Carotid atherosclerosis: where we have been and where we are going

Abstract

Objective While carotid atherosclerosis (CA) biomarkers are valuable surrogates for cardiovascular events, a significant gap exists between predicted and actual event rates. Recent advances in carotid plaque imaging may have a transformative impact on this issue. We performed an interdisciplinary systematic review and bibliometric analysis to understand the future role of CA in cardiovascular diseases (CVDs) prevention.

Methods We applied a comprehensive search strategy to construct a representative dataset of the bibliographic records of CA from 1997 to 2017. A total of 31793 retrieved articles and 407473 cited references were included in the analysis. The co-word network and co-citation network were derived to describe the intellectual structure of CA. Milestones detected by burst analysis were reviewed to delineate the dynamic patterns of CA. Interdisciplinary studies detected by structural variation analysis were used to help understand the emerging trends of CA.

Results CA is a multidisciplinary field of study that could be divided into three communities concerning the early prevention of subclinical atherosclerosis, revascularization of carotid stenosis and imaging techniques. A specialty in CA may go through three stages: the exploration stage, the verification stage and the calibration stage. Carotid plaque imaging had become a converging trend in pathology, epidemiology and clinical practice of CA.

Conclusions The role of CA in CVDs prevention is now undergoing a paradigm shift from “luminal narrowing” to “vulnerable plaques”. An advanced treatment and evaluation system based on a series of carotid plaque imaging techniques is establishing.

Keywords: carotid atherosclerosis, carotid intimal-medial thickness, carotid plaque, carotid stenosis, bibliometric analysis

1. Introduction

Carotid atherosclerosis (CA) is a chronic vascular disease with a narrowing of the carotid artery walls caused by atherosclerotic lesion formation[1]. About 10-15% of all strokes follow thromboembolism from a previously asymptomatic carotid artery stenosis >50%[2]. This relation has promoted the use of CA biomarkers to aid the best individually tailored preventive strategy for cardiovascular events.

The most widely used CA biomarker in the past two decades is carotid artery stenosis. A fundamental role of carotid stenosis severity is established in stroke risk and indication of clinical intervention by current guidelines[3,4]. However, recent studies have highlighted its inadequacy in identifying high-risk groups among asymptomatic patients, given the uncertainty of net benefits based on this classification system[5,6]. Another widely adopted CA biomarker is carotid intimal-medial thickness (cIMT). Under the tacit assumption that we could prevent cardiovascular diseases (CVDs) by intervening subclinical atherosclerosis, cIMT was included as a surrogate in pharmacotherapy trials. But a growing body of evidence proved that cIMT is only a mild reclassification modifier at best and interventions including cIMT as a primary outcome to indicate cardiovascular risk might be "inherently misleading"[7,8].

On the contrary, noninvasive imaging of carotid plaques has experienced a prosperity in the past decade. Emerging evidence shows that the characterization of the carotid plaque by various methods are stroke risk factors independent of stenosis severity[9,10]. It is believed that we are now undergoing a paradigm shift towards a new era of plaque-based risk stratifications driven by imaging technologies[11]. However, studies using novel carotid plaque imaging markers to predict patient outcome are relatively small and scattered. A comprehensive interdisciplinary review is needed to understand the past and future role of CA in the prevention of CVDs.

Previous reviews have been methodologically limited to relatively small ranges, which makes it difficult to identify the scientific changes hidden in the process of interdisciplinary interaction. Recent advances in scientometrics and bibliometrics have made it possible to deal with a large amount of literature simultaneously, so as to clearly reveal the hidden patterns of disciplinary evolution, and therefore, to provide a quantitative visualization method for trend prediction. The purpose of this study is to identify the past and the future role of CA in the prevention of CVDs with visualized bibliometric analysis.

2. Method

2.1 Data collection

We searched the Web of Science with “Carotid” AND (“atherosclerosis” OR “thick*” OR “plaque” OR “stenosis”) on 22 February 2018 to include publications related to “Carotid atherosclerosis”, “Carotid artery atherosclerosis”, “Carotid intima-media thickness”, “Carotid wall thickness”, “Carotid wall thickening” “Carotid plaque”, “Carotid atherosclerotic plaque”, “Carotid stenosis” or “Carotid artery stenosis”. We included original articles and reviews in English, published between Jan 1, 1997 and Dec 31, 2017. This query generated 31,793 records with 407,473 valid references, which accounted for 99.34% of all cited references and was considered generic enough to be applicable to a science mapping study.

2.2 Visualization and Analysis

We used co-word analysis to summarize the major disciplines related to CA. Top 8 subject categories in each year from 1997 to 2017 were used to generate a co-word network. Pathfinder network scaling, which retains the most significant connections, was used to simplify the subject category network. Co-word frequency and betweenness centrality of the categories were used to describe the connections between different disciplines.

We used co-citation analysis to identify the major topics in CA. Top 100 most cited references in each year from 1997 to 2017 were selected to generate a progressively synthesized co-citation network, which was then divided into co-citation clusters. Each cluster represented the intellectual base of a certain topic. We used two visualization techniques - the landscape view and the timeline view - to show the relationship and temporal characteristics of co-citation clusters. Each node in the network represented a highly cited reference. The co-citation relations between nodes were represented by colored curves. Top-ranked keywords by Log-likelihood ratio test method were selected as cluster labels[12].

We used burst analysis to detect the milestones in the major topics. Burst detection is a computational technique that has been used to identify abrupt changes of events[13]. This technique is based on the number of citations a reference received in the corresponding year of publication[14]. The shift of fast-increasing citation indicates the evolution history of active areas. The burst strength and duration of references were used as a valuable indicator of the most active research topics. The article with the strongest burst strength in a cluster is the landmark of a research topic. We summarized the research designs, topics and conclusions of burst references to reveal the evolution history of the major topics.

We used structural variation analysis (SVA), in addition to citation-based patterns, to detect the interdisciplinary studies of CA in recent years. According to the theory of structural variation, the transformative potential of an article may be reflected by the extent to which it varies the existing intellectual structure[15]. SVA could identify the extraordinary connections across clusters made by certain articles. We summarized the articles with transformative potentials between 2012 and 2017.

We visualize and analyze the dataset with CiteSpace V. Figure 1 shows the overview of the analytic framework.

3. Result

3.1 Intellectual structure of CA

Figure 2 shows the subject category co-word network with 14 frequent categories from 1997 to 2017 in CA. The most common category in CA was "Cardiovascular system & Cardiology", followed by "Peripheral Vascular Disease". "Neurosciences & Neurology", "Medicine, Research & Experimental", "Radiology, Nuclear Medicine & Medical Imaging" and "Endocrinology & Metabolism" had high degree of centrality, which means these categories tend to bridge different subareas of CA.

Figure 3 shows the timeline view of the co-citation network, which contains 853 cited references published from 1989 to 2016. The network had a modularity of 0.778, suggesting that the topics in CA were clearly defined. This map shows the main research branches of CA with 11 significantly aggregated co-citation clusters. Table 1 shows the size, temporal characteristics and main themes of each cluster. The largest cluster (#0) included 132 nodes, which accounted for 15.47% of the network. The top 11 largest clusters accounted for 77.84% of the entire network. The average silhouette score of these major clusters was 0.921, suggesting a high level of homogeneity. The most enduring cluster spanned 25 years, while the shortest cluster lasted only 10 years. Clusters that were still active include #2, #4, #5, #8 and #9. Figure 4 shows the landscape view of the co-citation network. The 11 clusters could be divided into three communities according to their spatial clustering the relevance of themes:

- Community 1, which consists of #0, #2, #6 and #8, focused on the early prevention of subclinical atherosclerosis.
- Community 2, including #1, #3, and #4, focused on the revascularization of carotid stenosis and its comparation with medical therapies
- Community 3, including #5, #7, #9, and #11, showed the most commonly used imaging techniques in CA.

3.2 Evolution history of CA

A total of 472 burst references were detected, of which 87.08% belonged to the 11 major clusters. Table 2 shows the distribution of burst references in the major clusters. The strongest burst article appeared in cluster #0, and Cluster #4 had the highest average burst strength (51.21).

3.2.1 Community 1 – Early prevention of subclinical atherosclerosis

Clusters in Community 1 covered 3 specialties related to the early prevention of subclinical atherosclerosis, including cIMT (#0 and #2), inflammation of atherosclerosis (#6) and artery stiffness (#8). We will particularly focuse on the first specialty and give a brief introduction to inflammation of atherosclerosis, given their relevance with CA.

Cluster #0 & #2 - Carotid intima–media thickness

Cluster #0 and #2 depicted the evolution history of research on cIMT, the most concerned imaging biomarker of CA in the past two decades. Cluster #0 revealed the early history, while #2 showed the latest developments.

Cluster #0 was the largest cluster, containing 132 references across a 17-year period from 1989 to 2005. This cluster could be divided into two stages according to the 89 burst references detected. Figure 5 shows the top 5 burst references in each stage.

In the first stage (1989-1996), population-based cross-sectional and case-control studies accounted for the majority of burst references. A variety of ultrasonic measurement methods of wall thickness in the carotid artery, including the common carotid artery, carotid bifurcation and inner carotid artery, were developed and applied[16-25]. The morphological characteristics, population distribution, determinants and the association with CVDs of carotid artery wall thickness were found[26-37]. Pharmaceutical studies started to use the imaging indicators of carotid artery wall thickness as the basis for evaluation[38-46].

In the second stage (1997-2005), cohort studies began to dominate. Ultrasonic measured cIMT became known as a noninvasive marker for atherosclerosis, a powerful predictor and a potential risk reclassification tool of CVDs[47]. The most influential studies in this cluster demonstrated the association between increases in cIMT and increased risk of myocardial infarction, stroke or coronary heart disease[48-56]. Therapeutic trials showed that overall statins and antihypertensive drugs may have a beneficial effect on cIMT progression and reduce the incidence of cardiovascular events[57-64].

Cluster #2 was the largest currently active cluster, containing 75 references across a 14-year period from 2002 till 2015. More than fifty burst references were detected in this cluster, including 20 cohort studies, 12 systematic reviews and 9 consensus or guidelines. The perception of the relationship between cIMT and CVDs was further deepened and solidified in this cluster. The year 2008 seemed to be a turning point to this perception. On the one hand, the strongest burst reference in this cluster showed that cIMT is a strong predictor of future vascular events[65]. The predictive value of cIMT on future vascular events was further confirmed in the younger population[66]. On the other hand, however, cIMT had been proved only a mild reclassification modifier in head to head comparation with other biomarkers since 2008, which made its clinical utility open to question[8,67-75].

The shift in the perception of cIMT could also be observed by the development of guidelines, consensuses and pathological studies[76-82]. The latest "European Guidelines on cardiovascular disease prevention in clinical practice (version 2016)" downgraded the recommendation for cIMT screening from "should be considered (Class IIa/B)" to "not recommended (Class III/A)"[3,79]. The only burst pathological article in cluster #2, published in 2010 by Finn AV, specifically pointed out the limitations of cIMT and the potential of plaque in cardiovascular risk assessment[7]. In the end of this cluster, the greater incremental value of measures that include plaque area and thickness, rather than cIMT alone, received considerable attention[83-87].

The application of cIMT in pharmacology seemed less controversial. The progression of cIMT had long been accepted a surrogate for CVDs endpoints in statin trials[88]. After the efficacy and safety of statin therapy were confirmed by systematic reviews[89,90], the combined medication of statins with other drugs, such as torcetrapib, ezetimibe or niacin, became the next focus between 2008 and 2012[91-93]. In the last few years, the clinical application of statins had expanded to populations such as low-risk individuals with subclinical atherosclerosis[94] and apparently healthy persons without hyperlipidemia but with elevated C-reactive protein[95].

Cluster #6 - Inflammation in atherosclerosis

Cluster #6 revealed the early history of inflammation research in atherosclerosis. This cluster contained 48 references across a 14-year period from 1992 till 2005. At first, it was discovered that inflammation related factors, such as chlamydia pneumoniae infection, serum antibodies and circulating adhesion molecules, were associated with CA or coronary heart disease[96-105]. A fundamental role was then established for inflammation in mediating atherosclerosis by basic science and epidemiological studies[106-112]. In the end of this cluster, the incremental value of inflammatory markers, including C-reactive protein, fibrinogen, serum antibodies, cytokines and soluble adhesion molecules, became the major focus. As a summery, a statement suggested to limit the assays of inflammatory markers to hypersensitive C-reactive protein, given their stability, consistency and predictive abilities[113]. But it was also pointed out that inflammatory markers might still be able to measure the characteristics of plaques.

3.2.2 Community 2 – Revascularization of carotid artery stenosis

Cluster #1, #3 and #4 showed the development and competition history of carotid endarterectomy (CEA) and carotid angioplasty and stenting (CAS). Custer #1 showed the early history of evaluation and technological development of CAS, while Cluster #3 focuses on the efficiency evaluation of CEA for a wider population, especially patients with asymptomatic carotid stenosis. A series of studies comparing these two techniques were presented in Cluster #4. The top 25 strongest burst references showed the major milestones in Community 2 (Table 3).

Cluster #1 - Carotid angioplasty and stenting

Cluster #1 was the second largest cluster with 91 cited references that covered a 19-year duration from 1990 to 2008. This cluster could be divided into two stages according to the 51 burst reference detected. Figure 6 shows the top 5 burst references in each stage.

The first stage (1990-2000) mainly consisted of nonrandomized or non-controlled trials, evaluating the feasibility, safety, and efficacy of CAS in the treatment of carotid artery occlusive disease. Refinement techniques for high-risk patient identification and embolic complications elimination were developed[114-117]. CAS became a potential alternative to CEA, especially for patients with severe medical comorbidity or recurrent carotid artery stenosis following CEA[118-129]. However, a randomized trial of CEA vs CAS was stopped primarily because of problems with informed consent[130]. CAS generated widely divergent opinions about its therapeutic role and called for results from randomized trials[131].

The second stage (2001-2008) appeared several high-impact contributions, including 5 randomized controlled trials[132-136]. The strongest burst reference in this cluster reported a similar effectiveness between CAS and CEA among patients with severe carotid-artery stenosis[135]. A Cochrane systematic review also found no significant difference in the major risks between these two treatments[137]. Short and long-term effectiveness of embolic protection devices were evaluated[138-143], and the preoperative identification of carotid ulceration and thrombus became the next emphasis in high-risk patient identification[144,145]. However, in the end of this cluster, a competitive result attracted wide attention that the rates of death and stroke at 1 and 6 months were lower with CEA than with CAS among patients with symptomatic carotid stenosis of 60% or more[136].

Cluster #3 - Carotid endarterectomy

Cluster #3 was the most durable cluster, containing 71 highly cited references across a 25-year period from 1989 till 2013. This cluster could also be divided into two stages according to the 42 burst references detected. Figure 7 shows the top 5 burst references in each stage.

In the first stage (1989-2002), the beneficial effect of CEA in different groups of patients were evaluated by multicenter randomized controlled trials. Research among patients with severe carotid stenosis yielded highly consistent results, while the benefit of CEA in asymptomatic patients or symptomatic moderate carotid stenosis patients remained controversial[146-155]. The strongest burst article in this cluster demonstrated that asymptomatic patients could benefit from CEA under several restrictions[151]. New diagnostic tools, especially noninvasive imaging of carotid artery stenosis and vulnerable plaques, became the next hotspot[156-165].

The second stage (2003-2013) witnessed the emerging of systematic reviews, consensus and guidelines. Researches based on real world data defined the boundaries of CEA in clinical practice. Pooled data analysis confirmed the beneficial effect of CEA for symptomatic moderate and severe carotid stenosis patients, but not for patients with carotid near-occlusion[166,167]. Factors affecting the benefit from CEA mainly included overall rate of perioperative stroke and death[168], timing of surgery[169], operative indications of patients[170,171] and causes of stroke[172]. In the end of this cluster, the early assessment and the urgent treatment of stroke after transient ischemic attack or minor stroke attracted extensive interest[173-178].

Cluster #4 - CAS VS CEA

Cluster #4 was the second largest currently active cluster, with 69 highly cited references from 2004 to 2016. Over forty burst references were detected, including 20 RCTs, 10 guidelines or consensus statements and 7 systematic reviews. This cluster showed an interesting phenomenon of the competition between two technologies.

In the first stage (2004-2010), CEA versus CAS RCTs taked the majority of burst articles, in which the perioperative safety and long-term outcomes were the major focuses[179-188]. The strongest burst reference in this cluster demonstrated that there were no significant differences between the primary outcomes of CEA and CAS, except for a higher risk of stroke with CAS and a higher risk of myocardial infarction with CEA during the periprocedural period[188]. Meanwhile, magnetic resonance imaging (MRI) were increasingly used in the detection of ischemic brain injury after CAS or CEA[189,190]. Best practices for the management of asymptomatic carotid stenosis patients was another focus in this stage. Evidence accumulated from epidemiological studies and therapeutic studies comparing medical and surgical treatment[191-199].

The second stage (2011-2016) witnessed the burst of guidelines[4,200-204]. While the short-term and long-term outcomes of CAS versus CEA were still controversial[205-209], a latest guideline downgraded the recommendation for CAS, in certain group of symptomatic patients, from Class I to Class IIa based on a meta-analysis of comparative trails[4,210]. Recent studies focused on issues such as subgroup analysis for risk factors identification[211,212], MRI characterization of carotid plaque[10], and the embolic reducing technological optimization in CAS[213].

3.2.2 Community 3 – Imaging Techniques in CA

Cluster #5, #7, #9 and #11 revealed the evolution history of imaging techniques. Cluster #11 and #7 show the earlier imaging technologies, while #5 and #9 reveal the latest development of plaque imaging techniques.

Cluster #11 - Transcranial doppler sonography

Cluster #11 was the shortest cluster, containing 13 highly cited references from 1990 till 1999. The primary focus of this cluster was on the application of transcranial doppler sonography in CEA preoperative assessment, intraoperative monitoring and postoperative evaluation. At first, the transcranial doppler ultrasound was used to measure the disease activity of extracranial carotid artery stenosis in medical and surgical treatments, for its ability to detect emboli associated with platelet thrombus and ulcerations in the carotid artery[214-216]. Prospective pilot studies then proved that asymptomatic embolization is an independent predictor of future stroke risk in both symptomatic and asymptomatic carotid stenosis patients, thus made this technology a potential tool in the definition of a high-risk subgroup for CEA [217,218]. However, this application was hampered due to the problem of sensitivity and specificity in the end of this cluster[219,220].

Cluster #7 - Noninvasive imaging of carotid stenosis

The primary focus of Cluster #7 (from 1990 to 2001) was on the noninvasive imaging of carotid stenosis, primarily in response to the high complication rate of cerebral angiography[221]. Studies in this cluster focused on the standardization of ultrasonic measured carotid stenosis and the comparison of angiography with noninvasive methods, including duplex ultrasound, computed tomography (CT) angiography and magnetic resonance angiography[222-235]. In the end of this cluster, the predictive value of ultrasonic measured hypoechoic carotid plaques on ischemic cerebrovascular events became the next focous[236-239].

Cluster #5 - MRI characterization of carotid plaque

Cluster #5 was the biggest cluster in Community 3, with 65 highly cited references from 1993 till 2013. The primary focus of this cluster was on the application of MRI in the characterization of carotid plaque. This cluster could be divided into two stages according to the 37 burst references detected.

The first stage was from 1993 to 2005. As the first noninvasive imaging technique that allowed the characterization of intraplaque hemorrhage and acute thrombosis[240-246], MRI was used in the detection of carotid plaques, which in turn led to the classification of atherosclerotic lesions[247-249]. Pathogenic studies based on MRI demonstrated that repeated bleeding into the plaque and rupture of the atherosclerotic plaque play an important role in the pathogenesis of ischemic stroke caused by carotid artery stenosis[250,251]. Epidemiological studies found the correlations between carotid plaque characteristics and subsequent ischemic cerebrovascular events[252-256].

In the second stage (2006-2013), prospective studies proved the association between intraplaque hemorrhage (IPH) and cerebrovascular events. IPH, as detected by MRI, predicts cerebrovascular events in both symptomatic and asymptomatic carotid stenosis patients[9,257-259].

Cluster #9 - Positron emission tomography imaging of plaque inflammation

Cluster #9 was a currently active cluster, containing 23 highly cited references from 2002 till 2014. The pathophysiology of atherosclerotic lesion had undergone a research renaissance in the past decade[1,260-262]. Positron emission tomography (PET) imaging provided a noninvasive measure of atherosclerosis inflammation[263], which plays a key role in progression and destabilization of atherosclerotic plaque[264]. The first burst article in this cluster demonstrated that atherosclerotic plaque inflammation can be imaged with 18FDG-PET, and symptomatic unstable plaques accumulated more 18FDG than asymptomatic lesions[164]. In recent years, the technology of visually monitoring plaque inflammation by 18FDG-PET had been applied in the evaluation of therapeutic effectiveness in plaque-based therapy trails[265-267].

3.3 Emerging Trends in CA

Table 4 lists the 30 articles with transformative potentials from 2012 to 2017. These articles had the highest geometric mean of three structural variation variables generated by Citespace. We detected three transformative topics in this 6-year period.

Debate on the expanded application of CAS peaked between 2012 and 2013. The focus of the debate was whether the United States Center for Medicare and Medicaid Services should extend reimbursement indications for CAS. And it was concluded that the expansion would have disastrous health and economic consequences[268,269]. However, the role of age and gender in choosing therapeutic modality gained additional evidence[270], and studies are still working on the better selection criteria for individually tailored treatment[271].

The role of cIMT for cardiovascular risk stratification was the major transformative topic from 2014 to 2015. Population-based studies demonstrated that incremental predictive value of cIMT was very limited compared with coronary calcium score[272], and cIMT was even no longer significantly associated with carotid stenosis after adjustments for plaque and systolic blood pressure[273]. Systolic blood pressure appeared to be a pathological mechanism, indirectly affecting cIMT[274]. Furthermore, limitations still exist in the clearly defined threshold value of cIMT and how the presence of high risk cIMT findings in a patient affects management decisions[275-277]. However, a number of carotid imaging parameters had been shown to be predictive in the identification of high-risk asymptomatic carotid stenosis patients, including ultrasonic measured hypoechoic carotid plaques and MRI detected intraplaque hemorrhage[6,278].

Plaque imaging had become the most concentrated transformative topic since 2016. A growing body of evidence shows that noninvasive imaging of the carotid plaque by various methods reliably identifies structural correlates of plaque vulnerability and is now used to decide on optimal treatment[5,11,279-282].

4. Discussion

At present, patients with carotid atherosclerotic disease are selected for revascularization or medical therapies mainly based on the degree of carotid stenosis and the presence or absence of recent ischemic symptoms[3,4]. However, there is increasing evidence that active, unstable plaques in the carotid arteries are more likely to cause symptoms, regardless of stenosis severity[9,10]. Behind these evidences may implicate an important shift in the perception of CA-mediated CVDs. In our study, we mapped the intellectual structure, evolution history and emerging trends of CA through multiple bibliometric analysis based on extensive literature available. To the best of our knowledge, this is the first science mapping study on CA.

We found the hidden patterns in the major specialties and proved that plaque imaging had become a converging trend in CA. These interdisciplinary findings are particularly useful for sponsors and future researchers to choose the best research topics in CA. It is also important for clinical practitioners to be aware of these promising imaging techniques for clinical decision-making.

A specialty of CA may go through 3 stages: the exploration stage, the verification stage and the calibration stage (Table 5). In the exploration stage, new tools or therapeutic methods will be developed. Exploratory studies, such as cross-sectional studies, case control studies and nonrandomized trails, take the majority of influential literatures. In the verification stage, high-impact cohort studies or RCTs will dominate. An important task in this stage is the standardization of heterogeneous methods. In the calibration stage, the applicable boundaries of the new method, as well as competitive theories will be tested. Previously accumulated knowledge will be summarized and solidified in form of pooled data analysis, systematic reviews, guidelines or consensus. A surrogate biomarker or a novel therapeutic method might be routinely applied in clinical practice or widely questioned and declined. The latter may continue to contribute to another area of research.

CA is a multidisciplinary field of study and medical imaging plays a transformative role in the revolution of this discipline. Advances in imaging techniques bridged the gaps between pathology, epidemiology and clinical practice to form a spiral cycle, thus gradually deepening our understanding of the relationship between CA and CVDs. The application of imaging techniques - such as ultrasound, CT, MRI and PET - enables researchers to further explore the pathogenic mechanisms of CA, evaluate the effects of treatments, predict future cardiovascular events and classify patients into different risk groups in clinical practice. The standardization of these methods establishes the basis for further systematic analysis and clinical application. Pathology, on the other hand, plays an inspiring and explanatory role in CA. New pathological hypothesis provides insights into CA. The incomprehensible phenomena found in epidemiological and therapeutic studies in turn raise new questions for pathological research, thus cyclically promotes our understanding and treatment of carotid atherosclerotic diseases. In fact, influential pathological literature often indicates the transform of research stages. The shift in scientific research may happen several years before the publication of large study results or systematic reviews. Guidelines and consensus are only confirmations and manifestations of such shifts. According to the above patterns, we can identify the current evolutionary stages of subdomains of CA (Figure 8).

Effective CA surrogates are essential for clinical decision-making. The benefits, risks and costs of prevention strategies must be weighed to choose the best individually tailored preventive strategy. In the end of Cluster #2, the shift in perception of cIMT and the emphasis on plaque ultrasound measurements occurred almost simultaneously. A similar phenomenon appeared in Community 2 that MRI characterization of carotid plaque became a promising tool in the competition between CEA and CAS in the end of Cluster #4. On the other hand, although early studies on inflammation in atherosclerosis in Cluster #6 had gradually declined, carotid plaque inflammation measured by PET allowed this basic study to continue in another way. For the first time, plaque imaging became a converging trend in pathology, epidemiology and clinical practice in CA.

5. Limitations

Our systematic search was comprehensive and carefully conducted but we restricted our search strategy to the web of science and we may have missed relevant articles that are not accessible in the web of science. However, we extend the object of analysis to the reference these articles cited, which totaled 407,473. We believe that these references have covered most of the milestones of CA in the past two decades.

It is relying on the analysis of burst references of major clusters that we identified the hidden patterns of CA and the current stages of each sub areas. We therefore may have overlooked other influential studies, as well as some important progress made in other related but less aggregated branches. However, we must make a trade-off between the main research lines and the scattered details. The evolution process of research focuses could be clearly reflected by the citation behavior to burst references, thus better maps the main research lines of CA. When we focus on the citation behavior of researchers, we could actually "see" the cognition changing process of academic communities in a new light, thus avoiding falling into the details of bias checking based on limited information. In addition, we used co-word analysis and structural variation analysis to help understand the intellectual structure and interdisciplinary frontiers of CA, thus providing other perspectives for the interpretation of the hidden patterns.

There have been many theories of scientific change[283,284], but it is still difficult to divide a particular field of research into distinct stages. Our phased approach to CA is a new attempt to quantitatively predict the future directions of medical research. Medical research is a very practical subject that new theories and techniques are often constantly tested and refined in practice. Therefore, it is difficult to distinguish the boundaries between theoretical research, tool development and practical application. However, the patterns of discipline evolution could still be observed from the commonness of high-impact literature in different periods. In fact, the boundaries between different stages are not strict, and we adopted the important milestones as the boundaries of different stages. For instance, the first burst RCT or cohort study marks the beginning of the verification stage, while the concentrated publication of system review and guidelines is the symbol of calibration stage.

6. Future perspective

Our understanding of the mechanism of CA-mediated cardiovascular events is undergoing a transition from “luminal narrowing” to “vulnerable plaques”. In the first era, we reduced cardiovascular events mainly by curing carotid stenosis. But this paradigm faces enormous difficulties in treating patients with asymptomatic or mild to moderate symptomatic carotid stenosis, which account for the majority of CA patients. In the second era, we might be able to solve this problem by establishing a new treatment and evaluation system based on a series of plaque imaging techniques. The intersection of future carotid plaque studies will deepen our understanding of the relationship between CA and cardiovascular events, stimulate new treatment strategies, and create new diagnostic, assessment and classification tools for clinical practice. Major breakthroughs might be expectable in the near future, which may have a revolutionary impact on the role of CA in CVDs prevention.

The rapid accumulation and updating of scientific knowledge poses a great challenge to the methodology of systematic review. It has become a major problem, how to understand the overall progress and new frontier areas of multiple disciplines. Citespace allows us to simultaneously process a huge number of literatures and map the sub-areas of a certain discipline through co-citation analysis, thus makes the quantitative exploration of academic frontiers possible.

References

1 Libby, P., Ridker, P. M. & Hansson, G. K. Progress and challenges in translating the biology of atherosclerosis. *Nature* **473**, 317-325, doi:10.1038/nature10146 (2011).

2 Naylor, A. R. Why is the management of asymptomatic carotid disease so controversial? *The surgeon : journal of the Royal Colleges of Surgeons of Edinburgh and Ireland* **13**, 34-43, doi:10.1016/j.surge.2014.08.004 (2015).

3 Piepoli, M. F. *et al.* 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts)Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *European heart journal* **37**, 2315-2381, doi:10.1093/eurheartj/ehw106 (2016).

4 Kernan, W. N. *et al.* Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* **45**, 2160-2236, doi:10.1161/str.0000000000000024 (2014).

5 Sun, J. & Hatsukami, T. S. Plaque Imaging to Decide on Optimal Treatment: Medical Versus Carotid Endarterectomy Versus Carotid Artery Stenting. *Neuroimaging clinics of North America* **26**, 165-173, doi:10.1016/j.nic.2015.09.011 (2016).

6 Paraskevas, K. I., Spence, J. D., Veith, F. J. & Nicolaides, A. N. Identifying which patients with asymptomatic carotid stenosis could benefit from intervention. *Stroke* **45**, 3720-3724, doi:10.1161/strokeaha.114.006912 (2014).

7 Finn, A. V., Kolodgie, F. D. & Virmani, R. Correlation between carotid intimal/medial thickness and atherosclerosis: a point of view from pathology. *Arteriosclerosis, thrombosis, and vascular biology* **30**, 177-181, doi:10.1161/atvbaha.108.173609 (2010).

8 Yeboah, J. *et al.* Comparison of novel risk markers for improvement in cardiovascular risk assessment in intermediate-risk individuals. *Jama* **308**, 788-795, doi:10.1001/jama.2012.9624 (2012).

9 Saam, T. *et al.* Meta-analysis and systematic review of the predictive value of carotid plaque hemorrhage on cerebrovascular events by magnetic resonance imaging. *Journal of the American College of Cardiology* **62**, 1081-1091, doi:10.1016/j.jacc.2013.06.015 (2013).

10 Gupta, A. *et al.* Carotid plaque MRI and stroke risk: a systematic review and meta-analysis. *Stroke* **44**, 3071-3077, doi:10.1161/strokeaha.113.002551 (2013).

11 Brinjikji, W. *et al.* Contemporary carotid imaging: from degree of stenosis to plaque vulnerability. *Journal of neurosurgery* **124**, 27-42, doi:10.3171/2015.1.Jns142452 (2016).

12 Chen, C., Ibekwe-SanJuan, F. & Hou, J. The structure and dynamics of cocitation clusters: A multiple-perspective cocitation analysis. *Journal of the American Society for Information Science and Technology* **61**, 1386-1409, doi:doi:10.1002/asi.21309 (2010).

13 Kleinberg, J. Bursty and Hierarchical Structure in Streams. *Data Mining and Knowledge Discovery* **7**, 373-397, doi:10.1023/A:1024940629314 (2003).

14 Chen, C. *Science Mapping: A Systematic Review of the Literature*. Vol. 2 (2017).

15 Chen, C., Hu, Z., Liu, S. & Tseng, H. Emerging trends in regenerative medicine: a scientometric analysis in CiteSpace. *Expert opinion on biological therapy* **12**, 593-608, doi:10.1517/14712598.2012.674507 (2012).

16 High-resolution B-mode ultrasound scanning methods in the Atherosclerosis Risk in Communities Study

(ARIC). The ARIC Study Group. *Journal of neuroimaging : official journal of the American Society of Neuroimaging* **1**, 68-73 (1991).

17 Bots, M. L., Mulder, P. G., Hofman, A., van Es, G. A. & Grobbee, D. E. Reproducibility of carotid vessel wall thickness measurements. The Rotterdam Study. *Journal of clinical epidemiology* **47**, 921-930 (1994).

18 O'Leary, D. H. *et al.* Use of sonography to evaluate carotid atherosclerosis in the elderly. The Cardiovascular Health Study. CHS Collaborative Research Group. *Stroke* **22**, 1155-1163 (1991).

19 Riley, W. A. *et al.* Reproducibility of noninvasive ultrasonic measurement of carotid atherosclerosis. The Asymptomatic Carotid Artery Plaque Study. *Stroke* **23**, 1062-1068 (1992).

20 Salonen, J. T. & Salonen, R. Ultrasound B-mode imaging in observational studies of atherosclerotic progression. *Circulation* **87**, Ii56-65 (1993).

21 Selzer, R. H. *et al.* Evaluation of computerized edge tracking for quantifying intima-media thickness of the common carotid artery from B-mode ultrasound images. *Atherosclerosis* **111**, 1-11 (1994).

22 Veller, M. G. *et al.* Measurement of the ultrasonic intima-media complex thickness in normal subjects. *Journal of vascular surgery* **17**, 719-725 (1993).

23 Wendelhag, I., Gustavsson, T., Suurkula, M., Berglund, G. & Wikstrand, J. Ultrasound measurement of wall thickness in the carotid artery: fundamental principles and description of a computerized analysing system. *Clinical physiology (Oxford, England)* **11**, 565-577 (1991).

24 Wong, M., Edelstein, J., Wollman, J. & Bond, M. G. Ultrasonic-pathological comparison of the human arterial wall. Verification of intima-media thickness. *Arteriosclerosis and thrombosis : a journal of vascular biology* **13**, 482-486 (1993).

25 O'Leary, D. H. *et al.* Thickening of the carotid wall. A marker for atherosclerosis in the elderly? Cardiovascular Health Study Collaborative Research Group. *Stroke* **27**, 224-231 (1996).

26 Heiss, G. *et al.* Carotid atherosclerosis measured by B-mode ultrasound in populations: associations with cardiovascular risk factors in the ARIC study. *American journal of epidemiology* **134**, 250-256 (1991).

27 Howard, G. *et al.* Carotid artery intimal-medial thickness distribution in general populations as evaluated by B-mode ultrasound. ARIC Investigators. *Stroke* **24**, 1297-1304 (1993).

28 O'Leary, D. H. *et al.* Distribution and correlates of sonographically detected carotid artery disease in the Cardiovascular Health Study. The CHS Collaborative Research Group. *Stroke* **23**, 1752-1760 (1992).

29 Prati, P. *et al.* Prevalence and determinants of carotid atherosclerosis in a general population. *Stroke* **23**, 1705-1711 (1992).

30 Salonen, J. T. & Salonen, R. Ultrasonographically assessed carotid morphology and the risk of coronary heart disease. *Arteriosclerosis and thrombosis : a journal of vascular biology* **11**, 1245-1249 (1991).

31 Salonen, R. & Salonen, J. T. Determinants of carotid intima-media thickness: a population-based ultrasonography study in eastern Finnish men. *Journal of internal medicine* **229**, 225-231 (1991).

32 Bots, M. L., Hofman, A., de Bruyn, A. M., de Jong, P. T. & Grobbee, D. E. Isolated systolic hypertension and vessel wall thickness of the carotid artery. The Rotterdam Elderly Study. *Arteriosclerosis and thrombosis : a journal of vascular biology* **13**, 64-69 (1993).

33 Bots, M. L., Hofman, A. & Grobbee, D. E. Common carotid intima-media thickness and lower extremity arterial atherosclerosis. The Rotterdam Study. *Arteriosclerosis and thrombosis : a journal of vascular biology* **14**, 1885-1891 (1994).

34 Celermajer, D. S. *et al.* Non-invasive detection of endothelial dysfunction in children and adults at risk of atherosclerosis. *Lancet (London, England)* **340**, 1111-1115 (1992).

35 Gariepy, J., Massonneau, M., Levenson, J., Heudes, D. & Simon, A. Evidence for in vivo carotid and femoral wall thickening in human hypertension. Groupe de Prevention Cardio-vasculaire en Medecine

du Travail. *Hypertension (Dallas, Tex. : 1979)* **22**, 111-118 (1993).
36 Roman, M. J. *et al.* Parallel cardiac and vascular adaptation in hypertension. *Circulation* **86**, 1909-1918 (1992).
37 Wendelhag, I., Wiklund, O. & Wikstrand, J. Arterial wall thickness in familial hypercholesterolemia. Ultrasound measurement of intima-media thickness in the common carotid artery. *Arteriosclerosis and thrombosis : a journal of vascular biology* **12**, 70-77 (1992).
38 Blankenhorn, D. H. *et al.* Beneficial effects of colestipol-niacin therapy on the common carotid artery. Two- and four-year reduction of intima-media thickness measured by ultrasound. *Circulation* **88**, 20-28 (1993).
39 Crouse, J. R., 3rd *et al.* Pravastatin, Lipids, and Atherosclerosis in the Carotid Arteries (PLAC-II). *The American journal of cardiology* **75**, 455-459 (1995).
40 Furberg, C. D. *et al.* Effect of lovastatin on early carotid atherosclerosis and cardiovascular events. Asymptomatic Carotid Artery Progression Study (ACAPS) Research Group. *Circulation* **90**, 1679-1687 (1994).
41 Grobbee, D. E. & Bots, M. L. Carotid artery intima-media thickness as an indicator of generalized atherosclerosis. *Journal of internal medicine* **236**, 567-573 (1994).
42 Hodis, H. N. *et al.* Reduction in carotid arterial wall thickness using lovastatin and dietary therapy: a randomized controlled clinical trial. *Annals of internal medicine* **124**, 548-556 (1996).
43 Mercuri, M. *et al.* Pravastatin reduces carotid intima-media thickness progression in an asymptomatic hypercholesterolemic mediterranean population: the Carotid Atherosclerosis Italian Ultrasound Study. *The American journal of medicine* **101**, 627-634 (1996).
44 Sacks, F. M. *et al.* The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. *The New England journal of medicine* **335**, 1001-1009, doi:10.1056/nejm199610033351401 (1996).
45 Salonen, R. *et al.* Kuopio Atherosclerosis Prevention Study (KAPS). A population-based primary preventive trial of the effect of LDL lowering on atherosclerotic progression in carotid and femoral arteries. *Circulation* **92**, 1758-1764 (1995).
46 Shepherd, J. *et al.* Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. *The New England journal of medicine* **333**, 1301-1307, doi:10.1056/nejm199511163332001 (1995).
47 Simon, A., Gariepy, J., Chironi, G., Megnien, J. L. & Levenson, J. Intima-media thickness: a new tool for diagnosis and treatment of cardiovascular risk. *Journal of hypertension* **20**, 159-169 (2002).
48 O'Leary, D. H. *et al.* Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. Cardiovascular Health Study Collaborative Research Group. *The New England journal of medicine* **340**, 14-22, doi:10.1056/nejm199901073400103 (1999).
49 Bots, M. L., Hoes, A. W., Koudstaal, P. J., Hofman, A. & Grobbee, D. E. Common carotid intima-media thickness and risk of stroke and myocardial infarction: the Rotterdam Study. *Circulation* **96**, 1432-1437 (1997).
50 Chambless, L. E. *et al.* Association of coronary heart disease incidence with carotid arterial wall thickness and major risk factors: the Atherosclerosis Risk in Communities (ARIC) Study, 1987-1993. *American journal of epidemiology* **146**, 483-494 (1997).
51 Hodis, H. N. *et al.* The role of carotid arterial intima-media thickness in predicting clinical coronary events. *Annals of internal medicine* **128**, 262-269 (1998).
52 Allan, P. L., Mowbray, P. I., Lee, A. J. & Fowkes, F. G. Relationship between carotid intima-media thickness

and symptomatic and asymptomatic peripheral arterial disease. The Edinburgh Artery Study. *Stroke* **28**, 348-353 (1997).

53 Chambless, L. E. *et al.* Carotid wall thickness is predictive of incident clinical stroke: the Atherosclerosis Risk in Communities (ARIC) study. *American journal of epidemiology* **151**, 478-487 (2000).

54 Davis, P. H., Dawson, J. D., Riley, W. A. & Lauer, R. M. Carotid intimal-medial thickness is related to cardiovascular risk factors measured from childhood through middle age: The Muscatine Study. *Circulation* **104**, 2815-2819 (2001).

55 Ebrahim, S. *et al.* Carotid plaque, intima media thickness, cardiovascular risk factors, and prevalent cardiovascular disease in men and women: the British Regional Heart Study. *Stroke* **30**, 841-850 (1999).

56 Raitakari, O. T. *et al.* Cardiovascular risk factors in childhood and carotid artery intima-media thickness in adulthood: the Cardiovascular Risk in Young Finns Study. *Jama* **290**, 2277-2283, doi:10.1001/jama.290.17.2277 (2003).

57 de Groot, E. *et al.* B-mode ultrasound assessment of pravastatin treatment effect on carotid and femoral artery walls and its correlations with coronary arteriographic findings: a report of the Regression Growth Evaluation Statin Study (REGRESS). *Journal of the American College of Cardiology* **31**, 1561-1567 (1998).

58 Downs, J. R. *et al.* Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. *Jama* **279**, 1615-1622 (1998).

59 MacMahon, S. *et al.* Effects of lowering average of below-average cholesterol levels on the progression of carotid atherosclerosis: results of the LIPID Atherosclerosis Substudy. LIPID Trial Research Group. *Circulation* **97**, 1784-1790 (1998).

60 Pitt, B. *et al.* Effect of amlodipine on the progression of atherosclerosis and the occurrence of clinical events. PREVENT Investigators. *Circulation* **102**, 1503-1510 (2000).

61 Lonn, E. *et al.* Effects of ramipril and vitamin E on atherosclerosis: the study to evaluate carotid ultrasound changes in patients treated with ramipril and vitamin E (SECURE). *Circulation* **103**, 919-925 (2001).

62 MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet (London, England)* **360**, 7-22, doi:10.1016/s0140-6736(02)09327-3 (2002).

63 Taylor, A. J. *et al.* ARBITER: Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol: a randomized trial comparing the effects of atorvastatin and pravastatin on carotid intima medial thickness. *Circulation* **106**, 2055-2060 (2002).

64 Taylor, A. J., Sullenberger, L. E., Lee, H. J., Lee, J. K. & Grace, K. A. Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol (ARBITER) 2: a double-blind, placebo-controlled study of extended-release niacin on atherosclerosis progression in secondary prevention patients treated with statins. *Circulation* **110**, 3512-3517, doi:10.1161/01.Cir.0000148955.19792.8d (2004).

65 Lorenz, M. W., Markus, H. S., Bots, M. L., Rosvall, M. & Sitzer, M. Prediction of clinical cardiovascular events with carotid intima-media thickness: a systematic review and meta-analysis. *Circulation* **115**, 459-467, doi:10.1161/circulationaha.106.628875 (2007).

66 Lorenz, M. W., von Kegler, S., Steinmetz, H., Markus, H. S. & Sitzer, M. Carotid intima-media thickening indicates a higher vascular risk across a wide age range: prospective data from the Carotid Atherosclerosis Progression Study (CAPS). *Stroke* **37**, 87-92, doi:10.1161/01.STR.0000196964.24024.ea (2006).

67 Den Ruijter, H. M. *et al.* Common carotid intima-media thickness measurements in cardiovascular risk

prediction: a meta-analysis. *Jama* **308**, 796-803, doi:10.1001/jama.2012.9630 (2012).

68 Folsom, A. R. *et al.* Coronary artery calcification compared with carotid intima-media thickness in the prediction of cardiovascular disease incidence: the Multi-Ethnic Study of Atherosclerosis (MESA). *Archives of internal medicine* **168**, 1333-1339, doi:10.1001/archinte.168.12.1333 (2008).

69 Inaba, Y., Chen, J. A. & Bergmann, S. R. Carotid plaque, compared with carotid intima-media thickness, more accurately predicts coronary artery disease events: a meta-analysis. *Atherosclerosis* **220**, 128-133, doi:10.1016/j.atherosclerosis.2011.06.044 (2012).

70 Johnsen, S. H. *et al.* Carotid atherosclerosis is a stronger predictor of myocardial infarction in women than in men: a 6-year follow-up study of 6226 persons: the Tromso Study. *Stroke* **38**, 2873-2880, doi:10.1161/strokeaha.107.487264 (2007).

71 Lorenz, M. W. *et al.* Carotid intima-media thickness progression to predict cardiovascular events in the general population (the PROG-IMT collaborative project): a meta-analysis of individual participant data. *Lancet (London, England)* **379**, 2053-2062, doi:10.1016/s0140-6736(12)60441-3 (2012).

72 Lorenz, M. W., Schaefer, C., Steinmetz, H. & Sitzer, M. Is carotid intima media thickness useful for individual prediction of cardiovascular risk? Ten-year results from the Carotid Atherosclerosis Progression Study (CAPS). *European heart journal* **31**, 2041-2048, doi:10.1093/eurheartj/ehq189 (2010).

73 Peters, S. A., den Ruijter, H. M., Bots, M. L. & Moons, K. G. Improvements in risk stratification for the occurrence of cardiovascular disease by imaging subclinical atherosclerosis: a systematic review. *Heart (British Cardiac Society)* **98**, 177-184, doi:10.1136/heartjnl-2011-300747 (2012).

74 Polak, J. F., Pencina, M. J., O'Leary, D. H. & D'Agostino, R. B. Common carotid artery intima-media thickness progression as a predictor of stroke in multi-ethnic study of atherosclerosis. *Stroke* **42**, 3017-3021, doi:10.1161/strokeaha.111.625186 (2011).

75 van den Oord, S. C. *et al.* Carotid intima-media thickness for cardiovascular risk assessment: systematic review and meta-analysis. *Atherosclerosis* **228**, 1-11, doi:10.1016/j.atherosclerosis.2013.01.025 (2013).

76 Goff, D. C., Jr. *et al.* 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* **129**, S49-73, doi:10.1161/01.cir.0000437741.48606.98 (2014).

77 Greenland, P. *et al.* 2010 ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Journal of the American College of Cardiology* **56**, e50-103, doi:10.1016/j.jacc.2010.09.001 (2010).

78 Mancia, G. *et al.* 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *European heart journal* **34**, 2159-2219, doi:10.1093/eurheartj/eht151 (2013).

79 Perk, J. *et al.* European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). *European heart journal* **33**, 1635-1701, doi:10.1093/eurheartj/ehs092 (2012).

80 Stein, J. H. *et al.* Use of carotid ultrasound to identify subclinical vascular disease and evaluate cardiovascular disease risk: a consensus statement from the American Society of Echocardiography Carotid Intima-Media Thickness Task Force. Endorsed by the Society for Vascular Medicine. *Journal of the American Society of Echocardiography : official publication of the American Society of Echocardiography* **21**, 93-111; quiz 189-190, doi:10.1016/j.echo.2007.11.011 (2008).

81 Touboul, P. J. *et al.* Mannheim carotid intima-media thickness consensus (2004-2006). An update on behalf of the Advisory Board of the 3rd and 4th Watching the Risk Symposium, 13th and 15th European Stroke Conferences, Mannheim, Germany, 2004, and Brussels, Belgium, 2006. *Cerebrovascular diseases (Basel, Switzerland)* **23**, 75-80, doi:10.1159/000097034 (2007).

82 Touboul, P. J. *et al.* Mannheim carotid intima-media thickness and plaque consensus (2004-2006-2011). An update on behalf of the advisory board of the 3rd, 4th and 5th watching the risk symposia, at the 13th, 15th and 20th European Stroke Conferences, Mannheim, Germany, 2004, Brussels, Belgium, 2006, and Hamburg, Germany, 2011. *Cerebrovascular diseases (Basel, Switzerland)* **34**, 290-296, doi:10.1159/000343145 (2012).

83 Gonzalez-Juanatey, C., Llorca, J., Martin, J. & Gonzalez-Gay, M. A. Carotid intima-media thickness predicts the development of cardiovascular events in patients with rheumatoid arthritis. *Seminars in arthritis and rheumatism* **38**, 366-371, doi:10.1016/j.semarthrit.2008.01.012 (2009).

84 Nambi, V. *et al.* Carotid intima-media thickness and presence or absence of plaque improves prediction of coronary heart disease risk: the ARIC (Atherosclerosis Risk In Communities) study. *Journal of the American College of Cardiology* **55**, 1600-1607, doi:10.1016/j.jacc.2009.11.075 (2010).

85 Mathiesen, E. B. *et al.* Carotid plaque area and intima-media thickness in prediction of first-ever ischemic stroke: a 10-year follow-up of 6584 men and women: the Tromso Study. *Stroke* **42**, 972-978, doi:10.1161/strokeaha.110.589754 (2011).

86 Nambi, V. *et al.* Common carotid artery intima-media thickness is as good as carotid intima-media thickness of all carotid artery segments in improving prediction of coronary heart disease risk in the Atherosclerosis Risk in Communities (ARIC) study. *European heart journal* **33**, 183-190, doi:10.1093/eurheartj/ehr192 (2012).

87 Polak, J. F. *et al.* The value of carotid artery plaque and intima-media thickness for incident cardiovascular disease: the multi-ethnic study of atherosclerosis. *Journal of the American Heart Association* **2**, e000087, doi:10.1161/jaha.113.000087 (2013).

88 Espeland, M. A. *et al.* Carotid intimal-media thickness as a surrogate for cardiovascular disease events in trials of HMG-CoA reductase inhibitors. *Current controlled trials in cardiovascular medicine* **6**, 3, doi:10.1186/1468-6708-6-3 (2005).

89 Amarenco, P., Labreuche, J., Lavallee, P. & Touboul, P. J. Statins in stroke prevention and carotid atherosclerosis: systematic review and up-to-date meta-analysis. *Stroke* **35**, 2902-2909, doi:10.1161/01.STR.0000147965.52712.fa (2004).

90 Baigent, C. *et al.* Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet (London, England)* **366**, 1267-1278, doi:10.1016/s0140-6736(05)67394-1 (2005).

91 Kastelein, J. J. *et al.* Effect of torcetrapib on carotid atherosclerosis in familial hypercholesterolemia. *The New England journal of medicine* **356**, 1620-1630, doi:10.1056/NEJMoa071359 (2007).

92 Kastelein, J. J. *et al.* Simvastatin with or without ezetimibe in familial hypercholesterolemia. *The New England journal of medicine* **358**, 1431-1443, doi:10.1056/NEJMoa0800742 (2008).

93 Taylor, A. J. *et al.* Extended-release niacin or ezetimibe and carotid intima-media thickness. *The New England journal of medicine* **361**, 2113-2122, doi:10.1056/NEJMoa0907569 (2009).

94 Crouse, J. R., 3rd *et al.* Effect of rosuvastatin on progression of carotid intima-media thickness in low-risk individuals with subclinical atherosclerosis: the METEOR Trial. *Jama* **297**, 1344-1353, doi:10.1001/jama.297.12.1344 (2007).

95 Ridker, P. M. *et al.* Rosuvastatin to prevent vascular events in men and women with elevated C-reactive

protein. *The New England journal of medicine* **359**, 2195-2207, doi:10.1056/NEJMoa0807646 (2008).

96 Kuo, C. C. *et al.* Demonstration of Chlamydia pneumoniae in atherosclerotic lesions of coronary arteries. *The Journal of infectious diseases* **167**, 841-849 (1993).

97 Xu, Q. *et al.* Association of serum antibodies to heat-shock protein 65 with carotid atherosclerosis. *Lancet (London, England)* **341**, 255-259 (1993).

98 Campbell, L. A. *et al.* Detection of Chlamydia pneumoniae TWAR in human coronary atherectomy tissues. *The Journal of infectious diseases* **172**, 585-588 (1995).

99 Grayston, J. T. *et al.* Chlamydia pneumoniae (TWAR) in atherosclerosis of the carotid artery. *Circulation* **92**, 3397-3400 (1995).

100 Chiu, B., Viira, E., Tucker, W. & Fong, I. W. Chlamydia pneumoniae, cytomegalovirus, and herpes simplex virus in atherosclerosis of the carotid artery. *Circulation* **96**, 2144-2148 (1997).

101 Danesh, J., Collins, R. & Peto, R. Chronic infections and coronary heart disease: is there a link? *Lancet (London, England)* **350**, 430-436, doi:10.1016/s0140-6736(97)03079-1 (1997).

102 Gupta, S. *et al.* Elevated Chlamydia pneumoniae antibodies, cardiovascular events, and azithromycin in male survivors of myocardial infarction. *Circulation* **96**, 404-407 (1997).

103 Hwang, S. J. *et al.* Circulating adhesion molecules VCAM-1, ICAM-1, and E-selectin in carotid atherosclerosis and incident coronary heart disease cases: the Atherosclerosis Risk In Communities (ARIC) study. *Circulation* **96**, 4219-4225 (1997).

104 Muhlestein, J. B. *et al.* Infection with Chlamydia pneumoniae accelerates the development of atherosclerosis and treatment with azithromycin prevents it in a rabbit model. *Circulation* **97**, 633-636 (1998).

105 Rohde, L. E. *et al.* Circulating cell adhesion molecules are correlated with ultrasound-based assessment of carotid atherosclerosis. *Arteriosclerosis, thrombosis, and vascular biology* **18**, 1765-1770 (1998).

106 Ridker, P. M., Cushman, M., Stampfer, M. J., Tracy, R. P. & Hennekens, C. H. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. *The New England journal of medicine* **336**, 973-979, doi:10.1056/nejm199704033361401 (1997).

107 Ridker, P. M., Hennekens, C. H., Roitman-Johnson, B., Stampfer, M. J. & Allen, J. Plasma concentration of soluble intercellular adhesion molecule 1 and risks of future myocardial infarction in apparently healthy men. *Lancet (London, England)* **351**, 88-92, doi:10.1016/s0140-6736(97)09032-6 (1998).

108 Xu, Q. *et al.* Association of serum antibodies to heat-shock protein 65 with carotid atherosclerosis : clinical significance determined in a follow-up study. *Circulation* **100**, 1169-1174 (1999).

109 Ridker, P. M., Hennekens, C. H., Buring, J. E. & Rifai, N. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. *The New England journal of medicine* **342**, 836-843, doi:10.1056/nejm200003233421202 (2000).

110 Ridker, P. M., Rifai, N., Stampfer, M. J. & Hennekens, C. H. Plasma concentration of interleukin-6 and the risk of future myocardial infarction among apparently healthy men. *Circulation* **101**, 1767-1772 (2000).

111 Ross, R. Atherosclerosis--an inflammatory disease. *The New England journal of medicine* **340**, 115-126, doi:10.1056/nejm199901143400207 (1999).

112 Libby, P., Ridker, P. M. & Maseri, A. Inflammation and atherosclerosis. *Circulation* **105**, 1135-1143 (2002).

113 Pearson, T. A. *et al.* Markers of inflammation and cardiovascular disease: application to clinical and public health practice: A statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. *Circulation* **107**, 499-511 (2003).

114 Theron, J. G., Payelle, G. G., Coskun, O., Huet, H. F. & Guimaraens, L. Carotid artery stenosis: treatment with protected balloon angioplasty and stent placement. *Radiology* **201**, 627-636,

doi:10.1148/radiology.201.3.8939208 (1996).
115 Mathur, A. *et al.* Predictors of stroke complicating carotid artery stenting. *Circulation* **97**, 1239-1245 (1998).
116 Jordan, W. D., Jr. *et al.* Microemboli detected by transcranial Doppler monitoring in patients during carotid angioplasty versus carotid endarterectomy. *Cardiovascular surgery (London, England)* **7**, 33-38 (1999).
117 Ohki, T., Roubin, G. S., Veith, F. J., Iyer, S. S. & Brady, E. Efficacy of a filter device in the prevention of embolic events during carotid angioplasty and stenting: An ex vivo analysis. *Journal of vascular surgery* **30**, 1034-1044 (1999).
118 Kachel, R., Basche, S., Heerklotz, I., Grossmann, K. & Endler, S. Percutaneous transluminal angioplasty (PTA) of supra-aortic arteries especially the internal carotid artery. *Neuroradiology* **33**, 191-194 (1991).
119 Diethrich, E. B., Ndiaye, M. & Reid, D. B. Stenting in the carotid artery: initial experience in 110 patients. *Journal of endovascular surgery : the official journal of the International Society for Endovascular Surgery* **3**, 42-62, doi:10.1583/1074-6218(1996)003<0042:Sitcai>2.0.Co;2 (1996).
120 Roubin, G. S., Yadav, S., Iyer, S. S. & Vitek, J. Carotid stent-supported angioplasty: a neurovascular intervention to prevent stroke. *The American journal of cardiology* **78**, 8-12 (1996).
121 Yadav, J. S., Roubin, G. S., King, P., Iyer, S. & Vitek, J. Angioplasty and stenting for restenosis after carotid endarterectomy. Initial experience. *Stroke* **27**, 2075-2079 (1996).
122 Wholey, M. H. *et al.* Endovascular stents for carotid artery occlusive disease. *Journal of endovascular surgery : the official journal of the International Society for Endovascular Surgery* **4**, 326-338, doi:10.1583/1074-6218(1997)004<0326:Esfcao>2.0.Co;2 (1997).
123 Yadav, J. S. *et al.* Elective stenting of the extracranial carotid arteries. *Circulation* **95**, 376-381 (1997).
124 Henry, M. *et al.* Angioplasty and stenting of the extracranial carotid arteries. *Journal of endovascular surgery : the official journal of the International Society for Endovascular Surgery* **5**, 293-304, doi:10.1583/1074-6218(1998)005<0293:Aasote>2.0.Co;2 (1998).
125 Wholey, M. H. *et al.* Current global status of carotid artery stent placement. *Catheterization and cardiovascular diagnosis* **44**, 1-6 (1998).
126 Hobson, R. W., 2nd *et al.* Carotid restenosis: operative and endovascular management. *Journal of vascular surgery* **29**, 228-235; discussion 235-228 (1999).
127 Lanzino, G. *et al.* Percutaneous transluminal angioplasty and stent placement for recurrent carotid artery stenosis. *Journal of neurosurgery* **90**, 688-694, doi:10.3171/jns.1999.90.4.0688 (1999).
128 Shawl, F. *et al.* Safety and efficacy of elective carotid artery stenting in high-risk patients. *Journal of the American College of Cardiology* **35**, 1721-1728 (2000).
129 Wholey, M. H. *et al.* Global experience in cervical carotid artery stent placement. *Catheterization and cardiovascular interventions : official journal of the Society for Cardiac Angiography & Interventions* **50**, 160-167 (2000).
130 Naylor, A. R. *et al.* Randomized study of carotid angioplasty and stenting versus carotid endarterectomy: a stopped trial. *Journal of vascular surgery* **28**, 326-334 (1998).
131 Veith, F. J. *et al.* Current status of carotid bifurcation angioplasty and stenting based on a consensus of opinion leaders. *Journal of vascular surgery* **33**, S111-116 (2001).
132 Endovascular versus surgical treatment in patients with carotid stenosis in the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS): a randomised trial. *Lancet (London, England)* **357**, 1729-1737 (2001).
133 Brooks, W. H., McClure, R. R., Jones, M. R., Coleman, T. C. & Breathitt, L. Carotid angioplasty and stenting

versus carotid endarterectomy: randomized trial in a community hospital. *Journal of the American College of Cardiology* **38**, 1589-1595 (2001).

134 Brooks, W. H., McClure, R. R., Jones, M. R., Coleman, T. L. & Breathitt, L. Carotid angioplasty and stenting versus carotid endarterectomy for treatment of asymptomatic carotid stenosis: a randomized trial in a community hospital. *Neurosurgery* **54**, 318-324; discussion 324-315 (2004).

135 Yadav, J. S. *et al.* Protected carotid-artery stenting versus endarterectomy in high-risk patients. *The New England journal of medicine* **351**, 1493-1501, doi:10.1056/NEJMoa040127 (2004).

136 Mas, J. L. *et al.* Endarterectomy versus stenting in patients with symptomatic severe carotid stenosis. *The New England journal of medicine* **355**, 1660-1671, doi:10.1056/NEJMoa061752 (2006).

137 Coward, L. J., Featherstone, R. L. & Brown, M. M. Safety and efficacy of endovascular treatment of carotid artery stenosis compared with carotid endarterectomy: a Cochrane systematic review of the randomized evidence. *Stroke* **36**, 905-911, doi:10.1161/01.Str.0000158921.51037.64 (2005).

138 Al-Mubarak, N. *et al.* Effect of the distal-balloon protection system on microembolization during carotid stenting. *Circulation* **104**, 1999-2002 (2001).

139 Reimers, B. *et al.* Cerebral protection with filter devices during carotid artery stenting. *Circulation* **104**, 12-15 (2001).

140 Cremonesi, A., Manetti, R., Setacci, F., Setacci, C. & Castriota, F. Protected carotid stenting: clinical advantages and complications of embolic protection devices in 442 consecutive patients. *Stroke* **34**, 1936-1941, doi:10.1161/01.Str.0000081000.23561.61 (2003).

141 Kastrup, A. *et al.* Early outcome of carotid angioplasty and stenting with and without cerebral protection devices: a systematic review of the literature. *Stroke* **34**, 813-819, doi:10.1161/01.Str.0000058160.53040.5f (2003).

142 Safian, R. D. *et al.* Protected carotid stenting in high-risk patients with severe carotid artery stenosis. *Journal of the American College of Cardiology* **47**, 2384-2389, doi:10.1016/j.jacc.2005.12.076 (2006).

143 White, C. J., Iyer, S. S., Hopkins, L. N., Katzen, B. T. & Russell, M. E. Carotid stenting with distal protection in high surgical risk patients: the BEACH trial 30 day results. *Catheterization and cardiovascular interventions : official journal of the Society for Cardiac Angiography & Interventions* **67**, 503-512, doi:10.1002/ccd.20689 (2006).

144 Biasi, G. M. *et al.* Carotid plaque echolucency increases the risk of stroke in carotid stenting: the Imaging in Carotid Angioplasty and Risk of Stroke (ICAROS) study. *Circulation* **110**, 756-762, doi:10.1161/01.Cir.0000138103.91187.E3 (2004).

145 Fisher, M. *et al.* Carotid plaque pathology: thrombosis, ulceration, and stroke pathogenesis. *Stroke* **36**, 253-257, doi:10.1161/01.Str.0000152336.71224.21 (2005).

146 Barnett, H. J. M. *et al.* Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. *The New England journal of medicine* **325**, 445-453, doi:10.1056/nejm199108153250701 (1991).

147 Mayberg, M. R. *et al.* Carotid endarterectomy and prevention of cerebral ischemia in symptomatic carotid stenosis. Veterans Affairs Cooperative Studies Program 309 Trialist Group. *Jama* **266**, 3289-3294 (1991).

148 Warlow, C. MRC European Carotid Surgery Trial: interim results for symptomatic patients with severe (70-99%) or with mild (0-29%) carotid stenosis. *The Lancet* **337**, 1235-1243, doi:https://doi.org/10.1016/0140-6736(91)92916-P (1991).

149 Hobson, R. W., 2nd *et al.* Efficacy of carotid endarterectomy for asymptomatic carotid stenosis. The Veterans Affairs Cooperative Study Group. *The New England journal of medicine* **328**, 221-227,

doi:10.1056/nejm199301283280401 (1993).
150 Risk of stroke in the distribution of an asymptomatic carotid artery. The European Carotid Surgery Trialists Collaborative Group. *Lancet (London, England)* **345**, 209-212 (1995).
151 Walker, M. D., Marler, J. R., Goldstein, M. & et al. Endarterectomy for asymptomatic carotid artery stenosis. *Jama* **273**, 1421-1428, doi:10.1001/jama.1995.03520420037035 (1995).
152 Endarterectomy for moderate symptomatic carotid stenosis: interim results from the MRC European Carotid Surgery Trial. *Lancet (London, England)* **347**, 1591-1593 (1996).
153 Randomised trial of endarterectomy for recently symptomatic carotid stenosis: final results of the MRC European Carotid Surgery Trial (ECST). *Lancet (London, England)* **351**, 1379-1387 (1998).
154 Barnett, H. J. *et al.* Benefit of carotid endarterectomy in patients with symptomatic moderate or severe stenosis. North American Symptomatic Carotid Endarterectomy Trial Collaborators. *The New England journal of medicine* **339**, 1415-1425, doi:10.1056/nejm199811123392002 (1998).
155 Benavente, O., Moher, D. & Pham, B. Carotid endarterectomy for asymptomatic carotid stenosis: a meta-analysis. *BMJ (Clinical research ed.)* **317**, 1477-1480 (1998).
156 Huston, J., 3rd *et al.* Carotid artery: prospective blinded comparison of two-dimensional time-of-flight MR angiography with conventional angiography and duplex US. *Radiology* **186**, 339-344, doi:10.1148/radiology.186.2.8421731 (1993).
157 Rothwell, P. M., Gibson, R. & Warlow, C. P. Interrelation between plaque surface morphology and degree of stenosis on carotid angiograms and the risk of ischemic stroke in patients with symptomatic carotid stenosis. On behalf of the European Carotid Surgery Trialists' Collaborative Group. *Stroke* **31**, 615-621 (2000).
158 Fayad, Z. A. & Fuster, V. Clinical imaging of the high-risk or vulnerable atherosclerotic plaque. *Circulation research* **89**, 305-316 (2001).
159 Johnston, D. C. & Goldstein, L. B. Clinical carotid endarterectomy decision making: noninvasive vascular imaging versus angiography. *Neurology* **56**, 1009-1015 (2001).
160 Nederkoorn, P. J. *et al.* Preoperative diagnosis of carotid artery stenosis: accuracy of noninvasive testing. *Stroke* **33**, 2003-2008 (2002).
161 Nederkoorn, P. J., van der Graaf, Y. & Hunink, M. G. Duplex ultrasound and magnetic resonance angiography compared with digital subtraction angiography in carotid artery stenosis: a systematic review. *Stroke* **34**, 1324-1332, doi:10.1161/01.Str.0000068367.08991.A2 (2003).
162 Wardlaw, J. M., Chappell, F. M., Best, J. J., Wartolowska, K. & Berry, E. Non-invasive imaging compared with intra-arterial angiography in the diagnosis of symptomatic carotid stenosis: a meta-analysis. *Lancet (London, England)* **367**, 1503-1512, doi:10.1016/s0140-6736(06)68650-9 (2006).
163 Randoux, B. *et al.* Carotid artery stenosis: prospective comparison of CT, three-dimensional gadolinium-enhanced MR, and conventional angiography. *Radiology* **220**, 179-185, doi:10.1148/radiology.220.1.r01jl35179 (2001).
164 Rudd, J. H. *et al.* Imaging atherosclerotic plaque inflammation with [18F]-fluorodeoxyglucose positron emission tomography. *Circulation* **105**, 2708-2711 (2002).
165 Cai, J. *et al.* In vivo quantitative measurement of intact fibrous cap and lipid-rich necrotic core size in atherosclerotic carotid plaque: comparison of high-resolution, contrast-enhanced magnetic resonance imaging and histology. *Circulation* **112**, 3437-3444, doi:10.1161/circulationaha.104.528174 (2005).
166 Rothwell, P. M. *et al.* Analysis of pooled data from the randomised controlled trials of endarterectomy for symptomatic carotid stenosis. *Lancet (London, England)* **361**, 107-116 (2003).
167 Rothwell, P. M., Gutnikov, S. A. & Warlow, C. P. Reanalysis of the final results of the European Carotid

Surgery Trial. *Stroke* **34**, 514-523 (2003).
168 Ferguson, G. G. *et al.* The North American Symptomatic Carotid Endarterectomy Trial : surgical results in 1415 patients. *Stroke* **30**, 1751-1758 (1999).
169 Rothwell, P. M., Eliasziw, M., Gutnikov, S. A., Warlow, C. P. & Barnett, H. J. Endarterectomy for symptomatic carotid stenosis in relation to clinical subgroups and timing of surgery. *Lancet (London, England)* **363**, 915-924, doi:10.1016/s0140-6736(04)15785-1 (2004).
170 Rothwell, P. M. & Warlow, C. P. Prediction of benefit from carotid endarterectomy in individual patients: a risk-modelling study. European Carotid Surgery Trialists' Collaborative Group. *Lancet (London, England)* **353**, 2105-2110 (1999).
171 Bond, R., Rerkasem, K. & Rothwell, P. M. Systematic review of the risks of carotid endarterectomy in relation to the clinical indication for and timing of surgery. *Stroke* **34**, 2290-2301, doi:10.1161/01.Str.0000087785.01407.Cc (2003).
172 Inzitari, D. *et al.* The causes and risk of stroke in patients with asymptomatic internal-carotid-artery stenosis. North American Symptomatic Carotid Endarterectomy Trial Collaborators. *The New England journal of medicine* **342**, 1693-1700, doi:10.1056/nejm200006083422302 (2000).
173 Johnston, S. C., Gress, D. R., Browner, W. S. & Sidney, S. Short-term prognosis after emergency department diagnosis of TIA. *Jama* **284**, 2901-2906 (2000).
174 Coull, A. J., Lovett, J. K. & Rothwell, P. M. Population based study of early risk of stroke after transient ischaemic attack or minor stroke: implications for public education and organisation of services. *BMJ (Clinical research ed.)* **328**, 326, doi:10.1136/bmj.37991.635266.44 (2004).
175 Rothwell, P. M. *et al.* Effect of urgent treatment of transient ischaemic attack and minor stroke on early recurrent stroke (EXPRESS study): a prospective population-based sequential comparison. *Lancet (London, England)* **370**, 1432-1442, doi:10.1016/s0140-6736(07)61448-2 (2007).
176 Ois, A., Cuadrado-Godia, E., Rodriguez-Campello, A., Jimenez-Conde, J. & Roquer, J. High risk of early neurological recurrence in symptomatic carotid stenosis. *Stroke* **40**, 2727-2731, doi:10.1161/strokeaha.109.548032 (2009).
177 Johnston, S. C. *et al.* Validation and refinement of scores to predict very early stroke risk after transient ischaemic attack. *Lancet (London, England)* **369**, 283-292, doi:10.1016/s0140-6736(07)60150-0 (2007).
178 Easton, J. D. *et al.* Definition and evaluation of transient ischemic attack: a scientific statement for healthcare professionals from the American Heart Association/American Stroke Association Stroke Council; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; and the Interdisciplinary Council on Peripheral Vascular Disease. The American Academy of Neurology affirms the value of this statement as an educational tool for neurologists. *Stroke* **40**, 2276-2293, doi:10.1161/strokeaha.108.192218 (2009).
179 Chaturvedi, S. *et al.* Carotid endarterectomy--an evidence-based review: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology* **65**, 794-801, doi:10.1212/01.wnl.0000176036.07558.82 (2005).
180 Ringleb, P. A. *et al.* 30 day results from the SPACE trial of stent-protected angioplasty versus carotid endarterectomy in symptomatic patients: a randomised non-inferiority trial. *Lancet (London, England)* **368**, 1239-1247, doi:10.1016/s0140-6736(06)69122-8 (2006).
181 Eckstein, H. H. *et al.* Results of the Stent-Protected Angioplasty versus Carotid Endarterectomy (SPACE) study to treat symptomatic stenoses at 2 years: a multinational, prospective, randomised trial. *The Lancet. Neurology* **7**, 893-902, doi:10.1016/s1474-4422(08)70196-0 (2008).
182 Gurm, H. S. *et al.* Long-term results of carotid stenting versus endarterectomy in high-risk patients. *The*

New England journal of medicine **358**, 1572-1579, doi:10.1056/NEJMoa0708028 (2008).
183 Mas, J. L. *et al.* Endarterectomy Versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S) trial: results up to 4 years from a randomised, multicentre trial. *The Lancet. Neurology* **7**, 885-892, doi:10.1016/s1474-4422(08)70195-9 (2008).
184 Bonati, L. H. *et al.* Long-term risk of carotid restenosis in patients randomly assigned to endovascular treatment or endarterectomy in the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS): long-term follow-up of a randomised trial. *The Lancet. Neurology* **8**, 908-917, doi:10.1016/s1474-4422(09)70227-3 (2009).
185 Bonati, L. H. *et al.* Short-term outcome after stenting versus endarterectomy for symptomatic carotid stenosis: a preplanned meta-analysis of individual patient data. *Lancet (London, England)* **376**, 1062-1073, doi:10.1016/s0140-6736(10)61009-4 (2010).
186 Mantese, V. A., Timaran, C. H., Chiu, D., Begg, R. J. & Brott, T. G. The Carotid Revascularization Endarterectomy versus Stenting Trial (CREST): stenting versus carotid endarterectomy for carotid disease. *Stroke* **41**, S31-34, doi:10.1161/strokeaha.110.595330 (2010).
187 Ederle, J. *et al.* Carotid artery stenting compared with endarterectomy in patients with symptomatic carotid stenosis (International Carotid Stenting Study): an interim analysis of a randomised controlled trial. *Lancet (London, England)* **375**, 985-997, doi:10.1016/s0140-6736(10)60239-5 (2010).
188 Brott, T. G. *et al.* Stenting versus endarterectomy for treatment of carotid-artery stenosis. *The New England journal of medicine* **363**, 11-23, doi:10.1056/NEJMoa0912321 (2010).
189 Schnaudigel, S., Groschel, K., Pilgram, S. M. & Kastrup, A. New brain lesions after carotid stenting versus carotid endarterectomy: a systematic review of the literature. *Stroke* **39**, 1911-1919, doi:10.1161/strokeaha.107.500603 (2008).
190 Bonati, L. H. *et al.* New ischaemic brain lesions on MRI after stenting or endarterectomy for symptomatic carotid stenosis: a substudy of the International Carotid Stenting Study (ICSS). *The Lancet. Neurology* **9**, 353-362, doi:10.1016/s1474-4422(10)70057-0 (2010).
191 Halliday, A. *et al.* Prevention of disabling and fatal strokes by successful carotid endarterectomy in patients without recent neurological symptoms: randomised controlled trial. *Lancet (London, England)* **363**, 1491-1502, doi:10.1016/s0140-6736(04)16146-1 (2004).
192 Goessens, B. M., Visseren, F. L., Kappelle, L. J., Algra, A. & van der Graaf, Y. Asymptomatic carotid artery stenosis and the risk of new vascular events in patients with manifest arterial disease: the SMART study. *Stroke* **38**, 1470-1475, doi:10.1161/strokeaha.106.477091 (2007).
193 de Weerd, M. *et al.* Prevalence of asymptomatic carotid artery stenosis in the general population: an individual participant data meta-analysis. *Stroke* **41**, 1294-1297, doi:10.1161/strokeaha.110.581058 (2010).
194 Halliday, A. *et al.* 10-year stroke prevention after successful carotid endarterectomy for asymptomatic stenosis (ACST-1): a multicentre randomised trial. *Lancet (London, England)* **376**, 1074-1084, doi:10.1016/s0140-6736(10)61197-x (2010).
195 Markus, H. S. *et al.* Asymptomatic embolisation for prediction of stroke in the Asymptomatic Carotid Emboli Study (ACES): a prospective observational study. *The Lancet. Neurology* **9**, 663-671, doi:10.1016/s1474-4422(10)70120-4 (2010).
196 Marquardt, L., Geraghty, O. C., Mehta, Z. & Rothwell, P. M. Low risk of ipsilateral stroke in patients with asymptomatic carotid stenosis on best medical treatment: a prospective, population-based study. *Stroke* **41**, e11-17, doi:10.1161/strokeaha.109.561837 (2010).
197 Nicolaides, A. N. *et al.* Asymptomatic internal carotid artery stenosis and cerebrovascular risk

stratification. *Journal of vascular surgery* **52**, 1486-1496.e1481-1485, doi:10.1016/j.jvs.2010.07.021 (2010).

198 Spence, J. D. *et al.* Effects of intensive medical therapy on microemboli and cardiovascular risk in asymptomatic carotid stenosis. *Archives of neurology* **67**, 180-186, doi:10.1001/archneurol.2009.289 (2010).

199 Abbott, A. L. Medical (nonsurgical) intervention alone is now best for prevention of stroke associated with asymptomatic severe carotid stenosis: results of a systematic review and analysis. *Stroke* **40**, e573-583, doi:10.1161/strokeaha.109.556068 (2009).

200 Brott, T. G. *et al.* 2011 ASA/ACCF/AHA/AANN/AANS/ACR/ASNR/CNS/SAIP/SCAI/SIR/SNIS/SVM/SVS guideline on the management of patients with extracranial carotid and vertebral artery disease: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American Stroke Association, American Association of Neuroscience Nurses, American Association of Neurological Surgeons, American College of Radiology, American Society of Neuroradiology, Congress of Neurological Surgeons, Society of Atherosclerosis Imaging and Prevention, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of NeuroInterventional Surgery, Society for Vascular Medicine, and Society for Vascular Surgery. *Journal of the American College of Cardiology* **57**, 1002-1044, doi:10.1016/j.jacc.2010.11.005 (2011).

201 Furie, K. L. *et al.* Guidelines for the prevention of stroke in patients with stroke or transient ischemic attack: a guideline for healthcare professionals from the american heart association/american stroke association. *Stroke* **42**, 227-276, doi:10.1161/STR.0b013e3181f7d043 (2011).

202 Goldstein, L. B. *et al.* Guidelines for the primary prevention of stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* **42**, 517-584, doi:10.1161/STR.0b013e3181fcb238 (2011).

203 Ricotta, J. J. *et al.* Updated Society for Vascular Surgery guidelines for management of extracranial carotid disease: executive summary. *Journal of vascular surgery* **54**, 832-836, doi:10.1016/j.jvs.2011.07.004 (2011).

204 Tendera, M. *et al.* [ESC guidelines for the treatment and diagnosis of peripheral artery disease. Guideline includes extracranial carotid artery, vertebral, mesenteric, renal, upper and lower extremity arteries]. *Turk Kardiyoloji Dernegi arsivi : Turk Kardiyoloji Derneginin yayin organidir* **40 Suppl 1**, 5-60 (2012).

205 Economopoulos, K. P., Sergentanis, T. N., Tsivgoulis, G., Mariolis, A. D. & Stefanadis, C. Carotid artery stenting versus carotid endarterectomy: a comprehensive meta-analysis of short-term and long-term outcomes. *Stroke* **42**, 687-692, doi:10.1161/strokeaha.110.606079 (2011).

206 Silver, F. L. *et al.* Safety of stenting and endarterectomy by symptomatic status in the Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST). *Stroke* **42**, 675-680, doi:10.1161/strokeaha.110.610212 (2011).

207 Lal, B. K. *et al.* Restenosis after carotid artery stenting and endarterectomy: a secondary analysis of CREST, a randomised controlled trial. *The Lancet. Neurology* **11**, 755-763, doi:10.1016/s1474-4422(12)70159-x (2012).

208 Bonati, L. H. *et al.* Long-term outcomes after stenting versus endarterectomy for treatment of symptomatic carotid stenosis: the International Carotid Stenting Study (ICSS) randomised trial. *Lancet (London, England)* **385**, 529-538, doi:10.1016/s0140-6736(14)61184-3 (2015).

209 Brott, T. G. *et al.* Long-Term Results of Stenting versus Endarterectomy for Carotid-Artery Stenosis. *The New England journal of medicine* **374**, 1021-1031, doi:10.1056/NEJMoa1505215 (2016).

210 Bonati, L. H., Lyrer, P., Ederle, J., Featherstone, R. & Brown, M. M. Percutaneous transluminal balloon angioplasty and stenting for carotid artery stenosis. *The Cochrane database of systematic reviews*, Cd000515, doi:10.1002/14651858.CD000515.pub4 (2012).

211 Howard, V. J. *et al.* Influence of sex on outcomes of stenting versus endarterectomy: a subgroup analysis of the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST). *The Lancet. Neurology* **10**, 530-537, doi:10.1016/s1474-4422(11)70080-1 (2011).

212 Voeks, J. H. *et al.* Age and outcomes after carotid stenting and endarterectomy: the carotid revascularization endarterectomy versus stenting trial. *Stroke* **42**, 3484-3490, doi:10.1161/strokeaha.111.624155 (2011).

213 Bijuklic, K., Wandler, A., Hazizi, F. & Schofer, J. The PROFI study (Prevention of Cerebral Embolization by Proximal Balloon Occlusion Compared to Filter Protection During Carotid Artery Stenting): a prospective randomized trial. *Journal of the American College of Cardiology* **59**, 1383-1389, doi:10.1016/j.jacc.2011.11.035 (2012).

214 Spencer, M. P., Thomas, G. I., Nicholls, S. C. & Sauvage, L. R. Detection of middle cerebral artery emboli during carotid endarterectomy using transcranial Doppler ultrasonography. *Stroke* **21**, 415-423 (1990).

215 Siebler, M., Sitzer, M., Rose, G., Bendfeldt, D. & Steinmetz, H. Silent cerebral embolism caused by neurologically symptomatic high-grade carotid stenosis. Event rates before and after carotid endarterectomy. *Brain : a journal of neurology* **116 (Pt 5)**, 1005-1015 (1993).

216 Siebler, M., Kleinschmidt, A., Sitzer, M., Steinmetz, H. & Freund, H. J. Cerebral microembolism in symptomatic and asymptomatic high-grade internal carotid artery stenosis. *Neurology* **44**, 615-618 (1994).

217 Siebler, M. *et al.* Cerebral microembolism and the risk of ischemia in asymptomatic high-grade internal carotid artery stenosis. *Stroke* **26**, 2184-2186 (1995).

218 Molloy, J. & Markus, H. S. Asymptomatic embolization predicts stroke and TIA risk in patients with carotid artery stenosis. *Stroke* **30**, 1440-1443 (1999).

219 Basic identification criteria of Doppler microembolic signals. Consensus Committee of the Ninth International Cerebral Hemodynamic Symposium. *Stroke* **26**, 1123 (1995).

220 Ringelstein, E. B. *et al.* Consensus on microembolus detection by TCD. International Consensus Group on Microembolus Detection. *Stroke* **29**, 725-729 (1998).

221 Hankey, G. J., Warlow, C. P. & Sellar, R. J. Cerebral angiographic risk in mild cerebrovascular disease. *Stroke* **21**, 209-222 (1990).

222 Norris, J. W., Zhu, C. Z., Bornstein, N. M. & Chambers, B. R. Vascular risks of asymptomatic carotid stenosis. *Stroke* **22**, 1485-1490 (1991).

223 Kleiser, B. & Widder, B. Course of carotid artery occlusions with impaired cerebrovascular reactivity. *Stroke* **23**, 171-174 (1992).

224 Alexandrov, A. V., Bladin, C. F., Maggisano, R. & Norris, J. W. Measuring carotid stenosis. Time for a reappraisal. *Stroke* **24**, 1292-1296 (1993).

225 Bock, R. W. *et al.* The natural history of asymptomatic carotid artery disease. *Journal of vascular surgery* **17**, 160-169; discussion 170-161 (1993).

226 Dillon, E. H., van Leeuwen, M. S., Fernandez, M. A., Eikelboom, B. C. & Mali, W. P. CT angiography: application to the evaluation of carotid artery stenosis. *Radiology* **189**, 211-219, doi:10.1148/radiology.189.1.8372196 (1993).

227 Fox, A. J. How to measure carotid stenosis. *Radiology* **186**, 316-318, doi:10.1148/radiology.186.2.8421726 (1993).

228 Moneta, G. L. *et al.* Correlation of North American Symptomatic Carotid Endarterectomy Trial (NASCET) angiographic definition of 70% to 99% internal carotid artery stenosis with duplex scanning. *Journal of vascular surgery* **17**, 152-157; discussion 157-159 (1993).
229 Cumming, M. J. & Morrow, I. M. Carotid artery stenosis: a prospective comparison of CT angiography and conventional angiography. *AJR. American journal of roentgenology* **163**, 517-523, doi:10.2214/ajr.163.3.8079836 (1994).
230 Faught, W. E. *et al.* Color-flow duplex scanning of carotid arteries: new velocity criteria based on receiver operator characteristic analysis for threshold stenoses used in the symptomatic and asymptomatic carotid trials. *Journal of vascular surgery* **19**, 818-827; discussion 827-818 (1994).
231 Neale, M. L. *et al.* Reappraisal of duplex criteria to assess significant carotid stenosis with special reference to reports from the North American Symptomatic Carotid Endarterectomy Trial and the European Carotid Surgery Trial. *Journal of vascular surgery* **20**, 642-649 (1994).
232 Eliasziw, M., Rankin, R. N., Fox, A. J., Haynes, R. B. & Barnett, H. J. Accuracy and prognostic consequences of ultrasonography in identifying severe carotid artery stenosis. North American Symptomatic Carotid Endarterectomy Trial (NASCET) Group. *Stroke* **26**, 1747-1752 (1995).
233 Moneta, G. L. *et al.* Screening for asymptomatic internal carotid artery stenosis: duplex criteria for discriminating 60% to 99% stenosis. *Journal of vascular surgery* **21**, 989-994 (1995).
234 Patel, M. R. *et al.* Preoperative assessment of the carotid bifurcation. Can magnetic resonance angiography and duplex ultrasonography replace contrast arteriography? *Stroke* **26**, 1753-1758 (1995).
235 Hood, D. B. *et al.* Prospective evaluation of new duplex criteria to identify 70% internal carotid artery stenosis. *Journal of vascular surgery* **23**, 254-261; discussion 261-252 (1996).
236 Geroulakos, G. *et al.* Characterization of symptomatic and asymptomatic carotid plaques using high-resolution real-time ultrasonography. *The British journal of surgery* **80**, 1274-1277 (1993).
237 Polak, J. F. *et al.* Hypoechoic plaque at US of the carotid artery: an independent risk factor for incident stroke in adults aged 65 years or older. Cardiovascular Health Study. *Radiology* **208**, 649-654, doi:10.1148/radiology.208.3.9722841 (1998).
238 Gronholdt, M. L., Nordestgaard, B. G., Schroeder, T. V., Vorstrup, S. & Sillesen, H. Ultrasonic echolucent carotid plaques predict future strokes. *Circulation* **104**, 68-73 (2001).
239 Mathiesen, E. B., Bonaa, K. H. & Joakimsen, O. Echolucent plaques are associated with high risk of ischemic cerebrovascular events in carotid stenosis: the tromso study. *Circulation* **103**, 2171-2175 (2001).
240 Toussaint, J. F., LaMuraglia, G. M., Southern, J. F., Fuster, V. & Kantor, H. L. Magnetic resonance images lipid, fibrous, calcified, hemorrhagic, and thrombotic components of human atherosclerosis in vivo. *Circulation* **94**, 932-938 (1996).
241 Hatsukami, T. S., Ross, R., Polissar, N. L. & Yuan, C. Visualization of fibrous cap thickness and rupture in human atherosclerotic carotid plaque in vivo with high-resolution magnetic resonance imaging. *Circulation* **102**, 959-964 (2000).
242 Yuan, C., Mitsumori, L. M., Beach, K. W. & Maravilla, K. R. Carotid atherosclerotic plaque: noninvasive MR characterization and identification of vulnerable lesions. *Radiology* **221**, 285-299, doi:10.1148/radiol.2212001612 (2001).
243 Chu, B. *et al.* Hemorrhage in the atherosclerotic carotid plaque: a high-resolution MRI study. *Stroke* **35**, 1079-1084, doi:10.1161/01.Str.0000125856.25309.86 (2004).
244 Saam, T. *et al.* Quantitative evaluation of carotid plaque composition by in vivo MRI. *Arteriosclerosis, thrombosis, and vascular biology* **25**, 234-239, doi:10.1161/01.Atv.0000149867.61851.31 (2005).

245 Yuan, C. *et al.* Contrast-enhanced high resolution MRI for atherosclerotic carotid artery tissue characterization. *Journal of magnetic resonance imaging : JMRI* **15**, 62-67 (2002).
246 Moody, A. R. *et al.* Characterization of complicated carotid plaque with magnetic resonance direct thrombus imaging in patients with cerebral ischemia. *Circulation* **107**, 3047-3052, doi:10.1161/01.Cir.0000074222.61572.44 (2003).
247 Cai, J. M. *et al.* Classification of human carotid atherosclerotic lesions with in vivo multicontrast magnetic resonance imaging. *Circulation* **106**, 1368-1373 (2002).
248 Yuan, C. *et al.* In vivo accuracy of multispectral magnetic resonance imaging for identifying lipid-rich necrotic cores and intraplaque hemorrhage in advanced human carotid plaques. *Circulation* **104**, 2051-2056 (2001).
249 Saam, T. *et al.* Comparison of symptomatic and asymptomatic atherosclerotic carotid plaque features with in vivo MR imaging. *Radiology* **240**, 464-472, doi:10.1148/radiol.2402050390 (2006).
250 Carr, S., Farb, A., Pearce, W. H., Virmani, R. & Yao, J. S. Atherosclerotic plaque rupture in symptomatic carotid artery stenosis. *Journal of vascular surgery* **23**, 755-765; discussion 765-756 (1996).
251 Takaya, N. *et al.* Presence of intraplaque hemorrhage stimulates progression of carotid atherosclerotic plaques: a high-resolution magnetic resonance imaging study. *Circulation* **111**, 2768-2775, doi:10.1161/circulationaha.104.504167 (2005).
252 Stary, H. C. *et al.* A definition of advanced types of atherosclerotic lesions and a histological classification of atherosclerosis. A report from the Committee on Vascular Lesions of the Council on Arteriosclerosis, American Heart Association. *Circulation* **92**, 1355-1374 (1995).
253 Hatsukami, T. S. *et al.* Carotid plaque morphology and clinical events. *Stroke* **28**, 95-100 (1997).
254 Shinnar, M. *et al.* The diagnostic accuracy of ex vivo MRI for human atherosclerotic plaque characterization. *Arteriosclerosis, thrombosis, and vascular biology* **19**, 2756-2761 (1999).
255 Golledge, J., Greenhalgh, R. M. & Davies, A. H. The symptomatic carotid plaque. *Stroke* **31**, 774-781 (2000).
256 Yuan, C. *et al.* Identification of fibrous cap rupture with magnetic resonance imaging is highly associated with recent transient ischemic attack or stroke. *Circulation* **105**, 181-185 (2002).
257 Altaf, N., MacSweeney, S. T., Gladman, J. & Auer, D. P. Carotid intraplaque hemorrhage predicts recurrent symptoms in patients with high-grade carotid stenosis. *Stroke* **38**, 1633-1635, doi:10.1161/strokeaha.106.473066 (2007).
258 Altaf, N. *et al.* Detection of intraplaque hemorrhage by magnetic resonance imaging in symptomatic patients with mild to moderate carotid stenosis predicts recurrent neurological events. *Journal of vascular surgery* **47**, 337-342, doi:10.1016/j.jvs.2007.09.064 (2008).
259 Takaya, N. *et al.* Association between carotid plaque characteristics and subsequent ischemic cerebrovascular events: a prospective assessment with MRI--initial results. *Stroke* **37**, 818-823, doi:10.1161/01.Str.0000204638.91099.91 (2006).
260 Weber, C. & Noels, H. Atherosclerosis: current pathogenesis and therapeutic options. *Nature medicine* **17**, 1410-1422, doi:10.1038/nm.2538 (2011).
261 Libby, P. Inflammation in atherosclerosis. *Arteriosclerosis, thrombosis, and vascular biology* **32**, 2045-2051, doi:10.1161/ATVBAHA.108.179705 (2012).
262 Virmani, R., Burke, A. P., Farb, A. & Kolodgie, F. D. Pathology of the vulnerable plaque. *Journal of the American College of Cardiology* **47**, C13-18, doi:10.1016/j.jacc.2005.10.065 (2006).
263 Tawakol, A. *et al.* In vivo 18F-fluorodeoxyglucose positron emission tomography imaging provides a noninvasive measure of carotid plaque inflammation in patients. *Journal of the American College of*

Cardiology **48**, 1818-1824, doi:10.1016/j.jacc.2006.05.076 (2006).
264 Hansson, G. K. & Hermansson, A. The immune system in atherosclerosis. *Nature immunology* **12**, 204-212, doi:10.1038/ni.2001 (2011).
265 Tahara, N. *et al.* Simvastatin attenuates plaque inflammation: evaluation by fluorodeoxyglucose positron emission tomography. *Journal of the American College of Cardiology* **48**, 1825-1831, doi:10.1016/j.jacc.2006.03.069 (2006).
266 Rudd, J. H. *et al.* Atherosclerosis inflammation imaging with 18F-FDG PET: carotid, iliac, and femoral uptake reproducibility, quantification methods, and recommendations. *Journal of nuclear medicine : official publication, Society of Nuclear Medicine* **49**, 871-878, doi:10.2967/jnumed.107.050294 (2008).
267 Fayad, Z. A. *et al.* Safety and efficacy of dalcetrapib on atherosclerotic disease using novel non-invasive multimodality imaging (dal-PLAQUE): a randomised clinical trial. *Lancet (London, England)* **378**, 1547-1559, doi:10.1016/s0140-6736(11)61383-4 (2011).
268 Cambria, R. P. Centers for Medicare and Medicaid Services conducts a medical evidence development and coverage advisory committee meeting on carotid atherosclerosis. *Journal of vascular surgery* **56**, e1-16, doi:10.1016/j.jvs.2012.04.051 (2012).
269 Why the United States Center for Medicare and Medicaid Services (CMS) should not extend reimbursement indications for carotid artery angioplasty/stenting. *Brain and behavior* **2**, 200-207, doi:10.1002/brb3.32 (2012).
270 Giannopoulos, S. *et al.* Age and gender disparities in the risk of carotid revascularization procedures. *Neurological sciences : official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology* **34**, 1711-1717, doi:10.1007/s10072-013-1453-2 (2013).
271 Eckstein, H. H. *et al.* The diagnosis, treatment and follow-up of extracranial carotid stenosis. *Deutsches Arzteblatt international* **110**, 468-476, doi:10.3238/arztebl.2013.0468 (2013).
272 Ferket, B. S. *et al.* Predictive value of updating Framingham risk scores with novel risk markers in the U.S. general population. *PloS one* **9**, e88312, doi:10.1371/journal.pone.0088312 (2014).
273 Martinsson, A. *et al.* Carotid plaque, intima-media thickness, and incident aortic stenosis: a prospective cohort study. *Arteriosclerosis, thrombosis, and vascular biology* **34**, 2343-2348, doi:10.1161/atvbaha.114.304015 (2014).
274 Dratva, J. *et al.* Early detection of subjects at risk for vascular remodelling - results from the Swiss population-based study SAPALDIA. *Swiss medical weekly* **144**, w14052, doi:10.4414/smw.2014.14052 (2014).
275 Lee, C. J. & Park, S. The role of carotid ultrasound for cardiovascular risk stratification beyond traditional risk factors. *Yonsei medical journal* **55**, 551-557, doi:10.3349/ymj.2014.55.3.551 (2014).
276 Vlachopoulos, C. *et al.* The role of vascular biomarkers for primary and secondary prevention. A position paper from the European Society of Cardiology Working Group on peripheral circulation: Endorsed by the Association for Research into Arterial Structure and Physiology (ARTERY) Society. *Atherosclerosis* **241**, 507-532, doi:10.1016/j.atherosclerosis.2015.05.007 (2015).
277 Polak, J. F., Szklo, M. & O'Leary, D. H. Associations of Coronary Heart Disease with Common Carotid Artery Near and Far Wall Intima-Media Thickness: The Multi-Ethnic Study of Atherosclerosis. *Journal of the American Society of Echocardiography : official publication of the American Society of Echocardiography* **28**, 1114-1121, doi:10.1016/j.echo.2015.04.001 (2015).
278 Naylor, A. R., Schroeder, T. V. & Sillesen, H. Clinical and imaging features associated with an increased risk of late stroke in patients with asymptomatic carotid disease. *European journal of vascular and endovascular surgery : the official journal of the European Society for Vascular Surgery* **48**, 633-640,

doi:10.1016/j.ejvs.2014.08.017 (2014).
279 Maier, A. *et al.* A molecular intravascular ultrasound contrast agent allows detection of activated platelets on the surface of symptomatic human plaques. *Atherosclerosis* **267**, 68-77, doi:10.1016/j.atherosclerosis.2017.10.029 (2017).
280 Chowdhury, M. M., Tawakol, A. & Jaffer, F. A. Molecular Imaging of Atherosclerosis: A Clinical Focus. *Current cardiovascular imaging reports* **10**, doi:10.1007/s12410-017-9397-1 (2017).
281 Sakamoto, S. *et al.* Carotid artery stenting for vulnerable plaques on MR angiography and ultrasonography: utility of dual protection and blood aspiration method. *Journal of neurointerventional surgery* **8**, 1011-1015, doi:10.1136/neurintsurg-2015-012052 (2016).
282 Bonati, L. H. & Nederkoorn, P. J. Clinical Perspective of Carotid Plaque Imaging. *Neuroimaging clinics of North America* **26**, 175-182, doi:10.1016/j.nic.2015.09.012 (2016).
283 Kuhn, T. S. *The Structure of Scientific Revolutions. Chicago (University of Chicago Press)* (1962).
284 Shneider, A. M. Four stages of a scientific discipline; four types of scientist. *Trends in Biochemical Sciences* **34**, 217-223 (2009).
285 Roubin, G. S. *et al.* Immediate and late clinical outcomes of carotid artery stenting in patients with symptomatic and asymptomatic carotid artery stenosis: a 5-year prospective analysis. *Circulation* **103**, 532-537 (2001).
286 Hobson, R. W., 2nd *et al.* Carotid artery stenting is associated with increased complications in octogenarians: 30-day stroke and death rates in the CREST lead-in phase. *Journal of vascular surgery* **40**, 1106-1111, doi:10.1016/j.jvs.2004.10.022 (2004).
287 Liapis, C. D. *et al.* ESVS guidelines. Invasive treatment for carotid stenosis: indications, techniques. *European journal of vascular and endovascular surgery : the official journal of the European Society for Vascular Surgery* **37**, 1-19, doi:10.1016/j.ejvs.2008.11.006 (2009).
288 Fent, G. J., Greenwood, J. P., Plein, S. & Buch, M. H. The role of non-invasive cardiovascular imaging in the assessment of cardiovascular risk in rheumatoid arthritis: where we are and where we need to be. *Annals of the rheumatic diseases* **76**, 1169-1175, doi:10.1136/annrheumdis-2016-209744 (2017).
289 Atchaneeyasakul, K. *et al.* Safety Outcomes Using a Proximal Protection Device in Carotid Stenting of Long Carotid Stenoses. *Interventional neurology* **5**, 123-130, doi:10.1159/000447022 (2016).
290 Calvet, D. & Mas, J. L. Recent advances in carotid angioplasty and stenting. *International journal of stroke : official journal of the International Stroke Society* **11**, 19-27, doi:10.1177/1747493015616637 (2016).
291 Frerix, M., Stegbauer, J., Kreuter, A. & Weiner, S. M. Atherosclerotic plaques occur in absence of intima-media thickening in both systemic sclerosis and systemic lupus erythematosus: a duplexsonography study of carotid and femoral arteries and follow-up for cardiovascular events. *Arthritis research & therapy* **16**, R54, doi:10.1186/ar4489 (2014).
292 Doig, D. & Brown, M. M. Carotid stenting versus endarterectomy. *Annual review of medicine* **63**, 259-276, doi:10.1146/annurev-med-081210-101714 (2012).
293 Koennecke, H. C. Revascularization of carotid artery stenosis - a brief update on current evidence. *VASA. Zeitschrift fur Gefasskrankheiten* **41**, 5-10, doi:10.1024/0301-1526/a000157 (2012).
294 Touze, E. Treatment of carotid stenosis. *Current vascular pharmacology* **10**, 734-738 (2012).
295 Kerekes, G. *et al.* Validated methods for assessment of subclinical atherosclerosis in rheumatology. *Nature reviews. Rheumatology* **8**, 224-234, doi:10.1038/nrrheum.2012.16 (2012).
296 Habersberger, J., Brott, T. G. & Roubin, G. S. Carotid artery stenting: a clinical update. *Current opinion in cardiology* **27**, 565-571, doi:10.1097/HCO.0b013e3283587506 (2012).

297 Tulip, H. H. *et al.* Cerebral embolization in asymptomatic versus symptomatic patients after carotid stenting. *Journal of vascular surgery* **56**, 1579-1584; discussion 1584, doi:10.1016/j.jvs.2012.06.074 (2012).

298 Kakisis, J. D. *et al.* The European Society for Vascular Surgery guidelines for carotid intervention: an updated independent assessment and literature review. *European journal of vascular and endovascular surgery : the official journal of the European Society for Vascular Surgery* **44**, 238-243, doi:10.1016/j.ejvs.2012.04.015 (2012).

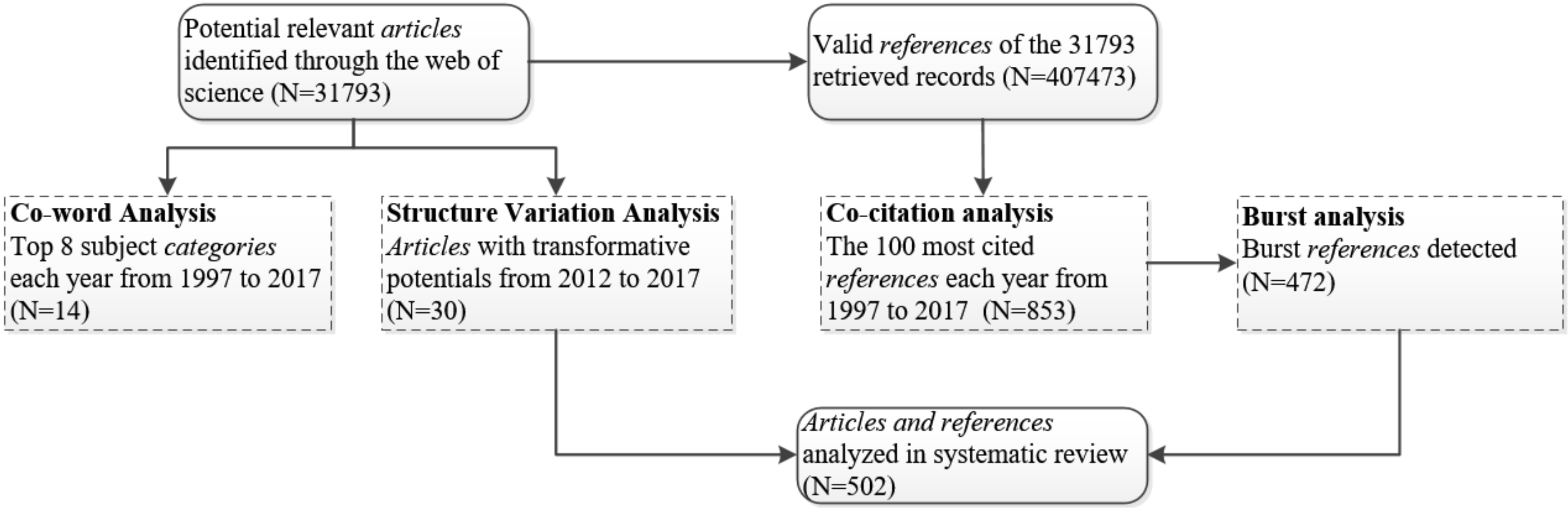

Figure 1 The overview of the analytic framework.

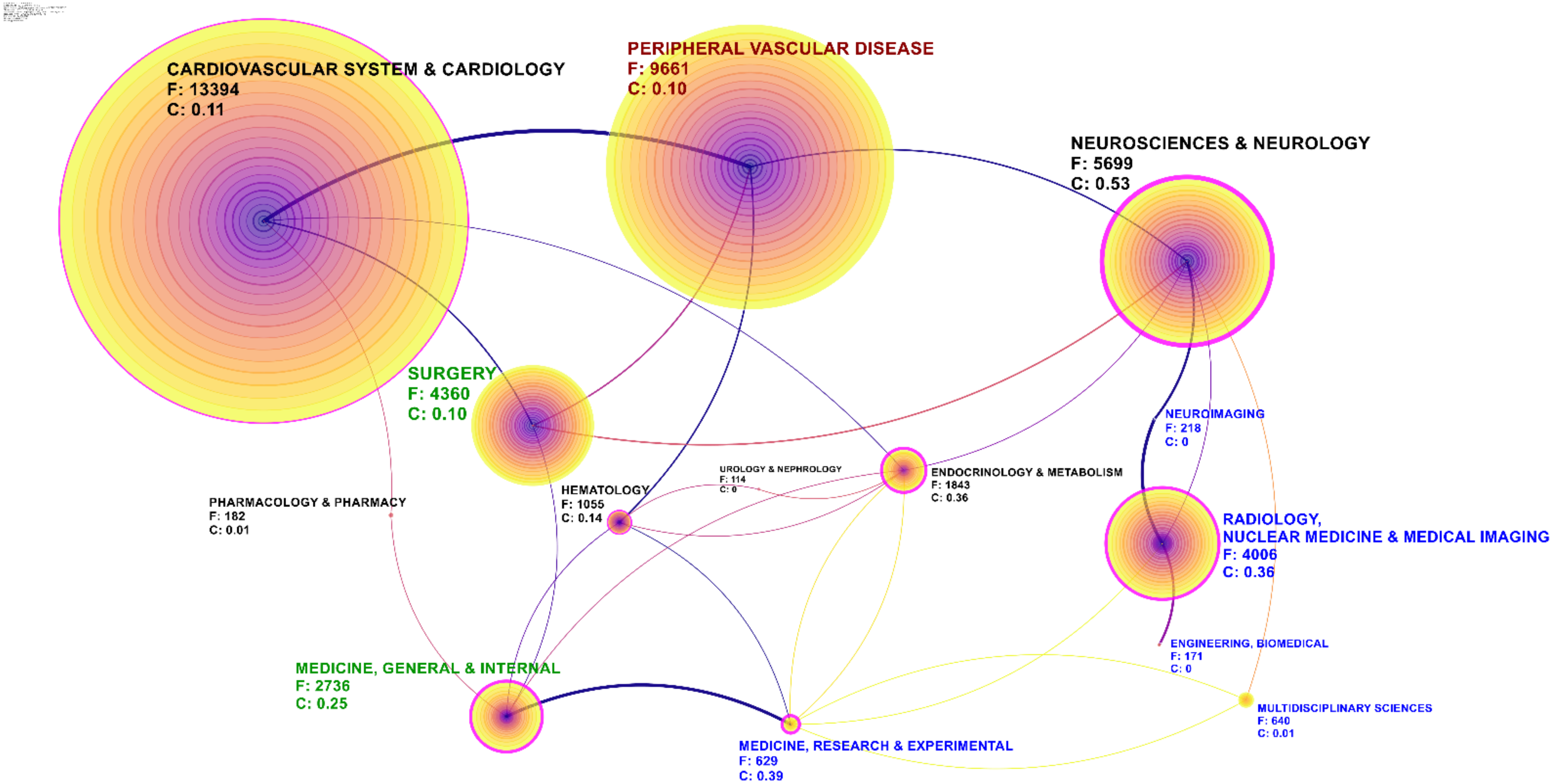

Figure 2 Co-word network of the major subject categories. Each node represents a common category. The size of a circle represents the co-citation frequency and the purple rims of the circles represent the high betweenness centralities. F indicates co-citation frequency; and C, betweenness centrality.

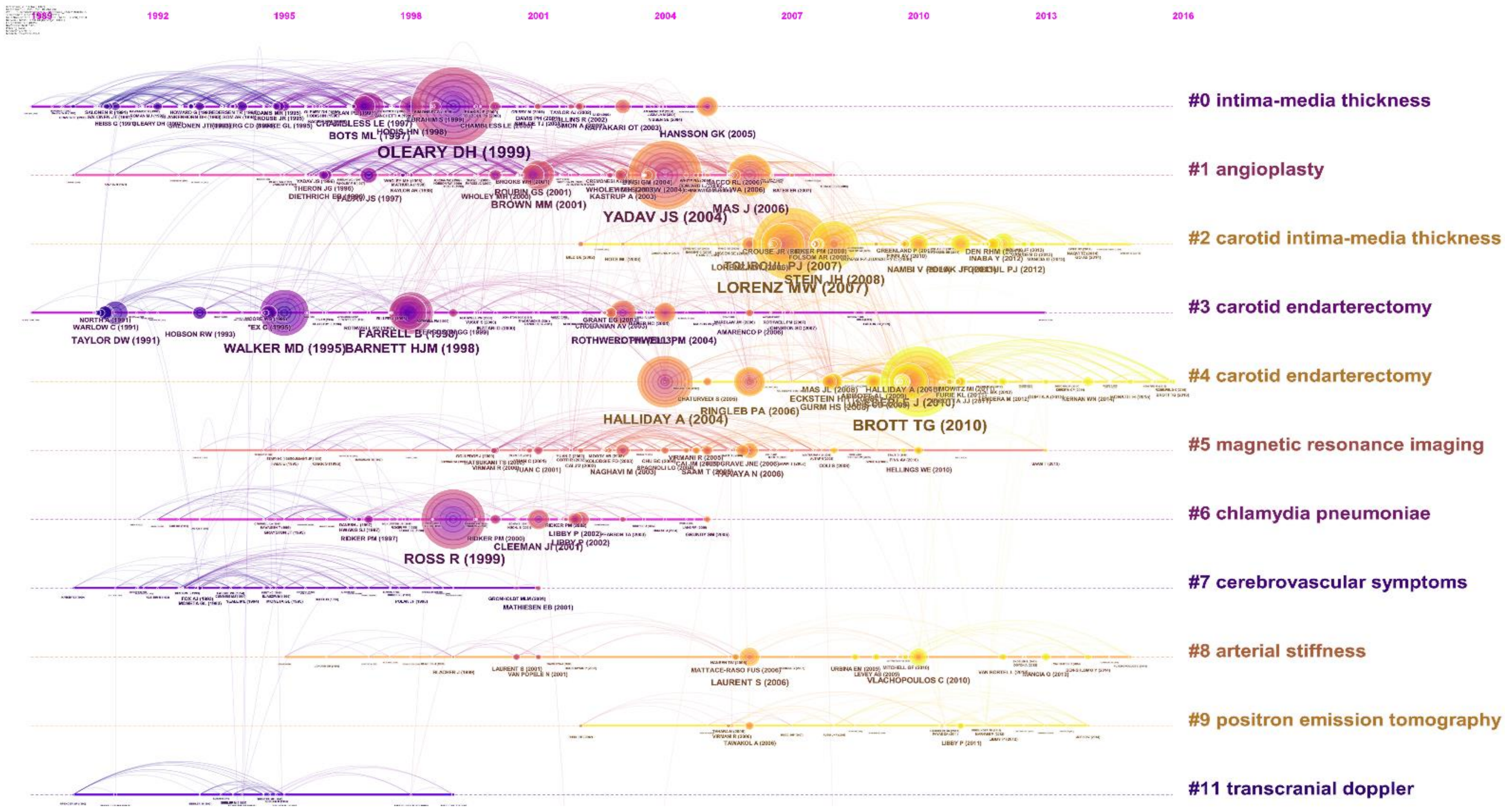

Figure 3 Timeline view of the co-citation network. Clusters are depicted along horizontal timelines and arranged vertically in descending order according to the size of the nodes. Large-sized nodes are highly cited references with more conspicuous labels below. The publication time of each reference is presented by the colour of the node. The top-ranked keyword by Log-likelihood ratio test is selected as cluster label.

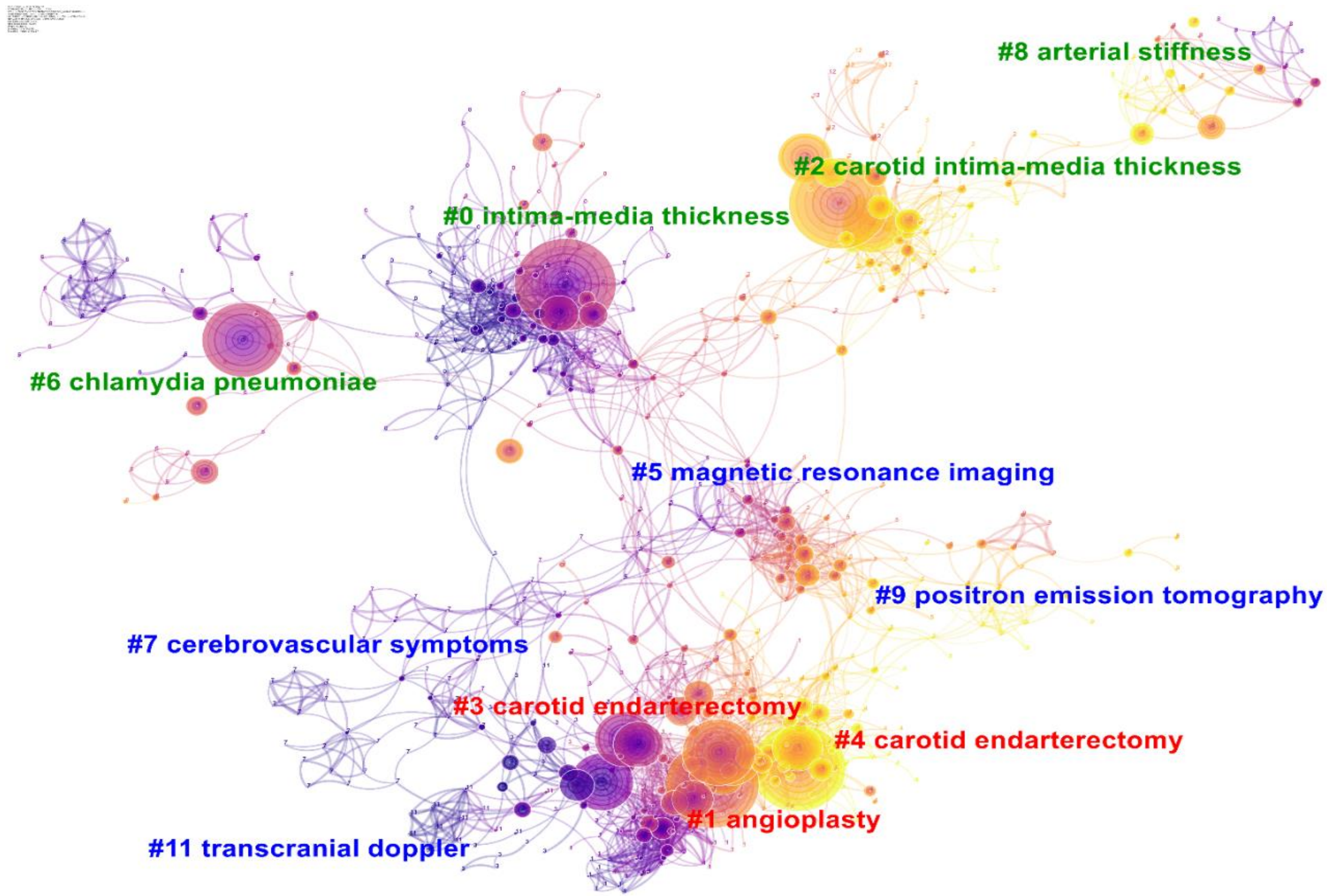

Figure 4 Landscape view of the co-citation network. The co-citation relationship between points is represented by their spatial position. Clusters are naturally formed by the spatial aggregation of nodes. The cluster label for the Community 1 is marked green, Community 2, red, and Community 3, blue. Cluster #2, #4 and #9 are the latest active clusters dyed in light yellow.

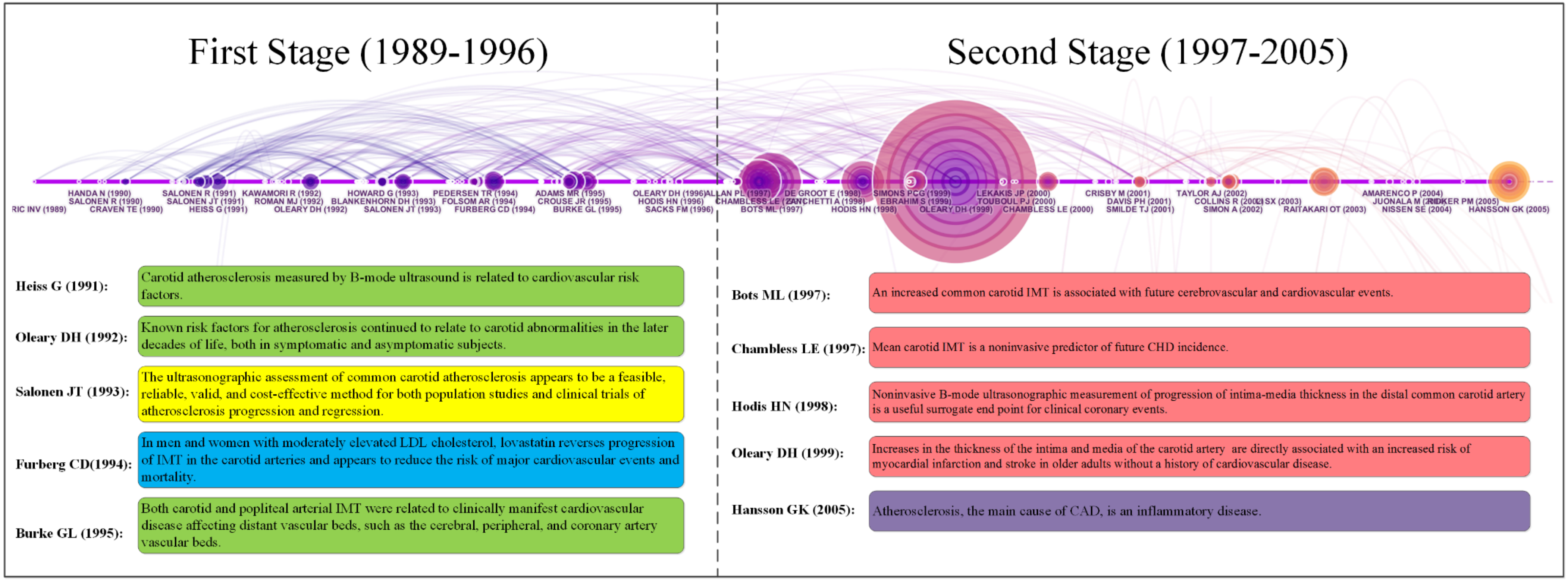

Figure 5 The top 5 burst references in each stage of Cluster #0. Cross-sectional studies and case-control studies were marked in green, pharmacological studies in blue, imaging studies in yellow, cohort studies in red, and pathological studies in purple.

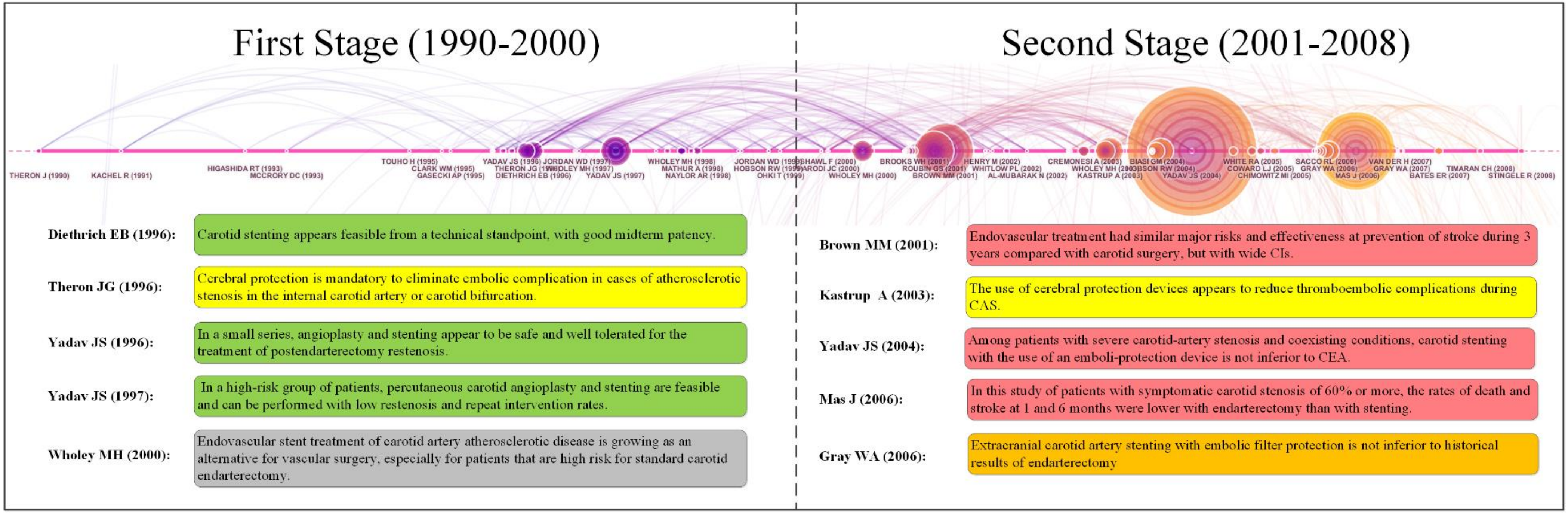

Figure 6 The top 5 burst references in each stage of Cluster #1. Non-randomized studies were marked in green, imaging studies in yellow, pooled data analysis and systematic reviews in grey, randomized controlled trails in red, and guidelines in orange.

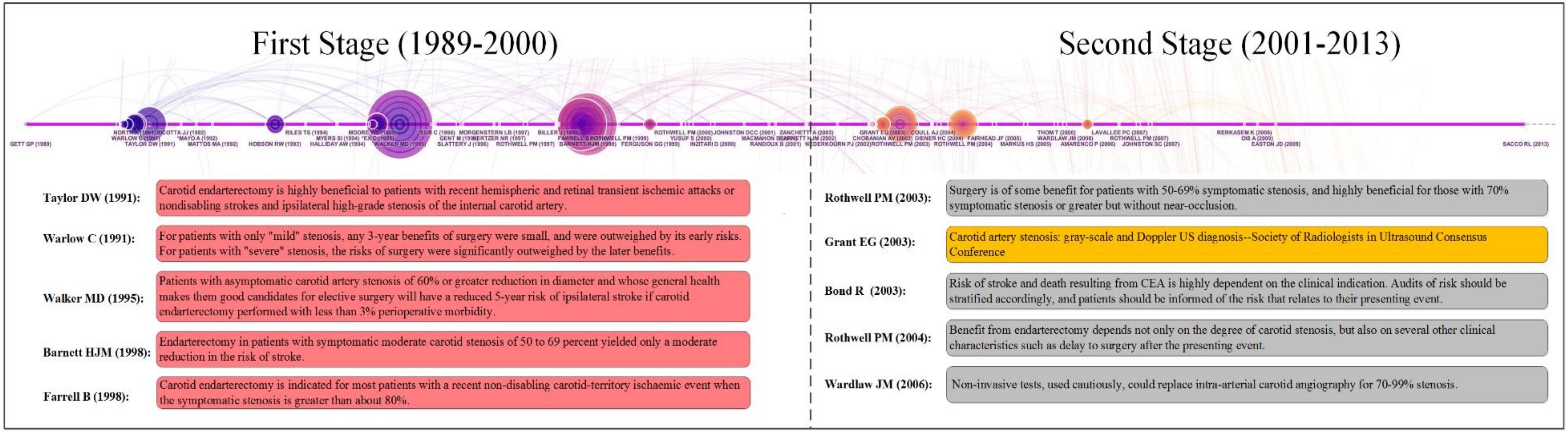

Figure 7 **The top 5 burst references in each stage of Cluster #3.** Randomized controlled trails were marked in red, pooled data analysis and systematic reviews in grey, and guidelines in orange.

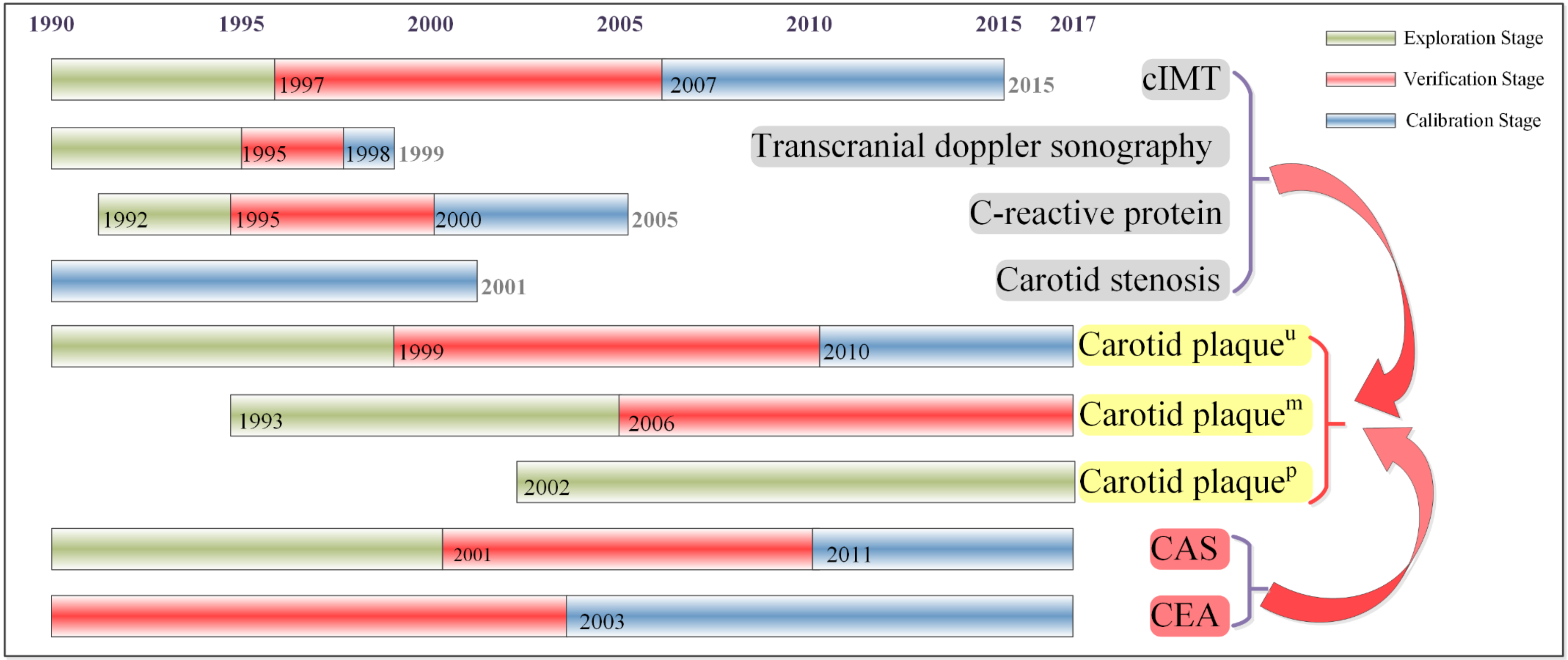

Figure 8 Evolutionary stages of major specialties in CA.

Table 1 Basic information of the top 11 significantly aggregated co-citation clusters.

Cluster ID	Size	% of the network	Silhouette	From	To	Duration	Median	Activeness	Top 3 keywords selected by Log-likelihood ratio test
#0	132	15.47	0.911	1989	2005	17	1996	Inactive	intima-media thickness; carotid stenosis; ultrasound
#1	91	10.67	0.866	1990	2008	19	2001	Inactive	angioplasty; stent; atherosclerosis
#2	75	8.79	0.939	2002	2015	14	2009	Active	carotid intima-media thickness; cardiovascular disease; rheumatoid arthritis
#3	72	8.56	0.799	1989	2013	25	1999	Inactive	carotid endarterectomy; carotid stenosis; atherosclerosis
#4	69	8.09	0.873	2004	2016	13	2010	Active	carotid endarterectomy; stroke; carotid artery stenting
#5	65	7.62	0.873	1993	2013	21	2003	Active	magnetic resonance imaging; vulnerable plaque; intraplaque hemorrhage
#6	48	5.63	0.997	1992	2005	14	1998	Inactive	chlamydia pneumoniae; inflammation; infection
#7	46	5.39	0.935	1990	2001	12	1994	Inactive	cerebrovascular symptoms; atherosclerosis; duplex
#8	29	3.40	0.998	1995	2015	21	2006	Active	arterial stiffness; pulse wave velocity; augmentation index
#9	23	2.70	0.975	2002	2014	13	2009	Active	positron emission tomography; inflammation; molecular imaging
#11	13	1.52	0.968	1990	1999	10	1994	Inactive	transcranial doppler; cerebral embolism; ultrasonics

Table 2 Article with the strongest burst in the top 11 clusters.

Cluster ID	Cluster label	No.	Mean strength	Max strength	Article with strongest burst
#0	intima-media thickness	89	34.63	296.78	Oleary DH, 1999
#1	angioplasty	53	38.69	223.95	Yadav JS, 2004
#2	carotid intima-media thickness	52	44.59	250.19	Lorenz MW, 2007
#3	carotid endarterectomy	46	48.16	255.10	Walker MD, 1995
#4	carotid endarterectomy	42	51.21	265.28	Brott TG, 2010
#5	magnetic resonance imaging	37	31.10	64.38	Takaya N, 2006
#6	chlamydia pneumoniae	30	34.87	239.42	Ross R, 1999
#7	cerebrovascular symptoms	22	20.85	46.87	Mathiesen EB, 2001
#8	arterial stiffness	20	35.90	90.93	Laurent S, 2006
#9	positron emission tomography	10	26.66	50.25	Libby P, 2011
#11	transcranial doppler	10	16.89	24.27	Eliasziw M, 1994

Table 3 Top 25 strongest burst references in Community 2.

Cited references	Citation burst				Cluster ID
	Begin	End	Duration (1997-2017)	Strength	
Taylor DW, 1991, New Engl J Med[146]	1997	1999		**171.36**	**#3**
Warlow C, 1991, Lancet[148]	1998	1999		**103.49**	**#3**
Hobson RW, 1993, New Engl J Med[149]	1997	2001		**84.50**	**#3**
Walker MD, 1995, Jama[151]	1998	2003		**255.10**	**#3**
Diethrich EB, 1996, J Endovasc Surg[119]	1998	2004		**67.50**	**#1**
Yadav JS, 1997, Circulation[123]	1998	2005		**82.74**	**#1**
Barnett HJM, 1998, New Engl J Med[154]	2000	2006		**190.07**	**#3**
Farrell B, 1998, Lancet[153]	2000	2006		**154.53**	**#3**
Brown MM, 2001, Lancet[132]	2003	2009		**118.24**	**#1**
Roubin Gs, 2001, Circulation[285]	2003	2008		**85.32**	**#1**
Rothwell PM, 2003, Lancet[166]	2004	2011		**96.43**	**#3**
Yadav JS, 2004, New Engl J Med[135]	2005	2012		**223.95**	**#1**
Halliday A, 2004, Lancet[191]	2005	2012		**179.10**	**#4**
Rothwell PM, 2004, Lancet[169]	2005	2012		**80.80**	**#3**
Hobson RW, 2004, J Vasc Surg[286]	2006	2012		**64.63**	**#1**
Mas J, 2006, New Engl J Med[136]	2007	2014		**138.71**	**#1**
Ringleb PA, 2006, Lancet[180]	2008	2014		**101.38**	**#4**
Gurm HS, 2008, New Engl J Med[182]	2009	2017		**69.79**	**#4**
Eckstein HhH 2008, Lancet Neurol[181]	2009	2017		**67.31**	**#4**
Abbott AL, 2009, Stroke[199]	2011	2017		**65.65**	**#4**
Liapis CD, 2009, Eur J Vasc Endovasc[287]	2010	2017		**64.03**	**#4**
Brott TG, 2010, New Engl J Med[188]	2011	2017		**265.28**	**#4**
Ederle J, 2010, Lancet[187]	2011	2017		**133.53**	**#4**
Halliday A, 2010, Lancet[194]	2011	2017		**69.32**	**#4**
Kernan WN, 2014, Stroke[4]	2015	2017		**62.81**	**#4**

Table 4 Articles with transformative potential published in recent years (2012–2017).

Citing Articles	F	▵M	∆C	ILs	TLs
Fent Gj, 2017, Ann Rheum Dis[288]	5	1.36	0.21	1	2
Maier A, 2017, Atherosclerosis[279]	0	0.94	0.02	0	2
Chowdhury MM, 2017, Curr Cardiovasc Imag[280]	0	0.93	0	0	2
Sun J, 2016, Neuroimag Clin N Am[5]	2	2.82	0.04	0	5
Bonati Lh, 2016, Neuroimag Clin N Am[282]	5	1.47	0.03	1	2
Brinjikji W, 2016, J Neurosurg[11]	31	0.95	0.04	0	2
Atchaneeyasakul K, 2016, Interv Neurol[289]	1	0.75	0.51	0	1
Sakamoto S, 2016, J Neurointerv Surg[281]	2	0.71	0.01	0	1
Calvet D, 2016, Int J Stroke[290]	5	0.7	0.02	0	1
Vlachopoulos C, 2015, Atherosclerosis[276]	182	2.16	0.12	0	6
Polak JF, 2015, J Am Soc Echocardiog[277]	7	1.33	0.01	0	3
Paraskevas Ki, 2014, Stroke[6]	32	1.84	0.25	0	3
Naylor Ar, 2014, Eur J Vasc Endovasc[278]	33	1.12	0.07	0	2
Martinsson A, 2014, Arterioscl Throm Vas[273]	13	0.85	0	0	2
Lee Cj, 2014, Yonsei Med J[275]	7	0.85	0	0	2
Dratva J, 2014, Swiss Med Wkly[274]	4	0.85	0	0	2
Frerix M, 2014, Arthritis Res Ther[291]	24	0.75	0.01	1	2
Ferket BS, 2014, Plos One[272]	11	0.75	0.01	1	2
Giannopoulos S, 2013, Neurol Sci[270]	10	1.32	0.04	0	2
Eckstein Hh, 2013, Dtsch Arztebl Int[271]	56	1.32	0.04	0	2
Cambria Rp, 2012, J Vasc Surg[268]	3	3.29	0.08	2	6
Abbott Al, 2012, Brain Behav[269]	0	3.29	0.08	2	6
Doig D, 2012, Annu Rev Med[292]	4	2.02	0.09	2	4
Koennecke HC, 2012, Vasa[293]	4	1.5	0.04	1	3
Touze E, 2012, Curr Vasc Pharmacol[294]	7	1.33	0.01	0	2
Kerekes G, 2012, Nat Rev Rheumatol[295]	66	1.33	0.01	0	5
Habersberger J, 2012, Curr Opin Cardiol[296]	4	1.33	0.01	0	2
Tulip HH, 2012, J Vasc Surg[297]	9	1.26	0	0	2
Kakisis JD, 2012, Eur J Vasc Endovasc[298]	43	1.26	0	0	2
Bonati LH, 2012, Cochrane Db Syst Rev[210]	26	1.24	0.05	1	2

F=Frequency; ▵M=▵Modularity; ∆C=∆Centrality; ILs=Incremental Links; TLs=Transformative Links.

Table 5 The three evolutionary stages of CA

	Surrogate markers			New therapeutic methods		
	Main types of burst articles	**Research topics**	**Level of concern**	**Main types of burst articles**	**Research topics**	**Level of concern**
Exploration stage	Cross sectional and case control study	Association discovery; Development of techniques	+	Non-randomized trail	Technical assessment; Development of techniques	+
Verification stage	Cohort study	Association confirmation; Standarlization of measurement technology	++++	RCT	Comparison with traditional therapies; Technical refinement	++++
Calibration stage	Systematic review, Guideline, consensus, Cohort study	Knowledge aggregation; Risk Reclassification	+++	Pooled data analysis, Systematic review, Guideline, consensus, RCT	Comparison with competitive therapies; Knowledge aggregation	++