

Study Protocol: Diagnostic Accuracy of Computed Tomographic Angiography for Blunt Cerebrovascular Injury Screening in Trauma Patients: A Systematic Review and Meta-Analysis

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1. Background and Rationale:

Blunt trauma to the carotid and/or vertebral arteries, collectively termed blunt cerebrovascular injury (BCVI), occurs in approximately 1% of all hospitalized, blunt trauma victims.^{1,2} Although BCVI was previously linked with early, unavoidable, and often devastating neurological deficits, it is now recognized that a latent period of 10- to 72-hours between injury and development of neurological sequelae frequently exists.^{3,4} Moreover, as the pathophysiology of BCVI-related stroke involves arterial intimal disruption, platelet aggregation, and subsequent vessel thrombosis or distal thromboembolism, antithrombotic therapy appears to effectively prevent adverse neurological sequelae in many patients.^{2,5} Therefore, radiological screening for BCVI may ultimately permit initiation of therapy early or in the latent period and result in improved neurological outcome and mortality.⁶⁻⁹

Although four-vessel digital subtraction angiography (DSA) remains the gold- or reference-standard test for BCVI screening and diagnosis, this investigation is labor intensive, invasive, and linked with several procedural complications.¹⁰ These limitations have led clinicians to investigate the validity of alternate BCVI screening or diagnostic tests, including duplex Doppler ultrasonography (US), magnetic resonance angiography (MRA), and single- or multidetector-row (or “slice”) computed tomographic angiography (CTA).¹¹⁻¹⁶ Duplex US was abandoned after an investigation involving 1400 blunt trauma patients reported an overall sensitivity of only 39% for BCVI and a high incidence of stroke among patients with false negative results.¹⁶ Furthermore, MRA has been limited by poor sensitivity and specificity for detection of BCVI, delays in availability, and incompatibility of equipment.^{11,15}

Several investigations have therefore focused on CTA as an alternative to DSA for BCVI screening or diagnosis.^{1,10,15,17-24} Advantages of this imaging modality include its non-invasive nature, short study times, relatively small intravascular contrast loads, and the ability to manipulate the product image in three-dimensions.²⁵ Moreover, many critically injured patients at risk for BCVI have additional indications for CT of other anatomical regions, making concurrent CTA of the cervical vasculature an attractive diagnostic approach.²⁵ However, possibly because CTA can be limited by the interpreting radiologist’s experience, streak and motion artifacts, and beam hardening by venous contrast, its reported accuracy has been highly variable.²⁶

Initial studies of one- and two-detector row scanners reported poor sensitivities of CTA for BCVI diagnosis.^{1,15} However, four- and eight-slice CTA were associated with sensitivities ranging from 83% to 92% for identification of carotid artery injury and 40% to 60% for vertebral artery injury.¹⁷ Excellent sensitivity and specificity using 16-slice multidetector CTA for BCVI screening was also observed in two studies.^{10,18} However, six other trials that evaluated the accuracy of 16-, 32-, or 64-slice CTA for detection of BCVI reported sensitivities and specificities ranging from poor to excellent, resulting in heterogeneous recommendations by injury experts for use of CTA for BCVI screening or diagnosis.¹⁹⁻²⁴ Some have advocated that CTA should be widely adopted while others suggested it be abandoned in favour of continued use of DSA. Although a previous review that employed a systematic search and study validity assessment attempted to assimilate the present cumulative knowledge of CTA use for BCVI, this investigation had several methodological limitations.²⁷ It lacked clear inclusion and exclusion criteria, included studies that did not examine the test validity of CTA, and did not investigate between studies for sources of heterogeneity or determine summary estimates of relevant outcomes. Thus, we seek to conduct a systematic review and meta-analysis of all diagnostic

cohort studies that report on the test accuracy of CTA versus DSA for detection of blunt carotid and/or vertebral artery injuries in blunt trauma patients.

2. Structured Clinical Question:

In blunt trauma patients with at least one BCVI associated risk factor or sign, is CTA as accurate as DSA for detection of blunt carotid or vertebral artery injuries?

2.1 PICOD Components:

P: Blunt trauma patients with at least one BCVI associated risk factor or sign as defined by the Western Trauma Association (WTA) and the Eastern Association for the Surgery of Trauma (EAST).^{5,28}

- Risk factors for BCVI (as described by the WTA and EAST) include: 1) an injury mechanism likely involving severe cervical hyperextension with rotation or hyperflexion; 2) Lefort II or III mid-face fractures; 3) basilar skull fracture involving the carotid canal; 4) closed head trauma with diffuse axonal injury and Glasgow Coma Scale (GCS) score ≤ 8 ; 5) cervical spine fracture of C1 to C3 or through the foramen transversarium or with associated subluxation or ligamentous injury; 6) near-hanging resulting in cerebral anoxia; or 7) seat belt or other clothesline-type injury with significant cervical pain, swelling, or altered mental status.^{5,28}
- Signs used as screening criteria for BCVI (as described by the WTA and EAST) include: 1) arterial hemorrhage from the neck, nose, or mouth; 2) expanding neck hematoma; 3) audible cervical bruit in a patient < 50 years of age; 4) focal neurological deficit, including transient ischemic attack (TIA), hemiparesis, vertebrobasilar symptoms, Horner's syndrome; or stroke on CT or MRI.^{5,28}

I: CTA of the carotid and vertebral arteries, either single- or multidetector-row slice

C: Percutaneous catheter-based four-vessel DSA of both carotid and vertebral arteries

O: Test accuracy (see below for definition) for detection of any BCVI (carotid and/or vertebral artery injury) or carotid or vertebral artery injury alone

D: Diagnostic cohort studies

3. Outcomes:

3.1. Primary Outcome:

Test accuracy of CTA for detection of any BCVI or carotid or vertebral artery injury alone on a per-patient, per-artery, and combined (per-patient and per-artery) basis.

- We define test accuracy as true and false positives, true and false negatives, sensitivity and specificity, and positive and negative likelihood ratios. The per-patient analysis addresses whether there is at least one BCVI detected among patients with one or more carotid or vertebral artery injuries, or whether a patient is correctly classified as uninjured. In contrast, the per-artery assessment addresses whether each of the examined extracranial cerebral arteries is correctly classified as injured or uninjured.

3.2. Secondary Outcomes:

1. Test accuracy of CTA for detection of different grades of carotid or vertebral artery injury will also be determined, if possible.
 - BCVIs will be graded according to the Denver grading scale.³⁰ Grade I injuries are defined as vessel wall irregularity or dissection/hematoma with less than 25% luminal stenosis. Grade II injuries are characterized by an intraluminal thrombus, dissection, or raised intraluminal flap with greater than 25% luminal narrowing. Grade III and IV injuries involve pseudoaneurysm formation and vessel occlusion, respectively, while grade V injuries are vessel transections with active arterial extravasation or arteriovenous fistulae.

4. Protocol:

This protocol will be made publicly available on the Trauma Association of Canada website (www.traumacanada.org). Methods for inclusion and analysis of articles and reporting of study results will follow recommendations from the Meta-analysis of Observational Studies in Epidemiology (MOOSE) proposal,³¹ the Preferred Reporting Items in Systematic Reviews and Meta-analyses statement,^{32,33} and the Cochrane Diagnostic Test Accuracy Working Group.^{34,35}

5. Search Strategy:

With the assistance of a medical librarian, two investigators (D.J.R., V.P.C.) will conduct the search using strategies previously recommended for systematic reviews of diagnostic and screening tests.²⁹ Using Ovid, we will search MEDLINE (1950 to present), EMBASE (1977 to present), and the Cochrane Database of Systematic Reviews. We will also query PubMed, the Cochrane Central Register of Controlled Trials (CENTRAL), and Web of Science. No publication date or language restrictions will be imposed. To identify unpublished/ongoing studies, we will write experienced colleagues, investigate two clinical trials registries (ClinicalTrials.gov and Current Controlled Trials), and search abstracts from the American Association for the Surgery of Trauma (AAST), Trauma Association of Canada (TAC), EAST, and WTA meetings (2008 to 2011). We will also use the PubMed “related articles” feature and hand-survey personal files and reference lists of included articles and identified review papers.

For our MEDLINE search, we will construct search filters for the themes BCVI, CTA or DSA, and diagnostic and screening tests using a combination of exploded Medical Subject Heading (MeSH) terms and text words, each combined through use of the Boolean operator “OR.” Each of the below search themes will subsequently be combined with use of the Boolean operator “AND” (similar searches will be conducted in remaining databases):

1. The BCVI search theme will contain the exploded MeSH terms “Carotid Artery Injuries,” “Cerebrovascular Trauma,” “Neck Injuries,” “Vertebral Artery/Injuries,” “Wounds and Injuries,” “Wounds, Nonpenetrating,” OR “Multiple Trauma” as well as the key words “carotid injur*,” “cerebrovascular injur*,” “neck injur*,” “vertebral artery injur*,” OR “blunt cervical vascular injur*”
2. The CTA or DSA search theme will contain the MeSH terms “Angiography, Digital Subtraction,” “Cerebral Angiography,” “Angiography,” “Tomography, X-Ray Computed,” “Tomography Scanners, X-Ray Computed,” OR “Image Processing, Computer-Assisted” as well as the key words “computed tomography,” “computed tomographic angiography,” “computed tomography angiography,” “multi-detector computed tomographic angiography,” OR “multidetector computed tomographic angiography”

3. Although their utility has been questioned, the diagnostic and screening tests theme will utilize a search filter that has been validated to yield the highest sensitivity for locating diagnostic studies in MEDLINE³⁶ and EMBASE.³⁷

6. Selection Criteria:

Following removal of duplicate citations, two reviewers (D.J.R., V.P.C.) will independently screen all identified titles and abstracts. As the initial screen is intended to be broad, these investigators will select all potentially relevant citations in which CTA may have been used for screening or diagnosis of BCVI in trauma patients. All of these citations will then be obtained and read in full so that inclusion and exclusion criteria can be applied.

We will use the following inclusion criteria: 1) design was a prospective or retrospective diagnostic cohort study; 2) study participants were adult (mean age \geq 16-years-old) blunt trauma patients with at least one BCVI associated risk factor or sign (see section 2.1); 3) experimental test included one-slice and/or multidetector row CTA; 4) gold- or reference-standard test included percutaneous four-vessel DSA; 5) either all or a proportion (at least 10) of the study participants underwent both CTA and DSA; and 6) the study presented 2 X 2 contingency tables or data allowing their construction. As all grades of BCVI require treatment (and thus a change in clinical management),^{5,28} the 5-grades of injury will be combined and dichotomous “injury” or “no injury” (i.e. grade I or higher BCVI versus no injury) 2 X 2 tables will be separately constructed on both a per-patient and per-artery basis. Similarly, separate descriptions of injury detection across segments of the carotid or vertebral arteries will be combined into a single carotid or vertebral artery injury detection accuracy measure.²² We will exclude non-original studies, animal model investigations, investigations utilizing test phantoms (plastic tubes that mimic vessels with pulsatile flow generators), and studies in which either all or a proportion (at least 10) of the study participants did not receive both CTA and DSA.

Agreement between reviewers will be quantified using the Kappa statistic.²⁹ Any disagreement regarding inclusion or exclusion of articles between reviewers will be resolved by consensus or arbitration by a third reviewer (M.T.J.) if necessary.

7. Data Extraction:

In duplicate, the same two reviewers will independently extract data using a pre-designed data extraction spreadsheet (Excel spreadsheet available upon individual request), which will be piloted on three identified studies. We will extract data on: 1) trial design; 2) participant inclusion and exclusion criteria; 3) study participant characteristics, including age, mechanism of injury [e.g., motor vehicle collision (MVC), motor bike collision (MBC), assault, fall, motor vehicle versus pedestrian, and hanging, among others], injury severity score (ISS), regional bodily abbreviated injury score (AIS), and distribution of associated risk factors or signs used as indications for BCVI screening; 4) distribution of identified BCVI injury grades on CTA or DSA across the study population; 5) the experimental CTA test, including CT scanner model/brand, imaging technique, volume and type of contrast agent, and number of CT rows or slices; 6) the DSA test, including technique and type and volume of contrast agent; 7) study methodology (see below); 8) the rate of true and false positive and negatives for the detection of any BCVI or carotid or vertebral artery injury alone across injury grades and on a per-patient and per-artery basis in order to populate 2 X 2 contingency tables; and 9) reported sensitivities and specificities.

Interpreters will be enlisted to translate non-English language studies as necessary. Agreement between reviewers (D.J.R., V.P.C.) on data extraction will be quantified using the

Kappa statistic. Any disagreement regarding inclusion or exclusion between reviewers will be resolved by consensus or arbitration by a third reviewer (M.T.J.) if necessary.

8. Assessment of Methodological Quality:

The methodological quality of studies will also be assessed independently and in duplicate by the same two reviewers using the 14 question Quality Assessment of Diagnostic Accuracy Studies (QUADAS) tool (Appendix I).³⁸ Questions 3, 6, and 7 (differential verification bias and accurate, independent reference standard) will be omitted as only studies utilizing DSA as the reference standard will be included. For question 4 of the QUADAS tool (“[i]s the time period between reference standard and the index test short enough to be reasonably sure that the target condition did not change between the two tests?”), we will define the time interval as ≤ 48 -hours. For question 8 (“[w]as the execution of the index test described in sufficient detail to permit replication of the test?”), the CT scanner model/brand, general imaging technique, volume and type of intravenous contrast, and number of CT rows or slices must be afforded to consider the description of the index test sufficient. Similarly, in question 9 (“[w]as the execution of the reference standard described in sufficient detail to permit its replication?”), the procedure and type of and volume of intra-arterial contrast must be explained. We will define verification bias as occurring when not all of the carotid and/or vertebral arteries imaged during CTA are subsequently subselected and examined during DSA.

Three methodological characteristics of diagnostic studies that are largely unaddressed by the QUADAS tool will also be assessed. These include: 1) data collection (prospective versus retrospective), 2) patient selection (consecutive versus non-consecutive), and 3) training of the interpreting radiologist (neuroradiologist versus non-neuroradiologist). Studies will also be examined as to whether a “learning curve” in evaluation existed (i.e., a difference in test accuracy between the beginning and a subsequent time point of a diagnostic study).

9. Data Synthesis/Analysis:

3.1. Primary Analysis:

- Meta-analysis of individual studies will be conducted using Stata V12.0 (Stata Corp., College Station, TX). As was described above, we will begin by dividing the extracranial cerebrovascular arterial system into two groups of vessels: the carotid and vertebral arteries. Abstracted data will be used to populate 2 X 2 tables for each group of vessels and for the overall combined group of vessels on a per-patient and per-artery basis. The 5-grades of injury will be combined and a dichotomous “injury” or “no injury” (i.e. grade I or higher BCVI versus no injury) and a 2 X 2 table will be constructed for each level of analysis. For each study, sensitivity, specificity, and positive and negative likelihood ratios for detection of any BCVI or carotid or vertebral artery injury alone will be calculated from our populated 2 X 2 tables. If possible, summary estimates of CTA test accuracy will also be produced for each of the described BCVI grades (I to V).
- A pooled analysis of included studies will be conducted using bivariate mixed-effects regression models.^{39,40} Results will be represented graphically using Forest plots with one plot for each diagnostic accuracy estimate of interest with data

available. Hierarchical summary receiver operating curves (ROC) will also be constructed in order to assess for a variation in determining CTA test positivity across studies (either explicit or implicit).⁴¹ The potential for publication bias will be assessed using funnel plots and the funnel plot asymmetry test described by Deek.⁴²

3.2. Subgroup Analysis and Investigation of Heterogeneity:

- Heterogeneity between studies could be related to diagnostic test characteristics, study quality, or test interpretation. Subgroup analyses will be conducted to determine if these explain heterogeneity if heterogeneity is detected.
- Heterogeneity will be explored using univariate meta-regression using the diagnostic odds ratio as the outcome and with diagnostic test characteristics, study quality, and test interpretation explored in univariate analyses. A type I error rate of 0.10 will be used to identify significant differences in meta-regression.
 1. Characteristics of the diagnostic test:
 - a) < 16-slices
 - b) 16-slices
 - c) > 16-slices
 3. Quality of the study (including the five characteristics that determine design-related bias as identified by Lijmer and colleagues⁴³):
 - a) Case-control design
 - b) Presence of partial verification bias
 - c) Independent, blind assessment of CTA and/or DSA results
 - d) Adequate reporting of the index test characteristics
 - e) Adequate reporting of the reference test characteristics
 - f) Prospective study design
 - g) Consecutive patient enrollment
 4. Test interpretation
 - a) Neuroradiologist
 - b) Non-neuroradiologist
 - c) Studies in which a “learning curve” was evident (see above)

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Appendix I. Quality Assessment of Diagnostic Accuracy Studies (QUADAS) tool.

Item		Yes	No	Unclear
1.	Was the spectrum of patients representative of the patients who will receive the test in practice?			
2.	Were selection criteria clearly described?			
3.	Is the reference standard likely to correctly classify the target condition?			
4.	Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?			
5.	Did the whole sample or a random selection of the sample, receive verification using a reference standard of diagnosis?			
6.	Did patients receive the same reference standard regardless of the index test result?			
7.	Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?			
8.	Was the execution of the index test described in sufficient detail to permit replication of the test?			
9.	Was the execution of the reference standard described in sufficient detail to permit its replication?			
10.	Were the index test results interpreted without knowledge of the results of the index test?			
11.	Were the reference standard results interpreted without knowledge of the results of the index test?			
12.	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?			
13.	Were interpretable/intermediate test results reported?			
14.	Were withdrawals from the study explained?			

Taken from Whiting P, Rutjes AW, Reitsma JB, et al. The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. BMC Med Res Methodol 2003;3:25.