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. About 10-15% of all strokes follow thromboembolism from a previously asymptomatic carotid artery stenosis >50%. 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. 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. 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”.

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. It is believed that we are now undergoing a paradigm shift towards a new era of plaque-based risk stratifications driven by imaging technologies. 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.

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. This technique is based on the number of citations a reference received in the corresponding year of publication. 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\textsuperscript{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 focus 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\textsuperscript{16-25}. The morphological characteristics, population distribution, determinants and the association with CVDs of carotid artery wall thickness were found\textsuperscript{26-37}. Pharmaceutical studies started to use the imaging indicators of carotid artery wall thickness as the basis for evaluation\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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. The predictive value of cIMT on future vascular events was further confirmed in the younger population. 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.

The year 2008 seemed to be a turning point to this perception. 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. 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. 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.

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. After the efficacy and safety of statin therapy were confirmed by systematic reviews, the combined medication of statins with other drugs, such as torcetrapib, ezetimibe or niacin, became the next focus between 2008 and 2012. In the last few years, the clinical application of statins had expanded to populations such as low-risk individuals with subclinical atherosclerosis.
and apparently healthy persons without hyperlipidemia but with elevated C-reactive protein\textsuperscript{95}.

\textbf{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\textsuperscript{96-105}. A fundamental role was then established for inflammation in mediating atherosclerosis by basic science and epidemiological studies\textsuperscript{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\textsuperscript{113}. But it was also pointed out that inflammatory markers might still be able to measure the characteristics of plaques.

\textbf{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\textsuperscript{114-117}. CAS became a potential alternative to CEA, especially for patients with severe medical comorbidity or recurrent carotid artery stenosis following CEA\textsuperscript{118-129}. However, a randomized trial of CEA vs CAS was stopped primarily because of problems with informed consent\textsuperscript{130}. CAS generated widely divergent opinions about its therapeutic role and called for results from randomized trials\textsuperscript{131}.

The second stage (2001-2008) appeared several high-impact contributions, including 5 randomized controlled trials\textsuperscript{132-136}. The strongest burst reference in this cluster reported a similar effectiveness between CAS and CEA among patients with severe carotid-artery stenosis\textsuperscript{135}. A Cochrane systematic review also found no significant difference in the major risks between these two treatments\textsuperscript{137}. Short and long-term effectiveness of embolic protection devices were evaluated\textsuperscript{138-143}, and the preoperative identification of carotid ulceration and thrombus became the next emphasis in high-risk patient identification\textsuperscript{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\textsuperscript{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. The strongest burst article in this cluster demonstrated that asymptomatic patients could benefit from CEA under several restrictions. New diagnostic tools, especially noninvasive imaging of carotid artery stenosis and vulnerable plaques, became the next hotspot.

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. Factors affecting the benefit from CEA mainly included overall rate of perioperative stroke and death, timing of surgery, operative indications of patients, and causes of stroke. 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.

**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 took the majority of burst articles, in which the perioperative safety and long-term outcomes were the major focuses.\textsuperscript{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.\textsuperscript{188} Meanwhile, magnetic resonance imaging (MRI) were increasingly used in the detection of ischemic brain injury after CAS or CEA.\textsuperscript{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.\textsuperscript{191-199}

The second stage (2011-2016) witnessed the burst of guidelines.\textsuperscript{4,200-204} While the short-term and long-term outcomes of CAS versus CEA were still controversial,\textsuperscript{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.\textsuperscript{4,210} Recent studies focused on issues such as subgroup analysis for risk factors identification,\textsuperscript{211,212} MRI characterization of carotid plaque,\textsuperscript{10} and the embolic reducing technological optimization in CAS.\textsuperscript{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
hyperechoic carotid plaques on ischemic cerebrovascular events became the next focus.\textsuperscript{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,\textsuperscript{240-246} MRI was used in the detection of carotid plaques, which in turn led to the classification of atherosclerotic lesions.\textsuperscript{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.\textsuperscript{250,251} Epidemiological studies found the correlations between carotid plaque characteristics and subsequent ischemic cerebrovascular events.\textsuperscript{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.\textsuperscript{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.\textsuperscript{1,260-262} Positron emission tomography (PET) imaging provided a noninvasive
measure of atherosclerosis inflammation\textsuperscript{263}, which plays a key role in progression and destabilization of atherosclerotic plaque\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{268,269}. However, the role of age and gender in choosing therapeutic modality gained additional evidence\textsuperscript{270}, and studies are still working on the better selection criteria for individually tailored treatment\textsuperscript{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\textsuperscript{272}, and cIMT was even no longer significantly associated with carotid stenosis after adjustments for plaque and systolic blood pressure\textsuperscript{273}. Systolic blood pressure appeared to be a pathological mechanism, indirectly affecting cIMT\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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.
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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.

<table>
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<th>Cluster ID</th>
<th>Size</th>
<th>% of the</th>
<th>Silhouette</th>
<th>From</th>
<th>To</th>
<th>Duration</th>
<th>Median</th>
<th>Activeness</th>
<th>Top 3 keywords selected by Log-likelihood ratio test</th>
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<td>1990</td>
<td>2008</td>
<td>19</td>
<td>2001</td>
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<td>angioplasty; stent; atherosclerosis</td>
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Table 2 Article with the strongest burst in the top 11 clusters.

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Table 3 Top 25 strongest burst references in Community 2.

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<th>Cluster ID</th>
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### Table 4 Articles with transformative potential published in recent years (2012–2017).

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F=Frequency; ΔM=ΔModularity; ΔC=ΔCentrality; ILS=Incremental Links; TLs=Transformative Links.
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<th>Research topics</th>
<th>Level of concern</th>
<th>Main types of burst articles</th>
<th>Research topics</th>
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<td>Non-randomized trail</td>
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<td><strong>Verification stage</strong></td>
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<td>Standardization of measurement technology</td>
<td>+++</td>
<td>RCT</td>
<td>Comparison with competitive therapies; Knowledge aggregation</td>
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