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Recurrence of cervical artery dissection: protocol for a systematic review

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ABSTRACT

Introduction Cervical artery dissection, including carotid and vertebral artery dissection, is an important cause of stroke in the young. Risk of developing cervical artery dissection has been associated with physical activity in various forms and has been presumed to be related to minor trauma and mechanical stretching of the cervical arteries. This systematic review will aim to synthesise data on the risk of recurrent cervical artery dissection after an initial dissection. This information may be applied to further understand the natural history of this disease, and potentially to help direct evidence-based discussions on safe return to activity after dissection.

Methods and analysis A broad search of multiple electronic databases (Medline, Embase, Cochrane Central Register of Controlled Trials and Web of Science) will be conducted to identify studies published as of 13 November 2019, examining all-comers with cervical artery dissection observed over time. Studies will be screened by two independent reviewers in a two-level process to determine eligibility for inclusion. Data will be pooled from eligible articles and the main outcome of recurrent cervical artery dissection at 5 years will be determined using quantitative analysis.

Ethics and dissemination Ethics approval is not necessary as no primary data are being collected. The information will be disseminated in the form of a systematic review article which will be submitted to a peer-reviewed medical journal.

PROSPERO registration number CRD42020166105.

Strengths and limitations of this study

► This systematic review protocol was developed in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols checklist.
► This a priori protocol will allow for a standardised and predetermined method of rigorously collecting and assessing data.
► The broad search strategy employed will aim to amalgamate all available data on this subject to answer an important clinical question.
► Given the relative rarity of initial and recurrent dissections, there may be a limited number of eligible studies on this topic, and potential publication bias could reduce the confidence in the cumulative evidence.
► Subgroup analysis on incidence of recurrent dissection in different patient populations may be challenging depending on the extent of patient-level data reported, which could limit the clinical applicability to individual patients.

INTRODUCTION

Cervical artery dissection, including carotid and vertebral artery dissection, has an estimated incidence of 3.5–4.5 per 100 000.[1] It is an important cause of stroke in the young, particularly in otherwise healthy patients without traditional vascular risk factors. It has been identified as the cause of up to 1 in 4 strokes in young adults,[2] but can affect patients of any age, with a peak incidence in the fifth decade of life.[1] Cervical artery dissection may also be associated with Horner's syndrome, head or neck pain, or may be discovered incidentally. Known risk factors for cervical artery dissection include connective tissue disorders, hypertension, certain infections and major trauma.[3] Cervical artery dissection is frequently associated with participation in sports and physical activity, presumably related to minor trauma or neck movements causing mechanical stretching of these vessels.[4 5] In case reports, cervical artery dissection has been associated with running,[6 7] swimming,[8] golf,[9] extreme conditioning programmes,[10] waterskiing[11] and volleyball,[12] among other examples.[4]

Patients who have sustained a cervical artery dissection frequently ask physicians how likely they are to suffer from another dissection in the future. There are individual studies examining the risk of recurrent cervical artery dissection, but no systematic reviews exist on this topic. This systematic review will aim to aggregate and synthesise previously published results to address the following question: In all-comers who have had a cervical artery dissection, what is the incidence of recurrent dissection? The main goal of this systematic review will be to report the incidence of recurrent cervical artery dissection with a larger sample size than in previous individual

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studies. If possible, we will aim to report on incidences within different subgroups (detailed in the data synthesis section) to improve the clinical utility of results, however limited patient-level data may preclude this analysis.

The information gathered from this systematic review may enable physicians to advise patients on what to expect after a cervical artery dissection with a greater degree of confidence, and may be helpful when counselling patients on safe return to activity after a dissection. At present, there is no consensus on how to direct evidence-based discussions on return to activity, but an accurate estimation of the risk of recurrent cervical artery dissection may be a helpful starting point.

METHODS AND ANALYSIS

This a priori protocol for a systematic review was developed in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols guidelines (see online supplemental appendix for checklist). Any important amendments to the protocol will be documented clearly in the final systematic review.

Eligibility criteria
Study characteristics
In order to be eligible for inclusion in this systematic review, the following elements (Population, Intervention, Comparison, Outcome) will be evaluated:

Population
All-comers (male and female children and adults of all ethnicities) who have been diagnosed with cervical artery dissection, with or without resultant stroke. Cervical artery dissection will be defined as an extracranial dissection of one or more of the carotid (common or internal) or vertebral arteries at any location. Patients with multiple cervical artery dissections at the time of initial imaging will not be excluded, including patients with both carotid and vertebral artery dissections. Diagnosis should be confirmed by imaging (including conventional angiography, CT angiography, magnetic resonance angiography or Doppler ultrasound imaging). Of note, 20% of cases of dissection in the CADISS trial could not be confirmed following central review of imaging,[13] highlighting the challenges in definitive diagnosis. Studies that do not list their radiological diagnostic criteria will not be excluded but any specific criteria used for diagnosis will be noted in the data extraction form and this will be considered in the final interpretation of results. Patients known for concomitant diagnosis of connective tissue disease will not be excluded.

Intervention
Watchful waiting, in addition to any secondary prevention measures instituted at the discretion of the practitioner, including antiplatelet agents, anticoagulation and cervical artery stenting. This information will be captured in our data extraction form.

Comparison
Not applicable in this case, given that the goal is to accumulate data on the natural history of cervical artery dissection rather than compare the efficacy of one treatment to another or to placebo.

Outcome
Incidence of a recurrent event of cervical artery dissection, in the same or another vessel, diagnosed at any point after the initial imaging study confirming diagnosis of dissection.

Eligible study types will include case series, prospective and retrospective observational studies, and arms of randomised controlled trials. Case reports and review articles will be excluded. A study follow-up of a minimum of 1 month will be required for inclusion, in order to adequately assess for recurrence risk. This minimum follow-up interval was chosen as some studies suggest that in cases of recurrence, early recurrence within the first month is most common, so a period of 1 month is likely to capture the majority of incidences of recurrence.[14 15]

Report characteristics
Articles in languages other than English or French will be excluded to reflect the functional capabilities of the reviewers. Abstracts without full text will be excluded, as will protocols, supplements and articles in press. There will be no restrictions on publication date in order to garner the most data possible on natural history of cervical artery dissection, so any articles published prior to the search date of 13 November 2019 will be included.

Information sources
We will employ the search strategy detailed below in the following electronic databases: Ovid Medline, Embase, Cochrane Central Register of Controlled Trials and Web of Science.

Search strategy
Full search strategies for all databases above are included in the online supplemental appendix.

Study records
Data management
Covidence software program will be used to manage records and data.

Selection process
The process of study selection will be completed in a two-level process by two independent reviewers. During both phases, reviewers will make reference to a predesigned screening form (figure 1). These forms will be tested with a pilot exercise in which it is applied by each reviewer to the first 100 articles obtained, to ensure adequate inter-rater reliability, at which point it will be further refined as necessary. In the first level of screening, each reviewer will screen the title and abstract of the article to determine potential eligibility. If potentially eligible, the article will be then assessed in the second phase. In

1. **Is this study in a language other than English or French?**
   Yes: stop here, article is excluded
   No: proceed to next item

2. **Is this study an abstract only, a supplement, a protocol, or currently in press?**
   Yes: stop here, article is excluded
   No: proceed to next item

3. **Is this study a review article?**
   Yes: stop here, article is excluded
   No: proceed to next item

4. **Is this study a case report?**
   Yes: stop here, article is excluded
   No: proceed to next item

5. **Does this study include patients who have had a cervical (carotid or vertebral) artery dissection?**
   Yes: proceed to next item
   No: stop here, article is excluded

6. **Was the cervical artery dissection confirmed with imaging?**
   Yes: proceed to next item
   No: stop here, article is excluded

7. **Does this study's outcomes include recurrence of cervical artery dissection?**
   Yes: proceed to next item
   No: stop here, article is excluded

8. **Does this study include follow-up for a minimum of 1 month?**
   Yes: article is eligible for inclusion
   No: stop here, article is excluded

Figure 1 Predesigned screening form to be used in both phases of screening to determine eligibility for inclusion in the systematic review.

the second phase, each reviewer will examine the full text of the article to determine final eligibility and candidacy for data extraction. Any disagreements between the two reviewers during either phase will be adjudicated by a third reviewer. In the event that the full text of an article is not available, it will be requested through an interlibrary loan or purchased.

Data collection process
Data will be extracted in a systematic way from eligible articles by two independent reviewers using a preconceived data extraction form (figure 2).

Data items
The data items listed in figure 2 will be collected where available. We acknowledge that some items may not be documented, for instance certain data on patient-specific individual recurrence events, however we anticipate that in some studies, the number of incidences of recurrent dissection may be small enough that authors may choose to report qualitative data for those cases.

Outcomes and prioritisation
The main outcome of this review will be the incidence of recurrent dissection at 5 years. Secondary outcomes will include incidence of early and intermediate recurrent dissection at 1 month and 1 year respectively, and risk of recurrent stroke, defined as incidence of diagnosis of stroke attributed to recurrent cervical artery dissection at any point during the follow-up period. Collection of data for stratification of early

compared with late recurrence will be helpful in reinforcing evidence from studies that suggest early recurrence is more common.[14 15] If recurrence risk is front-loaded, this would in turn be useful information in counselling patients on how best to return to activity safely. Data will also be collected, where possible, on items that are potential risk factors for recurrent dissection, including coexistence of known connective tissue disease. If available, data will be collected on mechanism of initial dissection, which will be labelled as traumatic (defined based on existing literature as any identified preceding event in the 1 month prior to diagnosis of dissection, including motor vehicle accident, cervical manipulation, sports or physical activity, extreme neck movements or positions, or lifting heavy loads) or spontaneous, in which there is no identified preceding event.[16] Analysis of this data could provide interesting insights, as an initial spontaneous dissection may imply greater susceptibility to vessel injury and possibly increased risk of recurrent dissection.

Risk of bias in individual studies
As we anticipate that most eligible studies will be observational, risk of bias will be assessed using Hoy *et al*'s risk of bias tool for prevalence studies. This information will be used to stratify studies into low-quality and high-quality subgroups, for subsequent subgroup analysis.

Data synthesis
Data will be descriptively summarised by reporting the number of studies excluded and the final number of studies included, categorised into the type of study design employed. We will also descriptively synthesise the demographic and clinical characteristics of the included studies. Incidence rates at 5 years, 1 year and 1 month will be calculated for each of the studies and presented along with their respective 95% CIs. In the absence of clinical and methodological heterogeneity, pooling of incidence rates will be undertaken by weighting by the inverse of the variance. Subgroup analysis will be performed on the higher quality studies following assessment of risk of bias. We anticipate that subgroup analysis of clinical factors will likely not be possible as there will likely be limited patient-level or stratified data available. If sufficient data are reported, we will conduct subgroup analysis of the main outcome of recurrent dissection at 5 years in each of the following subgroups: male patients, female patients, patients younger than 50 years old, patients older than 50 years old, patients with connective tissue disease, patients without connective tissue disease, patients with carotid artery dissections, patients with vertebral artery dissections, patients with traumatic dissections and patients with spontaneous dissections. Subgroup-specific incidence rates and 95% CIs will be calculated and presented. There is no planned formal comparison between the subgroups.

Meta-bias
We acknowledge the effect of publication bias, particularly in case series, which may lead to increased reporting of recurrences of dissection, rather than the absence of recurrence.

Bibliographic data	Article title	
	First author last name	
	Publication year	
	Country	
	Funding source	
Study design data	Study design	
	Length of follow-up period	
Study population data	Number of participants	
	Age data	
	Gender data	
	Does the article include patients with connective tissue disease?	
	Prevalence of connective tissue disease	
	Vessel(s) affected by initial dissection (carotid versus vertebral artery versus multiple vessels)	
	Specified radiologic diagnostic criteria?	
	Diagnosis of stroke at the time of dissection?	
	Mechanism of initial dissection (traumatic versus spontaneous)	
	Treatment with antithrombotics (none, single antiplatelet, dual antiplatelet therapy, or anticoagulation)	
	Treatment with stenting?	
Outcome data	Incidence of recurrent dissection at 5 years	
	Incidence of recurrent dissection at 1 year	
	Incidence of recurrent dissection at 1 month	
	Incidence of stroke from recurrent dissection	
	If specified, any further qualitative data on individual recurrences, including time since initial dissection, vessel affected, mechanism of recurrent dissection	

Figure 2 Data extraction form to be used for systematic data collection from eligible articles.

We recognise this as a possible pitfall and will consider this in the ultimate interpretation of the evidence.

Confidence in cumulative evidence
The potential for publication bias above, as well as an anticipated small number of eligible studies, will diminish our confidence in the cumulative evidence.

PATIENT AND PUBLIC INVOLVEMENT
The initial development of the research question was informed by several clinical experiences involving young, healthy patients who sustained cervical artery dissections during physical activity. The question arose on how to advise patients on return to activity, which in the cumulative experience of the authors, is a common question from this patient population. Patients were not directly involved in design or dissemination of the study.

ETHICS AND DISSEMINATION
No research ethics board approval is required for this study as no primary data are being collected. Once data are collected and analysed, the systematic review will be submitted to a peer-reviewed medical or neurological journal.

data extraction items. EL and DAF developed a data synthesis strategy. EL drafted the protocol manuscript, and it was reviewed by BD, DAF, MS and DD. EL acts as the guarantor of the review.

Author note Study dates: Study was commenced in October 2019 with expected completion before June 2022.

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