Effective Health Care Program

Technical Brief
Number 3

Vulnerable Atherosclerotic Plaque

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Vulnerable Atherosclerotic Plaque

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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.

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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 approach[5] 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 concept[6] 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; angioscopy; Raman spectroscopy; optical coherence tomography; palpography-elastography; magnetic resonance imaging; and variations of these terms. After inspection, the most relevant and

[a]According 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) database[7] by either product name, or applicant name (or the manufacturer). For drugs, we searched the Drugs@FDA database[8] 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 imdividuals 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 A_2 (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 report[4] 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 (±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 ≥ 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 study[39] enrolled apparently healthy individuals and compared the Apoliporotein (Apo) B/ApoA1 ratio to carotid plaque echoluceny (as an imaging feature of plaque vulnerability), whereas another study[40] 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 angioscopy 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 report[4] 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 studies[41-56] 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 A_2 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 angioscopy,[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 ads 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

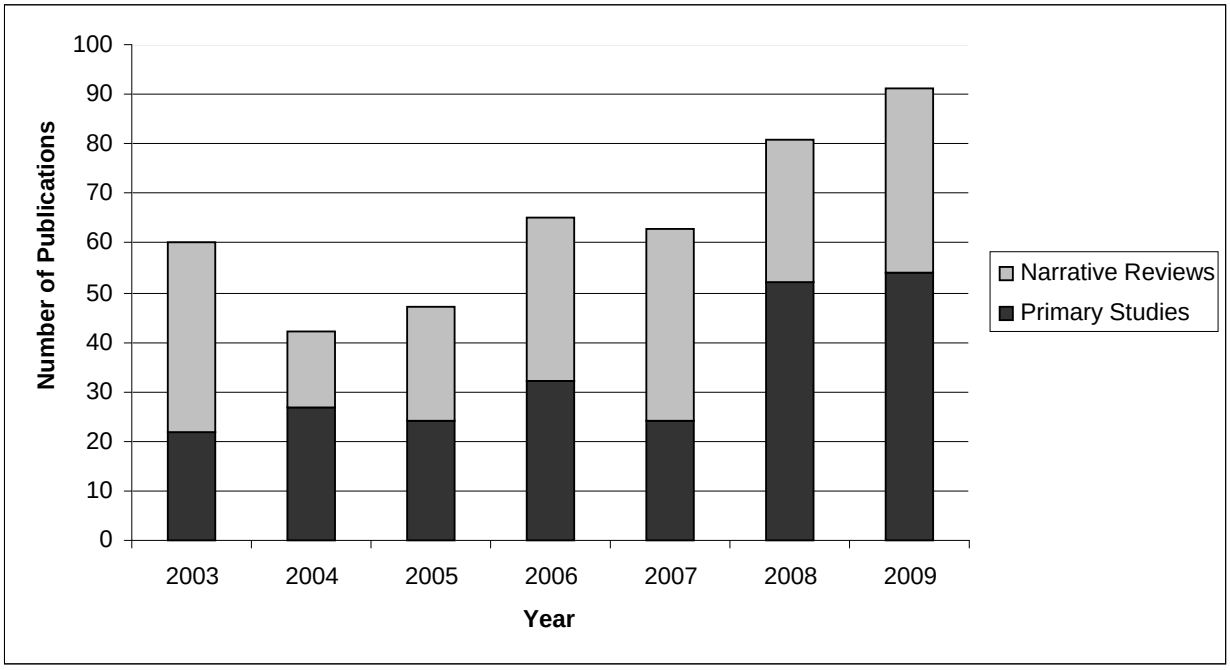

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Table 2. Basic study features of included studies

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 Information from the manufacturer's website is included if no FDA information could be found.
C-Reactive Protein (Latex) (CRP)	Roche Diagnostics, Inc.	YES	NO	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 *vitro* diagnostic use only.
Advia Chemistry Cardiophase High Sensitivity C-Reactive ProteinADVIA CHEMISTRY CARDIOPHASE HIGH SENSITIVITY C-REACTIVE PROTEIN (HSCRP), Calibrators	Siemens Healthcare Diagnostics, Inc.	YES	NO	FDA: The ADVIA Chemistry CardioPhaseTM High Sensitivity C-Reactive Protein assay is for *in vitro* 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 CardioPhaseTM High Sensitivity C-Reactive Protein Calibrators are for *in vitro* 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.
Immage 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 *in vitro* 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 in vitro diagnostic product intended to be used to calibrate the Dimension® *CardioPhase*® 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 Information from the manufacturer's website is included if no FDA information could be found.
MMP-9, Human, Biotrak Assay (MMP-9)	GE Healthcare, Inc.	NO DATA	NO DATA	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). 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. 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. http://www1.gelifesciences.com/aptrix/upp01077.nsf/Content/Products?OpenDocument&parentid=658500&moduleid=165915&zone
MMP9 Protein (MMP-9)	Abcam, Plc.	NO DATA	NO DATA	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." http://www.abcam.com/MMP9-protein-ab39309.html

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.
MMP-9 Colorimetric Drug Discovery Kit: AK-410 (MMP-9)	EnzoLife Sciences Inc.	NO DATA	NO DATA	Product info from company website: The *MMP-9 Colorimetric Drug Discovery Kit: AK-410* 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_2H_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 (ε=13,600 $M^{-1}cm^{-1}$ 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/2ea0c3ed6ecddcc785257306007241bb/$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 Information from the manufacturer's website is included if no FDA information could be found.
Maternal Serum Screen, First Trimester (PAPP-A)	Quest Diagnostics, Inc.	NO DATA	NO DATA	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-ß hCG, and NT combination for Down syndrome screening. http://www.questdiagnostics.com/hcp/topics/genetictesting/mss_t1.html
Dai PAPP-A Elisa EIA-2397 (PAPP-A)	Diagnostic Automation, Inc.	NO DATA	NO DATA	Product info from company website: The *Diagnostic Automation Inc. PAPP-A ELISA* 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 ß-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. http://www.rapidtest.com/ELISA%20Inserts%202009%20052209/PAPP-A_4229-6.pdf

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.
PAPP-A Elisa (PAPP-A)	Alpco Diagnostics	NO DATA	NO DATA	Product info from company website: The *PAPP-A ELISA* 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. http://www.alpco.com/pdfs/38/38-PAPHU-E01.pdf

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 (>=.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	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. 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.	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 *(This company does not currently sell products in the USA)*	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 Information from the manufacturer's website is included if no FDA information could be found
Lipitor Active Ingredient: Atorvastatin calcium	Pfizer	FDA Application No. (NDA): 020702 Original Approval Date: December 17, 1996	NO	LIPITOR is an inhibitor of HMG-CoA reductase (statin) indicated as adjunct therapy to diet to: • 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. 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.

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	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. • Primary Prevention of Coronary Events In hypercholesterolemic patients without clinically evident CHD, PRAVACHOL is indicated to: – 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: – 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 phospholi-pase A_2) inhibitor	GlaxoSmith Kline	NO DATA	NO DATA	Product info from company website: Results of the Integrated Biomarkers and Imaging Study-2 (IBIS-2) demonstrated that darapladib: − 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-PLA_2, 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 usIng 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

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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