable” plaque was the one responsible for the clinical event during follow-up.^{21-28,36,37} This may be challenging since plaques within a given patient may progress largely independently.³⁸ This adds to the complexity of predicting events from plaque imaging, and suggests local effects (e.g., physical forces) in addition to any systemic effects influencing plaque progression.

Once it is prospectively validated that certain plaque features are independently predictive of a future cardiovascular event, demonstrating the incremental utility of such a concept will be required. In applying the concept in individuals who are not considered high-risk by current criteria (typical of a primary prevention population), the positive predictive value of “plaque vulnerability” will be constrained by the prevalence or pretest probability of cardiovascular disease in the screened population.

Finally, once the incremental predictive utility of detecting a vulnerable plaque is established, it will have to be demonstrated that certain treatments (novel or currently in use) in patients who would otherwise not have been candidates will indeed improve outcomes. For example, would a statin reduce the risk of a future cardiovascular event in a patient who does not meet current treatment indications, but is found to have a “vulnerable plaque” on imaging? Would screening for such patients followed by selective treatment be more cost-effective than unselective treatment without screening? Such questions will need to be answered before the “vulnerable plaque” paradigm is routinely considered in the prevention and treatment of cardiovascular disease.

Figure 1. Publication trends of vulnerable plaque articles for the period 2003-2009

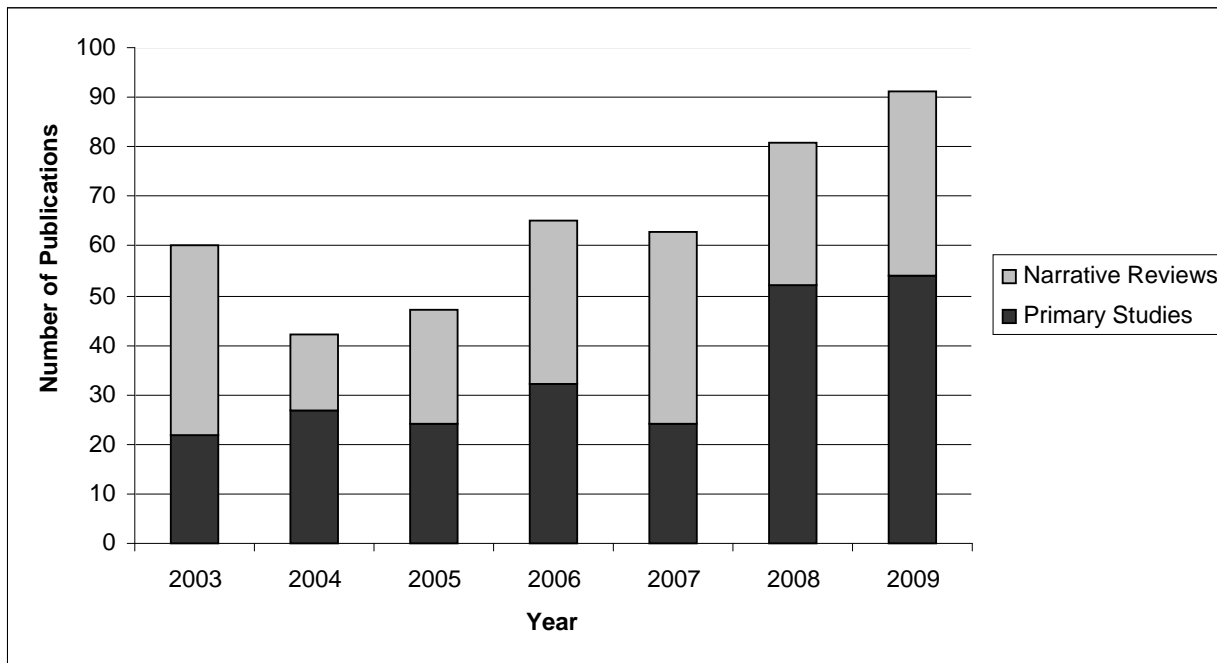


Table 1. References of primary studies and narrative review articles

References of primary studies

1. Adetiloye VA, Al DS. Sonographic evaluation of plaque morphology in haemodynamic and non-haemodynamic symptomatic carotid artery stenoses. *Afr J Med Med Sci* 2003;32:381-385.
2. Akabame S, Hamaguchi M, Tomiyasu K, et al. Evaluation of vulnerable coronary plaques and non-alcoholic fatty liver disease (NAFLD) by 64-detector multislice computed tomography (MSCT). *Circ J* 2008;72:618-625.
3. Altaf N, MacSweeney ST, Gladman J, et al. Carotid intraplaque hemorrhage predicts recurrent symptoms in patients with high-grade carotid stenosis. *Stroke* 2007;38:1633-1635.
4. Altaf N, Beech A, Goode SD, et al. Carotid intraplaque hemorrhage detected by magnetic resonance imaging predicts embolization during carotid endarterectomy. *J Vasc Surg* 2007;46:31-36.
5. Altaf N, Morgan PS, Moody A, MacSweeney ST, Gladman JR, Auer DP. Brain white matter hyperintensities are associated with carotid intraplaque hemorrhage. *Radiology* 2008;248:202-209.
6. Alvarez B, Ruiz C, Chacon P, et al. Serum values of metalloproteinase-2 and metalloproteinase-9 as related to unstable plaque and inflammatory cells in patients with greater than 70% carotid artery stenosis. *J Vasc Surg* 2004;40:469-475.
7. Alvarez GB, Ruiz C, Chacon P, et al. High-sensitivity C-reactive protein in high-grade carotid stenosis: risk marker for unstable carotid plaque. *J Vasc Surg* 2003;38:1018-1024.
8. Amano T, Matsubara T, Uetani T, et al. Impact of metabolic syndrome on tissue characteristics of angiographically mild to moderate coronary lesions integrated backscatter intravascular ultrasound study. *J Am Coll Cardiol* 2007;20:49:1149-1156.
9. Amano T, Matsubara T, Uetani T, et al. Abnormal glucose regulation is associated with lipid-rich coronary plaque: relationship to insulin resistance. *JACC Cardiovasc Imaging* 2008;1:39-45.
10. Angheloiu GO, Arendt JT, Muller MG, et al. Intrinsic fluorescence and diffuse reflectance spectroscopy identify superficial foam cells in coronary plaques prone to erosion. *Arterioscler Thromb Vasc Biol* 2006;26:1594-1600.
11. Annovazzi A, Bonanno E, Arca M, et al. 99mTc-interleukin-2 scintigraphy for the in vivo imaging of vulnerable atherosclerotic plaques. *Eur J Nucl Med Mol Imaging* 2006;33:117-126.
12. Anselmi M, Garbin U, Agostoni P, et al. Plasma levels of oxidized-low-density lipoproteins are higher in patients with unstable angina and correlated with angiographic coronary complex plaques. *Atherosclerosis* 2006;185:114-120.
13. Anzidei M, Napoli A, Marincola BC, et al. Gadofosveset-enhanced MR angiography of carotid arteries: does steady-state imaging improve accuracy of first-pass imaging? Comparison with selective digital subtraction angiography. *Radiology* 2009;251:457-466.
14. Avanzas P, Arroyo-Espliguero R, Cosin-Sales J, et al. Markers of inflammation and multiple complex stenoses (pancoronary plaque vulnerability) in patients with non-ST segment elevation acute coronary syndromes. *Heart* 2004;90:847-852.
15. Barlis P, Serruys PW, Gonzalo N, et al. Assessment of culprit and remote coronary narrowings using optical coherence tomography with long-term outcomes. *Am J Cardiol* 2008;102:391-395.

-
16. Bayturan O, Tuzcu EM, Nicholls SJ, et al. Attenuated plaque at nonculprit lesions in patients enrolled in intravascular ultrasound atherosclerosis progression trials. *JACC Cardiovasc Interv* 2009;2:672-678.
 17. Beaudoux JL, Burc L, Imbert-Bismut F, et al. Serum plasma pregnancy-associated protein A: a potential marker of echogenic carotid atherosclerotic plaques in asymptomatic hyperlipidemic subjects at high cardiovascular risk. *Arterioscler Thromb Vasc Biol* 2003;23:e7-e10.
 18. Bernard S, Loffroy R, Serusclat A, et al. Increased levels of endothelial microparticles CD144 (VE-Cadherin) positives in type 2 diabetic patients with coronary noncalcified plaques evaluated by multidetector computed tomography (MDCT). *Atherosclerosis* 2009;203:429-435.
 19. Bobryshev YV, Killingsworth MC, Lord RS, et al. Matrix vesicles in the fibrous cap of atherosclerotic plaque: possible contribution to plaque rupture. *J Cell Mol Med* 2008;12:2073-2082.
 20. Bot PT, Hofer IE, Sluijter JP, et al. Increased expression of the transforming growth factor-beta signaling pathway, endoglin, and early growth response-1 in stable plaques. *Stroke* 2009;40:439-447.
 21. Brajovic MD, Markovic N, Loncar G, et al. The influence of various morphologic and hemodynamic carotid plaque characteristics on neurological events onset and deaths. *ScientificWorldJournal* 2009;9:509-521.
 22. Brevetti G, Sirico G, Giugliano G, et al. Prevalence of hypoechoic carotid plaques in coronary artery disease: relationship with coexistent peripheral arterial disease and leukocyte number. *Vasc Med* 2009;14:13-19.
 23. Brodoefel H, Burgstahler C, Heuschmid M, et al. Accuracy of dual-source CT in the characterisation of non-calcified plaque: use of a colour-coded analysis compared with virtual histology intravascular ultrasound. *Br J Radiol* 2009;82:805-812.
 24. Broedl UC, Lebherz C, Lehrke M, et al. Low adiponectin levels are an independent predictor of mixed and non-calcified coronary atherosclerotic plaques. *PLoS One* 2009;4:e4733.
 25. Cai J, Hatsukami TS, Ferguson MS, et al. In vivo quantitative measurement of intact fibrous cap and lipid-rich necrotic core size in atherosclerotic carotid plaque: comparison of high-resolution, contrast-enhanced magnetic resonance imaging and histology. *Circulation* 2005;112:3437-3444.
 26. Cappendijk VC, Cleutjens KB, Kessels AG, et al. Assessment of human atherosclerotic carotid plaque components with multisequence MR imaging: initial experience. *Radiology* 2005;234:487-492.
 27. Cappendijk VC, Kessels AG, Heeneman S, et al. Comparison of lipid-rich necrotic core size in symptomatic and asymptomatic carotid atherosclerotic plaque: Initial results. *J Magn Reson Imaging* 2008;27:1356-1361.
 28. Caussin C, Ohanessian A, Ghostine S, et al. Characterization of vulnerable nonstenotic plaque with 16-slice computed tomography compared with intravascular ultrasound. *Am J Cardiol* 2004;94:99-104.
 29. Chen F, Eriksson P, Kimura T, et al. Apoptosis and angiogenesis are induced in the unstable coronary atherosclerotic plaque. *Coron Artery Dis* 2005;16:191-197.
 30. Chen F, Eriksson P, Hansson GK, et al. Expression of matrix metalloproteinase 9 and its regulators in the unstable coronary atherosclerotic plaque. *Int J Mol Med* 2005;15:57-65.
-

-
31. Cheng C, Noordeloos AM, Jeney V, et al. Heme oxygenase 1 determines atherosclerotic lesion progression into a vulnerable plaque. *Circulation*. 2009;119:3017-3027.
 32. Choi BJ, Kang DK, Tahk SJ, et al. Comparison of 64-slice multidetector computed tomography with spectral analysis of intravascular ultrasound backscatter signals for characterizations of noncalcified coronary arterial plaques. *Am J Cardiol* 2008;102:988-993.
 33. Chu B, Kampschulte A, Ferguson MS, et al. Hemorrhage in the atherosclerotic carotid plaque: a high-resolution MRI study. *Stroke* 2004;35:1079-1084.
 34. Cipollone F, Fazio M, Mincione G, et al. Increased expression of transforming growth factor-beta1 as a stabilizing factor in human atherosclerotic plaques. *Stroke* 2004;35:2253-2257.
 35. Cipollone F, Mezzetti A, Fazio ML, et al. Association between 5-lipoxygenase expression and plaque instability in humans. *Arterioscler Thromb Vasc Biol* 2005;25:1665-1670.
 36. Coli S, Magnoni M, Sangiorgi G, et al. Contrast-enhanced ultrasound imaging of intraplaque neovascularization in carotid arteries: correlation with histology and plaque echogenicity. *J Am Coll Cardiol* 2008;52:223-230.
 37. Cui S, Lu SZ, Chen YD, et al. Relationship among soluble CD105, hypersensitive C-reactive protein and coronary plaque morphology: an intravascular ultrasound study. *Chin Med J (Engl)* 2008;20;121:128-132.
 38. Daskalopoulou SS, Daskalopoulos ME, Theocharis S, et al. Metallothionein expression in the high-risk carotid atherosclerotic plaque. *Curr Med Res Opin* 2007;23:659-670.
 39. de Weert TT, Cretier S, Groen HC, et al. Atherosclerotic plaque surface morphology in the carotid bifurcation assessed with multidetector computed tomography angiography. *Stroke* 2009;40:1334-1340.
 40. De PR, Del GF, Abbate G, et al. Patients with acute coronary syndrome show oligoclonal T-cell recruitment within unstable plaque: evidence for a local, intracoronary immunologic mechanism. *Circulation* 2006;113:640-646.
 41. Diethrich EB, Pauliina MM, Reid DB, et al. Virtual histology intravascular ultrasound assessment of carotid artery disease: the Carotid Artery Plaque Virtual Histology Evaluation (CAPITAL) study. *J Endovasc Ther* 2007;14:676-686.
 42. Ding S, Zhang M, Zhao Y, et al. The role of carotid plaque vulnerability and inflammation in the pathogenesis of acute ischemic stroke. *Am J Med Sci* 2008;336:27-31.
 43. Dunmore BJ, McCarthy MJ, Naylor AR, et al. Carotid plaque instability and ischemic symptoms are linked to immaturity of microvessels within plaques. *J Vasc Surg* 2007;45:155-159.
 44. Ehara S, Kobayashi Y, Yoshiyama M, et al. Spotty calcification typifies the culprit plaque in patients with acute myocardial infarction: an intravascular ultrasound study. *Circulation* 2004;110:3424-3429.
 45. Erbel C, Sato K, Meyer FB, et al. Functional profile of activated dendritic cells in unstable atherosclerotic plaque. *Basic Res Cardiol* 2007;102:123-132.
 46. Fabiano S, Mancino S, Stefanini M, et al. High-resolution multicontrast-weighted MR imaging from human carotid endarterectomy specimens to assess carotid plaque components. *Eur Radiol* 2008;18:2912-21.
-

-
47. Fiotti N, Altamura N, Orlando C, et al. Metalloproteinases-2, -9 and TIMP-1 expression in stable and unstable coronary plaques undergoing PCI. *Int J Cardiol* 2008;127:350-357.
 48. Fisher M, Paganini-Hill A, Martin A, et al. Carotid plaque pathology: thrombosis, ulceration, and stroke pathogenesis. *Stroke* 2005;36:253-257.
 49. Formato M, Farina M, Spirito R, et al. Evidence for a proinflammatory and proteolytic environment in plaques from endarterectomy segments of human carotid arteries. *Arterioscler Thromb Vasc Biol* 2004;24:129-135.
 50. Fujii K, Kobayashi Y, Mintz GS, et al. Intravascular ultrasound assessment of ulcerated ruptured plaques: a comparison of culprit and nonculprit lesions of patients with acute coronary syndromes and lesions in patients without acute coronary syndromes. *Circulation* 2003;108:2473-2478.
 51. Furukado S, Sakaguchi M, Yamagami H, et al. Cyclo-oxygenase-2 -765G > C promoter variants are associated with lower carotid plaque echogenicity in Japanese. *Cerebrovasc Dis* 2009;27:91-98.
 52. Gao T, Zhang Z, Yu W, et al. Atherosclerotic carotid vulnerable plaque and subsequent stroke: a high-resolution MRI study. *Cerebrovasc Dis* 2009;27:345-352.
 53. Giacconi R, Caruso C, Lio D, et al. 1267 HSP70-2 polymorphism as a risk factor for carotid plaque rupture and cerebral ischaemia in old type 2 diabetes-atherosclerotic patients. *Mech Ageing Dev* 2005;126:866-873.
 54. Giannoni MF, Vicenzini E, Citone M, et al. Contrast carotid ultrasound for the detection of unstable plaques with neoangiogenesis: a pilot study. *Eur J Vasc Endovasc Surg* 2009;37:722-727.
 55. Giattina SD, Courtney BK, Herz PR, et al. Assessment of coronary plaque collagen with polarization sensitive optical coherence tomography (PS-OCT). *Int J Cardiol* 2006;107:400-409.
 56. Graebe M, Pedersen SF, Borgwardt L, et al. Molecular pathology in vulnerable carotid plaques: correlation with [18]-fluorodeoxyglucose positron emission tomography (FDG-PET). *Eur J Vasc Endovasc Surg* 2009;37:714-721.
 57. Grogan JK, Shaalan WE, Cheng H, et al. B-mode ultrasonographic characterization of carotid atherosclerotic plaques in symptomatic and asymptomatic patients. *J Vasc Surg* 2005;42:435-441.
 58. Haraguchi K, Houkin K, Koyanagi I, et al. Evaluation of carotid plaque composition by computed tomographic angiography and black blood magnetic resonance images. *Minim Invasive Neurosurg* 2008;51:91-94.
 59. Hashimoto H, Tagaya M, Niki H, et al. Computer-assisted analysis of heterogeneity on B-mode imaging predicts instability of asymptomatic carotid plaque. *Cerebrovasc Dis* 2009;28:357-364.
 60. Hatakeyama K, Hao H, Imamura T, et al. Relation of CD39 to plaque instability and thrombus formation in directional atherectomy specimens from patients with stable and unstable angina pectoris. *Am J Cardiol* 2005;95:632-635.
 61. Heliopoulos J, Vadikolias K, Mitsias P, et al. A three-dimensional ultrasonographic quantitative analysis of non-ulcerated carotid plaque morphology in symptomatic and asymptomatic carotid stenosis. *Atherosclerosis* 2008;198:129-135.
 62. Hellings WE, Moll FL, de Vries JP, et al. Histological characterization of restenotic carotid plaques in relation to recurrence interval and clinical presentation: a cohort study. *Stroke* 2008;39:1029-1032.
-

-
63. Higashida T, Kanno H, Nakano M, et al. Expression of hypoxia-inducible angiogenic proteins (hypoxia-inducible factor-1alpha, vascular endothelial growth factor, and E26 transformation-specific-1) and plaque hemorrhage in human carotid atherosclerosis. *J Neurosurg* 2008;109:83-91.
 64. Hirano M, Nakamura T, Kitta Y, et al. Rapid improvement of carotid plaque echogenicity within 1 month of pioglitazone treatment in patients with acute coronary syndrome. *Atherosclerosis* 2009;203:483-488.
 65. Hirayama A, Saito S, Ueda Y, et al. Qualitative and quantitative changes in coronary plaque associated with atorvastatin therapy. *Circ J* 2009;73:718-725.
 66. Honda M, Kitagawa N, Tsutsumi K, et al. High-resolution magnetic resonance imaging for detection of carotid plaques. *Neurosurgery* 2006;58:338-346.
 67. Honda O, Sugiyama S, Kugiyama K, et al. Echolucent carotid plaques predict future coronary events in patients with coronary artery disease. *J Am Coll Cardiol* 2004;43:1177-1184.
 68. Hong MK, Mintz GS, Lee CW, et al. Comparison of virtual histology to intravascular ultrasound of culprit coronary lesions in acute coronary syndrome and target coronary lesions in stable angina pectoris. *Am J Cardiol* 2007;100:953-959.
 69. Hong YJ, Jeong MH, Choi YH, et al. Plaque characteristics in culprit lesions and inflammatory status in diabetic acute coronary syndrome patients. *JACC Cardiovasc Imaging* 2009;2:339-349.
 70. Hong YJ, Ahn Y, Sim DS, et al. Relation between N-terminal pro-B-type natriuretic peptide and coronary plaque components in patients with acute coronary syndrome: virtual histology-intravascular ultrasound analysis. *Coron Artery Dis* 2009;20:518-524.
 71. Howarth SP, Tang TY, Trivedi R, et al. Utility of USPIO-enhanced MR imaging to identify inflammation and the fibrous cap: a comparison of symptomatic and asymptomatic individuals. *Eur J Radiol* 2009;70:555-560.
 72. Hur J, Kim YJ, Lee HJ, et al. Quantification and characterization of obstructive coronary plaques using 64-slice computed tomography: a comparison with intravascular ultrasound. *J Comput Assist Tomogr* 2009;33:186-192.
 73. Ikuta T, Naruko T, Ikura Y, et al. Immunolocalization of platelet glycoprotein IIb/IIIa and P-selectin, and neutrophil-platelet interaction in human coronary unstable plaques. *Int J Mol Med* 2005;15:573-577.
 74. Inoue F, Sato Y, Matsumoto N, et al. Evaluation of plaque texture by means of multislice computed tomography in patients with acute coronary syndrome and stable angina. *Circ J* 2004;68:840-844.
 75. Inoue T, Kato T, Uchida T, et al. Local release of C-reactive protein from vulnerable plaque or coronary arterial wall injured by stenting. *J Am Coll Cardiol* 2005;19:46:239-245.
 76. Ishikawa T, Hatakeyama K, Imamura T, et al. Increased adrenomedullin immunoreactivity and mRNA expression in coronary plaques obtained from patients with unstable angina. *Heart* 2004;90:1206-1210.
 77. Ishikawa Y, Satoh M, Itoh T, et al. Local expression of Toll-like receptor 4 at the site of ruptured plaques in patients with acute myocardial infarction. *Clin Sci (Lond)* 2008;115:133-140.
 78. Isoviita PM, Nuotio K, Saksi J, et al. An imbalance between CD36 and ABCA1 protein expression favors lipid accumulation in stroke-prone ulcerated carotid plaques. *Stroke* 2010;41:389-393.
-

-
79. Jiang X, Zeng HS, Guo Y, et al. The expression of matrix metalloproteinases-9, transforming growth factor-beta1 and transforming growth factor-beta receptor I in human atherosclerotic plaque and their relationship with plaque stability. *Chin Med J (Engl)* 2004;117:1825-1829.
 80. Jo JA, Fang Q, Papaioannou T, et al. Diagnosis of vulnerable atherosclerotic plaques by time-resolved fluorescence spectroscopy and ultrasound imaging. *Conf Proc IEEE Eng Med Biol Soc* 2006;1:2663-2666.
 81. Kadoglou NP, Gerasimidis T, Golemati S, The relationship between serum levels of vascular calcification inhibitors and carotid plaque vulnerability. *J Vasc Surg* 2008;47:55-62.
 82. Kadoglou NP, Gerasimidis T, Moutzouglou A, et al. Intensive lipid-lowering therapy ameliorates novel calcification markers and GSM score in patients with carotid stenosis. *Eur J Vasc Endovasc Surg* 2008;35:661-668.
 83. Kampschulte A, Ferguson MS, Kerwin WS, et al. Differentiation of intraplaque versus juxtalumenal hemorrhage/thrombus in advanced human carotid atherosclerotic lesions by in vivo magnetic resonance imaging. *Circulation* 2004;110:3239-3244.
 84. Kanai H, Hasegawa H, Ichiki M, et al. Elasticity imaging of atheroma with transcutaneous ultrasound: preliminary study. *Circulation* 2003;107:3018-3021.
 85. Kashiwagi M, Tanaka A, Kitabata H, et al. Relationship between coronary arterial remodeling, fibrous cap thickness and high-sensitivity C-reactive protein levels in patients with acute coronary syndrome. *Circ J* 2009;73:1291-1295.
 86. Katritsis DG, Pantos I, Korovesis S, et al. Three-dimensional analysis of vulnerable segments in the left anterior descending artery. *Coron Artery Dis* 2009;20:199-206.
 87. Katsargyris A, Theocharis SE, Tsiodras S, et al. Enhanced TLR4 endothelial cell immunohistochemical expression in symptomatic carotid atherosclerotic plaques. *Expert Opin Ther Targets* 2010;14:1-10.
 88. Kawahara I, Kitagawa N, Tsutsumi K, et al. The expression of vascular dendritic cells in human atherosclerotic carotid plaques. *Hum Pathol* 2007;38:1378-1385.
 89. Kawahara I, Morikawa M, Honda M, et al. High-resolution magnetic resonance imaging using gadolinium-based contrast agent for atherosclerotic carotid plaque. *Surg Neurol* 2007;68:60-65.
 90. Kawano T, Honye J, Takayama T, et al. Compositional analysis of angioscopic yellow plaques with intravascular ultrasound radiofrequency data. *Int J Cardiol* 2008;125:74-78.
 91. Kenji K, Hironori U, Hideya Y, et al. Tenascin-C is associated with coronary plaque instability in patients with acute coronary syndromes. *Circ J* 2004;68:198-203.
 92. Kerwin W, Hooker A, Spilker M, et al. Quantitative magnetic resonance imaging analysis of neovasculature volume in carotid atherosclerotic plaque. *Circulation* 2003;107:851-856.
 93. Khan T, Soller B, Naghavi M, et al. Tissue pH determination for the detection of metabolically active, inflamed vulnerable plaques using near-infrared spectroscopy: an in-vitro feasibility study. *Cardiology* 2005;103:10-16.
 94. Kietzelaer BL, Reutelingsperger CP, Heidendal GA, et al. Noninvasive detection of plaque instability with use of radiolabeled annexin A5 in patients with carotid-artery atherosclerosis. *N Engl J Med* 2004;350:1472-1473.
-

-
95. Kim SH, Hong MK, Park DW, et al. Impact of plaque characteristics analyzed by intravascular ultrasound on long-term clinical outcomes. *Am J Cardiol* 2009;103:1221-1226.
 96. Kitagawa T, Yamamoto H, Horiguchi J, et al. Characterization of noncalcified coronary plaques and identification of culprit lesions in patients with acute coronary syndrome by 64-slice computed tomography. *JACC Cardiovasc Imaging* 2009;2:153-160.
 97. Knollmann F, Ducke F, Krist L, et al. Quantification of atherosclerotic coronary plaque components by submillimeter computed tomography. *Int J Cardiovasc Imaging* 2008;24:301-310.
 98. Knollmann FD, Wieltch A, Peters S, et al. Flat panel volume computed tomography of the coronary arteries. *Acad Radiol* 2009;16:1251-1262.
 99. Kobayashi S, Inoue N, Ohashi Y, et al. Interaction of oxidative stress and inflammatory response in coronary plaque instability: important role of C-reactive protein. *Arterioscler Thromb Vasc Biol* 2003;23:1398-1404.
 100. Kock SA, Nygaard JV, Eldrup N, et al. Mechanical stresses in carotid plaques using MRI-based fluid-structure interaction models. *J Biomech* 2008;41:1651-1658.
 101. Kolodgie FD, Gold HK, Burke AP, et al. Intraplaque hemorrhage and progression of coronary atheroma. *N Engl J Med* 2003;349:2316-2325.
 102. Kolodgie FD, Burke AP, Skorija KS, et al. Lipoprotein-associated phospholipase A2 protein expression in the natural progression of human coronary atherosclerosis. *Arterioscler Thromb Vasc Biol* 2006;26:2523-2529.
 103. Kotani J, Mintz GS, Castagna MT, et al. Intravascular ultrasound analysis of infarct-related and non-infarct-related arteries in patients who presented with an acute myocardial infarction. *Circulation* 2003;107:2889-2893.
 104. Koutouzis M, Nomikos A, Nikolidakis S, et al. Statin treated patients have reduced intraplaque angiogenesis in carotid endarterectomy specimens. *Atherosclerosis* 2007;192:457-463.
 105. Krupinski J, Turu MM, Martinez-Gonzalez J, et al. Endogenous expression of C-reactive protein is increased in active (ulcerated noncomplicated) human carotid artery plaques. *Stroke* 2006;37:1200-1204.
 106. Krupinski J, Catena E, Miguel M, et al. D-dimer local expression is increased in symptomatic patients undergoing carotid endarterectomy. *Int J Cardiol* 2007; 20;116:174-179.
 107. Kubo T, Imanishi T, Takarada S, et al. Assessment of culprit lesion morphology in acute myocardial infarction: ability of optical coherence tomography compared with intravascular ultrasound and coronary angiography. *J Am Coll Cardiol* 2007;50:933-939.
 108. Kubo T, Imanishi T, Takarada S, et al. Implication of plaque color classification for assessing plaque vulnerability: a coronary angiography and optical coherence tomography investigation. *JACC Cardiovasc Interv* 2008;1:74-80.
 109. Kubo T, Imanishi T, Kashiwagi M, et al. Multiple coronary lesion instability in patients with acute myocardial infarction as determined by optical coherence tomography. *Am J Cardiol* 2010;105:318-322.
 110. Kume T, Akasaka T, Kawamoto T, et al. Measurement of the thickness of the fibrous cap by optical coherence tomography. *Am Heart J* 2006;152:755-754.
-

-
111. Kunimasa T, Sato Y, Sugi K, et al. Evaluation by multislice computed tomography of atherosclerotic coronary artery plaques in non-culprit, remote coronary arteries of patients with acute coronary syndrome. *Circ J* 2005;69:1346-1351.
 112. Kunte H, Amberger N, Busch MA, et al. Markers of instability in high-risk carotid plaques are reduced by statins. *J Vasc Surg.* 2008;47:513-522.
 113. Lal BK, Hobson RW, Hameed M, et al. Noninvasive identification of the unstable carotid plaque. *Ann Vasc Surg* 2006;20:167-174.
 114. Lastas A, Graziene V, Barkauskas E, et al. Carotid artery atherosclerotic plaque: clinical and morphological-immunohistochemical correlation. *Med Sci Monit* 2004;10:CR606-CR614.
 115. Lavezzi AM, Milei J, Grana DR, et al. Expression of c-fos, p53 and PCNA in the unstable atherosclerotic carotid plaque. *Int J Cardiol* 2003;92:59-63.
 116. Lavi S, Bae JH, Rihal CS, et al. Segmental coronary endothelial dysfunction in patients with minimal atherosclerosis is associated with necrotic core plaques. *Heart* 2009;95:1525-1530.
 117. Lee SG, Lee CW, Hong MK, et al. Change of multiple complex coronary plaques in patients with acute myocardial infarction: a study with coronary angiography. *Am Heart J* 2004;147:281-286.
 118. Lee WS, Kim SW, Hong SA, et al. Atherosclerotic progression attenuates the expression of Nogo-B in autopsied coronary artery: pathology and virtual histology intravascular ultrasound analysis. *J Korean Med Sci* 2009;24:596-604.
 119. Lapedda AJ, Cigliano A, Cherchi GM, et al. A proteomic approach to differentiate histologically classified stable and unstable plaques from human carotid arteries. *Atherosclerosis* 2009;203:112-118.
 120. Li W, Kornmark L, Jonasson L, et al. Cathepsin L is significantly associated with apoptosis and plaque destabilization in human atherosclerosis. *Atherosclerosis* 2009;202:92-102.
 121. Li XM, Huang CX, Wang TS, et al. Comparison of coronary plaque composition among patients with acute coronary syndrome and stable coronary artery disease. *Chin Med J (Engl)* 2008;20;121:534-539.
 122. Li ZY, Tang T, King-Im J, et al. Assessment of carotid plaque vulnerability using structural and geometrical determinants. *Circ J* 2008;72:1092-1099.
 123. Lilledahl MB, Haugen OA, de Lange DC, et al. Characterization of vulnerable plaques by multiphoton microscopy. *J Biomed Opt* 2007;12:044005.
 124. Lin K, Zhang ZQ, Detrano R, et al. Carotid vulnerable lesions are related to accelerated recurrence for cerebral infarction magnetic resonance imaging study. *Acad Radiol* 2006;13:1180-1186.
 125. Liu F, Xu D, Ferguson MS, et al. Automated in vivo segmentation of carotid plaque MRI with Morphology-Enhanced probability maps. *Magn Reson Med* 2006;55:659-668.
 126. Lombardo A, Biasucci LM, Lanza GA, et al. Inflammation as a possible link between coronary and carotid plaque instability. *Circulation.* 2004;109:3158-3163.
 127. Lovett JK, Gallagher PJ, Hands LJ, et al. Histological correlates of carotid plaque surface morphology on lumen contrast imaging. *Circulation* 2004;110:2190-2197.
-

-
128. Low AF, Kawase Y, Chan YH, et al. In vivo characterisation of coronary plaques with conventional grey-scale intravascular ultrasound: correlation with optical coherence tomography. *EuroIntervention* 2009;4:626-632.
 129. Marcu L, Jo JA, Fang Q, et al. Detection of rupture-prone atherosclerotic plaques by time-resolved laser-induced fluorescence spectroscopy. *Atherosclerosis* 2009;204:156-164.
 130. Marfella R, D'Amico M, Di FC, et al. Increased activity of the ubiquitin-proteasome system in patients with symptomatic carotid disease is associated with enhanced inflammation and may destabilize the atherosclerotic plaque: effects of rosiglitazone treatment. *J Am Coll Cardiol* 2006;20;47:2444-2455.
 131. Martin RM, Gunnell D, Whitley E, et al. Associations of insulin-like growth factor (IGF)-I, IGF-II, IGF binding protein (IGFBP)-2 and IGFBP-3 with ultrasound measures of atherosclerosis and plaque stability in an older adult population. *J Clin Endocrinol Metab* 2008;93:1331-1338.
 132. Mattock KL, Gough PJ, Humphries J, et al. Legumain and cathepsin-L expression in human unstable carotid plaque. *Atherosclerosis* 2010;208:83-89.
 133. Mauriello A, Sangiorgi G, Fratoni S, et al. Diffuse and active inflammation occurs in both vulnerable and stable plaques of the entire coronary tree: a histopathologic study of patients dying of acute myocardial infarction. *J Am Coll Cardiol* 2005;45:1585-1593.
 - 134/ Meijs MF, Meijboom WB, Bots ML, et al. Comparison of frequency of calcified versus non-calcified coronary lesions by computed tomographic angiography in patients with stable versus unstable angina pectoris. *Am J Cardiol* 2009;104:305-311.
 135. Meuwissen M, van der Wal AC, Koch KT, et al. Association between complex coronary artery stenosis and unstable angina and the extent of plaque inflammation. *Am J Med* 2003;114:521-527.
 136. Meuwissen M, van der Wal AC, Niessen HW, et al. Colocalisation of intraplaque C reactive protein, complement, oxidised low density lipoprotein, and macrophages in stable and unstable angina and acute myocardial infarction. *J Clin Pathol* 2006;59:196-201.
 137. Mitsumori LM, Hatsukami TS, Ferguson MS, et al. In vivo accuracy of multisequence MR imaging for identifying unstable fibrous caps in advanced human carotid plaques. *J Magn Reson Imaging* 2003;17:410-420.
 138. Miyagi M, Ishii H, Murakami R, et al. Impact of renal function on coronary plaque composition. *Nephrol Dial Transplant* 2010;25:175-181.
 139. Miyamoto S, Ueda M, Ikemoto M, et al. Increased serum levels and expression of S100A8/A9 complex in infiltrated neutrophils in atherosclerotic plaque of unstable angina. *Heart* 2008;94:1002-1007.
 140. Miyata K, Nakayama M, Mizuta S, et al. Elevated mature macrophage expression of human ABHD2 gene in vulnerable plaque. *Biochem Biophys Res Commun* 2008;365:207-213.
 141. Molinari F, Liboni W, Pavanelli E, et al. Accurate and automatic carotid plaque characterization in contrast enhanced 2-d ultrasound images. *Conf Proc IEEE Eng Med Biol Soc* 2007;2007:335-338.
 142. Molloy KJ, Thompson MM, Jones JL, et al. Unstable carotid plaques exhibit raised matrix metalloproteinase-8 activity. *Circulation* 2004; 20;110:337-343.
 143. Morioka M, Hamada J, Hashiguchi A, et al. Contribution of angiotensin-converting enzyme and angiotensin II to ischemic stroke: their role in the formation of stable and unstable carotid atherosclerotic plaques. *Surg Neurol* 2004;62:292-301.
-

-
144. Motoyama S, Kondo T, Sarai M, et al. Multislice computed tomographic characteristics of coronary lesions in acute coronary syndromes. *J Am Coll Cardiol* 2007;50:319-326.
 145. Motoyama S, Sarai M, Harigaya H, et al. Computed tomographic angiography characteristics of atherosclerotic plaques subsequently resulting in acute coronary syndrome. *J Am Coll Cardiol* 2009;54:49-57.
 146. Motz JT, Fitzmaurice M, Miller A, et al. In vivo Raman spectral pathology of human atherosclerosis and vulnerable plaque. *J Biomed Opt* 2006;11:021003.
 147. Murashige A, Hiro T, Fujii T, et al. Detection of lipid-laden atherosclerotic plaque by wavelet analysis of radiofrequency intravascular ultrasound signals: in vitro validation and preliminary in vivo application. *J Am Coll Cardiol* 2005;45:1954-1960.
 148. Muscari A, Martignani C, Bastagli L, et al. A comparison of acute phase proteins and traditional risk factors as markers of combined plaque and intima-media thickness and plaque density in carotid and femoral arteries. *Eur J Vasc Endovasc Surg* 2003;26:81-87.
 149. Myoishi M, Hao H, Minamino T, et al. Increased endoplasmic reticulum stress in atherosclerotic plaques associated with acute coronary syndrome. *Circulation* 2007;116:1226-1233.
 150. Nakamura T, Obata JE, Kitta Y, et al. Rapid stabilization of vulnerable carotid plaque within 1 month of pitavastatin treatment in patients with acute coronary syndrome. *J Cardiovasc Pharmacol* 2008;51:365-371.
 151. Nakamura T, Kubo N, Funayama H, et al. Plaque characteristics of the coronary segment proximal to the culprit lesion in stable and unstable patients. *Clin Cardiol* 2009;32:E9-E12.
 152. Nasu K, Tsuchikane E, Katoh O, et al. Accuracy of in vivo coronary plaque morphology assessment: a validation study of in vivo virtual histology compared with in vitro histopathology. *J Am Coll Cardiol* 2006; 20;47:2405-1242.
 153. Navarro Estrada JL, Gabay JM, Alvarez J, et al. Relation of C-reactive protein to extent and complexity of coronary narrowing in patients with non-ST elevation acute coronary syndromes. A prospective cohort study. *Coron Artery Dis* 2004;15:477-484.
 154. Navarro Estrada JL, Rubinstein F, Bahit MC, et al. NT-probrain natriuretic peptide predicts complexity and severity of the coronary lesions in patients with non-ST-elevation acute coronary syndromes. *Am Heart J* 2006;151:1093-1097.
 155. Nijmeijer R, Meuwissen M, Krijnen PA, et al. Secretory type II phospholipase A2 in culprit coronary lesions is associated with myocardial infarction. *Eur J Clin Invest* 2008;38:205-210.
 156. Nishibe A, Kijima Y, Fukunaga M, et al. Increased isoprostane content in coronary plaques obtained from vulnerable patients. *Prostaglandins Leukot Essent Fatty Acids*. 2008;78:257-263.
 157. Nishihira K, Imamura T, Yamashita A, et al. Increased expression of interleukin-10 in unstable plaque obtained by directional coronary atherectomy. *Eur Heart J* 2006;27:1685-1689.
 158. Nishihira K, Yamashita A, Imamura T, et al. Thioredoxin in coronary culprit lesions: possible relationship to oxidative stress and intraplaque hemorrhage. *Atherosclerosis* 2008;201:360-367.
 159. Norja S, Nuutila L, Karhunen PJ, et al. C-reactive protein in vulnerable coronary plaques. *J Clin Pathol* 2007;60:545-548.
-

-
160. O'Malley SM, Vavuranakis M, Naghavi M, et al. Intravascular ultrasound-based imaging of vasa vasorum for the detection of vulnerable atherosclerotic plaque. *Med Image Comput Comput Assist Interv* 2005;8:343-51.
 161. Ohtani T, Ueda Y, Shimizu M, et al. Association between cardiac troponin T elevation and angiographic morphology of culprit lesion in patients with non-ST-segment elevation acute coronary syndrome. *Am Heart J* 2005;150:227-233.
 162. Ohtani T, Ueda Y, Mizote I, et al. Number of yellow plaques detected in a coronary artery is associated with future risk of acute coronary syndrome: detection of vulnerable patients by angiography. *J Am Coll Cardiol* 2006;47:2194-2200.
 163. Okada K, Ueda Y, Oyabu J, et al. Plaque color analysis by the conventional yellow-color grading system and quantitative measurement using LCH color space. *J Interv Cardiol* 2007;20:324-334.
 164. Otsuka F, Sugiyama S, Kojima S, et al. Plasma adiponectin levels are associated with coronary lesion complexity in men with coronary artery disease. *J Am Coll Cardiol* 2006;19:48:1155-1162.
 165. Panayiotou A, Griffin M, Georgiou N, et al. ApoB/ApoA1 ratio and subclinical atherosclerosis. *Int Angiol* 2008;27:74-80.
 166. Papalambros E, Sigala F, Georgopoulos S, et al. Vascular endothelial growth factor and matrix metalloproteinase 9 expression in human carotid atherosclerotic plaques: relationship with plaque destabilization via neovascularization. *Cerebrovasc Dis* 2004;18:160-165.
 167. Papas TT, Maltezos CK, Papanas N, et al. High-sensitivity CRP is correlated with neurologic symptoms and plaque instability in patients with severe stenosis of the carotid bifurcation. *Vasc Endovascular Surg* 2008;42:249-255.
 168. Papaspyridonos M, Smith A, Burnand KG, et al. Novel candidate genes in unstable areas of human atherosclerotic plaques. *Arterioscler Thromb Vasc Biol* 2006;26:1837-1844.
 169. Papaspyridonos M, McNeill E, de Bono JP, et al. Galectin-3 is an amplifier of inflammation in atherosclerotic plaque progression through macrophage activation and monocyte chemoattraction. *Arterioscler Thromb Vasc Biol* 2008;28:433-440.
 170. Parahuleva MS, Kanse SM, Parviz B, et al. Factor Seven Activating Protease (FSAP) expression in human monocytes and accumulation in unstable coronary atherosclerotic plaques. *Atherosclerosis* 2008;196:164-171.
 171. Peeters W, Hellings WE, de Kleijn DP, et al. Carotid atherosclerotic plaques stabilize after stroke: insights into the natural process of atherosclerotic plaque stabilization. *Arterioscler Thromb Vasc Biol* 2009;29:128-133.
 172. Pelisek J, Rudelius M, Zepper P, et al. Multiple biological predictors for vulnerable carotid lesions. *Cerebrovasc Dis* 2009;28:601-610.
 173. Pilarczyk K, Sattler KJ, Galili O, et al. Placenta growth factor expression in human atherosclerotic carotid plaques is related to plaque destabilization. *Atherosclerosis* 2008;196:333-340.
 174. Prabhudesai V, Phelan C, Yang Y, et al. The potential role of optical coherence tomography in the evaluation of vulnerable carotid atheromatous plaques: a pilot study. *Cardiovasc Intervent Radiol* 2006;29:1039-1045.
 175. Pucci A, Sheiban I, Formato L, et al. In vivo coronary plaque histology in patients with stable and acute coronary syndromes: relationships with hyperlipidemic status and statin treatment. *Atherosclerosis* 2007;194:189-195.
-

-
176. Pucci A, Brscic E, Tessitore E, et al. C-reactive protein and coronary composition in patients with percutaneous revascularization. *Eur J Clin Invest* 2008;38:281-289.
 177. Puppini G, Furlan F, Ciota N, et al. Characterisation of carotid atherosclerotic plaque: comparison between magnetic resonance imaging and histology. *Radiol Med* 2006;111:921-930.
 178. Raman SV, Winner III MW, Tran T, et al. In vivo atherosclerotic plaque characterization using magnetic susceptibility distinguishes symptom-producing plaques. *JACC Cardiovasc Imaging* 2008;1:49-57.
 179. Randi AM, Biguzzi E, Falciani F, et al. Identification of differentially expressed genes in coronary atherosclerotic plaques from patients with stable or unstable angina by cDNA array analysis. *J Thromb Haemost* 2003;1:829-835.
 180. Redgrave JN, Lovett JK, Gallagher PJ, et al. Histological assessment of 526 symptomatic carotid plaques in relation to the nature and timing of ischemic symptoms: the Oxford plaque study. *Circulation* 2006;113:2320-2328.
 181. Reiter M, Effenberger I, Sabeti S, et al. Increasing carotid plaque echolucency is predictive of cardiovascular events in high-risk patients. *Radiology* 2008;248:1050-1055.
 182. Ren MY, Sui SJ, Zhang Y, et al. Increased plasma osteoprotegerin levels are associated with the presence and severity of acute coronary syndrome. *Acta Cardiol* 2008;63:615-622.
 183. Ribichini F, Pugno F, Ferrero V, et al. Cellular immunostaining of angiotensin-converting enzyme in human coronary atherosclerotic plaques. *J Am Coll Cardiol* 2006;47:1143-1149.
 184. Rivera JJ, Nasir K, Cox PR, et al. Association of traditional cardiovascular risk factors with coronary plaque sub-types assessed by 64-slice computed tomography angiography in a large cohort of asymptomatic subjects. *Atherosclerosis* 2009;206:451-457.
 185. Russell DA, Abbott CR, Gough MJ. Vascular endothelial growth factor is associated with histological instability of carotid plaques. *Br J Surg* 2008;95:576-581.
 186. Russell DA, Wijeyaratne SM, Gough MJ. Relationship of carotid plaque echomorphology to presenting symptom. *Eur J Vasc Endovasc Surg* 2010;39:134-138.
 187. Saba L, Caddeo G, Sanfilippo R, et al. CT and ultrasound in the study of ulcerated carotid plaque compared with surgical results: potentialities and advantages of multidetector row CT angiography. *AJNR Am J Neuroradiol* 2007;28:1061-1066.
 188. Saba L, Caddeo G, Sanfilippo R, et al. Efficacy and sensitivity of axial scans and different reconstruction methods in the study of the ulcerated carotid plaque using multidetector-row CT angiography: comparison with surgical results. *AJNR Am J Neuroradiol* 2007;28:716-723.
 189. Saba L, Mallarini G. Fissured fibrous cap of vulnerable carotid plaques and symptomatology: are they correlated? Preliminary results by using multi-detector-row CT angiography. *Cerebrovasc Dis* 2009;27:322-327.
 190. Saba L, Montisci R, Sanfilippo R, et al. Multidetector row CT of the brain and carotid artery: a correlative analysis. *Clin Radiol* 2009;64:767-778.
 191. Sadat U, Li ZY, Young VE, et al. Finite element analysis of vulnerable atherosclerotic plaques: a comparison of mechanical stresses within carotid plaques of acute and recently symptomatic patients with carotid artery disease. *J Neurol Neurosurg Psychiatry* 2010;81:286-289.
-

-
192. Sangiorgi G, Mauriello A, Bonanno E, et al. Pregnancy-associated plasma protein-a is markedly expressed by monocyte-macrophage cells in vulnerable and ruptured carotid atherosclerotic plaques: a link between inflammation and cerebrovascular events. *J Am Coll Cardiol* 2006;47:2201-2211.
 193. Sano K, Kawasaki M, Ishihara Y, et al. Assessment of vulnerable plaques causing acute coronary syndrome using integrated backscatter intravascular ultrasound. *J Am Coll Cardiol* 2006;47:734-741.
 194. Sapienza P, di ML, Borrelli V, et al. Basic fibroblast growth factor mediates carotid plaque instability through metalloproteinase-2 and -9 expression. *Eur J Vasc Endovasc Surg* 2004;28:89-97.
 195. Sapienza P, di ML, Borrelli V, et al. Metalloproteinases and their inhibitors are markers of plaque instability. *Surgery* 2005;137:355-63.
 196. Sarno G, Vanhoenacker P, Decramer I, et al. Characterisation of the "vulnerable" coronary plaque by multi-detector computed tomography: a correlative study with intravascular ultrasound-derived radiofrequency analysis of plaque composition. *EuroIntervention* 2008;4:318-323.
 197. Sarzynska-Dlugosz I, Nowaczenko M, Blazejewska-Hyzorek B, et al. Echolucent internal carotid artery plaques are a risk factor for stroke. *Neurol Neurochir Pol* 2008;42:91-98.
 198. Sayed S, Cockerill GW, Torsney E, et al. Elevated tissue expression of thrombomodulatory factors correlates with acute symptomatic carotid plaque phenotype. *Eur J Vasc Endovasc Surg* 2009;38:20-25.
 199. Schaar JA, De Korte CL, Mastik F, et al. Characterizing vulnerable plaque features with intravascular elastography. *Circulation* 2003;108:2636-2641.
 200. Schmidt C, Fagerberg B, Wikstrand J, et al. Multiple risk factor intervention reduces cardiovascular risk in hypertensive patients with echolucent plaques in the carotid artery. *J Intern Med* 2003;253:430-438.
 201. Serruys PW, Garcia-Garcia HM, Buszman P, et al. Effects of the direct lipoprotein-associated phospholipase A(2) inhibitor darapladib on human coronary atherosclerotic plaque. *Circulation* 2008;118:1172-1182.
 202. Shaalan WE, Cheng H, Gewertz B, et al. Degree of carotid plaque calcification in relation to symptomatic outcome and plaque inflammation. *J Vasc Surg* 2004;40:262-269.
 203. Shi H, Mitchell CC, McCormick M, et al. Preliminary in vivo atherosclerotic carotid plaque characterization using the accumulated axial strain and relative lateral shift strain indices. *Phys Med Biol* 2008;53:6377-6394.
 204. Sigala F, Vourliotakis G, Georgopoulos S, et al. Vascular endothelial cadherin expression in human carotid atherosclerotic plaque and its relationship with plaque morphology and clinical data. *Eur J Vasc Endovasc Surg* 2003;26:523-528.
 205. Staub D, Patel MB, Tibrewala A, et al. Vasa vasorum and plaque neovascularization on contrast-enhanced carotid ultrasound imaging correlates with cardiovascular disease and past cardiovascular events. *Stroke* 2010;41:41-47.
 206. Takano M, Jang IK, Inami S, et al. In vivo comparison of optical coherence tomography and angioscopy for the evaluation of coronary plaque characteristics. *Am J Cardiol* 2008;101:471-476.
-

-
207. Takarada S, Imanishi T, Kubo T, et al. Effect of statin therapy on coronary fibrous-cap thickness in patients with acute coronary syndrome: assessment by optical coherence tomography study. *Atherosclerosis* 2009;202:491-497.
 208. Takaya N, Yuan C, Chu B, et al. Presence of intraplaque hemorrhage stimulates progression of carotid atherosclerotic plaques: a high-resolution magnetic resonance imaging study. *Circulation* 2005;111:2768-2775.
 209. Takeuchi H, Morino Y, Matsukage T, et al. Impact of vascular remodeling on the coronary plaque compositions: an investigation with in vivo tissue characterization using integrated backscatter-intravascular ultrasound. *Atherosclerosis* 2009;202:476-482.
 210. Tang D, Yang C, Zheng J, et al. Local maximal stress hypothesis and computational plaque vulnerability index for atherosclerotic plaque assessment. *Ann Biomed Eng* 2005;33:1789-1801.
 211. Tang D, Teng Z, Canton G, et al. Local critical stress correlates better than global maximum stress with plaque morphological features linked to atherosclerotic plaque vulnerability: an in vivo multi-patient study. *Biomed Eng Online* 2009;8:15.
 212. Tang D, Teng Z, Canton G, et al. Sites of rupture in human atherosclerotic carotid plaques are associated with high structural stresses: an in vivo MRI-based 3D fluid-structure interaction study. *Stroke* 2009;40:3258-3263.
 213. Tang TY, Howarth SP, Miller SR, et al. The ATHEROMA (Atorvastatin Therapy: Effects on Reduction of Macrophage Activity) Study. Evaluation using ultrasmall superparamagnetic iron oxide-enhanced magnetic resonance imaging in carotid disease. *J Am Coll Cardiol* 2009;53:2039-2050.
 214. Tavora FR, Ripple M, Li L, et al. Monocytes and neutrophils expressing myeloperoxidase occur in fibrous caps and thrombi in unstable coronary plaques. *BMC Cardiovasc Disord* 2009;9:27.
 215. Tearney GJ, Yabushita H, Houser SL, et al. Quantification of macrophage content in atherosclerotic plaques by optical coherence tomography. *Circulation* 2003;107:113-119.
 216. Thies F, Garry JM, Yaqoob P, et al. Association of n-3 polyunsaturated fatty acids with stability of atherosclerotic plaques: a randomised controlled trial. *Lancet* 2003;361:477-485.
 217. Trivedi RA, King-Im JM, Graves MJ, et al. MRI-derived measurements of fibrous-cap and lipid-core thickness: the potential for identifying vulnerable carotid plaques in vivo. *Neuroradiology* 2004;46:738-743.
 218. Trivedi RA, King-Im JM, Graves MJ, et al. In vivo detection of macrophages in human carotid atheroma: temporal dependence of ultrasmall superparamagnetic particles of iron oxide-enhanced MRI. *Stroke* 2004;35:1631-1635.
 219. Trivedi RA, Mallawarachi C, King-Im JM, et al. Identifying inflamed carotid plaques using in vivo USPIO-enhanced MR imaging to label plaque macrophages. *Arterioscler Thromb Vasc Biol* 2006;26:1601-1606.
 220. Trivedi RA, Li ZY, King-Im J, et al. Identifying vulnerable carotid plaques in vivo using high resolution magnetic resonance imaging-based finite element analysis. *J Neurosurg* 2007;107:536-542.
 221. Trostdorf F, Buchkremer M, Harmjanz A, et al. Fibrous cap thickness and smooth muscle cell apoptosis in high-grade carotid artery stenosis. *Eur J Vasc Endovasc Surg* 2005;29:528-535.
 222. Ueda Y, Ohtani T, Shimizu M, et al. Assessment of plaque vulnerability by angioscopic classification of plaque color. *Am Heart J* 2004;148:333-335.
-

-
223. Valgimigli M, Rodriguez-Granillo GA, Garcia-Garcia HM, et al. Distance from the ostium as an independent determinant of coronary plaque composition in vivo: an intravascular ultrasound study based radiofrequency data analysis in humans. *Eur Heart J* 2006;27:655-663.
 224. van der Hoeven BL, Liem SS, Oemrawsingh PV, et al. Role of calcified spots detected by intravascular ultrasound in patients with ST-segment elevation acute myocardial infarction. *Am J Cardiol* 2006;98:309-313.
 225. van Velzen JE, Schuijf JD, de Graaf FR, et al. Plaque type and composition as evaluated non-invasively by MSCT angiography and invasively by VH IVUS in relation to the degree of stenosis. *Heart* 2009;95:1990-1996.
 226. Verhoeven B, Hellings WE, Moll FL, et al. Carotid atherosclerotic plaques in patients with transient ischemic attacks and stroke have unstable characteristics compared with plaques in asymptomatic and amaurosis fugax patients. *J Vasc Surg* 2005;42:1075-1081.
 227. Waddington EI, Croft KD, Sienuarine K, et al. Fatty acid oxidation products in human atherosclerotic plaque: an analysis of clinical and histopathological correlates. *Atherosclerosis* 2003;167:111-120.
 228. Wahlgren CM, Zheng W, Shaalan W, et al. Human carotid plaque calcification and vulnerability. Relationship between degree of plaque calcification, fibrous cap inflammatory gene expression and symptomatology. *Cerebrovasc Dis* 2009;27:193-200.
 229. Wainstein M, Costa M, Ribeiro J, et al. Vulnerable plaque detection by temperature heterogeneity measured with a guidewire system: clinical, intravascular ultrasound and histopathologic correlates. *J Invasive Cardiol* 2007;19:49-54.
 230. Waki H, Masuyama T, Mori H, et al. Ultrasonic tissue characterization of the atherosclerotic carotid artery: histological correlates or carotid integrated backscatter. *Circ J* 2003;67:1013-1016.
 231. Wang HB, Kang WQ, Song DL, et al. Relationship between tissue type plasminogen activator and coronary vulnerable plaque in patients with acute coronary syndrome: virtual histological study. *Chin Med J (Engl)* 2008;20;121:540-543.
 232. Watanabe K, Sugiyama S, Kugiyama K, et al. Stabilization of carotid atheroma assessed by quantitative ultrasound analysis in nonhypercholesterolemic patients with coronary artery disease. *J Am Coll Cardiol* 2005;46:2022-2030.
 233. Waxman S, Mittleman MA, Zarich SW, et al. Plaque disruption and thrombus in Ambrose's angiographic coronary lesion types. *Am J Cardiol* 2003;92:16-20.
 234. White AJ, Duffy SJ, Walton AS, et al. Compliance mismatch between stenotic and distal reference segment is associated with coronary artery disease instability. *Atherosclerosis* 2009;206:179-185.
 235. Wintermark M, Jawadi SS, Rapp JH, et al. High-resolution CT imaging of carotid artery atherosclerotic plaques. *AJNR Am J Neuroradiol* 2008;29:875-882.
 236. Yamada K, Yoshimura S, Kawasaki M, et al. Effects of atorvastatin on carotid atherosclerotic plaques: a randomized trial for quantitative tissue characterization of carotid atherosclerotic plaques with integrated backscatter ultrasound. *Cerebrovasc Dis* 2009;28:417-424.
 237. Yamamoto M, Takano M, Okamatsu K, et al. Relationship between thin cap fibroatheroma identified by virtual histology and angioscopic yellow plaque in quantitative analysis with colorimetry. *Circ J* 2009;73:497-502.
 238. Yoshida K, Narumi O, Chin M, et al. Characterization of carotid atherosclerosis and detection of soft plaque with use of black-blood MR imaging. *AJNR Am J Neuroradiol* 2008;29:868-874.
-

-
239. Yunoki K, Naruko T, Komatsu R, et al. Enhanced expression of haemoglobin scavenger receptor in accumulated macrophages of culprit lesions in acute coronary syndromes. *Eur Heart J* 2009;30:1844-1852.
 240. Zhang XW, Ge JB, Yang JM, et al. Relationship between hs-CRP, proMMP-1, TIMP-1 and coronary plaque morphology: intravascular ultrasound study. *Chin Med J (Engl)* 2006;20;119:1689-1694.
 241. Zheng J, El N, I, Rowold FE, et al. Quantitative assessment of coronary artery plaque vulnerability by high-resolution magnetic resonance imaging and computational biomechanics: a pilot study ex vivo. *Magn Reson Med* 2005;54:1360-1368.
 242. Zuromskis T, Wetterholm R, Lindqvist JF, et al. Prevalence of micro-emboli in symptomatic high grade carotid artery disease: a transcranial Doppler study. *Eur J Vasc Endovasc Surg* 2008;35:534-540.

References of narrative review articles

1. Identifying the vulnerable plaque. *J Invasive Cardiol* 2003;15:280-284.
 2. What really causes heart attacks. In most cases, it's not a plugged artery, according to the "vulnerable plaque" theory. But searching for the vulnerable plaque may also be a mistake. *Harv Health Lett* 2003;28:6.
 3. Vulnerable Plaque Symposium, Boston, Massachusetts, USA, October 2003. *J Am Coll Cardiol* 2006;47:C1-C103.
 4. Aidinian G, Weiswasser JM, Arora S, et al. Carotid plaque morphologic characteristics. *Perspect Vasc Surg Endovasc Ther* 2006;18:63-70.
 5. Aikawa M, Libby P. The vulnerable atherosclerotic plaque: pathogenesis and therapeutic approach. *Cardiovasc Pathol* 2004;13:125-138.
 6. Akdim F, van Leuven SI, Kastelein JJ, et al. Pleiotropic effects of statins: stabilization of the vulnerable atherosclerotic plaque? *Curr Pharm Des* 2007;13:1003-1012.
 7. Ambrose JA, D'Agate DJ. Classification of systemic therapies for potential stabilization of the vulnerable plaque to prevent acute myocardial infarction. *Am J Cardiol* 2005;95:379-382.
 8. Ambrose JA. In search of the "vulnerable plaque": can it be localized and will focal regional therapy ever be an option for cardiac prevention? *J Am Coll Cardiol* 2008;51:1539-1542.
 9. Ambrose JA, Srikanth S. Vulnerable plaques and patients: improving prediction of future coronary events. *Am J Med* 2010;123:10-16.
 10. Baldewsing RA, Schaar JA, Mastik F, et al. Local elasticity imaging of vulnerable atherosclerotic coronary plaques. *Adv Cardiol* 2007;44:35-61
 11. Bardelli M. Ultrasonographic investigation of the mechanics of vulnerable atherosclerotic plaques: significance of the volume strain. *J Hypertens* 2009;27:219-220.
 12. Ben-Haim S, Israel O. PET/CT for atherosclerotic plaque imaging. *Q J Nucl Med Mol Imaging* 2006;50:53-60.
 13. Bhatia V, Bhatia R, Dhindsa S, et al. Vulnerable plaques, inflammation and newer imaging modalities. *J Postgrad Med* 2003;49:361-368.
-

-
14. Bhatia V, Bhatia R, Dhindsa S, et al. Imaging of the vulnerable plaque: new modalities. *South Med J* 2003;96:1142-1147.
 15. Biasucci LM, Leo M, De Maria GL. Local and systemic mechanisms of plaque rupture. *Angiology* 2008;59:73S-76S.
 16. Blum A. The vulnerable patient; not the vulnerable plaque. *Isr Med Assoc J* 2008;10:909.
 17. Bochaton-Piallat ML, Gabbiani G. Smooth muscle cell: a key cell for plaque vulnerability regulation? *Circ Res* 2006;98:448-449.
 18. Braunwald E. Noninvasive detection of vulnerable coronary plaques: Locking the barn door before the horse is stolen. *J Am Coll Cardiol* 2009;54:58-59.
 19. Brezinski ME. Optical coherence tomography for identifying unstable coronary plaque. *Int J Cardiol* 2006;107:154-165.
 20. Briley-Saebo KC, Mulder WJ, Mani V, et al. Magnetic resonance imaging of vulnerable atherosclerotic plaques: current imaging strategies and molecular imaging probes. *J Magn Reson Imaging* 2007;26:460-479.
 21. Brodoefel H, Burgstahler C, Heuschmid M, et al. Accuracy of dual-source CT in the characterisation of non-calcified plaque: use of a colour-coded analysis compared with virtual histology intravascular ultrasound. *Br J Radiol* 2009;82:805-812.
 22. Broz P, Marsch S, Hunziker P. Targeting of vulnerable plaque macrophages with polymer-based nanostructures. *Trends Cardiovasc Med* 2007;17:190-196.
 23. Bruggink JL, Meerwaldt R, van Dam GM, et al. Spectroscopy to improve identification of vulnerable plaques in cardiovascular disease. *Int J Cardiovasc Imaging* 2010;26:111-119.
 24. Burgstahler C, Hombach V, Rasche V. Molecular imaging of vulnerable plaque by cardiac magnetic resonance imaging. *Semin Thromb Hemost* 2007;33:165-172.
 25. Cademartiri F, La GL, Palumbo A, et al. Imaging techniques for the vulnerable coronary plaque. *Radiol Med* 2007;112:637-659.
 26. Caplan JD, Waxman S, Nesto RW, et al. Near-infrared spectroscopy for the detection of vulnerable coronary artery plaques. *J Am Coll Cardiol* 2006;47:C92-C96.
 27. Carlier S, Kakadiaris IA, Dib N, et al. Vasa vasorum imaging: a new window to the clinical detection of vulnerable atherosclerotic plaques. *Curr Atheroscler Rep* 2005;7:164-169.
 28. Casscells W, Naghavi M, Willerson JT. Vulnerable atherosclerotic plaque: a multifocal disease. *Circulation* 2003;107:2072-2075.
 29. Castillo M. From the vulnerable plaque to the vulnerable patient: imaging and clinical implications. *Acad Radiol* 2006;13:1177-1179.
 30. Cevik C, Otahbachi M, Nugent K, et al. Effect of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibition on serum matrix metalloproteinase-13 and tissue inhibitor matrix metalloproteinase-1 levels as a sign of plaque stabilization. *J Cardiovasc Med (Hagerstown)* 2008;9:1274-1278.
 31. Chalela JA. Evaluating the carotid plaque: going beyond stenosis. *Cerebrovasc Dis.* 2009;27(Suppl 1):19-24.
 32. Chen JW, Wasserman BA. Vulnerable plaque imaging. *Neuroimaging Clin N Am* 2005;15:609-621, xi.
-

-
33. Chen W, Bural GG, Torigian DA, et al. Emerging role of FDG-PET/CT in assessing atherosclerosis in large arteries. *Eur J Nucl Med Mol Imaging* 2009;36:144-151.
 34. Choi SH, Chae A, Chen CH, et al. Emerging approaches for imaging vulnerable plaques in patients. *Curr Opin Biotechnol* 2007;18:73-82.
 35. Cilingiroglu M, Ozer K. Optical coherence tomography and its use in detection of vulnerable plaque. *Curr Atheroscler Rep* 2006;8:140-143.
 36. Cilingiroglu M, Khan F. Drug-eluting stents and vulnerable plaque. *Curr Atheroscler Rep* 2009;11:146-148.
 37. Cipollone F, Fazio M, Mezzetti A. Novel determinants of plaque instability. *J Thromb Haemost* 2005;3:1962-1975.
 38. Cola C, Clementi E, Biondi-Zoccai G, et al. From carotid plaque biology to serologic markers of vulnerability to predict the risk of cerebrovascular events. *Acta Chir Belg* 2007;107:129-142.
 39. Corsten MF, Reutelingsperger CP, Hofstra L. Imaging apoptosis for detecting plaque instability: rendering death a brighter facade. *Curr Opin Biotechnol* 2007;18:83-89.
 40. Corti R, Fuster V, Badimon JJ. Pathogenetic concepts of acute coronary syndromes. *J Am Coll Cardiol* 2003;19;41:7S-14S.
 41. Corti R, Hutter R, Badimon JJ, et al. Evolving concepts in the triad of atherosclerosis, inflammation and thrombosis. *J Thromb Thrombolysis* 2004;17:35-44.
 42. Crea F, Andreotti F. The unstable plaque: a broken balance. *Eur Heart J* 2009;30:1821-1823.
 43. Cyrus T, Lanza GM, Wickline SA. Molecular imaging by cardiovascular MR. *J Cardiovasc Magn Reson* 2007;9:827-843.
 44. Cyrus T, Gropler RJ, Woodard PK. Coronary CT angiography (CCTA) and advances in CT plaque imaging. *J Nucl Cardiol* 2009;16:466-473.
 45. Dandona S, Roberts R. Genomic view of factors leading to plaque instability. *Curr Cardiol Rep* 2009;11:282-287.
 46. Davies JR, Rudd JF, Fryer TD, et al. Targeting the vulnerable plaque: the evolving role of nuclear imaging. *J Nucl Cardiol* 2005;12:234-246.
 47. Davies JR, Rudd JH, Weissberg PL, et al. Radionuclide imaging for the detection of inflammation in vulnerable plaques. *J Am Coll Cardiol* 2006;47:C57-C68.
 48. de Korte CL, Schaar JA, Mastik F, et al. Intravascular elastography: from bench to bedside. *J Interv Cardiol* 2003;16:253-259.
 49. DeMaria AN, Narula J, Mahmud E, et al. Imaging vulnerable plaque by ultrasound. *J Am Coll Cardiol* 2006;47:C32-C39.
 50. Di SR, Felice F, Balbarini A. Angiogenesis as risk factor for plaque vulnerability. *Curr Pharm Des* 2009;15:1095-1106.
 51. Diamantopoulos L. Arterial wall thermography. *J Interv Cardiol* 2003;16:261-266.
 52. Dickson BC, Gotlieb AI. Towards understanding acute destabilization of vulnerable atherosclerotic plaques. *Cardiovasc Pathol* 2003;12:237-248.
-

-
53. Didangelos A, Simper D, Monaco C, et al. Proteomics of acute coronary syndromes. *Curr Atheroscler Rep* 2009;11:188-195.
 54. Dunphy MP, Strauss HW. Molecular imaging of atherosclerosis. *Curr Cardiol Rep* 2008;10:121-127.
 55. Eijgelaar WJ, Heeneman S, Daemen MJ. The vulnerable patient: refocusing on the plaque? *Thromb Haemost* 2009;102:231-239.
 56. Elkhawad M, Rudd JH. Radiotracer imaging of atherosclerotic plaque biology. *Cardiol Clin* 2009;27:345-354, Table.
 57. Farooq MU, Khasnis A, Majid A, et al. The role of optical coherence tomography in vascular medicine. *Vasc Med* 2009;14:63-71.
 58. Finet G, Ohayon J, Rioufol G, et al. Morphological and biomechanical aspects of vulnerable coronary plaque. *Arch Mal Coeur Vaiss* 2007;100:547-553.
 59. Fishbein MC. The vulnerable and unstable atherosclerotic plaque. *Cardiovasc Pathol* 2010;19:6-11.
 60. Foin N, Evans P, Krams R. Atherosclerosis: cell biology and lipoproteins—new developments in imaging of inflammation of the vulnerable plaque. *Curr Opin Lipidol* 2008;19:98-100.
 61. Fox JJ, Strauss HW. One step closer to imaging vulnerable plaque in the coronary arteries. *J Nucl Med* 2009;50:497-500.
 62. Friedewald VE, Ambrose JA, Stone GW, et al. The editor's roundtable: the vulnerable plaque. *Am J Cardiol* 2008;102:1644-1653.
 63. Frutkin AD, Mehta SK, McCrary JR, et al. Limitations to the use of virtual histology-intravascular ultrasound to detect vulnerable plaque. *Eur Heart J* 2007;28:1783-1784.
 64. Fuster V, Moreno PR, Fayad ZA, et al. Atherothrombosis and high-risk plaque: part I: evolving concepts. *J Am Coll Cardiol* 2005;20;46:937-954.
 65. Galis ZS. Vulnerable plaque: the devil is in the details. *Circulation* 2004;20;110:244-246.
 66. Garcia-Garcia HM, Gonzalo N, Granada JF, et al. Diagnosis and treatment of coronary vulnerable plaques. *Expert Rev Cardiovasc Ther* 2008;6:209-222.
 67. Giannoni MF, Vicenzini E. Focus on the "unstable" carotid plaque: detection of intraplaque angiogenesis with contrast ultrasound. Present state and future perspectives. *Curr Vasc Pharmacol* 2009;7:180-184.
 68. Gillard JH. Advances in atheroma imaging in the carotid. *Cerebrovasc Dis* 2007;24(Suppl 1):40-48.
 69. Goldberg SL. The burden of "vulnerable plaque": more plaque burden. *J Invasive Cardiol* 2008;20:640-641.
 70. Gossl M, Versari D, Hildebrandt H, et al. Vulnerable plaque: detection and management. *Med Clin North Am* 2007;91:573-601.
 71. Granada JF, Kaluza GL, Raizner AE, et al. Vulnerable plaque paradigm: prediction of future clinical events based on a morphological definition. *Catheter Cardiovasc Interv* 2004;62:364-374.
-

-
72. Halvorsen B, Otterdal K, Dahl TB, et al. Atherosclerotic plaque stability—what determines the fate of a plaque? *Prog Cardiovasc Dis* 2008;51:183-194.
 73. Hamdan A, Assali A, Fuchs S, et al. Imaging of vulnerable coronary artery plaques. *Catheter Cardiovasc Interv* 2007;70:65-74.
 74. Hartung D, Schafers M, Fujimoto S, et al. Targeting of matrix metalloproteinase activation for noninvasive detection of vulnerable atherosclerotic lesions. *Eur J Nucl Med Mol Imaging* 2007;34(Suppl 1):S1-S8.
 75. Hazen SL. Myeloperoxidase and plaque vulnerability. *Arterioscler Thromb Vasc Biol* 2004;24:1143-1146.
 76. Heistad DD. Unstable coronary-artery plaques. *N Engl J Med* 2003;349:2285-2287.
 77. Hellings WE, Peeters W, Moll FL, et al. From vulnerable plaque to vulnerable patient: the search for biomarkers of plaque destabilization. *Trends Cardiovasc Med* 2007;17:162-171.
 78. Hennerici MG. The unstable plaque. *Cerebrovasc Dis* 2004;17(Suppl 3):17-22.
 79. Hermus L, van Dam GM, Zeebregts CJ. Advanced carotid plaque imaging. *Eur J Vasc Endovasc Surg* 2010;39:125-133.
 80. Holm PW, Slart RH, Zeebregts CJ, et al. Atherosclerotic plaque development and instability: a dual role for VEGF. *Ann Med* 2009;41:257-264.
 81. Hurks R, Peeters W, Derksen WJ, et al. Biobanks and the search for predictive biomarkers of local and systemic outcome in atherosclerotic disease. *Thromb Haemost* 2009;101:48-54.
 82. Ishibashi F, Aziz K, Abela GS, et al. Update on coronary angiography: review of a 20-year experience and potential application for detection of vulnerable plaque. *J Interv Cardiol* 2006;19:17-25.
 83. Jain RK, Finn AV, Kolodgie FD, et al. Antiangiogenic therapy for normalization of atherosclerotic plaque vasculature: a potential strategy for plaque stabilization. *Nat Clin Pract Cardiovasc Med* 2007;4:491-502.
 84. Jialal I, Devaraj S, Singh U. C-reactive protein and the vascular endothelium: implications for plaque instability. *J Am Coll Cardiol* 2006;47:1379-1381.
 85. Kahn J. Beyond IVUS: new imaging methods zero in on vulnerable plaque—part I. *J Interv Cardiol* 2005;18:375-377.
 86. Kahn J. Beyond IVUS: new imaging methods zero in on vulnerable plaque—part II. *J Interv Cardiol* 2006;19:27-29.
 87. Katritsis DG, Pantos J, Efsthopoulos E. Hemodynamic factors and atheromatic plaque rupture in the coronary arteries: from vulnerable plaque to vulnerable coronary segment. *Coron Artery Dis* 2007;18:229-237.
 88. Kavurma MM, Bhindi R, Lowe HC, et al. Vessel wall apoptosis and atherosclerotic plaque instability. *J Thromb Haemost* 2005;3:465-472.
 89. Kelly P, Bhatt DL. Identification of vulnerable plaque—the quest continues. *J Invasive Cardiol* 2007;19:55-57.
 90. Kereiakes DJ. The Emperor's clothes: in search of the vulnerable plaque. *Circulation* 2003;107:2076-2077.
-

-
91. King-Im JM, Tang T, Moustafa RR, et al. Imaging the cellular biology of the carotid plaque. *Int J Stroke* 2007;2:85-96.
 92. King-Im JM, Young V, Gillard JH. Carotid-artery imaging in the diagnosis and management of patients at risk of stroke. *Lancet Neurol* 2009;8:569-580.
 93. Klein LW. Clinical implications and mechanisms of plaque rupture in the acute coronary syndromes. *Am Heart Hosp J* 2005;3:249-255.
 94. Koenig W, Khuseyinova N. Biomarkers of atherosclerotic plaque instability and rupture. *Arterioscler Thromb Vasc Biol* 2007;27:15-26.
 95. Kolodgie FD, Virmani R, Burke AP, et al. Pathologic assessment of the vulnerable human coronary plaque. *Heart* 2004;90:1385-1391.
 96. Konig A, Margolis MP, Virmani R, et al. Technology insight: in vivo coronary plaque classification by intravascular ultrasonography radiofrequency analysis. *Nat Clin Pract Cardiovasc Med* 2008;5:219-229.
 97. Kopp AF. Angio-CT: heart and coronary arteries. *Eur J Radiol* 2003;45(Suppl 1):S32-S36.
 98. Kovanen PT, Mayranpaa M, Lindstedt KA. Drug therapies to prevent coronary plaque rupture and erosion: present and future. *Handb Exp Pharmacol* 2005;745-776.
 99. Krams R, Segers D, Mousavi GB, et al. Inflammation and atherosclerosis: mechanisms underlying vulnerable plaque. *J Interv Cardiol* 2003;16:107-113.
 100. Kuchulakanti P, Rha SW, Cheneau E, et al. Identification of "vulnerable plaque" using virtual histology in angiographically benign looking lesion of proximal left anterior descending artery. *Cardiovasc Radiat Med* 2003;4:225-227.
 101. Kukreja N, Garcia-Garcia HM, Serruys PW. Invasive imaging techniques for the assessment of vulnerable plaque. *Minerva Cardioangiol* 2006;54:603-617.
 102. Kwee RM, van Oostenbrugge RJ, Hofstra L, et al. Identifying vulnerable carotid plaques by noninvasive imaging. *Neurology* 2008;70:2401-2409.
 103. Ia-Korpela M, Sipola P, Kaski K. Characterization and molecular detection of atherothrombosis by magnetic resonance—potential tools for individual risk assessment and diagnostics. *Ann Med* 2006;38:322-336.
 104. LaBelle EF, Tulenko TN. LDL, IGF-1, and VSMC apoptosis: linking atherogenesis to plaque rupture in vulnerable lesions. *Cardiovasc Res* 2004;61:204-205.
 105. Lafont A. Basic aspects of plaque vulnerability. *Heart* 2003;89:1262-1267.
 106. Langer H, Schonberger T, Bigalke B, et al. Where is the trace? Molecular imaging of vulnerable atherosclerotic plaques. *Semin Thromb Hemost* 2007;33:151-158.
 107. Langer HF, Haubner R, Pichler BJ, et al. Radionuclide imaging: a molecular key to the atherosclerotic plaque. *J Am Coll Cardiol* 2008;52:1-12.
 108. Laufer EM, Winkens MH, Narula J, et al. Molecular imaging of macrophage cell death for the assessment of plaque vulnerability. *Arterioscler Thromb Vasc Biol* 2009;29:1031-1038.
 109. Laufer EM, Winkens HM, Corsten MF, et al. PET and SPECT imaging of apoptosis in vulnerable atherosclerotic plaques with radiolabeled Annexin A5. *Q J Nucl Med Mol Imaging* 2009;53:26-34.
-

-
110. Lerakis S, Synetos A, Toutouzas K, et al. Imaging of the vulnerable plaque: noninvasive and invasive techniques. *Am J Med Sci* 2008;336:342-348.
 111. Lerman A, Vogel J, Fischell T, et al. AGS proceedings. The biology of plaque and patient vulnerability. Panel discussion. *J Invasive Cardiol* 2005;17:239-242.
 112. Levin RI. Plaque vulnerability pathologic form and patient fate. *J Am Coll Cardiol* 2010;55:133-134.
 113. Libby P, Aikawa M. Effects of statins in reducing thrombotic risk and modulating plaque vulnerability. *Clin Cardiol* 2003;26:111-114.
 114. Libby P. Act local, act global: inflammation and the multiplicity of "vulnerable" coronary plaques. *J Am Coll Cardiol* 2005;45:1600-1602.
 115. Lindstedt KA, Kovanen PT. Mast cells in vulnerable coronary plaques: potential mechanisms linking mast cell activation to plaque erosion and rupture. *Curr Opin Lipidol* 2004;15:567-573.
 116. Lindstedt KA, Mayranpaa MI, Kovanen PT. Mast cells in vulnerable atherosclerotic plaques—a view to a kill. *J Cell Mol Med* 2007;11:739-758.
 117. Low AF, Tearney GJ, Bouma BE, et al. Technology Insight: optical coherence tomography—current status and future development. *Nat Clin Pract Cardiovasc Med* 2006;3:154-162.
 118. Lutgens E, van Suylen RJ, Faber BC, et al. Atherosclerotic plaque rupture: local or systemic process? *Arterioscler Thromb Vasc Biol* 2003;23:2123-2130.
 119. MacNeill BD, Lowe HC, Takano M, et al. Intravascular modalities for detection of vulnerable plaque: current status. *Arterioscler Thromb Vasc Biol* 2003;23:1333-1342.
 120. MacNeill BD, Bouma BE, Yabushita H, et al. Intravascular optical coherence tomography: cellular imaging. *J Nucl Cardiol* 2005;12:460-465.
 121. Madjid M, Zarrabi A, Litovsky S, et al. Finding vulnerable atherosclerotic plaques: is it worth the effort? *Arterioscler Thromb Vasc Biol* 2004;24:1775-1782.
 122. Madjid M, Willerson JT, Casscells SW. Intracoronary thermography for detection of high-risk vulnerable plaques. *J Am Coll Cardiol* 2006;47:C80-C85.
 123. Madjid M, Toutouzas K, Stefanadis C, et al. Coronary thermography for detection of vulnerable plaques. *J Nucl Cardiol* 2007;14:244-249.
 124. Martinet W, Kockx MM. Apoptosis in atherosclerosis: implications for plaque destabilization. *Verh K Acad Geneesk Belg* 2004;66:61-79.
 125. Maseri A, Fuster V. Is there a vulnerable plaque? *Circulation* 2003;107:2068-2071.
 126. Mehta SK, McCrary JR, Frutkin AD, et al. Intravascular ultrasound radiofrequency analysis of coronary atherosclerosis: an emerging technology for the assessment of vulnerable plaque. *Eur Heart J* 2007;28:1283-1288.
 127. Mezzetti A. Pharmacological modulation of plaque instability. *Lupus* 2005;14:769-772.
 128. Mitra AK, Dhume AS, Agrawal DK. "Vulnerable plaques"—ticking of the time bomb. *Can J Physiol Pharmacol* 2004;82:860-871.
-

-
129. Monroe VS, Kerensky RA, Rivera E, et al. Pharmacologic plaque passivation for the reduction of recurrent cardiac events in acute coronary syndromes. *J Am Coll Cardiol* 2003;19;41:23S-30S.
 130. Montecucco F, Steffens S, Mach F. The immune response is involved in atherosclerotic plaque calcification: could the RANKL/RANK/OPG system be a marker of plaque instability? *Clin Dev Immunol* 2007;75805.
 131. Montecucco F, Steffens S, Mach F. Insulin resistance: a proinflammatory state mediated by lipid-induced signaling dysfunction and involved in atherosclerotic plaque instability. *Mediators Inflamm* 2008;767623.
 132. Montero I, Orbe J, Varo N, et al. C-reactive protein induces matrix metalloproteinase-1 and -10 in human endothelial cells: implications for clinical and subclinical atherosclerosis. *J Am Coll Cardiol* 2006;47:1369-1378.
 133. Moreno PR, Muller JE. Detection of high-risk atherosclerotic coronary plaques by intravascular spectroscopy. *J Interv Cardiol* 2003;16:243-252.
 134. Moreno PR. Vulnerable plaque: definition, diagnosis, and treatment. *Cardiol Clin* 2010;28:1-30.
 135. Muller JE, Tawakol A, Kathiresan S, et al. New opportunities for identification and reduction of coronary risk: treatment of vulnerable patients, arteries, and plaques. *J Am Coll Cardiol* 2006;47:C2-C6.
 136. Nadkarni SK, Bouma BE, de BJ, et al. Evaluation of collagen in atherosclerotic plaques: the use of two coherent laser-based imaging methods. *Lasers Med Sci* 2009;24:439-445.
 137. Naghavi M, Libby P, Falk E, et al. From vulnerable plaque to vulnerable patient: a call for new definitions and risk assessment strategies: Part II. *Circulation*. 2003;108:1772-1778.
 138. Naghavi M, Libby P, Falk E, et al. From vulnerable plaque to vulnerable patient: a call for new definitions and risk assessment strategies: Part I. *Circulation*. 2003;108:1664-1672.
 139. Naghavi M, Falk E, Hecht HS, et al. From vulnerable plaque to vulnerable patient—Part III: Executive summary of the Screening for Heart Attack Prevention and Education (SHAPE) Task Force report. *Am J Cardiol* 2006;98:2H-15H.
 140. Nakamura M, Lee DP, Yeung AC. Identification and treatment of vulnerable plaque. *Rev Cardiovasc Med* 2004;5(Suppl 2):S22-S33.
 141. Narula J, Garg P, Achenbach S, et al. Arithmetic of vulnerable plaques for noninvasive imaging. *Nat Clin Pract Cardiovasc Med*. 2008;5(Suppl 2):S2-10.
 142. Narula J. Who gets the heart attack: noninvasive imaging markers of plaque instability. *J Nucl Cardiol* 2009;16:860-868.
 143. Nemirovsky D. Imaging of high-risk plaque. *Cardiology* 2003;100:160-175.
 144. Newby AC. Do metalloproteinases destabilize vulnerable atherosclerotic plaques? *Curr Opin Lipidol* 2006;17:556-561.
 145. Newby AC. Metalloproteinases and vulnerable atherosclerotic plaques. *Trends Cardiovasc Med* 2007;17:253-258.
 146. Newby AC. Metalloproteinase expression in monocytes and macrophages and its relationship to atherosclerotic plaque instability. *Arterioscler Thromb Vasc Biol* 2008;28:2108-114.
-

-
147. Nighoghossian N, Derex L, Douek P. The vulnerable carotid artery plaque: current imaging methods and new perspectives. *Stroke* 2005;36:2764-2772.
 148. Nilsson J, Glazer S, Carlsson R. Antibodies against oxidized low-density lipoprotein for the treatment of vulnerable plaques. *Curr Opin Investig Drugs* 2006;7:815-819.
 149. Nissen SE. The vulnerable plaque "hypothesis": promise, but little progress. *JACC Cardiovasc Imaging* 2009;2:483-485.
 150. Oikawa M, Ota H, Takaya N, et al. Carotid magnetic resonance imaging. A window to study atherosclerosis and identify high-risk plaques. *Circ J* 2009;73:1765-1773.
 151. Ozer K, Cilingiroglu M. Vulnerable plaque: definition, detection, treatment, and future implications. *Curr Atheroscler Rep* 2005;7:121-126.
 152. Paoletti R, Cignarella A. Can we stabilize unstable plaque? *Curr Atheroscler Rep* 2003;5:423-424.
 153. Paramo JA, Rodriguez JA, Orbe J. Vulnerable plaque versus vulnerable patient: emerging blood biomarkers for risk stratification. *Endocr Metab Immune Disord Drug Targets* 2007;7:195-201.
 154. Parthasarathy S, Litvinov D, Selvarajan K, et al. Lipid peroxidation and decomposition—conflicting roles in plaque vulnerability and stability. *Biochim Biophys Acta* 2008;1781:221-231.
 155. Pasterkamp G, Daemen M. Stabilizing the vulnerable plaque: the search for the magic bullet. *Curr Pharm Des* 2007;13:979-982.
 156. Qian JY. Detection of vulnerable plaques rather than the culprit lesions in patients with acute coronary syndrome using virtual histology intravascular ultrasound imaging. *Chin Med J (Engl)* 2009;20;122:610-611.
 157. Rammos G, Kondomerkos D. The role of CD4+CD28(null) T-lymphocytes and statins in rheumatoid arthritis and unstable atherosclerotic plaque. *Hellenic J Cardiol* 2007;48:165-174.
 158. Ravnskov U, McCully KS. Review and Hypothesis: Vulnerable plaque formation from obstruction of Vasa vasorum by homocysteinyllated and oxidized lipoprotein aggregates complexed with microbial remnants and LDL autoantibodies. *Ann Clin Lab Sci* 2009;39:3-16.
 159. Riou LM, Broisat A, Dimastromatteo J, et al. Pre-clinical and clinical evaluation of nuclear tracers for the molecular imaging of vulnerable atherosclerosis: an overview. *Curr Med Chem* 2009;16:1499-1511.
 160. Rohde LE, Lee RT. Pathophysiology of atherosclerotic plaque development and rupture: an overview. *Semin Vasc Med* 2003;3:347-354.
 161. Rudd JH, Davies JR, Weissberg PL. Imaging of atherosclerosis—can we predict plaque rupture? *Trends Cardiovasc Med* 2005;15:17-24.
 162. Saam T, Hatsukami TS, Takaya N, et al. The vulnerable, or high-risk, atherosclerotic plaque: noninvasive MR imaging for characterization and assessment. *Radiology* 2007;244:64-77.
 163. Sadat U, Li ZY, Graves MJ, et al. Noninvasive imaging of atheromatous carotid plaques. *Nat Clin Pract Cardiovasc Med* 2009;6:200-209.
 164. Saia F, Schaar J, Regar E, et al. Clinical imaging of the vulnerable plaque in the coronary arteries: new intracoronary diagnostic methods. *J Cardiovasc Med (Hagerstown)* 2006;7:21-28.
 165. Saloner D, cevedo-Bolton G, Wintermark M, et al. MRI of geometric and compositional features of vulnerable carotid plaque. *Stroke* 2007;38:637-641.
-

-
166. Sangiorgi GM, Clementi F, Cola C, et al. Plaque vulnerability and related coronary event prediction by intravascular ultrasound with virtual histology: "it's a long way to tipperary"? *Catheter Cardiovasc Interv* 2007;70:203-210.
 167. Schaar JA, de Korte CL, Mastik F, et al. Intravascular palpography for high-risk vulnerable plaque assessment. *Herz* 2003;28:488-495.
 168. Schaar JA, Muller JE, Falk E, et al. Terminology for high-risk and vulnerable coronary artery plaques. Report of a meeting on the vulnerable plaque, June 17 and 18, 2003, Santorini, Greece. *Eur Heart J* 2004;25:1077-1082.
 169. Schaar JA, van der Steen AF, Mastik F, et al. Intravascular palpography for vulnerable plaque assessment. *J Am Coll Cardiol* 2006;47:C86-C91.
 170. Schaar JA, Mastik F, Regar E, et al. Current diagnostic modalities for vulnerable plaque detection. *Curr Pharm Des* 2007;13:995-1001.
 171. Schiro BJ, Wholey MH. The expanding indications for virtual histology intravascular ultrasound for plaque analysis prior to carotid stenting. *J Cardiovasc Surg (Torino)* 2008;49:729-736.
 172. Schoenhagen P, Nissen SE. Assessing coronary plaque burden and plaque vulnerability: atherosclerosis imaging with IVUS and emerging noninvasive modalities. *Am Heart Hosp J* 2003;1:164-169.
 173. Schwartz RS, Bayes-Genis A, Lesser JR, et al. Detecting vulnerable plaque using peripheral blood: inflammatory and cellular markers. *J Interv Cardiol* 2003;16:231-242.
 174. Shah PK. Mechanisms of plaque vulnerability and rupture. *J Am Coll Cardiol* 2003;19;41:15S-22S.
 175. Shah PK. Molecular mechanisms of plaque instability. *Curr Opin Lipidol* 2007;18:492-499.
 176. Shah PK. Inflammation and plaque vulnerability. *Cardiovasc Drugs Ther* 2009;23:31-40.
 177. Sharif F, Murphy RT. Current status of vulnerable plaque detection. *Catheter Cardiovasc Interv* 2010;75:135-144.
 178. Shin J, Edelberg JE, Hong MK. Vulnerable atherosclerotic plaque: clinical implications. *Curr Vasc Pharmacol* 2003;1:183-204.
 179. Sibinga NE. Stable protein, unstable plaque? *J Mol Cell Cardiol* 2009;46:289-291.
 180. Sipahi I, Nicholls SJ, Tuzcu EM. Recent trends in coronary intravascular ultrasound: tracking atherosclerosis, pursuit of vulnerable plaques, and beyond. *J Nucl Cardiol* 2006;13:91-96.
 181. Slager CJ, Wentzel JJ, Gijzen FJ, et al. The role of shear stress in the destabilization of vulnerable plaques and related therapeutic implications. *Nat Clin Pract Cardiovasc Med* 2005;2:456-464.
 182. Slager CJ, Wentzel JJ, Gijzen FJ, et al. The role of shear stress in the generation of rupture-prone vulnerable plaques. *Nat Clin Pract Cardiovasc Med* 2005;2:401-407.
 183. Smeglin A, Frishman WH. Elastolytic matrix metalloproteinases and their inhibitors as therapeutic targets in atherosclerotic plaque instability. *Cardiol Rev* 2004;12:141-150.
 184. SoRelle R. Detecting vulnerable plaque. *Circulation* 2003;108:e9066-e9070.
 185. Sosnovik DE. Will molecular MR imaging play a role in identification and treatment of patients with vulnerable atherosclerotic plaques? *Radiology* 2009;251:309-310.
-

-
186. Stamper D, Weissman NJ, Brezinski M. Plaque characterization with optical coherence tomography. *J Am Coll Cardiol* 2006;47:C69-C79.
 187. Staniloae CS, Ambrose JA. Identification of vulnerable atherosclerotic plaques. *Expert Rev Cardiovasc Ther* 2003;1:353-365.
 188. Stefanadis C, Vavuranakis M, Toutouzas P. Vulnerable plaque: the challenge to identify and treat it. *J Interv Cardiol* 2003;16:273-280.
 189. Sztajzel R. Ultrasonographic assessment of the morphological characteristics of the carotid plaque. *Swiss Med Wkly* 2005;135:635-643.
 190. Tabas I, Seimon T, Timmins J, et al. Macrophage apoptosis in advanced atherosclerosis. *Ann N Y Acad Sci* 2009;1173(Suppl 1):E40-E45.
 191. Tabas I. Macrophage apoptosis in atherosclerosis: consequences on plaque progression and the role of endoplasmic reticulum stress. *Antioxid Redox Signal* 2009;11:2333-2339.
 192. Tahara N, Imaizumi T, Virmani R, Narula J. Clinical feasibility of molecular imaging of plaque inflammation in atherosclerosis. *J Nucl Med* 2009;50:331-334.
 193. Tan KT, Lip GY. Imaging of the unstable plaque. *Int J Cardiol* 2008;127:157-165.
 194. Tearney GJ, Jang IK, Bouma BE. Optical coherence tomography for imaging the vulnerable plaque. *J Biomed Opt* 2006;11:021002.
 195. Thim T, Hagensen MK, Bentzon JF, et al. From vulnerable plaque to atherothrombosis. *J Intern Med* 2008;263:506-516.
 196. Thorn EM, Khan IA. Pregnancy-associated plasma protein-A: an emerging cardiac biomarker. *Int J Cardiol* 2007;117:370-372.
 197. Toutouzas K, Drakopoulou M, Stefanadi E, et al. Intracoronary thermography: does it help us in clinical decision making? *J Interv Cardiol* 2005;18:485-489.
 198. Toutouzas K, Stefanadis C. Advances in vulnerable plaque detection and treatment: how far have we gone? *Hellenic J Cardiol* 2006;47:129-131.
 199. Trivedi RA, Gillard JH, Kirkpatrick PJ. Modern methods for imaging carotid atheroma. *Br J Neurosurg* 2008;22:350-359.
 200. Tuzcu EM, Schoenhagen P. Acute coronary syndromes, plaque vulnerability, and carotid artery disease: the changing role of atherosclerosis imaging. *J Am Coll Cardiol* 2003;42:1033-1036.
 201. Ueda Y, Hirayama A, Kodama K. Plaque characterization and atherosclerosis evaluation by coronary angioscopy. *Herz* 2003;28:501-504.
 202. Vaina S, Stefanadis C. Detection of the vulnerable coronary atheromatous plaque. Where are we now? *Int J Cardiovasc Intervent* 2005;7:75-87.
 203. Valgimigli M, Agostoni P, Serruys PW. Acute coronary syndromes: an emphasis shift from treatment to prevention; and the enduring challenge of vulnerable plaque detection in the cardiac catheterization laboratory. *J Cardiovasc Med (Hagerstown)* 2007;8:221-229.
 204. van der Wal AC, Li X, de Boer OJ. Tissue factor expression in the morphologic spectrum of vulnerable atherosclerotic plaques. *Semin Thromb Hemost* 2006;32:40-47.
-

-
205. Vicenzini E, Giannoni MF, edetti-Valentini F, et al. Imaging of carotid plaque angiogenesis. *Cerebrovasc Dis* 2009;27(Suppl 2):48-54.
 206. Vink A, Pasterkamp G. Atherosclerotic plaques: how vulnerable is the definition of "the vulnerable plaque"? *J Interv Cardiol* 2003;16:115-122.
 207. Virani SS, Ballantyne CM. How to identify patients with vulnerable plaques. *Diabetes Obes Metab* 2008;10:824-833.
 208. Virmani R, Burke AP, Kolodgie FD, et al. Pathology of the thin-cap fibroatheroma: a type of vulnerable plaque. *J Interv Cardiol* 2003;16:267-272.
 209. Virmani R, Kolodgie FD, Burke AP, et al. Atherosclerotic plaque progression and vulnerability to rupture: angiogenesis as a source of intraplaque hemorrhage. *Arterioscler Thromb Vasc Biol* 2005;25:2054-2061.
 210. Virmani R, Burke AP, Farb A, et al. Pathology of the vulnerable plaque. *J Am Coll Cardiol* 2006;47:C13-C18.
 211. Wallis d V, van Dam GM, Tio RA, et al. Current imaging modalities to visualize vulnerability within the atherosclerotic carotid plaque. *J Vasc Surg* 2008;48:1620-1629.
 212. Wasserman EJ, Shipley NM. Atherothrombosis in acute coronary syndromes: mechanisms, markers, and mediators of vulnerability. *Mt Sinai J Med* 2006;73:431-439.
 213. Waxman S, Ishibashi F, Muller JE. Detection and treatment of vulnerable plaques and vulnerable patients: novel approaches to prevention of coronary events. *Circulation* 2006;114:2390-2411.
 214. Waxman S, Ishibashi F, Caplan JD. Rationale and use of near-infrared spectroscopy for detection of lipid-rich and vulnerable plaques. *J Nucl Cardiol* 2007;14:719-728.
 215. Weintraub HS. Identifying the vulnerable patient with rupture-prone plaque. *Am J Cardiol* 2008;101:3F-10F.
 216. Wilensky RL, Song HK, Ferrari VA. Role of magnetic resonance and intravascular magnetic resonance in the detection of vulnerable plaques. *J Am Coll Cardiol* 2006;47:C48-C56.
 217. Wilensky RL, Hamamdzcic D. The molecular basis of vulnerable plaque: potential therapeutic role for immunomodulation. *Curr Opin Cardiol* 2007;22:545-551.
 218. Wilensky RL. Vulnerable plaque: scope of the problem. *J Interv Cardiol* 2008;21:443-451.
 219. Young JJ. Detection of vulnerable coronary artery plaques: lesion level risk assessment within the coronary arterial tree? *JACC Cardiovasc Imaging* 2008;1:649-651.
 220. Young JJ, Phillips HR, Marso SP, et al. Vulnerable plaque intervention: State of the art. *Catheter Cardiovasc Interv* 2008;71:367-374.
 221. Zaninotto M, Mion MM, Novello E, et al. New biochemical markers: from bench to bedside. *Clin Chim Acta* 2007;381:14-20.
-

Table 2. Basic study features of included studies

Study Design	N (%) *
1. All studies included	463 (100%)
1.1. Primary Studies	242 (52%)
1.1.1. Study Design	
1.1.1.1. Cross-sectional	216 (89%)
1.1.1.2. Longitudinal	26 (11%)
1.1.1.2.1. Prospective	24 (9.9%)
1.1.1.2.2. Retrospective	2 (0.8%)
1.1.2. Disease investigated	
1.1.2.1. Coronary artery disease	114 (47%)
1.1.2.2. Carotid artery disease	130 (54%)
1.1.2.3. Participants with no history of cardiovascular disease	3 (1.2%)
1.1.3. Populations included	
1.1.3.1. Living	143 (59%)
1.1.3.2. Tissue sample from living person	79 (33%)
1.1.3.3. Autopsy	20 (8.3%)
1.1.4. Predictors used	
1.1.4.1. Imaging	120 (50%)
1.1.4.2. Histopathology	60 (25%)
1.1.4.3. Biomarkers	36 (15%)
1.1.4.4. Treatment	17 (7.0%)
1.1.4.5. Combination	2 (0.8%)
1.1.4.6. Other †	7 (2.9%)
1.1.5. No. Patients: median (IQR)	60 (30-114)
1.2. Narrative Reviews	221 (48%)

IQR = interquartile range; N = number of abstracts.

*The percentages of primary studies (1.1) and narrative reviews (1.2) are of total number of studies. The remaining percentages have been calculated for primary studies only.

†Other predictors: cardiovascular risk factors, kidney function, metabolic syndrome, peripheral arterial disease, diabetes mellitus, endothelial dysfunction, non-alcoholic fatty liver

Table 3. Study features of histopathology studies

Study Feature	N (%) *
2. Histopathology studies	60 (100%)
2.1. Coronary artery disease	28 (47%)
2.1.1. Populations Included	
2.1.1.1. Tissue sample from living person	19 (68%)
2.1.1.2. Autopsy	9 (32%)
2.1.2. Study Design	
2.1.2.1. Cross-sectional	28 (100%)
2.1.2.2. Longitudinal	0 (0%)
2.1.3. Histopathology Features Assessed	
2.1.3.1. Macrophage infiltration	4 (14%)
2.1.3.2. Combination	2 (7.1%)
2.1.3.3. Other †	2 (7.1%)
2.1.3.4. Tissue expression of molecules/cells within the plaque ‡	20 (71%)
2.1.4. Outcomes	
2.1.4.1. Clinical §	19 (68%)
2.1.4.2. Histopathological	8 (29%)
2.1.4.3. Imaging	1 (3.6%)
2.1.5. No. patients: median (IQR)	42 (27-71)
2.1.6. No. lesions: median (IQR)	44 (20-93)
2.2. Carotid artery disease	32 (53%)
2.2.1. Populations Included	
2.2.1.1. Tissue sample from living person	31 (97%)
2.2.1.2. Autopsy	1 (3.1%)
2.2.2. Study Design	
2.2.2.1. Cross-sectional	32 (100%)
2.2.2.2. Longitudinal	0 (0%)
2.2.3. Histopathology Features Assessed	
2.2.3.1. Macrophage infiltration	3 (9.4%)
2.2.3.2. Combination	2 (6.3%)
2.2.3.3. Other †	4(13%)
2.2.3.4. Tissue expression of molecules/cells within the plaque ‡	23 (72%)
2.2.4. Outcomes	
2.2.4.1. Clinical §	18 (56%)
2.2.4.2. Histopathological	14 (44%)
2.2.5. No. patients: median (IQR)	60 (38-200)
2.2.6. No. lesions: median (IQR)	48 (30-53)

IQR = interquartile range; N = number of abstracts.

*The percentages of coronary artery disease studies (2.1) and carotid artery disease studies (2.2) have been calculated for all histopathology studies, The remaining percentages have been calculated for coronary and carotid artery disease separately.

†Other histopathological features investigated by single studies included cap thickness, intraplaque hemorrhage, calcification, vasa vasorum, lipid core.

‡Molecules/cells investigated for increased expression/infiltration within the plaque: matrix metalloproteinases -1,-2,-8,-9,13; placenta growth factor; C-reactive protein ; angiotensin converting enzyme /angiotensin II; cadherin; hydroxyeicosatetraenoic acids; hydroxyoctadecadienoic acids; alpha/beta hydrolase domain containing 2; endoplasmic reticulum chaperones; lipoprotein-associated phospholipase A2; 8-iso-prostaglandin F(2)(alpha); factor VII activating protease; interleukin 10; membrane attack complex; oxidized low density lipoprotein; toll-like receptor 4; hypoxia inducible factor-1a; vascular endothelial growth factor; vascular endothelial growth factor receptor 1 and 2; secretory type-II phospholipase A(2); galectin-3; gene expression profiling; cluster of differentiation 68+ macrophages; cluster of differentiation 3+ T cells; paucity of alpha-actin smooth muscle cells; 5-lipo-oxygenase; cyclooxygenase 2; expression of apoptotic molecules; platelet glycoprotein IIb/IIIa and P-selectin; transforming growth factor beta; adrenomedullin; cFos (proto-oncogene); ; osteoprotegerin; monoclonal anti C. Pneumoniae antibodies; signal intensity of dendritic cells; third complementarity-determining region size; nogo-B; cluster of differentiation 36; ATP-binding cassette transporter.

§Clinical outcomes included acute coronary syndrome or ischemic symptoms for coronary artery disease and symptomatic carotid disease or stroke/transient ischemic attack for carotid artery disease.

Table 4. Study features of biomarker studies

Study Feature	N (%) *
3. Biomarker studies	36 (100%)
3.1. Coronary artery disease	19 (53%)
3.1.1. Populations Included	
3.1.1.1. Living	19 (100%)
3.1.2. Study Design	
3.1.2.1. Cross-sectional	19 (100%)
3.1.2.2. Longitudinal	0 (0%)
3.1.3. Biomarkers Investigated	
CRP, MMP2, MMP9, t-PA, TnT, ProMMP1, TIMP-1, CD39, oxLDL, S100A8/A9, NT-proBNP, adiponectin, neopterin, CD105	
3.1.4. Outcomes	
3.1.4.1. Clinical †	3 (16%)
3.1.4.2. Histopathological	1 (5.3%)
3.1.4.3. Imaging	15 (79%)
3.1.5. No. patients: median (IQR)	89 (49-172)
3.2. Carotid artery disease	15 (42%)
3.2.1. Disease/Populations Included	
3.2.1.1. Living	15 (100%)
3.2.2. Study Design	
3.2.2.1. Cross-sectional	15 (100%)
3.2.2.2. Longitudinal	0 (0%)
3.2.3. Biomarkers Investigated	
CRP, fibrinogen, C3 complement, HSP70-2 polymorphism, PAPP-A, MMP2, MMP9, Osteopontin, NFkB, D-Dimers, PGE2, PGD2, IGF-I, TIMP-1, PDGF, neopterin, IL-6,-8,-18, multimarker panel	
3.2.4. Outcomes	
3.2.4.1. Clinical †	4 (27%)
3.2.4.2. Histopathological	6 (40%)
3.2.4.3. Imaging	5 (33%)
3.2.5. No. patients: median (IQR)	88 (62-164)
3.3. Participants with no history of cardiovascular disease	2 (5%)
3.3.1. Populations Included	
3.3.1.1. Living	2 (100%)
3.3.2. Study Design	
3.3.2.1. Cross-sectional	2 (100%)
3.3.2.2. Longitudinal	0 (0%)
3.3.3. Biomarkers Investigated	
ApoB/ApoA1; IGF-I, IGF-II, IGFBP-2, IGFBP-3	
3.3.4. Outcomes	
3.3.4.1. Imaging	2 (100%)
3.3.5. No. patients: median (IQR)	518 (NA)

ApoB/ApoA1 = apolipoprotein B/A1; CD105 = cluster of differentiation 105 or endoglin; CD39 = cluster of differentiation 39 or ectonucleoside triphosphate diphosphohydrolase; CRP = C-reactive protein; HSP70-2 = heat-shock protein 70-2; IGF = insulin-like growth factor; IGFBP = insulin-like growth factor binding protein; IL = interleukin; IQR = interquartile range; MMP = matrix metalloproteinases; N = number of abstracts; NFkB = nuclear factor kappa-B; NT-proBNP = N-terminal-proBrain Natriuretic Peptide; oxLDL = oxidized low density lipoprotein; PAPP-A = plasma pregnancy-associated protein A; PDGF = platelet-derived growth factor; PGD2 = prostaglandin D2; PGE2 = prostaglandin E2; ProMMP1 = pro-matrix metalloproteinase 1; S100A8/A9 = calprotectin; TIMP-1 = tissue inhibitor of matrix metalloproteinases; TnT = troponin T; t-PA = tissue plasminogen activator = NA, non-applicable.

*The percentages of coronary artery disease studies (3.1), carotid artery disease studies (3.2), and no cardiovascular disease studies (3.3) have been calculated for all biomarker studies. The remaining percentages have been calculated for coronary artery disease, for carotid artery disease and for studies with patients with no history of cardiovascular disease, separately.

†Clinical outcomes included acute coronary syndrome or ischemic symptoms for coronary artery disease and symptomatic carotid disease or stroke/transient ischemic attack for carotid artery disease

Table 5. Grey literature search results for biomarker tests of potential use in the management of patients with vulnerable plaques

Biomarkers	Company	FDA clearance	FDA clearance for vulnerable plaque	FDA intended use or company indications for use
C-Reactive Protein (Latex) (CRP)	Roche Diagnostics, Inc.	YES	NO	Information from the manufacturer's website is included if no FDA information could be found. FDA: Immunoturbidometric assay for the in vitro quantitative determination of CRP in human serum and plasma on Roche automated clinical chemistry analyzers.
S-Test C-Reactive Protein (CRP)	Alfa Wassermann Diagnostic Technologies, Inc.	YES	NO	FDA: The S-Test C-Reactive Protein Reagent Cartridge is intended for the quantitative determination of C-reactive protein concentration in serum or heparin plasma using the S40 Clinical Analyzer. Measurement of C-reactive protein aids in evaluation of the amount of injury to body tissues. This test is intended for use in clinical laboratories or physician office laboratories. For in <i>vitro</i> diagnostic use only.
Advia Chemistry Cardiophase High Sensitivity C-Reactive ProteinADVIA CHEMISTRY CARDIOPHASE HIGH SENSITIVITY C-REACTIVE PROTEIN (HSCR), Calibrators	Siemens Healthcare Diagnostics, Inc.	YES	NO	FDA: The ADVIA Chemistry CardioPhase™ High Sensitivity C-Reactive Protein assay is for <i>in vitro</i> diagnostic use in the quantitative determination of the concentration of CRP in human serum and plasma (lithium heparin and potassium EDTA) on the ADVIA Chemistry systems. In acute phase response, increased levels of a number of plasma proteins, including CRP, are observed. Measurement of CRP is useful for the detection and evaluation of infection, tissue injury, inflammatory disorders, and associated diseases. High sensitivity CRP (hsCRP) measurements may be used as an independent risk marker for the identification of individuals at risk for future cardiovascular disease. Measurement of hsCRP, when used in conjunction with traditional clinical laboratory evaluation of acute coronary syndromes, may be useful as an independent marker of prognosis for recurrent events in patients with stable coronary disease or acute coronary syndromes. The ADVIA Chemistry CardioPhase™ High Sensitivity C-Reactive Protein Calibrators are for <i>in vitro</i> diagnostic use in the calibration of ADVIA Chemistry systems for the CardioPhase High Sensitivity C-Reactive Protein method.

Table 5. Grey literature search results for biomarker tests of potential use in the management of patients with vulnerable plaques (continued)

Biomarkers	Company	FDA clearance	FDA clearance for vulnerable plaque	FDA intended use or company indications for use Information from the manufacturer's website is included if no FDA information could be found.
Immagine Immunochemistry Systems High Sensitivity Cardiac C-Reactive Protein (CCRP) Reagent	Beckman Coulter, Inc.	YES	NO	FDA: High Sensitivity Cardiac CRP reagent, when used in conjunction with IMMAGE® 800 Immunochemistry Systems and Calibrator 5 Plus, is intended for the quantitative determination of CRP in human serum or plasma by rate turbidimetry. CAL 5 Plus (Calibrator 5 Plus), when used in conjunction with Beckman Coulter reagents, is intended for use on IMMAGE® Immunochemistry Systems for the calibration of Anti-Streptolysin 0 (ASO), CCRP and Rheumatoid Factor (RF).
Nanopia Wide Range C-Reactive Protein (CRP) Reagent Kit	Clinical Data, Inc.	YES	NO	FDA: The Nanopia Wide Range CRP Reagent is intended for the quantitative measurement of CRP concentration in serum or plasma. Measurement of CRP is useful for determining the existence of inflammatory lesions and to monitor treatment. The Nanopia Wide Range CRP Calibrator is intended for the calibration of the Nanopia Wide Range CRP assay. Special condition for use statement(s): For <i>in vitro</i> diagnostic use. Increases in CRP values are non-specific and should not be interpreted without a complete clinical history. Special instrument Requirements: Clinical chemistry analyzers (testing performed on Roche Hitachi 917 analyzer).
Dimension Cardiophase High Sensitivity C-Reactive Protein Calibrator (CRP)	Dade Behring, Inc.	YES	NO	FDA: The Dimension® CCRP Calibrator is an <i>in vitro</i> diagnostic product intended to be used to calibrate the Dimension® <i>CardioPhase</i> ® high sensitivity CRP (Cat. No. RC434) method for the Dimension® clinical chemistry system with the heterogeneous immunoassay module.
Human MMP-9 Elisa (MMP-9)	BioVendor: Laboratorní Medicína, a.s.	NO DATA	NO DATA	The human MMP-9 ELISA is an enzyme-linked immunosorbent assay for the quantitative detection of human MMP-9. The human MMP-9 ELISA is for research use only. Not for diagnostic or therapeutic procedures. http://www.biovendor.com/molecule/mmp-9

Table 5. Grey literature search results for biomarker tests of potential use in the management of patients with vulnerable plaques (continued)

Biomarkers	Company	FDA clearance	FDA clearance for vulnerable plaque	FDA intended use or company indications for use
MMP-9, Human, Biotrak Assay (MMP-9)	GE Healthcare, Inc.	NO DATA	NO DATA	<p>Information from the manufacturer's website is included if no FDA information could be found.</p> <p>Product info from company website: Many normal physiological and pathological processes such as embryogenesis, morphological growth changes, ovulation and pregnancy, wound healing, atherosclerosis, inflammation, tumor invasion, and metastasis involve breakdown and remodeling of the extracellular matrix. This degradation is due to the family of important enzymes known as the matrix metalloproteinases (MMPs).</p> <p>GE Healthcare has a range of Biotrak ELISA kits for the convenient measurement of MMP protein levels in human serum, plasma, and cell culture samples.</p> <p>The Biotrak range also includes MMP Activity Assays, which enable accurate measurement of the amount of active MMP enzyme present in complex biological samples in a convenient, plate-based method that is both sensitive and specific.</p> <p>http://www1.gelifesciences.com/aptrix/upp01077.nsf/Content/Products?OpenDocument&parentid=658500&moduleid=165915&zone</p>
MMP9 Protein (MMP-9)	Abcam, Plc.	NO DATA	NO DATA	<p>Product info from company website: MMP9, also known as gelatinase B, is a secreted enzyme which degrades the interstitial collagens, types I, II, and III and is produced by normal alveolar macrophages and granulocytes. The expression of MMP9 increases in Epstein-Barr virus infected lymphoma derived cell lines and may be of significance in typically invasive nasopharyngeal carcinomas. MMP9 is constitutively produced by some tumor cell lines (e.g.: HT1080, HL60, U937) but not by most quiescent cells and tissues. Treatment of cells with the phorbol ester TPA stimulates production of MMP9 in some cell types, but the low protein levels produced (pg/ml) often require concentration of cell culture media to visualize the bands by Western blotting. All products are "for research use only and are not intended for diagnostic or therapeutic use."</p> <p>http://www.abcam.com/MMP9-protein-ab39309.html</p>

Table 5. Grey literature search results for biomarker tests of potential use in the management of patients with vulnerable plaques (continued)

Biomarkers	Company	FDA clearance	FDA clearance for vulnerable plaque	FDA intended use or company indications for use
MMP-9 Colorimetric Drug Discovery Kit: AK-410 (MMP-9)	EnzoLife Science: Inc.	NO DATA	NO DATA	Information from the manufacturer's website is included if no FDA information could be found. Product info from company website: The <i>MMP-9 Colorimetric Drug Discovery Kit: AK-410</i> is a complete assay system designed to measure protease activity of MMP-9 using a thiopeptide as a chromogenic substrate (Ac-PLG-[2-mercapto-4-methyl-pentanoyl]-LG-OC ₂ H ₅). ^{9,10} The MMP cleavage site peptide bond is replaced by a thioester bond in the thiopeptide. Hydrolysis of this bond by an MMP produces a sulfhydryl group, which reacts with DTNB [5,5'-dithiobis(2-nitrobenzoic acid), Ellman's reagent] to form 2-nitro-5-thiobenzoic acid, which can be detected by its absorbance at 412 nm ($\epsilon = 13,600 \text{ M}^{-1} \text{ cm}^{-1}$ at pH 6.0 and above). ¹¹ The assays are performed in a convenient 96-well microplate format. The kit is useful to screen inhibitors of MMP-9, a potential therapeutic target. An inhibitor, NNGH, ¹² is also included as a prototypic control inhibitor. http://www.biomol.com/SiteData/docs/productdata/ak410.pdf
Human MMP-9 Immunoassay Kit Cat. No. ECM494 (MMP-9)	Chemicon International	NO DATA	NO DATA	Product info from company website: The MMP-9 immunoassay kit is useful for the determination of MMP-9 (pro-MMP-9) levels in fresh human plasma and conditioned medium of human cells. Human serum is not an acceptable sample for evaluation. This system recognizes free pro-MMP-9, intermediate 83 kDa MMP-9, and MMP-9 in complex with TIMP-1 with the same efficiency. The assay does not recognize active MMP-9 (67 kDa). Contents of this kit are sufficient for assay of 100 samples, including standard curve. Testing of samples in duplicate or triplicate is strongly recommended. This kit is intended for research use only; not for diagnostic or therapeutic applications. http://www.millipore.com/publications.nsf/a73664f9f981af8c852569b9005b4eee/2ea0c3ed6ecdcc785257306007241bb/\$FILE/ECM494.pdf
PAPP-A and cPAPP-A (for research only) (PAPP-A)	Diagnostic Systems Laboratories, Inc.	NO DATA	NO DATA	Unable to obtain product information from company website. Diagnostic Systems Laboratories, Inc is a Beckman Coulter company. http://www.dslabs.com/about_us/Default.aspx

Table 5. Grey literature search results for biomarker tests of potential use in the management of patients with vulnerable plaques (continued)

Biomarkers	Company	FDA clearance	FDA clearance for vulnerable plaque	FDA intended use or company indications for use
Maternal Serum Screen, First Trimester (PAPP-A)	Quest Diagnostics, Inc.	NO DATA	NO DATA	<p>Information from the manufacturer's website is included if no FDA information could be found.</p> <p>Product info from company website: This first-trimester maternal serum screening test includes maternal age, pregnancy-associated plasma protein-A (PAPP-A), invasive trophoblast antigen (ITA), and nuchal translucency (NT). PAPP-A is a placental protein generally present in lower concentrations in Down syndrome-affected pregnancies relative to unaffected pregnancies. ITA is a hyperglycosylated form of human chorionic gonadotropin (hCG) that is produced by cytotrophoblasts during embryonic implantation and trophoblast invasion of the uterine wall. Levels tend to be increased in Down syndrome-affected pregnancies. NT is an ultrasonographic measurement of a fluid-filled space at the back of the fetal neck. NT tends to be elevated in cases of fetal aneuploidy. Palomaki and colleagues showed that this screening test is equivalent to the PAPP-A, free-β hCG, and NT combination for Down syndrome screening.</p> <p>http://www.questdiagnostics.com/hcp/topics/geneticstesting/mss_t1.html</p>
Dai PAPP-A Elisa EIA-2397 (PAPP-A)	Diagnostic Automation, Inc.	NO DATA	NO DATA	<p>Product info from company website: The <i>Diagnostic Automation Inc. PAPP-A ELISA</i> is an enzyme immunoassay for the quantitative in vitro diagnostic measurement of Pregnancy associated plasma protein A (PAPP-A) in serum and plasma. In the United States, this kit is intended for Research Use Only. The DAI PAPP-A ELISA EIA-2397 may be used for the risk assessment of Down's syndrome (trisomy 21) in the first trimester of pregnancy. For the risk assessment of trisomy 21 and other fetal aneuploidies PAPP-A should always be measured in combination with other analytes (for example free β-HCG and NT, see above) and a special software for the risk assessment of trisomy 21. According to the IVD Directive (98/79/EC) both software and kits for the additional analytes must be suitable for trisomy 21 screening and CE-certified by a notified body, indicated by the identification number of the notified body on the CE-mark on software and kits.</p> <p>http://www.rapidtest.com/ELISA%20Inserts%202009%20052209/PAPP-A_4229-6.pdf</p>

Table 5. Grey literature search results for biomarker tests of potential use in the management of patients with vulnerable plaques (continued)

Biomarkers	Company	FDA clearance	FDA clearance for vulnerable plaque	FDA intended use or company indications for use
PAPP-A Elisa (PAPP-A)	Alpco Diagnostics	NO DATA	NO DATA	<p>Information from the manufacturer's website is included if no FDA information could be found.</p> <p>Product info from company website: The <i>PAPP-A ELISA</i> is a solid phase enzyme-linked immunosorbent assay (ELISA) based on the sandwich principle. The microtiter wells are coated with a polyclonal anti PAPP-A antibody. An Aliquot of sample containing endogenous PAPP-A is incubated in the coated well with sample buffer. After incubation the unbound material is washed off. In the second incubation step a sandwich complex is formed with anti PAPP-A antibody peroxidase conjugate. Having added the substrate solution, the intensity of color developed is proportional to the concentration of PAPP-A in the sample.</p> <p>http://www.alpco.com/pdfs/38/38-PAPHU-E01.pdf</p>

CRP = C-reactive protein; MMP-9 = matrix-metalloproteinase; PAPP-A = pregnancy-associated plasma protein A.

Table 6. Grey literature search results for imaging devices of potential use in the management of patients with vulnerable plaques

Company	Test modality	Test name	Indications per company literature	FDA clearance	FDA clearance for vulnerable plaque
Volcano, Inc,	Intravascular ultrasound-virtual histology (IVUS)	Eagle Eye Gold IVUS Imaging Catheter	Intravascular Ultrasound (IVUS) is a catheter based system that allows physicians to acquire images of diseased vessels from inside the artery. IVUS provides detailed and accurate measurements of lumen and vessel size, plaque area and volume, and the location of key anatomical landmarks. Volcano's proprietary VH™ IVUS technology helps differentiate the four plaque types: fibrous, fibro-fatty, necrotic core and dense calcium.	To provide an image of the vessel lumen and wall structures	NO
Volcano, Inc,	Intravascular ultrasound-virtual histology (IVUS)	Revolution 45MHZ IVUS Imaging Catheter	Intravascular Ultrasound (IVUS) is a catheter based system that allows physicians to acquire images of diseased vessels from inside the artery. IVUS provides detailed and accurate measurements of lumen and vessel size, plaque area and volume, and the location of key anatomical landmarks. Volcano's proprietary VH™ IVUS technology helps differentiate the four plaque types: fibrous, fibro-fatty, necrotic core and dense calcium.	For the IVUS examination of coronary arteries	NO
Volcano, Inc,	Intravascular ultrasound-virtual histology (IVUS)	Visions PV 8.2 IVUS Imaging Catheter	Intravascular Ultrasound (IVUS) is a catheter based system that allows physicians to acquire images of diseased vessels from inside the artery. IVUS provides detailed and accurate measurements of lumen and vessel size, plaque area and volume, and the location of key anatomical landmarks. Volcano's proprietary VH™ IVUS technology helps differentiate the four plaque types: fibrous, fibro-fatty, necrotic core and dense calcium.	To provide an image of the vessel lumen and wall structures	NO

Table 6. Grey literature search results for imaging devices of potential use in the management of patients with vulnerable plaques (continued)

Company	Test modality	Test name	Indications per company literature	FDA clearance	FDA clearance for vulnerable plaque
Boston Scientific, Inc.	Intravascular ultrasound-virtual histology (IVUS)	iLab [®] System	Provides full cross-section IVUS images alone or in combination with a LongView™ Image Facilitates measurement of lesion length on LongView Image. Automatically determines vessel and lumen borders, which gives plaque burden and percent area stenosis measurement for clinical decision making	Intended for ultrasound examinations of intravascular pathology	NO
Boston Scientific, Inc.	Intravascular ultrasound-virtual histology (IVUS)	Atlantis [®] SR Pro Imaging Catheter	40 MHz catheter provides excellent image resolution and clarity. Redesigned transducer housing and drive shaft for more uniform imaging core rotation. Larger imaging window clearance to decrease friction in tortuous anatomy. Improved tip design (in-line vs. side port flush) provides increased kink resistance. 6F guide catheter compatibility ($\geq .064$ ") for convenience and ease of use. Tapered tip with .022 entry profile. Naturally compatible with all Boston Scientific IVUS imaging systems.	Intended for ultrasound examination of coronary intravascular pathology only	NO

Table 6. Grey literature search results for imaging devices of potential use in the management of patients with vulnerable plaques (continued)

Company	Test modality	Test name	Indications per company literature	FDA clearance	FDA clearance for vulnerable plaque
InfraReDx	Near-Infrared spectroscopy	Infraredx NIR Imaging System and Infraredx NIR Imaging System MC-5	<p>The LipiScan Coronary Imaging System utilizes advanced optical technology, much of it developed for telecom uses, to deliver and retrieve NIR light from coronary plaques. The light reflected back at different wavelengths is analyzed to detect the chemical composition of the coronary plaques. At the completion of the catheter pullback, the LipiScan console instantly displays the scan results on a “chemogram”, a digital color-coded map of the location and intensity of lipid core containing plaques of interest in the artery. A Lipid Core Burden Index is also reported, which is a measure of the total amount of lipid core containing plaques of interest in the coronary artery. The LipiScan catheter interrogates each artery in less than 2 minutes and does not require the interruption of the flow of blood.</p> <p>Near Infrared (NIR) diffuse spectroscopy is a technique based on the absorption of light in the NIR spectrum, in a specific manner, by organic molecules. NIR spectroscopy has demonstrated the ability to identify plaques with lipid pools through blood in our laboratories. Clinical research studies are underway to determine the ability of the InfraReDx system to determine the chemical composition of plaques in patients undergoing cardiac catheterization.</p>	Lipid-core containing plaques	NO

Table 6. Grey literature search results for imaging devices of potential use in the management of patients with vulnerable plaques (continued)

Company	Test modality	Test name	Indications per company literature	FDA clearance	FDA clearance for vulnerable plaque
Toshiba America Medical Systems	320-multidetector computed tomography	Aquilion ONE TSX-301A and Aquilion ONE TSX-301A.2	The Aquilion ONE has a coverage area of 320 detector rows, can capture actual organ movement (like blood flowing through the heart) and can image an entire organ in one gantry rotation. Additionally, the Aquilion ONE can capture the heart in one heart beat. Toshiba's Aquilion ONE dynamic volume CT system utilizes 320 ultra-high resolution detector rows (0.5 mm in width) to image an entire organ in a single gantry rotation. The result is unparalleled in diagnostic imaging today and produces a 4D clinical video showing up to 16 cm of anatomical coverage, enough to capture the entire brain or heart, and show its movement such as blood flow.	Device is indicated to acquire and display cross sectional volumes of the whole body	NO
Nihon Kohden	Angioscope	Angioscope MC-800 E	Unable to access product information on company website. Company website does not provide product/device info.	NO DATA	NO DATA
Renishaw	Raman Spectroscopy	Invia Raman and AFM Raman and SEM Raman and FT-1R Raman	Renishaw manufactures a wide range of optical spectroscopy products, including: Raman microscopes, compact process monitoring Raman spectrometers, Raman analyzers for scanning electron microscopes, lasers for spectroscopy, and state-of-the-art cooled CCD detectors. The Renishaw Raman systems exploit the Raman effect to identify and characterize the chemistry and structure of materials in a non-contacting, non-destructive manner.	NO DATA	NO DATA

Table 6. Grey literature search results for imaging devices of potential use in the management of patients with vulnerable plaques (continued)

Company	Test modality	Test name	Indications per company literature	FDA clearance	FDA clearance for vulnerable plaque
Kaiser Optical Systems, Inc.	Raman Spectroscopy	RAMANRXN Systems™	The RAMANRXN Systems™ family of Raman analyzers are the instruments of choice for Raman spectroscopy, both in the laboratory and on the process line. All of Kaiser's Raman systems use the same spectrograph and probe head technology, allowing for easy transfer of protocol from the laboratory to the pilot plant to the production environment. Kaiser's RAMANRXN SYSTEMS™ family represents the state of the art in Raman spectroscopic analyzers.	NO DATA	NO DATA
Hitachi Medical Systems, Inc.	Spectroscopy and Magnetic Resonance Imaging (MRI)	Echelon Package: Neuro imaging, Spectroscopy, Contrast-enhanced angiography, Cardiac imaging	Echelon is a fully featured high-field performance MRI, incorporating powerful imaging tools to meet your current and future demands. Its core is a high- performance, short-bore, super-conductive magnet with high homogeneity and low cryogenic boil-off.	Provides information based on relative concentrations of metabolites in body tissues	NO
GE Medical Systems, Inc.	Spectroscopy	Hydrogen Spectroscopy Option-probe #M104	Unable to access product information on company website. Company website does not provide product/device info.	FDA: Statement/Summary/Purged Status: purged 510(k)	NO
Philips Medical Systems, Inc.	Nuclear magnetic resonance spectroscopic system	MR Spectroscopy Package	The package includes an option supporting diffusion, perfusion, and functional brain imaging, which can help in the early detection of stroke. On the cardiac side, the package enables a Gyroscan NT site to conduct cardiac MRI without purchasing additional hardware. One feature of the package, MotionTrak, enables users to control motion artifacts through gating and slice tracking. Other features of the new package include advancements in MR angiography, MR spectroscopy, and coil technology.	Provides information based on relative concentrations of metabolites in body tissues	NO

Table 6. Grey literature search results for imaging devices of potential use in the management of patients with vulnerable plaques (continued)

Company	Test modality	Test name	Indications per company literature	FDA clearance	FDA clearance for vulnerable plaque
VP Diagnostics, Inc	Magnetic Resonance Imaging (MRI)	MRI-Plaque View, Version 1.1.2003	The MRI Plaque View software provides a set of post-processing tools to assist trained cardiologists and radiologists in the quantitative analysis of atherosclerotic carotid arteries from 1.5 T or 3.0 T MRI studies acquired with a combination of one or more contrast weightings such as T1, T2, Proton Density, and Time of Flight. Users of MRI-Plaque View perform semi-automatic delineation of lumen, and outer vessel wall boundaries, and also perform semi-automatic, user configurable segmentation or manual drawing for delineation of atherosclerotic plaque components within the vessel wall.	Delineation of atherosclerotic plaque components within the vessel wall	NO
Siemens Medical Solutions, Inc.	Spectroscopy	MAGNETOM Vision Family: Concerto Trio Sonata Harmony, etc.	The MAGNETOM VISION is a magnetic resonance imaging and spectroscopy system which uses time-varying magnetic field gradients and rf energy to spacially encode the anatomy of a patient	Analysis of energy metabolites in muscle, liver and heart tissue.	NO
Prescient Medical, Inc, Doylestown, PA	(stent not a test)	vProtect™ Luminal Shield	The vProtect™ Luminal Shield is designed to treat soft, atherosclerotic lesions that may be at risk of rupture, or recently ruptured. Using a unique and proprietary platform, we plan to bring a series of products to market with a focus on plaque stabilization and intravascular healing. Today, current practices and available technologies for the treatment of coronary artery disease are solely focused on improving luminal diameter and the restoration of blood flow. We believe these devices are not well suited for the treatment of non-calcified or vulnerable plaques. The company goal is to provide interventional cardiologists with treatment devices designed to address different plaque types. We believe that our products will finally enable cardiologists to more accurately treat patients at risk and, for the first time, treat the cause of heart attacks before they occur.	NO DATA	NO DATA

Table 6. Grey literature search results for imaging devices of potential use in the management of patients with vulnerable plaques (continued)

Company	Test modality	Test name	Indications per company literature	FDA clearance	FDA clearance for vulnerable plaque
Prescient Medical, Inc, Doylestown, P	Optical Catheter	vPredict™ Optical Catheter	The vPredict™ Optical Catheter System is being designed to rapidly analyze materials within arterial walls during a procedure referred to as an Optiography™ Scan. Using advanced optical analysis techniques, the system is intended to detect and display the chemical composition of atherosclerotic plaques. The company goal is to provide interventional cardiologists with the real-time critical information they currently lack regarding atherosclerotic plaque – its precise chemical composition.	NO DATA	NO DATA
Goodman, Co. LightLab Imaging	Optical coherence tomography	LightLab M2x OCT <i>(This company does not currently sell products in the USA)</i>	LightLab Imaging, Inc., is the pioneer in the development of Optical Coherence Tomography (OCT). OCT is a high-resolution imaging modality that applies advanced photonics to medical imaging applications. With the ability to resolve real-time images to 15 micrometers, the LightLab Imaging OCT Imaging Systems offer physicians more information, and more precise information, than ever before available	NO DATA	NO DATA

Table 7. Grey literature search results for therapeutic options of potential use in the management of patients with vulnerable plaques

Treatment	Company	FDA clearance	FDA clearance for vulnerable plaque	Company indications and use
Lipitor Active Ingredient: Atorvastatin calcium	Pfizer	FDA Application No. (NDA): 020702 Original Approval Date: December 17, 1996	NO	<p>LIPITOR is an inhibitor of HMG-CoA reductase (statin) indicated as adjunct therapy to diet to:</p> <ul style="list-style-type: none"> • Reduce the risk of MI, stroke, revascularization procedures, and angina in patients without CHD, but with multiple risk factors. • Reduce the risk of MI and stroke in patients with type 2 diabetes without a higher incidence of hemorrhagic stroke was seen in patients without CHD, but with multiple risk factors. • Reduce the risk of non-fatal MI, fatal and non-fatal stroke, revascularization procedures, hospitalization for CHF, and angina in patients with CHD. • Reduce elevated total-C, LDL-C, apo B, and TG levels and increase HDL-C in adult patients with primary hyperlipidemia (heterozygous familial and nonfamilial) and mixed dyslipidemia. • Reduce elevated TG in patients with hypertriglyceridemia and primary dysbetalipoproteinemia. <p>Reduce total-C and LDL-C and apo B levels in boys and postmenarchal girls, 10 to 17 years of age, with heterozygous familial hypercholesterolemia after failing an adequate trial of diet therapy.</p>

Table 7. Grey literature search results for therapeutic options of potential use in the management of patients with vulnerable plaques (continued)

Treatment	Company	FDA clearance	FDA clearance for vulnerable plaque	Company indications and use Information from the manufacturer's website is included if no FDA information could be found
Pravachol Active Ingredient: Pravastatin sodium	Bristol Myers Squibb	FDA Application No. (NDA): 019898 Original Approval Date: October 31, 1991	NO	<p>Therapy with PRAVACHOL (pravastatin sodium) should be considered in those individuals at increased risk for atherosclerosis-related clinical events as a function of cholesterol level, the presence or absence of CHD, and other risk factors.</p> <ul style="list-style-type: none"> • Primary Prevention of Coronary Events In hypercholesterolemic patients without clinically evident CHD, PRAVACHOL is indicated to: <ul style="list-style-type: none"> – Reduce the risk of MI – Reduce the risk of undergoing myocardial revascularization procedures – Reduce the risk of cardiovascular mortality with no increase in death from noncardiovascular causes. • Secondary Prevention of Cardiovascular Events In patients with clinically evident CHD, PRAVACHOL is indicated to: <ul style="list-style-type: none"> – Reduce the risk of total mortality by reducing coronary death – Reduce the risk of MI – Reduce the risk of undergoing myocardial revascularization procedures – Reduce the risk of stroke and stroke/transient ischemic attack – Slow the progression of coronary atherosclerosis. • Hyperlipidemia PRAVACHOL is indicated as an adjunct to diet to reduce elevated Total-C, LDL-C, ApoB, and TG levels and to increase HDL-C in patients with primary hypercholesterolemia and mixed dyslipidemia (Fredrickson Type IIa and IIb). PRAVACHOL is indicated as adjunctive therapy to diet for the treatment of patients with elevated serum triglyceride levels (Fredrickson Type IV). PRAVACHOL is indicated for the treatment of patients with primary dysbetalipoproteinemia (Fredrickson Type III) who do not respond adequately to diet.
Darapladib selective Lp-PLA ₂ (lipoprotein-associated phospholipase A ₂) inhibitor	GlaxoSmith Kline	NO DATA	NO DATA	<p>Product info from company website: Results of the Integrated Biomarkers and Imaging Study-2 (IBIS-2) demonstrated that darapladib:</p> <ul style="list-style-type: none"> – Prevented expansion of the necrotic core in human coronary plaques, potentially reducing the risk of plaque rupture and subsequent cardiovascular events – Inhibited activity of plasma Lp-PLA₂, an emerging risk factor for cardiovascular events

MI = myocardial infarction; CHD = coronary heart disease, CHF = chronic heart failure, TG = triglycerides; LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol.

Table 8. Study features of imaging studies

Study Feature	N (%) *
4. Imaging studies	120 (100%)
4.1. Coronary artery disease	52 (43%)
4.1.1. Populations Included	
4.1.1.1. Living	41 (79%)
4.1.1.2. Tissue sample from living person	1 (1.9%)
4.1.1.3. Autopsy	10 (19%)
4.1.2. Study design	
4.1.2.1. Cross-sectional	45 (87%)
4.1.2.2. Longitudinal	7 (13%)
4.1.2.2.1. Prospective	6 (12%)
4.1.2.2.2. Retrospective	1 (1.9%)
4.1.3. Imaging modalities used	
4.1.3.1. Angiography	3 (5.8%)
4.1.3.2. Angioscopy	5 (9.6%)
4.1.3.3. Intravascular ultrasonography	17 (33%)
4.1.3.4. Multi-detector computed tomography	13 (25%)
4.1.3.5. Magnetic resonance imaging	2 (3.8%)
4.1.3.6. Optical coherence tomography	6 (11%)
4.1.3.7. Other	6 (11%)
Intrinsic fluorescence and diffuse reflectance spectroscopy, multiphoton microscopy, dual source CT, flat-panel volumetric CT, thermography, elastography	
4.1.4. Imaging feature detected	
4.1.4.1. Combination of features	20 (38%)
4.1.4.2. Single features	
4.1.4.2.1. Calcification	3 (5.8%)
4.1.4.2.2. Cap thickness	4 (7.7%)
4.1.4.2.3. Lipid core	3 (5.8%)
4.1.4.2.4. Vessel remodeling	2 (3.8%)
4.1.4.2.5. Plaque density	3 (5.8%)
4.1.4.2.6. Yellow color	5 (9.6%)
4.1.4.2.7. Other	11 (21%)
Vulnerable plaque (not defined), stress-based computational plaque vulnerability index, distance from ostium and plaque composition, macrophage infiltration, superficial foam cells in atheromas and intimal thickening, cross-sectional compliance, plaque echolucency, plaque temperature, ulceration-complex lesion, elasticity imaging, vasa vasorum	
4.1.5. Outcomes	
4.1.5.1. Clinical †	19 (37%)
4.1.5.2. Histopathological	13 (25%)
4.1.5.3. Imaging	19 (37%)
4.1.5.4. Descriptive studies (no outcome)	1 (1.9%)
4.1.6. No. patients: median (IQR)	58 (30-140)
4.1.7. No. lesions: median (IQR)	50 (31-132)
4.2. Carotid artery disease	68 (57%)
4.2.1. Populations included	
4.2.1.1. Living	46 (68%)
4.2.1.2. Tissue sample from living person	22 (32%)
4.2.2. Study Design	
4.2.2.1. Cross-sectional	62 (91%)
4.2.2.2. Longitudinal	6 (8.8%)
4.2.2.2.1. Prospective	5 (7.4%)
4.2.2.2.2. Retrospective	1 (1.5%)

Table 8. Study features of imaging studies (continued)

Study Feature	N (%) *
4.2.3. Imaging Modalities Used	
4.2.3.1. Magnetic resonance imaging	31 (46%)
4.2.3.2. Carotid ultrasonography	16 (24%)
4.2.3.3. Multi-detector computed tomography	6 (8.8%)
4.2.3.4. Intravascular ultrasonography	4 (5.9%)
4.2.3.5. Elastography	2 (2.9%)
4.2.3.6. Other	8 (11.8%)
	Single photon emission computed tomography, positron emission tomography, fluorescence spectroscopy, combination of computed tomography angiography and black blood magnetic resonance imaging, near-infrared spectroscopy, optical coherence tomography, Raman spectroscopy, angiography
4.2.4. Imaging feature detected	
4.2.4.1. Combination of features	18 (26%)
4.2.4.2. Single features	
4.2.4.2.1. Plaque echolucency	8 (12%)
4.2.4.2.2. Ulceration-complex lesion	8 (12%)
4.2.4.2.3. Intraplaque hemorrhage	6 (8.8%)
4.2.4.2.4. Lipid core	3 (4.4%)
4.2.4.2.5. Plaque density	3 (4.4%)
4.2.4.2.6. Other	23 (34%)
	Cap thickness, elasticity imaging, vasa vasorum, vulnerable plaque (not defined), annexin A5 uptake, macrophage infiltration (detected by [18]-fluorodeoxyglucose uptake positron emission tomography, tissue pH, plaque collagen, shear stress and plaque composition, inflammation/macrophages with ultra small superparamagnetic particles of iron oxide, superficial foam cells in atheromas and intimal thickening, histologic state of fibrous cap
4.2.5. Outcomes	
4.2.5.1. Clinical †	18 (26%)
4.2.5.2. Histopathological	31 (46%)
4.2.5.3. Imaging	9 (13%)
4.2.5.4. Descriptive studies (no outcome)	10 (15%)
4.2.6. No. patients: median (IQR)	39 (18-92)
4.2.7. No. lesions: median (IQR)	45 (12-206)

IQR = interquartile range; N = number of abstracts.

*The percentages of coronary artery disease studies (4.1) and carotid artery disease studies (4.2) have been calculated for all histopathology studies, The remaining percentages have been calculated for coronary and carotid artery disease separately.
 †Clinical outcomes included acute coronary syndrome, ischemic symptoms or composite outcomes for coronary artery disease and symptomatic carotid disease or stroke/transient ischemic attack for carotid artery disease.

Table 9. Study features of treatment studies

Study Feature	N (%) *
5. Treatment studies	17 (100%)
5.1. Coronary artery disease	5 (29%)
5.1.1. Populations Included	
5.1.1.1. Living	4 (80%)
5.1.1.2. Tissue sample from living person	1 (20%)
5.1.2. Study design	
5.1.2.1. Cross-sectional	1 (20%)
5.1.2.2. Longitudinal	4 (80%)
5.1.2.2.1. Prospective	4 (80%)
5.1.2.2.2. Retrospective	0 (0%)
5.1.3. Treatments examined	
5.1.3.1. Statins	4 (80%)
5.1.3.2. Darapladib	1 (20%)
5.1.4. Outcomes	
5.1.4.1. Histopathological	1 (20%)
5.1.4.2. Imaging	4 (80%)
5.1.5. No. patients: median (IQR)	48 (4-75)
5.2. Carotid artery disease	9 (53%)
5.2.1. Populations Included	
5.2.1.1. Living	6 (67%)
5.2.1.2. Tissue sample from living person	3 (33%)
5.2.2. Study design	
5.2.2.1. Cross-sectional	3 (33%)
5.2.2.2. Longitudinal	6 (67%)
5.2.2.2.1. Prospective	6 (67%)
5.2.2.2.2. Retrospective	0 (0%)
5.2.3. Treatments examined	
5.2.3.1. Statins	6 (67%)
5.2.3.2. Rosiglitazone	1 (11%)
5.2.3.3. n-3 PUFA	1 (11%)
5.2.3.4. multiple risk factor intervention	1 (11%)
5.2.4. Outcomes	
5.2.4.1. Histopathological	2 (22%)
5.2.4.2. Imaging	5 (56%)
5.2.4.3. Clinical†	3 (33%)
5.2.5. No. patients: median (IQR)	78 (47-97)
5.3. Both carotid and coronary artery disease	3 (18%)
5.3.1. Populations Included	
5.3.1.1. Living	3 (100%)
5.3.2. Study design	
5.3.2.1. Longitudinal	3 (100%)
5.3.2.1.1. Prospective	3 (100%)
5.3.2.1.2. Retrospective	0 (0%)
5.3.3. Treatments examined	
5.3.3.1. Statins	2 (67%)
5.3.3.2. Pioglitazone	1 (33%)
5.3.4. Outcomes	
5.3.4.1. Imaging	3 (100%)
5.3.5. No. patients: median (range)	61 (60-65)

IQR = interquartile range; N = number of abstracts.

*The percentages of coronary artery disease studies (5.1), carotid artery disease studies (5.2) and both carotid and coronary artery disease have been calculated for all histopathology studies. The remaining percentages have been calculated for each type of disease separately.

†Clinical outcomes included composite outcome and stroke/transient ischemic attack for carotid artery disease.

Table 10. ClinicalTrials.gov search results for trials related to vulnerable plaque*

ClinicalTrials.gov Identifier	Title	Recruitment	Conditions	Study Types	Interventions or Predictors used	Enrollment	Study Designs
NCT00172419	The Effects of Atorvastatin on Vulnerable Plaques in Untreated Dyslipidemic Patients.	Completed	Coronary Artery Disease	Interventional	Atorvastatin	43	Treatment Open Label Uncontrolled Single Group Assignment Efficacy Study
NCT00173927	Images in Extracranial Artery Stenosis	Recruiting	Carotid Artery Disease	Observational	PET/MRI fusion imaging	100	Prospective
NCT00214006	Carotid Atherosclerotic Plaque Study	Recruiting	Carotid Artery Disease	Observational	US elastography, MRI, trans-cranial doppler	200	Case-Only Prospective
NCT00330928	SPECTACL: SPECTroscopic Assessment of Coronary Lipid	Completed	Coronary Artery Disease	Interventional	NIRS, IVUS	106	Diagnostic Non-Randomized Open Label Uncontrolled Single Group Assignment Efficacy Study
NCT00388843	Carotid Plaque Regression With Statin Treatment Assessed by High Field Magnetic Resonance Imaging (MRI)	Recruiting	Carotid Atherosclerosis	Observational	3 Tesla MRI	52	Cohort Prospective
NCT00416065	PET/CT to Identify "Vulnerable" Arterial Plaque	Recruiting	Coronary Artery Disease	Interventional	PET, CT	800	Randomized Open Label Uncontrolled Single Group Assignment
NCT00451529	Predictive Value for Stroke	Recruiting	Carotid Artery Disease	Observational	MRI, FDG-PET	200	Cohort Prospective
NCT00456950	Magnetic Resonance Imaging of the Coronary Vessel Wall	Completed	Coronary Artery Disease	Observational	MRI, IVUS	75	Cohort Prospective

Table 10. ClinicalTrials.gov search results for trials related to vulnerable plaque* (continued)

ClinicalTrials.gov Identifier	Title	Recruitment	Conditions	Study Types	Interventions or Predictors used	Enrollment	Study Designs
NCT00466050	Correlation Between Serum Markers of Unstable Plaque and Virtual Histology of Unstable Plaque Visualized by IVUS	Completed	Coronary Artery Disease	Observational	IVUS	30	Case-Only Prospective
NCT00482651	Imaging of Vulnerable Plaques in Coronary Artery Disease by Multidetector Computed Tomography	Recruiting	Coronary Artery Disease	Interventional	MDCT	80	Diagnostic Non-Randomized Open Label Uncontrolled Single Group Assignment
NCT00540761	Identifying Vulnerable Plaques in Blood Vessels of the Heart Using a New Imaging Technique	Recruiting	Coronary Arteriosclerosis	Observational	OFDI	100	Cohort Prospective
NCT00576576	Evaluation of Atorvastatin on Atherosclerosis Composition	Recruiting	Coronary Artery Disease	Interventional	Atorvastatin	20	Treatment Non-Randomized Open Label Single Group Assignment Efficacy Study
NCT00636766	Diagnosis and Therapy of Vulnerable Atherosclerotic Plaque	Completed	Carotid Artery Disease	Interventional	atorvastatin, rimonabant, rosiglitazone, metformin	300	Other Randomized Open Label Active Control Factorial Assignment Efficacy Study
NCT00738725	BioImage Study: A Clinical Study of Burden of Atherosclerotic Disease in an At-Risk Population	Active, not recruiting	Both	Observational	Non-Invasive Imaging Modalities	7300	Cohort Prospective

Table 10. ClinicalTrials.gov search results for trials related to vulnerable plaque* (continued)

ClinicalTrials.gov Identifier	Title	Recruitment	Conditions	Study Types	Interventions or Predictors used	Enrollment	Study Designs
NCT00798122	Study of Women With Acute Coronary Syndromes and Nonobstructive Coronary Artery Disease	Recruiting	Coronary Artery Disease	Interventional	IVUS, MRI		Diagnostic Single Group Assignment
NCT00799903	The Stabilization of Atherosclerotic Plaque by Initiation of Darapladib Therapy Trial	Recruiting	Coronary Artery Disease	Interventional	Darapladib	15500	Treatment Randomized Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor) Parallel Assignment Safety/Efficacy Study
NCT00822302	Trial to Evaluate the Ability of a Single Infusion of High-Density Lipoprotein (HDL) to Modulate Markers of Cerebral Ischaemia	Active, not recruiting	Carotid Artery Disease	Interventional	Reconstituted HDL	40	Basic Science Randomized Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor) Placebo Control Parallel Assignment
NCT00905671	Intravascular Near Infrared Spectroscopy (NIRS) Bifurcation - Lipid Core Plaque Shift Study	Recruiting	Coronary Artery Disease	Interventional	LipiScan Coronary Imaging Catheter	20	Basic Science Non-Randomized Open Label Single Group Assignment
NCT00962416	Comparison of Biomatrix Versus Gazelle in ST-Elevation Myocardial Infarction (STEMI)	Recruiting	Coronary Artery Disease	Interventional	Biolimus eluted from an erodable stent coating (Biomatrix)	1100	Treatment Randomized Single Blind (Outcomes Assessor) Parallel Assignment Safety/Efficacy Study

Table 10. ClinicalTrials.gov search results for trials related to vulnerable plaque* (continued)

ClinicalTrials.gov Identifier	Title	Recruitment	Conditions	Study Types	Interventions or Predictors used	Enrollment	Study Designs
NCT00965185	Statin Therapy to Improve Atherosclerosis in HIV Patients	Not yet recruiting	Coronary Artery Disease	Interventional	Atorvastatin	40	Treatment Randomized Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor) Placebo Control Parallel Assignment Efficacy Study
NCT00984776	Detection of Coronary Vulnerable Plaque With Contrast-enhanced Magnetic Resonance Imaging	Completed	Coronary Artery Disease	Interventional	Contrast enhanced MRI with Gadofosveset	20	Diagnostic
NCT00991835	Plaque Registration and Event Detection In Computed Tomography	Recruiting	Coronary Artery Disease	Observational	MDCT	6000	Cohort Prospective
NCT01000181	Imaging 61CuATSM Uptake in Atherosclerotic Plaque Using PET-CT	Not yet recruiting	Carotid Artery Disease	Observational	PET-CT with CuATSM	10	Case-Only Prospective
NCT01000701	Inflammation and Acute Coronary Syndromes	Recruiting	Coronary Artery Disease	Observational	IVUS, OCT	2400	Cohort Prospective
NCT01000727	The Stabilization Of pLaques uslng Darapladib-Thrombolysis In Myocardial Infarction 52 Trial	Recruiting	Coronary Artery Disease	Interventional	Darapladib	11500	Treatment Randomized Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor) Parallel Assignment Safety/Efficacy Study

Table 10. ClinicalTrials.gov search results for trials related to vulnerable plaque* (continued)

ClinicalTrials.gov Identifier	Title	Recruitment	Conditions	Study Types	Interventions or Predictors used	Enrollment	Study Designs
NCT01023607	Evaluation of Statin-induced Lipid-rich Plaque Progression by Optical Coherence Tomography (OCT) Combined With Intravascular Ultrasound (IVUS)	Recruiting	Coronary Artery Disease	Interventional	Atorvastatin, Rosuvastatin	120	Treatment Randomized Single Blind (Outcomes Assessor) Active Control Single Group Assignment Safety/Efficacy Study
NCT01024179	Relationship Between Initial Plaque Characteristics and Stent Surface Coverage Patterns	Recruiting	Coronary Artery Disease	Interventional	Polymer-based sirolimus-eluting stent (Partner stent)	90	Treatment Non-Randomized Open Label Uncontrolled Single Group Assignment Safety/Efficacy Study
NCT00180466	PROSPECT: An Imaging Study in Patients With Unstable Atherosclerotic Lesions	Active, not recruiting	Coronary Artery Disease	Observational	IVUS	697	Other Prospective
NCT00860184	SmartRisk Stroke Prediction by MRI of Carotid Disease	Recruiting	Carotid Artery Disease	Observational	MRI	300	Cohort Prospective

*Search results as of 02/10/2010.

Abbreviations: US = ultrasonography; IVUS = intravascular ultrasonography; MDCT = multi-detector computed tomography, MRI = Magnetic resonance imaging, OCT = optical coherence tomography, PET = positron emission tomography; CuATSM = diacetyl-bis(N4-methylthiosemicarbazone); HDL = high density lipoprotein; OFDI = optical frequency-domain imaging; FDG = fluorodeoxyglucose; CT = computed tomography; NIRS = Near-infrared spectroscopy

References

1. Heart Disease and Stroke Statistics—2009 Update (All Charts) American Heart Association. Available at: <http://www.americanheart.org/presenter.jhtml?identifier=3018163>. Accessed August 17, 2009.
2. World Health Organization, Cardiovascular Diseases Fact Sheet. Available at: <http://www.who.int/mediacentre/factsheets/fs317/en/print.html>. Accessed August 17, 2009.
3. Cannon CP, Braunwald E, McCabe CH, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med* 2004;350:1495-1504.
4. Vulnerable Plaques. A Brief Review of the Concept and Proposed Approaches to Diagnosis and Treatment. Technology Assessment. January 2004. Rockville, MD: Agency for Healthcare Research and Quality. Available at: <http://www.ahrq.gov/clinic/ta/plaque/>.
5. Fourth International Conference on Grey Literature, Washington DC. 1999.
6. Waxman S, Ishibashi F, Muller JE. Detection and treatment of vulnerable plaques and vulnerable patients: novel approaches to prevention of coronary events. *Circulation* 2006;114:2390-2411.
7. US Food and Drug Administration Premarket Notifications (510(k)s) Database. Available at: <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm>. 2009.
8. Drugs@FDA Database. Available at: <http://www.accessdata.fda.gov/scripts/cder/DrugsatFDA/>. 2009.
9. Muller JE, Tofler GH, Stone PH. Circadian variation and triggers of onset of acute cardiovascular disease. *Circulation* 1989;79:733-743.
10. Ambrose JA, Winters SL, Arora RR, et al. Angiographic evolution of coronary artery morphology in unstable angina. *J Am Coll Cardiol* 1986;7:472-478.
11. Little WC, Constantinescu M, Applegate RJ, et al. Can coronary angiography predict the site of a subsequent myocardial infarction in patients with mild-to-moderate coronary artery disease? *Circulation* 1988;78:1157-1166.
12. Hackett D, Davies G, Maseri A. Pre-existing coronary stenoses in patients with first myocardial infarction are not necessarily severe. *Eur Heart J* 1988;9:1317-1323.
13. Giroud D, Li JM, Urban P, et al. Relation of the site of acute myocardial infarction to the most severe coronary arterial stenosis at prior angiography. *Am J Cardiol* 1992;69:729-732.
14. Naqvi TZ, Hachamovitch R, Berman D, et al. Does the presence and site of myocardial ischemia on perfusion scintigraphy predict the occurrence and site of future myocardial infarction in patients with stable coronary artery disease? *Am J Cardiol* 1997;79:1521-1524.
15. Kolodgie FD, Virmani R, Burke AP, et al. Pathologic assessment of the vulnerable human coronary plaque. *Heart* 2004;90:1385-1391.
16. Narula J, Garg P, Achenbach S, et al. Arithmetic of vulnerable plaques for noninvasive imaging. *Nature Clinical Practice Cardiovascular Medicine* 2008;5(Suppl-10).
17. Virmani R, Burke AP, Farb A, et al. Pathology of the vulnerable plaque. *J Am Coll Cardiol* 2006;47:C13-C18.
18. Naghavi M, Libby P, Falk E, et al. From vulnerable plaque to vulnerable patient: a call for new definitions and risk assessment strategies: Part I. *Circulation* 2003;108:1664-1672.
19. Virmani R, Kolodgie FD, Burke AP, et al. Lessons from sudden coronary death: a comprehensive morphological classification scheme for atherosclerotic lesions. *Arterioscler Thromb Vasc Biol* 2000;20:1262-1275.
20. Kolodgie FD, Virmani R, Burke AP, et al. Pathologic assessment of the vulnerable human coronary plaque. *Heart* 2004;90:1385-1391.

21. Motoyama S, Sarai M, Harigaya H, et al. Computed tomographic angiography characteristics of atherosclerotic plaques subsequently resulting in acute coronary syndrome. *J Am Coll Cardiol* 2009;54:49-57.
22. Kim SH, Hong MK, Park DW, et al. Impact of plaque characteristics analyzed by intravascular ultrasound on long-term clinical outcomes. *Am J Cardiol* 2009;103:1221-1226.
23. Lee SG, Lee CW, Hong MK, et al. Change of multiple complex coronary plaques in patients with acute myocardial infarction: a study with coronary angiography. *Am Heart J* 2004;147:281-286.
24. Ohtani T, Ueda Y, Mizote I, et al. Number of yellow plaques detected in a coronary artery is associated with future risk of acute coronary syndrome: detection of vulnerable patients by angioscopy. *J Am Coll Cardiol* 2006;47:2194-2200.
25. Bayturan O, Tuzcu EM, Nicholls SJ, et al. Attenuated plaque at nonculprit lesions in patients enrolled in intravascular ultrasound atherosclerosis progression trials. *Jacc: Cardiovasc Interv* 2009;2:672-678.
26. Reiter M, Effenberger I, Sabeti S, et al. Increasing carotid plaque echolucency is predictive of cardiovascular events in high-risk patients. *Radiology* 2008;248:1050-1055.
27. Hashimoto H, Tagaya M, Niki H, et al. Computer-assisted analysis of heterogeneity on B-mode imaging predicts instability of asymptomatic carotid plaque. *Cerebrovasc Dis* 2009;28:357-364.
28. Brajovic MD, Markovic N, Loncar G, et al. The influence of various morphologic and hemodynamic carotid plaque characteristics on neurological events onset and deaths. *ScientificWorldJournal* 2009;9:509-521.
29. Takaya N, Yuan C, Chu B, et al. Association between carotid plaque characteristics and subsequent ischemic cerebrovascular events: a prospective assessment with MRI—initial results. *Stroke* 2006;37:818-823.
30. Takaya N, Yuan C, Chu B, et al. Association between carotid plaque characteristics and subsequent ischemic cerebrovascular events: a prospective assessment with MRI—initial results. *Stroke* 2006;37:818-823.
31. Takaya N, Yuan C, Chu B, et al. Presence of intraplaque hemorrhage stimulates progression of carotid atherosclerotic plaques: a high-resolution magnetic resonance imaging study. *Circulation* 2005;111:2768-2775.
32. Underhill HR, Yuan C, Yarnykh VL, et al. Predictors of Surface Disruption with MR Imaging in Asymptomatic Carotid Artery Stenosis. *AJNR Am J Neuroradiol* 2009.
33. Altaf N, MacSweeney ST, Gladman J, et al. Carotid intraplaque hemorrhage predicts recurrent symptoms in patients with high-grade carotid stenosis. *Stroke* 2007;38:1633-1635.
34. Davies MJ. Pathology of arterial thrombosis. *Br Med Bull* 1994;50:789-802.
35. Burke AP, Kolodgie FD, Farb A, et al. Healed plaque ruptures and sudden coronary death: evidence that subclinical rupture has a role in plaque progression. *Circulation* 2001;103:934-940.
36. Altaf N, MacSweeney ST, Gladman J, et al. Carotid intraplaque hemorrhage predicts recurrent symptoms in patients with high-grade carotid stenosis. *Stroke* 2007;38:1633-1635.
37. Barlis P, Serruys PW, Gonzalo N, et al. Assessment of culprit and remote coronary narrowings using optical coherence tomography with long-term outcomes. *Am J Cardiol* 2008;102:391-395.
38. Gibson CM, Sandor T, Stone PH, et al. Quantitative angiographic and statistical methods to assess serial changes in coronary luminal diameter and implications for atherosclerosis regression trials. *Am J Cardiol* 1992;69:1286-1290.
39. Panayiotou A, Griffin M, Georgiou N, et al. ApoB/ApoA1 ratio and subclinical atherosclerosis. *Int Angiol* 2008;27:74-80.
40. Martin RM, Gunnell D, Whitley E, et al. Associations of insulin-like growth factor (IGF)-I, IGF-II, IGF binding protein (IGFBP)-2 and IGFBP-3 with ultrasound measures of atherosclerosis and plaque stability in an older adult population. *J Clin Endocrinol Metab* 2008;93:1331-1338.
41. Serruys PW, Garcia-Garcia HM, Buszman P, Effects of the direct lipoprotein-associated phospholipase A(2) inhibitor darapladib on human coronary atherosclerotic plaque. *Circulation* 2008;118:1172-1182.

42. Thies F, Garry JM, Yaqoob P, et al. Association of n-3 polyunsaturated fatty acids with stability of atherosclerotic plaques: a randomised controlled trial. *Lancet* 2003;361:477-485.
43. Schmidt C, Fagerberg B, Wikstrand J, et al. Multiple risk factor intervention reduces cardiovascular risk in hypertensive patients with echolucent plaques in the carotid artery. *J Intern Med* 2003;253:430-438.
44. Marfella R, D'Amico M, Di FC, et al. Increased activity of the ubiquitin-proteasome system in patients with symptomatic carotid disease is associated with enhanced inflammation and may destabilize the atherosclerotic plaque: effects of rosiglitazone treatment. *J Am Coll Cardiol* 2006;47:2444-2455.
45. Okada K, Ueda Y, Oyabu J, et al. Plaque color analysis by the conventional yellow-color grading system and quantitative measurement using LCH color space. *J Interv Cardiol* 2007;20:324-334.
46. Annovazzi A, Bonanno E, Arca M, et al. 99mTc-interleukin-2 scintigraphy for the in vivo imaging of vulnerable atherosclerotic plaques. *Eur J Nucl Med Mol Imaging* 2006;33:117-126.
47. Nakamura T, Obata JE, Kitta Y, et al. Rapid stabilization of vulnerable carotid plaque within 1 month of pitavastatin treatment in patients with acute coronary syndrome. *J Cardiovasc Pharmacol* 2008;51:365-371.
48. Watanabe K, Sugiyama S, Kugiyama K, et al. Stabilization of carotid atheroma assessed by quantitative ultrasound analysis in nonhypercholesterolemic patients with coronary artery disease. *J Am Coll Cardiol* 2005;46:2022-2030.
49. Kadoglou NP, Gerasimidis T, Moutzouoglou A, et al. Intensive lipid-lowering therapy ameliorates novel calcification markers and GSM score in patients with carotid stenosis. *Eur J Vasc Endovasc Surg* 2008;35:661-668.
50. Kunte H, Amberger N, Busch MA, et al. Markers of instability in high-risk carotid plaques are reduced by statins. *J Vasc Surg* 2008;47:513-522.
51. Koutouzis M, Nomikos A, Nikolidakis S, et al. Statin treated patients have reduced intraplaque angiogenesis in carotid endarterectomy specimens. *Atherosclerosis* 2007;192:457-463.
52. Pucci A. In vivo coronary plaque histology in patients with stable and acute coronary syndromes: relationships with hyperlipidemic status and statin treatment. *Atherosclerosis* 2007;189-195.
53. Hirano M, Nakamura T, Kitta Y, et al. Rapid improvement of carotid plaque echogenicity within 1 month of pioglitazone treatment in patients with acute coronary syndrome. *Atherosclerosis* 2009;203:483-488.
54. Hirayama A, Saito S, Ueda Y, et al. Qualitative and quantitative changes in coronary plaque associated with atorvastatin therapy. *Circulation Journal* 2009;73:718-725.
55. Takarada S, Imanishi T, Kubo T, et al. Effect of statin therapy on coronary fibrous-cap thickness in patients with acute coronary syndrome: assessment by optical coherence tomography study. *Atherosclerosis* 2009;202:491-497.
56. Tang TY, Howarth SP, Miller SR, et al. The ATHEROMA (Atorvastatin Therapy: Effects on Reduction of Macrophage Activity) Study. Evaluation using ultrasmall superparamagnetic iron oxide-enhanced magnetic resonance imaging in carotid disease. *Journal of the American College of Cardiology* 2009;53:2039-2050.
57. Yamada K, Yoshimura S, Kawasaki M, et al. Effects of atorvastatin on carotid atherosclerotic plaques: a randomized trial for quantitative tissue characterization of carotid atherosclerotic plaques with integrated backscatter ultrasound. *Cerebrovasc Dis* 2009;28:417-424.
58. Koutouzis M, Nomikos A, Nikolidakis S, Tzavara V, Andrikopoulos V, Nikolaou N et al. Statin treated patients have reduced intraplaque angiogenesis in carotid endarterectomy specimens. *Atherosclerosis* 2007;192:457-463.
59. Tang TY, Howarth SP, Miller SR, et al. The ATHEROMA (Atorvastatin Therapy: Effects on Reduction of Macrophage Activity) Study. Evaluation using ultrasmall superparamagnetic iron oxide-enhanced magnetic resonance imaging in carotid disease. *Journal of the American College of Cardiology* 2009;53:2039-2050.
60. Waxman S, Ishibashi F, Muller JE. Detection and treatment of vulnerable plaques and vulnerable patients: novel approaches to prevention of coronary events. *Circulation* 2006;114:2390-2411.

61. Ramcharitar S, Gonzalo N, van Geuns RJ, et al. First case of stenting of a vulnerable plaque in the SECRITT I trial-the dawn of a new era? *Nature Reviews Cardiology* 2009;6:374-378.
62. Koutouzis M, Nomikos A, Nikolidakis S, et al. Statin treated patients have reduced intraplaque angiogenesis in carotid endarterectomy specimens. *Atherosclerosis* 2007;192:457-463.
63. Tang TY, Howarth SP, Miller SR, et al. The ATHEROMA (Atorvastatin Therapy: Effects on Reduction of Macrophage Activity) Study. Evaluation using ultrasmall superparamagnetic iron oxide-enhanced magnetic resonance imaging in carotid disease. *Journal of the American College of Cardiology* 2009;53:2039-2050.
64. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes [Erratum appears in *N Engl J Med* 2007 Jul 5;357(1):100]. *N Engl J Med* 2007;356:2457-2471.
65. Lincoff AM, Wolski K, Nicholls SJ, et al. Pioglitazone and risk of cardiovascular events in patients with type 2 diabetes mellitus: a meta-analysis of randomized trials. *JAMA* 2007;298:1180-1188.
66. Nighoghossian N, Derex L, Douek P. The vulnerable carotid artery plaque: current imaging methods and new perspectives. *Stroke* 2005;36:2764-2772.

List of Acronyms/Abbreviations

Abbreviation/acronym	Explanation
ACS	acute coronary syndrome
CMS	Centers for Medicare & Medicaid Services
CRP	C-reactive protein
MDCT	multi-detector computed tomography
FDA	Food & Drug Administration
IL-2	Interleukin-2
IL-2R	Interleukin-2 Receptor
IQR	interquartile range
IVUS	intravascular ultrasound
KQ	key question
Lp-PLA ₂	lipoprotein-associated phospholipase A ₂
MMP	matrix metalloproteinase
MRI	magnetic resonance imaging
PAPP-A	pregnancy-associated plasma protein A
PPAR-g	peroxisome proliferator-activated receptor-gamma
VEGF	vascular endothelial growth factor