Cervical artery dissection

Evidence update

May 2017

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Version	Final

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Abbreviations

AE	Adverse Event
ASA	American Stroke Association
AHA	American Heart Association
CAD/ CeAD	Cervical Artery Dissection
CADISP	Cervical Artery Dissections and Ischemic Stroke Patients
CMT	Cervical Manipulative Therapy
cSMT	Cervical Spinal Manipulation Therapy
iCAD	internal Carotid Artery Dissection
OR	Odds Ratio
PCT	Prior Cervical Trauma
SR	Systematic Review
VAD	vertebral artery dissection

1 Background and purpose

1.1 Objective

The objective of this review is to update the 2012 ACC report on cervical artery dissection (CAD) and focus on reports on whether techniques like cervical manipulation that may be applied by physiotherapists, chiropractors, or osteopaths is associated with the occurrence of an arterial dissection of the internal carotid or vertebral arteries.

This is a rapid review of the peer-reviewed academic literature that reports the results of a systematic search of the academic literature and critical appraisal of the included papers related to the objective of the report.

1.2 Background

Cervical artery dissection (CAD) is a collective term that includes internal carotid artery dissection (iCAD) and/or vertebral artery dissection (VAD). A dissection is a tear or haematoma in the wall of either the vertebral or internal carotid artery, and can lead to serious events like stroke. The incidence of CAD is relatively low (based on large hospital cohorts it is estimated at 2.6 – 3 / 100,000 individuals a year)[1], with the incidence of iCAD more common (1.7 / 100,000 per year) than VAD (1.0 / 100,000)[2]. The symptoms of a dissection can present as neck or head pain (most common); other clinical features include: visual, speech or balance disturbance; facial palsy; ptosis; paresthesiae in face/tongue or limbs; and limb weakness[3]. One analysis showed that cervical pain is about twice as common in patients with VAD, while headache at admission is more frequent in patients with iCAD[2], however it can be difficult to determine the causation of CAD.

The causation of CAD is unclear but has been attributed to both traumatic (where a severe blunt or penetrating trauma has occurred) or spontaneous events[4]. It is described as a multifactorial disease and identified risk factors include cervical trauma, recent infection, hypertension and migraine[1, 2]. Cervical artery dissection is seen more often younger populations(under 65)[1, 4], and is reported to account for 10 – 25% of ischemic strokes in young and middle aged patients[4]. Cohorts of people with CAD and other underlying vascular disorders like: fibromuscular dysplasia; reversible cerebral vasoconstriction syndrome; Ehlers-Danlos syndrome[1]; or a family history of CAD[5] are shown to have increased incidence of CAD compared to people who had CAD but no underlying disorders or family history.

Cervical manipulation is suggested to lead to CAD. This is hard to investigate as the initial symptoms of a CAD can present as musculoskeletal pain for which patients may go to a health professional to treat. So if the CAD was already developed and the patient did not know; the chiropractor / physiotherapist, osteopath or other health professional may perform the manipulation, then when the CAD is diagnosed it is misattributed to the manipulation rather than being a spontaneous event (see Figure 1 below adapted from Church et al, 2016).

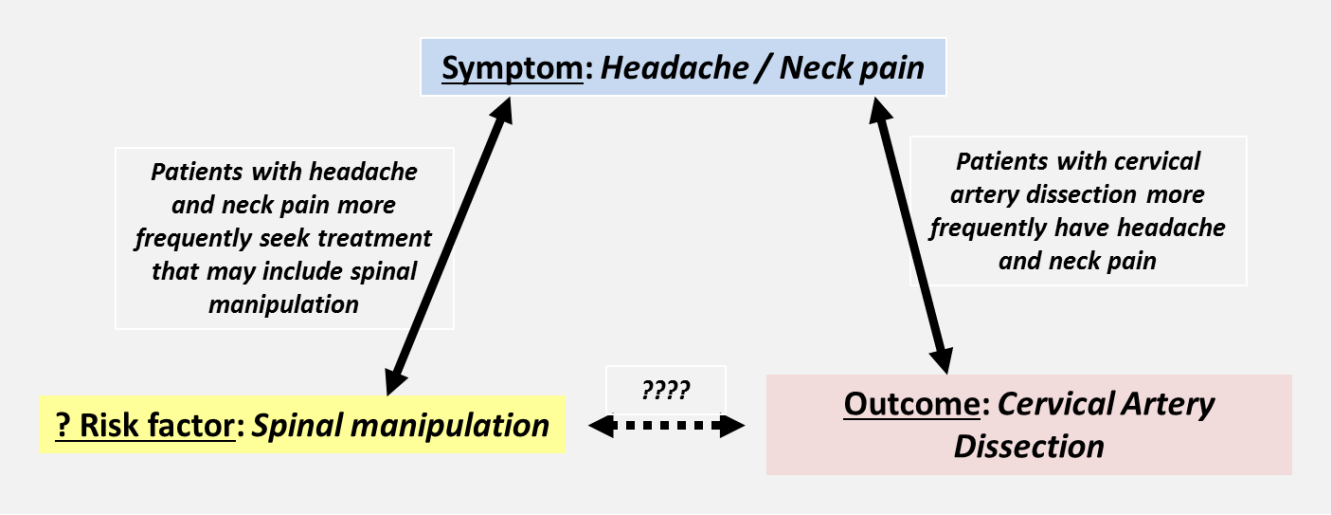


Figure 1. Potential relationship between CAD and symptoms [6]

1.3 2012 ACC Report on Cervical Artery Dissection

A previous report was completed by the Evidence-based Health group in ACC research in 2012[7]. This report focused on the evidence for causation of CAD by trauma and what degree of trauma is required; and if the symptoms of CAD could be confused with the symptoms of a traumatic event. The summary of this report is quoted as follows:

- "Without major trauma it is unlikely that a CAD is an injury caused by accident;
- It is unlikely that a recent minor event such as lifting or twisting is the cause of a CAD;
- Symptoms of spontaneous CAD (neck, face or head pain in the preceding minutes, hours or days while the intimal split evolves into a dissection) can be misattributed to a CAD caused by trauma."
- Careful consideration should be given to the history and clinical records, particularly known predisposing factors to the risk of dissection (although these are rare): heritable connective tissue disorders such as Ehlers-Danlos syndrome; arterial anomalies; genetic risk factors; oral contraceptives; smoking; hypertension and respiratory tract infections.

Cervical artery dissection was largely categorised as a traumatic cause by the studies included in this report or reported as a separate category.

Findings specifically related to CAD reported initial symptoms of dissection commonly imitated musculoskeletal pain for which patients typically consult chiropractors; and that some of these patients may have already been developing a CAD before having chiropractic treatment. However the association of CAD and cervical manipulation (high velocity low amplitude thrusts) was not the focus of this review.

2 Methods

2.1 Search Strategy

A standard systematic search was conducted over multiple databases using search terms as described below. This search was aimed to build on information previously reported by ACC [7].

Two searches were conducted in April 2016 and in November 2016 across the following databases:

- Medline
- Medline Inprocess & ePub Ahead of Print,
- Embase
- Cochrane Library
- Amed
- Ovid Nursing Database

Search terms included: Carotid artery; internal, dissection; carotid artery injuries; vertebral artery dissection; spinal manipulation; manipulation osteopathic; chiropractic physical therapists. (Full search strategy can be found in Appendix 1).

2.2 Inclusion and exclusion criteria

A total of 42 studies were found related to this topic, the inclusion criterion outlined below were used to select studies for the review. Studies selected were systematic reviews published from November 2011 and any studies conducted after May 2013 (see Church et al, 2016).

2.2.1 Inclusion Criteria

- *Study design:* Systematic reviews published after November 2011, reviews of case reports and primary studies that included cohort studies and case control studies published after May 2013

- *Participant:* Human participants with arterial dissection of the carotid or vertebral arteries
- *Intervention:* cervical manipulation / high velocity, low amplitude thrust
- *Type of outcome measures*: radiographic analysis, clinical outcome measures

2.2.2 *Exclusion criteria*

- Grey literature, conference proceedings
- Arterial dissection of other arteries not in cervical spine
- Animal or laboratory studies
- Single case reports and literature reviews
- Cadaver studies
- Non-English studies

2.3 Level of Evidence

Studies that met the criteria for inclusion in this report were assessed for their methodological quality using the Scottish Intercollegiate Guideline Network (SIGN) level of evidence system[i], as outlined below.

Levels of evidence	
1++	High quality meta analyses, systematic reviews of randomized controlled trials (RCTs), or RCTs with a very low risk of bias
1+	Well conducted meta analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1-	Meta analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
2++	High quality systematic reviews of case-control or cohort studies. High quality case-control or cohort studies with a very low risk of confounding, bias, or chance and a high probability that the relationship is causal
2+	Well conducted case control or cohort studies with a high risk of confounding, bias, or chance and a significant risk that the relationship is not causal
3	Non-analytic studies, e.g. case reports, case series
4	Expert opinion

[i] Scottish Intercollegiate Guidelines Network: http://www.sign.ac.uk/

3 Results

3.1 Study selection

Five systematic reviews, two retrospective analyses and two reviews of case reports met the inclusion criteria of this report. A brief description of these studies and their level of evidence are outlined below in Tables 2 – 4, further details of the studies can be found in the evidence tables at the end of this document (Appendix 4).

The study designs included in this report, including those analysed in the systematic reviews, are predominantly retrospective analyses of data and case-control studies. This means that information from the primary studies cannot determine if manipulative techniques like high velocity low amplitude thrusts cause cervical artery dissection. However, it can outline which variables or patient characteristics are present when a carotid artery or vertebral artery dissection has occurred, and under what circumstances there are increased odds of CAD occurring.

3.1.1 Systematic reviews (SRs)

A total of five systematic reviews fit the inclusion criteria for this review. There is cross-over (outlined in Appendix 4) of the cohort of primary studies included in the systematic reviews; one review (Dittrich et al, 2007) had been included in all reviews including the review produced in-house by ACC in 2012 [7]. The systematic analyses were of moderate to good quality (graded as 2+ to 1-) however the primary studies analysed by the systematic reviews were largely retrospective analyses and case control studies indicating that available primary evidence is of moderate to low quality (graded as 2- to 3).

Table 1. Brief description of included systematic reviews

Study	Overview	Study types	SIGN grade
Church et al, 2016[6]	Evaluate the evidence by performing a systematic review and meta-analysis of published data on chiropractic manipulation and CAD.	N = 6 case-control studies. Five were retrospective analyses and one consisted of face-to-face interviews. *Studies were of moderate (n = 2) to low (n = 4) quality, graded using GRADE tool*	**1-**
Gottesman et al, 2012[8]	SR of studies reporting clinical and radiographic data on individuals with vertebral artery dissection	Out of 75 studies included in this review, 16 investigated VAD related to chiropractic treatment. N = 12 of these were retrospective analyses; N = 3 were prospective analyses. *Most of these studies were of moderate quality*	**1-**
Chung et al, 2015[9]	SR of studies investigating internal carotid artery dissection after cervical spine manipulation, and whether there are any associations or increased incidence of CAD with manipulation.	Out of 99 identified studies, no studies were found that met the author's pre-determined inclusion criteria.	**1-**
Haynes et al, 2012[10]	Update of SR by Rubenstein et al (2005) and to determine if there Is conclusive evidence of a strong association between cervical manipulation and CAD stroke	N = 5 case control studies N = 3 retrospective analyses; N = 1 prospective case-control study; N = 1 Case control and case crossover	**2+**

		study.	
Wynd et al, 2013[10]	To collect and synthesise reports of CAD associated with cervical manipulation	N = 43 studies including case reports and case studies Due to study design (case reports) these data are of low quality, however are directly related to this report	**2+**

3.1.2 Primary studies

Four primary studies were found that were published after publication of the systematic reviews, or met our inclusion criteria but were not included in the 2012 ACC report[7]. These were mostly retrospective analyses of pre-existing datasets, no studies of higher quality (eg. prospective cohort studies) that met the inclusion criteria were found. One study is an analysis of compensation claims from adverse events arising from chiropractic treatment [11] the other is an analysis of a population known to have an arterial dissection in which the demographics were retrospectively examined[12].

Table 2. Brief description of primary studies

Study	Overview	Diagnosis of CAD	Comparisons and demographics included	SIGN grade
Bejot et al, 2014[13]	Retrospective analysis of data from the Cervical Artery Dissections and Ischemic Stroke Patients (CADISP) consortium that compares baseline characteristics and short-term outcomes between patients with single CAD and multiple CAD.	Radiological presentation of dissection .(see Appendix 4 for further description) Pure intracranial and iatrogenic dissection after a procedure or CAD due to vascular disorders (eg. Ehlers-Danlos syndrome)	N = 983 participants from the CADISP population compared to N = 659 patients as well as 281 health subjects. Characteristics examined included Hypertension, diabetes mellitus, smoking, obesity, recent trauma, prior manipulation, recent infection and hypercholesterolemia	**2-**
Jevne et al, 2014[11]	Retrospective analysis of compensation claims from claims following consultation with chiropractors reported to the Danish Patient Compensation Association and Norwegian System of Compensation from 2004 - 2012	Not described, report included claims that described CAD as the diagnosis	Analysis of N = 300 claims 17 of these for CAD (5.7%); 11 were approved. Costs for financial compensation were high (88.7% of whole complain category were for the CAD cases, which was €2,044,523)	**2-**
Moon et al, 2016[12]	Retrospective review of endovascular treatment (stent placement or coil occlusion of parent vessel conducted) for cervical dissection from 2006 – 2016.	Population of confirmed CAD patients undergoing stent placement for the dissection	Data extracted on demographics, procedural details, radiographic and angiographic studies. Data on restricted population, N = 93 with carotid artery dissection; N = 23 with vertebral artery dissection that underwent a surgical procedure. N = 67 who had a spontaneous dissection had a chiropractic manipulation within the	**2-**

			past 30 days	
Thomas et al, 2015[3]	Cross-sectional case control study comparing participants (<55yrs) with CAD with age and sex-matched comparison group with ischaemic stroke but no CAD.	Radiological diagnosis of CAD, retrospective analyses of medical record reviews and interviews	N = 45 participants (24 with dissection, 21 controls). Review of medical records and detailed structured interview of participants regarding potential risk factors for CAD including minor mechanical trauma to the neck.	**2-**

3.1.3 Reviews of single case reports

Two reviews that collated the findings of single case reports of adverse events arising from cervical manipulative therapy[14] or 'massage' therapy techniques that can include manipulation[15] (n = 177 individual cases) published in the literature were included. Although single case reports represent low quality evidence these reviews were included because they are directly related to this review, there is limited volume published evidence from higher quality study design available and highlight that the large volume of these case reports existing in academic literature could create a publication bias within the literature.

These reviews specifically searched for adverse events related to manipulation. This shows that although a high number of individual cases of manipulation with CAD exist, as these researchers did not search for outcomes related from manipulation in general they many not present a true representation of the population, inferring publication bias. These reviews reported that CAD featured predominantly as an adverse event from manipulation (Table 3) however details of diagnosis were not included.

Table 3. Brief description of reviews of single case reports

Study	Overview	Comparisons and demographics included	SIGN grade
Yin et al, 2014 [15]	To evaluate all data published between 2003 – 2013 on adverse effects of massage therapy (including manipulation)	Review of single case reports from a number of different countries. Of the 43 case reports included, 10 were adverse events of the vertebral artery.	**3+**
Puentedura et al, 2012 [14]	Retrospective analysis of all available case reports in the literature published from 1950 - 2010	N = 134 cases reported across 93 articles. Arterial dissection was the most common adverse event (AE) reported (37.3% of cases; N = 50); Chiropractors involved in the majority of injuries (69.4%; n = 93) following manipulation, followed by osteopathic physicians (8.2%), physical therapists (3.7%)	**3+**

3.2 Cervical artery dissection occurrence in cases that have had a cervical manipulation

Results outlining findings from three systematic reviews, two primary studies and the two reviews of case reports are presented in Table 4 below. Two SRs did not report data that could be used for statistical analyses so occurrence are not reported in this section[9, 16]. Some initial observations were that manipulations mainly reported to be performed by a chiropractor, however one study did report manipulation and dissection from other professions as well[17]; and that carotid artery dissection was more common than vertebral artery dissection[12, 19].

Two SRs show although there is a positive association between CAD and cervical manipulation however there is a high amount of heterogeneity within the sample[6, 18]. The positive associations were reported across a number of primary studies within the SRs, which indicates increased odds of CAD when a cervical manipulation is performed, however it is noted that the confidence intervals were wide in some of the reports, and that some of these were not statistically significant (see Table 4 below). This could be because where population numbers were reported[13] the

numbers and percentages of dissection sampled were low, and the number of dissection from manipulation was even lower (Dittrich et al, 2007 and Thomas et al, 2011 reported in the Haynes et al, 2012[10]).

Table 4. Reports of manipulation related to cervical artery dissection

Study	Comparison	Finding
Systematic Reviews		
Church et al, 2016	Association between dissection and chiropractic care	*Pooled OR for all studies (n = 6 case-control studies)* **Odds Ratio (OR)** 1.74 (95% CI 1.26 – 2.41) – *However it should be noted there was significant heterogeneity for this sample (I^2 84%)* Excluded Class III studies (n = 2 studies) **OR** 3.17 (95% CI 1.30 – 7.74)
Gottesman et al, 2012	Report of vertebral artery dissection in relation to a chiropractic injury	46 out of 283 patients from across 14 studies reported chiropractic related injuries. Pooled proportion: 0.16 (0.07 – 0.3); pooled SE 0.36
Haynes et al, 2012	Reported results from studies separately	Smith et al, 2003 *VAD and exposure to manipulation in last 30 days* **OR(adj)** 6.62 (95%CI 1.4 – 30) Dittrich et al, 2007 *Odds of CAD in included sample* **OR(adj)** 1.5 (95%CI 0.3 – 6.9) Thomas et al, 2011 *Cases of CAD when exposed to manipulation within 3 weeks of stroke* **OR (adj)** 12.7 (95%CI1.43 – 112.0) *Association with recent head or neck trauma* **OR(adj)**23.5 (95%CI 5.7 – 96.9)
Primary Studies		
Bejot et al, 2014[13]	Occurrence of multiple CAD with manipulation prior to onset of stroke	Odds of multiple CeAD vs single CeAD after cervical manipulation OR 2.23; 95% CI 1.26 – 3.95) 6% of the single CAD population (n = 49 out of 834) had had a prior cervical manipulation 13.6% of the multiple CAD population (n = 20 out of 149) had had a prior cervical manipulation
Moon et al, 2016	Incidence of manipulation in a population of CAD cases undergoing endovascular stent placement	6 of 67 (9%) of patients with spontaneous dissection had a chiropractic manipulation within the past 30 days
Thomas et al, 2015 [3]	Incidence of cervical manipulation in a population of CAD cases	4 out of 24 had a neck manipulation in the month prior to CAD. In two cases high-velocity thrusts were administered, another case deep massage to the sub occipital region and the final unknown. No participant reported stroke. N = 3 were VAD, N = 1 was iCAD. Not statistically significant (OR 5.2, 95% CI 0.6 - ∞)
Reviews of case reports		
Puentedura et al, 2012 [14]	Results of case reports in patients with severe adverse events after cervical spine manipulation	Arterial dissection most common adverse event reported (n =37.3% of cases); 7 of these resulted in death (5 from dissection, 2 from practitioner continuing to perform manipulation) Chiropractors involved in majority of reported injuries (n = 64.9%); followed by osteopathic physicians (8.2%) and physical therapists (3.7%). Temporal relationship of manipulation and adverse event not reported
Yin et al, 2014 [15]	Results of case reports describing adverse events and if a manipulation was or was not mentioned in the case notes.	10 out of 43 case reports were due to vertebral artery dissection, 5 of these were from a manipulation. Details of the case, temporal relationship and health profession not included.

3.3 Mechanical trauma or neck strain

Thomas et al (2015) reported 17 out of the 24 patients with CAD reported a recent history of minor mechanical trauma (including cervical manipulation) [3]. The type of trauma or neck strain varied within this group, the most common was activities or sports with jerky head movements.

Other risk factors for single [3] and recurring CAD [13] are presented in Appendix 3 of this document.

3.4 Identification of CAD from compensation claims[11]

One included primary study was a retrospective analysis of compensation claims in Denmark and Norway from 2004 – 2012[11]. Different adverse events were investigated with a cohort of claims that undergone chiropractic treatment. CAD made up 17 of 300 (5.7%) of adverse events, 11 of these claims were funded and contributed to 88.7% (€2,044,523) of financial compensation for the whole complaint category from both the Danish and Norwegian compensation organisations. Within this paper although spinal manipulative therapy is discussed it is not stated in the paper that the chiropractic treatment included manipulation.

4 Discussion

4.1 Quality of Evidence

Both secondary and primary research articles were included in this report. These included systematic reviews of case control studies and retrospective analyses of administrative data, primary case-control studies and retrospective analyses as well as reviews of single case studies. There was some overlap in the primary studies that the SRs covered (Appendix 5) and it should be noted that some of the information reported in these reviews was already reported in the previous ACC report[7]. The quality of these data ranged from low (3+) to moderate (2+), however none of these study designs are able to determine if causation of CAD is from cervical manipulation as they only report the prevalence of CAD. It should also be noted that although a positive association was reported across some studies between CAD and manipulation, that the heterogeneity was high and not all studies showed statistical significance; and also that a positive association between manipulation and CAD does not equal causation. To determine if a manipulation leads to dissection a before and after study design with imaging techniques would have to be used, however this would be difficult as CAD occurs after a period of time rather than straight after a manipulation.

Two reviews of low quality data (single case studies) were also included as the content was in alignment with the research question of this review. Both of these reviews reported a combined 177 single cases of CAD after chiropractic treatment that had been reported within the published literature. It should be noted that the higher percentages of CAD (37.3% and 23.2%) reported due to chiropractic treatment are not representative of a general population due to publication bias as the search strategy of these reviews were designed to focus on adverse events from spinal manipulation; not a general search. These reviews were included to highlight the publication bias as the volume of case reports (compared to articles of higher quality study design) in the literature could lead to a perception CAD is associated with chiropractic treatment without understanding the paucity of high quality of study designs available on this topic in general.

Diagnosis of CAD did differ between studies. Radiological diagnosis was mentioned in two primary studies[3, 13] whereas one other primary study was from claims data that had coded for CAD[11], and another was a study on a known CAD population. The most common health profession mentioned with regards to CAD was chiropractic, however it has been stated this could be because chiropractors are more likely to perform this procedure than other professions (physiotherapists, osteopaths) trained in the technique[11].

4.1.1 Identification using ICD-9 codes

There has been some contention regarding identification of CAD within a primary article included in two of the SRs [6 16]. The primary study used ICD-9 codes to identify cases of CAD who had had a visit to a chiropractor during the 30 days before CAD diagnosis[20]. It is recently contested that the coding used in this study underestimated the true number of cases[21]. Cai et al 2014 used the same search strategy as Cassidy et al, (2009) [20] and added specific dissection ICD codes they had available within their dataset that the database used by Cassidy et al (2009[20]) did not. They used these codes to identify patients in a Veterans Health Administration (VA) electronic database. They found that the previous study may have underestimated the number of CAD cases in general, and that the ORs calculated for CAD and a visit to the chiropractor within 30 days of diagnosis are likely to be larger. This means that reports using statistics from this study[6, 16] may underestimate the association between CAD and chiropractic treatment.

4.1.2 Limitation of studies

The main limitation of these studies is that they cannot answer whether cervical dissection is caused by cervical manipulation techniques. One SR did not find any studies that fitted the researchers' pre-determined inclusion criteria regarding the causation of internal carotid artery dissection[9]. However these studies do show, from different primary sources and different populations, that there is a positive association between the occurrence of CAD and cervical manipulation. This means that although there are higher odds of CAD in populations of people receiving cervical spine manipulation, it cannot be determined if the CAD was pre-existing or if the manipulation caused the CAD to occur.

4.1.3 Future study

To determine if cervical manipulation does cause a cervical artery (internal carotid or vertebral artery) dissection a well-designed intervention study (ie. randomised control trial) with high quality imaging would be required before and after the manipulative procedure. These participants would have to be followed up at specific time points in the following weeks to determine if cervical manipulation did lead to an arterial dissection occurring; however the feasibility of this study design may be low due to cost, the resources required and other variables (ie. individual lifestyle or patient risk factors) that may contribute to CAD occurring in individual cases.

4.2 Scientific Statement from the American Heart Association (AHA) / American Stroke Association (ASA) [22]

A statement published in 2014 was endorsed by the American Association of Neurological Surgeons and Congress of Neurological Surgeons regarding CAD and cervical manipulative therapy (CMT) [22]. It is not included with this analysis as it is not a systematic review and no critical appraisal or structured systematic literature search is reported in the methodology so does not meet the pre-determined search criteria. However as the paper is in direct alignment with this report and has undergone extensive AHA internal peer-review the findings are briefly outlined below.

The report discusses four case-control studies that report on the association of stroke and CMT. All four of these studies are included within the primary studies assessed in Church et al (2016), one of the SR's included in this report[6] (Appendix 4). The main conclusions from these studies in the statement were that CMT is associated with CAD and that while CAD may be of low incidence, there could be serious complications. Also as people with VAD commonly present with neck pain, they can seek therapy for this. This can make it appear that CMT was causal to VAD, when it may have spontaneously occurred.

It was recommended that patients with neck pain and no neurological symptoms after trauma should be informed about potential risks of CMT, and that this CAD should be considered by the health professional before performing CMT.

5 Conclusion

The main limitation of the studies critiqued for this report is that they cannot answer whether cervical dissection is caused by cervical manipulation techniques due to study design. To determine if a manipulation leads to dissection a before and after study design with imaging techniques would have to be used, however this would be difficult as CAD occurs after a period of time rather than straight after a manipulation.

There are some positive associations between the occurrence of CAD and cervical manipulation reported, however it is unable to be determined if the CAD occurred before or after the manipulation was performed.

6 Appendices

6.1 Appendix 1. Search Strategies

First batch of searches, general etiology, April 2016:

2016 ICAD 0.1

Medline, 27 April (an Emtree-adapted version was also run on Embase)

1. Carotid Artery, Internal, Dissection/
2. exp *carotid artery injuries/ or vertebral artery dissection/
3. (carotid artery adj3 (dissect$ or injur$)).tw.
4. or/1-3
5. limit 4 to (english language and humans)
6. limit 5 to ed=20111019-20160427
7. 6 and (exp risk factors/ or exp causality/ or exp genetic predisposition to disease/)
8. 6 and (risk factor$ or causal$ or causat$ or predispos$ or aetiolog$ or etiolog$).tw.
9. limit 6 to ("reviews (maximizes specificity)" or "causation-etiology (maximizes specificity)")
10. 6 and (exp *carotid artery injuries/ep, et, ge or vertebral artery dissection/ep, et, ge or Carotid Artery, Internal, Dissection/ep, et, ge)
11. or/7-10

2016 ICAD 0.2

Medline In-Process & ePub Ahead of Print, 27 April

1. ((carotid or cervical or vertebral) adj artery adj3 (dissect$ or injur$)).tw. 1.
2. limit 1 to english language
3. limit 2 to yr="2015 - 2016" 2.
4. limit 3 to (in process or "pubmed not medline")

Second batch of searches, focus on manipulation, September 2016:

2016 ICAD Cochrane

Cochrane Library, 28 September

#1 (carotid or cervical or vertebral) and artery and (dissection or injur*)

#2 MeSH descriptor: [Carotid Artery, Internal, Dissection] explode all trees

#3 MeSH descriptor: [Carotid Artery Injuries] explode all trees

#4 MeSH descriptor: [Vertebral Artery Dissection] explode all trees

#5 #1 or #2 or #3 or #4

#6 spinal manipulation*

#7 MeSH descriptor: [Spinal] explode all trees

#8 MeSH descriptor: [Manipulation, Osteopathic] explode all trees

#9 MeSH descriptor: [Manipulation, Chiropractic] explode all trees

#10 MeSH descriptor: [Musculoskeletal Manipulations] this term only

#11 chiropract*

#12 osteopath*

#13 MeSH descriptor: [Physical Therapists] explode all trees

#14 #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13

#15 #5 and #14

2016 ICAD 0.3

Medline, Medline In-Process & ePub Ahead of Print, AMED and Ovid Nursing Database, 28 September

1. (((carotid or cervical or vertebral) adj3 arter$) and (dissect$ or injur$)).mp.

2. exp Carotid Artery Injuries/

3. Vertebral Artery Dissection/

4. or/1-3

5. ((spinal or spine) adj3 manipulat$).mp.

6. exp Manipulation, Chiropractic/ or exp Manipulation, Spinal/ or exp Manipulation, Osteopathic/

7. chiropract$.af.

8. osteopath$.af.

9. Physical Therapists/

10. or/5-9

11. 4 and 10

2016 ICAD 0.4

Embase, 28 September 3.

1. (((carotid or cervical or vertebral) adj3 arter$) and (dissect$ or injur$)).mp.
2. exp carotid artery injury/
3. exp artery dissection/
4. 1 or 2 or 3
5. ((spinal or spine) adj3 manipulat$).mp.
6. exp chiropractic/ or exp manipulative medicine/
7. exp osteopathic medicine/
8. (chiropract$ or osteopath$).af.
9. 5 or 6 or 7 or 8
10. 4

6.2 Appendix 2. Description of the CADISP Consortium

Two retrospective analyses included in this review sourced data from the CADISP (Cervical Artery Dissections and Ischemic Stroke Patients) consortium[ii]. Although both studies are likely to be reporting the same individuals both are included in this review as the direction of the analyses is different for each study.

The CADISP consortium is a multinational network based across 19 centres in 9 countries in Europe. The main aim of the project is to increase knowledge of the pathophysiological mechanisms of cervical artery dissection from analysis of data obtained from a large number of patients. Of relevance to this review the CADISP network is also intended to provide data on environmental risk factors and genetic susceptibility to CAD. Patients were recruited consecutively and CAD was matched on age and gender with the ischaemic stroke and healthy groups. They were also strictly matched on geographical origin to avoid stratification bias.

Table 5. Inclusion and exclusion factors for CADISP participants *(adapted from Debette et al, 2009[23])*

	CAD	Ischaemic stroke	Healthy controls
Inclusion criteria	Radiological presentation of dissection	Recent stroke, no sign of CAD (on ultrasound, MRI or CT)	Individuals from general population without a history of vascular disease (MI, stroke or peripheral artery disease).
Exclusion criteria	Purely intracranial dissection, latrogenic dissection after a endovascular procedure, and disorders known to cause CAD (eg. vascular Ehlers-Danlos syndrome)	Where CAD cannot be ruled out, endovascular or surgical procedures on coronary, cervical or cerebral arteries. Cardiopathies with a very high embolic risk, arterial vasospasm after subarachnoid haemorrhage. Auto immune or monogenic disease explaining stroke	

[ii] http://cadisp.com/topic/index.html

6.3 Appendix 3: Risk factors associated with CAD

Other risk factors are associated with occurrence of CAD. Below are findings from two primary reports from retrospective analyses[13] [3].

The study by Thomas et al, 2015[3] was a retrospective analysis of data collected using a cross-sectional case-control design. A detailed interview close to time of admission about risk factors was performed. The main findings are presented in Table 7 below. The ORs compare the CAD group with the ischemic stroke group. However none of these are statistically significant, possibly due to very small sample sizes and? it should be noted the risk factors described are similar to those reported in Bejot et al, 2014[13] in Table 8.

Table 6. Risk factors analysis from Thomas et al, 2015[3]

Risk factor	VAD (n = 10)	iCAD (n = 14)	Total CAD (n = 24)	Odds Ratio OR(95% CI)
Recent infection	1	4	5	2.5(0.4 – 14.5)
Vascular anomaly	1	3	4	1.9(0.3 – 11.6)
Hypertension	1	4	5	0.8(0.2 – 3.1)
Smoking	3	2	5	0.4(0.09 – 1.3)
Cholesterol	0	1	1	0.6(0.01 -0.5)
Family history	1	0	1	0.9(0.05 – 14.8)
Migraine	4	6	10	6.7(1.3 – 38.0)

The study by Bejot et al, 2014[13] reported an analysis of data from the CADISP consortium (for further description see Appendix 7.1). This outlined other participant characteristics that had positive associations with the recurrence of CAD (Table 5). Positive associations for multiple CAD vs single CAD were seen for hypertension, recent infection and recent traumatism (not including cervical manipulation). Findings are presented in Table 7 below.

Table 7. Patient characteristics analysis from Bejot et al, 2014 for multiple vs single CAD

Characteristic	Multiple CeAD (n = 149 (15.2%)	Single CeAD (N=834, 84.8%)	Adjusted analyses (adj for age, sex and country of inclusion) OR (95% CI)
Hypertension (n=249)	43 (29.1%)	206 (25%)	1.53 (1.01-2.31)
Hypercholesterolemia (n = 182)	21 (14.6%)	161(19.7%)	0.75(0.45-1.25)
Diabetes mellitus (n = 21, 2.2%)	5 (3.4%)	16 (1.9%)	1.87(0.66-5.32)
Active smoking (n=269, 27.7%)	31(20.9%)	238(28.9%)	0.63 (0.40-0.99)
Obesity (BMI >31kg/m^2) (n = 68, 7.3%)	11 (7.7%)	57 (7.2%)	1.13(0.58-2.24)
Recent infection n = 187	38 (26%)	149 (18.3%)	1.71(1.12 – 2.61)
Recent traumatism, n = 391 (40.5%)	66 (44.9%)	325(39.7%)	2.23(1.26-3.95)

6.4 Appendix 4: Evidence Tables

6.4.1 Evidence Tables: Systematic Reviews

<table>
<tr><th colspan="5">Systematic Review</th></tr>
<tr><th>Study</th><th>Methodology</th><th>Outcomes & results</th><th colspan="2">Quality assessment</th><th>Reviewer comments and evidence level</th></tr>
<tr>
<td>Church et al, 2016[6]

Cureus. 8 (2)

Study design:
Systematic review

Research question:
To evaluate the evidence by performing a systematic review and meta-analysis of published data on chiropractic manipulation and CAD.

Funding
No conflicts of interest</td>
<td>Total of 6 studies of included:

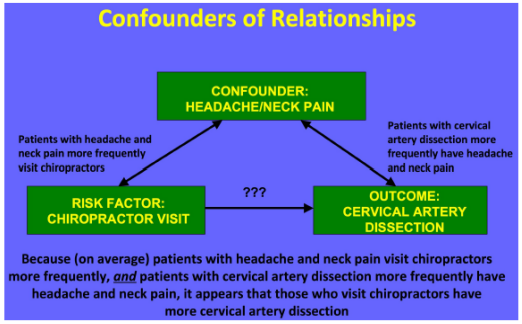
N = 5 studies include in quantitative synthesis (meta-analysis)

N = 6 studies included in qualitative synthesis

N = 2 class II studies of case-control design:
- Smith et al, 2003 (retrospective analyses)
- Dittrich et al, 2007 (face-to-face interviews with blinding)

N = 4 class III studies of Case control design
- Rothwell et al, 2001 (retrospective analyses)
- Cassidy et al, 2008 (retrospective case control design)
- Thomas et al, 2011 (Retrospective analyses of records)
- Engelter et al, 2013 (data evaluated from the CADISP study which consists of both retrospective and prospectively collected data)

Studies graded using GRADE system

Included databases:
Medline and Cochrane</td>
<td> 

Meta-analysis
A meta-analysis was done for the association between dissection and chiropractic care.

The pooled ORs for all studies showed a positive association, however the heterogeneity between the studies was high (I^2 84%):

OR 1.74 (95% CI 1.26 – 2.41)

With Class III studies excluded association still remained however this only included two studies:
OR 3.17 (95% CI 1.30 – 7.74)

Evidence Grading: Very low due to:
- Controversial nature of the topic, legal ramifications of results and potential from bias

Authors conclusions:</td>
<td colspan="2">
<table>
<tr><td>Clearly defined research question</td><td>Y</td></tr>
<tr><td>Two people selected studies and extracted data</td><td>Y</td></tr>
<tr><td>Comprehensive literature search carried out</td><td>Y</td></tr>
<tr><td>Authors clearly state how limited review by publication type</td><td>Y</td></tr>
<tr><td>Included and excluded studies listed</td><td>N</td></tr>
<tr><td>Characteristics of included studies are provided</td><td>N</td></tr>
<tr><td>Scientific quality of included studies assessed and documented</td><td>Y</td></tr>
<tr><td>Scientific quality of included studies assessed appropriately</td><td>Y</td></tr>
<tr><td>Appropriate methods used to combine individual study findings</td><td>Y</td></tr>
<tr><td>Likelihood of publication bias assessed</td><td>Y</td></tr>
<tr><td>Conflicts of interest declared</td><td>Y</td></tr>
<tr><td>Are results of study directly applicable to patient group targeted by guideline?</td><td>Y</td></tr>
</table>
</td>
<td>SIGN evidence level:

1-

Reviewer comments:
Good critique of low quality studies. A comprehensive search was performed however only two databases were searched which may have limited the number of included studies. Univariate analyses for OR used meaning considerations within cohorts that could have an effect on the occurrence of CAD (eg. population demographics, patient history) weren't taken into account for pooled OR</td>
</tr>
</table>

	Two authors independently reviewed all articles	Found no evidence of a causal link and quality of information is very low. Meta-analysis shows a small association but there is considerable risk of bias and confounding factors in these studies. There is no convincing evidence to support a causal link.			

Systematic Reviews

Study	Methodology	Outcomes & results	Quality assessment		Reviewer comments and evidence level
Gottesman et al 2012[8] *The Neurologist 18(5). Pg 245.* **Study design:** Systematic Review **Research question:** To conduct a systematic review of studies reporting clinical and radiographic data on individuals with Vertebral Artery Dissection (VAD) to determine level of evidence available for this	**Total of 75 studies of included:** - Out of these 16 studies were included that investigated VAD related to chiropractic injury 12 of these studies were retrospective analyses: - Ahmad et al, 1999 - Bartels et al, 2006 - Chiche et al, 2005 - De Bray et al, 1997 - Dziewas et al, 2003 - Hicks et al, 1994 - Josien et al, 1992 - Lu et al, 2000 - Mas et al, 1987 - Pugliese et al, 2007 - Saeed et al, 2000 - Sturzenegger et al, 1994 The rest of the studies were prospective	***Only trauma related variables reported in this table from the article*** **Symptoms associated with VAD:** Dizziness/vertigo most common symptom (58% of VAD) followed by headache (51%) and neck pain (46%).Frequency reported was variable (between 24% and 100%). Reported standard errors large for pooled proportions due to significant heterogeneity across studies. Minor trauma was relatively uncommon in association with VAD. **Results for Chiropractic related injuries** N = 14 studies providing a total sample size of 46 out of 283 patients with symptoms. Pooled proportion: 0.16; Pooled SE: 0.36 Range of proportions (7 – 30%)	Clearly defined research question	Y	**SIGN evidence level:** **1-** **Reviewer comments:** Pragmatic assessment of low quality studies.
			Two people selected studies and extracted data	Y	
			Comprehensive literature search carried out	Y	
			Authors clearly state how limited review by publication type	Y	
			Included and excluded studies listed	N	
			Characteristics of included studies are provided	N	
			Scientific quality of included studies assessed and documented	Y	
			Scientific quality of included studies assessed appropriately	Y	
			Appropriate methods used to combine individual study findings	Y	

topic and identify core clinical features. **Funding** No conflicts of interest	analyses: - Wessels et al, 2008 - Sturzenegger et al, 1993 - Hicks et al, 1994 **Included databases (**Up to February 2009)**:** MEDLINE (through Pubmed), EMBASE Three reviewers independently reviewed all articles using the Standards for Reporting Diagnostic accuracy statement **Exclusion** Non-english, duplicating data from other publications, not about vascular disease or dissection, <5 subjects **Inclusion** Studies with radiological or pathological confirmation of dissection	**Evidence Grading:** Most studies met medium quality criteria because of adequacy of subject recruitment or case ascertainment. Most did not provide adequate information on data collection or masking of examiners. **Authors conclusions:** VAD associated with nonspecific symptoms such as dizziness, vertigo, and headache or neck pain should be considered in the diagnostic assessment of patients presenting with these symptoms even in the absence of other risk factors. A history of trauma or connective tissue disease is not found in the majority of symptomatic cases.	Likelihood of publication bias assessed	Y	
			Conflicts of interest declared	Y	
			Are results of study directly applicable to patient group targeted by guideline?	Y	

Systematic Reviews

Study	Methodology	Outcomes & results	Quality assessment		Reviewer comments and evidence level
Haynes et al 2012[10] *International Journal of Clinical Practice. 66(10)940 -947.* **Study design:** Systematic Review	**Total of 5 case control studies (2001 – 2011) were included:** - Rothwell et al, 2001 - Smith et al, 2003 - Dittrich et al,2006 - Cassidy et al,2008 - Thomas et al, 2011	***Results reported from each individual paper included in this review*** **Results for Chiropractic related injuries** *Rothwell et al, 2001:* Retrospective population-based nested case-control:	Clearly defined research question	Y	**SIGN evidence level:** **2+** **Reviewer comments:** Systematic review of case control studies. Review critiqued comprehensively for bias and confounders, however minimal comments were made regarding large confidence intervals
			Two people selected studies and extracted data	Y	
			Comprehensive literature search carried out	Y	
			Authors clearly state how limited review by publication type	Y	

Research question: To update a previous SR by Rubinstein et al(2005) as well as determine whether there is conclusive evidence of a strong association between cervical spinal manipulation therapy (cSMT) and CAD stroke **Funding** No conflicts of interest	**Included databases** PUBMED, EMBASE, CINAHL, PLUS and AMED 5 reviewers independently reviewed all articles using clear criteria that is outlined in the paper and is in alignment with GRADE and SIGN. Criteria include: Objective of study, population characteristics, identification of potential confounders and risk factors, outcome assessment. Data analysis methodologies **Exclusion** Case reports, case series, abstracts and letters to the editor; dissections were from surgery, arteriography or major trauma **Inclusion** RCTs, Cohort, case-control and case-crossover; had a population with confirmed or assumed diagnosis of CAD and control group; had individuals exposed to specific incidences of cSMT or mild neck trauma; and were full reports. **Data extracted** Characteristics of the study population, risk factors (including spinal manipulation), potential confounders and strength of association	OR(crude): 3.94 (95% CI 0.99-15.78) OR(non-parametric bootstrap 95% CI: 0.64-46.28) *Smith et al, 2003* Retrospective population-based nested case-control: Exposure to manipulation within 30 days compared. Small Ns – n = 7 of VAD and 3 controls OR (adj): 6.62 (95% CI 1.4 – 30) *Dittrich et al, 2006* Prospective case-control study. Small sample sizes: n = 7 cases of CAD, vs 3 controls. OR(adj) 1.5 (95% CI 0.3 – 6.9) *Cassidy et al, 2008* Extension of Rothwell paper. Population-based, case-control and case-crossover study. *Thomas et al, 2011* Retrospective case-control using hospital records to identify cases of CAD and exposures to manipulation within 3 weeks of the stroke. N = 11 cases compared with controls OR(adj) 12.7 (1.43 – 112.0) Association found with recent head or neck trauma with 30 cases compared with n = 3 controls OR(adj) 23.5 (95% CI 5.71 – 96.9). **Evidence Grading:** No evidence grades given, **Authors conclusions:** Inconclusive evidence regarding a strong association or no association between manipulation and CAD related stroke. Future studies need to aim to eliminate or at least	Included and excluded studies listed	N	reported in studies likely due to the small numbers. Inconclusive results stated are justifiable.
			Characteristics of included studies are provided	N	
			Scientific quality of included studies assessed and documented	Y	
			Scientific quality of included studies assessed appropriately	Y	
			Appropriate methods used to combine individual study findings	Y	
			Likelihood of publication bias assessed	Y	
			Conflicts of interest declared	Y	
			Are results of study directly applicable to patient group targeted by guideline?	Y	

		minimise bias and confounding factors			

Evidence Tables: Systematic Reviews

Study	Methodology	Outcomes & results	Quality assessment		Reviewer comments and evidence level
Wynd et al, 2013 Public Library of Science, 10(6): e0130221 **Study design** Systematic review **Objective** To systematically collect and synthesise reports of CAD associated with cSMT and assess the quality of these reports **Funding** No conflicts mentioned in report	**Number of studies:** N = 43 studies of 901 participants **Inclusion:** All study designs, including case reports and case studies **Populations:** Adults and children of any gender **Diagnosis:** Methods included angiography (34%); MRI with and without angiography (34%), CT (9%). The remaining 23% used Doppler ultrasonography, and duplex sonography. Criteria such as appearance of stenotic vessels, flow abnormalities, presence of intimal flap. 49 cases did not report an imaging method for diagnosis. **Data extracted** Quality was evaluated against 21 factors from the Bradford-Hill criteria to measure cause and effect as there is a lack of an existing tool to measure case report quality in this topic area. However the tool did not analyse the quality of the studies but the quality of data and how it attributed to CAD.	**Stroke type:** 707 (85%) reported stroke type. Strokes reported post cSMT were all ischemic (674 /706 cases), one haemorrhagic. 56 cases had vascular compromise without infarct, 3 cases where CAD caused neurovascular compromise leading to Horner's syndrome. **Main results showed:** 93% cases reported time to onset symptoms, 70% reported vertebrobasilar injuries, 10% reported presence of head or neck pain. Other variables under Hill's criteria were very low. Under type of cSMT performed only 8% (69) reported type of cSMT. No study reported more than eight variables under Hill's criteria. **Author conclusions:** Overall case reports examined in this study was low in that they infrequently contained more than 5 of the 11 relevant factors. Literature infrequently reports useful data towards understanding the association between cSMT, CADs and stroke. The value of these reports toward informing understanding of the relationship between cSMT and CAD is minimal. It is important to standardisation of the	Clearly defined research question	Y	**SIGN evidence level:** **2+** **Reviewer comments:** Review of predominantly low quality studies (case reports). Due to this criteria used to assess quality was based on what factors were reported in the diagnosis of CAD, guided by variables that fall under the Bradford-Hill criteria. Outcome showed reporting of factors contributing to diagnosis of CAD were lacking making it hard to determine if cSMT leads to CAD.
			Two people selected studies and extracted data	Y	
			Comprehensive literature search carried out	Y	
			Authors clearly state how limited review by publication type	Y	
			Included and excluded studies listed	N	
			Characteristics of included studies are provided	N	
			Scientific quality of included studies assessed and documented	N	
			Scientific quality of included studies assessed appropriately	N	
			Appropriate methods used to combine individual study findings	?	
			Likelihood of publication bias assessed	N	
			Conflicts of interest declared	N	
			Are results of study directly applicable to patient group targeted by guideline?	Y	

		diagnostic criteria for CADs is important for reporting of case reports.			

Evidence Tables: Systematic Reviews

Study	Methodology	Outcomes & results	Quality assessment		Reviewer comments and evidence level
Chung et al, 2015 Journal of Manipulative Physiological Therapeutics 38 (9) **Study design** Systematic review **Objective** To determine the incidence of internal carotid artery dissection after cervical spine manipulation in patients who experience neck pain and its associated disorders. Determine whether cervical spine manipulation is associated with an increased risk of ICA dissection in patients with neck	**Inclusion criteria** - French or English language; human subject studies; published in a peer-reviewed journal; RCT, Cohort studies, case-crossover or case control studies **Exclusion criteria** - Studies that combined carotid and vertebral arteries into one category unless a stratified analysis was conducted for carotid artery dissections - Cross-sectional studies, biomechanical studies, case reports, case series, reviews, opinions, editorials and conference proceedings **Databases** MEDLINE, CINAHL, Alternative health, AMED, Index to Chiropractic literature, EMBASE. From 1970 to November 2012	Of the 99 studies identified through the original search. No studies were found within their systematic search that met the pre-determined inclusion criteria. Studies found were: 37% case reports or case series, 28% literature reviews, 27% trials, 4% were commentaries and 3% were epidemiologic studies no related to ICA. **Conclusions** Study did not find any epidemiologic studies that measured incidence of cervical spine manipulation and CAD Did not find any literature quantifying association between cervical spine manipulation and carotid artery dissection Incidence of carotid artery dissection after cervical spine manipulation is unknown.	Clearly defined research question	Y	**SIGN evidence level:** **1-** **Reviewer comments:** Appears to be well conducted SR, however excluded studies are not listed so cannot be compared against criteria.
			Two people selected studies and extracted data	Y	
			Comprehensive literature search carried out	Y	
			Authors clearly state how limited review by publication type	Y	
			Included and excluded studies listed	N	
			Characteristics of included studies are provided	NA	
			Scientific quality of included studies assessed and documented	NA	
			Scientific quality of included studies assessed appropriately	NA	
			Appropriate methods used to combine individual study findings	NA	
			Likelihood of publication bias assessed	Y	
			Conflicts of interest declared	Y	
			Are results of study directly applicable to patient group targeted by guideline?	Y	

pain, upper back pain or headaches. **Funding** No conflicts mentioned in report					

6.4.2 Evidence Tables: Primary studies

Evidence table 2. Primary Studies

Study	Methodology	Findings	Quality assessment		Conclusions
Bejot et al, 2014[13] *Stroke, 45, pg 37 – 41* **Study design:** Retrospective analysis of data from the CADISP consortium (Cervical Artery Dissection and Ischemic Stroke Patients) **Objective:** To compare the baseline characteristics and short-term outcome	As described in Engelter et al, 2013. *Observational study* Retrospectively recruited patients had either a CeAD or non-CeAD ischaemic stroke before the study was enrolled in the CADISP clinical study. Clinical data were systematically collected from local databases or registries. N = 983 CeAD patients and n = 659 non-CeAD-IS patients from the CADISP clinical study as well as 281 health subjects enrolled prospsectively.	***Participants:*** N = 983 participants with CeAD Of these 149 (15.2%) presented with multiple artery involvement. Multiple CeAD was more often associated with cervical pain at admission (OR 1.59; 95% CI 1.10 – 2.30), prior infection (OR 1.71; 95% CI 1.12-2.61) and cervical manipulation (OR 2.23; 95% CI 1.26 – 3.95). Carotid location was more frequent in patients with single CeAD. **Analyses** **Characteristic** | **Multiple CeAD (n = 149 (15.2%)** | **Single CeAD (N=834, 84.8%)** | **Adjusted analyses (adj for age, sex and country**	Appropriate and clearly focused question	Y	**Reviewer comments:** Focus of this study is to compare the characteristics and short-term outcomes of patients with multiple dissections vs single dissections as part of the CADISP study. **Level of evidence:** 2 – (graded down due to retrospective study design's potential susceptibility to bias, however it is a high quality analysis of retrospective data)
			The two groups being studied are selected from source populations that are comparable in all respects other than factor under investigation	Y	
			Study indicates how many people asked to take part did so	na	
			Likelihood some eligible subjects have the outcome assessed and taken into account in analysis	Y	
			Percentage of recruits dropped out	n/a	

between patients with single CeAD and multiple CeAD in the CADISP study.

Funding:
As part of the CADISP study funding has been received from research funds from Helsinki University, and the Academy of Finland, as well as multiple foundations (see paper)

Primary author has affiliations with Bayer and Boehringer, and Pfizer and on editorial boards of academic journals

Standard questionnaire was used for all participants and completed during visits to outpatient clinics.

Definition of Prior Cervical Trauma (PCT): included direct mechanical impact to the neck or head region and must have occurred within 1 month prior to first symptoms of CeAD or prior to ischemic stroke. Cervical manipulation was classified as a subtype of PCT and results for these were reported together as well as separately.

CeAD diagnosis
Presence of mural hematoma, aneurysmal dilatation, long tapering stenosis, intimal flap, double lumen, occlusion >2cm above carotid bifurcation .

Exclusions
Intracranial or iatrogenic dissections not included

Functional outcomes:
Modified Rankin Scale – favourable 3 month outcome was functional independence as defined by a modified Rankin Scale score of

As data was sourced from the CADISP it is likely that this study includes the same cohort of participants.

			of inclusion)
Hypertension (n=249)	43 (29.1%)	206 (25%)	1.53 (1.01-2.31)
Hypercholesterolemia (n = 182)	21 (14.6%)	161(19.7%)	0.75(0.45-1.25)
Diabetes mellitus (n = 21, 2.2%)	5 (3.4%)	16 (1.9%)	1.87(0.66-5.32)
Active smoking (n=269, 27.7%)	31(20.9%)	238(28.9%)	0.63 (0.40-0.99)
Obesity (BMI >31kg/m^2) n = 68, 7.3%)	11 (7.7%)	57 (7.2%)	1.13(0.58-2.24)
Recent infection n = 187	38 (26%)	149 (18.3%)	1.71(1.12 – 2.61)
Recent traumatism, n = 391 (40.5%)	66 (44.9%)	325(39.7%)	2.23(1.26-3.95)
Prior manipulation **69(7.2%)**	20 (13.6%)	49(6%)	2.23(1.26-3.95)

Author conclusions

- Retrospective recruitment of patients may have biased assessment of risk factors
- If multiple dissections more often lead to a poor short-term outcome, the outcome severity may be underestimated.
- Features suggestive of underlying vasculopathy (fibromuscular dysplasia) and environmental triggers (recent infection, cervical manipulation and remote history of head or neck surgery) are preferentially associated with multiple CeAD.

Comparison made between participants and those lost to follow up	n/a
Outcomes clearly defined	Y
Assessment of outcome made blind to exposure status	n/a
Recognition that knowledge of exposure status could influence assessment of outcome	n/a
Measure of exposure assessment is reliable	Y
Evidence from other sources used to demonstrate method of outcome assessment is valid and reliable	Y
Exposure level or prognostic factor assessed more than once	c/s
Main potential confounders identified and taken into account	Y
Confidence intervals provided	Y
Quality of study in minimising risk of bias or confounding	Y
Clear evidence of association between exposure and outcome	Y
Study results directly applicable to patient group targeted	Y

Evidence table 2. Primary Studies

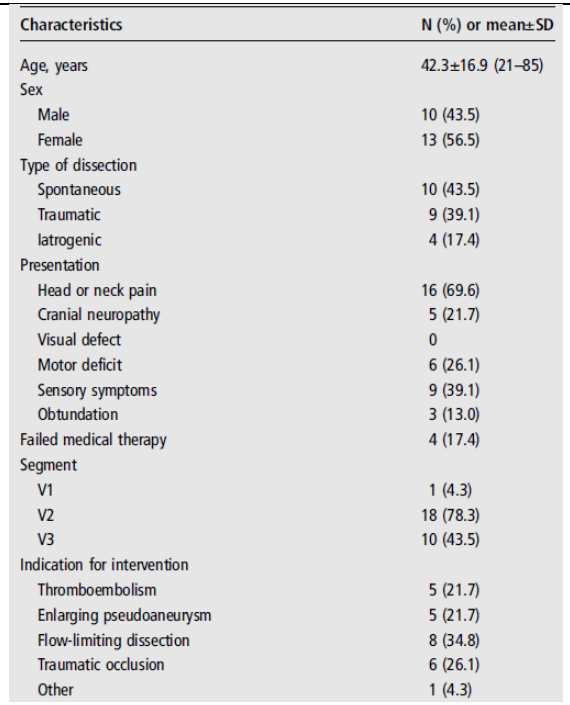
Study	Methodology	Findings	Quality assessment		Conclusions
Jevne et al, 2014[11] *Chiropractic and Manual therapies, 22(2), 37.* **Study design:** A retrospective study of compensation claims following consultations with chiropractors reported to the Danish and Norwegian compensation associations **Objective:** To describe claims reported to the Danish Patient Compensation Association and the Norwegian System of Compensation to Patients related to chiropractic form 2004 - 2012 **Funding:** None disclosed	**Observational study.** Retrospective analysis of 300 claims (n = 269 from Denmark Patient Compensation Association – DPCA; n = 31 from Norwegian PCA) lodged between 2004 – 2012. **Inclusion:** Cases included in analysis if they involved a chiropractor and they were finalised at the time of the review. **Exclusion:** Patient insurance law did not cover them; patients withdrew claims, if claims wrongly assigned to chiropractors, and if there are duplicates. **Assessment of claims:** Both Denmark and Norway have a no fault compensation system. For claims related to CAD: **Denmark**: Rule of reason applies: where the patient leaves in a worse condition than they entered after treatment by a professional *eg. in cases of CVAs following manipulation even when no causal connection can be established,* they receive compensation even in	***Participants:*** N = 300 claims, N = 17 of these were for cervical artery dissection (5.7%); and n = 11 were approved. Cost of financial compensation was €2,044,523 (88.7% of costs for the whole complaint category) ***Limitations*** Detailed analysis of chiropractor and treatment characteristics was not possible, it should be considered that several different interventions on most patients including SMT, mobilisation, massage etc can be performed, so in some instances it might not be possible to discern which part of the treatment package is responsible for the complaint. ***Author conclusions:*** While the causality between manipulation and CAD remains uncertain, these events will continue to occur in association with cervical spine manipulation. Evidence based frameworks have recently been published.	Appropriate and clearly focused question	Y	**Reviewer comments:** Good retrospective analysis of claims data. Limitations of data store in these circumstances are clearly outlined, and likely to be similar to those faced by ACC. Data specifically searched for consultation with chiropractors, no comparisons with other health professionals who also perform cervical manipulative techniques were included. How CAD was diagnosed is not explained, report simply describes claims for CAD and numbers of claims accepted that are attributed to CAD **Level of evidence:** 2-
			The two groups being studied are selected from source populations that are comparable in all respects other than factor under investigation	CS	
			Study indicates how many people asked to take part did so	Y	
			Likelihood some eligible subjects have the outcome assessed and taken into account in analysis	Y	
			Percentage of recruits dropped out	Y	
			Comparison made between participants and those lost to follow up	Y	
			Outcomes clearly defined	Y	
			Assessment of outcome made blind to exposure status	NA	
			Recognition that knowledge of exposure status could influence assessment of outcome	NA	
			Measure of exposure assessment is reliable	CS	

	cases where the health care professional adhered to the specialist standard, - acceptance of the claim does not imply causality, or lack of function but reflects the statutory function of the compensation association **Norway:** Causation criteria must be fulfilled including: 1) causal relationship between the treatment and observed injury; 2) treatment should clearly not have been provided as there were clear signs of contraindication; and 3) there has to be financial loss because of the injury		Evidence from other sources used to demonstrate method of outcome assessment is valid and reliable	N	
			Exposure level or prognostic factor assessed more than once	CS	
			Main potential confounders identified and taken into account	Y	
			Confidence intervals provided	N	
			Quality of study in minimising risk of bias or confounding	N	
			Clear evidence of association between exposure and outcome	N	
			Study results directly applicable to patient group targeted	Y	

Evidence table 2. Primary Studies

Study	Methodology	Findings	Quality assessment		Conclusions
Moon et al, 2016[12] *Journal of Neuro Interventional Surgery 0, pg 1 – 7. doi:10.1136/ neurintsurg-2016-012565.* **Study design:** A retrospective review	**Observational study.** Retrospective analysis of patients with extracranial dissection who underwent endovascular intervention between January 1996 – January 2016. Data extracted on demographics, procedural details, radiographic and angiographic studies,	***Surgery outcomes reported in study not reported in this evidence table. Below are reported demographics of patients who had CAD or VAD. Please note results do not represent proportion of CAD or VAD of a whole population, but characteristics of this particular population.*** ***Participants*** N = 93 with carotid artery dissection, n = 23 with vertebral artery dissection	Appropriate and clearly focused question	Y	**Reviewer comments:** 9% of patients with CAD or VAD had recently undergone chiropractic manipulation; however the chronology of events could not be determined. Restricted population as cause of dissection not the main aim of this paper,
			The two groups being studied are selected from source populations that are comparable in all respects other than factor under investigation	Y	
			Study indicates how many people asked to take part did so	n/a	

of a prospectively maintained database **Objective:** To review institutional experience with endovascular treatment of cervical dissections over the past 20 years to examine indications for treatment, interventional methods and outcomes **Funding:** None disclosed	procedure-related complications and outcomes **Inclusion:** Patients in which stent placement or coil occlusion of parent vessel were conducted. **Exclusion:** Undergone formal angiography or medical management alone	***Carotid artery dissection participants*** **Characteristics** — **N (%) or mean±SD** Age, years — 45.4±14.5 (5–78) Sex Male — 52 (55.9) Female — 41 (44.1) Type of dissection Spontaneous — 57 (61.3) Traumatic — 27 (29.0) Iatrogenic — 9 (9.7) Presentation Head or neck pain — 29 (31.2) Cranial neuropathy — 11 (11.8) Visual deficit — 17 (18.3) Motor deficit — 50 (53.8) Sensory symptoms — 27 (29.0) Obtundation — 16 (17.2) Failed medical therapy — 47 (50.5) Segment CCA — 6 (6.5) ICA — 89 (95.7) Petrous segment — 24 (25.8) Indication for intervention Thromboembolism — 53 (57.0) Enlarging pseudoaneurysm — 48 (51.6) Flow-limiting dissection — 40 (43.0) Traumatic occlusion — 2 (2.2) ***Vertebral artery dissection participants***	Likelihood some eligible subjects have the outcome assessed and taken into account in analysis	c/s	**Level of evidence:** 2-
			Percentage of recruits dropped out	n/a	
			Comparison made between participants and those lost to follow up	n/a	
			Outcomes clearly defined	y	
			Assessment of outcome made blind to exposure status	n/a	
			Recognition that knowledge of exposure status could influence assessment of outcome	y	
			Measure of exposure assessment is reliable	y	
			Evidence from other sources used to demonstrate method of outcome assessment is valid and reliable	y	
			Exposure level or prognostic factor assessed more than once	c/s	
			Main potential confounders identified and taken into account	y	
			Confidence intervals provided	n	
			Quality of study in minimising risk of bias or confounding	y	
			Clear evidence of association between exposure and outcome	n	

		 6 of 67 (9%) patients with spontaneous dissection had a chiropractic manipulation within the past 30 days, 2 of these were vertebral artery dissections ***Authors note*** The relationship between dissections and chiropractic manipulation remains controversial because of limited populations studies and potential confounding factors such as underlying connective-tissue disorders and symptoms overlapping those of musculoskeletal disorders	Study results directly applicable to patient group targeted	y	

Evidence table 2. Primary Studies

Study

Thomas et al, 2015

Journal of Orthopaedic and Sports Physical Therapy, 45(7), Pg 503 - 511

Study design:
Cross-sectional case control study

Objective:
To identify risk factors and clinical presentation of individuals with cervical arterial dissection

Funding:
No affiliations or financial involvement with any organisation or entity with direct financial interest

Methodology

Cohort:
Aged 55years or younger from the Hunter region of NSW, Australia

Case control analysis:
Age and sex-matched comparison, medical work-up similar to those with CAD but no CAD present

Patient interview
Participants were interviewed about risk factors, preceding events and clinical features of their stroke

2 participants with CAD died as a result of dissection, medical records were used in these cases for data collection.

CAD diagnosis
Radiological diagnosis:

Exclusions
Intracranial or iatrogenic dissections not included

Cervical manipulation description:
Undergone recent

Findings

Participants:
N = 24 participants with CAD, and 21 controls (ischemic stroke but no dissection)

Recruited over 3 years due to relatively low occurrence of CAD

Analyses
Risk factors for participants with CAD and those with ischemic stroke by no dissection (adapted from original published in article)

Risk factor	VAD (n = 10)	iCAD (n = 14)	Total CAD (n = 24)	Odds Ratio OR(95% CI)
Neck manipulation	3	1	4	5.2(0.6-∞)
Minor mechanical trauma	9	8	17	60.0(8.7 - ∞)
Recent infection	1	4	5	2.5(0.4 – 14.5)
Vascular anomaly	1	3	4	1.9(0.3 – 11.6)
Hypertension	1	4	5	0.8(0.2 – 3.1)
Smoking	3	2	5	0.4(0.09 – 1.3)
Cholesterol	0	1	1	0.6(0.01 -0.5)
Family history	1	0	1	0.9(0.05 – 14.8)
Migraine	4	6	10	6.7(1.3 – 38.0)

Frequency and presentation of pain
*(A) Vertebral artery (n = 10) (B)**Internal Carotid Artery Dissection (n = 14)***

Quality assessment

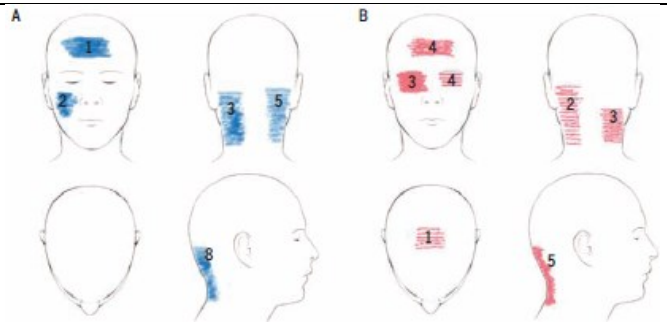
Appropriate and clearly focused question	Y
The two groups being studied are selected from source populations that are comparable in all respects other than factor under investigation	Y
Study indicates how many people asked to take part did so	na
Likelihood some eligible subjects have the outcome assessed and taken into account in analysis	Y
Percentage of recruits dropped out	N
Comparison made between participants and those lost to follow up	n/a
Outcomes clearly defined	Y
Assessment of outcome made blind to exposure status	n/a
Recognition that knowledge of exposure status could influence assessment of outcome	n/a
Measure of exposure assessment is reliable	Y

Conclusions

Reviewer comments:
Low sample sizes due to low numbers of CAD in population – results considered as preliminary as desired sample size (n = 40 CAD) was not met.

Level of evidence:
2 –

(graded down due to small sample size)

	chiropractic treatment in neck in month prior to dissection. N = 2 had rotary high-velocity thrust manipulation, n = 1had a deep massage to suboccipital region, and n = 1 was unknown No participants in control group had undergone a cervical, manipulative procedure within the same timeframe.	 **Early Warning Signs** **Clinical features in month preceding CAD diagnosis included:** Unusual headache or neck pain (most common in 14/ 16 CAD cases), Facial palsy, visual and speech disturbances, dizziness, imbalance, upper limb paresthesia and weakness. **Author conclusions** - *Recent prior minor mechanical trauma or strain to the neck is an important feature of CAD (including manipulation also vigorous manual techniques or exercise* - *Patients can present for treatment of acute-onset headache or neck pain as dissection develops* - *CAD may present as transient ischemic signs and symptoms in preceding few weeks before diagnosis*	Evidence from other sources used to demonstrate method of outcome assessment is valid and reliable	Y	
			Exposure level or prognostic factor assessed more than once	N/A	
			Main potential confounders identified and taken into account	Y	
			Confidence intervals provided	Y	
			Quality of study in minimising risk of bias or confounding	Y	
			Clear evidence of association between exposure and outcome	Y	
			Study results directly applicable to patient group targeted	Y	

6.4.3 Evidence Table: Review of single case studies

Evidence table 2. Reviews of single case studies					
Study	**Methodology**	**Findings**	**Quality assessment**		**Conclusions**
Puentedura et al, 2012	***Review***	***Participants:*** *N = 134 cases, reported in 93 articles*	Clearly defined research question	Y	**Reviewer comments:** Review of cases cannot

Journal of manual and manipulative therapy, 20 (2) pg 66 - 74 **Study design:** A review of 134 case reports **Objective:** To retrospectively analyse all available case reports in the literature on patients who had experience severe adverse events after receiving CSM to determine if CSM was used appropriately, and if these type of AEs could have been prevented **Funding:** None disclosed	*Review of case reports published in academic literature from 1950 – 2010.* ***Inclusion:*** *published between 1950 – 2010; case reports or case series; CSM as an intervention* ***Exclusion:*** *Spontaneous adverse event; systematic or literature reviews; in a language that was not English, German, Spanish, polish, French or Norwegian.* *Data extracted by 3 reviewers*	*Arterial dissection was the most common AE reported (37.3% of cases, n = 50).* *Chiropractors were involved in the majority of injuries (69.4%; n = 93) following manipulation, followed by osteopathic physicians (8.2%), physical therapists (3.7%)* 7 Cases resulted in death, 5 were from arterial dissection, 2 were from the practitioner continuing to perform the manipulation. ***Author conclusions:*** *There is no significant association between appropriateness of CSM and preventability of adverse events. Patients may be at increased risk due to the lack of reliable and valid screening tools, history taking*	Two people selected studies and extracted data	Y	distinguish causality, and cannot determine if dissection was caused by the cervical spine manipulation **Level of evidence:** 3+
			Comprehensive literature search carried out	Y	
			Authors clearly state how limited review by publication type	Y	
			Included and excluded studies listed	N	
			Characteristics of included studies are provided	N	
			Scientific quality of included studies assessed and documented	N	
			Scientific quality of included studies assessed appropriately	N	
			Appropriate methods used to combine individual study findings	Y	
			Likelihood of publication bias assessed	N	
			Evidence from other sources used to demonstrate method of outcome assessment is valid and reliable	NA	
			Main potential confounders identified and taken into account	Y	
			Confidence intervals provided	NA	

			Quality of study in minimising risk of bias or confounding	N	
			Clear evidence of association between exposure and outcome	N	
			Study results directly applicable to patient group targeted	Y	

Evidence table: Review of single case studies

Study	Methodology	Outcomes & results	Quality assessment		Reviewer comments and evidence level
Yin et al, 2014[15] Complementary and Alternative Medicine: eCAM. 480956 **Study design** Systematic review **Objective** To evaluate all published data (between 2003 and 2013) about adverse effects of massage therapy (including manipulation) **Funding** The work in Austria was supported by the Federal Ministries of	**Number of studies:** N = 40 articles (138 cases included) These articles varied in content: 33 articles reporting a total of 43 case reports, and 7 reports containing 95 adverse events in case series associated with 'massage'. **Definitions of massage:** Massage therapy in this paper included modalities like chiropractic manipulation, neck manipulation and rotation Of these N = 10 (6.5% of all cases) were diagnosed as arterial dissections **Databases** PubMED incl: MEDLINE, EMBASE, Cochrane Library, CNKI, CQVIP and Wanfang digital databases **Inclusion:** Only original case reports of complications or adverse events related to massage, manual therapy, and tuina published between January	**Main results showed:** Of the 43 case reports 10 of the adverse events were dissection of the vertebral artery. Of these 5 were reported as having a manipulation however the details of the case regarding diagnosis of dissection and time of manipulation were not reported. Reports were from a mixture of countries (US, Germany, Japan, Denmark, Spain and China) and clinicians were either not reported, 3 were chiropractors or one was a GP. In the majority of cases, problems were related to spinal manipulations, including rotational movements, which seem to the probable cause of AE's. **Author conclusions:** Spinal manipulation in massage has repeatedly been associated with serious adverse events. Clearly they are not totally devoid of risks, but the incidence of such events is low.	Clearly defined research question	N	**SIGN evidence level:** **3+** **Reviewer comments:** Systematic review of single case reports. Studies included based on content, however there is no clear justification why only case reports were analysed. Quality of the individual case reports was not reported, and details of the cases were missing. Reporting of the included studies has brief and did not go into detail. Although overall findings are aligned with other studies (incidence is low) this review provides little information that helps inform the primary research question regarding causation of cervical dissection.
			Two people selected studies and extracted data	Y	
			Comprehensive literature search carried out	Y	
			Authors clearly state how limited review by publication type	N	
			Included and excluded studies listed	N	
			Characteristics of included studies are provided	N	
			Scientific quality of included studies assessed and documented	N	
			Scientific quality of included studies assessed appropriately	CS	
			Appropriate methods used to combine individual study findings	N	
			Likelihood of publication bias assessed	N	

Science, Research and Economy of Health	2003 to June 2013 included **Exclusions:** Conference proceedings, cross-sectional and other descriptive designs and narrative reviews were excluded. **Populations:** Predominantly Chinese nationals but does include Germany, USA, Spain, and Australia. Lumbar and thoracic areas were included as well as different manual therapies, however cases were reported individually. **Diagnosis:** Just the adverse event was labelled, but method of diagnosis was not mentioned. Some papers described symptoms and attributed those symptoms to dissection as a way of diagnosis. Clinician types included chiropractors, GPs, , self-treatment, **Data extracted** Details of therapy, clinician type, adverse event, and follow up				
			Conflicts of interest declared	Y	
			Are results of study directly applicable to patient group targeted by guideline?	Y	

Evidence table 2. Primary Studies – already included in systematic review so excluded from analysis

Study	Methodology	Findings	Quality assessment	Conclusions

<table>
<tr>
<td>Engelter et al, 2013[19]

Neurology, 80 (21), pg 1950 – 1957

Study design:
Retrospective analysis of data from the CADISP consortium (Cervical Artery Dissection and Ischemic Stroke Patients)

Objective:
To examine the import of prior cervical (PCT) in patients with cervical artery dissection (CeAD)

Funding:
As part of the CADISP study funding has been received from research funds from Helsinki University, and the Academy of Finland, as well as multiple foundations (see paper)

Primary author has affiliations with Bayer and Boehringer, and Pfizer and on editorial boards of academic journals</td>
<td>Observational study.

Retrospectively recruited patients had either a CeAD or non-CeAD ischaemic stroke before the study was enrolled in the CADISP clinical study. Clinical data were systematically collected from local databases or registries.

N = 983 CeAD patients and n = 659 non-CeAD-IS patients from the CADISP clinical study as well as 281 health subjects enrolled prospectively.

Standard questionnaire was used for all participants and completed during visits to outpatient clinics.

Definition of Prior Cervical Trauma (PCT): included direct mechanical impact to the neck or head region and must have occurred within 1 month prior to first symptoms of CeAD or prior to ischemic stroke. Cervical manipulation was classified as a subtype of PCT and results for these were reported together as well as separately.

Functional outcomes:
Modified Rankin Scale – favourable 3 month outcome was functional independence as defined by a modified Rankin Scale score of 0 to 2.</td>
<td>Participants:
N = 1,897 included (n = 966 with CeAD; n = 651 with non-CeAD ischaemic stroke; n = 280 health subjects)

880 participants were recruited retrospectively. 26 participants were excluded because of missing information.

In CeAD participants:

<table>
<tr><th>Dissected artery</th><th>Without PCT n(%)</th><th>With PCT n(%)</th></tr>
<tr><td>ICAD</td><td>379 (66)</td><td>229 (58.4)</td></tr>
<tr><td>VAD</td><td>176 (30.5)</td><td>147 (37.5)</td></tr>
<tr><td>Both</td><td>19 (3.3)</td><td>16 (3.6)</td></tr>
<tr><td>Multiple CeADs</td><td>81 (14.1)</td><td>66 (16.9)</td></tr>
</table>

Risk factors:
Higher incidence of migraine in CeAD patients vs ischemic stroke or healthy subjects:

OR (95%CI)
Vs. IS: 1.589 (1.280 – 1.974)
Vs. Healthy: 1.841 (1.359- 2.493)

Lower incidence of diabetes:
Vs IS: 0.251 (0.150 – 0.420)
Vs. healthy: 0.324 (0.170 – 0.617)

Odds of trauma:
Significantly higher across all centres for:
Any trauma
Mild trauma
Severe trauma

Odds of prior cervical trauma:
(only cervical manipulative therapy reported for this</td>
<td>
<table>
<tr><td>Appropriate and clearly focused question</td><td>Y</td></tr>
<tr><td>The two groups being studied are selected from source populations that are comparable in all respects other than factor under investigation</td><td>Y</td></tr>
<tr><td>Study indicates how many people asked to take part did so</td><td>Y</td></tr>
<tr><td>Likelihood some eligible subjects have the outcome assessed and taken into account in analysis</td><td>Y</td></tr>
<tr><td>Percentage of recruits dropped out</td><td>n/a</td></tr>
<tr><td>Comparison made between participants and those lost to follow up</td><td>n</td></tr>
<tr><td>Outcomes clearly defined</td><td>Y</td></tr>
<tr><td>Assessment of outcome made blind to exposure status</td><td>n/a</td></tr>
<tr><td>Recognition that knowledge of exposure status could influence assessment of outcome</td><td>n/a</td></tr>
<tr><td>Measure of exposure assessment is reliable</td><td>Y</td></tr>
<tr><td>Evidence from other sources used to demonstrate method of outcome assessment is valid and reliable</td><td>Y</td></tr>
</table>
</td>
<td>Reviewer comments:
Some differences between healthy population and CeAD and nonCeAD IS populations which could have introduced bias.

High quality analysis of retrospectively analysed data.

Level of evidence:
2 –

(graded down due to retrospective study design's potential susceptibility to bias)</td>
</tr>
</table>

		review) CeAD vs NonCeADIS: Non-adjusted: 12.1(4.37 – 33.2), p <0.001 Adjusted (age, sex, centre): 11.9 (4.28 – 33.2) CeAD vs Healthy Non-adjusted: 4.1 (1.64 – 10.3) Adjusted (age, sex, centre): 3.6 (1.23 – 10.7) **Author conclusions:** CMT and extreme head movements were reported more frequently in CeAD patients than in healthy subjects according to crude adjusted analyses. Findings suggest a clear association between CeAD and cervical manipulation therapy.	Exposure level or prognostic factor assessed more than once	c/s	
			Main potential confounders identified and taken into account	Y	
			Confidence intervals provided	Y	
			Quality of study in minimising risk of bias or confounding	✓	
			Clear evidence of association between exposure and outcome	✓	
			Study results directly applicable to patient group targeted	Y	

6.5 Appendix 5. Primary studies included in Systematic Reviews

	SR	Primary study																						
SR	Rubenstein, 2005	Smith et al, 2003	Dittrich et al, 2007	Rothwell et al, 2001	Cassidy et al, 2008	Thomas et al, 2011	Engelter et al, 2013	Beletski et al, 2003	Debette et al, 2011	Dziewas et al, 2003	Hauser et al, 2010	Ahmad et al, 1999	Bartels et al, 2006	Chiche et al, 2005	De Bray et al, 1997	Hicks et al, 1994	Hufnagel et al, 199	Lu et al, 2000	Mas et al, 1987	Pugliese et al, 2007	Saeed e tal, 2000	Sturzenegger et al, 1994	Sturzenegger et al, 1993	Wessels et al, 2008	Gross et al, 2004
Conlon, 2012	✓		✓			✓	✓	✓	✓	✓	✓													
Church et al,		✓	✓	✓	✓	✓	✓																	
Haynes et al,		✓	✓	✓		✓																		
Gottesman et al,			✓									✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Wynd et al, 2013		✓	✓	✓	✓					✓			✓								✓			✓

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