Comparison of drug-coated balloon angioplasty versus standard medical therapy on recurrent stroke and mortality rates among patients with symptomatic intracranial atherosclerotic stenosis: protocol for a systematic review and meta-analysis

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ABSTRACT

Introduction Stroke remains the second leading cause of death worldwide, a common cause of which is intracranial atherosclerotic stenosis (ICAS). Medical treatment is recommended as first-line therapy for treating ICAS, but the recurrence rate remains high. Drug-coated balloon (DCB) angioplasty has been designed to lower the risk of recurrent stenosis, holding therapeutic promise in the treatment of ICAS. However, the benefits of DCB require further evaluation.

Methods and analysis The Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols was followed to develop this protocol. We will systematically search online databases including Cochrane Central Register of Controlled Trials, PubMed, Web of Science, EMBASE, China Biological Medicine Database, ClinicalTrials.gov and WHO ICTRP from 1 January 2011 to the date of search. This will be supplemented by a manual search of unpublished and ongoing trials to manually select articles for inclusion. Inclusion criteria are randomised or quasi-randomised clinical trials and observational studies that investigated DCB or medical treatment for patients with a symptomatic ICAS of 50%–99%. The primary outcome is short-term composite safety including death of any cause, or non-fatal stroke. Secondary outcomes include long-term death or stroke, restenosis, neurological rehabilitation, quality of life and other complications. The available data will be analysed using meta-analysis, if appropriate. The evaluation of heterogeneity and biases will be guided by the Cochrane Handbook for Systematic Reviews of Interventions.

Ethics and dissemination This systematic review does not require ethical approval as all available data from eligible studies will be anonymous with no concerns regarding privacy. Our findings will be disseminated through international conferences and peer-reviewed publications. Additional data from the study are available on request to corresponding authors via email.

PROSPERO registration number CRD42022341607.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The protocol has a clearly established aim, a rigorous study design, reasonable methods and scientific and feasible processes.
⇒ The well-designed search strategies with no language or country restriction will offer a comprehensive and precise search.
⇒ The Grading of Recommendations Assessment, Development, and Evaluation approach will be used to evaluate the overall quality of evidence.
⇒ Included observational studies may be unexpectedly heterogeneous.
⇒ The potential publication bias and limited available studies could reduce the reliability of conclusions.

BACKGROUND

Description of condition Globally, 6.55 million people died of stroke in 2019, making it the second leading cause of death.1 2 Intracranial atherosclerotic stenosis (ICAS) accounts for approximately 10%–20% and up to 50% of ischaemic strokes in Western and Eastern countries, respectively.3–7 ICAS is a chronic inflammatory process leading to progressive stenosis, cerebral hypoperfusion and neurological dysfunction.8 9 For patients with ICAS of more than 70% luminal stenosis, the recurrent risk of stroke exceeds 20% within 1 year.10 With population growth, ageing and lifestyle changes, it is expected that the incidence of ICAS and the resulting stroke burden will continue to increase in the coming years, especially in developing countries.11 12
Description of the interventions

The treatment of ICAS mainly includes medical and endovascular approaches. According to the latest guidelines from the American Stroke Association, medical treatment is preferred as the first-line therapy for treating ICAS and preventing stroke or transient ischaemic attack (TIA) recurrence. Specifically, it includes short-term dual antiplatelet therapy (aspirin and clopidogrel), statins, blood glucose and pressure control, combined with lifestyle modifications such as dietary interventions, physical activity and smoking cessation. Among patients with symptomatic ICAS, aggressive medical treatment has shown benefit in prevention of subsequent stroke, but the stroke recurrence and death rates remain relatively high. There is an urgent need to explore more effective treatments, including endovascular therapy (EVT), also referred to as percutaneous transluminal angioplasty and stenting (PTAS).

EVT is a minimally invasive technique to recanalise narrowed or obstructed blood vessels. Typical approaches for ICAS include percutaneous transluminal balloon angioplasty (PTA), self-expanding stents (SES) or balloon-mounted stents (BMS). When suffering acute cerebral vascular events, some patients undergo EVT as rescue therapy. PTA alone may apply pressure to the stenotic artery wall through balloon dilation, effectively dilating the lumen and restoring blood supply. Despite more frequent postoperative residual stenosis, PTA alone may offer higher short-term safety and comparable long-term mortality and stroke rate compared with SES or BMS. In the Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) trial, the occurrence of stroke or death in the PTA with SES group was significantly higher than the medical group at 30 days (14.7% vs 5.8%, p=0.0016) and at 3 years (23.9% vs 14.9%, p=0.0193). Similarly, the Vitesse Intracranial Stent Study for Ischaemic Stroke Therapy (VISSIT) trial demonstrated that aggressive medical therapy alone was superior to BMS for patients with ICAS and was terminated owing to safety concerns about high adverse event rates within 30 days in the stenting group (24.1%).

With refined patient selection and improved surgeon experience, the China Angioplasty and Stenting for Symptomatic Intracranial Severe Stenosis (CASSISS) trial reported a reduced 30-day rate of stroke or death in the PTAS group (5.1%) compared with SAMMPRIS and VISSIT. However, no significant difference in the 30-day rate of stroke or death or stroke rate up to 1 year was reported (p=0.82). Altogether, these three multicentre randomised controlled trials (RCTs) did not support stent implantation for treating ICAS, which was attributable to high peri-procedural complication rates and in-stent restenosis rate.

The underlying mechanism of in-stent restenosis is associated with intracranial arterial intimal hyperplasia and smooth muscle cell proliferation due to dilation trauma, thrombogenicity and the inflammatory response. To overcome this limitation of PTAS, drug-coated balloons (DCBs) have been developed and successfully used to treat small coronary artery disease. DCBs are mostly semicompliant balloons, allowing a rapid and homogeneous release of antiproliferative drugs from the balloon matrix to the vessel wall after the inflated balloon contacts it. At present, several studies have demonstrated the safety and effectiveness of DCB in ICAS treatment, with a low intracranial complication rate (0%–6.7%) and a low recurrence rate (0%–3.2%). DCB is related to slow progression of stenosis and able to effectively lower the degree of restenosis and total restenosis risk, making it a promising alternative treatment with benefits to patients.

Rationale for the current systematic review

Currently, medical treatment is the primary option for patients with ICAS, but for patients suffering symptomatic ICAS, there remains a high risk of recurrent cerebral ischaemic events and death, making PTAS a potential alternative therapy. Nevertheless, PTAS may cause in-stent restenosis and severe complications such as bleeding and have no advantage over medical therapy alone. High restenosis rates of 18%–20% and 23%–30% have been reported for BMS and SES, respectively, making DCB a potentially lower-risk option for patients suffering symptomatic high-grade ICAS. One study reported that compared with SES, DCB resulted in a significantly lower rate of occurrence of recurrent ischaemic events and/or restenosis (13% vs 64%; p=0.03). Furthermore, DCBs have been applied to resolve in-stent stenosis, showing a lower restenosis rate of 9% vs 50% of conventional balloons. With the advantage of no permanent implants and relatively simple procedure, DCB can not only avoid the risks of in-stent restenosis, stent thrombosis, stent fracture and metal allergy, but also shorten the duration of postoperative dual antiplatelet therapy, thereby reducing bleeding complications. DCB appears to be a superior endovascular strategy for treating patients with ICAS. We believe that the potential of DCB warrants collation and analysis of the existing data in a systematic review and meta-analysis as:

- To date, the reported rates of peri-procedural complications and restenosis among patients undergoing DCB angioplasty have varied widely, ranging from 0% to 11.4% and 0% to 15%, respectively.
- The sample size of current studies is small, and the quality of single-study evidence is limited.
- The safety and efficacy of DCB requires further investigation.
- Whether DCB is superior, inferior or equal to medical therapy for ICAS is unclear.
- Insufficient evidence exists to include DCB within treatment guidelines.
- Additional evidence is needed to help clinicians and patients make informed decisions about treating ICAS with DCB.
OBJECTIVES
We aim to compare the safety and efficacy of DCB angioplasty versus standard medical treatment in patients with symptomatic ICAS.

METHODS
This protocol is completed under the guidance of Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) Protocols and the checklist items are detailed in online supplemental file 1. Our systematic review has obtained a registration number CRD42022341607 from the PROSPERO database, where we will record any revision and update our study process. We will conduct the study following the recommendations of the Cochrane Handbook.

Criteria for considering studies for this review
Types of studies
The first attempt to treat intracranial stenoses with DCBs published in 2011. In order to compare DCBs with medical therapy since both have been available treatments, we will include clinical trials (RCTs or quasi-RCTs), and observational trials (cohort studies, case–control trials, case series reports with sample size ≥n=10) that investigated DCB or medical treatment for patients with symptomatic ICAS from 1 January 2011 to the present. There will be no restrictions on language, and we will translate articles as necessary. Other articles including reviews, comments, protocols, editorials, letters, case reports or case series reports with sample size <10, experimental studies and conference abstracts without exhaustive data will be excluded (table 1).

Types of participants
Studies that include patients meeting the following criteria will be included:
► Age ≥18 years.
► Any gender or race.
► Symptomatic ICAS of 50%–99%.
► At least one major intracranial artery, including vertebral artery, basilar artery, middle cerebral artery, internal carotid artery and their major branches, is stenosed.
► Digital subtraction angiography (DSA) and the standard Warfarin–Aspirin Symptomatic Intracranial Disease method are used to verify the degree of stenosis.
► Clinical manifestations: stroke and/or TIA attributable to hypoperfusion in the territory of the stenosed vessel. A TIA is defined as a transient episode of neurological dysfunction caused by focal brain, spinal cord or retinal ischaemia, with no acute infarction but high risk of early stroke and recovery of symptoms within 24 hours.

Exclusion criteria include non-atherosclerotic lesions, asymptomatic stenosis, no follow-up and indistinguishable data (see table 1 for more details).

Types of interventions
DCB angioplasty is defined as a balloon carrying anti-proliferative drugs implemented by a percutaneous endovascular catheter to dilate the vascular lumen and prevent restenosis. Medical treatment aims to prevent the progression of stenosis through antithrombotic therapy (antiplatelet drugs or anticoagulant drugs alone or in combination) along with aggressive management of risk factors.

Table 1 The criteria for inclusion and exclusion of studies
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<th>Criteria</th>
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<tr>
<td>Inclusion</td>
<td>1. Studies investigating DCB or medical treatment for ICAS. 2. Patients (≥18 years) with a symptomatic ICAS of 50%–99%.</td>
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<td>- Symptoms: stroke and/or TIA. - Involved sites: ICA, MCA, VA, BA or their major branches. - Imaging: DSA.</td>
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<tr>
<td>Exclusion</td>
<td>1. Patients with asymptomatic stenosis or without follow-up. 2. The intracranial stenosis caused by non-atherosclerotic lesions: cardiac embolism, moyamoya disease, vasculitis, arterial dissection, fibromuscular dysplasia, sickle-cell disease, neurofibromatosis. 3. Impossible to distinguish between intracranial and extracranial stenosis, or between atherosclerotic and non-atherosclerotic stenosis. 4. Impossible to differentiate DCB from other endovascular treatments for ICAS. 5. The detailed outcome information is not available. 6. Repetitive publications or overlapping populations. We will retain the most recent and complete report with the largest sample size. 7. Reviews, comments, protocols, editorials, letters, case reports or case series reports (sample size &lt;10), animal trials and conference abstracts without exhaustive data.</td>
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BA, basilar artery; DCB, drug-coated balloon; DSA, digital subtraction angiography; ICA, internal carotid artery; ICAS, intracranial atherosclerotic stenosis; MCA, middle cerebral artery; TIA, transient ischaemic attack; VA, vertebral artery.
Studies evaluating DGB or standard medical treatment for ICAS will be included according to the following characteristics:
1. Studies reporting on angioplasty groups should involve DGB angioplasty, regardless of whether there exists a background of medical treatment.
2. Studies reporting on standard medication groups should consist of medical treatment only and be dominated by antithrombotic therapy.

Types of outcome measures
Studies considered for inclusion should report at least one of the following primary and secondary outcomes:
- Short-term safety and/or efficacy in the perioperative period, or follow-up ≥30 days.
- Long-term safety and/or efficacy with follow-up ≥30 days.
- Restenosis, defined as a stenosis of ≥50% from no stenosis or ≤50% stenosis assessed by DSA, ultrasound or other detection methods during the follow-up period with/or without clinical symptoms.

Primary outcomes
- Short-term safety of DGB angioplasty, compared with standard medical treatment including death of any cause, or non-fatal stroke (either ischaemic or haemorrhagic) in the territory of stenosed artery.

Secondary outcomes
- Death or stroke of any type (long term).
- Stroke in the qualifying artery territory.
- The short-term or long-term restenosis of the involved vessel, classified as: (1) symptomatic or (2) asymptomatic.
- Types of recurrent events (TIA, ischaemic stroke, haemorrhagic stroke).
- Other complications, classified as: (1) major complications requiring additional therapy or causing death, (2) minor complications including haematoma, wound infection, nerve palsy.
- Functional status and neurological rehabilitation evaluated using the modified Ranking Scale (mRS). We consider mRS Score ≤2 within 90 days as favourable prognosis.
- Health-related quality of life.

Search methods for identification of reviews

Electronic searches
The following online databases will be systematically searched:
- Cochrane Central Register of Controlled Trials.
- PubMed.
- Science Citation Index (Web of Science).
- EMBASE.
- China Biological Medicine Database.

Considering inappropriate randomisation procedures reported in many RCTs published in Chinese journals, we will review their study design and decide on their inclusion.45 Two investigators will independently retrieve relevant studies published from 1 January 2011 to the date of the searches, with no restrictions on language or country. Translation will be arranged if required. Search keywords include: ‘drug-coated balloon’, ‘antithrombotic therapy’, ‘intracranial stenosis’ and ‘intracranial arteriosclerosis’. The detailed search string is provided in online supplemental file 2, which has been drafted and revised by an experienced doctor according to the Peer Review of Electronic Search Strategies Evidence-Based Checklist.46

We will also visit the following websites of trial registries for ongoing trials:
- US National Institutes of Health Ongoing Trials Register (www.clinicaltrials.gov/).
- WHO International Clinical Trials Registry Platform (https://trialssearch.who.int/).

Searching other sources
Electronic searches will be complemented by manual searches of other sources. Selective reporting of clinical trial results leads to unrealistic and exaggerated estimates of effectiveness, thus the inclusion of unpublished data is of importance.47 In an effort to search for studies as extensively as possible to reduce potential publication bias, we plan to:
- Hand-search the reference lists of all identified relevant articles and previous reviews on the same topic for additional studies.
- Use OpenGrey (https://opengrey.eu/) to identify grey literature such as reports, dissertations and conference proceedings, where negative results are more likely to be reported.
- Contact relevant manufacturers and experts in the field about unpublished or ongoing studies and request raw data from the corresponding authors, if necessary.

The search will be rerun prior to assessing studies for inclusion to ensure the comprehensiveness of our searches.

Data collection and analysis

Selection of studies
We will initially remove duplicates from the studies retrieved by the search and calculate inter-rater reliability through predesigned screening pilot-test forms (online supplemental file 3). The following selection process will be performed at high consistency: kappa statistic ≥80%.48 First, two reviewers (YS and HG) will independently screen the titles and abstracts of the obtained literature to determine whether a study meets the inclusion criteria and exclude obviously irrelevant references. Then, the full text of the remaining articles will be retrieved and assessed for inclusion or exclusion by two independent reviewers. Study authors may be contacted for more adequate information and the reasons for study exclusion will be recorded. In cases of repetitive publications or overlapping populations, we will retain the most recent and complete report with the largest sample size. Any disagreements will be resolved by discussion or, when
necessary, by the involvement of a third reviewer (TW). We will also complete a PRISMA flow diagram on the basis of the selection process (figure 1).

Data extraction and management
A standard information extraction form will be designed in advance to ensure consistency of information extracted from each included study. Two reviewers will independently extract the following items from eligible studies:
1. Article characteristics: title, first author, journal, publication date, study design, sample size, region, funding and volume of the study centre.
2. Outcome data: number of outcome events (e.g., stroke, TIA, death and restenosis), total number of patients and duration of follow-up.
3. Participant characteristics: gender (%), age (median or mean), lesion location, the length of the lesion, preprocedural degree of stenosis, number of strokes, pathogenesis, time from symptoms to intervention, and history of hypertension, diabetes mellitus, medicine, smoking and alcohol intake.
4. Intervention characteristics: types of DCBs, success rate of angioplasty, ratio of degree of stenosis before and after treatment, residual stenosis, types and dosage of drug used.

A pilot test to calculate inter-rater reliability will be conducted to achieve high agreement (≥80%) before formal data extraction. A third reviewer will be consulted if disagreements cannot be resolved through discussion. We will contact the principal investigators to request missing details or clarify ambiguous information. The completed data collection form will be reviewed by the third author for accuracy.

Assessment of risk of bias in included studies
The risk-of-bias assessment for each study will be performed by two raters independently. For RCTs, the following domains will be evaluated with ‘high risk’, ‘low risk’ or ‘unclear’ using the Cochrane Collaboration risk-of-bias tool:\41

- Random sequence generation.
- Allocation concealment.
- Blinding of participants and personnel.
- Blinding of outcome assessment.
- Incomplete outcome data.
- Selective outcome reporting.
- Other biases such as the trial not being registered.

Figure 1 Flow diagram of the study selection process.
For observational studies (cohort and case–control studies), we will assess their risk of bias by the Newcastle-Ottawa Scale (NOS) (online supplemental file 4). Studies with NOS scores more than 5 will be considered high-quality studies. We will resolve any discrepancies between the two raters by discussion or by inviting another reviewer. The summary and judgement process for each study will be recorded in detail in the ‘risk-of-bias’ tables.

Assessment of heterogeneity
Poor overlap of the CIs across studies indicates statistical heterogeneity, which reduces the confidence of the recommended treatment. We will quantitatively assess heterogeneity between studies using $I^2$ statistic in RevMan software and consider $p<0.05$ to be statistically significant. $I^2$, ranging from 0%–100%, illustrates the percentage of the variability in effect estimates resulting from differences between studies rather than sampling error. The value of ≤50% represents acceptable heterogeneity. If $I^2$ statistic is >50%, we will explore possible sources of any substantial heterogeneity through: (1) examining the intervention types and participant characteristics to evaluate clinical heterogeneity quantitatively; (2) conducting subgroup analysis to investigate hidden heterogeneity qualitatively.

Dealing with missing data
We will try to contact corresponding authors in an attempt to obtain missing data of the included studies, as necessary. If there is no response to our request, we will carry out intention-to-treat (ITT) analysis according to the Cochrane Handbook. If ITT is not feasible, we will only analyse the available data. Furthermore, a sensitivity analysis will be performed to probe the impact on the final results, which will be presented in the discussion section of the review.

Assessment of reporting biases
A systematic literature retrieval, inclusion of unpublished studies when eligible and appropriate, and the use of trial registries, are intended to minimise reporting biases in the review. Correspondence is also a recommended source of additional information about unpublished studies. When at least 10 studies are included, a funnel plot will be used for qualitatively assessing reporting biases or small study effects, and funnel plot asymmetry testing, such as Egger’s test, will measure biases quantitatively. Nevertheless, a symmetrical funnel plot cannot exclude publication bias.

Data synthesis and analysis
We will describe dichotomous variables as OR or risk ratio (RR) with 95% CI and describe continuous variables as standardised mean differences or weighted mean differences with 95% CI. Clinically, it is common to interpret OR as RR; however, this overestimates the effect. We will perform meta-analyses of the primary and secondary endpoints, based on sufficient available data from clinically similar target populations and outcome measures. We plan to compute pooled estimates of data corresponding to outcomes by fixed-effect models using RevMan software (V.5.4.1, The Cochrane Collaboration). We will rerun any meta-analysis under random effects models in the presence of significant heterogeneity in the results ($I^2$ statistic>50%). RStudio with R language (V.4.2.2) may be used for more complex analyses, if required. If it is not possible to perform a meta-analysis due to insufficient data or inappropriate quantitative synthesis, we will narratively report the results.

Sensitivity analysis
To support the stability of our findings, we will carry out a sensitivity analysis of the primary endpoint with a sufficient number of eligible studies. The impact of bias on results will be evaluated by analysing studies with low risk of bias.

Subgroup analysis
As previously described, subgroup analyses will be undertaken to further investigate potential causes of substantial heterogeneity. The following subgroup analyses are planned, dependent on sufficient available data:
1. Types of DCB.
2. Degree of stenosis.
3. Location of stenosis.
4. Volume of the study centre or number of recruiting centres (single-centre vs multicentric studies).
5. Timing of the procedure.

Certainty of the body of evidence
For all outcomes, the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach will be used to appraise the quality of evidence. Generally, RCTs and observational studies areas high-quality and low-quality evidence, respectively.

There are five factors for downgrading a rating:
► Study limitations.
► Imprecision.
► Inconsistency of results.
► Indirectness of evidence.
► Publication bias likely.

There are three factors for upgrading a rating:
► Large magnitude of effect.
► Dose–response.
► Confounders likely minimise the effect.

Ultimately, the GRADE quality will be judged by two independent reviewers as one of four categories—high, moderate, low and very low—for each body of evidence, not a single study.

DISCUSSION
Currently, there are many challenges in the treatment of ICAS despite advances made in medical treatment. Although guidelines recommend dual antiplatelet therapy plus risk factor management as the preferred treatment for preventing stroke or TIA, their efficacy is...
not satisfactory because of a high recurrence rate. DCB angioplasty shows promise in reducing restenosis rate, is easy to use, and is relatively safe for patients because there is no permanent implant, compared with stenting.

To the best of our knowledge, this will be the first systematic review and meta-analysis comparing DCB angioplasty with medical therapy for recurrent stroke and mortality among patients with symptomatic ICAS. Our review will offer a comprehensive assessment of DCB and medical therapy in the treatment of ICAS with the aim to help clinicians and patients choose optimal interventions and provide a new evidence base that supports the development of future clinical guidelines and trial designs.

We should acknowledge several limitations of this review. The results will be based on and also restricted by the included studies. There may be a limited number of eligible studies on this topic with mixed quality. Included observational studies may be unexpectedly heterogeneous. In cases of insufficient data, the quantitative evidence synthesis will be challenging.

Biases are inevitable and cannot be removed completely, although we will choose the optimal methodology to reduce the bias according to the specific conditions. The potential publication bias can reduce the reliability of the cumulative evidence. To obtain adequate statistical power, observational studies will be included. There is no doubt that they will affect the quality of the evidence. We will consider only synthesising the results of RCTs to assess the robustness of the final findings and discuss variation.

In the time span of the selected articles, the development of DCB type and medical therapy could have influence on the therapeutic effect. We will continue to track the field and update the results. Moreover, a further verification by RCTs or cohort studies will need to be conducted in the future.

Ethics and dissemination
This systematic review does not require ethical approval as all available data from eligible studies will be anonymous with no concerns regarding privacy. Our findings will be disseminated through international conferences and peer-reviewed publications. Additional data from the study are available on request to corresponding authors via email.

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Contributors YS, JL and HG contributed equally to this paper. LJ and TW conceived this protocol. YS and HG accomplished the study design under the supervision of YM and XZ. LJ and TW were consulted about clinical issues and responsible for important intellectual content. BY, YS, JL and TW were involved in the development of search strategy. The original manuscript was drafted by YS and JL, and critically revised by TW, HG and RX. All authors read and approved the final manuscript.

Funding This work was supported by the Beijing Hospitals Authority’s Ascent Plan (DFL20220702), Xuanwu Hospital Talent Seed Program (YCY2020120) and Beijing Municipal Health Commission (11000023T000002036320).

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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