รายงานวิจัยฉบับสมบูรณ์

โครงการ การศึกษา systematic review ด้านผลของเทคนิคด้านวิสัญญี การใส่ shunting และเทคนิคการปิดหลอดเลือดต่อภาวะแทรกซ้อนหลัง การผ่าตัด carotid endarterectomy

โดย ศ.ดร.นพ.กิตติพันธุ์ ฤกษ์เกษม

กรกฎาคม 2558

สัญญาเลขที่ RSA5580008

รายงานวิจัยฉบับสมบูรณ์

โครงการการศึกษา systematic review ด้านผลของเทคนิคด้านวิสัญญี การใส่ shunting และเทคนิคการปิดหลอดเลือดต่อภาวะแทรกซ้อนหลังการผ่าตัด carotid endarterectomy

ศ.นพ.กิตติพันธุ์ ฤกษ์เกษม
ภาควิชาศัลยศาสตร์ คณะแพทยศาสตร์
มหาวิทยาลัยเชียงใหม่

สนับสนุนโดยสำนักงานกองทุนสนับสนุนการวิจัย
คณะแพทยศาสตร์ มหาวิทยาลัยเชียงใหม่ และมหาวิทยาลัยเชียงใหม่
(ความเห็นในรายงานนี้เป็นของผู้วิจัย สกว. และ มหาวิทยาลัยเชียงใหม่
ไม่จำเป็นต้องเห็นด้วยเสมอไป)

กิตติกรรมประกาศ (Acknowledgement)

ผู้จัดทำขอขอบคุณ

สำนักงานกองทุนสนับสนุนการวิจัย

คณะแพทยศาสตร์ มหาวิทยาลัยเชียงใหม่

และมหาวิทยาลัยเชียงใหม่

ที่ให้ทุนในการศึกษานี้

รูปแบบ Abstract (บทคัดย่อ)

Project Code : **(รหัสโครงการ)**	RSA5580008
Project Title : **(ชื่อโครงการ)**	การศึกษา systematic review ด้านผลของเทคนิคด้านวิสัญญี การใส่ shunting และเทคนิคการปิดหลอดเลือดต่อภาวะแทรกซ้อนหลังการผ่าตัด carotid endarterectomy
Investigator : **(ชื่อนักวิจัย)**	ศ.นพ.กิตติพันธุ์ ฤกษ์เกษม ภาควิชาศัลยศาสตร์ คณะแพทยศาสตร์ มหาวิทยาลัยเชียงใหม่
E-mail Address :	rerkase@gmail.com
Project Period : **(ระยะเวลาโครงการ)**	3 ปี

Abstract

Background

Carotid endarterectomy reduces the risk of stroke in people with recently symptomatic, severe carotid artery stenosis. However, there are significant perioperative risks which may be lessened by performing the operation under local rather than general anaesthetic. Also the perioperative risk might be lower by using intraluminal shunting rather than without shunt. This study aimed to assess the risks of endarterectomy under local compared with general anaesthetic. Also to assess the effect of routine versus selective or no shunting during carotid endarterectomy, and to assess the effect of different methods for selection of people for shunting.

Methods

We searched the Cochrane Stroke Group Trials Register (last searched August 2013), the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library, Issue 8, 2013), MEDLINE (1966 to August 2013), EMBASE (1980 to August 2013) and Index to Scientific and Technical Proceedings (1980 to August 2013). We handsearched journals and conference proceedings, checked reference lists, and contacted experts in the field. In terms of selection criteria, randomised trials comparing carotid endarterectomy under local versus general anaesthetic. Also randomised and quasi-randomised trials of routine shunting compared with no shunting or selective shunting, and trials that compared different shunting policies in people undergoing carotid endarterectomy. Two review authors assessed trial quality and extracted the data independently.

Main results

For study in anesthetic aspect, ten randomised trials involving 4335 operations were included, of which 3526 were from the single largest trial (GALA). Meta-analysis of the randomised studies showed that there was no evidence of a reduction in the odds of operative stroke or death (odds ratio (OR) 0.85, 95% confidence interval (CI) 0.63 to 1.16). For study in shunting, We included three trials involving 686 participants compared routine shunting with no shunting, For routine versus no shunting, there was no significant difference in the rate of all stroke, ipsilateral stroke or death up to 30 days after surgery, although data were limited.

Authors' conclusions

The risk of stroke and death did not differ significantly between the two types of anaesthetic technique during carotid endarterectomy. This review provides evidence to support a policy that patients and surgeons can choose either anaesthetic technique, depending on the clinical situation and their own preferences. This review concluded that the data available were too limited to either support or refute the use of routine or selective shunting in carotid endarterectomy. Large scale randomised trials of routine shunting versus selective shunting are required.

Key word: carotid endarterectomy, stroke, anesthetic, shunt

บทคัดย่อ

บทนำ

การผ่าตัด Carotid endarterectomy (CEA) สามารถลดการเกิดอัมพาตในคนที่มีหลอดเลือดแดง carotid ตีบรุนแรงได้ แต่เนื่องจากเทคนิคการผ่าตัดมีความแตกต่างกันเพื่อลดการเกิดอัมพาตในเกิดน้อยที่สุดในระหว่างการผ่าตัดในแต่ละศัลยแพทย์ ได้มีข้อถกเถียงกันถึงเทคนิคทางวิสัญญีวิทยาว่าจะใช้ยาระงับความรู้สึกเฉพาะที่หรือจะให้ยาระงับความรู้สึกทั้งตัว และในระหว่างการผ่าตัดหนีบหลอดเลือดควรใส่ shunt ซึ่งเป็นท่อพลาสติกกลวงที่สามารถโค้งงอได้มาใส่ไว้ในหลอดเลือดเพื่อให้เลือดไหลผ่านลัดข้ามบริเวณที่กำลังทำผ่าตัดไปหรือไม่

วิธีการศึกษา

การศึกษาใช้เทคนิค systematic review และ meta-analysis ที่หาข้อมูลจากฐานข้อมูล MEDLINE (คศ.1966 ถึง 2013), EMBASE (คศ1980 ถึง 2013) ได้หาข้อมูลจาก Index to Scientific and Technical Proceedings (ISTP) (คศ.1980 ถึง 2013) ได้ทำการค้นหาข้อมูลเพิ่มเติมโดยละเอียดในเอกสารประกอบการประชุมใน 6 วารสาร และค้นหาจากเอกสารอ้างอิงในงานวิจัยที่นำมาวิเคราะห์

โดยเลือกเฉพาะการศึกษาแบบ randomised controlled trial (RCT) (รวมถึง quasi-RCT) ที่เปรียบเทียบระหว่างเทคนิคทางวิสัญญีวิทยาว่าจะใช้ยาระงับความรู้สึกเฉพาะที่หรือจะให้ยาระงับความรู้สึกทั้งตัว และในระหว่างการผ่าตัดหนีบหลอดเลือดใส่ shunt หรือไม่ใส่ shunt การศึกษาทำโดย 2 นักวิจัยที่ทำโดยอิสระต่อกันในทุกขั้นตอน

ผลการศึกษา

ในด้านเทคนิคทางวิสัญญี พบ 10 RCT มีจำนวนการผ่าตัดในการศึกษาทั้งหมด 4335 ครั้ง การศึกษาพบว่าไม่พบความแตกต่างของอัตราการเกิดอัมพาตและเสียชีวิตระหว่าง 2 เทคนิคทางวิสัญญี (odds ratio 0.85, 95% confidence interval 0.63 ถึง 1.16) ในด้านการศึกษา shunt พบ 3 RCT มีจำนวนการผ่าตัดทั้งหมด 686 ครั้ง จากข้อมูลที่มีไม่พบว่ามีความแตกต่างระหว่างการใส่ shunt และการไม่ใส่ shunt แต่ข้อมูลที่มีในการวิเคราะห์มีจำนวนน้อยเกิดกว่าที่จะสรุปได้อย่างมั่นใจ

สรุป

การศึกษานี้ไม่พบว่าเทคนิคทางวิสัญญีวิทยาว่าจะใช้ยาระงับความรู้สึกเฉพาะที่หรือจะให้ยาระงับความรู้สึกทั้งตัวมีความแตกต่างด้านอัตราการเกิดอัมพาต ดังนั้นผู้ป่วยและศัลยแพทย์

สามารถเลือกวิธีใดก็ได้ในการผ่าตัด ในด้านการใส่ shunt พบว่าจำนวนผู้ป่วยในการศึกษามีจำนวนจำกัด ไม่สามารถสรุปได้ จึงต้องรอการศึกษาให้มีจำนวนที่พอเพียงก่อนจะสรุปได้

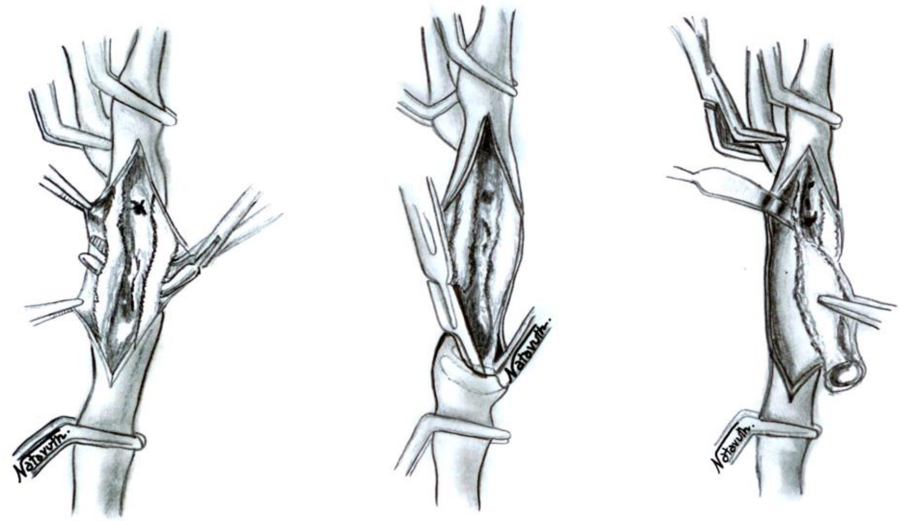
คำสำคัญ อัมพาต หลอดเลือดแดงตีบ วิสัญญี การใส่ท่อเลือด

สารบัญ

1. บทนำ ความสำคัญและที่มาของปัญหา

โรคหลอดเลือดสมองหรือ stroke นำมาสู่การเสียชีวิตและความพิการ เป็นโรคที่แต่ละประเทศต้องใช้งบประมาณอย่างมากในการดูแลผู้ป่วย แต่ถึงอย่างไรก็ตาม stroke เป็นโรคที่รักษาและป้องกันได้ จากข้อมูลกระทรวงสาธารณสุข พ.ศ.2547 [1] ซึ่งได้รายงานโรคที่เป็นภาระของคนไทยฉบับล่าสุด พบว่า stroke คือโรคที่เป็นสาเหตุการตายหนึ่งในสิบของคนไทยโดยในเพศหญิงเป็นสาเหตุการตายที่สูงเป็นอันดับหนึ่ง (14%) และในเพศชายเป็นอันดับสาม (8%) รองจากโรคเอดส์และอุบัติเหตุ โรค stroke ทำให้ประเทศชาติสูญเสียทรัพยากรมนุษย์ที่จะทำงานหรือถ้ายังไม่เสียชีวิต ก็เสียความสามารถในการทำงานอย่างมีประสิทธิภาพ จากข้อมูลเบื้องต้นพบว่า stroke เป็นโรคที่ทำให้จำนวนปีที่สุขภาพดีสูญเสียไป (disability adjusted life year) สูงเป็นอันดับสองในเพศหญิงและเป็นอันดับสามในเพศชาย [1]

การตีบของหลอดเลือดเลี้ยงสมองบริเวณคอ (Carotid artery stenosis-CAS) เป็นสาเหตุโรคหลอดเลือดสมอง 17% [2] การศึกษาในอดีตพบว่า CAS ก่อให้เกิดก้อนเลือดบริเวณหลอดเลือดที่ตีบและส่งผลให้เกิดหลอดเลือดไปอุดเส้นเลือดในสมอง (cerebral embolism) เป็นกลไกหลักของการเกิดโรคหลอดเลือดสมองจาก CAS การผ่าตัด Carotid endarterectomy (CEA) (รูปที่ 1) เป็นการผ่าตัดเพื่อลอก atherosclerotic plaque ออกจากผนังหลอดเลือด CEA สามารถป้องกันการเกิด stroke ในอนาคตออก ในราวปี ค.ศ. 1991 มีการศึกษา randomsied controlled trial (RCT) ขนาดใหญ่อยู่สองการศึกษา ในยุโรปชื่อ European Carotid Surgery Trial –ECST (3018 คน) [3] และในสหรัฐอเมริกา ชื่อ North American Symptomatic Carotid Endarterectomy Trial [4]–NASCET (2885 คน) เป็นการศึกษาในผู้ป่วยที่มีอาการขาดเลือดเลี้ยงสมองร่วมกับมี CAS ได้ศึกษาเปรียบเทียบระหว่างการผ่าตัด CEA กับการได้ยารักษา พบว่าการผ่าตัด CEA สามารถลดโอกาสเสี่ยงการเกิด stroke ได้มากกว่าการได้ยาเพียงอย่างเดียว [5] แต่ถึงอย่างไรก็ตามแม้มีการศึกษาขนาดใหญ่ดังกล่าว การผ่าตัด CEA ยังมีข้อถกเถียงในเรื่องเทคนิคการผ่าตัด ด้านผลของเทคนิคด้านวิสัญญี การใส่ shunting และเทคนิคการปิดหลอดเลือด และเป็นที่มาการศึกษาวิจัยหัวข้อต่างในการศึกษานี้



ก ข ค

รูปที่ 1 แสดงการเลาะ atherosclerotic plaque จากผนังหลอดเลือด ก) แสดงเลาะ plaque ทะลุไปอีกด้านโดย right angle clamp ข) แสดงการตัด plaque ในแนว CCA ค) ลอก plaque ออกไปทาง distal

1.1 วิธีการให้ยาระงับความรู้สึกในการผ่าตัด CEA

ในการผ่าตัด CEA ได้มีข้อถกเถียงกันถึงเทคนิคทางวิสัญญีวิทยาว่าจะใช้ยาระงับความรู้สึกเฉพาะที่ (locoregional anesthesia หรือ LA) หรือจะให้ยาระงับความรู้สึกทั้งตัว (general anesthesia หรือ GA)[6] แพทย์บางกลุ่มให้เหตุผลว่า GA สามารถป้องกันการขาดเลือดในสมองได้เพราะยาดมสลบบางตัว เช่น isoflurane สามารถลด neuronal activity ทำให้เซลล์สมองมีความต้องการออกซิเจนลดลง[7] ส่วน fast-acting barbiturate สามารถลด oxygen metabolism ทำให้เซลล์สมองใช้ออกซิเจนลดลง นอกจากนั้น barbiturate ยังเพิ่มเลือดไปเลี้ยงสมองส่วนต่างๆ ให้มีประสิทธิภาพยิ่งขึ้น ลด intracranial pressure และป้องกันสมองบวม อย่างไรก็ตามผลของ barbiturate ดังกล่าวจะเกิดเมื่อให้ยาในปริมาณที่สูงกว่าระดับปกติที่ใช้กัน ส่วนผลของ barbiturate ปริมาณปกติที่ให้ผู้ป่วยมีอยู่เพียงการศึกษาเดียวที่แสดงให้เห็นประโยชน์ของการป้อง

การสมองขาดเลือด[7] ข้อดีของ GA อีกประการหนึ่งคือทำให้ผู้ป่วยไม่ต้องกระวนกระวายในขณะผ่าตัด ความกังวลของผู้ป่วยจะมีผลต่อการทำงานของระบบหัวใจและหลอดเลือด

ในทางตรงกันข้ามแพทย์อีกกลุ่มหนึ่งให้เหตุผลว่า LA เป็นวิธีที่ดีกว่าเพราะสามารถตรวจระบบการทำงานของสมองได้ตลอดเวลาเพราะผู้ป่วยรู้สึกตัวอยู่ตลอดและใช้ในการประเมินว่าจะต้องใส่ shunt หรือไม่ หากเป็นการผ่าตัดโดยใช้ GA จะไม่สามารถประเมินการทำงานของสมองได้จึงให้อัตราการใส่ shunt สูงกว่ามาก หากอัตราการใส่ shunt ลดลงจะทำให้ภาวะแทรกซ้อนจากการใส่ shunt ลดลงไปด้วย นอกจากนี้ LA ยังรักษากระบวนการ physiological protective mechanisms ของ cerebrovascular reflex ส่งผลให้มีเลือดไปเลี้ยงสมองอย่างสม่ำเสมอ[8]

สรุปข้อดีของการผ่าตัด CEA โดยใช้ GA

- สามารถลด cerebral metabolic rate ในขณะผ่าตัดได้
- ลดความกังวลในผู้ป่วยลง ทำให้ผ่าตัดได้สะดวก ผู้ป่วยอยู่ในท่านิ่งตลอดเวลา
- ความเครียดของศัลยแพทย์ลดลงทำให้การสอนนักศึกษาแพทย์หรือศัลยแพทย์ฝึกหัดทำได้สะดวกขึ้น
- แนวโน้มที่ผู้ป่วยจะมีความดันโลหิตสูงในระหว่างผ่าตัดมีต่ำกว่า
- หากเกิดปัญหารุนแรงในระหว่างผ่าตัดสามารถดูแลทางเดินหายใจได้ง่ายกว่าเพราะมีท่อช่วยหายใจอยู่แล้ว

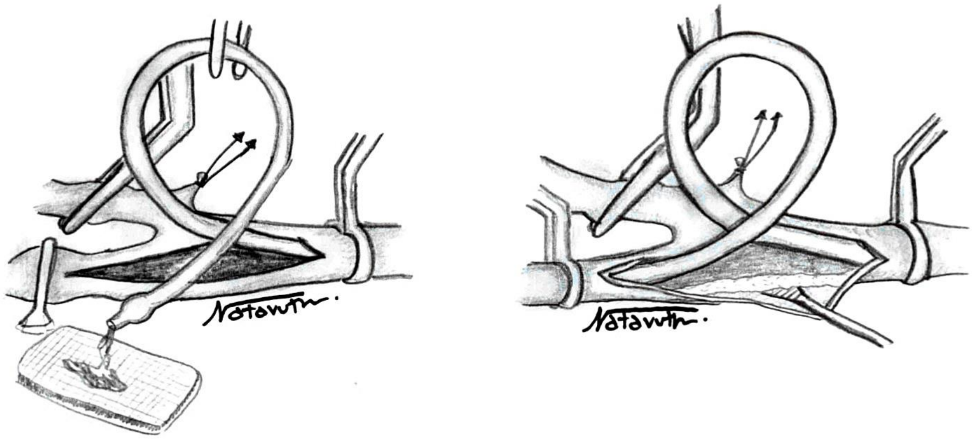
สรุปข้อดีของการผ่าตัด CEA โดยใช้ LA[9]

- ทำให้รักษากระบวนการ cerebral antoregulation เป็นไปอย่างปกติ
- ป้องกันการเกิดความดันโลหิตต่ำในระหว่างผ่าตัด
- สามารถให้การวินิจฉัยได้อย่างชัดเจนว่าผู้ป่วยต้องการการใส่ shunt หรือไม่ในระหว่างหนีบหลอดเลือด carotid artery
- หลังผ่าตัดผู้ป่วยจะฟื้นตัวได้เร็วสามารถกลับบ้านได้ไวกว่าจึงลดค่าใช้จ่ายในโรงพยาบาลได้ดีกว่า

สรุปการผ่าตัดยังไม่สามารถสรุปได้ว่าควรผ่าตัด CEA ใต้ LA หรือ GA จึงนำมาสู่การศึกษาวิจัยนี้

1.2 การใส่ shunt ขณะผ่าตัด

ในการผ่าตัด CEA จะต้องมีการหนีบหลอดเลือด carotid artery ซึ่งมีส่วนไปเลี้ยงสมองทำให้ผู้ป่วยอาจมีอาการสมองขาดเลือดได้ ซึ่งเรียกว่า hemodynamic stroke ทำให้มีการคิดค้นวิธีใส่ shunt ขึ้นโดยนำท่อพลาสติกกลวงที่สามารถโค้งงอได้มาใส่ไว้ในหลอดเลือดเพื่อให้เลือดไหลผ่านลัดข้ามบริเวณที่กำลังทำผ่าตัดไป เพื่อป้องกันสมองขาดเลือดเรียกเทคนิคนี้ว่า temporary intraluminal shunting[10] (รูปที่ 2) การใส่ shunt ในระหว่างผ่าตัดทำให้การทำ endarterectomy ไม่ต้องรีบร้อนมากและยังมีเวลาที่จะสอนศัลยแพทย์ฝึกหัดได้อีกด้วย ในบางครั้งอาจทำให้การผ่าตัดที่ค่อนข้างยุ่งยากซับซ้อนง่ายดายขึ้น เช่น การมี high carotid dissection ข้อดีอีกอย่างหนึ่งคือ shunt ยังทำหน้าที่เหมือนเป็น stent คอยถ่างหลอดเลือดไว้ขณะกำลังเย็บปิดผนังหลอดเลือด



ก ข

รูปที่ 2 แสดงขั้นตอนการใส่ Javid shunt ก) แสดงการใส่ shunt เข้าไปในส่วนของ common carotid artery และปล่อยให้เลือดไหลออกมาสู่ guaze เพื่อลด emboli ข) ใส่ shunt ลงไปในส่วน internal carotid artery และเริ่มลอก plaque

(รูปดัดแปลงจาก Greenhalgh และ Becquemin. Vascular and endovascular surgical techniques. London : W. B. Saunders, 2001, p37.)

สามารถแบ่งกลุ่มของการใส่ shunt ตามความนิยมของศัลยแพทย์ออกเป็น 3 ประเภทคือ (1) ใส่ shunt ทุกราย (routine shunter) (2) ใส่ shunt ในบางกรณี (selective shunter) (3) ไม่นิยมใส่ shunt (rare shunter) ในกลุ่มแรกที่นิยมใส่ shunt เนื่องจากข้อดีของ shunt มีมากมายในขณะที่บางคนนิยมใส่ shunt ในบางกรณีเท่านั้น เนื่องจากผู้ป่วยบางคนมีอาการสมองขาดเลือดขณะหนีบหลอดเลือด carotid artery เนื่องจากมีหลอดเลือดสำรองจากด้านตรงข้ามมาเลี้ยงไม่เพียงพอ จากงานวิจัย meta-analysis (ตารางที่ 4) พบว่าผู้ป่วยเพียงประมาณ 25-30% เท่านั้นที่ต้องการการใส่ shunt[11]

ส่วนศัลยแพทย์ที่ไม่นิยมใส่ shunt ในทุกกรณีเนื่องจากสามารถผ่าตัด endarterectomy ได้เสร็จในระยะเวลาอันสั้นและมีความเสี่ยงน้อยต่อการเกิด hemodynamic stroke ในขณะที่ shunt ก็สามารถทำให้เกิดอันตรายต่อผนังหลอดเลือดชั้น tunica intima และเกิด embolism ตามมาได้ 0.002 % - 5 %[12] อีกทั้งการใส่ shunt ก็อาจไปกีดขวางการผ่าตัดทำให้ขั้นตอนการลอก plaque และการเย็บผนังหลอดเลือดทำได้ลำบาก

จากข้อมูลดังกล่าวจะเห็นว่าประเด็นการจะใส่ shunt หรือไม่ ระหว่างการผ่าตัด CEA ยังเป็นที่ถกเถียง ผู้วิจัยจึงสนใจเพื่อแก้ปัญหาดังกล่าว

2. วัตถุประสงค์

เป็นการศึกษาเปรียบเทียบว่าเทคนิคใดต่อไปนี้ให้ผลการรักษาดีที่สุด (ภาวะแทรกซ้อนจากการผ่าตัดต่ำสุด) ในการผ่าตัด CEA

- Local versus general anesthesia
- Shunting versus non-shunting

3. วิธีการทดลอง

3.1 ระเบียบวิธีวิจัย

Systematic review and meta-analysis of randomized controlled trial ซึ่งการศึกษานี้เป็นส่วนหนึ่งของ update Cochrane Systematic Review

3.2 วิธีการค้นหาและคัดเลือกการศึกษา

3.2.1 เกณฑ์ในการคัดเลือกการศึกษามีดังต่อไปนี้

Type of studies

All RCTs that compared LA with GA for CEA and that measured clinically relevant outcome

Types of participants

Any trials that included any type of patients undergoing unilateral or bilateral CEA to be eligible

Types of interventions

We sought to identify all trials comparing CEA under GA of any type with CEA under LA of any type, including epidural and cervical nerve block

3.2.2 เกณฑ์ในการคัดเลือกการศึกษามีดังต่อไปนี้

โดยการศึกษาเหล่านั้นต้องมี outcome ดังนี้

Type of outcome measure

Outcome 30 days

Primary outcome: อัตราจำนวนผู้ป่วยที่มี stroke/ death

Secondary outcome รวมสิ่งต่อไปนี้

- Ipsilateral strokes, death, stroke/death
- Other complications เช่น Myocardial infarction

– ภาวะแทรกซ้อนอื่นๆ เช่น

- rupture or haemorrhage,
- infection,
- occlusion of the artery operated on

3.2.3 วิธีการ Searching มีในฐานข้อมูลดังนี้

- the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library Issue 3, 2013)
- MEDLINE (1966 to 2013)
- EMBASE (1980 to 2013)
- Index to Scientific and Technical Proceedings (1980 to 2013)
- Hand searched ใน 6 วารสารที่มักมีงานวิจัยนี้อยู่ รวมถึง conference supplements
- ทบทวน the reference lists ในงานวิจัยที่เข้าเกณฑ์ รnclusion criteria
- ติดต่อผู้ชำนาญการในด้านนี้

- นอกจากนี้ Managing Editor (Mrs Hazel), Cochrane Stroke Group ได้หาข้อมูลจาก Cochrane registry

3.3 Data collection

- นักวิจัยทั้ง 3 คน (ศ.ดร.นพ.กิตติพันธุ์, อ.นพ. ธนัฐ วานิยะพงศ์, ดร.วิไลวรรณ จงรักษ์สัตย์) ได้ทำการอ่าน title, abstract และคัดงานวิจัยที่เข้าได้กับเรื่องที่จะทำวิจัย โดยในการทำงานวิจัยทั้งหมดได้สำเนาเอกสารเป็นอย่างน้อย 3 ชุด เพื่อให้การอ่าน โดยหลักการเลือกการศึกษาต้องมีลักษณะดังต่อไปนี้

โดยการทำการวิจัยระหว่าง 3 นักวิจัยในขั้นตอนนี้ เป็นแบบ independent ซึ่งนักวิจัยแต่ละคนจะเลือกงานวิจัยตามลำพัง แล้วเมื่อเลือกเสร็จก็นำมาเปรียบเทียบกัน ในกรณีที่ไม่ตรงกันได้วิเคราะห์ วิจารณ์กันในกรณีที่ไม่สามารถสรุปไม่ได้ให้ใช้การ vote เสียงส่วนมากเป็นตัวตัดสิน Extract data/ analysis

นักวิจัยได้ extract data ทั้งผลการเปรียบเทียบ ทั้งในแง่ภาวะแทรซ้อนจากการผ่าตัดและ คุณภาพของงานวิจัย

3.4 Risk of bias assessment

Random sequence generation (selection bias)

Allocation concealment (selection bias)

Blinding of participants/personel (performance bias)

Blinding outcome assessor (detection bias)

Incomplete outcome data (attribution bias)

Selective reporting (reporting bias)

Other bias

3.5 Analysisss

3.5.1 การวิเคราะห์เปรียบเทียบประสิทธิภาพแต่ละวิธี (Measures of treatment effect)

ได้ใช้วิธี Peto odds ratio and 95% confidence interval (95% CI) ในการคำนวน

3.5.2. การวิเคราะห์ heterogeneity between study

ได้ใช้วิธี I^2 statistic เพื่อประเมิน heterogeneity ในแต่ละการศึกษา ถ้า I^2 > 75% ถือว่ามี significant heterogeneity.

4 ผลการศึกษา

4.1 ด้านข้อถกเถียงทางเทคนิคทางวิสัญญี

4.1.1 ผลการค้นหางานวิจัยที่เข้าเกณฑ์ในการวิเคราะห์

สุดท้ายได้งานวิจัยที่คาดว่าจะเข้าเกณฑ์ 14 การศึกษา มีการผ่าตัดทั้งหมด 4596 การผ่าตัด โดยการศึกษาหนึ่งชื่อ GALA trial[13] มีผู้ร่วมวิจัยมากสุดคือ 3526การผ่าตัด ซึ่งการศึกษานี้มี 95 ศูนย์การแพทย์ร่วมในการศึกษานี้ใน 24 ประเทศทุกงานวิจัยตีพิมพ์ในภาษาอังกฤษ ยกเว้น 4 งานวิจัยที่มาจากภาษา French, Sebian, German และ Czech

4.1.2 คุณภาพงานวิจัยที่เข้าร่วมการวิเคราะห์

คุณภาพการวิจัยโดยรวมยังไม่ดี ดังตารางที่ 1 ยกเว้นการศึกษา GALA ซึ่งดีหมดยกเว้นในแง่ blinding ทั้ง participant และ personnel ซึ่งทำไม่ได้ ซึ่งเป็นธรรมชาติการศึกษา RCT ทางศัลยศาสตร์ ซึ่งในด้านผู้ป่วยระหว่างการผ่าตัดที่หลับ (GA) กับอีกกลุ่มซึ่งผ่าตัดโดยผู้ป่วยตื่นอยู่ย่อมรู้ว่าตนเองอยู่ในกลุ่ม LA (personnel bias) และเช่นเดียวกันศัลยแพทย์ที่ทำ blind ก็ไม่ได้ระหว่างกลุ่มหนึ่งศัลยแพทย์สามารถพูดคุยกับผู้ป่วยเพื่อประเมินว่ามี cerebral ischemia หรือไม่ระหว่างการทำ carotid artery clamping ในกลุ่ม LA กับอีกกลุ่มที่เป็น GA ที่ผู้ป่วยหลับและใส่ endotracheal tube และ on respirator

ตารางที่ 1 แสดงคุณภาพของงานแต่ละงาน โดยแต่ละการศึกษาระบุตามชื่อนักวิจัยชื่อแรกและปีในการตีพิมพ์ (แกน y) Risk of bias assessment (แกน x) สีในตารางแสดงสีเขียวบ่งว่า good สีเหลือง ยังไม่ชัดเจน ยังเกิดคำถาม สีแดง ไม่ดี

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding (performance bias and detection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Binder 1999	+	?	?	-	?	?	?	?
Forssell 1989	+	?	?	-	?	?	?	?
GALA 2008	+	+	-	-	+	+	+	+
Gimenez 2004	+	?	?	-	?	?	?	?
Kasprzak 2006	+	?	?	-	+	+	?	?
Luchetti 2008	+	?	?	-	?	?	?	?
Mazul-Sunko 2010	+	?	?	-	?	?	?	?
McCarthy 2004	+	?	?	-	?	?	?	?
Moritz 2010	+	?	?	-	?	+	?	?
Mrozek 2007	+	?	?	-	?	?	?	?
Pluskwa 1989	+	?	?	-	?	?	?	?
Prough 1989	+	?	?	-	?	?	?	?
Sbarigia 1999	+	?	?	-	?	+	+	?
Sindelic 2004	+	?	?	-	?	+	-	?

4.1.3 ผลของ intervention

จากการศึกษาไม่พบว่าไม่มีความแตกต่างผลใน 30 วัน ในด้าน stroke, death, stroke/death, myocardial infarction, local hemorrhage, cranial nerve injuries ระหว่าง LA กับ GA แต่ที่ต่างกันชัดเจนคืออัตราการใส่ shunt ใน LA พบน้อยกว่า GA อย่างชัดเจน (ตารางที่ 2, รูปที่ 3-9)

ตารางที่ 2 แสดงสรุปผลเปรียบเทียบระหว่าง LA และ GA ในการผ่าตัด CEA

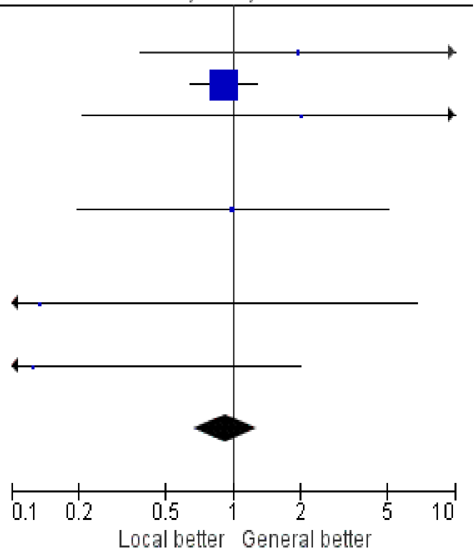
Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
1.1 Any stroke within 30 days of operation	12	4453	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.92 [0.67, 1.28]
1.2 Death within 30 days of operation	10	4181	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.61 [0.35, 1.06]
1.3 Stroke or death within 30 days of operation	10	4181	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.85 [0.62, 1.16]
1.4 Myocardial infraction within 30 days of operation	11	4357	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.53 [0.67, 3.47]
1.5 Local haemorrhage	5	3976	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.95 [0.75, 1.19]
1.6 Cranial nerve injuries	4	3865	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.17 [0.95, 1.44]
1.7 Arteries shunted	8	4133	Odds Ratio (M-H, Random, 95% CI)	0.24 [0.08, 0.73]

รูปที่ 3 แสดง forest plot ระหว่างการรักษาโดย LA และ GA ในด้านการเกิด Stroke

	Local		General			Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI	Peto, Fixed, 95% CI
Binder 1999	0	27	0	19		Not estimable	
Forssell 1989	4	56	2	55	4.0%	1.97 [0.38, 10.15]	
GALA 2008	63	1771	68	1752	87.8%	0.91 [0.64, 1.30]	
Kasprzak 2006	2	91	1	95	2.1%	2.05 [0.21, 19.96]	
Luchetti 2008	0	14	0	14		Not estimable	
Mazul-Sunko 2010	0	29	0	28		Not estimable	
McCarthy 2004	3	88	3	88	4.1%	1.00 [0.20, 5.07]	
Moritz 2010	0	48	0	48		Not estimable	
Mrozek 2007	0	40	0	40		Not estimable	
Pluskwa 1989	0	10	1	10	0.7%	0.14 [0.00, 6.82]	
Prough 1989	0	13	0	10		Not estimable	
Sbarigia 1999	0	55	2	52	1.4%	0.13 [0.01, 2.03]	
Total (95% CI)		**2242**		**2211**	**100.0%**	**0.92 [0.67, 1.28]**	
Total events	72		77				

Heterogeneity: Chi² = 4.21, df = 5 (P = 0.52); I² = 0%

Test for overall effect: Z = 0.48 (P = 0.63)

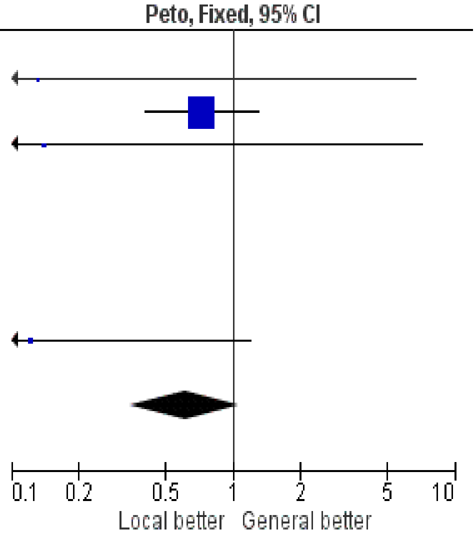


รูปที่ 4 แสดง forest plot ระหว่างการรักษาโดย LA และ GA ในด้านการเกิด Death

	Local		General			Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI	Peto, Fixed, 95% CI
Binder 1999	0	27	0	19		Not estimable	
Forssell 1989	0	56	1	55	2.0%	0.13 [0.00, 6.70]	
GALA 2008	19	1771	26	1752	90.0%	0.72 [0.40, 1.30]	
Kasprzak 2006	0	91	1	95	2.0%	0.14 [0.00, 7.12]	
Luchetti 2008	0	14	0	14		Not estimable	
Mazul-Sunko 2010	0	29	0	28		Not estimable	
Mrozek 2007	0	40	0	40		Not estimable	
Pluskwa 1989	0	10	0	10		Not estimable	
Prough 1989	0	13	0	10		Not estimable	
Sbarigia 1999	0	55	3	52	6.0%	0.12 [0.01, 1.21]	
Total (95% CI)		**2106**		**2075**	**100.0%**	**0.61 [0.35, 1.06]**	
Total events	19		31				

Heterogeneity: Chi² = 3.32, df = 3 (P = 0.34); I² = 10%

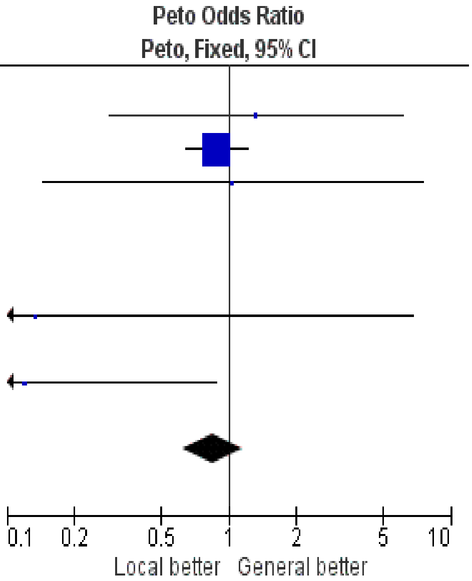
Test for overall effect: Z = 1.75 (P = 0.08)



รูปที่ 5 แสดง forest plot ระหว่างการรักษาโดย LA และ GA ในด้านการเกิด stroke/death

Study or Subgroup	Local Events	Local Total	General Events	General Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Binder 1999	0	27	0	19		Not estimable
Forssell 1989	4	56	3	55	4.2%	1.33 [0.29, 6.09]
GALA 2008	71	1771	79	1752	90.3%	0.88 [0.64, 1.23]
Kasprzak 2006	2	91	2	95	2.5%	1.04 [0.14, 7.54]
Luchetti 2008	0	14	0	14		Not estimable
Mazul-Sunko 2010	0	29	0	28		Not estimable
Mrozek 2007	0	40	0	40		Not estimable
Pluskwa 1989	0	10	1	10	0.6%	0.14 [0.00, 6.82]
Prough 1989	0	13	0	10		Not estimable
Sbarigia 1999	0	55	4	52	2.4%	0.12 [0.02, 0.88]
Total (95% CI)		**2106**		**2075**	**100.0%**	**0.85 [0.62, 1.16]**
Total events	77		89			

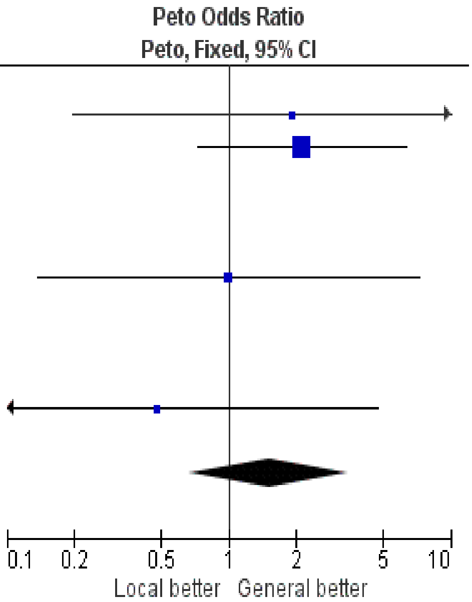
Heterogeneity: Chi² = 4.98, df = 4 (P = 0.29); I² = 20%
Test for overall effect: Z = 1.02 (P = 0.31)



รูปที่ 6 แสดง forest plot ระหว่างการรักษาโดย LA และ GA ในด้านการเกิด Myocardial infarction

Study or Subgroup	Local Events	Local Total	General Events	General Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Binder 1999	0	27	0	19		Not estimable
Forssell 1989	2	56	1	55	12.9%	1.94 [0.20, 19.01]
GALA 2008	9	1771	4	1752	56.9%	2.14 [0.72, 6.36]
Kasprzak 2006	0	91	0	95		Not estimable
Luchetti 2008	0	14	0	14		Not estimable
Mazul-Sunko 2010	0	29	0	28		Not estimable
McCarthy 2004	2	88	2	88	17.3%	1.00 [0.14, 7.22]
Mrozek 2007	0	40	0	40		Not estimable
Pluskwa 1989	0	10	0	10		Not estimable
Prough 1989	0	13	0	10		Not estimable
Sbarigia 1999	1	55	2	52	12.9%	0.48 [0.05, 4.70]
Total (95% CI)		**2194**		**2163**	**100.0%**	**1.53 [0.67, 3.47]**
Total events	14		9			

Heterogeneity: Chi² = 1.58, df = 3 (P = 0.66); I² = 0%
Test for overall effect: Z = 1.01 (P = 0.31)

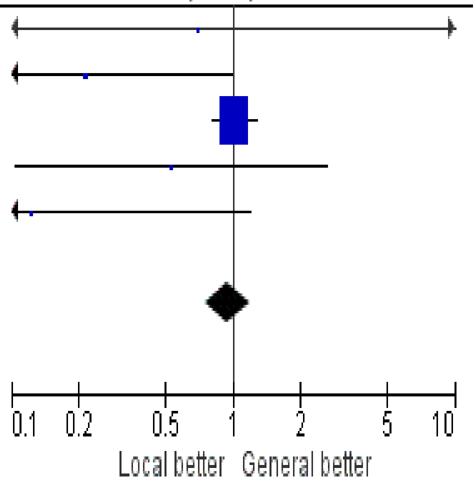


รูปที่ 7 แสดง forest plot ระหว่างการรักษาโดย LA และ GA ในด้านการเกิด Cranial nerve injury

	Local		General			Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI
Binder 1999	1	27	1	19	0.7%	0.69 [0.04, 11.94]
Forssell 1989	1	56	6	55	2.3%	0.22 [0.05, 0.99]
GALA 2008	150	1773	146	1753	94.0%	1.02 [0.80, 1.29]
Kasprzak 2006	2	91	4	95	2.0%	0.53 [0.10, 2.67]
Sbarigia 1999	0	55	3	52	1.0%	0.12 [0.01, 1.21]
Total (95% CI)		**2002**		**1974**	**100.0%**	**0.95 [0.75, 1.19]**
Total events	154		160			

Heterogeneity: Chi² = 7.57, df = 4 (P = 0.11); I² = 47%
Test for overall effect: Z = 0.47 (P = 0.64)

Peto Odds Ratio
Peto, Fixed, 95% CI

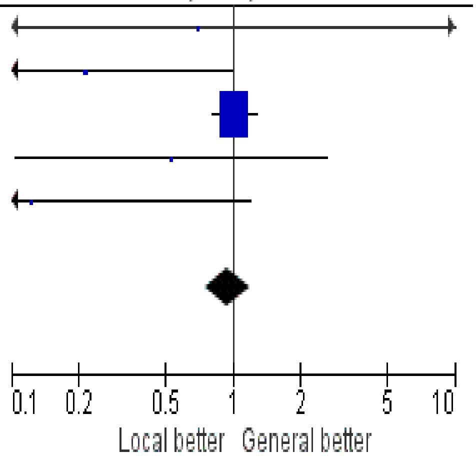


รูปที่ 8 แสดง forest plot ระหว่างการรักษาโดย LA และ GA ในด้านการเกิด Local hemorrhage

	Local		General			Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI
Binder 1999	1	27	1	19	0.7%	0.69 [0.04, 11.94]
Forssell 1989	1	56	6	55	2.3%	0.22 [0.05, 0.99]
GALA 2008	150	1773	146	1753	94.0%	1.02 [0.80, 1.29]
Kasprzak 2006	2	91	4	95	2.0%	0.53 [0.10, 2.67]
Sbarigia 1999	0	55	3	52	1.0%	0.12 [0.01, 1.21]
Total (95% CI)		**2002**		**1974**	**100.0%**	**0.95 [0.75, 1.19]**
Total events	154		160			

Heterogeneity: Chi² = 7.57, df = 4 (P = 0.11); I² = 47%
Test for overall effect: Z = 0.47 (P = 0.64)

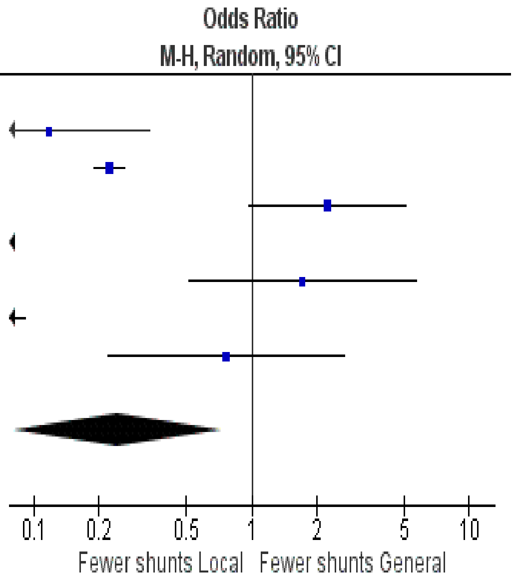
Peto Odds Ratio
Peto, Fixed, 95% CI



รูปที่ 9 แสดง forest plot ระหว่างการรักษาโดย LA และ GA ในด้านการใช้ Shunting

	Local		General			Odds Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**
Binder 1999	27	27	19	19		Not estimable
Forssell 1989	5	56	25	55	14.8%	0.12 [0.04, 0.34]
GALA 2008	248	1730	738	1720	17.1%	0.22 [0.19, 0.26]
Kasprzak 2006	19	91	10	95	15.7%	2.24 [0.98, 5.13]
Mazul-Sunko 2010	1	29	23	28	10.1%	0.01 [0.00, 0.07]
Moritz 2010	8	48	5	48	14.3%	1.72 [0.52, 5.70]
Mrozek 2007	6	40	35	40	14.0%	0.03 [0.01, 0.09]
Sbarigia 1999	5	55	6	52	14.1%	0.77 [0.22, 2.68]
Total (95% CI)		**2076**		**2057**	**100.0%**	**0.24 [0.08, 0.73]**
Total events	319		861			

Heterogeneity: Tau² = 1.84; Chi² = 65.40, df = 6 (P < 0.00001); I² = 91%
Test for overall effect: Z = 2.51 (P = 0.01)



4.2 Shunting

4.2.1 ผลการค้นหางานวิจัยที่เข้าเกณฑ์ในการวิเคราะห์

การศึกษานี้พบ 3 RCT มีจำนวนผู้เข้าร่วมการศึกษาทั้งหมด 686 คน ซึ่งเป็นการเปรียบเทียบระหว่าง routine shunting กับการไม่ใส่ shunt เลย with no shunting (Gumerlock 1988; Palombo 2007; Sandmann 1993). โดยการศึกษาของ Sandmann ในกลุ่มที่ไม่ใส่ shunt ทำโดยการ monitor โดย EEG and SEP[14] ในขณะการศึกษาของ Palombo ใช้ stump pressure เป็นการ monitor[15] ส่วนการศึกษาของ Gumerlock ไม่มี montoring ระหว่างการศึกษา[16]

4.2.2 คุณภาพงานวิจัยที่เข้าร่วมการวิเคราะห์

คุณภาพโดยรวมของทั้งการศึกษาค่อนข้างต่ำ (ตารางที่ 3) โดยงานวิจัยของ Sandmann เป็นการตีพิมพ์ในลักษณะ 'Letter to the editor[14] ดังนั้นการศึกษานี้มีข้อจำกัดมากในการได้ข้อมูลมาวิเคราะห์

ตารางที่ 3 แสดงคุณภาพของงานแต่ละงาน โดยแต่ละการศึกษาระบุตามชื่อนักวิจัยชื่อแรกและปีในการตีพิมพ์ (แกน y) Risk of bias assessment (แกน x) สีในตารางแสดงสีเขียวบ่งว่า good สีเหลือง ยังไม่ชัดเจน ยังเกิดคำถาม สีแดง ไม่ดี

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Gumerlock 1988	−	−	−	−	+	−	−
Palombo 2007	+	−	−	?	+	+	−
Sandmann 1993	+	−	+	+	+	−	−

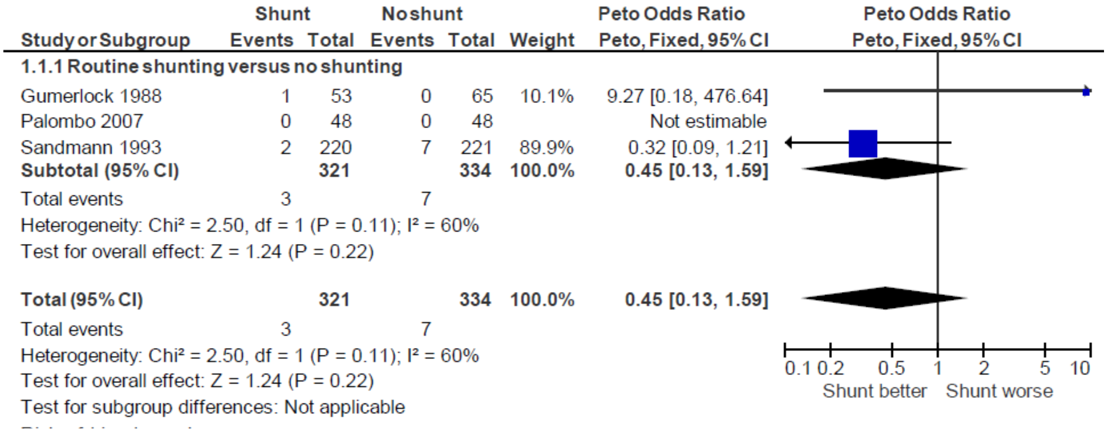
4.2.3 ผลของ intervention

จากการศึกษาพบว่าไม่มีความแตกต่างผลใน 30 วัน ในด้าน stroke, death, stroke/death, myocardial infarction, local hemorrhage, cranial nerve injuries ระหว่าง shunting กับ Non shunting แต่สังเกตว่าจำนวนการศึกษามีน้อยมาก สังเกตจากการที่มี confidence interval ที่กว้างมาก ที่ต่างกันชัดเจนคืออัตราการใส่ shunt ใน LA พบน้อยกว่า GA อย่างชัดเจน (ตารางที่ 4, รูป 10-16)

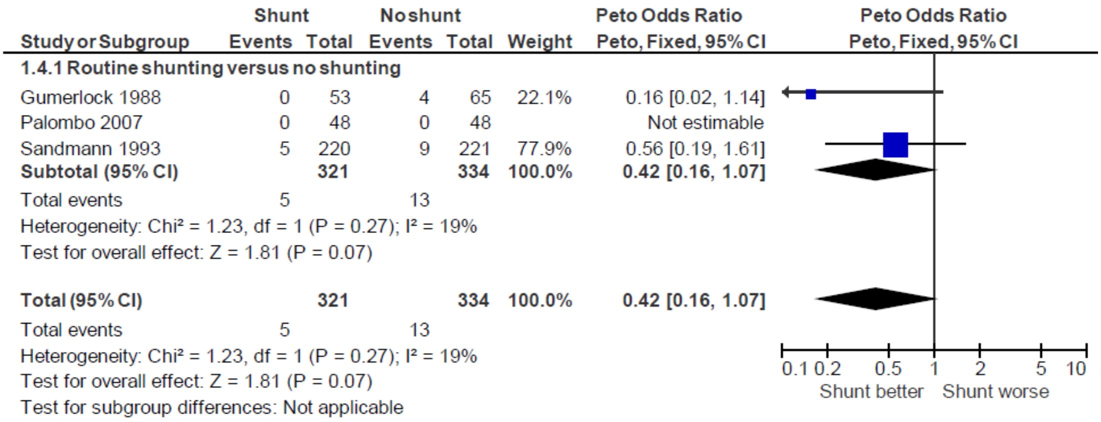
ตารางที่ 4 แสดงสรุปผลเปรียบเทียบระหว่าง Shunt และ non shunting ในการผ่าตัด CEA

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
1.1 Death from all causes within 30 days of surgery	3	655	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.45 [0.13, 1.59]
1.2 Any stroke during surgery	3	655	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.42 [0.16, 1.07]
1.3 Ipsilateral stroke during surgery	3	737	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.42 [0.17, 1.08]
1.4 Stroke or death within 30 days of surgery	3	655	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.62 [0.31, 1.27]
1.5 Haemorrhage from operation site	2	641	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.19 [0.07, 19.47]
1.6 Infection of operation site	2	641	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.16 [0.00, 8.12]
1.7 Nerve palsy post-operatively	1	138	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.81 [0.30, 10.82]

รูปที่ 10 แสดง forest plot ระหว่างการรักษาโดย shunting และ non shuntingในด้านการเกิด Death

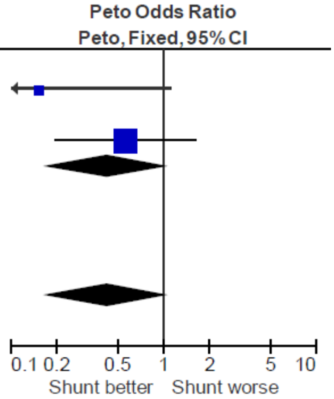


รูปที่ 11 แสดง forest plot ระหว่างการรักษาโดย shunting และ non shuntingในด้านการเกิด Any Stroke



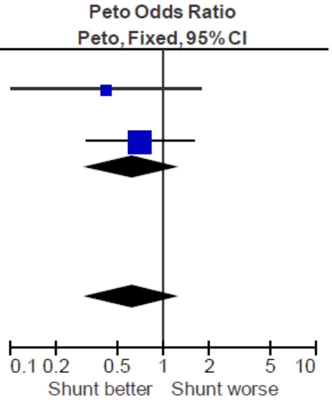
รูปที่ 12 แสดง forest plot ระหว่างการรักษาโดย shunting และ non shuntingในด้านการเกิด Ipsilataral stroke

Study or Subgroup	Shunt Events	Shunt Total	No shunt Events	No shunt Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
1.8.1 Routine shunting versus no shunting						
Gumerlock 1988	0	63	4	75	22.2%	0.15 [0.02, 1.11]
Palombo 2007	0	48	0	48		Not estimable
Sandmann 1993	5	250	9	253	77.8%	0.56 [0.19, 1.63]
Subtotal (95% CI)		**361**		**376**	**100.0%**	**0.42 [0.17, 1.08]**
Total events	5		13			
Heterogeneity: Chi² = 1.29, df = 1 (P = 0.26); I² = 22%						
Test for overall effect: Z = 1.81 (P = 0.07)						
Total (95% CI)		**361**		**376**	**100.0%**	**0.42 [0.17, 1.08]**
Total events	5		13			
Heterogeneity: Chi² = 1.29, df = 1 (P = 0.26); I² = 22%						
Test for overall effect: Z = 1.81 (P = 0.07)						
Test for subgroup differences: Not applicable						



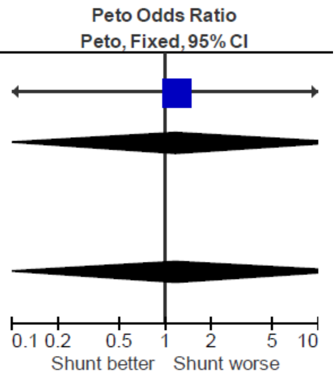
รูปที่ 13 แสดง forest plot ระหว่างการรักษาโดย shunting และ non shuntingในด้านการเกิด Stroke or death

Study or Subgroup	Shunt Events	Shunt Total	No shunt Events	No shunt Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
1.12.1 Routine shunting versus no shunting						
Gumerlock 1988	2	53	6	65	24.7%	0.42 [0.10, 1.79]
Palombo 2007	0	48	0	48		Not estimable
Sandmann 1993	10	220	14	221	75.3%	0.71 [0.31, 1.61]
Subtotal (95% CI)		**321**		**334**	**100.0%**	**0.62 [0.31, 1.27]**
Total events	12		20			
Heterogeneity: Chi² = 0.36, df = 1 (P = 0.55); I² = 0%						
Test for overall effect: Z = 1.30 (P = 0.19)						
Total (95% CI)		**321**		**334**	**100.0%**	**0.62 [0.31, 1.27]**
Total events	12		20			
Heterogeneity: Chi² = 0.36, df = 1 (P = 0.55); I² = 0%						
Test for overall effect: Z = 1.30 (P = 0.19)						
Test for subgroup differences: Not applicable						



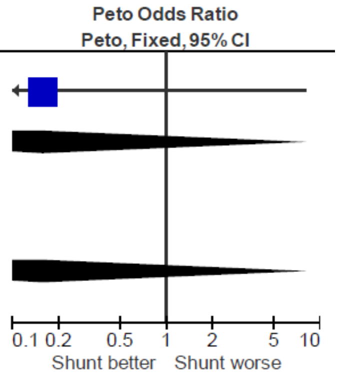
รูปที่ 14 แสดง forest plot ระหว่างการรักษาโดย shunting และ non shuntingในด้านการเกิด Haemorrhage

Study or Subgroup	Shunt Events	Shunt Total	No shunt Events	No shunt Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
1.14.1 Routine shunting versus no shunting						
Gumerlock 1988	1	63	1	75	100.0%	1.19 [0.07, 19.47]
Sandmann 1993	0	250	0	253		Not estimable
Subtotal (95% CI)		**313**		**328**	**100.0%**	**1.19 [0.07, 19.47]**
Total events	1		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.12 (P = 0.90)						
Total (95% CI)		**313**		**328**	**100.0%**	**1.19 [0.07, 19.47]**
Total events	1		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.12 (P = 0.90)						
Test for subgroup differences: Not applicable						



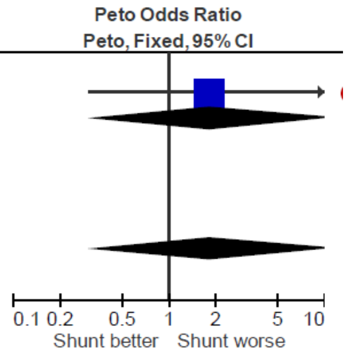
รูปที่ 15 แสดง forest plot ระหว่างการรักษาโดย shunting และ non shuntingในด้านการเกิด Infection

Study or Subgroup	Shunt Events	Shunt Total	No shunt Events	No shunt Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
1.15.1 Routine shunting versus no shunting						
Gumerlock 1988	0	63	1	75	100.0%	0.16 [0.00, 8.12]
Sandmann 1993	0	250	0	253		Not estimable
Subtotal (95% CI)		**313**		**328**	**100.0%**	**0.16 [0.00, 8.12]**
Total events	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.92 (P = 0.36)						
Total (95% CI)		**313**		**328**	**100.0%**	**0.16 [0.00, 8.12]**
Total events	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.92 (P = 0.36)						
Test for subgroup differences: Not applicable						



รูปที่ 16 แสดง forest plot ระหว่างการรักษาโดย shunting และ non shuntingในด้านการเกิด Cranial nerve injury

Study or Subgroup	Shunt Events	Shunt Total	No shunt Events	No shunt Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
1.16.1 Routine shunting versus no shunting						
Gumerlock 1988	3	63	2	75	100.0%	1.81 [0.30, 10.82]
Subtotal (95% CI)		**63**		**75**	**100.0%**	**1.81 [0.30, 10.82]**
Total events	3		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.65 (P = 0.51)						
Total (95% CI)		**63**		**75**	**100.0%**	**1.81 [0.30, 10.82]**
Total events	3		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.65 (P = 0.51)						
Test for subgroup differences: Not applicable						



5. สรุปและบทวิจารณ์

5.1 ในด้านเทคนิควิสัญญี

จากข้อมูลของ systematic review ที่ได้ศึกษางานวิจัยแบบ non-RCT ทั้งหมด 45 รายงานซึ่งเป็นการเปรียบเทียบกันระหว่างการผ่าตัด CEA โดยใช้ LA กับ GA[17] พบว่าการใช้ LA มีโอกาสลดการเกิด stroke , MI , pulmonary complication การใส่ shunt และการเสียชีวิตได้อย่างมีในสำคัญทางสถิติ นอกจากนั้นยังมีการศึกษาดูระดับ inflammatory mediator interleukin-6 (IL- 6) ในกระแสเลือดของผู้ป่วยที่ได้รับการผ่าตัด CEA พบว่าระดับ IL – 6 หลังผ่าตัดโดยใช้ LA มีค่าที่ต่ำกว่า GA อย่างมีนัยสำคัญ[18] ซึ่งว่านับเป็นผลดีเนื่องจากการที่ IL – 6 มีค่าสูงมักจะสัมพันธ์กับการเกิด systemic inflammatory response syndromes ซึ่งทำให้เกิดภาวะแทรกซ้อนต่างๆ ที่รุนแรงมากมาย เช่น sepsis และ shock เป็นต้น และยังมีรายงานถึง LA อีกว่าผู้ป่วยให้ความร่วมมืออย่างดีและอัตราการเปลี่ยนจาก LA เป็น GA ในระหว่างผ่าตัดค่อนข้างต่ำ[17] ส่วนเรื่องค่ารักษาพยาบาลและวันที่ต้องอยู่โรงพยาบาลแสดงเห็นว่า LA มีค่ารักษาที่ต่ำกว่าและนอนโรงพยาบาลสั้นกว่า[19] แต่การนำผลวิจัยของ non– RCT มาวิเคราะห์ต้องระมัดระวังเรื่องอคติในการเลือกกลุ่ม เช่น ผู้ป่วยที่มีความเสี่ยงสูงอาจอยู่ในกลุ่มที่ผ่าตัดโดยการใช้ GA มากกว่าเป็นต้น[17]

ตารางที่ 5 แสดงผลของความเสี่ยงต่อภาวะแทรกซ้อนต่างๆ ของ CEA ภายใน 30 วันหลังผ่าตัด ในการศึกษา Systematic Review ใน nonRCT ระหว่างเทคนิค Locoregional Anesthesia (LA) กับ General Anesthetic (GA)[17] *

	LA	GA	*P-value*
การเสียชีวิต	84/8945 (0.9%)	119/9939 (1.2%)	0.04
Stroke	173/9480 (1.8%)	426/9081 (4.7%)	<0.001
Stroke และการเสียชีวิต	114/4611 (2.5%)	522/10034 (5.2%)	<0.001
Myocardial infarction	84/8061 (1.0%)	240/7810 (3.1%)	<0.001
Neck hematoma	54/3002 (1.8%)	156/5344 (2.9%)	0.11
ภาวะแทรกซ้อนในทางเดินหายใจ	6/1635 (0.4%)	27/1292 (2.1%)	<0.05
การบาดเจ็บต่อ Cranial nerve	58/2461 (2.4%)	234/4960 (4.7%)	0.78
การใส่ shunt	1056/8011 (13.2%)	4057/8211 (49.4%)	<0.001

*ดัดแปลงจาก Rerkasem K, Rothwell PM. Local versus general anaesthesia for carotid endarterectomy. Cochrane Database Syst Rev 2008;CD000126.

ส่วนงานวิจัยที่เป็นแบบ RCT ในการศึกษานี้ (ตารางที่ 2) พบว่า LA มีอัตราการเกิดภาวะแทรกซ้อนไม่แตกต่างจาก GA ซึ่งผลการศึกษานี้ตรงข้ามกับ non RCT โดยเป็นที่ยอมรับกันทั่วไปว่าผลการศึกษา RCT ซึ่งน่าเชื่อถือกว่าและการศึกษานี้นับว่ามีขนาดตัวอย่างที่ใหญ่สามารถสรุปได้อย่างมั่นใจว่าเทคนิคการให้ยาระงับความรู้สึกไม่มีวิธีใดดีกว่ากัน ศัลยแพทย์และผู้ป่วยสามารถเลือกใช้เทคนิคใดก็ได้ในการผ่าตัด CEA จากการศึกษานี้ทำให้เห็นความจริงอีกประการว่าการจะสรุปว่าการรักษาใด ดีกว่าอะไรต้องมาจาก RCT เพราะจะเห็นว่า non RCT ออกผลมาตรงข้ามซึ่งทำให้ศัลยแพทย์คิดว่าการรักษาแบบ LA ดีกว่า ดังนั้นประเด็นนี้สรุปได้ว่าศัลยแพทย์สามารถใช้เทคนิคใดก็ได้อย่างมั่นใจในการผ่าตัด CEA[12]

5.2 Shunt

มีงานวิจัยที่เป็น RCT เกี่ยวกับการใส่ shunt อยู่ 3 รายงาน ซึ่งไม่พบว่ามีความแตกต่างอย่างมีนัยสำคัญจากการศึกษาเปรียบเทียบกันระหว่างผู้ป่วยที่ใส่ shunt ทุกรายกับไม่ใส่ shunt ถึงแม้พบว่าในผู้ป่วยที่ใส่ shunt จะมีอัตราการเกิด stroke และเสียชีวิตภายใน 30 วันหลังผ่าตัดลดลง 40 % เทียบกับไม่ได้ใส่ shunt แต่ไม่พบความแตกต่างอย่างมีนัยสำคัญทางสถิติ จากข้อมูลดังกล่าวมีผู้เข้าร่วมการศึกษาน้อยเกินไป หากต้องการให้ได้ข้อสรุปที่ชัดเจนจะต้องมีผู้ป่วยอย่างน้อย 5,000 คนขึ้นไปและยังพบว่าผู้ป่วยบางคนในรายงานดังกล่าวมี contralateral CAS อย่างรุนแรง ทำให้ผลของการศึกษาอาจโน้มเอียงไปว่าการใส่ shunt ช่วยลดภาวะแทรกซ้อนได้ดีกว่าไม่ใส่ shunt

ส่วนในรายละเอียดของเทคนิคการผ่าตัดพบว่ากลุ่มที่ใส่ shunt มีการปิดหลอดเลือดด้วยวิธีการ patch มากกว่ากลุ่มที่ไม่ใส่ shunt ซึ่งอาจทำให้กลุ่มที่ไม่ใส่ shunt เกิด stroke มากกว่าเนื่องจากการปิดหลอดเลือดด้วยวิธี primary closure อาจทำให้หลอดเลือดตีบส่งผลให้เลือดไปเลี้ยงสมองไม่เพียงพอมากกว่าที่จะเกิดจากการไม่ใส่ shunt ในการศึกษาของ Sandman[14] พบว่าผู้ป่วยที่สุ่มว่าไม่ต้องใส่ shunt 10 คนกลับต้องเปลี่ยนมาใส่ shunt เนื่องจาก neuromonitoring แสดงให้เห็นว่าสมองเริ่มขาดเลือดอย่างมากขณะหนีบหลอดเลือด ในปัจจุบันยังไม่มีการศึกษาเปรียบเทียบการทำ selective shunting กับกลุ่มอื่น เนื่องจากการที่จะตัดสินใจว่าผู้ป่วยจะใส่ shunt หรือไม่ใน selective shunting ต้องตัดสินใจจาก intraoperative monitoring method ซึ่งปัจจุบันยังไม่มีวิธีใดที่ตัดสินได้แม่นยำที่สุด[12]

การใส่ shunt นับว่าเป็นอีกประเด็นหนึ่งที่มีการถกเถียงกันอย่างกว้างขวางในช่วงหลายปีที่ผ่านมาและยังไม่มีข้อมูลทั้ง RCT และ non – RCT ที่เป็นข้อสรุปที่ชัดเจน ควรมีการศึกษาเพิ่มเติมด้านนี้จึงจะสรุปได้[12]

6. ข้อเสนอแนะในอนาคต

ในด้านเทคนิควิสัญญีจะพบว่ามี non-significant trend แนวโน้มว่าจะมีการลดการเสียชีวิตในกลุ่ม LA แต่การศึกษาของเรายังมี power ไม่พอที่สรุปผลทางด้านนี้ได้อย่างมั่นใจ ดังนั้นการมี RCT ในอนาคตเปรียบเทียบ LA กับ GA ที่มีผลประโยชน์ต่ออัตราการเสียชีวิตยังควรมีเพื่อให้ข้อสรุปด้านนี้

ในด้านการศึกษา RCT ว่า shunting ดีกว่า non shunting ยังต้องการการศึกษา RCT ขนาดใหญ่เพิ่มเติม ที่น่าสนใจคือแม้ว่าการใส่ shunt จะสามารถลดการเกิด stroke และ death (relative risk) ได้ 25% ส่งผลทำให้ลดการเกิด stroke/death 15 คนต่อพันคนที่ได้รับการการผ่าตัด CEA ถึงอย่างไรก็ตามเพื่อให้สามารถ detect ความแตกต่างดังกล่าวอย่างน่าเชื่อถือ ให้ได้ 80% power และ 5% significance level การศึกษานี้ต้องการผู้ร่วมในการวิจัย 3000-5000 คน โดยการศึกษาเหล่านี้ต้องเป็น RCT ที่มีคุณภาพที่ดีและมี

- blind assessor โดยเฉพาะจะดีที่สุดโดย blind neurologist
- การศึกษาควรมีการ stratified โดย age, sex, degree of ipsilateral and contralateral internal carotid stenosis, รวมถึงระดับประสบการณ์ของศัลยแพทย์ อัตราการใช้ patching และวิธี monitoring of cerebral ischaemia.

7. หนังสืออ้างอิง

1. Burden of disease and injuries in Thailand. Prioriy setting for policy. 2002.

2. Dharmasaroja P. Baseline characteristics of patients with acute ischemic stroke in a suburban area of Thailand. Journal of stroke and cerebrovascular diseases : the official journal of National Stroke Association. 2008;17:82-5.

3. MRC European Carotid Surgery Trial: interim results for symptomatic patients with severe (70-99%) or with mild (0-29%) carotid stenosis. European Carotid Surgery Trialists' Collaborative Group. Lancet (London, England). 1991;337:1235-43.

4. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. The New England journal of medicine. 1991;325:445-53.

5. Rerkasem K, Rothwell PM. Carotid endarterectomy for symptomatic carotid stenosis. The Cochrane database of systematic reviews. 2011:Cd001081.

6. Vaniyapong T, Chongruksut W, Rerkasem K. Local versus general anaesthesia for carotid endarterectomy. The Cochrane database of systematic reviews. 2013;12:CD000126.

7. McCleary AJ, Maritati G, Gough MJ. Carotid endarterectomy; local or general anaesthesia? European journal of vascular and endovascular surgery : the official journal of the European Society for Vascular Surgery. 2001;22:1-12.

8. McCleary AJ, Dearden NM, Dickson DH, Watson A, Gough MJ. The differing effects of regional and general anaesthesia on cerebral metabolism during carotid endarterectomy. European journal of vascular and endovascular surgery : the official journal of the European Society for Vascular Surgery. 1996;12:173-81.

9. Hans SS, Jareunpoon O. Prospective evaluation of electroencephalography, carotid artery stump pressure, and neurologic changes during 314 consecutive carotid endarterectomies performed in awake patients. Journal of vascular surgery. 2007;45:511-5.

10. Bond R, Rerkasem K, Counsell C, Salinas R, Naylor R, Warlow CP, et al. Routine or selective carotid artery shunting for carotid endarterectomy (and different methods of monitoring in selective shunting). The Cochrane database of systematic reviews. 2002:CD000190.

11. Rerkasem K, Bond R, Rothwell PM. Local versus general anaesthesia for carotid endarterectomy. The Cochrane database of systematic reviews. 2004:CD000126.

12. Brott TG, Halperin JL, Abbara S, Bacharach JM, Barr JD, Bush RL, et al. 2011 ASA/ACCF/AHA/AANN/AANS/ACR/ASNR/CNS/SAIP/SCAI/SIR/SNIS/SVM/SVS guideline on the management of patients with extracranial carotid and vertebral artery disease: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American Stroke Association, American Association of Neuroscience Nurses, American Association of Neurological Surgeons, American College of Radiology, American Society of Neuroradiology, Congress of Neurological Surgeons, Society of Atherosclerosis Imaging and Prevention, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of NeuroInterventional Surgery, Society for Vascular Medicine, and Society for Vascular Surgery. Developed in collaboration with the American Academy of Neurology and Society of Cardiovascular Computed Tomography. Catheterization and cardiovascular interventions : official journal of the Society for Cardiac Angiography & Interventions. 2013;81:E76-123.

13. Lewis SC, Warlow CP, Bodenham AR, Colam B, Rothwell PM, Torgerson D, et al. General anaesthesia versus local anaesthesia for carotid surgery (GALA): a multicentre, randomised controlled trial. Lancet (London, England). 2008;372:2132-42.

14. Sandman WF. Current critical problems in vascular surgery In: FJ V, editor.: Quality Medical Publishing; 1994. p. 434-40.

15. Palombo D, Lucertini G, Mambrini S, Zettin M. Subtle cerebral damage after shunting vs non shunting during carotid endarterectomy. European journal of vascular and endovascular surgery : the official journal of the European Society for Vascular Surgery. 2007;34:546-51.

16. Gumerlock MK, Neuwelt EA. Carotid endarterectomy: to shunt or not to shunt. Stroke; a journal of cerebral circulation. 1988;19:1485-90.

17. Rerkasem K, Rothwell PM. Local versus general anaesthesia for carotid endarterectomy. The Cochrane database of systematic reviews. 2008:CD000126.

18. Rerkasem KS, CP. Garry, JM. Yaqoob, P. Grimble,P. Calder,PC. . Effect of the type of anaesthesia fot carotid carotid endarterectomy. J Thai Vascular Society. 2004;1:3.

19. McCarthy RJ, Walker R, McAteer P, Budd JS, Horrocks M. Patient and hospital benefits of local anaesthesia for carotid endarterectomy. European journal of vascular and endovascular surgery : the official journal of the European Society for Vascular Surgery. 2001;22:13-8.

8. Output จากโครงการวิจัยที่ได้รับทุนจาก สกว.

1. ผลงานตีพิมพ์ในวารสารวิชาการนานาชาติ (ระบุชื่อผู้แต่ง ชื่อเรื่อง ชื่อวารสาร ปี เล่มที่ เลขที่ และหน้า) พร้อมแจ้งสถานะของการตีพิมพ์ เช่น submitted, accepted, in press, published

- Chongruksut W, Vaniyapong T, **Rerkasem K**. Routine or selective carotid arteryshunting for carotid endarterectomy (and different methods of monitoring inselective shunting). Cochrane Database Syst Rev. 2014 ;6:CD000190. Published
- Vaniyapong T, Chongruksut W, **Rerkasem K**. Local versus general anaesthesia for carotid endarterectomy. Cochrane Database Syst Rev. 2013;12:CD000126. published
- Touzé E, Trinquart L, Felgueiras R, **Rerkasem K**, Bonati LH, Meliksetyan G, Ringleb PA, Mas JL, Brown MM, Rothwell PM; Carotid Stenting Trialists' Collaboration. A clinical rule (sex, contralateral occlusion, age, and restenosis) to select patients for stenting versus carotid endarterectomy: systematic review of observational studies with validation in randomized trials. Stroke. 2013;44:3394-400. Published (ผลงานจากความร่วมมือการทำ systematic review กับทีมกลุ่มวิจัยที่ University of Oxford ตาม proposal)

- **Rerkasem K**, Rattanatanyong P, Rerkasem A, Wongthanee A, Rungruengthanakit K,Mangklabruks A, Mutirangura A. Higher alu methylation levels in catch-up growth in twenty-year-old offsprings. PLoS One. 2015;10:e0120032. Published (เป็นผลงานสืบเนื่องจากการทำวิจัยในทุนนักวิจัยรุ่นใหม่ อันเกี่ยวข้องกับการเกิดโรคหลอดเลือดแดงอุดตันและได้ทุนจากการวิจัยในสัญญานี้ ได้รับการสนับสนุนไปเสนอผลงานที่ประเทศเยอรมัน)

- Boulanger M, Camelière L, Felgueiras R, Berger L, **Rerkasem K**, Rothwell PM, I Touzé E. Risk and risk factors of periprocedural myocardial infarction after Carotid Endarterectomy and Carotid Angioplasty and Stenting: systematic review and meta-analysis. Stroke Submitted (under first revision)

(ผลงานจากความร่วมมือการทำ systematic review กับทีมกลุ่มวิจัยที่ University of Oxford ตาม proposal)

2. การนำผลงานวิจัยไปใช้ประโยชน์

เนื่องจากงานวิจัยนี้เป็นงาน update ของ systematic review เดิม จึงได้สรุปรายงานผลประโยชน์ รวมประโยชน์ทั้ง version นี้และ version เดิม

- เชิงพาณิชย์ (มีการนำไปผลิต/ขาย/ก่อให้เกิดรายได้ หรือมีการนำไปประยุกต์ใช้โดยภาคธุรกิจ/บุคคลทั่วไป) -ยังไม่มี-
- เชิงนโยบาย (มีการกำหนดนโยบายอิงงานวิจัย/เกิดมาตรการใหม่/เปลี่ยนแปลงระเบียบข้อบังคับหรือวิธีทำงาน) -ยังไม่มี –
- เชิงสาธารณะ (มีเครือข่ายความร่วมมือ/สร้างกระแสความสนใจในวงกว้าง) -ยังไม่มี -
- เชิงวิชาการ (มีการพัฒนาการเรียนการสอน/สร้างนักวิจัยใหม่)

1. ได้รับการ citation ใน 6 ครั้ง ในบทความการตีพิมพ์ในวารสารวิชาการระดับนานาชาติ ซึ่งมี peer review

- Vaniyapong T, Chongruksut W, **Rerkasem K**. Local versus general anaesthesia for carotid endarterectomy. Cochrane Database Syst Rev. 2013;12:CD000126. **(Citation 1 ครั้ง)**

- Ringleb PA, Mas JL, Brown MM, Rothwell PM; Carotid Stenting Trialists' Collaboration. A clinical rule (sex, contralateral occlusion, age, and restenosis) to select patients for stenting versus carotid endarterectomy:systematic review of observational studies with validation in randomized trials. Stroke. 2013;44:3394-400. (Citation 5 ครั้ง)

2. ได้สร้างนักวิจัยใหม่ 2 คนในฐานะเป็น mentor และเป็น corresponding author ให้

- อ.นพ.ธนัฐ วานิยะพงศ์ แพทย์เฉพาะทางด้านศัลยศาสตร์ประสาทและนักศึกษาระดับปริญญาเอกทางระบาดวิทยา ภาควิชาศัลยศาสตร์ คณะแพทยศาสตร์ มหาวิทยาลัยเชียงใหม่

- ดร.วิไลวรรณ จงรักษ์สัตย์ PhD (ระบาดวิทยา) เลขาหน่วยวิจัย ภาควิชาศัลยศาสตร์ คณะแพทยศาสตร์ มหาวิทยาลัยเชียงใหม่

3. ได้ใช้ในการสอนนักศึกษาแพทย์ แพทย์ประจำบ้าน และแพทย์ต่อยอดสาขาศัลยศาสตร์หลอดเลือด คณะแพทยศาสตร์ มหาวิทยาลัยเชียงใหม่

บัณฑิตศึกษา	พ.ศศ.731
	พ.ศศ.736
	พ.ศศ.738
	พย.พศ.566899
ปริญญาตรี	พ.วป.602
	พ.คพ.502
	พ.คพ.402,412
	พ.คพ.301
	พ.ศศ.351

3. อื่น ๆ (เช่น ผลงานตีพิมพ์ในวารสารวิชาการในประเทศ การเสนอผลงานในที่ประชุมวิชาการ หนังสือ การจดสิทธิบัตร)

เสนอผลงานวิชาการภายใต้การสนับสนุนของ สกว. และคณะแพทยศาสตร์ มหาวิทยาลัยเชียงใหม่ ดังนี้

Rerkasem K, Rattanatanyong P, Rerkasem A, Wongthanee A, Rungruengthanakit K, Mangklabruks A, Mutirangura A. Higher alu methylation levels in catch-up growth in twenty-year-old offsprings. International conference on developmental origins of adiposity and long term health “The power of Programming 2014” Munich, Germany, 13-15 March 2014 (Poster presentation).

9. Appendix

Appendix 1: Chongruksut W, Vaniyapong T, **Rerkasem K**. Routine or selective carotid artery shunting for carotid endarterectomy (and different methods of monitoring inselective shunting). Cochrane Database Syst Rev. 2014 ;6:CD000190.

Appendix 2: Vaniyapong T, Chongruksut W, **Rerkasem K**. Local versus general anaesthesia for carotid endarterectomy. Cochrane Database Syst Rev. 2013;12:CD000126.

Appendix 3: Touzé E, Trinquart L, Felgueiras R, **Rerkasem K**, Bonati LH, Meliksetyan G, Ringleb PA, Mas JL, Brown MM, Rothwell PM; Carotid Stenting Trialists’ Collaboration. A clinical rule (sex, contralateral occlusion, age, and restenosis) to select patients for stenting versus carotid endarterectomy: systematic review of observational studies with validation in randomized trials. Stroke. 2013;44:3394-400.

Appendix 4: **Rerkasem K**, Rattanatanyong P, Rerkasem A, Wongthanee A, Rungruengthanakit K,Mangklabruks A, Mutirangura A. Higher alu methylation levels in catch-up growth in twenty-year-old offsprings. PLoS One. 2015;10:e0120032.

Appendix 5: Boulanger M, Camelière L, Felgueiras R, Berger L, **Rerkasem K**, Rothwell PM, l Touzé E. Risk and risk factors of periprocedural myocardial infarction after Carotid Endarterectomy and Carotid Angioplasty and Stenting: systematic review and meta-analysis. Stroke Submitted (under first revision)

Routine or selective carotid artery shunting for carotid endarterectomy (and different methods of monitoring in selective shunting) (Review)

Chongruksut W, Vaniyapong T, Rerkasem K

THE COCHRANE COLLABORATION®

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2014, Issue 6

http://www.thecochranelibrary.com

WILEY

T A B L E   O F   C O N T E N T S

[Intervention Review]

Routine or selective carotid artery shunting for carotid endarterectomy (and different methods of monitoring in selective shunting)

Wilaiwan Chongruksut[1], Tanat Vaniyapong[1], Kittipan Rerkasem[1,2]

[1]Department of Surgery, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand. [2]Center for Applied Science, Research Institute of Health Sciences, Chiang Mai University, Chiang Mai, Thailand

Contact address: Kittipan Rerkasem, rerkase@gmail.com.

Editorial group: Cochrane Stroke Group.
Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 6, 2014.
Review content assessed as up-to-date: 9 August 2013.

Citation: Chongruksut W, Vaniyapong T, Rerkasem K. Routine or selective carotid artery shunting for carotid endarterectomy (and different methods of monitoring in selective shunting). *Cochrane Database of Systematic Reviews* 2014, Issue 6. Art. No.: CD000190. DOI: 10.1002/14651858.CD000190.pub3.

ABSTRACT

Background

Temporary interruption of cerebral blood flow during carotid endarterectomy can be avoided by using a shunt across the clamped section of the carotid artery. This may improve outcome. This is an update of a Cochrane review originally published in 1996 and previously updated in 2009.

Objectives

To assess the effect of routine versus selective or no shunting during carotid endarterectomy, and to assess the best method for selecting people for shunting.

Search methods

We searched the Cochrane Stroke Group Trials Register (last searched August 2013), the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*, 2013, Issue 8), MEDLINE (1966 to August 2013), EMBASE (1980 to August 2013) and Index to Scientific and Technical Proceedings (1980 to August 2013). We handsearched journals and conference proceedings, checked reference lists, and contacted experts in the field.

Selection criteria

Randomised and quasi-randomised trials of routine shunting compared with no shunting or selective shunting, and trials that compared different shunting policies in people undergoing carotid endarterectomy.

Data collection and analysis

Three review authors independently performed the searches and applied the inclusion criteria. For this update, we identified two new relevant randomised controlled trials.

Main results

We included six trials involving 1270 participants in the review: three trials involving 686 participants compared routine shunting with no shunting, one trial involving 200 participants compared routine shunting with selective shunting, one trial involving 253 participants compared selective shunting with and without near-infrared refractory spectroscopy monitoring, and the other trial involving 131 participants compared shunting with a combination of electroencephalographic and carotid pressure measurement with shunting by carotid pressure measurement alone. In general, reporting of methodology in the included studies was poor. For most studies, the blinding of outcome assessors and the report of prespecified outcomes were unclear. For routine versus no shunting, there was no significant difference in the rate of all stroke, ipsilateral stroke or death up to 30 days after surgery, although data were limited. No significant difference was found between the groups in terms of postoperative neurological deficit between selective shunting with and without near-infrared refractory spectroscopy monitoring, However, this analysis was inadequately powered to reliably detect the effect. There was no significant difference between the risk of ipsilateral stroke in participants selected for shunting with the combination of electroencephalographic and carotid pressure assessment compared with pressure assessment alone, although again the data were limited.

Authors' conclusions

This review concluded that the data available were too limited to either support or refute the use of routine or selective shunting in carotid endarterectomy. Large scale randomised trials of routine shunting versus selective shunting are required. No method of monitoring in selective shunting has been shown to produce better outcomes.

P L A I N   L A N G U A G E   S U M M A R Y

Routine or selective carotid artery shunting for carotid endarterectomy (and different methods of monitoring in selective shunting)

Question

We wanted to compare the effect of routine shunting versus selective or no shunting during carotid endarterectomy, and to assess the effect of different methods for selection of people for shunting.

Background

About 20% of strokes result from narrowing of the carotid artery (the main artery supplying blood to the brain). Carotid endarterectomy is an operation to remove this narrowing and therefore reduce the risk of stroke. However, there is a 5% to 10% risk of the operation itself causing a stroke. The use of a silicon tube, or shunt, as a temporary bypass can reduce the length of time that blood flow to the brain is interrupted during the operation. This may reduce the risk of perioperative stroke but could also result in arterial wall damage and therefore increase the risk of stroke. Shunt surgery falls into three categories. Firstly, in routine shunting, the surgeon inserts a shunt in every patient. Secondly, in selective shunting, the surgeon only uses a shunt in patients with an inadequate blood supply to the brain following clamping; various cerebral monitoring techniques, such as ultrasound for predicting who needs a shunt, have been used in this policy. Thirdly, in no shunting, surgeons do not employ shunts at all.

Study characteristics

We identified six studies up to August 2013, for inclusion in the review. These studies included a total of 1270 participants. Three of the trials compared routine shunting with no shunting, one trial compared routine shunting versus selective shunting, and another two trials compared different methods of monitoring in selective shunting. We have not yet identified any trials that compared selective shunting with no shunting. All the included trials assessed the use of shunting in people undergoing endarterectomy under general anaesthetic. The age of the participants ranged from 40 to 89 years, and overall, there were more male than female participants. Where reported, participants were followed up for no longer than 30 days.

Key results

There is still no evidence for the use of a carotid shunt during carotid endarterectomy. This review suggests a benefit from the use of a shunt, but the overall results were not statistically significant. More trials are needed.

Quality of the evidence

There were significant problems with the quality of the randomised trials and, overall, the reporting of study methodology was poor.

BACKGROUND

Description of the condition

Around 20% of people presenting with a transient ischaemic attack (TIA) or non-disabling stroke have significant stenosis with unstable atheromatous plaque at or around the bifurcation of the ipsilateral carotid artery. This plaque can lead to the formation of emboli, which may cause a stroke. Carotid endarterectomy is an operation to remove this stenosis together with unstable plaque and, therefore, decrease the risk of stroke.

Description of the intervention

Carotid endarterectomy has been shown in large, well-conducted randomised controlled trials (RCTs) to substantially reduce the relative risk of stroke in people with recent TIAs or minor strokes related to severe symptomatic carotid artery stenosis (ECST 1991; NASCET 1991; Rerkasem 2011). To a lesser extent, benefit has also been shown for moderate symptomatic carotid artery stenosis (Rerkasem 2011). In these trials, the benefits were seen despite a stroke and death rate, within 30 days of the operation, of between 5% to 10%. Most of these strokes occurred during, or within, a few days of surgery, and were presumably related to surgery. More recently, it has been shown that people with asymptomatic carotid artery stenosis of greater than 60% may also benefit from carotid endarterectomy, but this relies on an average 30-day stroke and death rate of 3% or less (ACAS 1995; ACST 2004). Reducing the risk of perioperative stroke and death should therefore increase the number of people who can benefit from carotid endarterectomy. Most of the perioperative strokes are ischaemic and some (especially those that occur during the operation) may be caused by the temporary interruption of blood flow during the procedure whilst the carotid artery is clamped. This reduction in blood flow should be avoided if an intraluminal shunt is placed across the clamped section of the artery and this may reduce the perioperative stroke rate. When carotid endarterectomy is performed under local anaesthetic about 10% to 20% of people develop a transient neurological deficit after the artery is clamped, in which case the vast majority of surgeons would regard a shunt as mandatory. However, the routine or selective use of intraluminal shunting in carotid endarterectomy under general anaesthetic is more controversial. The publication of the results of the GALA trial has shown that the operative risk of stroke and death due to endarterectomy under local anaesthetic versus general anaesthetic is similar and so many operations will continue to be done under general anaesthetic (Lewis 2008).

How the intervention might work

Some advocate that routine shunting for all operations be done under general anaesthetic on the assumption that it reduces the risk of perioperative ischaemic strokes; it may also reduce the risk of minor cerebral ischaemic damage, and it also allows the surgeon time to perform an unhurried carotid endarterectomy or to teach a trainee carefully and in an unhurried manner (Javid 1979; Thompson 1979). Others advocate the selective use of shunting only in people who are at high risk of developing cerebral ischaemia during carotid clamping, but there is no consensus on how to identify which people need a shunt. Methods used to select which people to shunt include: using preoperative features such as a previous ipsilateral stroke or a contralateral carotid occlusion (Buche 1988); using indirect assessments of cerebral blood flow during the operation by monitoring electroencephalographic (EEG) activity (Whittemore 1983), somatosensory evoked potentials (SEP) (Schweiger 1988), carotid stump back pressure (Ricotta 1983), or combinations of these; using direct assessments of cerebral blood flow during the operation using intra-arterial radio-labelled xenon (Sundt 1986), or transcranial Doppler (Steiger 1989); and assessing the development of new neurological signs in awake patients who have their endarterectomy performed under local anaesthetic (Benjamin 1993; Connolly 1977; Evans 1985).

None of these monitoring techniques are perfect. Studies in people having endarterectomies performed under local anaesthetic have shown that both EEG monitoring and carotid stump pressure assessment may be normal in 6% to 30% of those who develop neurological signs and that they may be abnormal in 3% to 11% of those who do not develop signs of ischaemia (Benjamin 1993; Connolly 1977; Evans 1985). Many of these techniques also require additional technology and expert interpretation and so may not be practical in many situations. In addition, shunting may be associated with complications such as air embolism, plaque embolism, dissection of the carotid artery, acute occlusion of the carotid artery, and it also lengthens the time of the procedure and may make it technically more difficult (Green 1985; Ott 1980). All of these factors may be associated, paradoxically, with an increased risk of perioperative stroke (Salvian 1997). Several authors have, therefore, argued that shunting should be avoided (Ott 1980; Prioleau 1977; Reddy 1987). Shunting could also be associated with other complications due to increased manipulation of the artery such as an increased risk of cranial nerve palsy (Forssell 1995), arterial haemorrhage or infection, or long-term restenosis, perhaps because of intimal damage leading to intimal hyperplasia (Ouriel 1987), but accurate data on these risks are limited at present.

Why it is important to do this review

The lack of good evidence to support the use of shunts is reflected by a considerable variation in surgical practice. For UK surgeons (N = 76) performing carotid endarterectomy under general anaesthesia, a shunt was always, never, or selectively used by 73.6%, 4.2% and 22.2% respectively (Girn 2008). An earlier survey from North America showed that about one-third of carotid endarterectomies were performed with routine shunting, one-third with selective shunting and one-third without shunting (Fode 1986). Data from the European Carotid Surgery Trialists (ECST) showed highly significant variation in shunting practices for endarterectomy done under general anaesthetic both between individual surgeons and between countries (both $P < 0.001$) (Bond 2002). For example, shunts were used in 89% of operations performed in Germany versus 41% performed in Finland and 1% of those performed in France.

The best way to determine the perioperative (and long-term) risks and benefits of shunting during carotid endarterectomy is to compare shunting with no shunting in RCTs. We, therefore, reviewed all such trials, and the trials comparing different methods of selecting which people under general anaesthetic require selective shunting. A comparison of local versus general anaesthetic is dealt with in a separate review (Vaniyapong 2013).

This is an update of a Cochrane Review originally published in 1996 and previously updated in 2009.

O B J E C T I V E S

To assess the effect of routine versus selective or no shunting during carotid endarterectomy, and to assess the best method for selecting people for shunting. Specifically, to:

1. determine whether a policy of routine or selective shunting reduces the risk of perioperative stroke or death following carotid endarterectomy;

2. determine whether a policy of routine or selective shunting increases the complication rate (other than stroke or death) following carotid endarterectomy;

3. determine whether a policy of routine or selective shunting is associated with an increased risk of restenosis and, therefore, perhaps of stroke during long-term follow-up;

4. to assess the effect of different methods for selection of people for shunting.

Our primary hypothesis was that shunting reduced the risk of perioperative stroke but may be associated with an increased risk of other complications.

M E T H O D S

Criteria for considering studies for this review

Types of studies

We included all unconfounded RCTs and quasi-RCTs that compared shunting with no shunting, or one method of monitoring with another in selective shunting. Since foreknowledge of treatment allocation can bias the results of randomised trials (Schulz 1995), where there were sufficient data, we planned to perform sensitivity analyses including only trials where treatment allocation was securely concealed.

Types of participants

Trials that included any person undergoing unilateral or bilateral carotid endarterectomy (whether it was for symptomatic or asymptomatic carotid disease) were eligible.

Types of interventions

The following types of trials were eligible.

1. Trials comparing a policy of routine shunting in all participants using any type of carotid shunt with a policy of avoiding a shunt (never shunting).
2. Trials comparing a policy of selective shunting in only those participants identified as being at risk of cerebral ischaemia with a policy of avoiding a shunt. People could be identified as being at risk of ischaemia either on the basis of preoperative assessment (e.g. recent stroke), or assessment during the operation (e.g. assessment of stump pressure or EEG monitoring or near-infrared spectroscopy (NIRS) during a period of arterial occlusion).
3. Trials comparing a policy of selective shunting with routine shunting.
4. Trials in which participants were shunted selectively under general anaesthetic and that compared one method of assessment versus another to identify which people required a shunt.

Types of outcome measures

The intended measures of outcome were:

1. all strokes (ischaemic and haemorrhagic) that occurred during the operation (i.e. stroke apparent on recovery from anaesthetic), within 24 hours of surgery, within 30 days of surgery, and during the whole of follow-up. We did not include TIAs because these are less important to patients since they do not result in chronically impaired function. They are also more difficult to diagnose reliably, and so there is more potential for bias in their assessment (particularly if this is unblinded);
2. all ipsilateral strokes (ischaemic and haemorrhagic) that occurred within 24 hours and 30 days of surgery and during the whole of follow-up;
3. death from any cause within 30 days of surgery and during follow-up;
4. other complications within 30 days of surgery, such as rupture or haemorrhage from the endarterectomy site, infection

of the wound or artery, occlusion of the artery operated on, or ipsilateral nerve palsies;

5. long-term arterial complications, such as restenosis of the operated artery;
6. cognitive function at the end of follow-up.

Search methods for identification of studies

See the 'Specialized register' section in the Cochrane Stroke Group module. We searched for trials published in all languages and arranged translation of all possibly relevant non-English language publications.

Electronic searches

We searched the Cochrane Stroke Group Trials Register (last searched in August 2013), the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2013, Issue 8) (Appendix 1), MEDLINE (Ovid) (1966 to August 2013) (Appendix 1) and EMBASE (Ovid) (1980 to August 2013) (Appendix 2). We developed the search strategies with the help of the Cochrane Stroke Group Trials Search Co-ordinator.

We also systematically searched the conference proceedings database Index to Scientific and Technical Proceedings (ISTP) (BIDS) (1980 to August 2013) using the terms 'carotid' and 'trial or random*'.

Searching other resources

1. We handsearched the following journals:
   i) *Annals of Surgery* (1981 to 30 August 2013);
   ii) *Annals of Vascular Surgery* (1994 to 30 August 2013);
   iii) *Vascular* (previously *Cardiovascular Surgery*) (1994 to 30 August 2013);
   iv) *European Journal of Vascular and Endovascular Surgery* (previously *European Journal of Vascular Surgery*) (1987 to 30 August 2013);
   v) *Journal of Vascular Surgery* (1994 to 30 August 2013);
   vi) *Stroke* (1994 to 30 August 2013).
2. We reviewed the reference lists of all relevant studies.
3. We contacted experts in the field to identify further published and unpublished studies.
4. For a previous version of the review we handsearched the following journals and conference proceedings:
   i) *American Journal of Surgery* (1994 to 2001);
   ii) *British Journal of Surgery* (1985 to 2001);
   iii) *World Journal of Surgery* (1978 to 2001).
   iv) AGM of the Vascular Surgical Society (UK) (1995 to 2001);
   v) AGM of the Association of Surgeons of Great Britain and Ireland (1995 to 2001);
   vi) AHA Stroke Conference (1995 to 2001);
   vii) Annual Meeting of the Society for Vascular Surgery (USA) (1995 to 2001);
   viii) European Stroke Conference (1995 to 2001).

Data collection and analysis

All three review authors (WC, TV, KR) independently collected data. We collected the details of methods, participants, setting, context, interventions, outcomes, results, publications and investigators. We performed meta-analysis using RevMan 5.2 (RevMan 2012)

Selection of studies

All three review authors (WC, TV, KR) independently read the titles and abstracts of the records obtained from the electronic searches and excluded obviously irrelevant studies. We obtained the full texts of the remaining papers and the same authors independently selected studies for inclusion based on the predefined criteria. We resolved any disagreements through discussion.

Data extraction and management

We extracted details of the method of randomisation, the blinding of outcome assessments, losses to follow-up, cross-overs and exclusions after randomisation from the publications. We also compared participant characteristics (age, sex, vascular risk factors, indication for surgery) and details of the operation (type of cerebral monitoring, use of carotid patching, anaesthetic technique, use of perioperative antiplatelet therapy) between the treatment groups in each trial. Also, although people who were asymptomatic were included in some studies, the data were not available in sufficient detail to allow separate analysis of the outcomes of carotid endarterectomy in people with symptoms and those without symptoms. However, it is unlikely that the relative effect of shunting versus no shunting varied qualitatively with symptom status.

Assessment of risk of bias in included studies

We assessed risk of bias into three categories: low risk, high risk, and unclear risk in the 'Risk of bias' tables, as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). These risks of bias included random sequence generation (selection bias), allocation concealment (selection bias), blinding (performance bias and detection bias), blinding of participants and personnel (performance bias), blinding outcome assessment (detection bias), and incomplete outcome data (attrition bias).

Measures of treatment effect

We measured the treatment effect in the following outcomes within 30 days of surgery: stroke, death, myocardial infarction, local haemorrhage, cranial nerve injuries, and shunted arteries.

Unit of analysis issues

The unit of analysis is the onset of the adverse outcome. We extracted details of all the outcome events. Some studies included participants who had bilateral operations, but only reported the number of participants, and not the number of arteries, in each group. However, since bilateral carotid endarterectomy was unusual, we used the number of participants as the number of operations in such studies. Where possible we used the number of participants, not the number of arteries in the analysis. The unit of analysis was presented as odds ratios (OR).

Dealing with missing data

When data were missing, we contacted the corresponding author or co-author through the address given in the publication. If this information was not available, we searched for the study group via the Internet and contacted them for the missing data.

Assessment of heterogeneity

We assessed heterogeneity between study results using the I^2 statistic (Higgins 2003). We examined the percentage of total variations across the studies due to heterogeneity rather than to chance. Values of I^2 over 75% indicated a high level of heterogeneity.
We used I^2 methods for quantifying inconsistency across studies. A rough index to interpretation is as follows:

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: considerable heterogeneity.

Assessment of reporting biases

We identified all relevant trials, including unpublished trials, by searching not only MEDLINE and EMBASE, but also the Cochrane Stroke Group Trials Register. In addition, we handsearched relevant journals and reviewed the reference lists of all relevant studies. We also contacted experts in this field. We searched for trials published in all languages and arranged translation of all possibly relevant non-English language publications.

Data synthesis

We calculated proportional risk reductions based on a weighted estimate of the OR using the Peto method (APT 1994).

Subgroup analysis and investigation of heterogeneity

If there was considerable heterogeneity, we investigated the cause for such interactions.

Sensitivity analysis

When the decisions for the process undertaken in this systematic review were somewhat arbitrary or unclear, we undertook sensitivity analyses. For example, we performed both fixed-effect and random-effects meta-analyses to evaluate the consistency of the results, or we compared pooled estimates of all studies' results with the results of the excluded lower quality studies.

RESULTS

Description of studies

Results of the search

For this review we updated our previous searches of the Cochrane Stroke Group Trials Register, MEDLINE, EMBASE and ISTP. We also searched CENTRAL. We reviewed a total of 2853 references from the searches and obtained the full paper copy of 33 trial reports. We identified two new RCTs (AbuRahma 2010; Zogogiannis 2011). We identified a third RCT that compared the outcome of endarterectomy using one of two different types of shunt, the Pruitt-Inahara and Javid shunts (Wilkinson 1997), but this did not meet the inclusion criteria and so we disregarded it. This will be a topic of another review.

Included studies

In the included six trials, we identified three trials (including 686 participants) that compared routine shunting with no shunting (Gumerlock 1988; Palombo 2007; Sandmann 1993). One RCT compared the results of routine shunting versus selective shunting based on stump pressure. Two hundred participants were randomised into routine shunting (98 participants) or selective shunting (102 participants). In the selective shunting group, shunting was used only if systolic stump pressure was less than 40 mmHg. Clinical and demographic characteristics were comparable in both groups. In the selective shunting group, shunting was used in 29 participants (28%) (AbuRahma 2010). The other two trials compared monitoring methods in selective shunting: Fletcher 1988 (131 participants) compared the use of EEG monitoring combined with an assessment of the carotid stump back pressure with carotid back pressure assessment alone. In the former group, a shunt was only inserted if both the EEG showed significant ipsilateral change within three minutes of clamping and the carotid pressure was less than 50 mmHg, whilst in the latter group a shunt was inserted if the pressure was less than 50 mmHg; Zogogiannis 2011 (253 participants) evaluated whether the use of an intraoperative algorithm based on cerebral oximetry with NIRS monitoring, could help in the intraoperative decision for shunt placement, in people undergoing carotid endarterectomy. We have not yet identified any trials that compared selective shunting with no shunting. All trials looked at the use of shunting in people having carotid endarterectomy under general anaesthetic.

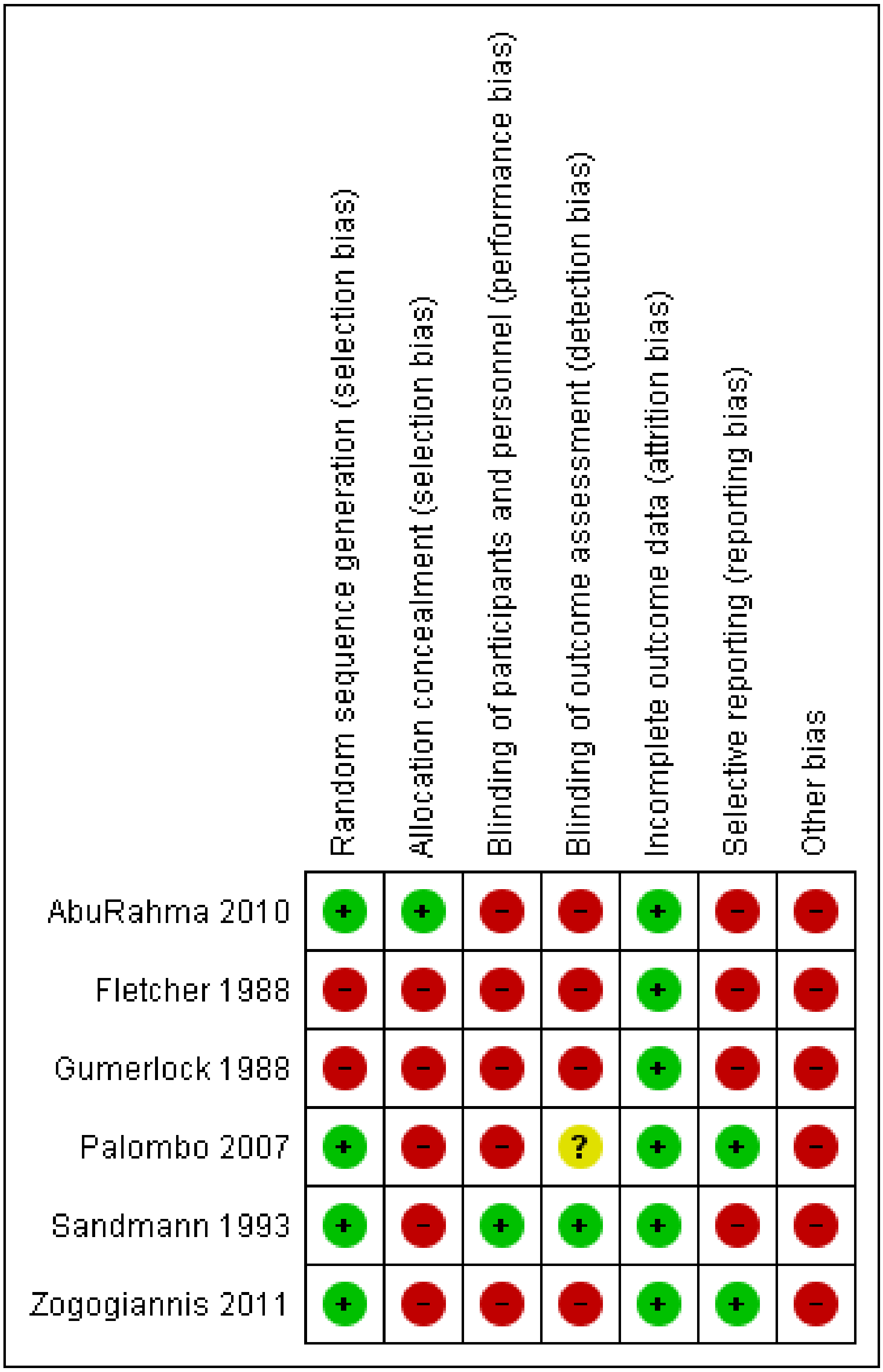
Excluded studies

We did not exclude any trials.

Risk of bias in included studies

One of the six RCTs was published in a journal as a 'Letter to the editor' (Sandmann 1993). For this study, only limited data from the short letter were available. In general, reporting of methodology was poor. The overall results of the 'Risk of bias' analysis are summarised in Figure 1.

Figure 1. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Allocation by randomisation was reported in all studies; however, only three studies reported the method of randomisation. This included odd/even hospital number (Gumerlock 1988), computer randomisation (Palombo 2007), and sequentially-numbered sealed envelopes (Sandmann 1993). The methods used for randomisation in the remaining trials were unclear. Gumerlock 1988 was not truly randomised as it used the patient hospital record number to allocate participants. There was an imbalance in the numbers of participants in each group in this trial (53 shunt versus 65 no shunt), which may have been due to selective inclusion of participants, although it was reported that consecutive patients were entered.

Blinding

Most studies did not report on blinding of participants, surgical teams and assessors to the randomised treatment allocation. In two trials, outcomes were assessed by independent neurologists (Sandmann 1993) and psychologists (Palombo 2007), but Palombo 2007 did not report whether these independent assessors knew the randomisation code.

Incomplete outcome data

Most studies did not report loss-to-follow-up or missing data except Sandmann 1993. There was no available information in this trial to indicate the loss to follow-up. Potentially important outcomes were not measured, such as stroke severity in terms of functional outcome, and long-term restenosis rate. One trial measured post-operative cognitive function (Palombo 2007). In addition, one trial randomised arteries rather than patients (Sandmann 1993), and the number of participants who had only unilateral procedures was not available by treatment group despite contact with the principal trialist. Overall, 441 participants had unilateral procedures and so we had to assume that these participants were roughly equally divided between the two treatment groups (the number of arteries randomised in each group was similar). In this trial the numbers of stroke-related deaths, strokes during surgery, and ipsilateral strokes were not reported by treatment group (and these data were not available from the authors). Therefore, we performed best- and worst-case analyses for these outcomes. This was possible because the total number of each of these events was known, as was the total number of deaths and strokes by treatment group. The best-case analysis assumed that the smallest possible number of events occurred in the shunted group, whilst the worst-case analysis assumed that the smallest number of events occurred in the unshunted group.

Selective reporting

Most studies did not indicate prespecified outcomes or report all prespecified outcomes. Only two studies reported all expected outcomes that were prespecified (Palombo 2007; Zogogiannis 2011).

Other potential sources of bias

Regarding allocation concealment, two trials used sealed envelopes that were opened just before surgery (AbuRahma 2010; Sandmann 1993). However, it was not reported if these were opaque. In the other four trials, the method of concealment of allocation was unclear.

We were not able to assess other biases, including measurement bias and funding bias in all studies.

Among the three trials comparing shunt versus no shunt (Gumerlock 1988; Palombo 2007; Sandmann 1993), one trial monitored participants in the unshunted group using EEG and SEP, and during the trial it was decided that participants randomised to no shunt should be shunted if they showed evidence of ipsilateral ischaemia (Sandmann 1993). Hence 3% of all operations in the no shunt group were in fact performed using a shunt. By comparison, in Gumerlock 1988 and Sandmann 1993 combined, 12% of the operations that were randomised to the shunt group were performed without shunting for technical reasons (usually because of difficulty in inserting a shunt). The most recent trial used stump pressure measurement and participants with stump pressure less than 50 mmHg required shunting (Palombo 2007).

The treatment groups were generally comparable in two trials (Gumerlock 1988; Palombo 2007). In one trial, those in the shunted group had more severe disease in the contralateral artery, which may have biased the results against shunting (Gumerlock 1988). The comparability of the groups with respect to age, sex, and vascular risk factors were not available for another trial (Sandmann 1993). However, there were imbalances in the surgical technique in this trial. Patching was performed more frequently in the shunted group (57% versus 39%). In addition, plication, resection or vein interposition was performed at the end of the operation to ensure laminar flow on Doppler, and these were performed more frequently in the unshunted group (56% versus 39%). This trial also noted that the outcome appeared to be better when the operation was performed by a more senior surgeon, and yet the experience of the surgeons was not given by treatment group. Neither trial reported on whether antithrombotic agents were used pre- or post-operatively.

There were other problems with the trials. Participants undergoing bilateral endarterectomies were included, and in one trial it was possible to be randomised twice to different operations (Sandmann 1993). The results of this trial were reported by artery rather than participant, which made analysis of the results using patient-based denominators (death or any stroke) difficult. Data on the comparability of the participants in this trial were not available and some outcomes were not reported by treatment group.

Effects of interventions

Shunt versus no shunt

NB. We had to calculate best- and worst-case scenarios for some outcomes because the number of events in each treatment group was not available for one trial.

Deaths within 30 days of surgery

The overall risk of deaths in participants who had unilateral operations or bilateral operations using the same procedure was 1.5% (10/655). All deaths were either due to stroke or coronary artery disease. There was a trend favouring a lower death rate in the shunted group but this was not significant (odds ratio (OR) 0.45, 95% confidence interval (CI) 0.13 to 1.59) (Analysis 1.1).
Only four patients died of stroke-related deaths (0.6%), so although there was a trend toward fewer stroke deaths in the shunted group, these data were not reliable (best case: Analysis 1.2; worst case: Analysis 1.3).

Any stroke (fatal or non-fatal, ischaemic or haemorrhagic, ipsilateral or contralateral, carotid or vertebrobasilar)

During surgery, the risk of stroke during surgery in both treatment groups combined was 2.7% (18/655). The best- and worst-case analyses gave qualitatively different results (that is, shunting was associated with a non-significant 58% reduction or 32% increase in the odds of stroke respectively) highlighting the instability of the data due to small numbers (best case: Analysis 1.4; worst case: Analysis 1.5).
During surgery or within 24 hours of surgery, data were available from only two trials, of which one trial showed a significant reduction in the risk of stroke with shunting (Gumerlock 1988), and the other trial reported no stroke in either treatment group (Palombo 2007). The pooled result showed a significant reduction in the risk of stroke with shunting (OR 0.15, 95% CI 0.03 to 0.78). However, this result is based on only six strokes in total and so is not reliable (Analysis 1.6).
During surgery or within 30 days of surgery, the overall risk of stroke within 30 days of surgery was 4.0% (26/655). There was a non-significant trend towards fewer strokes in the shunted group but the confidence interval was wide (OR 0.77, 95% CI 0.35 to 1.69) (Analysis 1.7).

Ipsilateral stroke (fatal and non-fatal, ischaemic and haemorrhagic)

During surgery, all strokes that occurred during surgery were ipsilateral. The risk of ipsilateral stroke in both groups combined was 2.4 per 100 operations (18/737). Again, the best- and worst-case analyses gave qualitatively different results (OR 0.42 and 1.32 respectively), although neither was significant (best case: Analysis 1.8; worst case: Analysis 1.9) .
During surgery or within 30 days of surgery, the risk of ipsilateral stroke was 3.0 per 100 operations (22/737). There was a trend for fewer strokes in the shunted group in both the best- and worst-case analyses (OR 0.41 and 0.88 respectively) but again, the small number of events makes these results difficult to interpret (best case: Analysis 1.10; worst case: Analysis 1.11).

Death or stroke within 30 days of surgery

The risk of death or stroke in patients (with unilateral or bilateral identical operations only) was 4.9% (32/655) overall. The best- and worst-case analyses showed non-significant trends favouring shunting (OR 0.62 and 0.81 respectively) but once again, the confidence intervals were wide (best case: Analysis 1.12; worst case: Analysis 1.13).

Other complications

The risks of wound haemorrhage or arterial rupture (0.3%) and wound infection (0.2%) were too small to reliably detect any difference between the two treatment groups. Nerve palsies were only recorded in one trial (Gumerlock 1988) and no significant difference was found between the two groups (3.6% risk overall) (Analysis 1.14; Analysis 1.15; Analysis 1.16).

Cognitive function

In the most recent trial, all participants underwent neuropsychological testing before the operation and three weeks after surgery (Palombo 2007). This study did not observe any statistical difference between the two groups before or after carotid surgery with regard to neuropsychological testing.

Comparison of routine shunting versus selective shunting

A single randomised controlled trial compared the results of routine shunting versus selective shunting based on stump pressure (AbuRahma 2010).There were no significant differences in clinical outcome between routine shunting and selective shunting. The perioperative stroke rate was 0% for routine shunting versus 2% for selective shunting (one major and one minor stroke, both related to carotid thrombosis) No participants died perioperatively. Combined perioperative TIA and stroke rates were 2% in routine shunting versus 2.9% in selective shunting. This study concluded that there were no significant differences between routine shunting and selective shunting.

Comparison of monitoring methods in selective shunting

EEG plus carotid stump pressure assessment versus stump pressure assessment alone

In Fletcher 1988 the risks of stroke or death per participant were not available from the published report. Five participants had a stroke within 24 hours of surgery (a risk of 3.5 per 100 operations.) There was no significant difference between combined EEG monitoring and carotid pressure assessment and carotid pressure assessment alone. In the combined monitoring group, two of the three strokes occurred in participants with abnormal EEGs who were not shunted because the carotid artery pressure was greater than 50 mmHg. The other stroke occurred in a participant with a normal EEG and a carotid pressure of greater than 55 mmHg. In the group with carotid stump pressure assessment alone, the two strokes occurred in participants with pressures greater than 55 mmHg. The risk of wound haemorrhage was too low (2.8%) to reliably detect any difference between the treatment groups. The risk of nerve palsies was higher (7.7%) but there was no apparent difference between the two groups. Combined monitoring results in about 50% fewer shunts being inserted (12 per 100 operations) than carotid artery pressure assessment alone (26 per 100 operations), but the numbers were small and so are not reliable.

The use of an intraoperative algorithm based on cerebral oximetry with near-infrared spectroscopy (NIRS) monitoring

Zogogiannis 2011 evaluated whether the use of an intraoperative algorithm based on cerebral oximetry with NIRS monitoring could help in the intraoperative decision for shunt placement, in people undergoing carotid endarterectomy. Two hundred and fifty-three participants who underwent carotid endarterectomy under general anaesthesia were randomly allocated to Group A (83 participants) using NIRS monitoring and the suggested algorithm, Group B (84 participants) using NIRS monitoring without the algorithm and Group C (86 participants) who served as controls. Shunt placement criterion for Groups A and B was a 20% drop in ipsilateral regional saturation from the baseline value recorded before surgery. The rate of shunting was 27.7% in group A, 59.5% in group B and 100% in group C. Regarding the rate of postoperative neurologic deficits, no significant difference was found between the three groups. This study concluded that the use of a specific algorithm based on NIRS monitoring, in people undergoing carotid endarterectomy, may reduce the rate for shunt placement. However, no significant effect of the reduced rate of shunting on the rate of neurological deficit was found.

DISCUSSION

Since the previous publication of this review there have been several new studies reporting the outcome of routine versus selective shunting in people undergoing carotid endarterectomy. However, most of these have been retrospective studies comparing the outcome of participants operated before and after a change in policy of shunt use (Bond 2002; Goodney 2012; Nguyen 2005; Woodworth 2007). Only two trials met the criteria for inclusion in this review (AbuRahma 2010; Zogogiannis 2011).

Of the six included trials, we identified three trials that compared routine shunting with no shunting (Gumerlock 1988; Palombo 2007; Sandmann 1993); only these three trials could be included in the meta-analysis. Two trials compared different monitoring methods in selective shunting (Fletcher 1988; Zogogiannis 2011), and one trial compared routine shunting with selective shunting (AbuRahma 2010). This trial showed no significant differences between routine shunting and selective shunting; however, too few outcomes were reported to detect any difference in the number of outcomes, especially strokes, between the two groups. More trials are needed.

Routine shunting versus no shunting

Summary of main results

The data from RCTs on the use of routine shunting were limited. There were promising but non-significant trends favouring a reduction in stroke-related deaths within 30 days of surgery with routine shunting.

Overall completeness and applicability of evidence

These analyses were based on very small numbers of outcome events. A large multicentre randomised trial is required to assess whether shunting reduces the risk of perioperative and long-term death and stroke. Even a modest 25% reduction in the relative risk of perioperative stroke or death would result in approximately 15 fewer strokes and deaths per 1000 people undergoing endarterectomy. However, detecting this reliably (80% power, 5% significance level) would require between 3000 and 5000 participants. The duration of follow-up in the included trials was very short. The main aim of shunting is to reduce the risk of perioperative stroke but it could possibly be associated with an increased risk of restenosis and late recurrent stroke. This risk was not assessed in the included trials.

Quality of the evidence

There were significant problems with the quality of the randomised trials. The method used for allocation concealment was inadequately reported in most of the included studies. The duration of follow-up was short in all included studies. It was also unclear in most of the studies whether the outcomes had been assessed blind to treatment allocation. It is well known that studies that have neurologists as assessors are associated with higher stroke and death rates (Rerkasem 2009; Rothwell 1996). Only two studies reported that they had independent assessors (psychologists, neurologists) (Palombo 2007; Sandmann 1993). Five of the trials reported complete outcome data.

Potential biases in the review process

There were several potential biases such as many cross-overs, imbalance in baseline characteristics and unavailable data for important baseline characteristics. These reduced the reliability of these results.

Agreements and disagreements with other studies or reviews

Our results showed that there were promising but non-significant trends favouring a reduction in both deaths and strokes within 30 days of surgery with the routine shunting policy. Opponents of this policy argue that insertion of a shunt can cause intimal injuries, embolisation, and difficulty in visualising the endpoint of endarterectomy, and that there might be a reduced incidence of stroke due to technical mistakes in patients who are not shunted (Halsey 1992). However, accurate data on these risks appear limited and anecdotal. In contrast, many studies reported that routine shunting by experienced surgeons results in a low rate of shunt-induced problems, and a low rate of stroke and death, and is a cost-effective procedure (Hamdan 1999; Hertzer 1997). Routine shunting avoids the need for test clamping of the common carotid artery (awake testing), which alone can cause embolic stroke. Also, routine shunting obviates the need to intubate urgently, which may force an attempt to place the shunt under less than ideal conditions, possibly raising the risk of technical errors.

Selective shunting versus no shunting

There are no data currently available from RCTs regarding the benefits (or hazards) of selective shunting versus no shunting.

Comparison of different methods of monitoring in selective shunting

Again, the data from randomised trials on which method should be used to select patients for selective shunting were very limited. We only identified two trials. The first trial (131 patients) compared the use of EEG monitoring combined with an assessment of the carotid stump back pressure with carotid back pressure assessment alone (Fletcher 1988). This study was small and did not report details of randomisation, blinding of outcome assessment and the numbers of participants in each group. Too few outcomes were reported to detect any difference in the number of strokes in the group that received EEG and carotid pressure assessment compared with the group that received carotid pressure assessment alone. However, from this limited data EEG monitoring did appear more sensitive to cerebral ischaemia than carotid stump pressure: two strokes occurred during the operation in participants who had EEG changes but whose carotid stump pressure remained greater than 50 mmHg, whilst no participants had reduced pressure without EEG changes. Combined EEG and pressure monitoring may reduce the number of shunts inserted but it is difficult to interpret these data without reliable evidence that this method of monitoring does not increase the risk of stroke. In addition, if EEG monitoring is not associated with fewer strokes, the costs of extra EEG monitoring may outweigh the costs saved by inserting fewer shunts.

The second trial assessed whether the use of an intraoperative algorithm based on cerebral oximetry with NIRS monitoring could help in the intraoperative decision for shunt placement, in people undergoing carotid endarterectomy (253 participants) (Zogogiannis 2011). Two hundred and fifty-three participants, who underwent CEA under general anaesthesia, were randomly allocated to Group A using NIRS monitoring and the suggested algorithm, Group B using NIRS monitoring without the algorithm and Group C who served as controls. This study was small and did not report details of randomisation, allocation concealment, blinding of the participants and personnel as well as outcome assessment. Shunt placement criterion for Group A and B was a 20% drop in ipsilateral regional saturation from the baseline value recorded before surgery. The rate of shunting was 27.7% in group A, 59.5% in group B and 100% in group C. For the rate of postoperative neurologic deficits, no significant difference was found between the three groups. However, too few outcomes (13 participants) were reported to detect any difference in the number of strokes in each group.

There are many other methods of monitoring for cerebral ischaemia that may be more sensitive than EEG, carotid pressure monitoring and NIRS but these have not been subjected to assessment in RCTs. The key question is not whether these methods can reliably detect cerebral ischaemia but whether shunting in these people results in lower perioperative morbidity and case fatality.

AUTHORS' CONCLUSIONS

Implications for practice

There is still insufficient evidence from randomised controlled trials to support the use of routine shunting in carotid endarterectomy, although a clinically important benefit from routine shunting cannot be excluded. There is no reliable evidence at present to support the use of selective shunting. In those who wish to use selective shunting in people under general anaesthetic, there is again little evidence to support the use of one form of monitoring over another. Much more data are required to prove this.

Implications for research

A large multicentre randomised trial is required to assess whether shunting reduces the risk of perioperative and long-term death and stroke. Even a modest 25% reduction in the relative risk of perioperative stroke or death would result in approximately 15 fewer strokes and deaths per 1000 people undergoing endarterectomy. However, to detect this reliably (80% power, 5% significance level) would require between 3000 and 5000 participants. Two policies could be considered: routine shunting for all people undergoing carotid endarterectomy or selective shunting in those at high risk of intraoperative cerebral ischaemia. The trial would have to be truly randomised, have long-term follow-up (several years) and have blinded outcome assessment preferably by neurologists. Patients should be stratified by age, sex, degree of ipsilateral and contralateral internal carotid stenosis, the experience of the surgeon, the use of patching and, in selective shunting, the method of monitoring of cerebral ischaemia.

As regards the method of monitoring in selective shunting, until the efficacy of shunting has been demonstrated, further trials of the method of monitoring are probably not merited. However, a systematic review of the sensitivity and specificity of the various methods of monitoring for cerebral ischaemia would be worthwhile to identify the best method of monitoring to be used in any trial of selective shunting (Irwig 1994).

ACKNOWLEDGEMENTS

We would like to thank: Hazel Fraser for providing us with references to relevant trials from the Cochrane Stroke Group's Trials Register; Brenda Thomas for helping with search strategy; Professor Peter Sandercock, Dr Eivind Berge and Devi Prasad Mohapatra for commenting on the manuscript; Mr Richard Bond and Professor Peter Rothwell for their contribution to previous versions of this review. Professor Kittipan Rerkasem was funded by The Thailand Research Fund (RSA5580008) and the Faculty of Medicine, Chiang Mai University.

Ongoing trials

If anyone is aware of any randomised trials that we have omitted please contact Professor Kittipan Rerkasem.

REFERENCES

References to studies included in this review

AbuRahma 2010 ***{published data only}***
Aburahma AF, Stone PA, Hass SM, Dean LS, Habib J, Keiffer T, et al.Prospective randomized trial of routine versus selective shunting in carotid endarterectomy based on stump pressure. *Journal of Vascular Surgery* 2010;**51**: 1133–8.

Fletcher 1988 ***{published data only}***
Fletcher JP, Morris JGL, Little JM, Kershaw LZ. EEG monitoring during carotid endarterectomy. *Australian and New Zealand Journal of Surgery* 1988;**58**:285–8.

Gumerlock 1988 ***{published and unpublished data}***
Gumerlock MK, Neuwelt EA. Carotid endarterectomy: to shunt or not to shunt. *Stroke* 1988;**19**:1485–90.

Palombo 2007 ***{published data only}***
Palombo D, Lucertini G, Mambrini S, Zettin M. Subtle cerebral damage after shunting vs non shunting during carotid endarterectomy. *European Journal of Vascular and Endovascular Surgery* 2007;**34**:546–51.

Sandmann 1993 ***{published and unpublished data}***
Sandmann W, Kolvenbach R, Willeke F. Risks and benefits of shunting in carotid endarterectomy. *Stroke* 1993;**24**: 1098.
* Sandmann W, Willeke F, Kovenbach R, Benecke R, Godehardt E. To shunt or not to shunt: the definite answer with a randomized study. In: Veith FJ editor(s). *Current Critical Problems in Vascular Surgery*. Vol. **5**, St Louis, Missouri: Quality Medical Publishing Inc, 1993:434–40.

Zogogiannis 2011 ***{published data only}***
Zogogiannis ID, Iatrou CA, Lazarides MK, Vogiatzaki TD, Wachtel MS, Chatzigakis PK, et al.Evaluation of an intraoperative algorithm based on near-infrared refracted spectroscopy monitoring, in the intraoperative decision for shunt placement, in patients undergoing carotid endarterectomy.. *Middle East Journal of Anesthesiology* 2011; **21**:367–73.

Additional references

ACAS 1995
Executive Committee for the Asymptomatic Carotid Atherosclerosis study. Endarterectomy for asymptomatic carotid artery stenosis. *JAMA* 1995;**273**:1421–8.

ACST 2004
ACST Collaborative Group. Prevention of disabling and fatal strokes by successful carotid endarterectomy in patients without recent neurological symptoms: randomised controlled trial. MRC Asymptomatic Carotid Surgery Trial (ACST) Collaborative Group. *Lancet* 2004;**363**:1491–502.

APT 1994
Antiplatelet Trialists Collaboration. Collaborative overview of trials of antiplatelet therapy - I: Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. *BMJ* 1994;**308**: 81–106.

Benjamin 1993
Benjamin ME, Silva MB, Watt C, McCaffrey MT, Burford-Foggs A, Flinn WR. Awake patient monitoring to determine the need for shunting during carotid endarterectomy. *Surgery* 1993;**114**:673–81.

Bond 2002
Bond R, Warlow C P, Naylor AR, Rothwell PM. Variation in surgical and anaesthetic technique and associations with operative risk in the European Carotid Surgery Trial: implications for trials of ancillary techniques. *European Journal of Vascular and Endovascular Surgery* 2002;**23**: 117–26.

Buche 1988
Buche M, Grenier Y, Schoevaerdts JC, Jaumin P, Ponlot R, Chalant CH. Comparative results after endarterectomy of internal carotid artery performed with or without a shunt. *Journal of Cardiovascular Surgery* 1988;**29**:428–31.

Connolly 1977
Connolly JE, Jack HM, Stemmer EA. Improved results with carotid endarterectomy. *Annals of Surgery* 1977;**186**: 334–42.

ECST 1991
European Carotid Surgery Trialists Collaborative Group. MRC Carotid Surgery Trial: interim results for symptomatic patients with severe (70-99%) or with mild (0-29%) carotid stenosis. *Lancet* 1991;**337**:1235–43.

Evans 1985
Evans WE, Hayes JP, Waltke, EA, Vermilion BD. Optimal cerebral monitoring during carotid endarterectomy: neurologic response under local anaesthetic. *Journal of Vascular Surgery* 1985;**2**:775–7.

Fode 1986
Fode NC, Sundt TM, Robertson JT, Peerless SJ, Shields CB. Multicenter retrospective review of results and complications of carotid endarterectomy in 1981. *Stroke* 1986;**17**:370–5.

Forssell 1995
Forssell C, Kitzing P, Bergqvist D. Cranial nerve injuries after carotid surgery. A prospective study of 663 operations. *European Journal of Vascular Surgery* 1995;**10**:445–9.

Girn 2008
Girn HR, Dellagrammaticas D, Laughlan K, Gough MJ, for the GALA Trial Collaborators. Carotid endarterectomy: technical practices of surgeons participating in the GALA trial. *European Journal of Vascular and Endovascular Surgery* 2008;**36**:385–9.

Goodney 2012
Goodney PP, Wallaert JB, Scali ST, Stone DH, Patel V, Shaw P, et al.Impact of practice patterns in shunt use during carotid endarterectomy with contralateral carotid occlusion. *Journal of Vascular Surgery* 2012;**55**:61–71.

Green 1985
Green RM, Messick WJ, Ricotta JJ, Charlton MH, Satran R, McBride MM, et al.Benefits, shortcomings, and costs of EEG monitoring. *Annals of Surgery* 1985;**201**:785–92.

Halsey 1992
Halsey JH Jr. Risks and benefits of shunting in carotid endarterectomy. The International Transcranial Doppler Collaborators. *Stroke* 1992;**23**:1583–7.

Hamdan 1999
Hamdan AD, Pomposelli FB Jr, Gibbons GW, Campbell DR, LoGerfo FW. Perioperative strokes after 1001 consecutive carotid endarterectomy procedures without an electroencephalogram: incidence, mechanism, and recovery. *Archives of Surgery* 1999;**134**:412–5.

Hertzer 1997
Hertzer NR, O'Hara PJ, Mascha EJ, Krajewski LP, Sullivan TM, Beven EG. Early outcome assessment for 2228 consecutive carotid endarterectomy procedures: the Cleveland Clinic experience from 1989 to 1995. *Journal of Vascular Surgery* 1997;**26**:1–10.

Higgins 2003
Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analysis. *BMJ* 2003;**327**: 557–60.

Higgins 2011
Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Irwig 1994
Irwig L, Tosteson ANA, Gatsonis C, Lau J, Colditz G, Chalmers TC, et al.Guidelines for meta-analyses evaluating diagnostic tests. *Annals of Internal Medicine* 1994;**120**: 667–76.

Javid 1979
Javid H, Julian OC, Dye WS, Hunter JA, Najafi H, Goldin MD, et al.Seventeen-year experience with routine shunting in carotid surgery. *World Journal of Surgery* 1979;**3**:167–77.

Lewis 2008
Lewis SC, Warlow CP, Bodenham AR, Colam B, Rothwell PM, Torgerson D, et al.General anaesthesia versus local anaesthesia for carotid surgery (GALA): a multicentre, randomised controlled trial. *Lancet* 2008;**372**:2132–42.

NASCET 1991
North American Symptomatic Carotid Endarterectomy Trial Collaborators. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. *New England Journal of Medicine* 1991; **325**:445–765.

Nguyen 2005
Nguyen TQ, Lind L, Harris EJ Jr. Selective shunting during carotid endarterectomy. *Vascular* 2005;**13**:23–7.

Ott 1980
Ott DA, Cooley DA, Chapa L, Coelho A. Carotid endarterectomy without temporary intraluminal shunt. Study of 309 consecutive operations. *Annals of Surgery* 1980;**191**:708–14.

Ouriel 1987
Ouriel K, Green RM. Clinical and technical factors influencing recurrent carotid stenosis and occlusion after endarterectomy. *Journal of Vascular Surgery* 1987;**5**:702–6.

Prioleau 1977
Prioleau WH, Aiken AF, Hairston P. Carotid endarterectomy. Neurologic complications as related to surgical techniques. *Annals of Surgery* 1977;**185**:678–83.

Reddy 1987
Reddy K, West M, Anderson B. Carotid endarterectomy without indwelling shunts and intraoperative electrophysiologic monitoring. *Canadian Journal of Neurological Sciences* 1987;**14**:131–5.

Rerkasem 2009
Rerkasem K, Rothwell PM. Temporal trends in the risks of stroke and death due to carotid endarterectomy for symptomatic carotid stenosis: an updated systematic review. *European Journal of Vascular and Endovascular Surgery* 2009; **37**:504–11.

Rerkasem 2011
Rerkasem K, Rothwell PM. Carotid endarterectomy for symptomatic carotid stenosis. *Cochrane Database of Systematic Reviews* 2011, Issue 4. [DOI: 10.1002/14651858.CD001081.pub2]

RevMan 2012
The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). 5.2. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012.

Ricotta 1983
Ricotta JJ, Charlton MH, DeWeese JA. Determining criteria for shunt placement during carotid endarterectomy. EEG versus back pressure. *Annals of Surgery* 1983;**198**: 642–5.

Rothwell 1996
Rothwell PM, Slattery J, Warlow CP. A systematic review of the risk of stroke and death due to endarterectomy for symptomatic carotid stenosis. *Stroke* 1996;**27**:260–5.

Salvian 1997
Salvian AJ, Taylor DC, Hsiang YN, Hildebrand HD, Litherland HK, Humer MF, et al.Selective shunting with EEG monitoring is safer than routine shunting for carotid endarterectomy. *Cardiovascular Surgery* 1997;**5**:481–5.

Schulz 1995
Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA* 1995;**273**:408–12.

Schweiger 1988
Schweiger H, Kamp H-D, Dinkel M. Somatosensory evoked potentials (SEP) during carotid endarterectomy - end of shunt debate?. In: Boccalon H editor(s). *Angiology: Strategy for Diagnosis and Therapeutics*. Paris: John Libbey Eurotext, 1988:353–5.

Steiger 1989
Steiger HJ, Schaffer L, Boll J, Liechti S. Results of microsurgical carotid endarterectomy. A prospective study with transcranial Doppler and EEG monitoring, and elective shunting. *Acta Neurochirurgica* 1989;**100**:31–8.

Sundt 1986
Sundt TM, Sharbrough FW, Marsh WR, Ebersold MJ, Piepgras DG, Messick JM. The risk-benefit ratio of intraoperative shunting during carotid endarterectomy. *Annals of Surgery* 1986;**203**:196–204.

Thompson 1979
Thompson JE. Complications of carotid endarterectomy and their prevention. *World Journal of Surgery* 1979;**3**: 155–65.

Vaniyapong 2013
Vaniyapong T, Chongruksut W, Rerkasem K. Local versus general anaesthesia for carotid endarterectomy. *Cochrane Database of Systematic Reviews* 2013, Issue 12. [DOI: 10.1002/14651858.CD000126]

Whittemore 1983
Whittemore AD, Kaufman JL, Kohler TR, Mannick JA. Routine electroencephalographic (EEG) monitoring during carotid endarterectomy. *Annals of Surgery* 1983;**197**: 707–13.

Wilkinson 1997
Wilkinson JM, Rochester JR, Sivaguru A, Cameron IC, Fisher R, Beard JD. Middle cerebral artery blood velocity, embolization, and neurological outcome during carotid endarterectomy. *European Journal of Vascular and Endovascular Surgery* 1997;**14**:402.

Woodworth 2007
Woodworth GF, McGirt MJ, Than KD, Huang J, Perler BA, Tamargo RJ. Selective versus routine intraoperative shunting during carotid endarterectomy: a multivariate outcome analysis. *Neurosurgery* 2007;**61**:1170–6.

References to other published versions of this review

Bond 2002a
Bond R, Rerkasem K, Rothwell PM. Routine or selective carotid artery shunting for carotid endarterectomy (and different methods of monitoring in selective shunting).

Cochrane Database of Systematic Reviews 2002, Issue 2. [DOI: 10.1002/14651858.CD000190]

Rerkasem 2009a

Rerkasem K, Rothwell PM. Routine or selective carotid artery shunting for carotid endarterectomy (and different methods of monitoring in selective shunting). *Cochrane Database of Systematic Reviews* 2009, Issue 4. [DOI: 10.1002/14651858.CD000190.pub2]

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

AbuRahma 2010

Methods	Method of randomisation: unknown Concealment: sealed envelops that were opened just before surgery Not blind Cross-overs: none (ITT analysis) Exclusions during trial: none Loss to follow-up: none
Participants	USA 200 participants, 200 operations Routine shunting: 98 operations Selective shunting: 102 operations Age: 45 to 89 years, mean 68 years Sex: 48% male, 52% female Comparability: age, sex, vascular risk factors similar between 2 groups More asymptomatic ipsilateral arteries in routine shunting group: 58% versus 53% Contralateral artery stenosis (mean %) routine shunting group: 38%; selective shunting group: 40%
Interventions	Treatment: selective shunting group; shunt selected if systolic stump pressure < 40 mmHg Control: routine shunting group All operations under general anaesthetic; unknown patching rate
Outcomes	TIA, stroke, combined stroke/TIA, death, bleeding, myocardial infarction, congestive, heart failure, asymptomatic carotid thrombosis, recurrent laryngeal injury, all complications, number of shunted artery
Notes	Exclusion: none Follow-up: 30 days

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "200 CEA patients were randomised into"
Allocation concealment (selection bias)	Low risk	Quote: "Randomization was done using sealed envelopes that were open just before surgery"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not reported

AbuRahma 2010 (*Continued)*

Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	High risk	Study authors did not report prespecified outcome
Other bias	High risk	Not reported

Fletcher 1988

Methods	Method of randomisation: unknown (artery or patient randomised?) Not blind Cross-overs: none Exclusions during trial: none Loss to follow-up: none
Participants	Australia 131 participants, 142 operations EEG/pressure monitoring: 72 operations Pressure assessment alone: 70 operations Age: 36 to 70 years, mean 58 years Sex: 70% male, 30% female Comparability: age, sex, vascular risk factors similar between 2 groups More asymptomatic ipsilateral arteries in pressure group: 1% versus 11% Contralateral artery stenosis unknown
Interventions	Treatment: EEG monitoring and carotid stump back pressure assessment; shunt selected if ipsilateral EEG change (loss of voltage/activity) within 3 minutes of clamping and back pressure < 50 mmHg Control: carotid stump back pressure assessment alone; shunt selected if back pressure < 50 mmHg All operations under general anaesthetic; unknown patching rate
Outcomes	Death plus stroke-related death, any stroke (during the operation), ipsilateral stroke, haemorrhage from operation site, nerve palsies, number of shunted artery
Notes	Exclusion: none Follow-up: duration unknown

Risk of bias

Bias	Authors' judgement	Support for judgement

Fletcher 1988 (*Continued)*

Random sequence generation (selection bias)	High risk	Quote: "Randomization was dependent on availability of an EEG technician"
Allocation concealment (selection bias)	High risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data
Selective reporting (reporting bias)	High risk	Study authors did not report prespecified outcome
Other bias	High risk	Not reported

Gumerlock 1988

Methods	Method of randomisation: odd/even hospital number (patient randomised) Not blind Cross-overs: shunt: 3 patients not shunted (analysed in original group) Exclusions during trial: none Loss to follow-up: none
Participants	USA Shunt: 53 participants (63 operations) No shunt: 65 participants (75 operations) Age: range 40 to 79 years Sex: unknown Comparability: age, vascular risk factors, indication for operation, degree of stenosis in operated artery similar between treatment and control More severe contralateral artery disease in shunt group: stenosis > 90% to 32% versus 19%
Interventions	Treatment: Javid shunt Control: no shunt All operations done under general anaesthetic; no monitoring; primary closure
Outcomes	Death plus stroke-related death, any stroke (during operation, within 24 hours and 30 days of operation), ipsilateral stroke, haemorrhage from operation site, infection at operation site, nerve palsy

Gumerlock 1988 (*Continued)*

Notes	Exclusions: none Follow-up: 30 days	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Not reported
Allocation concealment (selection bias)	High risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data
Selective reporting (reporting bias)	High risk	Study authors did not report prespecified outcome
Other bias	High risk	Quote: "All CEs were performed by either the attending neurosurgeon or by a senior neurosurgical resident under direct supervision". No data showed the percentage of operations done by residents in each arm. Obviously residents had less experience than the attending physician, even though such operations were done under direct supervision. This might be a risk of bias, if there was a significant proportion of residents as operators in 1 group

Palombo 2007

Methods	Randomisation was done by a random number generator using computational method Concealment: unclear Blind outcome assessment: unclear No cross-overs Exclusions during trial: unclear Loss to follow-up: unclear
Participants	Italy 96 participants Shunt: 48 participants; no shunt: 48 participants Age: mean 71.45 years Sex: 67% male, 33% female Comparability: age, sex, vascular risk factors, indication for operation, degree of ipsilateral/contralateral stenosis in each group not given Overall: all had 66% asymptomatic
Interventions	Treatment: Pruitt-Inahara shunt Control: no shunt (shunted if stump pressure < 50 mmHg) All operations done under general anaesthetic with stump pressure measurement All operations done by eversion carotid endarterectomy technique
Outcomes	Death and stroke, cerebral CT scan, serum concentration of S100 protein, neuron specific enolase, interleukin-6, neuropsychological test
Notes	Exclusions: contralateral severe carotid stenosis or carotid occlusion, right-side involvement, age greater than 80 years, dementia, previous disabling stroke, brain tumour, neuroleptic therapy and Mini Mental State Examination score < 24 points Follow-up: unclear

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomisation was done by a random number generator using computational method that was managed by a statistician."
Allocation concealment (selection bias)	High risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Neuropsychological test was done by psychologists but author did not report whether they knew the randomisation code

Incomplete outcome data (attrition bias) All outcomes	Low risk	No participants lost to follow-up
Selective reporting (reporting bias)	Low risk	Study authors reported all prespecified outcomes
Other bias	High risk	Not reported

Sandmann 1993

Methods	Method of randomisation: opaque, sequentially-numbered sealed envelopes (artery randomised) Blind outcome assessment Cross-overs: shunt: 35 participants not shunted; no shunt: 10 participants shunted (all participants analysed in original group) Exclusions during trial: none Loss to follow-up: none
Participants	Germany 472 participants, 441 with unilateral operations Shunt: 250 operations No shunt: 253 operations Age: mean 64 years Sex: 70% male, 30% female Comparability: age, sex, vascular risk factors, indication for operation, degree of ipsilateral/contralateral stenosis in each group not given Overall: all had ipsilateral stenosis > 70% (20% asymptomatic); 20% had contralateral stenosis > 80%
Interventions	Treatment: Javid shunt Control: no shunt (shunted if significant changes on monitoring) All operations done under general anaesthetic with EEG/SEP monitoring; at end of operation plication, resection, vein interposition was performed to achieve laminar flow on Doppler
Outcomes	Death plus stroke-related death, any stroke (during the operation and within 30 days), ipsilateral stroke, haemorrhage from operation site, infection at operation site
Notes	Exclusions: bilateral simultaneous endarterectomies, simultaneous reconstruction of supra-aortic branch and carotid bifurcation Follow-up: 30 days

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Sandmann 1993 (*Continued)*

Random sequence generation (selection bias)	Low risk	Quote: "the use of the intraluminal Javid shunt was prospectively randomised in a continuous series of 503 CEs"
Allocation concealment (selection bias)	High risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Based on unpublished data, a neurologist who was blind to treatment allocation assessed participants post-operatively
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "In 503 cases evaluated preoperatively and postoperatively by an independent neurologist, the use of a Javid shunt was prospectively randomised."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Based on unpublished data, there was no loss to follow-up in this study
Selective reporting (reporting bias)	High risk	Study authors did not report prespecified outcome
Other bias	High risk	Not reported

Zogogiannis 2011

Methods	Method of randomisation: unknown Not blind Cross-overs: none Exclusions during trial: none Loss to follow-up: none
Participants	Greece 253 participants, 253 operations Group A: using cerebral oximetry with the suggested algorithm (83 operations) Group B: using cerebral oximetry without the suggested algorithm (84 operations) Group C: control group - routine shunting (86 operations) Age: 48 to 82 years, mean 68.6 years Sex: 73% male, 27% female Comparability: age, sex, BMI, vascular risk factors, coronary artery disease, haemodialysis similar between 2 groups Asymptomatic ipsilateral arteries: 67.4% (group A), 66.7% (group B), 67.4 (group C) Contralateral artery stenosis unknown
Interventions	Treatment: Intervention group Group A: using cerebral oximetry with the suggested algorithm Group B: using cerebral oximetry without the suggested algorithm These 2 groups, surgeon was notified when a 20% drop from the baseline was found Group C control group - routine shunting

	All operations under general anaesthetic; unknown patching rate	
Outcomes	Number of shunted arteries, neurological deficit, cardiovascular ischaemia	
Notes	Exclusion: none Follow-up: duration unknown	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "This prospective, controlled, randomised study in two Greek institutions"
Allocation concealment (selection bias)	High risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data
Selective reporting (reporting bias)	Low risk	Study authors reported all prespecified outcomes
Other bias	High risk	Not reported

BMI: body mass index
CEA: carotid endarterectomy
CT: computerised tomography
EEG: electroencephalogram
ITT: intention to treat
SEP: somatosensory evoked potential
TIA: transient ischaemic attack

D A T A A N D A N A L Y S E S

Comparison 1. Shunting (routine or selective) versus no shunting

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death from all causes within 30 days of surgery	3	655	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.45 [0.13, 1.59]
1.1 Routine shunting versus no shunting	3	655	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.45 [0.13, 1.59]
2 Stroke-related death within 30 days of surgery (best case)	3	655	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.13 [0.02, 0.96]
2.1 Routine shunting versus no shunting	3	655	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.13 [0.02, 0.96]
3 Stroke-related death within 30 days of surgery (worst case)	3	655	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.37 [0.05, 2.62]
3.1 Routine shunting versus no shunting	3	655	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.37 [0.05, 2.62]
4 Any stroke during surgery (best case)	3	655	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.42 [0.16, 1.07]
4.1 Routine shunting versus no shunting	3	655	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.42 [0.16, 1.07]
5 Any stroke during surgery (worst case)	3	655	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.32 [0.52, 3.38]
5.1 Routine shunting versus no shunting	3	655	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.32 [0.52, 3.38]
6 Any stroke within 24 hours of surgery	2	214	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.15 [0.03, 0.78]
6.1 Routine shunting versus no shunting	2	214	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.15 [0.03, 0.78]
7 Any stroke within 30 days of surgery	3	655	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.77 [0.35, 1.69]
7.1 Routine shunting versus no shunting	3	655	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.77 [0.35, 1.69]
8 Ipsilateral stroke during surgery (best case)	3	737	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.42 [0.17, 1.08]
8.1 Routine shunting versus no shunting	3	737	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.42 [0.17, 1.08]
9 Ipsilateral stroke during surgery (worst case)	3	737	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.32 [0.52, 3.37]
9.1 Routine shunting versus no shunting	3	737	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.32 [0.52, 3.37]
10 Ipsilateral stroke within 30 days of surgery (best case)	3	737	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.41 [0.18, 0.97]
10.1 Routine shunting versus no shunting	3	737	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.41 [0.18, 0.97]
11 Ipsilateral stroke within 30 days of surgery (worst case)	3	737	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.88 [0.38, 2.05]

11.1 Routine shunting	3	737	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.88 [0.38, 2.05]
12 Stroke or death within 30 days of surgery (best case)	3	655	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.62 [0.31, 1.27]
12.1 Routine shunting versus no shunting	3	655	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.62 [0.31, 1.27]
13 Stroke or death within 30 days of surgery (worst case)	3	655	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.81 [0.40, 1.66]
13.1 Routine shunting versus no shunting	3	655	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.81 [0.40, 1.66]
14 Haemorrhage from operation site	2	641	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.19 [0.07, 19.47]
14.1 Routine shunting versus no shunting	2	641	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.19 [0.07, 19.47]
15 Infection of operation site	2	641	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.16 [0.00, 8.12]
15.1 Routine shunting versus no shunting	2	641	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.16 [0.00, 8.12]
16 Nerve palsy post-operatively	1	138	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.81 [0.30, 10.82]
16.1 Routine shunting versus no shunting	1	138	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.81 [0.30, 10.82]

WHAT'S NEW

Last assessed as up-to-date: 9 August 2013.

Date	Event	Description
9 August 2013	New citation required but conclusions have not changed	New first author.
9 August 2013	New search has been performed	The searches have been updated and completed to August 2013. We have identified and included two new randomised trials, bringing the total number of included studies to six, involving 1270 participants. The conclusions of the review have not changed

HISTORY

Protocol first published: Issue 1, 1995

Review first published: Issue 1, 1995

Date	Event	Description
3 May 2009	New search has been performed	The searches have been updated and completed to November 2008. In the years since the searches were last completed in 2000, we have identified one new

(*Continued*)

		randomised trial (Palombo 2007), which assesses the effect of shunting versus non-shunting during carotid endarterectomy. This new trial involved 48 patients in each group and there were no outcome events in either group. In this updated version, the conclusions have not therefore changed materially from the previous review
3 May 2009	New citation required but conclusions have not changed	Change of authorship.
12 September 2008	Amended	Converted to new review format.
10 August 2001	New search has been performed	In the six years since this review was first published there have been a number of retrospective comparisons of selective shunt use versus systematic shunt use, as well as a prospective comparison of different shunt types, but there have been no new prospective randomised controlled trials relevant to this review

CONTRIBUTIONS OF AUTHORS

Update of review

Wilaiwan Chongruksut, Tanat Vaniyapong, Kittipan Rerkasem: designed the protocol, performed searches, selected studies for inclusion or exclusion, extracted data and updated the review.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Faculty of Medicine, Chiang Mai University, Thailand.
- Reserach Institute for Health Sciences, Chiang Mai University, Chiang Mai, Thailand.

External sources

- Stroke Prevention Research Unit, Nuffield Department of Clinical Neurosciences, University of Oxford, UK.
- Thailand Research Fund, Thailand.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

None.

NOTES

None.

INDEX TERMS

Medical Subject Headings (MeSH)

Carotid Arteries [*surgery]; Endarterectomy, Carotid [adverse effects; *methods]; Randomized Controlled Trials as Topic; Stroke [prevention & control]

MeSH check words

Humans

Local versus general anaesthesia for carotid endarterectomy (Review)

Vaniyapong T, Chongruksut W, Rerkasem K

THE COCHRANE COLLABORATION®

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2013, Issue 12

http://www.thecochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Review]

Local versus general anaesthesia for carotid endarterectomy

Tanat Vaniyapong[1], Wilaiwan Chongruksut[1], Kittipan Rerkasem[1,2]

[1]Department of Surgery, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand. [2]Center for Applied Science, Research Institute of Health Sciences, Chiang Mai University, Chiang Mai, Thailand

Contact address: Kittipan Rerkasem, rerkase@gmail.com.

Editorial group: Cochrane Stroke Group.
Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 12, 2013.
Review content assessed as up-to-date: 30 September 2013.

Citation: Vaniyapong T, Chongruksut W, Rerkasem K. Local versus general anaesthesia for carotid endarterectomy. *Cochrane Database of Systematic Reviews* 2013, Issue 12. Art. No.: CD000126. DOI: 10.1002/14651858.CD000126.pub4.

ABSTRACT

Background

Carotid endarterectomy may significantly reduce the risk of stroke in people with recently symptomatic, severe carotid artery stenosis. However, there are significant perioperative risks that may be reduced by performing the operation under local rather than general anaesthetic. This is an update of a Cochrane Review first published in 1996, and previously updated in 2004 and 2008.

Objectives

To determine whether carotid endarterectomy under local anaesthetic: (1) reduces the risk of perioperative stroke and death compared with general anaesthetic; (2) reduces the complication rate (other than stroke) following carotid endarterectomy; and (3) is acceptable to patients and surgeons.

Search methods

We searched the Cochrane Stroke Group Trials Register (September 2013), MEDLINE (1966 to September 2013), EMBASE (1980 to September 2013) and Index to Scientific and Technical Proceedings (ISTP) (1980 to September 2013). We also handsearched relevant journals, and searched the reference lists of articles identified.

Selection criteria

Randomised trials comparing the use of local anaesthetic to general anaesthetic for carotid endarterectomy were considered for inclusion.

Data collection and analysis

Three review authors independently assessed trial quality and extracted data. We calculated a pooled Peto odds ratio (OR) and corresponding 95% confidence interval (CI) for the following outcomes that occurred within 30 days of surgery: stroke, death, stroke or death, myocardial infarction, local haemorrhage, cranial nerve injuries, and shunted arteries.

Main results

We included 14 randomised trials involving 4596 operations, of which 3526 were from the single largest trial (GALA). In general, reporting of methodology in the included studies was poor. All studies were unable to blind patients and surgical teams to randomised treatment allocation and for most studies the blinding of outcome assessors was unclear. There was no statistically significant difference in the incidence of stroke within 30 days of surgery between the local anaesthesia group and the general anaesthesia group. The incidence of strokes in the local anaesthesia group was 3.2% compared to 3.5% in the general anaesthesia group (Peto OR 0.92, 95% CI 0.67 to 1.28). There was no statistically significant difference in the proportion of patients who had a stroke or died within 30 days of surgery.

In the local anaesthesia group 3.6% of patients had a stroke or died compared to 4.2% of patients in the general anaesthesia group (Peto OR 0.85, 95% CI 0.63 to 1.16). There was a non-significant trend towards lower operative mortality with local anaesthetic. In the local anaesthesia group 0.9% of patients died within 30 days of surgery compared to 1.5% of patients in the general anaesthesia group (Peto OR 0.62, 95% CI 0.36 to 1.07). However, neither the GALA trial or the pooled analysis were adequately powered to reliably detect an effect on mortality.

Authors' conclusions

The proportion of patients who had a stroke or died within 30 days of surgery did not differ significantly between the two types of anaesthetic techniques used during carotid endarterectomy. This systematic review provides evidence to suggest that patients and surgeons can choose either anaesthetic technique, depending on the clinical situation and their own preferences.

PLAIN LANGUAGE SUMMARY

Local versus general anaesthesia for carotid endarterectomy

About 20% of strokes result from narrowing of the carotid artery, which is the main artery supplying blood to the brain. Blood clots can form at the point of narrowing. If a blood clot breaks off into the bloodstream, it can be carried into the brain, block the blood supply there and cause a stroke. A surgical operation known as carotid endarterectomy removes the inner lining and blood clot in the carotid artery and can lower the risk of stroke. However, even with very careful surgery, approximately one in 20 patients will suffer a stroke caused by the operation itself. The use of local anaesthesia rather than general anaesthesia might lower the risk of a stroke happening during or after surgery. This review includes 14 randomised trials, involving 4596 operations, comparing the use of local anaesthetic to general anaesthetic for carotid endarterectomy. There was no statistically significant difference between the anaesthetic techniques in the percentage of patients who had a stroke or died within 30 days of surgery. This systematic review provides evidence to suggest that patients and surgeons can choose either anaesthetic technique, depending on the clinical situation and their own preferences.

BACKGROUND

Description of the condition

Around 20% of patients presenting with transient ischaemic attack or non-disabling ischaemic stroke have a significant stenosis with unstable atheromatous plaque at or around the bifurcation of the ipsilateral carotid artery. This plaque gives rise to the embolus. Carotid endarterectomy is an operation to remove this stenosis together with unstable plaque and, therefore, decrease the risk of stroke.

Description of the intervention

Carotid endarterectomy has been shown in large, well-conducted randomised controlled trials (RCTs) to reduce the risk of stroke in patients with recently symptomatic, severe (greater than 70%) internal carotid artery stenosis (ECST 1991; NASCET 1991). In a pooled analysis of data from these RCTs of endarterectomy versus medical treatment, surgery was of marginal benefit in terms of the five-year risk of ipsilateral ischaemic stroke in those with 50% to 69% stenosis, and was highly beneficial in those with 70% stenosis or greater without near occlusion (Rothwell 2003; Rerkasem 2011). These benefits were seen despite the significant perioperative risks associated with carotid endarterectomy. The risk of stroke or death within 30 days of the operation was between 5% and 7% in the trials. If the risk of perioperative stroke could be reduced, the benefits from carotid endarterectomy would be greater. Thus it is important to make the operation as safe as possible.
Some perioperative strokes occur during the operative procedure and may relate to reduced blood flow during carotid artery clamping. If the onset of such strokes could be recognised early, it may be possible to reverse the ischaemia by placing a shunt across the clamped artery, thereby increasing blood flow. In patients operated on under general anaesthetic, the development of a new stroke is only recognised after recovery from the anaesthetic. In order to minimise the operative risk of stroke, several different approaches to shunting have been adopted when the procedure

is performed under general anaesthetic: namely the placement of a shunt in all patients (Javid 1979; Thompson 1979; Gumerlock 1988); the placement of a shunt in some patients thought to be at risk of an operative stroke (Ricotta 1983; Sundt 1986; Buche 1988; Schweiger 1988; Steiger 1989); or avoiding a shunt altogether (Prioleau 1977; Ott 1980; Reddy 1987). The avoidance of a shunt is based on the fact that only a small minority of patients do not tolerate arterial clamping without a shunt. Shunting may be associated with risks such as intimal damage promoting early postoperative thrombosis and late restenosis, which cause stroke. Thus, to many people, the selective method appears to be the most appropriate because it implies that only those patients who are at risk of having a stroke during carotid clamping are exposed to the risks of shunt placement. However, there is little consensus about the best way of identifying those patients who are at risk of stroke during the procedure. Several methods have been used to identify patients at risk of stroke including preoperative assessment (e.g. a history of recent stroke or occlusion of the contralateral artery), and a variety of techniques designed to directly or indirectly monitor cerebral blood flow during surgery. Techniques for monitoring blood flow during surgery include electroencephalographic monitoring, somatosensory evoked potential monitoring, transcranial Doppler monitoring, and measurement of the internal carotid artery back pressure (Rerkasem 2010). However, these methods are not reliable for detecting intraoperative stroke (Bass 1989; Gnanadev 1989; Kresowik 1991; Kearse 1992).

How the intervention might work

Performing carotid endarterectomy in awake patients under local anaesthetic offers the advantage of accurate assessment of the clinical state of the patient during surgery and during the early postoperative period (Benjamin 1993). Any neurological change, either during test clamping or during surgery itself, can be detected early and therefore allow more appropriate use of selective shunting in these patients. In addition, the cardiac and pulmonary morbidity of general anaesthetic may be avoided (Corson 1987; Becquemin 1991). There is also the suggestion that operation under local anaesthetic may be associated with an overall shorter hospital stay, and lower costs (Godin 1989; McCarthy 2001; Gurer 2003).

However, carotid endarterectomy under local anaesthetic may be associated with certain problems. The operation may be technically more difficult, which may increase the risk of a poor result from surgery. Patients may also undergo undue stress and pain during the operation, which may result in an increased risk of myocardial ischaemia. Finally, some surgeons may find performing the operation under local anaesthetic stressful. It is also possible that there may be certain advantages to operating under general anaesthetic. For example, there is some evidence that general anaesthetics reduce cerebral metabolic rate and may have a neuroprotective effect in the presence of ischaemia (Wells 1963; Michenfelder 1975; Markowitz 1984).

Why it is important to do this review

Carotid surgery is one of the most common types of vascular surgery. To date, there is no clear evidence that carotid endarterectomy performed under local anaesthesia is associated with reduced mortality. This issue is particularly important in older patients who comprise the majority of patients who need this type of surgery. The only reliable way to assess the relative risks and benefits of carotid endarterectomy under local anaesthetic versus general anaesthetic is by direct comparison in RCTs. We therefore undertook a systematic review of all such trials. This systematic review is an update of a Cochrane Review first published in 1996 and previously updated in 2004 and 2008 (Tangkanakul 1996; Rerkasem 2004; Rerkasem 2008).

OBJECTIVES

To determine whether carotid endarterectomy under local anaesthetic: (1) reduces the risk of perioperative stroke and death compared with general anaesthetic; (2) reduces the complication rate (other than stroke) following carotid endarterectomy; and (3) is acceptable to patients and surgeons.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised and quasi-randomised trials that compared local with general anaesthetic for carotid endarterectomy and that measured clinically relevant outcomes were eligible for inclusion.

Types of participants

We considered trials that included any type of patient undergoing unilateral or bilateral carotid endarterectomy to be eligible for inclusion, whether the initial indication was symptomatic or asymptomatic carotid disease.

Types of interventions

We sought to identify all trials comparing carotid endarterectomy under general anaesthetic of any type with carotid endarterectomy under local anaesthetic of any type, including both epidural and skin or deep infiltration.

Types of outcome measures

Primary outcomes

The primary outcome was the proportion of patients who had a stroke of any kind (i.e. fatal or non-fatal, contralateral or ipsilateral or brainstem, haemorrhage or infarction) within 30 days of surgery, and during long-term follow-up.

Secondary outcomes

Secondary outcomes included the following.

1. Stroke ipsilateral to the operated artery within 30 days of operation and during long-term follow-up.
2. Deaths from all causes within 30 days of surgery. We tried to classify each death as stroke-related, related to other vascular disease (cardiac disease, pulmonary embolism, haemorrhage or other vascular disease) or non-vascular.
3. The proportion of patients who had a stroke or died within 30 days of surgery.
4. Any myocardial infarction (fatal or non-fatal) within 30 days of surgery.
5. Other significant complications related to surgery (e.g. local haemorrhage from the artery or neck wound, pulmonary complications including pneumonia, pulmonary embolism, atelectasis, prolonged intubation and pulmonary oedema, and cranial nerve palsies).
6. The numbers of participants with raised or lower blood pressure (hypertension or hypotension) during or after surgery.
7. The percentage of participants in whom a shunt was used during surgery.
8. The total duration of hospital and intensive care unit stay.
9. The overall satisfaction and preference of participants with each type of procedure. We hoped this would indirectly assess outcomes such as pain and anxiety during and after the procedure.
10. The overall satisfaction and preference of surgeons.
11. The feasibility of carrying out carotid endarterectomy under local anaesthetic. This was assessed by calculating the percentage of participants allocated to have the surgery under local anaesthetic but who had crossed over to general anaesthetic. We tried to divide further into those patients who had their choice of anaesthetic changed before the procedure was started and those who converted from local to general anaesthesia once the procedure had started.

Search methods for identification of studies

See the 'Specialized register' section in the Cochrane Stroke Group module. No language restriction was used in the searches and we arranged for translation of all possibly relevant non-English language publications.

Electronic searches

We searched the Cochrane Stroke Group Trials Register in September 2013. In addition we searched the following electronic bibliographic databases from inception to 30 September 2013: the Cochrane Central Register of Controlled Trials (CENTRAL, *The Cochrane Library* 2013 Issue 8, Appendix 1), MEDLINE (Ovid, Appendix 2), and EMBASE (Ovid, Appendix 3). We developed the search strategies with the help of the Cochrane Stroke Group Trials Search Co-ordinator.
We also systematically searched the conference proceedings database Index to Scientific and Technical Proceedings (ISTP) (BIDS) (1980 to September 2013) using the terms 'carotid' and 'trial or random*'.

Searching other resources

1. We handsearched the following journals:
   i) *Annals of Surgery* (1981 to September 2013);
   ii) *Annals of Vascular Surgery* (1995 to September 2013);
   iii) *Vascular* (previously *Cardiovascular Surgery*) (1995 to September 2013);
   iv) *European Journal of Vascular and Endovascular Surgery* (previously *European Journal of Vascular Surgery*) (1988 to September 2013);
   v) *Journal of Vascular Surgery* (1995 to September 2013); and
   vi) *Stroke* (1995 to September 2013).
2. We reviewed the reference lists of all relevant studies.
3. For a previous version of the review we advertised the review in Vascular News, a newspaper for European vascular specialists (August 2001) and handsearched the following journals:
   i) *British Journal of Surgery* (1985 to 2002);
   ii) *International Journal of Angiology* (1995 to 2002);
   iii) *Journal of Cardiovascular Surgery* (1995 to 2002);
   iv) *Neurology* (1995 to 2002);
   v) *Neurosurgery* (1995 to 2002);
   vi) *Surgical Neurology* (1995 to 2002); and
   vii) *World Journal of Surgery* (1978 to 2002).

Data collection and analysis

Three authors (TV, WC, KR) independently collected data, including details of methods, participants, setting, context, interventions, outcomes, results, publications and investigators. We performed meta-analysis using RevMan 5.2 (RevMan 2012).

Selection of studies

Three authors (TV, WC, KR) independently read the titles and abstracts of the records obtained from the searches and excluded obviously irrelevant studies. We obtained the full-text articles of potentially relevant studies and the same authors independently selected studies for inclusion based on the predefined criteria. We resolved any disagreements through discussion.

Data extraction and management

We extracted details of the method of randomisation, the blinding of outcome assessments, losses to follow-up, cross-overs and exclusions after randomisation from the publications. We also compared patient characteristics (age, sex, vascular risk factors, and indication for surgery) and details of the operation (type of cerebral monitoring, use of carotid patching, use of shunts, use of perioperative antiplatelet therapy) between the treatment groups in each trial. Also, although asymptomatic patients were included in some studies, the data were not available in sufficient detail to allow separate analysis of the outcomes of carotid endarterectomy in symptomatic and asymptomatic patients. However, it is unlikely that the relative effect of local versus general anaesthesia will vary qualitatively with symptom status.

Assessment of risk of bias in included studies

Three authors (TV WC KR) independently assessed the methodological quality of the included trials using the Cochrane risk of bias tool (Higgins 2011). We resolved disagreements in the methodological assessment by reaching consensus through discussion. If an item was assessed as unclear, we contacted trialists for clarification and to request missing information.

Measures of treatment effect

We estimated treatment effect for the following outcomes within 30 days of surgery: stroke, death, stroke or death, myocardial infarction, local haemorrhage, cranial nerve injuries, and shunted arteries. Peto odds ratios (OR) and corresponding 95% confidence intervals were calculated for each outcome.

Unit of analysis issues

An event is the onset of an adverse outcome. We extracted the outcome events reported for each study. Some studies included patients who had bilateral operations, but only reported the number of patients, and not arteries, in each group. However, since bilateral carotid endarterectomy was unusual, we used the number of patients as the number of operations in such studies. Where possible we used the number of patients, not the number of arteries in the analysis.

Dealing with missing data

When data were missing, we contacted the corresponding author or a co-author to request missing information. When missing data could not be obtained, we analysed only the available data.

Assessment of heterogeneity

We assessed heterogeneity between study results using the I^2 statistic (Higgins 2003). This measure describes the percentage of total variation across studies due to heterogeneity rather than chance. An I^2 value over 75% was considered to indicate a high level of heterogeneity.

The I^2 statistic may be interpreted as follows:

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity; and
- 75% to 100%: considerable heterogeneity.

Assessment of reporting biases

In an effort to minimize the impact of reporting biases we sought to identify all relevant trials, including unpublished studies, by searching not only MEDLINE and EMBASE, but also the Cochrane Stroke Group Trials Register. In addition, we handsearched relevant journals and reviewed the reference lists of all relevant studies. In the previous version of this review we advertised the review in *Vascular News*, a newspaper for European vascular specialists. We did not impose any language restriction in the searches and we arranged translation of all relevant non-English language papers. Given a sufficient number of studies, publication bias was to be assessed by constructing funnel plots.

Data synthesis

We calculated proportional risk reductions based on a weighted estimate of the odds ratio using the Peto method (APT 1994). We calculated a pooled Peto OR and 95% CI for the following outcomes that occurred within 30 days of surgery: stroke, death, stroke or death, myocardial infarction, local haemorrhage, cranial nerve injuries, and shunted arteries.

Subgroup analysis and investigation of heterogeneity

Where there was considerable heterogeneity, we investigated the explanation for such interactions.

Sensitivity analysis

When the decisions for the process undertaken in this systematic review were arbitrary or unclear, we applied sensitivity analyses. For example, both fixed-effect and random-effects meta-analyses were performed to evaluate the consistency of the results, or pooled estimates of all studies' results compared with the results with studies of poorer quality excluded.

RESULTS

Description of studies

Results of the search

For this review we updated our previous searches of the Cochrane Stroke Group Trials Register, MEDLINE, EMBASE and ISTP. We also searched CENTRAL. We reviewed a total of 2392 references from the searches and obtained the full paper copy of 43 trial reports. We identified 14 RCTs.

Included studies

We included 14 RCTs, involving 4596 operations, which compared local and general anaesthetic for carotid endarterectomy. Most studies were small except the GALA trial, which reported on 3526 operations (GALA 2008). All studies were published in English except four, which were translated from French (Pluskwa 1989), German (Binder 1999), Serbian (Sindelic 2004), and Czech (Mrozek 2007) into English. There were two reports from one trial (McCarthy 2004). Initially the first report was published in 2002 with 67 participants and then, in 2004, another article was published including data from another hospital with a total of 176 participants (McCarthy 2004).

Since publication of the previous version of this review (Rerkasem 2008), we identified five new studies that appeared to meet the inclusion criteria (Mrozek 2007; Ebner 2008; Luchetti 2008; Mazul-Sunko 2010; Moritz 2010). Two studies were published in 2008, but they were not included in the previous version due to delayed publication (Ebner 2008; Luchetti 2008). One Czech paper was published in 2007, but this was missed because the journal was not included in MEDLINE or EMBASE (Mrozek 2007). This paper was retrieved from the Cochrane Stroke Group Trials Register. Another article was published in 2010 and was retrieved from the Cochrane Stroke Group Trials Register (Mazul-Sunko 2010). One trial was subsequently excluded (Ebner 2008), leaving four new studies for inclusion in the review (Luchetti 2008; Mrozek 2007; Moritz 2010; Mazul-Sunko 2010). We found no ongoing studies.

Thirteen studies used a cervical block and one study (Pluskwa 1989) used an epidural block to provide local anaesthesia. All studies used standard medication in the general anaesthetic group.

Ten trials reported the indication for shunting (Forssell 1989; Binder 1999; Sbarigia 1999; McCarthy 2004; Kasprzak 2006; Mrozek 2007; Luchetti 2008; GALA 2008; Moritz 2010; Mazul-Sunko 2010). One trial used intraluminal shunting in all patients (Binder 1999). One trial aimed to follow patients up to one year (GALA 2008). Four trials indicated the period of follow-up as follows: 30 postoperative days (Sbarigia 1999; Kasprzak 2006), two postoperative days (Binder 1999), and the time of hospital discharge (Forssell 1989). In the other trials, the period of follow-up was not stated but appeared to be up to the time of hospital discharge.

In most studies important outcomes were not assessed. Only the GALA trial determined whether the strokes were ipsilateral to the operated artery (GALA 2008). However, most strokes will have been ipsilateral. The GALA trial was the only study that reported the cause of death and the severity of stroke in terms of disability (GALA 2008). Patient satisfaction was formally assessed in only one trial (McCarthy 2004). Surgeon satisfaction was not formally assessed.

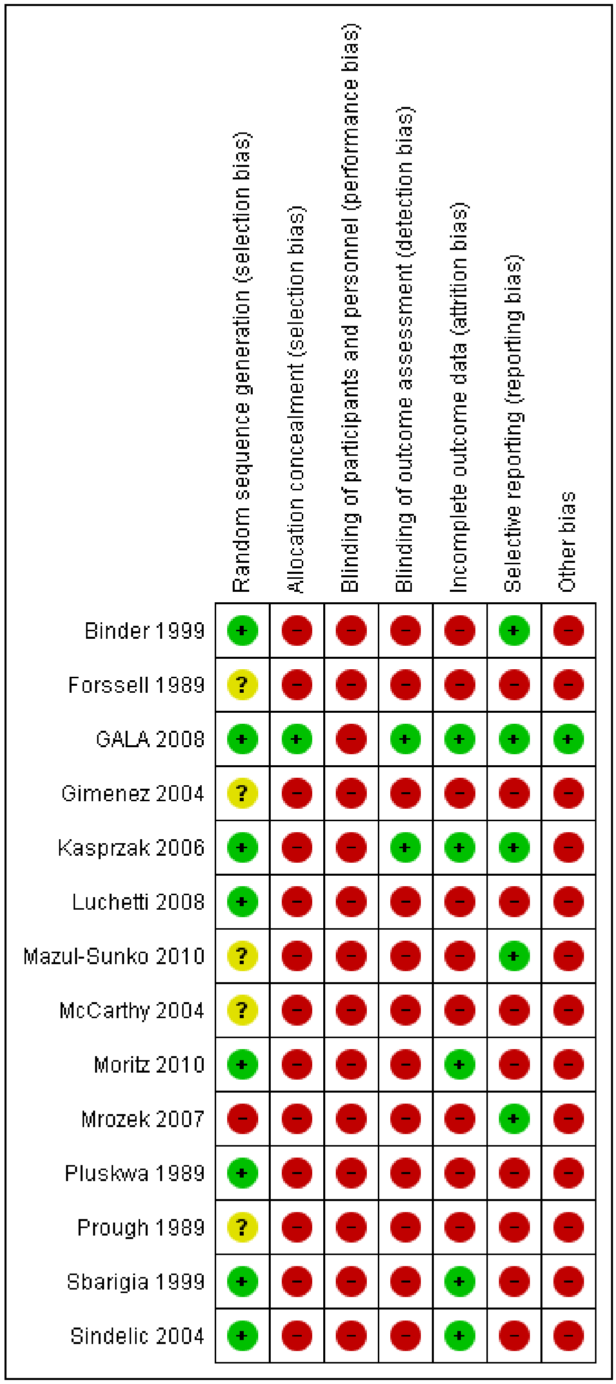
Excluded studies

We excluded one trial because the randomised allocation was based on the rotation of the two anaesthetists who could perform cervical plexus block (Ebner 2008).

Risk of bias in included studies

One of the 14 RCTs was published as an abstract (Gimenez 2004). For this study, only data from the abstract and oral presentation were available. In general, reporting of methodology was poor. The overall results of the risk of bias analysis are summarized in Figure 1.

Figure 1. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

In all studies, allocation by randomisation was reported. However, only six papers indicated the method of randomisation. This included block randomisation (Binder 1999; GALA 2008), computer randomisation (Kasprzak 2006; Luchetti 2008; Moritz 2010), and date of birth (Mrozek 2007). The methods used for randomisation in the remaining trials were unclear.

Blinding

All studies were unable to blind patients and surgical teams to randomised treatment allocation. In most trials, the blinding of outcome assessment was unclear. In three trials outcomes were assessed by neurologists who were blind to the type of anaesthesia used (Sbarigia 1999; Kasprzak 2006; GALA 2008).

Incomplete outcome data

Most studies did not report how incomplete outcome data was handled. However, six studies did report this information (Sbarigia 1999; McCarthy 2004; Sindelic 2004; Kasprzak 2006; GALA 2008; Moritz 2010). In six studies, some patients who were randomised to have surgery under local anaesthesia actually had surgery under general anaesthesia (Forssell 1989; Binder 1999; Sbarigia 1999; Kasprzak 2006; GALA 2008; Moritz 2010). Apart from two RCTs (GALA 2008; Moritz 2010), the reasons for the change were usually unclear, and these patients were excluded from the analysis in five trial reports (Forssell 1989; Binder 1999; Sbarigia 1999; GALA 2008; Moritz 2010). In one trial (Forssell 1989), 11 (11%) patients underwent staged bilateral endarterectomies and were randomised twice. Some of these patients may have had one operation under general anaesthesia and the other under local anaesthesia.

Selective reporting

Most studies did not indicate prespecified outcomes or report all prespecified outcomes. Only six studies reported all expected outcomes that were prespecified (Binder 1999; GALA 2008; Kasprzak 2006; Mazul-Sunko 2010; Moritz 2010; Mrozek 2007).

Other potential sources of bias

Regarding allocation concealment, two trials used sequentially numbered sealed envelopes but it was not stated if these were opaque (Forssell 1989; Sbarigia 1999). The GALA 2008 study utilised central allocation, while in 11 trials the method of concealment of allocation was unclear.
We were able to assess other bias, including measurement bias and funding bias in one study (GALA 2008).

Only the GALA trial clearly reported on the major differences in baseline prognostic factors between the two groups of patients (GALA 2008), although some studies provided limited data. Only four trials commented on the use of patching: two trials used a selective patch approach (Sbarigia 1999; Kasprzak 2006), one used patching in all patients (Binder 1999) and one study used various patching approaches (GALA 2008). Only the GALA trial reported on perioperative antiplatelet therapy (GALA 2008).

Effects of interventions

We included data from 14 randomised trials (4596 operations) in this review. We only assessed outcomes within 30 days of surgery, because none of the included studies reported long-term results.

Any stroke within 30 days of operation

There were 149 reported strokes of any type within 30 days of surgery. There was no statistically significant difference in the incidence of stroke between the local anaesthesia group and the general anaesthesia group. The incidence of strokes in the local anaesthesia group was 3.2% compared to 3.5% in the general anaesthesia group (Peto OR 0.92, 95% CI 0.67 to 1.28, Analysis 1.1). Only the GALA trial data allowed a comparison between ipsilateral and contralateral stroke (GALA 2008), and reported the rate of ipsilateral stroke as 57/1771 (3.2%) in local anaesthesia and 54/1752 (3.1%) in general anaesthesia.

Death within 30 days of operation

There were 52 deaths: 16 due to coronary artery diseases, 27 due to stroke and 9 due to other causes. There were 20 deaths (0.9%) in the local anaesthesia group compared to 32 deaths in the general anaesthesia group (1.5%). There was no statistically significant difference in death rates (Peto OR 0.62, 95% CI 0.36 to 1.07, Analysis 1.2).

Stroke or death within 30 days of operation

The rate of stroke or death in the local anaesthesia group was 3.6% compared with 4.2% in the general anaesthesia group. There was no statistically significant difference in the rate of stroke or death (Peto OR 0.85, 95% CI 0.63 to 1.16, Analysis 1.3).

Myocardial infarction within 30 days of operation

Twenty-three patients suffered a myocardial infarction within 30 days of surgery. Fourteen patients (0.6%) in the local anaesthesia group had a myocardial infarction compared with nine patients (0.4%) in the general anaesthesia group). There was no statistically significant difference between the groups in the rate of myocardial infarction (Peto OR 1.53, 95% CI 0.67 to 3.47, Analysis 1.4). The 95% CI was wide.

Other operative complications

Local haemorrhage

Five studies reported the rate of haemorrhage from the wound. There were 314 haemorrhages. Haemorrhage was reported in 7.7% of patients in the local anaesthesia group compared with 8.1% of patients in the general anaesthesia group. There was no statistically significant difference between the groups (Peto OR 0.95, 95% CI 0.75 to 1.19, Analysis 1.5). There was no indication of the severity of these bleeds.

Cranial nerve injuries

Four trials reported cranial nerve palsies. Eleven per cent of patients in the local anaesthesia group had cranial nerve injuries compared with 9.7% of general anaesthesia patients. There was no statistically significant difference between the groups (Peto OR 1.17, 95% CI 0.95 to 1.44, Analysis 1.6).

Pulmonary complications

One trial reported on pulmonary complications (Kasprzak 2006), and found no statistically significant difference in the rate of pneumonia under local anaesthesia compared with general anaesthesia. The GALA trial reported on pulmonary embolism as an outcome and reported no events in either treatment group (GALA 2008).

Blood pressure

Twelve trials recorded blood pressure during and after surgery. However, the studies did not consistently report the number of patients with significant hypotension or hypertension or mean arterial pressure during and after surgery. Furthermore, the definitions of hypertension and hypotension varied between trials. We have therefore simply described the results.

Six reported that blood pressure dropped in the general anaesthesia group after induction of anaesthesia (Forssell 1989; Pluskwa 1989; Prough 1989; McCarthy 2004; Sindelic 2004; GALA 2008). In one trial, more patients in the general anaesthesia group had significant hypotension during or after surgery compared with the local anaesthesia group (25% versus 7%) (Forssell 1989). However, this was not confirmed in another trial (Pluskwa 1989). The GALA trial reported on the manipulation of blood pressure (GALA 2008). More general anaesthesia than local anaesthesia patients had their blood pressure manipulated up (43% compared with 17%), and more local anaesthesia patients had their blood pressure manipulated down or not manipulated at all (74% compared with 41%) during or after surgery. The difference in blood pressure manipulation between the two trial arms was statistically significant (GALA 2008).

Five trials showed that blood pressure tended to increase during clamping of the carotid artery in the local anaesthesia group compared with the general anaesthesia group (Forssell 1989; Pluskwa 1989; Prough 1989; Gimenez 2004; Luchetti 2008) but this was not found in another trial (McCarthy 2004). In two trials, there were significantly more patients with hypertension in the local anaesthesia group during surgery than in the general anaesthesia group (Forssell 1989: 36% versus 0%; Pluskwa 1989: 80% versus 20%). Three trials reported that during surgery the mean arterial pressure in the local anaesthesia group was higher than in the general anaesthesia group (Mrozek 2007; Luchetti 2008; Moritz 2010). Two studies suggested that hypotension was more common in the postoperative period with local anaesthesia than with general anaesthesia (Pluskwa 1989; Prough 1989). Two trials found that patients operated on under general anaesthesia had more postoperative (within day one) hypertension than those operated on under local anaesthesia (Gimenez 2004; Kasprzak 2006).

Shunting

Eight studies reported the number of arteries shunted. The use of local anaesthetic was associated with significantly fewer shunts than general anaesthetic. Fifteen per cent of patients in the local anaesthesia group had their arteries shunted compared with 42% of of patients in the general anaesthesia group. As there was significant heterogeneity between studies (I^2 = 91%), we used the random-effects model to pool the results (OR 0.24, 95% CI 0.08 to 0.73, Analysis 1.7).

Hospital stay

The duration of hospital stay was reported in three trials (Binder 1999; McCarthy 2004; GALA 2008). The average time in hospital was not significantly different between the local and general anaesthesia groups.

Patient satisfaction

Patient satisfaction was formally assessed in one study (McCarthy 2004). There was no statistically significant difference in satisfaction between anaesthetic techniques. In Forssell 1989, of the three patients who had repeat carotid endarterectomies (having had a local anaesthetic for the first operation) none refused repeat randomisation (Forssell 1989). Forssell 1989 reported that one patient in the local anaesthesia group became extremely agitated during the procedure. Another trial evaluated patient satisfaction by a questionnaire (Binder 1999). They found that both types of anaesthesia were equally acceptable but the publication did not describe the questionnaire in detail. All patients preferred the same type of anaesthesia if they needed a second operation, except one patient in the local anaesthesia group (total 27 patients) who wished to have general anaesthesia for any further surgery. Mrozek 2007 asked patients about any unpleasant sensations after surgery and during the postoperative period. A minimum amount of unpleasant sensation was reported for both types of anaesthetic after surgery and during the postoperative period (Mrozek 2007).

Surgeon satisfaction

The satisfaction or preference of the surgeon was not assessed in any of the trials.

Feasibility of performing operation under local anaesthetic

One trial recorded the number of patients randomised to have surgery under local anaesthesia, but who had surgery under general anaesthesia (Forssell 1989). Eight patients crossed over from local to general anaesthesia whilst none switched from general to local anaesthesia. The most common reasons for cross-over were that the patient changed his or her consent or that the patient had unstable cardiac disease. Seven out of eight patients had their anaesthetic changed before the procedure was started. In another trial, six patients were switched from local to general anaesthesia due to severe agitation (three patients), insufficient anaesthesia under local anaesthesia (two patients), and intravascular injection during application of local anaesthetic agent (one patient) (Kasprzak 2006). Three out of six patients had their anaesthetic changed before the procedure was started. No general anaesthesia cases were switched to local anaesthesia in this study (Kasprzak 2006). In the GALA trial, 167 patients were crossed over before initiation of anaesthesia: 75 patients crossed over from local to general anaesthesia whilst 92 switched from general to local anaesthesia (GALA 2008). Patients allocated to general anaesthesia were more likely to cross over due to a medical decision, whereas patients allocated local anaesthesia were more likely to cross over due to the patient's preference. Sixty-nine out of 1771 (3.9%) local anaesthesia patients were switched to general anaesthesia after initiation of anaesthesia, 17 before and 52 after the start of surgery. In one trial, two patients switched from local to general anaesthesia (Moritz 2010) and in another trial, no patients switched from local anaesthesia to general anaesthesia (Mrozek 2007).

DISCUSSION

Summary of main results

We identified 14 studies comparing adverse outcomes for carotid endarterectomy performed under local anaesthesia with adverse outcomes for carotid endarterectomy performed under general anaesthesia. Meta-analysis of the randomised studies showed that there was no statistically significant difference between the anaesthesia groups in the proportion of patients who had a stroke, or died or a myocardial infarction within 30 days of surgery.

Overall completeness and applicability of evidence

The pooled analyses showed no statistically differences in the rate of stroke or death between the two types of anaesthetic technique used during carotid endarterectomy. There was a non-significant trend towards lower operative mortality with local anaesthesia (Peto OR 0.62, 95% CI 0.36 to 1.07), but neither the GALA 2008 study nor the pooled analysis were adequately powered to reliably detect an effect on mortality. It is unlikely that a sufficiently large (about 20,000 patients) randomised trial will be performed in the foreseeable future to confirm or refute this possible effect on mortality.

Twelve trials recorded blood pressure during and after surgery, but these data were difficult to interpret. It is interesting to note that two studies suggested that hypotension was more common in the postoperative period with local anaesthesia (Pluskwa 1989; Prough 1989). This is may be due to the high rate of blood pressure being manipulated down, but we could not find any hard evidence to support this at the present time.

The choice of anaesthetic technique will therefore depend on the clinical situation and the preferences of individual patients and their surgeon. In some patients the operation may be technically more difficult under local anaesthesia (e.g. in patients with short, wide necks). Some patients, perhaps as many as 10%, will refuse to have the operation under local anaesthesia (Forssell 1989), and some surgeons may feel more comfortable performing the operation under general anaesthesia.

GALA 2008 was also designed to determine whether the type of anaesthesia influenced the cost of endarterectomy. These data showed that the expected costs of carotid endarterectomy under local anaesthesia are less than those under general anaesthesia (mean difference GBP 178) (Gomes 2010). This difference was mainly due to the longer length of stay in an intensive care unit and the use of consumables such as shunts and patches. A post hoc subgroup analysis (40 patients) from the GALA 2008 study investigated the influence of local versus general anaesthesia on postoperative neurocognitive function. This study showed that local anaesthesia beneficially influenced early postoperative neurocognitive functions. Mazul-Sunko 2010 found shunting to be the only parameter associated with neurocognitive decline on the first day after carotid endarterectomy. Local anaesthesia was hypothesised to offer an indirect benefit due to the reduced rate of shunting (Mazul-Sunko 2010). However, given the small size of these studies, early postoperative neurocognitive function requires further investigation (Weber 2009).

Quality of the evidence

There were significant problems in the quality of the randomised trials. The method used for allocation concealment was inadequately reported in most of the included studies. The duration of follow-up was short in all included studies. It was also unclear in most of the studies whether the outcomes had been assessed blind to treatment allocation. It is well known that studies that have neurologists as assessors are associated with higher stroke and death rates (Rothwell 1996; Rerkasem 2009). Only two studies reported that they had neurologists as blinded assessors (Kasprzak 2006; GALA 2008). At least five of the trials excluded some randomised patients from the analysis, especially patients who crossed over anaesthetic type (Forssell 1989; Binder 1999; Sbarigia 1999; GALA 2008; Moritz 2010). If excluded patients differed from those patients who remained in the analysis, the results may be biased.

Potential biases in the review process

Many studies reported the number of arteries rather than the number of patients. Also, it was not clear how many of the strokes were ipsilateral, and how many were disabling. Few trials assessed patients' or surgeons' satisfaction or preference, or the duration of intensive care and overall hospital stay.

There was marked heterogeneity between studies in the use of shunts with both types of anaesthesia. This in part may be reflected by the different policies in shunting between studies. For example, in the Binder 1999 study all patients were shunted irrespective of treatment allocation. All patients in the local anaesthetic group were shunted despite the fact that surgeons preferred local anaesthetic due to the low rate of shunting. Apart from this trial, the remaining seven RCTs in the pooled analysis used selective shunting. For six RCTs, although the indication of shunting in the local anaesthesia group was not markedly different, the indication for shunting in the general anaesthesia group varied considerably. One study used stump pressure measurement and clinical judgment (Forssell 1989), while another study used a mix of transcranial Doppler, stump pressure measurement, EEG, and clinical judgment (GALA 2008). Although another two studies used somatosensory evoked potentials, the indication was not identical (Kasprzak 2006; Moritz 2010). One trial carried out shunting routinely, but the actual rate of shunting was 82% because of expected technical difficulties with shunt insertion in 18% of the cases in the general anaesthetic group (Mazul-Sunko 2010).The remaining three RCTs did not report the indication for shunting in the general anaesthesia group (Sbarigia 1999; Mrozek 2007; Moritz 2010). All of these differences may explain the considerable heterogeneity in the use of shunts.

Agreements and disagreements with other studies or reviews

It is also interesting to note that in our previous review, the non-randomised studies showed consistently lower risks of operative stroke and death when carotid endarterectomy was done under local anaesthesia (Rerkasem 2008). With the addition of GALA 2008 study the meta-analyses show that these apparent differences were probably due to biases in the non-randomised comparisons, illustrating the importance of adequately powered randomised controlled trials (Collins 2001).

AUTHORS' CONCLUSIONS

Implications for practice

The proportion of patients who had a stroke or died within 30 days of surgery did not differ significantly between the two types of anaesthetic techniques used during carotid endarterectomy. This systematic review provides evidence to suggest that patients and surgeons can choose either anaesthetic technique, depending on the clinical situation and their own preferences.

Implications for research

There was a non-significant trend towards lower operative mortality with local anaesthesia. However, our pooled analysis was not adequately powered to reliably detect an effect on mortality. More randomised controlled trials comparing local anaesthesia with general anaesthesia are needed to assess the potential beneficial effect on mortality.

ACKNOWLEDGEMENTS

We would like to thank Dr Chanpong Tangkanakul, Dr Carl Counsell, Professor Charles Warlow, Mr Richard Bond and Professor Peter Rothwell for their contribution to previous versions of this review; Hazel Fraser for providing us with references to relevant trials from the Cochrane Stroke Group's Trials Register; Professor Graeme Hankey, Ms Brenda Thomas, Dr Paul Nederkoorn, Mr Brian Stafford and Ms Ann Fonfa for commenting on the manuscript and Dr Branka Mazul-Sunko for providing unpublished data for a trial. Professor Kittipan Rerkasem was funded by The Thailand Research Fund (RSA5580008) and Faculty of Medicine, Chiang Mai University.

Ongoing trials

If anyone is aware of any randomised trials that we have omitted please contact Professor Kittipan Rerkasem.

R E F E R E N C E S

References to studies included in this review

Binder 1999 *{published and unpublished data}*

Binder M, Fitzgerald R, Fried H, Schwarz S. Carotid endarterectomy surgery in cervical block: an economic alternative to general anaesthesia? [Karotisdesobliteration in cervicalisblockade: eine okonomische alternative zur vollnarkose?]. *Gesundheitsökonomie und Qualitätsmanagement* 1999;**4**:19–24.

Forssell 1989 *{published data only}*

Forssell C. *Studies on risks and results in carotid artery surgery [dissertation]*. Malmo, Sweden: Lund University, 1991.

* Forssell C, Takolander R, Bergqvist D, Johansson A, Persson NH. Local versus general anaesthesia in carotid surgery. A prospective, randomised study. *European Journal of Vascular Surgery* 1989;**3**:503–9.

Takolander R, Bergqvist D, Hulthen L, Johansson A, Katzman PL. Carotid artery surgery. Local versus general anaesthetic as related to sympathetic activity and cardiovascular effects. *European Journal of Vascular Surgery* 1990;**4**:265–70.

GALA 2008 *{published and unpublished data}*

* GALA Trial Collaborative Group. General anaesthesia versus local anaesthesia for carotid surgery (GALA): a multicentre, randomised controlled trial. *Lancet* 2008;**372**: 2132–42.

Girn HRS, Dellagrammaticas D, Laughlan K, Gough MJ, GALA Trial Collaborators. Carotid endarterectomy: technical practices of surgeons participating in the GALA trial. *European Journal of Vascular and Endovascular Surgery* 2008;**36**:385–9.

Gomes M, Soares MO, Dumville JC, Lewis SC, Torgerson DJ, Bodenham AR, GALA Collaborative Group. Cost-effectiveness analysis of general anaesthesia versus local anaesthesia for carotid surgery (GALA Trial). *British Journal of Surgery* 2010;**97**:1218–25.

Gough MJ, Bodenham A, Horrocks M, Colam B, Lewis SC, Rothwell PM, et. al. GALA: an international multicentre randomised trial comparing general anaesthesiaversus local anaesthesia for carotid surgery. *Trials* 2008:doi: 10.1186/1745-6215-9-28.

Gough MJ, GALA trial Collaborators. The GALA trial - a summary of the findings. *European Journal of Vascular and Endovascular Surgery* 2008;**36**:505–6.

Weber CF, Friedl H, Hueppe M, Hintereder G, Schmitz-Rixen T, Zwissler B, et al.Impact of general versus local anesthesia on early postoperative cognitive dysfunction following carotid endarterectomy: GALA study subgroup analysis. *World Journal of Surgery* 2009;**33**:1526–32.

Wijeyaratne SM, Collins MA, Barth JH, Gough MJ. Jugular venous neurone specific enolase (NSE) increases following carotid endarterectomy under general, but not local, anaesthesia. *European Journal of Vascular and Endovascular Surgery* 2009;**38**:262–6.

Gimenez 2004 *{published data only}*

Gimenez A, Gonzales E, Lloret MD, Hospedales J, Bellmunt S, Vallespin J, et al.A comparison of general anaesthesia and loco-regional anaesthesia in surgery of the internal carotid artery and its repercussion on haemodynamic control. *Cardiovascular Surgery* 2003;**11**(Suppl 2):97.

Kasprzak 2006 *{published and unpublished data}*

Kasprzak P, Altmeppen J, Rosin L, Metz CH, Horn M, Jauch KW. Local versus general anaesthesia in carotid surgery - results of a prospective randomised study. *Cardiovascular Surgery* 1999;**7**(Suppl 1):16.

* Kasprzak PM, Altmeppen J, Angerer M, Mann S, Mackh J, Topel J. General versus locoregional anesthesia in carotid surgery: a prospective randomised trial. *VASA* 2006;**35**: 232–8.

Luchetti 2008 *{published data only}*

Luchetti M, Canella M, Zoppi M, Massei R. Comparison of regional anesthesia versus combined regional and general anesthesia for elective carotid endarterectomy: a small exploratory study. *Regional Anesthesia and Pain Medicine* 2008;**33**:340–5.

Mazul-Sunko 2010 *{published and unpublished data}*

Mazul-Sunko B, Hromatko I, Tadinac M, Sekulic A, Ivanec Z, Gvozdenovic A, et al.Subclinical neurocognitive dysfunction after carotid endarterectomy - the impact of shunting. *Journal of Neurosurgical Anesthesiology* 2010;**22**: 195–201.

McCarthy 2004 *{published data only}*

McCarthy RJ, Nasr MK, McAteer P, Horrocks M. Physiological advantages of cerebral blood flow during carotid endarterectomy under local anaesthesia.. *European Journal of Vascular and Endovascular Surgery* 2002;**24**: 215–21.

* McCarthy RJ, Trigg R, John C, Gough MJ, Horrocks M. Patient satisfaction for carotid endarterectomy performed under local anaesthesia. *European Journal of Vascular and Endovascular Surgery* 2004;**27**:654–9.

Moritz 2010 *{published data only}*

Moritz S, Schmidt C, Bucher M, Wiesenack C, Zimmermann M, Schebesch KM, et al.Neuromonitoring in carotid surgery: are the results obtained in awake patients transferable to patients under sevoflurane/fentanyl anesthesia?. *Journal of Neurosurgical Anesthesiology* 2010;**22**: 288–95.

Mrozek 2007 *{published data only}*

Mrozek Z, Koutna J, Marek O. Anesthesia options in carotid endarterectomy. *Anesteziologie a Intenzivni Medicina* 2007;**18**:202–9.

Pluskwa 1989 *{published data only}*

Pluskwa F, Bonnet F, Abhay K, Touboul C, Rey B, Marcandoro J, et al.Blood pressure profiles during carotid endarterectomy. Comparing flunitrazepam/fentanyl/nitrous oxide with epidural anaesthesia (author's translation).

Annales Françaises d'Anesthèsie et de Rèanimation 1989;**8**: 26–32.

Prough 1989 ***{published data only}***
Prough DS, Scuderi PE, McWhorter JM, Balestrieri FJ, Davis CH, Stullken EH. Hemodynamic status following regional and general anesthesia for carotid endarterectomy. *Journal of Neurosurgical Anesthesiology* 1989;**1**:35–40.

Sbarigia 1999 ***{published and unpublished data}***
* Sbarigia E, DarioVizza C, Antonini M, Speziale F, Maritti M, Fiorani B, et al.Locoregional versus general anesthesia in carotid surgery: is there an impact on perioperative myocardial ischemia? Results of a prospective monocentric randomized trial. *Journal of Vascular Surgery* 1999;**30**: 131–8.
Vizza C, Sbarigia E, Antonini M, Speziale F, Maritti M, Fiorani B, et al.Perioperative myocardial ischemia in patients treated with carotid surgery. Impact of the type of anesthesia (locoregional vs general). *Minerva Cardioangiologica* 1999; **47**(12):626–7.

Sindelic 2004 ***{published data only}***
Sindelic R, Viajkovic G, Davidovic L, Vujanac B, Vjestica M. Comparison of the influence of general and regional anesthesia on basic haemodynamic parameters during carotid endarterectomy. *Acta Chirurgica Iugoslavica* 2004; **51**:37–43.

References to studies excluded from this review

Ebner 2008 ***{published data only}***
Ebner FH, Trenti E, Baldinelli F, Natto M, Ebner H. Carotid endarterectomy: comparing anesthesia in awakened and intubated patients with general anesthesia. *Minerva Cardioangiologica* 2008;**56**(5 Suppl):29–34.

Additional references

APT 1994
Antiplatelet Trialists Collaboration. Collaborative overview of trials of antiplatelet therapy - I: Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. *BMJ* 1994;**308**: 81–106.

Bass 1989
Bass A, Krupski WC, Schneider PA, Otis SM, Dilley RB, Bernstein EF. Intraoperative transcranial doppler: limitations of the method. *Journal of Vascular Surgery* 1989; **10**:549–53.

Becquemin 1991
Becquemin JP, Paris E, Valverde A, Pluskwa F, Melliere D. Carotid surgery. Is regional anesthesia always appropriate?. *Journal of Cardiovascular Surgery* 1991;**32**:592–8.

Benjamin 1993
Benjamin ME, Silva MB, Watt C, McCaffrey MT, Burford-Foggs A, Flinn WR. Awake patient monitoring to determine the need for shunting during carotid endarterectomy. *Surgery* 1993;**114**:673–81.

Buche 1988
Buche M, Grenier Y, Schoevaerdts JC, Jaumin P, Ponlot R, Chalant CH. Comparative results after endarterectomy of internal carotid artery performed with or without a shunt. *Journal of Cardiovascular Surgery* 1988;**29**:428–31.

Collins 2001
Collins R, MacMahon S. Reliable assessment of the effects of treatment on mortality and major morbidity, I: clinical trials. *Lancet* 2001;**357**:373–80.

Corson 1987
Corson JD, Chang BB, Shah DM, Leather RP, DeLeo BM, Karmody AM. The influence of anesthetic choice on carotid endarterectomy outcome. *Archives of Surgery* 1987;**122**: 807–12.

ECST 1991
European Carotid Surgery Trialists Collaborative Group. MRC European Carotid Surgery Trial: interim results for symptomatic patients with severe (70-99%) or with mild (0-29%) carotid stenosis. *Lancet* 1991;**337**:1235–43.

Gnanadev 1989
Gnanadev DA, Wang N, Communale FL, Reile DA. Carotid artery stump pressure: how reliable is it in predicting the need for a shunt?. *Annals of Vascular Surgery* 1989;**3**:313–7.

Godin 1989
Godin MS, Bell WH, Schwedler M, Kerstein MD. Cost effectiveness of regional anesthesia in carotid endarterectomy. *American Surgeon* 1989;**55**:656–9.

Gomes 2010
Gomes M, Soares MO, Dumvile JC, Lewis SC, Torgerson DJ, Bodenham AR, et al.Cost-effectiveness analysis of general anaesthesia versus local anaesthesia for carotid surgery (GALA Trial). *British Journal of Surgery* 2010;**97**: 1218–25.

Gumerlock 1988
Gumerlock MK, Neuwelt EA. Carotid endarterectomy: to shunt or not to shunt. *Stroke* 1988;**19**:1485–90.

Gurer 2003
Gurer O, Yapici F, Enc Y, Cinar B, Ketenci B, Ozler A. Local versus general anaesthesia for carotid endarterectomy: report of 329 cases. *Vascular and Endovascular Surgery* 2003; **37**:171–7.

Higgins 2003
Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327**: 557–60.

Higgins 2011
Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Javid 1979
Javid H, Julian OC, Dye WS, Hunter JA, Najafi H, Goldin MD, et al.Seventeen-year experience with routine shunting in carotid surgery. *World Journal of Surgery* 1979;**3**:167–77.

Kearse 1992
Kearse LA, Brown EN, McPeck K. Somatosensory evoked potential sensitivity relative to electroencephalography for cerebral ischemia during carotid endarterectomy. *Stroke* 1992;**23**:498–505.

Kresowik 1991
Kresowik TF, Worsey MJ, Khoury MD, Krain LS, Shamma AR, Sharp WJ, et al.Limitations of electroencephalographic monitoring in the detection of cerebral ischemia accompanying carotid endarterectomy. *Journal of Vascular Surgery* 1991;**13**:439–43.

Markowitz 1984
Markowitz TP, Adinolfi MF, Kerstein MD. Barbiturate therapy in the postoperative endarterectomy patient with a neurologic deficit. *American Journal of Surgery* 1984;**148**: 221–3.

McCarthy 2001
McCarthy RJ, Walker R, McAteer P, Budd JS, Horrocks M. Patient and hospital benefits of local anaesthesia for carotid endarterectomy. *European Journal of Vascular and Endovascular Surgery* 2001;**22**:13–8.

Michenfelder 1975
Michenfelder JD, Milde JH. Cerebral protection by anesthetics during ischemia: (a review). *Resuscitation* 1975; **4**:219–33.

NASCET 1991
North American Symptomatic Carotid Endarterectomy Trial Collaborators. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. *New England Journal of Medicine* 1991; **325**:445–53.

Ott 1980
Ott DA, Cooley DA, Chapa L, Coelho A. Carotid endarterectomy without temporary intraluminal shunt. Study of 309 consecutive operations. *Annals of Surgery* 1980;**191**:708–14.

Prioleau 1977
Prioleau WH, Aiken AF, Hairston P. Carotid endarterectomy: neurologic complications as related to surgical techniques. *Annals of Surgery* 1977;**185**:678–83.

Reddy 1987
Reddy K, West M, Anderson B. Carotid endarterectomy without indwelling shunts and intraoperative electrophysiologic monitoring. *Canadian Journal of Neurological Sciences* 1987;**14**:131–5.

Rerkasem 2009
Rerkasem K, Rothwell PM. Temporal trends in the risks of stroke and death due to carotid endarterectomy for symptomatic carotid stenosis: an updated systematic review. *European Journal of Vascular and Endovascular Surgery* 2009; **37**:504–11.

Rerkasem 2010
Rerkasem K, Rothwell PM. Routine or selective carotid artery shunting for carotid endarterectomy and different methods of monitoring in selective shunting. *Stroke* 2010; **41**:e53–4.

Rerkasem 2011
Rerkasem K, Rothwell P. Carotid endarterectomy for symptomatic carotid stenosis. *Cochrane Database of Systematic Reviews* 2011, Issue 4. [DOI: 10.1002/14651858.CD001081.pub2]

RevMan 2012
The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). 5.2. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012.

Ricotta 1983
Ricotta JJ, Charlton MH, DeWeese JA. Determining criteria for shunt placement during carotid endarterectomy. EEG versus back pressure. *Annals of Surgery* 1983;**198**: 642–5.

Rothwell 1996
Rothwell PM, Slattery J, Warlow CP. A systematic review of the risk of stroke and death due to endarterectomy for symptomatic carotid stenosis. *Stroke* 1996;**27**:260–5.

Rothwell 2003
Rothwell PM, Eliasziw M, Gutnikov SA, Fox AJ, Taylor DW, Mayberg MR, et al.Analysis of pooled data from the randomised controlled trials of endarterectomy for symptomatic carotid stenosis. *Lancet* 2003;**361**:107–16.

Schweiger 1988
Schweiger H, Kamp HD, Dinkel M. Somatosensory evoked potentials (SEP) during carotid endarterectomy - end of shunt debate?. In: Boccalon H editor(s). *Angiology: strategy for diagnosis and therapeutics*. Paris: John Libbey Eurotext, 1988:353–5.

Steiger 1989
Steiger HJ, Schaffler L, Boll J, Liechti S. Results of microsurgical carotid endarterectomy. A prospective study with transcranial Doppler and EEG monitoring, and elective shunting. *Acta Neurochirurgica* 1989;**100**:31–8.

Sundt 1986
Sundt TM Jr, Ebersold MJ, Sharbrough FW, Piepgras DG, Marsh WR, Messick JM Jr. The risk-benefit ratio of intraoperative shunting during carotid endarterectomy. Relevancy to operative and postoperative results and complications. *Annals of Surgery* 1986;**203**:196–204.

Thompson 1979
Thompson JE. Complications of carotid endarterectomy and their prevention. *World Journal of Surgery* 1979;**3**: 155–65.

Weber 2009
Weber CF, Friedl H, Hueppe M, Hintereder G, Schmitz-Rixen T, Zwissler B, et al.Impact of general versus local anesthesia on early postoperative cognitive dysfunction following carotid endarterectomy: GALA study subgroup analysis. *World Journal of Surgery* 2009;**33**:1526–32.

Wells 1963
Wells BA, Keats AS, Cooly DA. Increased tolerance to cerebral ischemia produced by general anesthesia during temporary carotid occlusion. *Surgery* 1963;**54**:216–23.

References to other published versions of this review

Rerkasem 2004
Rerkasem K, Bond R, Rothwell PM. Local versus general anaesthesia for carotid endarterectomy. *Cochrane Database of Systematic Reviews* 2004, Issue 2. [DOI: 10.1002/14651858.CD000126]

Rerkasem 2008
Rerkasem K, Rothwell PM. Local versus general anaesthesia for carotid endarterectomy. *Cochrane Database of Systematic Reviews* 2008, Issue 4. [DOI: 10.1002/14651858.CD000126]

Tangkanakul 1996
Tangkanakul C, Counsell C, Warlow C. Carotid endarterectomy performed under local anaesthetic compared to general anaesthetic: a systematic review of the evidence. *Cochrane Database of Systematic Reviews* 1996, Issue 3. [DOI: 10.1002/14651858.CD000126]

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Binder 1999

Methods	RCT Block randomisation Blinding: unclear C: unclear Cross-over: yes, but number excluded during trial was unclear Losses to FU: none
Participants	Austria 1999 46 patients (46 operations) Age mean: 73 years (LA), 68 years (GA) Sex: unclear Comparability: unclear Indications for surgery: TIA, stroke, incidental diagnosis of carotid stenosis
Interventions	LA: superficial and deep block with bupivacaine GA: thiopental, vecuronium, fentanyl Patching: all cases Antiplatelet Rx: unclear Indication for shunting: all patients
Outcomes	Death, any stroke, TIA, myocardial infarction, time in hospital since surgery, bleeding, mean arterial blood pressure, shunted arteries
Notes	FU: 48 hours Ex: recent neurological deficit < 4 weeks, redo operation, recent myocardial infarction(< 2 months), ASA score $\geq$ 4, and any factor precluding randomisation such as pulmonary disease or refusal to participate in the study

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "46 Patienten nach Aufklarung and Unterzeichnung einer Einverstandniserklarung in die Studie aufgenommen und prospektiv randomisiert untersucht"
Allocation concealment (selection bias)	High risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Patients and surgeons were not blinded to treatment group

Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	Not reported
Selective reporting (reporting bias)	Low risk	All the study's prespecified outcomes of interest were reported
Other bias	High risk	Not reported

Forssell 1989

Methods	RCT C: unclear Blinding: unclear Sequentially numbered envelope Cross-overs: 8 LA performed under exclusions during trial: 8 cross-overs Losses to FU: none
Participants	Sweden 1985 to 1987 100 patients, 111 operations Age (mean): 66 years (LA), 63 years (GA) Male: 71% (LA), 64% (GA) Comparability: groups similar for vascular risk factors Indication for surgery: not reported
Interventions	LA: cervical block and skin infiltration with bupivacaine and mepivacaine or adrenaline GA: thiopental, isoflurane and bupivacaine or adrenaline skin infiltration Patching: not reported Antiplatelet Rx: not reported Indication for shunting: LA: neurological symptoms during/or after 1 minute test clamp; GA: stump pressure < 25 mmHg in TIA, stump pressure < 50 mmHg in vertebrobasilar insufficiency, always if previous stroke
Outcomes	Death, any stroke, myocardial infarction, wound haematoma, blood pressure, shunted arteries
Notes	FU: hospital stay Ex: consent refused, allergy to LA, ongoing heparin infusion, serious chronic cerebral insufficiency, uneasy during previous LA, randomisation miss, anxiety, simultaneous aortic repair, emergent operation

Risk of bias

Bias	Authors' judgement	Support for judgement

Random sequence generation (selection bias)	Unclear risk	Quote: "The remaining patients were randomised on 111 occasions into two groups, which were comparable (Table 2)"
Allocation concealment (selection bias)	High risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Patients and surgeons were not blinded to treatment group
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	Not reported
Selective reporting (reporting bias)	High risk	No prespecified outcomes were reported.
Other bias	High risk	Not reported

GALA 2008

Methods	RCT C: central trial office allocate and concealment Blinding: single blinding - independent assessor Block randomisation Cross-overs: 92/1751 (5.3%) GA patients and 75/1771 (4.2%) LA patients went to theatre, but received the opposite treatment allocation to that allocated at randomisation Losses to FU: 3/3523 (0.09%)
Participants	Multicentre RCT conducted mainly in Europe (95 centres), in 24 countries 2003 to 2008 3526 operations Age (mean): 69 years (LA), 70 years (GA) Male: 71% (LA), 70% (GA) Comparability: groups similar for vascular risk factors Indication for surgery: all patients with symptomatic or asymptomatic carotid stenosis for whom surgery was advised The reasons for using shunt varied in both the LA and GA groups depending on the practice of each trial site These reasons included: used routinely, drop velocity on TCD, unable to use TCD, contralateral occlusion or near occlusion, low stump pressure, contralateral carotid stenosis, recent stroke, unusual or damaged vein or arteries in head or neck, EEG or evoked potential change, blood pressure drop, falling brain oxygen level, operation converted to vein bypass and unknown
Interventions	LA versus GA

Outcomes	Primary outcome: proportion of patients alive, stroke free (including retinal infarction) and without myocardial infarction 30 days post-surgery Secondary outcomes: proportion alive and stroke free at 1 year and in the longer term, a comparison of health-related quality of life at 30 days and any surgical adverse events, re-operation and re-admission rates, the relative cost of the 2 methods of anaesthesia, length of stay and intensive and high dependency bed occupancy
Notes	FU: perioperative period (30 days after operation) and 1 year follow up Ex: a simultaneous bilateral carotid endarterectomy or carotid endarterectomy combined with another operative procedure such as coronary artery bypass surgery

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Central computerised randomisation
Allocation concealment (selection bias)	Low risk	Quote: "the office randomised patients to surgery under either general or local anaesthesia, stratified by centre and with balanced blocks of variable size, ensuring that allocation was completely concealed before the decision to randomise a patient and after baseline data were received"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "we could not blind patients or the surgical team to randomised treatment allocation"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "However, the independent stroke physician or neurologist who saw patients 1 month after surgery was unaware of the type of anaesthesia that the patients had received, although this blinding could be broken by the patient or by looking at hospital notes"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote in Figure 1: "21 incomplete follow-up, 1 no follow-up at all, 1 no post-surgery form, 19 no physician follow-up at one month five of these had patient follow-up at 1 year"
Selective reporting (reporting bias)	Low risk	All data were analysed and reported as predefined

Other bias	Low risk	Measurement bias: Quote: "a neurologist (CPW), unaware of treatment allocation, then prepared a summary for every patient that, depending on the outcome, was audited by an independent neurologist (PMR) or cardiologist (APB), who were also unaware of treatment allocation" Quote: "Data were analysed by the trial statistician (SCI) and reviewed annually in strict confidence by the Data Monitoring Committee. Everyone else involved in the study was unaware of the treatment allocation until the database was locked" Funding bias: Quote: "The funding source had no role in the study design, data collection, data analysis, data interpretation or writing of the report"

Gimenez 2004

Methods	RCT C: unclear Blinding: unclear Cross-over: unclear Exclusion during trial: unclear Losses to FU: unclear
Participants	Spain 1999 to 2001 93 patients and 93 operations Age: not indicated Male proportion: unclear Comparability: not reported Indication for surgery: not reported
Interventions	LA: not reported GA: not reported Patching and antiplatelet Rx: not reported Indication for shunting: reported
Outcomes	Blood pressure
Notes	FU: probably hospital discharge Ex: not reported Data were extracted only from abstract and we could not contact the authors of this publication

Gimenez 2004 *(Continued)*

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "In a prospective randomised study between 1999 and 2001, 93 patients underwent carotid endarterectomy, 47 under GA and 46 under LRA"
Allocation concealment (selection bias)	High risk	Not reported (only abstract available)
Blinding of participants and personnel (performance bias) All outcomes	High risk	Patients and surgeons were not blinded to treatment group
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported (only abstract available)
Incomplete outcome data (attrition bias) All outcomes	High risk	Not reported (only abstract available)
Selective reporting (reporting bias)	High risk	No prespecified outcomes were reported
Other bias	High risk	Not reported (only abstract available)

Kasprzak 2006

Methods	RCT C: unclear Blinding: independent neurologist Cross-over: 6 patients change from LA to GA Exclusion during trial: none Losses to FU: none
Participants	Germany 2006 186 patients,186 operations Age (mean): 69 years (LA), 69 years (GA) Male: 67% (LA), 61% (GA) Comparability: group similar for vascular risk factors Indication for surgery: asymptomatic carotid stenosis > 80% or symptomatic carotid stenosis > 70%
Interventions	LA: superficial and deep cervical plexus block by 0.5% bupivacaine + 1% prilocaine GA: fentanyl, etomidate, vecuronium, isoflurane Patching and antiplatelet: not reported Indication for shunting: LA: motor deficit, aphasia and loss of consciousness during carotid artery clamping; GA: decrease > 30% of amplitude in the baseline somatosensory

	evoked potential
Outcomes	Death, stroke, myocardial infarction, cranial nerve injury, blood pressure, shunting
Notes	FU: possibly hospital stay Ex: not meeting inclusion criteria, refused to participate, recalled consent, temporarily not operable, pilot study and other reason

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomized by computer random list for one type of anesthesia"
Allocation concealment (selection bias)	High risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Patients and surgeons were not blinded to treatment group
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "a neurological evaluation by a neurologist and a routine postoperative CT scan were done on day b2 or 3 after surgery. The neurologist was not informed about the type of anesthesia"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote in Figure 1: "received allocated treatment n = 95 analysed n = 95"
Selective reporting (reporting bias)	Low risk	All the study's prespecified outcomes of interest were reported
Other bias	High risk	Not reported

Luchetti 2008

Methods	RCT C: unclear Blinding: unclear Cross-over: unclear Exclusion during trial: unclear Losses to FU: unclear
Participants	Italy 2008 28 patients, 28 operations Age/male: unclear, but publication indicated that demographic data and baseline haemodynamic values are comparable

	Indication for surgery: unclear	
Interventions	LA: superficial cervical plexus block by 0.5% ropivacaine 30 cc GA: superficial cervical plexus block with continuous infusion of remifentanil, propofol with intubation and mechanical ventilation Patching and antiplatelet: not reported Indication for shunting: LA: following carotid clamping, change in mental evaluation defined as agitation, confusion, contralateral weakness, seizure, unresponsiveness	
Outcomes	Hemodynamic stability (mean arterial pressure), death, neurological deficit, cardiopulmonary complication	
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "They were randomly assigned by means of a computer-generated random number table to receive 1 of 2 anaesthesia techniques"
Allocation concealment (selection bias)	High risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Patients and surgeons were not blinded to treatment group
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	Not reported
Selective reporting (reporting bias)	High risk	Not all prespecified outcomes were reported, namely time to recovery of consciousness, perioperative complications such as nausea, vomiting, sweating, and grade on pain perception and comfort
Other bias	High risk	Not reported

Mazul-Sunko 2010

Methods	RCT C: unclear Blinding: unclear Cross-over: unclear Exclusion during trial: unclear Losses to FU: unclear
Participants	Croatia 2010 57 patients, 57 operations Mean age: 66.2 years (LA); 66 years (GA) Percentage of male: 89.6% (LA) and 85.7% (GA) Demographic data and baseline data are comparable Indication for surgery: carotid stenosis 70% or more
Interventions	LA: superficial cervical plexus block by levobupivacaine (1.5 mg/kg) and supplemental infiltration by surgeons with 1% lidocaine GA: etomidate in a dosage of 0.2 mg/kg and fentanyl (3 microgram/kg) for indication, vecuronium (0.08 mg/kg) for paralysis, maintain with isoflurane 0.7 to 1.2 MAC in a mixture of oxygen and nitrous oxide 50%:50%. Reversal with neostigmine (2.5 mg) and atropine (1 mg) Indication for shunting: LA: following carotid clamping, neurological deficit. GA : routine shunting was used except when technical difficulties
Outcomes	Stroke, death, myocardial infarction, shunting
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Elective carotid CEA were prospectively randomised to received either general or regional anaesthesia"
Allocation concealment (selection bias)	High risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Patients and surgeons were not blinded to treatment group
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	Not reported
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported

Other bias	High risk	Not reported

McCarthy 2004

Methods	RCT C: unclear Blinding: not reported Cross-over: not reported Exclusion during trial: none Losses to FU: none
Participants	UK 2004 176 patients and 176 operations Age (mean): 71 years (LA), 72 years (GA) Male: 61% (LA), 68% (GA) Comparability: groups similar for vascular risk factors Indication for surgery: not reported
Interventions	LA: not reported GA: not reported Patching: not reported Antiplatelet Rx: not reported Indication for shunting: not reported
Outcomes	Stroke, TIA, myocardial infarction, wound complication
Notes	FU: probably in-hospital stay Ex: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote:"The CEA-EQ questionnaire was administered to 176 CEA patients, prospectively randomised to either GA or LA in two hospitals, the Royal United Hospital Bath and The General Informary, Leeds"
Allocation concealment (selection bias)	High risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Patients and surgeons were not blinded to treatment group

Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	Not reported
Selective reporting (reporting bias)	High risk	No prespecified outcomes were reported
Other bias	High risk	Not reported

Moritz 2010

Methods	RCT Computer random Blinding: not reported Cross-over: 2 patients crossed over from LA to GA but these 2 patients were excluded from study Exclusion during trial: 6 (2 withdrawal of consent, 4 incomplete data) Losses to FU: not report
Participants	Germany 2010 96 patients, 96 operations Age (mean): of all participants, 69 years Male: 68.8% (LA), 70.8% (GA) Comparability for vascular risk factors, preoperative symptom, ASA classification Indication for surgery: symptomatic 70% to 99%, asymptomatic 80% to 99%
Interventions	LA: superficial + deep cervical block by 1% prilocaine GA: fentanyl, propofol, rocuronium and anaesthesia maintain by inspired sevoflurane, bolus fentanyl Patching: not reported Antiplatelet Rx: not reported Indication for shunting for LA group was any neurological deterioration like speech abnormality, hemiparesis, or impaired consciousness The indication for shunting in the GA group was N20/P25 amplitude of the somatosensory evoked potential decreased to or below 30% of the baseline value
Outcomes	Stroke, myocardial infarction, cardiopulmonary data (blood pressure, heart rate), comparison neuromonitoring various method i.e. stump pressure, transcranial Doppler, near-infrared spectroscopy, somatosensory evoked potentials
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Moritz 2010 (*Continued)*

Random sequence generation (selection bias)	Low risk	Quote: "All patients were randomised to either sevoflurane/fentanyl anaesthesia (GA = general anaesthesia) or regional anaesthesia (RAI) using a computerized system"
Allocation concealment (selection bias)	High risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Patients and surgeons were not blinded to treatment group
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "a total of 106 patients were randomised to the sevoflurane/ fentanyl (n=53) and regional (n=53) anaesthesia groups. Four patients were excluded because of withdrawal of consent (2 in each group), 2 patients because of conversion to general anaesthesia, and 4 patients because of incomplete data acquisition (3 in GA and 1 in RA). Thus, the final analysis was conducted in 96 patients (GA: n=48; RA: n=48)"
Selective reporting (reporting bias)	High risk	All prespecified outcome were reported
Other bias	High risk	Not reported

Mrozek 2007

Methods	RCT C: unclear Blinding: not reported Cross-over: no crossovers from LA to GA Exclusion during trial: not report Losses to FU: not report
Participants	Olomouc 2007 80 patients, 80 operations Age (mean): 67 years (LA), 67 years (GA) Male: 55% (LA), 87.5% (GA) Comparability for vascular risk factors: not reported Indication for surgery: not reported

Interventions	LA: superficial + deep cervical block by 0.5% bupivacaine under neurostimulator GA: intravenous etomide, thiopental, atracurium, midazolam, fentanyl and atracurium Patching: not reported Antiplatelet Rx: not reported Indication for shunting in LA group was loss of consciousness and loss of motor function following carotid clamping Indication for shunting in GA group: not reported
Outcomes	Hemodynamic parameter (blood pressure, pulse rate) death, stroke, myocardial infarction, patients' subjective feeling
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Quote: "the patients were randomised into two groups according to the first six digits of their date of birth (YYMMDD): odds to CB and even to GA"
Allocation concealment (selection bias)	High risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Patients and surgeons were not blinded to treatment group
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	Not reported
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported
Other bias	High risk	Not reported

Pluskwa 1989

Methods	RCT C: random number list Blinding: unclear Cross-overs: none Exclusions during trial: none Losses to FU: none
Participants	France 1989 20 patients, 20 operations Age (mean): 66 years (LA), 63 years (GA) Male: 90% (LA), 70% (GA) Comparability: groups similar for vascular risk factors Indication for surgery: not reported
Interventions	LA: epidural (C7-T1) by bupivacaine and fentanyl GA: flunitrazepam, fentanyl, vecuronium Patching: not reported Antiplatelet Rx: not reported Indication for shunting: not reported
Outcomes	Death, any stroke, myocardial infarction, blood pressure
Notes	FU: probably hospital discharge Ex: bleeding risk, on anticoagulants

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "La veille de l'intervention. ces patients ont ete repartis en deux groupes par tirage au sort a partir d'une serie de nombres au hasard"
Allocation concealment (selection bias)	High risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Patients and surgeons were not blinded to treatment group
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	Not reported
Selective reporting (reporting bias)	High risk	Not all prespecified outcomes were reported, namely heart rate

Other bias	High risk	Not reported

Prough 1989

Methods	RCT C: unclear Blinding: unclear Cross-overs: none Exclusions during trial: none Losses to FU: none
Participants	USA 1989 23 patients, 23 operations Age (mean): 67 years (LA), 61 years (GA) Male: 69% (LA), 40% (GA) Comparability: groups similar for preoperative physical status Indication for surgery: not reported
Interventions	LA: superficial cervical block GA: thiopental, pancuronium, isoflurane Patching and antiplatelet Rx: not reported Indication for shunting: not reported
Outcomes	Death, any stroke, myocardial infarction, blood pressure
Notes	FU: probable hospital discharge Ex: 5 patients refused GA so not randomised

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients who consented to either form of anaesthesia were randomised to received regional or general anaesthesia"
Allocation concealment (selection bias)	High risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Patients and surgeons were not blinded to treatment group
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported

Incomplete outcome data (attrition bias) All outcomes	High risk	Not reported
Selective reporting (reporting bias)	High risk	Not all prespecified outcomes were reported, namely intraoperative and post-operative intravenous fluid administration and urine output
Other bias	High risk	Not reported

Sbarigia 1999

Methods	RCT Randomisation: casual number C: unclear Blinding: assessor (neurologist) Cross-overs: 2 exclusions during trials Losses to FU: 18
Participants	Italy 1995 to 1998 107 patients, 107 operations Age (mean): 69.0 years (LA), 70.4 years (GA) Males: 87.3% (LA), 88.5% (GA) Comparability: groups similar for vascular risk factors Indication for surgery: TIA, asymptomatic carotid stenosis > 70%, stroke
Interventions	LA: superficial and deep cervical block with bupivacaine GA: alfentanil + propofol or sodium thiopental + fentanyl + isoflurane or vecuronium + nitrous oxide Patching: LA 36.4%, GA 23.1% Antiplatelet Rx: not reported Indication for shunting: LA: neurological test (toy-squeaker squeezing test); GA: not reported
Outcomes	Death, any stroke, myocardial infarction, TIA, bleeding, cranial nerve injuries, shunted arteries
Notes	FU: 30 days Ex: clinical signs of congestive heart disease, severe valvular heart disease, unstable angina, left bundle branch block (by ECG)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "randomization by means of causal numbers"

Sbarigia 1999 (*Continued)*

Allocation concealment (selection bias)	High risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Patients and surgeons were not blinded to treatment group
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 cross from LA to GA, no drop outs Quote: "two patients were excluded after randomisation and the operations were done under GA"; "in both cases, the anaesthesiologist considered the infiltration of LA to be dangerous"
Selective reporting (reporting bias)	High risk	No prespecified outcome was available
Other bias	High risk	Not reported

Sindelic 2004

Methods	RCT Randomisation, concealment and blinding of assessor: unclear Cross-over: unclear Losses to FU: unclear
Participants	Serbia 50 patients, 50 operations Mean age: 64.4 years (GA), 65.9 years (LA) Comparability of 2 groups in vascular risk factors Indication for surgery: unclear Males: 56% (GA), 52% (LA)
Interventions	LA: superficial and deep cervical plexus block: superficial block was done with 15 cc 0.5% bupivacaine and 5 cc 2% lidocaine injection along posterior border of sternocleidomastoid muscle Deep cervical block was performed with 3 injection techniques for blockages of C2, C3 and C4 segment GA: thiopental + fentanyl + rocuronium Patching and antiplatelet Rx and indication for shunting: not reported
Outcomes	Blood pressure
Notes	FU and Ex: unclear
Risk of bias	

Sindelic 2004 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: " Bolesnici su randomizirani u jednu od dve grupe, shodno anestezioloskim postupeima koji ce se sprovesti u toku operaciji: grupe opste anestezije (OA) i grupe regionalne anesezije (RA)."
Allocation concealment (selection bias)	High risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Patients and surgeons were not blinded to treatment group
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	No patients lost
Selective reporting (reporting bias)	High risk	Selected to report parameters only at T2 time which is the only one that is significant but not pre-specified Quote: "Zbog znacajna medjugrupna u grupi OA postojiu vremenu T2 i znacajna razlika u tom vremenu (OA vs RA,p < 0. 01)"
Other bias	High risk	Not reported

ASA: American Society of Anaesthesiologists
C: concealment of allocation
CABG: coronary artery bypass grafting
CT: computerised tomography
EEG: electroencephalography
Ex: exclusion criteria
FU: follow up
GA: general anaesthetic
ICA: internal carotid artery
ICU: intensive care unit
IHD: ischaemic heart disease
LA: local anaesthetic
MCA: middle cerebral artery
RCT: randomised controlled trial
Rx: therapy
TCD: transcranial doppler
TIA: transient ischaemic attack

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Ebner 2008	Randomised allocation was based on the rotation of two anaesthetists who could perform cervical plexus block

DATA AND ANALYSES

Comparison 1. Local versus general anaesthetic: randomised trials

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Any stroke within 30 days of operation	12	4453	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.92 [0.67, 1.28]
2 Death within 30 days of operation	10	4181	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.61 [0.35, 1.06]
3 Stroke or death within 30 days of operation	10	4181	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.85 [0.62, 1.16]
4 Myocardial infarction within 30 days of operation	11	4357	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.53 [0.67, 3.47]
5 Local haemorrhage	5	3976	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.95 [0.75, 1.19]
6 Cranial nerve injuries	4	3865	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.17 [0.95, 1.44]
7 Arteries shunted	8	4133	Odds Ratio (M-H, Random, 95% CI)	0.24 [0.08, 0.73]

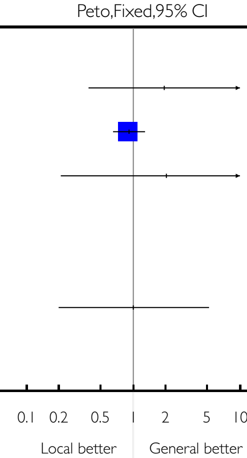
Analysis 1.1. Comparison 1 Local versus general anaesthetic: randomised trials, Outcome 1 Any stroke within 30 days of operation.

Review: Local versus general anaesthesia for carotid endarterectomy

Comparison: 1 Local versus general anaesthetic: randomised trials

Outcome: 1 Any stroke within 30 days of operation

Study or subgroup	Local n/N	General n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
Binder 1999	0/27	0/19		0.0 [0.0, 0.0]
Forssell 1989	4/56	2/55		1.97 [0.38, 10.15]
GALA 2008	63/1771	68/1752		0.91 [0.64, 1.30]
Kasprzak 2006	2/91	1/95		2.05 [0.21, 19.96]
Luchetti 2008	0/14	0/14		0.0 [0.0, 0.0]
Mazul-Sunko 2010	0/29	0/28		0.0 [0.0, 0.0]
McCarthy 2004	3/88	3/88		1.00 [0.20, 5.07]
Moritz 2010	0/48	0/48		0.0 [0.0, 0.0]



(*Continued . . .*)

(... *Continued*)

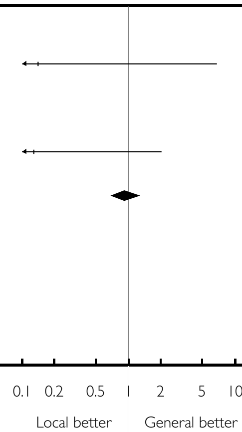
Study or subgroup	Local n/N	General n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
Mrozek 2007	0/40	0/40		0.0 [0.0, 0.0]
Pluskwa 1989	0/10	1/10		0.14 [0.00, 6.82]
Prough 1989	0/13	0/10		0.0 [0.0, 0.0]
Sbarigia 1999	0/55	2/52		0.13 [0.01, 2.03]
Total (95% CI)	**2242**	**2211**		**0.92 [0.67, 1.28]**

Total events: 72 (Local), 77 (General)

Heterogeneity: $Chi^2 = 4.21$, df = 5 (P = 0.52); $I^2 = 0.0\%$

Test for overall effect: Z = 0.48 (P = 0.63)

Test for subgroup differences: Not applicable



Analysis 1.2. Comparison 1 Local versus general anaesthetic: randomised trials, Outcome 2 Death within 30 days of operation.

Review: Local versus general anaesthesia for carotid endarterectomy

Comparison: 1 Local versus general anaesthetic: randomised trials

Outcome: 2 Death within 30 days of operation

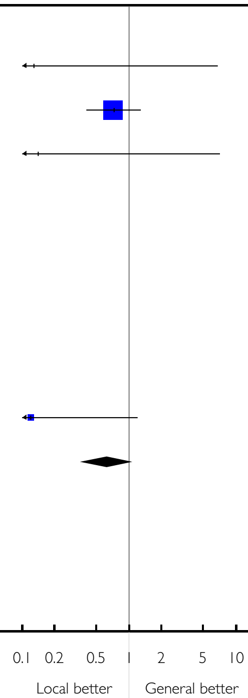
Study or subgroup	Local n/N	General n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
Binder 1999	0/27	0/19		0.0 [0.0, 0.0]
Forssell 1989	0/56	1/55		0.13 [0.00, 6.70]
GALA 2008	19/1771	26/1752		0.72 [0.40, 1.30]
Kasprzak 2006	0/91	1/95		0.14 [0.00, 7.12]
Luchetti 2008	0/14	0/14		0.0 [0.0, 0.0]
Mazul-Sunko 2010	0/29	0/28		0.0 [0.0, 0.0]
Mrozek 2007	0/40	0/40		0.0 [0.0, 0.0]
Pluskwa 1989	0/10	0/10		0.0 [0.0, 0.0]
Prough 1989	0/13	0/10		0.0 [0.0, 0.0]
Sbarigia 1999	0/55	3/52		0.12 [0.01, 1.21]
Total (95% CI)	**2106**	**2075**		**0.61 [0.35, 1.06]**

Total events: 19 (Local), 31 (General)

Heterogeneity: Chi^2 = 3.32, df = 3 (P = 0.34); I^2 =10%

Test for overall effect: Z = 1.75 (P = 0.080)

Test for subgroup differences: Not applicable



Analysis 1.3. Comparison 1 Local versus general anaesthetic: randomised trials, Outcome 3 Stroke or death within 30 days of operation.

Review: Local versus general anaesthesia for carotid endarterectomy

Comparison: 1 Local versus general anaesthetic: randomised trials

Outcome: 3 Stroke or death within 30 days of operation

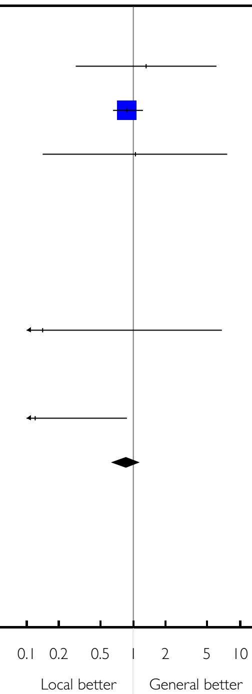
Study or subgroup	Local n/N	General n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
Binder 1999	0/27	0/19		0.0 [0.0, 0.0]
Forssell 1989	4/56	3/55		1.33 [0.29, 6.09]
GALA 2008	71/1771	79/1752		0.88 [0.64, 1.23]
Kasprzak 2006	2/91	2/95		1.04 [0.14, 7.54]
Luchetti 2008	0/14	0/14		0.0 [0.0, 0.0]
Mazul-Sunko 2010	0/29	0/28		0.0 [0.0, 0.0]
Mrozek 2007	0/40	0/40		0.0 [0.0, 0.0]
Pluskwa 1989	0/10	1/10		0.14 [0.00, 6.82]
Prough 1989	0/13	0/10		0.0 [0.0, 0.0]
Sbarigia 1999	0/55	4/52		0.12 [0.02, 0.88]
Total (95% CI)	**2106**	**2075**		**0.85 [0.62, 1.16]**

Total events: 77 (Local), 89 (General)

Heterogeneity: Chi^2 = 4.98, df = 4 (P = 0.29); I^2 =20%

Test for overall effect: Z = 1.02 (P = 0.31)

Test for subgroup differences: Not applicable



Analysis 1.4. Comparison 1 Local versus general anaesthetic: randomised trials, Outcome 4 Myocardial infarction within 30 days of operation.

Review: Local versus general anaesthesia for carotid endarterectomy

Comparison: 1 Local versus general anaesthetic: randomised trials

Outcome: 4 Myocardial infarction within 30 days of operation

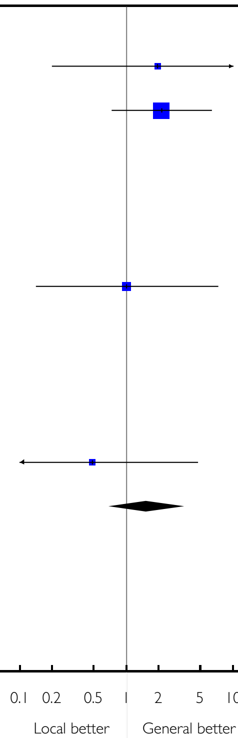
Study or subgroup	Local n/N	General n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
Binder 1999	0/27	0/19		0.0 [0.0, 0.0]
Forssell 1989	2/56	1/55		1.94 [0.20, 19.01]
GALA 2008	9/1771	4/1752		2.14 [0.72, 6.36]
Kasprzak 2006	0/91	0/95		0.0 [0.0, 0.0]
Luchetti 2008	0/14	0/14		0.0 [0.0, 0.0]
Mazul-Sunko 2010	0/29	0/28		0.0 [0.0, 0.0]
McCarthy 2004	2/88	2/88		1.00 [0.14, 7.22]
Mrozek 2007	0/40	0/40		0.0 [0.0, 0.0]
Pluskwa 1989	0/10	0/10		0.0 [0.0, 0.0]
Prough 1989	0/13	0/10		0.0 [0.0, 0.0]
Sbarigia 1999	1/55	2/52		0.48 [0.05, 4.70]
Total (95% CI)	**2194**	**2163**		**1.53 [0.67, 3.47]**

Total events: 14 (Local), 9 (General)

Heterogeneity: Chi^2 = 1.58, df = 3 (P = 0.66); I^2 =0.0%

Test for overall effect: Z = 1.01 (P = 0.31)

Test for subgroup differences: Not applicable



Analysis 1.5. Comparison 1 Local versus general anaesthetic: randomised trials, Outcome 5 Local haemorrhage.

Review: Local versus general anaesthesia for carotid endarterectomy

Comparison: 1 Local versus general anaesthetic: randomised trials

Outcome: 5 Local haemorrhage

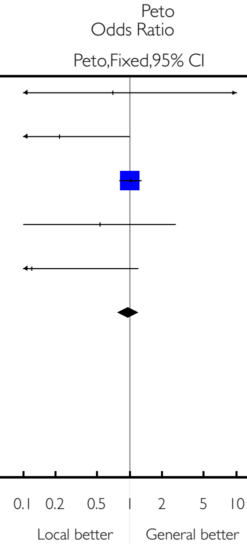
Study or subgroup	Local n/N	General n/N	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Binder 1999	1/27	1/19	0.7 %	0.69 [0.04, 11.94]
Forssell 1989	1/56	6/55	2.3 %	0.22 [0.05, 0.99]
GALA 2008	150/1773	146/1753	94.0 %	1.02 [0.80, 1.29]
Kasprzak 2006	2/91	4/95	2.0 %	0.53 [0.10, 2.67]
Sbarigia 1999	0/55	3/52	1.0 %	0.12 [0.01, 1.21]
Total (95% CI)	**2002**	**1974**	**100.0 %**	**0.95 [0.75, 1.19]**

Total events: 154 (Local), 160 (General)

Heterogeneity: $Chi^2 = 7.57$, df = 4 (P = 0.11); $I^2 = 47\%$

Test for overall effect: Z = 0.47 (P = 0.64)

Test for subgroup differences: Not applicable



Analysis 1.6. Comparison 1 Local versus general anaesthetic: randomised trials, Outcome 6 Cranial nerve injuries.

Review: Local versus general anaesthesia for carotid endarterectomy

Comparison: 1 Local versus general anaesthetic: randomised trials

Outcome: 6 Cranial nerve injuries

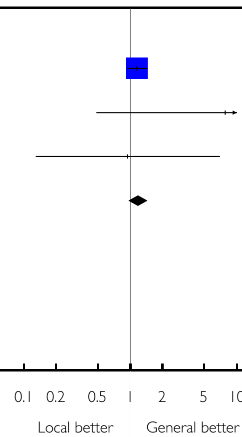
Study or subgroup	Local n/N	General n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
Binder 1999	0/27	0/19		0.0 [0.0, 0.0]
GALA 2008	213/1773	184/1753		1.16 [0.94, 1.43]
Kasprzak 2006	2/91	0/95		7.81 [0.48, 125.84]
Sbarigia 1999	2/55	2/52		0.94 [0.13, 6.90]
Total (95% CI)	**1946**	**1919**		**1.17 [0.95, 1.44]**

Total events: 217 (Local), 186 (General)

Heterogeneity: Chi² = 1.84, df = 2 (P = 0.40); I² =0.0%

Test for overall effect: Z = 1.52 (P = 0.13)

Test for subgroup differences: Not applicable



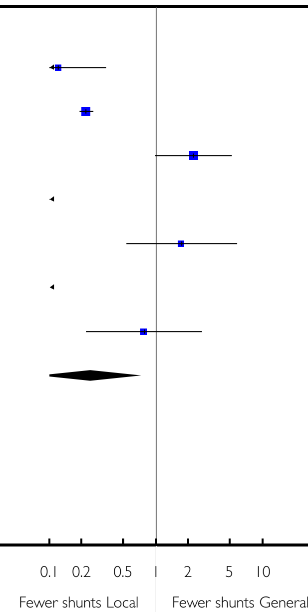
Analysis 1.7. Comparison 1 Local versus general anaesthetic: randomised trials, Outcome 7 Arteries shunted.

Review: Local versus general anaesthesia for carotid endarterectomy

Comparison: 1 Local versus general anaesthetic: randomised trials

Outcome: 7 Arteries shunted

Study or subgroup	Local n/N	General n/N	Odds Ratio M-H,Random,95% CI	Odds Ratio M-H,Random,95% CI
Binder 1999	27/27	19/19		0.0 [0.0, 0.0]
Forssell 1989	5/56	25/55		0.12 [0.04, 0.34]
GALA 2008	248/1730	738/1720		0.22 [0.19, 0.26]
Kasprzak 2006	19/91	10/95		2.24 [0.98, 5.13]
Mazul-Sunko 2010	1/29	23/28		0.01 [0.00, 0.07]
Moritz 2010	8/48	5/48		1.72 [0.52, 5.70]
Mrozek 2007	6/40	35/40		0.03 [0.01, 0.09]
Sbarigia 1999	5/55	6/52		0.77 [0.22, 2.68]
Total (95% CI)	**2076**	**2057**		**0.24 [0.08, 0.73]**



Total events: 319 (Local), 861 (General)

Heterogeneity: $Tau^2 = 1.84$; $Chi^2 = 65.40$, df = 6 (P<0.00001); I^2 =91%

Test for overall effect: Z = 2.51 (P = 0.012)

Test for subgroup differences: Not applicable

APPENDICES

Appendix 1. Cochrane Central Register of Controlled Trials (CENTRAL) search strategy

#1 [mh ˆ“endarterectomy, carotid”]
#2 [mh “carotid arteries”/SU]
#3 [mh “carotid artery diseases”/SU]
#4 [mh “carotid arteries”]
#5 [mh “carotid artery diseases”]
#6 carotid:ti,ab
#7 #4 or #5 or #6
#8 [mh êndarterectomy]
#9 (endarterectom* or surg*):ti,ab
#10 #8 or #9

#11 #7 and #10
#12 #1 or #2 or #3 or #11
#13 [mh anesthesia]
#14 [mh anesthetics]
#15 (anesthe* or anaesthe*):ti,ab
#16 [mh ^"cervical plexus"]
#17 (cervical NEXT block):ti,ab
#18 (bupivacaine or lidocaine or lignocaine or prilocaine or ropivacaine or mepivacaine or alfentanil or propofol or fentanyl or ketamine or midazolam or sevoflurane or desflurane or etomidate or isoflurane):ti,ab
#19 #13 or #14 or #15 or #16 or #17 or #18
#20 #12 and #19

Appendix 2. MEDLINE searcg strategy (OVID)

1 Endarterectomy, carotid/
2 exp carotid arteries/su
3 exp carotid artery diseases/su
4 exp carotid arteries/
5 exp carotid artery diseases/
6 carotid.tw.
7 4 or 5 or 6
8 endarterectomy/
9 (endarterectom$ or surg$).tw.
10 8 or 9
11 7 and 10
12 1 or 2 or 3 or 11
13 exp anesthesia/
14 exp anesthetics/
15 (anesthe$ or anaesthe$).tw.
16 cervical plexus/
17 cervical block.tw.
18 (bupivacaine or lidocaine or lignocaine or prilocaine or ropivacaine or mepivacaine or alfentanil or propofol or fentanyl or ketamine or midazolam or sevoflurane or desflurane or etomidate or isoflurane).tw.
19 or/13-18
20 12 and 19
21 exp animals/ not humans.sh
22. 20 not 21.

Appendix 3. EMBASE search strategy (OVID)

1. carotid artery surgery/ or carotid endarterectomy/
2. exp carotid artery/su [Surgery]
3. exp carotid artery disease/su [Surgery]
4. exp carotid artery/
5. exp carotid artery disease/
6. carotid.tw.
7. 4 or 5 or 6
8. endarterectomy/
9. (endarterectom$ or surg$).tw.
10. 8 or 9
11. 7 and 10
12. 1 or 2 or 3 or 11

13. exp anesthesia/
14. exp anesthetic agent/
15. exp local anesthetic agent/
16. (anesthe$ or anaesthe$).tw.
17. cervical plexus/
18. cervical block.tw.
19. (bupivacaine or lidocaine or lignocaine or prilocaine or ropivacaine or mepivacaine or alfentanil or propofol or fentanyl or ketamine or midazolam or sevoflurane or desflurane or etomidate or isoflurane).tw.
20. 13 or 14 or 15 or 16 or 17 or 18 or 19
21. 12 and 20
22. Randomized Controlled Trial/
23. Randomization/
24. Controlled Study/
25. control group/
26. clinical trial/ or phase 1 clinical trial/ or phase 2 clinical trial/ or phase 3 clinical trial/ or phase 4 clinical trial/ or controlled clinical trial/
27. Double Blind Procedure/
28. Single Blind Procedure/ or triple blind procedure/
29. drug comparison/ or drug dose comparison/
30. "types of study"/
31. random$.tw.
32. (controlled adj5 (trial$ or stud$)).tw.
33. (clinical$ adj5 trial$).tw.
34. ((control or treatment or experiment$ or intervention) adj5 (group$ or subject$ or patient$)).tw.
35. (quasi-random$ or quasi random$ or pseudo-random$ or pseudo random$).tw.
36. ((control or experiment$ or conservative) adj5 (treatment or therapy or procedure or manage$)).tw.
37. ((singl$ or doubl$ or tripl$ or trebl$) adj5 (blind$ or mask$)).tw.
38. versus.tw.
39. (assign$ or allocat$).tw.
40. controls.tw.
41. trial.ti. or (RCT or RCTs).tw.
42. or/22-41
43. 21 and 42
44. (exp animals/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/) not (human/ or normal human/ or human cell/)
45. 43 not 44

WHAT'S NEW

Last assessed as up-to-date: 30 September 2013.

Date	Event	Description
30 September 2013	New search has been performed	The searches have been updated to September 2013. We have identified four new randomised trials. The total number of included trials is now 14 randomised trials of 4596 operations. However, the four new trials did not have any stroke or death events in the perioperative period, so the results for these outcomes have

(*Continued*)

		not changed
30 September 2013	New citation required but conclusions have not changed	New first author. Conclusions unchanged

HISTORY

Review first published: Issue 1, 1996

Date	Event	Description
30 November 2008	New search has been performed	The searches have been updated and completed to November 2008. In the year since the searches were last completed in 2007, we have identified one new randomised trial. This most recent study is the biggest trial (3526 operations) in this systematic review. The total number of included trials is now 10 randomised trials of 4335 operations. The non-randomised studies, which are prone to bias and which were previously included in the review, have now been removed from this version
30 November 2008	New search has been performed	The searches have been completed to November 2008. In the three years since the previous version of this Cochrane Review was published, there have been three new randomised trials; the total number of included trials is now ten randomised trials involving 4335 operations
6 August 2008	New citation required but conclusions have not changed	There has been a change of authorship.
15 April 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Tanat Vaniyapong, Wilaiwan Chongruksut, Kittipan Rerkasem: designed the protocol, performed searches, selected studies for inclusion or exclusion, extracted data and updated the review.

D E C L A R A T I O N S O F I N T E R E S T

None known.

S O U R C E S O F S U P P O R T

Internal sources

- Faculty of Medicine, Chiang Mai University, Thailand.
- Center for Applied Science, Research Institute of Health Sciences, Chiang Mai University, Chiang Mai, Thailand.

External sources

- The Thailand Research Fund, Thailand.
- Stroke Prevention Research Unit, Nuffield Department of Clinical Neurosciences, University of Oxford, England, UK.

D I F F E R E N C E S B E T W E E N P R O T O C O L A N D R E V I E W

The non-randomised studies, which are prone to bias and which were previously included in the review, have been removed.

I N D E X T E R M S

Medical Subject Headings (MeSH)

*Anesthesia, General; *Anesthesia, Local; Clinical Trials as Topic; Endarterectomy, Carotid [*adverse effects; methods]; Myocardial Infarction [etiology]; Stroke [etiology]

MeSH check words

Humans

Stroke
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association | American Stroke Association

A Clinical Rule (Sex, Contralateral Occlusion, Age, and Restenosis) to Select Patients for Stenting Versus Carotid Endarterectomy: Systematic Review of Observational Studies With Validation in Randomized Trials

Emmanuel Touzé, Ludovic Trinquart, Rui Felgueiras, Kittipan Rerkasem, Leo H. Bonati, Gayané Meliksetyan, Peter A. Ringleb, Jean-Louis Mas, Martin M. Brown and Peter M. Rothwell
in collaboration with the Carotid Stenting Trialists Collaboration

Stroke. 2013;44:3394-3400; originally published online October 17, 2013;
doi: 10.1161/STROKEAHA.113.002756
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0039-2499. Online ISSN: 1524-4628

A Clinical Rule (Sex, Contralateral Occlusion, Age, and Restenosis) to Select Patients for Stenting Versus Carotid Endarterectomy

Systematic Review of Observational Studies With Validation in Randomized Trials

Emmanuel Touzé, MD, PhD*; Ludovic Trinquart, PhD*; Rui Felgueiras, MD; Kittipan Rerkasem, MD, PhD; Leo H. Bonati, MD, PhD; Gayané Meliksetyan, MD; Peter A. Ringleb, MD, PhD; Jean-Louis Mas, MD; Martin M. Brown, MD, FRCP; Peter M. Rothwell, MD, PhD, FRCP, FMedSci; in collaboration with the Carotid Stenting Trialists' Collaboration

Background and Purpose—Compared with carotid endarterectomy (CEA), carotid angioplasty and stenting (CAS) is associated with a higher risk of procedural stroke or death especially in patients with symptomatic stenosis. However, after the perioperative period, risk is similar with both treatments, suggesting that CAS could be an acceptable option in selected patients.

Methods—We performed systematic reviews of observational studies of procedural risks of CEA or CAS and extracted data on 9 predefined risk factors (age, contralateral carotid occlusion, coronary artery disease, diabetes mellitus, sex, hypertension, peripheral artery disease, and type and side of stenosis). We calculated pooled relative risks of procedural stroke or death. Factors with differential effects on risk of CAS versus CEA were identified by interaction tests and used to derive a rule. The rule was tested using individual patient data from randomized trials of CAS versus CEA from the Carotid Stenting Trialists' Collaboration (CSTC).

Results—We identified 170 studies. The effects of sex, contralateral occlusion, age, and restenosis (SCAR) on the procedural risk of stroke or death differed. Patients with contralateral occlusion or restenosis and women <75 years were at relatively low risk for CAS (SCAR negative), with all others being high risk (SCAR positive). Among the 3049 patients in the CSTC validation, 694 (23%) patients were SCAR negative. The pooled RR of procedural stroke and death with CAS versus CEA was 0.93 (0.49–1.77; P=0.83) in SCAR-negative and 2.41 (1.68–3.45; P<0.0001) in SCAR-positive patients (P [interaction]=0.05).

Conclusions—The SCAR rule is potentially useful to identify patients in whom CAS has a similar risk of perioperative stroke or death to CEA. **(*Stroke*. 2013;44:3394-3400.)**

Key Words: atherosclerosis ■ carotid endarterectomy ■ carotid stenosis ■ carotid stenting ■ meta-analysis ■ prevention ■ systematic review

Carotid artery stenting (CAS) is being evaluated as a potential alternative to carotid endarterectomy (CEA) in patients with severe carotid artery stenosis. However, to date, randomized clinical trials have shown that, on average, CAS is associated with a higher procedural risk of stroke than CEA in patients with symptomatic stenosis,[1,2] and that there are only limited data in patients with asymptomatic stenosis.[2] Nevertheless, because the risk of stroke after the perioperative

Received July 9, 2013; accepted September 4, 2013.

From the Université Paris Descartes, Sorbonne Paris Cité, INSERM UMR S894, Service de Neurologie, Hôpital Sainte-Anne, Paris, France (E.T., G.M., J.-L.M.); Université de Caen Basse Normandie, INSERM UMR-S U919, Service de Neurologie, CHU Côte de Nacre, Caen, France (E.T.); French Cochrane Centre, Université Paris Descartes, Sorbonne Paris Cité, INSERM U738, Assistance Publique-Hôpitaux de Paris, Hôpital Hôtel-Dieu, Centre d'Epidémiologie Clinique, Paris, France (L.T.); Neurology Department, Hospital Santo António, Centro Hospitalar do Porto, Largo Professor Abel Salazar, Porto, Portugal (R.F.); Department of Surgery, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand (K.R.); Department of Neurology and Stroke Unit, University Hospital Basel, Switzerland (L.H.B.); Department of Brain Repair and Rehabilitation, UCL Institute of Neurology, Queen Square, London, UK (L.H.B., M.M.B.); Department of Neurology, University Hospital Heidelberg, Im Neuenheimer Feld 400, Heidelberg, Germany (P.A.R.); and Stroke Prevention Research Unit, Nuffield Department of Clinical Neuroscience, University of Oxford, Oxford, UK (P.M.R.).

Guest Editor for this article was Miguel Perez-Pinzon, PhD.

*Drs Touzé and Trinquart contributed equally.

The online-only Data Supplement is available with this article at http://stroke.ahajournals.org/lookup/suppl/doi:10.1161/STROKEAHA.113.002756/-/DC1.

Correspondence to Emmanuel Touzé, MD, PhD, Université de Caen Basse Normandie, INSERM UMR-S U919, Service de Neurologie, CHU Côte de Nacre, Caen, France. E-mail touze-e@chu-caen.fr

Stroke **is available at http://stroke.ahajournals.org** **DOI: 10.1161/STROKEAHA.113.002756**

period seems to be similar for CAS and CEA,[3,4] it has been suggested that CAS may be an acceptable option in selected patients who have a low procedural risk of stroke or death, as indicated in European and American guidelines.[5,6] However, there is no indication as to how patients with a low procedural risk can be identified. The combined analysis of the large European trials and North American trials of CEA versus CAS has shown that CAS was potentially as safe as CEA in younger patients,[2,7] but there remains uncertainty whether age should be used alone as a selection criteria to identify potential candidates for CAS. Other clinical factors are likely to influence the relative procedural risks of the 2 techniques,[8–12] some of which were not addressed in analysis of the randomized trials, and other important groups, such as patients with restenosis, were either excluded from the trials or not reported separately.[13] Moreover, the trials lack the statistical power to detect clinically important interactions between patient characteristics and treatment effect.[7]

In contrast, numerous case series of patients undergoing CEA or CAS are available, and collectively provide data on the risk factors for procedural stroke and death for one or other procedure in several hundred thousand patients.[8–12] We have shown previously that meta-analysis of risk associations from such studies provides reliable and highly consistent data on the clinical characteristics associated with procedural risk of CEA and CAS independently.[7–18] To guide clinical decision making, we now aimed to use this approach to identify those predictors of procedural risk that differ significantly between CEA and CAS and might therefore be useful in determining which procedure is most appropriate in individual patients. We aimed to thereby derive a simple clinical risk rule to target CAS versus CEA and to validate the rule and determine its likely clinical use by using individual patient data from the randomized trials that directly compared CEA and CAS included in The Carotid Stenting Trialists' Collaboration (CSTC) Database.[7]

Methods

Systematic Review of Observational Data

We updated our previous systematic reviews using the same selection criteria and search strategy as previously published,[8–12,14] and following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations for reporting.[15]

Selection Criteria

Eligible studies were those which enrolled patients with symptomatic or asymptomatic stenosis located in the region of the carotid bifurcation, treated by CAS or CEA, and in which the numbers of stroke or death could be extracted for any subgroup among a predefined list of 9 risk factors: age (≥75–80 versus <75–80 years, ie, corresponding to the most common cutoffs used to separate elderly from nonelderly patients), contralateral carotid occlusion (severe stenosis was not considered), coronary artery disease, diabetes mellitus, sex (men versus women), hypertension, peripheral artery disease, type of stenosis (restenosis after CEA versus primary atherosclerotic disease), and side of stenosis (right versus left). These factors were identified as potentially relevant from previous systematic reviews or individual studies.[8–12] Studies were considered irrespective of setting and language. Observational studies were defined as cohorts or case series, including administrative databases, of patients undergoing CAS or CEA. We excluded studies that enrolled only specific populations (eg, postradiation stenosis, restenosis after CEA, and patients treated in an emergency context) and case reports.

Search Strategy

The search strategy was based primarily on an electronic search of 3 databases (Medical Literature Analysis and Retrieval System Online, Excerpta Medica, and the Cochrane Central Register of Controlled Trials databases) until July 1, 2011 (Table I in the online-only Data Supplement). We hand-searched the references of all included articles and any relevant reviews. We also searched books of abstracts from recent conferences that were available online (Table II in the online-only Data Supplement), the US Clinical Trial Register (http://www.clinicaltrials.gov), the US Food and Drug Administration (http://www.fda.gov), and the European Medicines Agency (http://www.emea.europa.eu) databases.

Study Selection and Data Collection

Assessment of eligibility of studies was performed by 2 independent reviewers for CAS and CEA separately, from the titles and abstracts as previously reported.[8–12] Final selection was made after reviewing full-text articles. Reviewers extracted information from the reports using a standardized data chart. For each report, a second reviewer ascertained the accuracy of data extracted by the first reviewer. Any disagreement was resolved by discussion.

The 3 large European randomized trials of CEA versus CAS in patients with symptomatic carotid stenosis (Endarterectomy Versus Angioplasty in Patients With Severe Symptomatic Carotid Stenosis [EVA-3S]; Stent-Protected Angioplasty versus Carotid Endarterectomy [SPACE]; International Carotid Stenting Study [ICSS]), which formed the CSTC,[7] were used for the validation analyses, and the data from these trials were therefore not included in the systematic review of risk associations.

Analysis

The primary outcome was the procedural risk of stroke or death (most commonly defined as the risk during the 30 days after the procedure). Secondary outcomes were stroke and any death separately. Nonfatal myocardial infarction was not included. For each of the 9 potential risk factors and separately for studies of CAS and of CEA, we calculated the relative risks (RR) of a procedural event in patients versus those without the risk factor. Because of differences between studies in which risk factor data were reported, the numbers of studies (and patients) included in each meta-analysis differed. In each meta-analysis, studies with no events occurring in all groups (ie, patients with and without the risk factor) did not contribute to the calculation of the pooled RR. However, when zero cell count was observed in 1 group only, we used a continuity correction, by adding a factor proportional to the reciprocal of the size of the contrasting study group to all cells.[16] Homogeneity of RRs across studies in each meta-analysis was assessed using the I^2 statistic. I^2>30% represents moderate heterogeneity, I^2>50% substantial heterogeneity, and I^2>70% considerable heterogeneity. We report pooled RRs computed through DerSimonian–Laird random effects meta-analyses, although analyses using fixed-effect meta-analysis models according to the Mantel–Haenszel method showed consistent results. For each risk factor, we assessed whether the effect on the procedural risk of event differed between CAS and CEA by performing an interaction test using random effects meta-regressions. As is recommended for such analyses, we considered a probability value of ≤0.10 as evidence of statistically significant interaction.[17]

Derivation of the Rule

From the set of risk factors with differing effects between CAS and CEA (ie, with statistically significant interactions), we took the magnitude and direction of interactions into account to determine the rule. If a large qualitative interaction was found (ie, when RRs were clearly in opposite directions or when the difference from unity was ≥0.50 for the factor with the greater effect and ≤0.10 for the factor with the effect close to the unity), such a risk factor was considered sufficient by itself to identify low-risk patients. Otherwise, factors associated with a high risk after CAS scored +1 and those with a low risk scored −1. Patients with a total score <0 were categorized into low risk. In a secondary analysis, an alternative rule was also derived, in which all factors were considered equivalent (high risk of CAS scores +1 and low risk for CAS scores −1), and patients were categorized according to the total score.

Validation of the Rule

After having derived the rule, P.M. Rothwell, E. Touzé, and L. Trinquart made a formal request to the CSTC to obtain a data set from EVA-3S, SPACE, and ICSS randomized trials to validate the rule.[7] At no time, did these researchers have access to the data set before they derived the rule. A per-protocol individual data set including the 30-day outcomes (stroke or death, stroke, death) occurrence and the risk factors selected for the clinical rule only were obtained. Definitions of outcomes and risk factors were already standardized across the 3 trials.[7] Patients were categorized into low or high risk according to the rule. We used a 2-stage meta-analytic approach.[18] First, in each low-risk and high-risk category and for CAS and CEA separately, we calculated combined absolute risks of procedural stroke or death. We used a DerSimonian–Laird random effects model to combine absolute risks across trials through the Freeman–Tukey variance stabilizing transformation.[19] Second, in each low-risk and high-risk category, we computed combined RR of stroke or death in patients treated with CAS compared with patients treated with CEA. We tested for interaction of treatment effect between low- and high-risk patients using meta-regression. Given the a priori prediction that the RR of stroke or death occurring in patients treated with CAS compared with patients treated with CEA would be higher in CAS-higher-risk than in CAS-lower-risk patients, we calculated a 1-sided probability value by using a Monte Carlo permutation test.[20]

Results

A total of 170 studies (227 articles, >70 000 patients) provided data for ≥1 of 9 potential risk factors: 115 studies (149 articles) relating to CEA and 68 studies (83 articles) relating to CAS, some being related to both CEA and CAS. The characteristics of these studies and the list of references are shown in Table I in the online-only Data Supplement.

The results of the meta-analyses of the RRs of stroke or death in relation to the 9 potential risk factors in CAS and CEA studies are shown in Figure 1. There was no or little heterogeneity between studies in RRs for age, contralateral occlusion, diabetes mellitus, sex, hypertension, and restenosis among either CAS or CEA studies. The effects of age, sex, contralateral occlusion, and restenosis on the procedural risk of stroke or death differed statistically significantly between CAS and CEA (interaction test probability value of <0.10). There was more heterogeneity in RR between CEA studies concerning coronary artery disease, stenosis side, and peripheral artery disease, but the effects of these variables on the procedural risk of stroke or death did not differ statistically significantly between CAS and CEA.

Age was associated with higher risks of procedural stroke or death for both CAS and CEA but the increase in risk was greater after CAS. Contralateral occlusion and female sex were associated with a higher risk of procedural stroke or death after CEA but had no significant influence on the risk after CAS. Compared with patients with primary atherosclerotic disease, those with restenosis after CEA had a higher risk of procedural stroke or death when treated by CEA but a lower risk when treated by CAS. Analyses based on stroke only yielded qualitatively similar results (Figure I in the online-only Data Supplement).

Therefore, the resulting rule was based on the presence or absence of the 4 following factors: sex, contralateral occlusion, age and restenosis (SCAR rule). Given the large qualitative

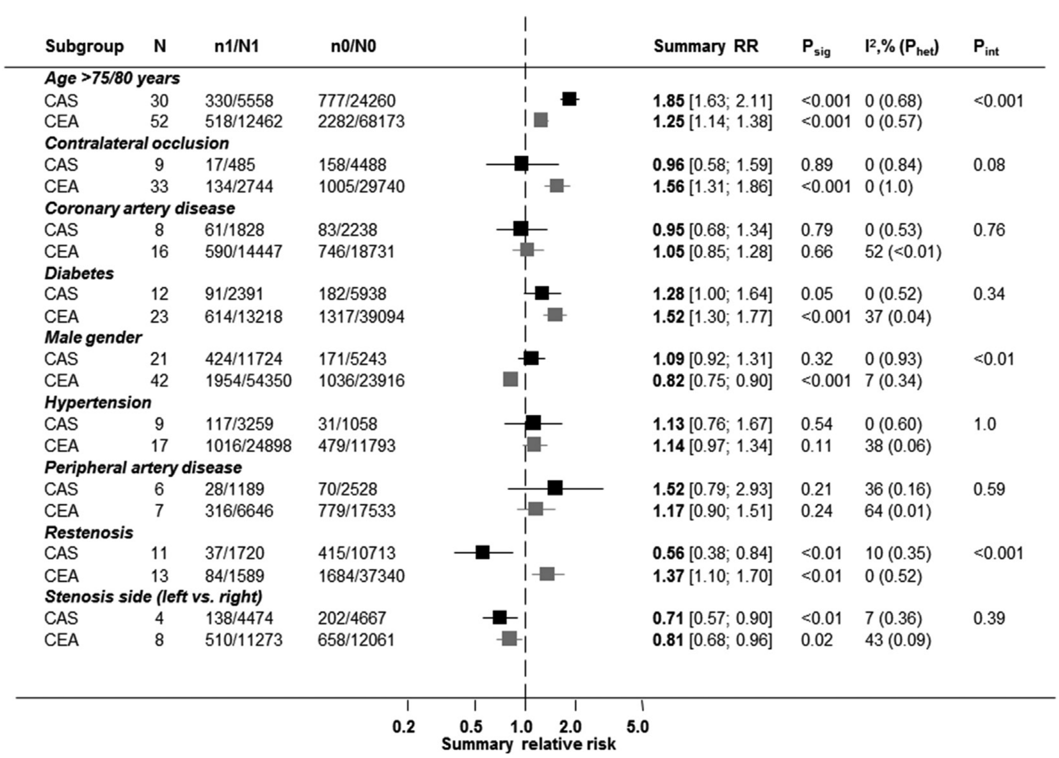


Figure 1. Meta-analyses of the relative risk of stroke or death after carotid angioplasty and stenting (CAS) and carotid endarterectomy (CEA) according to the 9 potential risk factors. N indicates number of studies; n1, number of events in patients with clinical factor; N1, number of patients with clinical factor; n0, number of events in patients without clinical factor; N0, number of patients without clinical factor; P_{het}, Cochran homogeneity test probability value; P_{int}, P interaction; P_{sig}, P significance; and RR, relative risk.

effect of contralateral occlusion and restenosis, we first considered that these risk factors were by themselves sufficient to identify patients in whom CAS would be relatively lower risk (SCAR negative) and comparable with CEA. Otherwise, given the smaller qualitative interaction for sex and the small quantitative interaction for age, only women <75 years would also be expected to be relatively at low risk for CAS (also SCAR negative), all other patients being categorized as higher risk (SCAR positive) for CAS and therefore as candidates for CEA preferentially. In a secondary analysis, we considered all factors equivalent, that is, that all patients with ≥2 factors (age <75 years, women, contralateral occlusion, or restenosis) would be SCAR negative and all others SCAR positive. The only difference between the 2 options being that men >75 years with contralateral carotid occlusion or restenosis are SCAR positive in the second option (Table II in the online-only Data Supplement).

Among the 4 components of the SCAR rule, effects of sex, contralateral occlusion, and age could be validated with the individual data from the CSTC, but patients with restenosis were excluded from the trials. Data on contralateral carotid occlusion were missing in 275 patients (262 from SPACE and 13 from ICSS). Exclusion of these patients left 3049 patients for the analyses. Using our primary definition of the SCAR rule, 694 (22·8%) patients were classified as SCAR negative: 135 patients had contralateral carotid occlusion, and the other 559 patients were women <75 years. Among these SCAR-negative patients, the absolute risks of any stroke or death were similar between CAS and CEA (absolute risks 5.6%, 95% confidence interval [3.0–9.0] versus 5.6% [3.4–8.4]). However, among SCAR-positive patients, the absolute risk of CAS was more than twice that of CEA (8.4%, 6.9–10.1 versus 3.5%, 2.6–4.6; Figure II in the online-only Data Supplement).

Figure 2 shows the RRs of any procedural stroke or death occurring in patients treated by CAS compared with patients treated by CEA. Among SCAR-negative patients, the pooled RR was 0.93 (95% confidence interval [0.49–1.76], I^2=0%; P (sig)=0.83) whereas, among SCAR-positive patients, it was 2.44 (1.71–3.48, I^2=0%; P (sig)<0.0001). The interaction was statistically significant (P=0.05). Analyses based on the procedural risk of stroke (RR=0.93; 0.48–1.80 in SCAR-negative patients versus 2.45; 1.70–3.64 in SCAR-positive patients; P for interaction=0.05; Figure III in the online-only Data Supplement) and death (RR=0.83; 0.15–4.52 in SCAR-negative patients versus 2.57; 1.00–6.62 in SCAR-positive patients; P=0.20) led to similar results. In the sensitivity analysis considering all 4 risk factors as equivalent, the results were similar (Figure IV in the online-only Data Supplement).

In the absence of contralateral occlusion and restenosis, only women <75 years are identified as low risk for CAS by the SCAR rule, consistent with the finding that men aged <75 years without contralateral carotid occlusion remained at higher risk of procedural stroke or death when treated by CAS versus CEA (RR=1.94; 95% confidence interval [1.22–3.07]).

Finally, considering that CSTC and CREST have both shown that CAS is not inferior to CEA in patients <70 years (rather than the 75-year cut point derived from our systematic review), we performed a sensitivity analysis including only patients who were SCAR positive and aged <70 years from the CSTC data set (data obtained secondarily from the CSTC). In this subset of patients, the trend toward a higher procedural risk of stroke or death with CAS compared with CEA remained (RR=1.77; 95% confidence interval [0.98–3.21]).

Discussion

We have derived and partially validated a simple rule to categorize patients with severe symptomatic carotid stenosis according to their RR of periprocedural stroke or death with CAS versus CEA and to thereby identify a subset of patients in whom CAS may be noninferior to CEA. We used the strongest evidence available from large systematic reviews to identify the relevant risk factors and then validated the resulting

Study	Events / Patients: Treatment	Control	RR	95% CI	Weight
SCAR negative					
EVA3S	5 / 55	3 / 38	1.15	0.29-4.53	21.83
SPACE	7 / 118	6 / 97	0.96	0.33-2.76	36.71
ICSS	7 / 200	8 / 186	0.81	0.30-2.20	41.45
TOTAL	19 / 373	17 / 321	0.93	0.49-1.76	100.00
Significance: p = 0.83					
Heterogeneity: p = 0.92					
SCAR positive					
EVA3S	20 / 205	7 / 219	3.05	1.32-7.07	18.21
SPACE	25 / 334	15 / 347	1.73	0.93-3.23	33.14
ICSS	52 / 622	19 / 628	2.76	1.65-4.62	48.65
TOTAL	97 / 1161	41 / 1194	2.44	1.71-3.48	100.00
Significance: p < 0.0001					
Heterogeneity: p = 0.44					

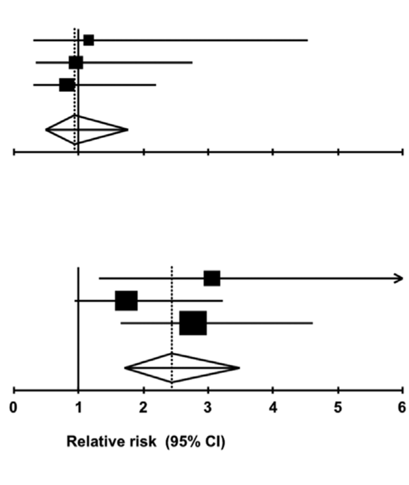


Figure 2. Application of the sex, contralateral occlusion, age, and restenosis (SCAR) rule to the pooled data on procedural risk of stroke and death from the 3 large randomized trials of carotid endarterectomy (CEA) versus carotid angioplasty and stenting (CAS) in the Carotid Stenting Trialists' Collaboration (CSTC).[1] CI indicates confidence interval; EVA3S, Endarterectomy Versus Angioplasty in Patients With Severe Symptomatic Carotid Stenosis; ICSS, International Carotid Stenting Study; RR, relative risk; and SPACE, Stent-Protected Angioplasty versus Carotid Endarterectomy.

rule in the largest available data set of randomized trial data comparing CAS with CEA. In this validation analysis, the results were highly consistent across trials. In the pooled data set of the 3 major European trials, the SCAR-negative patients accounted for about one fourth of the population, although patients with restenosis after previous CEA were excluded from the trials. Thus, in clinical practice, the rule would allow clinicians to identify those patients who might be able to undergo CAS without a higher procedural risk of stroke and death than with CEA (ie, patients with restenosis or contralateral occlusion and women aged <75 years).

In most trials and registries of patients with carotid stenosis, women account for about one third of the population recruited. Randomized trials of CEA for both symptomatic and asymptomatic carotid stenosis and systematic reviews of observational data have demonstrated that benefit is decreased in women, partly because of a high operative risk, which is independent of age.[8,21,22] By contrast, whether there are also sex differences in risk of CAS has remained uncertain.[11,23,24] By pooling all available data, we have confirmed that women are at higher risk of procedural stroke or death after CEA and shown that there is no evidence of an increased risk of periprocedural stroke or death after CAS, the risk being slightly higher in men. This sex difference between CEA and CAS mainly results from a higher risk of periprocedural complications after CEA in women, which has been attributed to sex differences in carotid size and in the nature of the atheromatous plaque.[25,26]

Less than 10% of patients with severe carotid artery stenosis have contralateral carotid occlusion. Most studies that analyzed the impact of contralateral carotid occlusion on procedural risks after CEA had limited statistical power, with inconsistent findings.[27] Although it has been suggested that routine use of shunts during CEA may reduce the risk of complications in this situation,[28] there is no strong evidence to support this view.[29] On the basis that the duration of carotid occlusion is shorter during CAS than during CEA, some authors have suggested that endovascular therapy might be preferable in patients with contralateral occlusion, but there was little evidence.[30–32] Our systematic review showing that patients with severe carotid stenosis and contralateral carotid occlusion are at high risk of periprocedural complications after CEA, but not after CAS, and the validation on RCTs provide useful new evidence and have practical implications.

Although previous meta-analyses of RCTs and registries have consistently shown that age has only a small impact on the risk of complications after CEA,[8] elderly patients have been considered at high surgical risk and therefore to be potentially good candidates for CAS by several authors.[13,33–35] However, as shown in our previous systematic reviews,[7–11] and more recently in RCTs,[2,7] increasing age has more impact on the procedural risk of CAS than CEA. This is also in agreement with studies showing that elderly patients are more likely to have tortuous and severely calcified vessels, resulting in an increased risk of embolization during wire manipulation and catheter exchanges at some stage in CAS.[12,36,37]

Restenosis occurs in ≥10% of patients treated by CEA,[38] and is generally attributed to neointimal hyperplasia during the early postoperative period or recurrent atherosclerosis thereafter. Although most carotid restenoses are asymptomatic, reoperation has been considered necessary in ≤8% of patients.[39] Surgical treatment for recurrent carotid stenosis is more technically difficult than primary procedures, notably because dissection of the neck tissues and the artery is more challenging. Several authors and guidelines have suggested that CAS may be the preferred treatment for post-CEA restenosis.[40,41] Using all available data, we have shown that in comparison with primary stenosis, restenosis is associated with a higher risk of stroke or death after CEA, but with a lower risk after CAS. We could not validate the finding in RCT data, but an RCT comparing CEA with CAS specifically in patients with carotid restenosis is unlikely to be performed in the future.

Our analysis has several potential limitations. First, because, the European RCTs did not include asymptomatic stenosis, further studies are required to validate the rule in this situation. However, there is no evidence from the literature suggesting a potential interaction between the clinical indication and any of the components of the SCAR rule concerning the periprocedural risk of stroke or death after CEA or CAS, and the components of the rule were identified from studies that included both symptomatic and asymptomatic patients. Second, a recent analysis of data from the CREST trials suggested that women have a higher risk of periprocedural stroke or death after CAS (5.5% versus 3.7%).[24] However, the treatment-by-sex interaction was not significant, and the results are not consistent with other trial data or case series, and no results were reported for women <75 years.[23] Moreover, these CREST data were included in our meta-analyses, with little effects on the overall estimates. Third, the cutoff we used for age may be questionable. Indeed, the pooled analysis of the European trials and CREST have detected an interaction between age and treatment effect, with a crossover at an age of ≈70 years; CAS being better at younger ages, and CEA better at older ages.[2,7] However, in most observational studies, the cutoffs used to categorize patients were either 75 or 80 years, and SCAR-positive patients <70 years were still at higher risk for procedural stroke or death after CAS compared with CEA in the CSTC data set. Fourth, we were unable to study some potential risk factors attributable to limited availability of published data from observational studies or lack of collection of data in the randomized trials. For instance, technical and anatomic factors, especially extreme angulation of the carotid artery or calcifications, can have an impact on the risks of CAS,[12] but there are few similar data published for CEA. We have also not been able to analyze patients according to both protection device systems and the risk factors simultaneously. However, there is no known interaction between the use of protection device systems and risk factors we examined. Leukoariaosis has been shown to be a risk factor for CEA in NASCET,[42] and also for CAS in ICSS,[43] but has not been widely studied. Similarly, the RR of periprocedural stroke or death in relation to the timing of the procedure might differ between CAS and CEA,[9,44] but definitions of early and late intervention differ widely in observational studies. Fifth, although the pooled absolute risks of periprocedural stroke or death in SCAR-negative patients were identical between CAS and CEA in the validation population, our approach cannot formally demonstrate noninferiority. Finally, although the rule can already be considered useful for clinical practice, further refinement will be required in the future, notably to identify the best option between the 2 potential rules we tested.

Appendix

CSTC Collaborators: The CSTC Steering Committee comprises A. Algra (independent chair); EVA-3S A. Branchereau, G. Chatellier, J.-L. Mas; SPACE G. Fraedrich, P.A. Ringleb, H. Zeumer; ICSS L.H. Bonati, M.M. Brown, W.P. Mali; J. Dobson (meta-analysis statistician). Steering committees of trials included in CSTC: EVA-3S J.-L. Mas (chair), G. Chatellier (cochair), J.-P. Becquemin, J.-F. Bonneville, A. Branchereau, D. Crochet, J.C. Gaux, V. Larrue, D. Leys, J. Watelet; SPACE W. Hacke (chair), M. Hennerici, J.R. Allenberg, P.C. Maurer, H.-H. Eckstein, H. Zeumer, O. Jansen; ICSS A. Algra, J. Bamford (chair), J. Beard, M. Bland, A.W. Bradbury, M.M. Brown (chief investigator), A. Clifton, P. Gaines, W. Hacke, A. Halliday, I. Malik, J.-L. Mas, A.J. McGuire, P. Sidhu, G. Venables.

Contributors: The study was conceived by P.M. Rothwell, and the protocol was drafted by E. Touzé and L. Trinquart. E. Touzé, L. Trinquart, R. Felgueiras, K. Rerkasem, and G. Meliksetyan were responsible for data collection. E. Touzé, L. Trinquart, and P.M. Rothwell were responsible for data analysis, data interpretation, and preparation of the report. L.H. Bonati, J.-L. Mas, P.A. Ringleb, and M.M. Brown provided data from the CSTC. All authors contributed to data interpretation, critical revision of the report, and approved the final version.

Role of the Funding Sources: This study was not funded. The sponsors of the contributing trials (EVA-3S, SPACE, ICSS) had no role in study design, data collection, data analysis, data interpretation, or the writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Sources of Funding

Dr Rothwell holds a National Institute of Health Research (NIHR) Senior Investigator Award and a Wellcome Trust Senior Investigator Award and is funded by the NIHR Biomedical Research Center, Oxford. ICSS was funded by grants from the Medical Research Council (MRC), The Stroke Association, Sanofi Synthelabo, and the European Commission. The funding from the MRC was managed by NIHR on behalf of the MRC-NIHR partnership. Dr Rerkasem has been funded by The Thailand Research Fund (RSA5580008) and Faculty of Medicine, Chiang Mai University. Dr Brown's Chair in Stroke Medicine at University College London is supported by the Reta Lila Weston Trust for Medical Research. Part of this work was undertaken at UCLH/UCL who received a proportion of funding from the Department of Health's NIHR Biomedical Research Centers funding scheme. Dr Bonati was supported by grants from the Swiss National Science Foundation (PBBSB-116873), the University of Basel, Switzerland, and The Stroke Association. EVA-3S was funded by the French Ministry of Health (Program Hospitalier de Recherche Clinique, Assitance Publique des Hôpitaux de Paris [AOM 97066]).

Disclosures

None.

References

1. Bonati LH, Lyrer P, Ederle J, Featherstone R, Brown MM. Percutaneous transluminal balloon angioplasty and stenting for carotid artery stenosis. *Cochrane Database Syst Rev*. 2012;9:CD000515.
2. Brott TG, Hobson RW II, Howard G, Roubin GS, Clark WM, Brooks W, et al; CREST Investigators. Stenting versus endarterectomy for treatment of carotid-artery stenosis. *N Engl J Med*. 2010;363:11–23.
3. Mas JL, Trinquart L, Leys D, Albucher JF, Rousseau H, Viguier A, et al; EVA-3S investigators. Endarterectomy Versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S) trial: results up to 4 years from a randomised, multicentre trial. *Lancet Neurol*. 2008;7:885–892.
4. Eckstein HH, Ringleb P, Allenberg JR, Berger J, Fraedrich G, Hacke W, et al. Results of the Stent-Protected Angioplasty versus Carotid Endarterectomy (SPACE) study to treat symptomatic stenoses at 2 years: a multinational, prospective, randomised trial. *Lancet Neurol*. 2008;7:893–902.
5. Brott TG, Halperin JL, Abbara S, Bacharach JM, Barr JD, Bush RL, et al; American College of Cardiology Foundation; American Stroke Association; American Association of Neurological Surgeons; American College of Radiology; American Society of Neuroradiology; Congress of Neurological Surgeons; Society of Atherosclerosis Imaging and Prevention; Society for Cardiovascular Angiography and Interventions; Society of Interventional Radiology; Society of NeuroInterventional Surgery; Society for Vascular Medicine; Society for Vascular Surgery. 2011 ASA/ACCF/AHA/AANN/AANS/ACR/ASNR/CNS/SAIP/SCAI/SIR/SNIS/SVM/SVS guideline on the management of patients with extracranial carotid and vertebral artery disease: executive summary. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American Stroke Association, American Association of Neuroscience Nurses, American Association of Neurological Surgeons, American College of Radiology, American Society of Neuroradiology, Congress of Neurological Surgeons, Society of Atherosclerosis Imaging and Prevention, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of NeuroInterventional Surgery, Society for Vascular Medicine, and Society for Vascular Surgery. *Circulation*. 2011;124:489–532.
6. Tendera M, Aboyans V, Bartelink ML, Baumgartner I, Clement D, Collet JP, et al. ESC Guidelines on the diagnosis and treatment of peripheral artery diseases: Document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteries: the Task Force on the Diagnosis and Treatment of Peripheral Artery Diseases of the European Society of Cardiology (ESC). *Eur Heart J*. 2011;32:2851–2906.
7. Bonati LH, Dobson J, Algra A, Branchereau A, Chatellier G, Fraedrich G, et al. Short-term outcome after stenting versus endarterectomy for symptomatic carotid stenosis: a preplanned meta-analysis of individual patient data. *Lancet*. 2010;376:1062–1073.
8. Bond R, Rerkasem K, Cuffe R, Rothwell PM. A systematic review of the associations between age and sex and the operative risks of carotid endarterectomy. *Cerebrovasc Dis*. 2005;20:69–77.
9. Bond R, Rerkasem K, Rothwell PM. Systematic review of the risks of carotid endarterectomy in relation to the clinical indication for and timing of surgery. *Stroke*. 2003;34:2290–2301.
10. Rerkasem K, Rothwell PM. Systematic review of the operative risks of carotid endarterectomy for recently symptomatic stenosis in relation to the timing of surgery. *Stroke*. 2009;40:e564–e572.
11. Touzé E, Trinquart L, Chatellier G, Mas JL. Systematic review of the perioperative risks of stroke or death after carotid angioplasty and stenting. *Stroke*. 2009;40:e683–e693.
12. Naggara O, Touzé E, Beyssen B, Trinquart L, Chatellier G, Meder JF, et al; EVA-3S Investigators. Anatomical and technical factors associated with stroke or death during carotid angioplasty and stenting: results from the endarterectomy versus angioplasty in patients with symptomatic severe carotid stenosis (EVA-3S) trial and systematic review. *Stroke*. 2011;42:380–388.
13. Yadav JS, Wholey MH, Kuntz RE, Fayad P, Katzen BT, Mishkel GJ, et al. Protected carotid-artery stenting versus endarterectomy in high-risk patients. *N Engl J Med*. 2004;351:1493–1501.
14. Rerkasem K, Rothwell PM. Temporal trends in the risks of stroke and death due to endarterectomy for symptomatic carotid stenosis: an updated systematic review. *Eur J Vasc Endovasc Surg*. 2009;37:504–511.
15. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med*. 2009;151:264–269.
16. Sweeting MJ, Sutton AJ, Lambert PC. What to add to nothing? Use and avoidance of continuity corrections in meta-analysis of sparse data. *Stat Med*. 2004;23:1351–1375.
17. Fleiss JL. Analysis of data from multiclinic trials. *Control Clin Trials*. 1986;7:267–275.
18. Koopman L, van der Heijden GJ, Hoes AW, Grobbee DE, Rovers MM. Empirical comparison of subgroup effects in conventional and individual patient data meta-analyses. *Int J Technol Assess Health Care*. 2008;24:358–361.
19. Freeman M, Tukey J. Transformations related to the angular and the square root. *Ann Math Stat*. 1950;21:607–611.

20. Higgins JP, Thompson SG. Controlling the risk of spurious findings from meta-regression. *Stat Med*. 2004;23:1663–1682.
21. Rothwell PM. ACST: which subgroups will benefit most from carotid endarterectomy? *Lancet*. 2004;364:1122–1123.
22. Rothwell PM, Eliasziw M, Gutnikov SA, Warlow CP, Barnett HJ; Carotid Endarterectomy Trialists Collaboration. Endarterectomy for symptomatic carotid stenosis in relation to clinical subgroups and timing of surgery. *Lancet*. 2004;363:915–924.
23. Brown MM, Raine R. Should sex influence the choice between carotid stenting and carotid endarterectomy? *Lancet Neurol*. 2011;10:494–497.
24. Howard VJ, Lutsep HL, Mackey A, Demaerschalk BM, Sam AD II, Gonzales NR, et al; CREST investigators. Influence of sex on outcomes of stenting versus endarterectomy: a subgroup analysis of the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST). *Lancet Neurol*. 2011;10:530–537.
25. Lee JW, Pomposelli F, Park KW. Association of sex with perioperative mortality and morbidity after carotid endarterectomy for asymptomatic carotid stenosis. *J Cardiothorac Vasc Anesth*. 2003;17:10–16.
26. Rockman CB, Castillo J, Adelman MA, Jacobowitz GR, Gagne PJ, Lamparello PJ, et al. Carotid endarterectomy in female patients: are the concerns of the Asymptomatic Carotid Atherosclerosis Study valid? *J Vasc Surg*. 2001;33:236–240.
27. Goodney PP, Wallaert JB, Scali ST, Stone DH, Patel V, Shaw P, et al. Impact of practice patterns in shunt use during carotid endarterectomy with contralateral carotid occlusion. *J Vasc Surg*. 2012;55:61–71.
28. Aburahma AF, Mousa AY, Stone PA. Shunting during carotid endarterectomy. *J Vasc Surg*. 2011;54:1502–1510.
29. Bond R, Rerkasem K, Counsell C, Salinas R, Naylor R, Warlow CP, et al. Routine or selective carotid artery shunting for carotid endarterectomy (and different methods of monitoring in selective shunting). *Cochrane Database Syst Rev*. 2002;2002:CD000190.
30. Touzé E, Calvet D, Chatellier G, Mas JL. Carotid stenting. *Curr Opin Neurol*. 2008;21:56–63.
31. Gray WA, Yadav JS, Verta P, Scicli A, Fairman R, Wholey M, et al; CAPTURE Trial Collaborators. The CAPTURE registry: predictors of outcomes in carotid artery stenting with embolic protection for high surgical risk patients in the early post-approval setting. *Catheter Cardiovasc Interv*. 2007;70:1025–1033.
32. Gray WA, Chaturvedi S, Verta P; Investigators and the Executive Committees. Thirty-day outcomes for carotid artery stenting in 6320 patients from 2 prospective, multicenter, high-surgical-risk registries. *Circ Cardiovasc Interv*. 2009;2:159–166.
33. Safian RD, Bresnahan JF, Jaff MR, Foster M, Bacharach JM, Maini B, et al; CREATE Pivotal Trial Investigators. Protected carotid stenting in high-risk patients with severe carotid artery stenosis. *J Am Coll Cardiol*. 2006;47:2384–2389.
34. Gray WA, Yadav JS, Verta P, Scicli A, Fairman R, Wholey M, et al. The CAPTURE registry: results of carotid stenting with embolic protection in the post approval setting. *Catheter Cardiovasc Interv*. 2007;69:341–348.
35. Katzen BT, Criado FJ, Ramee SR, Massop DW, Hopkins LN, Donohoe D, et al; CASES-PMS Investigators. Carotid artery stenting with emboli protection surveillance study: thirty-day results of the CASES-PMS study. *Catheter Cardiovasc Interv*. 2007;70:316–323.
36. Bazan HA, Pradhan S, Mojibian H, Kyriakides T, Dardik A. Increased aortic arch calcification in patients older than 75 years: implications for carotid artery stenting in elderly patients. *J Vasc Surg*. 2007;46:841–845.
37. Lam RC, Lin SC, DeRubertis B, Hynecek R, Kent KC, Faries PL. The impact of increasing age on anatomic factors affecting carotid angioplasty and stenting. *J Vasc Surg*. 2007;45:875–880.
38. Frericks H, Kievit J, van Baalen JM, van Bockel JH. Carotid recurrent stenosis and risk of ipsilateral stroke: a systematic review of the literature. *Stroke*. 1998;29:244–250.
39. AbuRahma AF, Jennings TG, Wulu JT, Tarakji L, Robinson PA. Redo carotid endarterectomy versus primary carotid endarterectomy. *Stroke*. 2001;32:2787–2792.
40. Lal BK, Hobson RW II. Management of carotid restenosis. *J Cardiovasc Surg (Torino)*. 2006;47:153–160.
41. Ricotta JJ, Aburahma A, Ascher E, Eskandari M, Faries P, Lal BK; Society for Vascular Surgery. Updated Society for Vascular Surgery guidelines for management of extracranial carotid disease. *J Vasc Surg*. 2011;54:e1–31.
42. Streifler JY, Eliasziw M, Benavente OR, Alamowitch S, Fox AJ, Hachinski VC, et al; North American Symptomatic Carotid Endarterectomy Trial Group. Prognostic importance of leukoaraiosis in patients with symptomatic internal carotid artery stenosis. *Stroke*. 2002;33:1651–1655.
43. Ederle J, Davagnanam I, van der Worp HB, Venables GS, Lyrer PA, Featherstone RL, et al; ICSS investigators. Effect of white-matter lesions on the risk of periprocedural stroke after carotid artery stenting versus endarterectomy in the International Carotid Stenting Study (ICSS): a prespecified analysis of data from a randomised trial. *Lancet Neurol*. 2013;12:866–872.
44. Collaboration CST. The risk of carotid artery stenting compared with carotid endarterectomy is greatest in patients treated within 7 days of symptoms. *J Vasc Surg*. 2013;57:619–626.

Supplemental Material

A clinical rule (SCAR) to select patients for stenting versus carotid endarterectomy: a systematic review of observational studies with validation in randomised trials

Supplementary table I – Characteristics of studies included in the systematic review and meta-analysis according to the 9 risk factors analysed.

Subgroup	Intervention	N studies (N)	Variable	Mean	Min	Max
Age (years)	**CAS**	30	Age (years)	71.1	63.0	74.0
			Male (%)	69.7	59.0	86.0
			Symptomatic (%)	40.8	14.0	100.0
			Study size (N patients)	410	15	5341
			Single-center studies (N)	14		
			Consecutive enrollment (N)	16		
			Prospective studies (N)	15		
	CEA	52	Age (years)	69.3	57.0	84.0
			Male (%) (%)	74.0	52.0	95.0
			Symptomatic (%)	55.8	0.0	100.0
			Study size (N patients)	523	79	13622
			Single-center studies (N)	34		
			Consecutive enrollment (N)	31		
			Prospective studies (N)	17		
Contralateral occlusion	**CAS**	9	Age (years)	71.3	69.0	73.0
			Male (%)	68.7	62.0	84.0
			Symptomatic (%)	32.0	26.0	61.0
			Study size (N patients)	471	58	2001
			Single-center studies (N)	6		
			Consecutive enrollment (N)	7		
			Prospective studies (N)	5		
	CEA	33	Age (years)	68.3	57.0	75.0
			Male (%)	67.8	58.0	93.0
			Symptomatic (%)	53.8	0.0	100.0
			Study size (N patients)	526	83	6038
			Single-center studies (N)	24		
			Consecutive enrollment (N)	19		
			Prospective studies (N)	11		
Coronary artery disease	**CAS**	8	Age (years)	70.8	61.0	72.0
			Male (%)	70.3	65.0	74.0
			Symptomatic (%)	39.7	24.0	100.0
			Study size (N patients)	353	26	1380
			Single-center studies (N)	7		
			Consecutive enrollment (N)	5		
			Prospective studies (N)	2		
	CEA	16	Age (years)	68.5	57.0	75.0
			Male (%)	66.1	58.0	76.0
			Symptomatic (%)	51.8	21.0	100.0
			Study size (N patients)	600	83	6038
			Single-center studies (N)	8		
			Consecutive enrollment (N)	7		
			Prospective studies (N)	4		

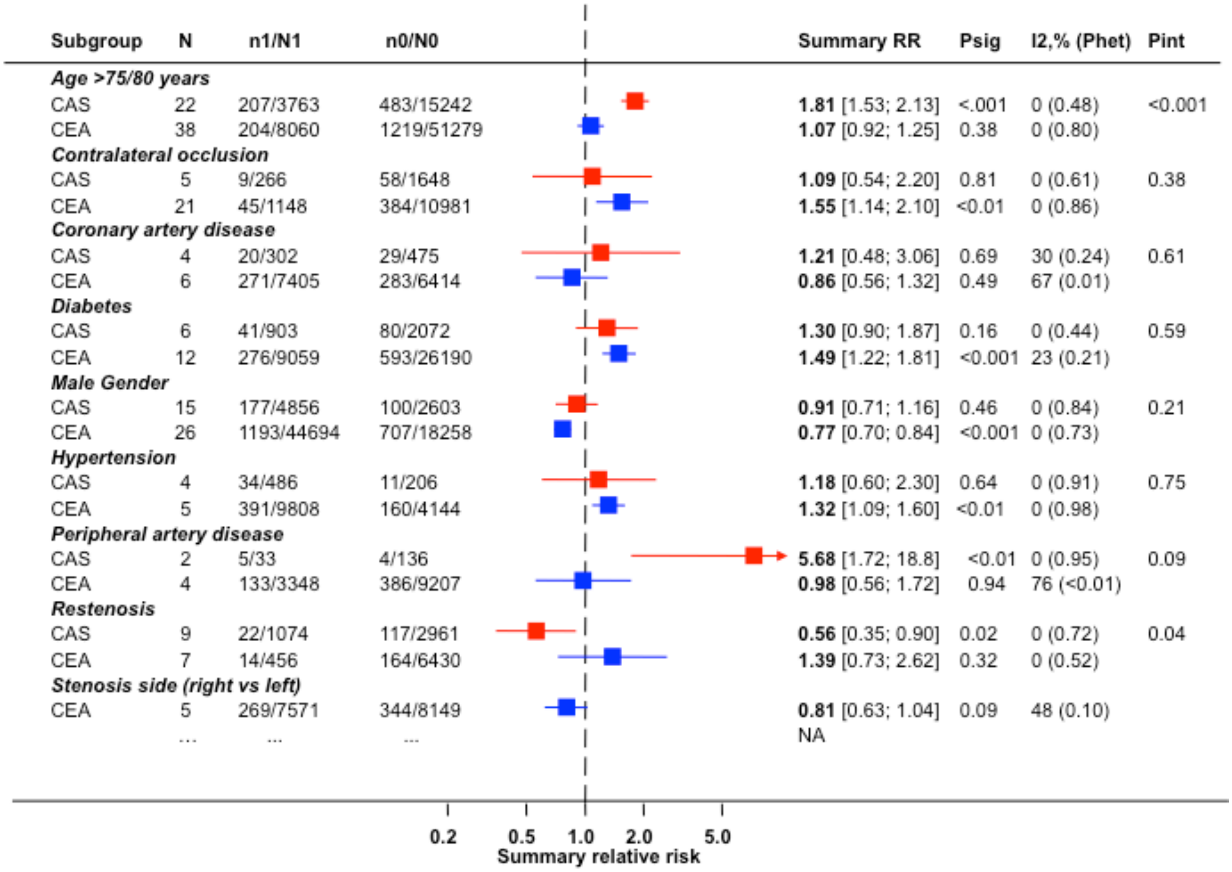
Supplementary table I – Characteristics of studies included in the systematic review and meta-analysis according to the 9 risk factors analysed (continued).

Subgroup	Intervention	N studies (N)	Variable	Mean	Min	Max
Diabetes	**CAS**	12	Age (years)	71.2	67.0	73.0
			Male (%)	69.5	63.0	84.0
			Symptomatic (%)	33.7	22.0	100.0
			Study size (N patients)	584	26	1729
			Single-center studies (N)	8		
			Consecutive enrollment (N)	7		
			Prospective studies (N)	3		
	CEA	23	Age (years)	68.4	57.0	75.0
			Male (%)	77.9	53.0	95.0
			Symptomatic (%)	53.6	0.0	100.0
			Study size (N patients)	678	57	13622
			Single-center studies (N)	12		
			Consecutive enrollment (N)	11		
			Prospective studies (N)	9		
Gender	**CAS**	21	Age (years)	70.1	61.0	73.0
			Male (%)	70.1	47.0	90.0
			Symptomatic (%)	47.3	24.0	100.0
			Study size (N patients)	418	15	5341
			Single-center studies (N)	13		
			Consecutive enrollment (N)	7		
			Prospective studies (N)	10		
	CEA	42	Age (years)	67.9	62.0	75.0
			Male (%)	72.4	43.0	95.0
			Symptomatic (%)	61.7	0.0	100.0
			Study size (N patients)	520	53	13622
			Single-center studies (N)	24		
			Consecutive enrollment (N)	22		
			Prospective studies (N)	13		
Hypertension	**CAS**	9	Age (years)	70.7	61.0	72.0
			Male (%)	71.1	65.0	84.0
			Symptomatic (%)	40.0	24.0	100.0
			Study size (N patients)	333	26	1380
			Single-center studies (N)	8		
			Consecutive enrollment (N)	6		
			Prospective studies (N)	1		
	CEA	17	Age (years)	68.7	62.0	75.0
			Male (%)	66.5	53.0	76.0
			Symptomatic (%)	49.3	0.0	100.0
			Study size (N patients)	752	252	6038
			Single-center studies (N)	6		
			Consecutive enrollment (N)	6		
			Prospective studies (N)	5		

Supplementary table I – Characteristics of studies included in the systematic review and meta-analysis according to the 9 risk factors analysed (continued).

Subgroup	Intervention	N studies (N)	Variable	Mean	Min	Max
Peripheral artery disease	**CAS**	6	Age (years)	71.3	69.0	72.0
			Male (%)	71.2	65.0	77.0
			Symptomatic (%)	27.5	24.0	50.0
			Study size (N patients)	470	26	1380
			Single-center studies (N)	5		
			Consecutive enrollment (N)	4		
			Prospective studies (N)	2		
	CEA	7	Age (years)	68.4	57.0	72.0
			Male (%)	67.5	65.0	74.0
			Symptomatic (%)	56.9	21.0	100.0
			Study size (N patients)	3056	83	6038
			Single-center studies (N)	2		
			Consecutive enrollment (N)	3		
			Prospective studies (N)	3		
Restenosis	**CAS**	11	Age (years)	70.7	61.0	74.0
			Male (%)	69.1	56.0	74.0
			Symptomatic (%)	44.3	17.0	96.0
			Study size (N patients)	418	47	5341
			Single-center studies (N)	6		
			Consecutive enrollment (N)	3		
			Prospective studies (N)	7		
	CEA	13	Age (years)	71.9	68.0	74.0
			Male (%)	59.5	51.0	70.0
			Symptomatic (%)	57.9	37.0	74.0
			Study size (N patients)	1341	352	20940
			Single-center studies (N)	11		
			Consecutive enrollment (N)	12		
			Prospective studies (N)	5		
Stenosis side	**CAS**	4	Age (years)	69.8	67.0	70.0
			Male (%)	70.8	68.0	71.0
			Symptomatic (%)	59.8	55.0	100.0
			Study size (N patients)	562	77	5341
			Single-center studies (N)	2		
			Consecutive enrollment (N)	3		
			Prospective studies (N)	1		
	CEA	8	Age (years)	66.6	57.0	69.0
			Male (%)	66.5	65.0	74.0
			Symptomatic (%)	72.2	60.0	100.0
			Study size (N patients)	1807	83	6038
			Single-center studies (N)	2		
			Consecutive enrollment (N)	4		
			Prospective studies (N)	2		

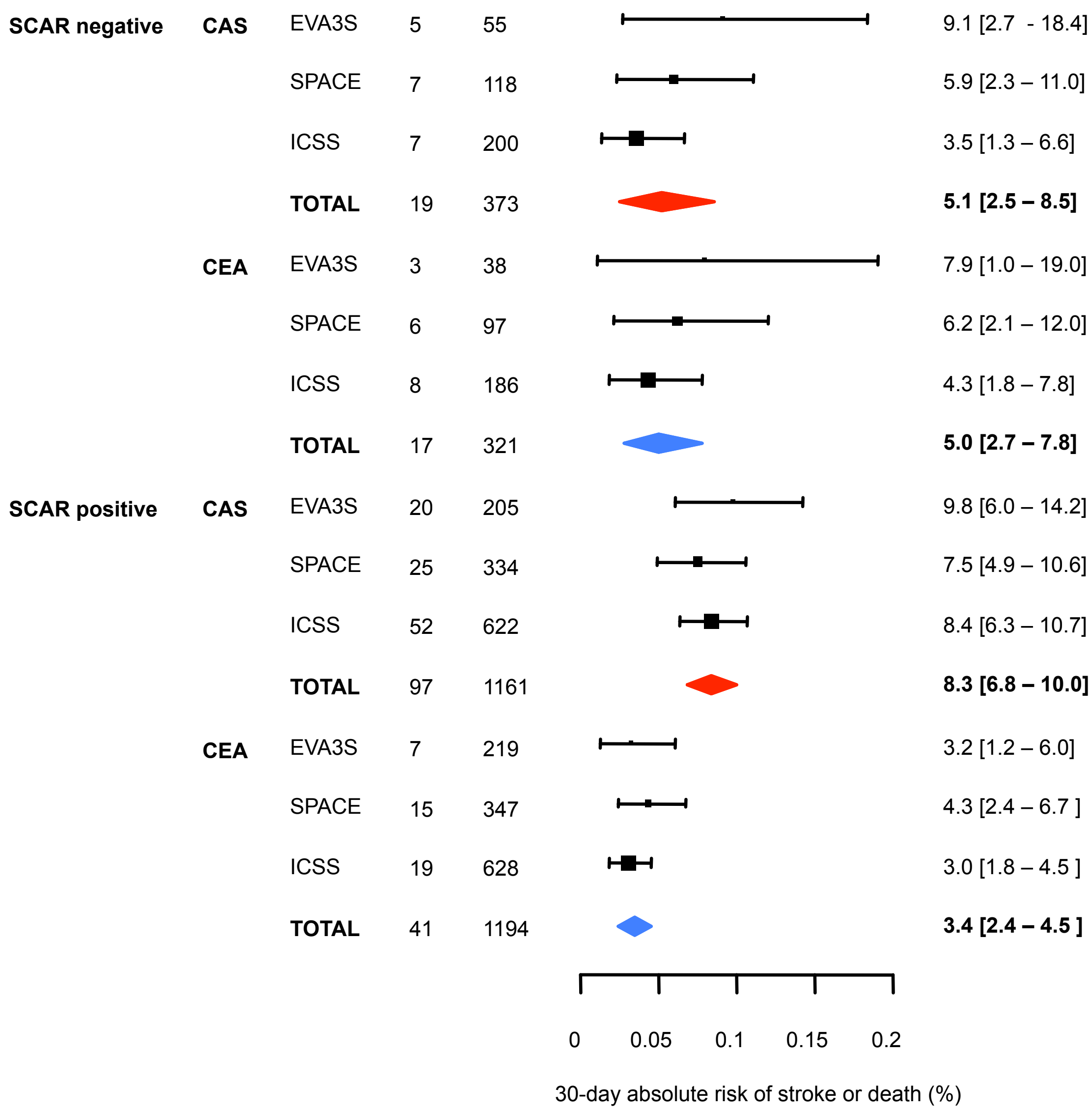
Supplementary figure I – Meta-analyses of the relative risk of stroke after CAS and CEA according to the 9 potential risk factors.



Supplementary table II – Categorization of patients according to the 2 potential definitions of the SCAR rule.

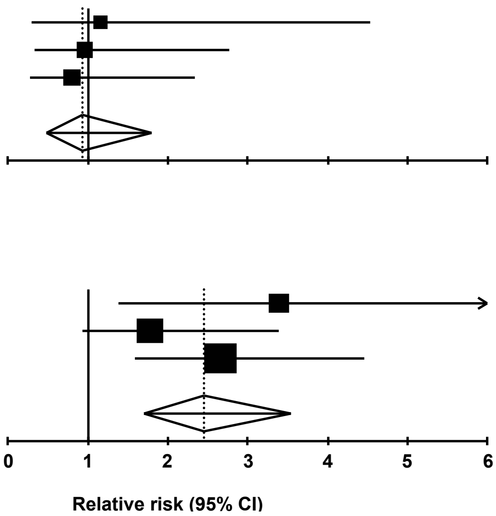
	Contralateral occlusion								No contralateral occlusion							
	Restenosis				No restenosis				Restenosis				No restenosis			
	Women		Men		Women		Men		Women		Men		Women		Men	
Age	<75	>75	<75	>75	<75	>75	<75	>75	<75	>75	<75	>75	<75	>75	<75	>75
SCAR primary option	-	-	-	-	-	-	-	-	-	-	-	-	-	+	+	+
SCAR secondary option	-	-	-	-	-	-	-	+	-	-	-	+	-	+	+	+

Supplementary figure II – Pooled absolute risks of stroke and death according to the SCAR rule in the three large randomised trials of CEA vs. CAS in the CSTC.



Supplementary figure III – Application of the SCAR rule (primary definition) to the pooled data on procedural risk of stroke from the three large randomised trials of CEA vs. CAS in the CSTC.

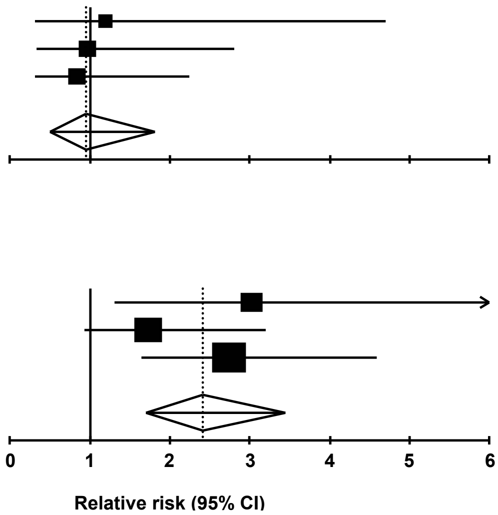
Study	Events / Patients: Treatment	Events / Patients: Control	RR	95% CI
SCAR negative				
EVA3S	5 / 55	3 / 38	1.15	0.29-4.53
SPACE	7 / 118	6 / 97	0.96	0.33-2.76
ICSS	6 / 200	7 / 186	0.80	0.27-2.33
TOTAL	18 / 373	16 / 321	0.93	0.48-1.80
Significance: p = 0.83				
Heterogeneity: p = 0.92				
SCAR positive				
EVA3S	19 / 205	6 / 219	3.38	1.38-8.30
SPACE	24 / 334	14 / 347	1.78	0.94-3.38
ICSS	50 / 622	19 / 628	2.66	1.59-4.45
TOTAL	93 / 1161	39 / 1194	2.45	1.70-3.54
Significance: p = <0.0001				
Heterogeneity: p = 0.46				



Supplementary figure IV – Application of the SCAR rule (secondary definition, i.e. all factors are considered as equivalent) to the pooled data on procedural risk of stroke and death (A) and stroke (B) from the three large randomised trials of CEA vs. CAS in the CSTC.

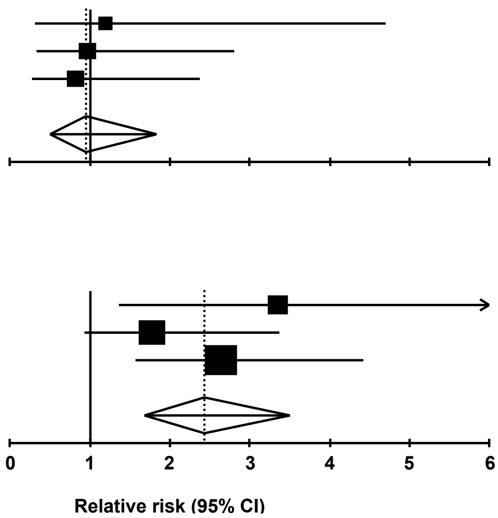
A – Stroke and death

Study	Events / Patients		RR	95% CI
	Treatment	Control		
SCAR negative				
EVA3S	5 / 53	3 / 38	1.19	0.30-4.70
SPACE	7 / 115	6 / 96	0.97	0.34-2.80
ICSS	7 / 189	8 / 180	0.83	0.31-2.25
TOTAL	19 / 357	17 / 314	0.95	0.50-1.80
Significance: p = 0.88				
Heterogeneity: p = 0.92				
SCAR positive				
EVA3S	20 / 207	7 / 219	3.02	1.31-7.00
SPACE	25 / 337	15 / 348	1.72	0.92-3.21
ICSS	52 / 633	19 / 634	2.74	1.64-4.58
TOTAL	97 / 1177	41 / 1201	2.42	1.69-3.45
Significance: p = <0.0001				
Heterogeneity: p = 0.44				



B – Stroke

Study	Events / Patients		RR	95% CI
	Treatment	Control		
SCAR negative				
EVA3S	5 / 53	3 / 38	1.19	0.30-4.70
SPACE	7 / 115	6 / 96	0.97	0.34-2.80
ICSS	6 / 189	7 / 180	0.82	0.28-2.38
TOTAL	18 / 357	16 / 314	0.95	0.49-1.84
Significance: p = 0.89				
Heterogeneity: p = 0.91				
SCAR positive				
EVA3S	19 / 207	6 / 219	3.35	1.36-8.22
SPACE	24 / 337	14 / 348	1.77	0.93-3.36
ICSS	50 / 633	19 / 634	2.64	1.57-4.42
TOTAL	93 / 1177	39 / 1201	2.43	1.69-3.51
Significance: p = <0.0001				
Heterogeneity: p = 0.47				



List of all references included in the systematic review.
Subgroup=Age
CAS

Zarins CK *et al*. J Endovasc Ther 2009;16:397-409.
Takayama K *et al*. Radiat Med 2008;26:348-354.
Stabile E *et al*. J Am Coll Cardiol 2010;55:1661-1667.
Randall MS *et al*. Circ Cardiovasc Interv 2010;3:50-56.
Perona F *et al*. Radiology 2009;250:178-183.
Kawabata Y *et al*. J Vasc Interv Radiol 2009;20:9-16.
Karkos CD *et al*. Cardiovasc Intervent Radiol 2010;33:34-40.
Henry M *et al*. Catheter Cardiovasc Interv 2008;72:309-317.
De Rango P *et al*. J Vasc Surg 2010;51:337-344.
Cremonesi A *et al*. EuroIntervention 2009;5:589-598.
Chaturvedi S *et al*. Stroke 2010;41:757-764.
Bacharach JM *et al*. Ann Vasc Surg 2010;24:153-159.
Almekhlafi MA *et al*. Can J Neurol Sci 2011;38:446-451.
Katzen B *et al*. Am J Cardiol 2006;98(suppl 1):11M.
Kastrup A *et al*. AJNR Am J Neuroradiol 2008;29:608-612.
Theiss W *et al*. Stroke 2008;39:2325-2330.
Kadkhodayan Y *et al*. Neuroradiology 2007;49:933-938.
Gray WA *et al*. Catheter Cardiovasc Interv 2007;70:1025-1033.
Zahn R *et al*. Eur Heart J 2007;28:370-375.
Teitelbaum GP *et al*. Surgical Neurology 1998;50:300-311.
Shawl F *et al*. J Am Coll Cardiol 2000;35:1721-1728.
Reimers B *et al*. Am J Med 2004;116:217-222.
Roubin GS *et al*. Circulation 2001;103:532-537.
Ahmadi R *et al*. J Endovasc Ther 2002;9:559-565.
Hobson RW *et al*. J Vasc Surg 2004;40:1106-1111.
Setacci C *et al*. J Endovasc Ther 2006;13:302-309.
Safian RD *et al*. J Am Coll Cardiol 2006;47:2384-2389.
Lam RC *et al*. J Vasc Surg 2007;45:875-880.
Topakian R *et al*. Eur J Neurol 2007;14:672-678.
Aydiner O *et al*. Anadolu Kardiyol Derg 2007;7:152-157.

CEA

Zarins CK *et al*. J Endovasc Ther 2009;16:397-409.
Young B *et al*. Stroke 1996;27:2216-2224.
Wong JH *et al*. Stroke 1997;28:891-898.
Van Damme H *et al*. Acta Chir Belg 1996;96:71-77.
Tu JV *et al*. Stroke 2003;34:2568-2573.
Tretter MJ *et al*. J Vasc Surg 1999;30:618-631.
Ting ACW *et al*. Cardiovasc Surg 2000;8:441-445.
Taylor DW *et al*. Lancet 1999;353:2179-2184.
Stoner MC *et al*. J Vasc Surg 2006;43:285-295.
Sternbergh WC *et al*. The Ochsner Journal 2003;5:24-30.
Sokol D *et al*. Acta Neurochir (Wien) 2011;153:363-369.
Schultz RD *et al*. Surg Gynecol Obstet 1988;166:245-251.
Schneider JR *et al*. J Vasc Surg 2000;31:927-935.
Salameh JR *et al*. Arch Surg 2002;137:1284-1288.
Rockman CB *et al*. Ann Vasc Surg 2003;17:9-14.
Reed AB *et al*. J Vasc Surg 2003;37:1191-1199.
Pulli R *et al*. Am J Surg 2005;189:714-719.
Pruner G *et al*. Cardiovasc Surg 2003;11:105-112.
Perler BA *et al*. J Am Coll Surg 1996;183:559-564.
Papachristou EA *et al*. Vasc Surg 1994;28:531-537.
Ouriel K *et al*. Surg Gynecol Obstet1986;162:334-336.
Organ N *et al*. Eur J Vasc Endovasc Surg 2008;35:273-279.
Ommer A *et al*. Cardiovasc Surg 2001;9:552-558.
Naylor AR *et al*. J Vasc Surg 2000;32:750-759.
Navas Vinagre I *et al*. Neurologia 2008;23:408-414.
Miller MT *et al*. J Vasc Surg 2005;41:231-237.

Maxwell JG *et al*. Am Surg 2000;66:773-780.
Magnadottir HB *et al*. Neurosurgery 1999;45:786-791.
Love A *et al*. Cardiovasc Surg 2000;8:429-435.
Lau D *et al*. Am J Surg 2005;190:795-799.
Kucey DS *et al*. J Vasc Surg 1998;28:1051-1058.
Kerdiles Y *et al*. J Cardiovasc Surg (Torino) 1997;38:327-334.
Hannan EL. Stroke 2001;32:2890-2897.
Halm EA *et al*. Stroke 2009;40:221-229.
Halliday A *et al*. Lancet 2004;363(9420):1491-1502.
Goldman KA *et al*. Vasc Surg 1999;33:451-460.
Fabiani A *et al*. Cardiovasc Surg 2001;9:2-2.
ECST. Lancet 1998;351:1379-1387.
Dorigo W *et al*. J Vasc Surg 2011;53:44-52.
Dorafshar AH *et al*. Ann Vasc Surg 2004;18:729-735.
De Rango P *et al*. J Vasc Surg 2010;51:337-344.
Debing E *et al*. Surg Neurol 2007;67:467-471.
Coyle KA *et al*. Ann Vasc Surg 1994;8:417-420.
Cebul RD *et al*. JAMA 1998;279:1282-1287.
Cartier B *et al*. Ann Vasc Surg 2002;16:751-755.
Brown MM *et al*. Pract Neurol 2008;8:39-45.
Barnett HJ *et al*. N Engl J Med 1998;339:1415-1425.
Ballotta E *et al*. J Vasc Surg 2009;50:518-525.
Aune S *et al*. Int Angiol 2003;22:421-425.
Ascher E *et al*. Ann Vasc Surg 2001;15:275-280.
Alozairi O *et al*. Eur J Vasc Endovasc Surg 2003;26:245-249.
Allcutt DA *et al*. Br J Neurosurg 1991;5:257-264.

Contralateral occlusion
CAS
Stabile E *et al*. J Am Coll Cardiol 2010;55:1661-1667.
Perona F *et al*. Radiology 2009;250:178-183.
Massop D *et al*. Catheter Cardiovasc Interv 2009;73:129-136.
Kawabata Y *et al*. J Vasc Interv Radiol 2009;20:9-16.
Silvestro A *et al*. J Cardiovasc Med (Hagerstown) 2008;9:137-141.
Reimers B *et al*. Am J Med 2004;116:217-222.
Sabeti S *et al*. Radiology 2004;230:70-76.
Lanzer P *et al*. Clin Res Cardiol 2006;95:4-12.
Hofmann R *et al*. Stroke 2006;37:2557-2561.

CEA
Tu JV *et al*. Stroke 2003;34:2568-2573.
Simo G *et al*. Cardiovasc Surg 2001;9:29-29.
Schneider JR *et al*. J Vasc Surg 2002;35:1114-1122.
Samson RH *et al*. Cardiovasc Surg 1998;6:475-484.
Pulli R *et al*. Am J Surg 2005;189:714-719.
Perler BA *et al*. J Vasc Surg 1992;16:347-352.
Naylor AR *et al*. J Vasc Surg 2000;32:750-759.
McCarthy WJ *et al*. Am J Surg 1993;166:168-171.
Mattos MA *et al*. Surgery 1992;112:670-679.
Magnan PE *et al*. Ann Vasc Surg 1993;7:521-529.
Magnadottir HB *et al*. Neurosurgery 1999;45:786-791.
Lacroix H *et al*. Cardiovasc Surg 1994;2:26-31.
Kerdiles Y *et al*. J Cardiovasc Surg (Torino) 1997;38:327-334.
Karmeli R *et al*. Cardiovasc Surg 2001;9:334-338.
Julia P *et al*. Ann Vasc Surg 1998;12:566-571.
Jordan WD *et al*. J Vasc Surg 2002;35:16-21.
Jansen C *et al*. Ann Vasc Surg 1993;7:95-101.
Hannan EL *et al*. Stroke 2001;32:2890-2897.
Halliday A *et al*. Lancet 2004;363:1491-1502.
Furst H *et al*. World J Surg 2001;25:969-974.
Fitzpatrick CM *et al*. Mil Med 2005;170:1069-1074.
ECST. Lancet 1998;351:1379-1387.

Dorigo W *et al*. J Vasc Surg 2011;53:44-52.
Domenig C *et al*. Ann Vasc Surg 2003;17:622-628.
Deriu GP *et al*. Ann Vasc Surg 1994;8:337-342.
da Silva AF *et al*. Br J Surg 1996;83:1370-1372.
Cao P *et al*. Eur J Vasc Endovasc Surg 1995;10:16-22.
Bunt TJ *et al*. Am Surg 1985;51:61-69.
Barnett HJ *et al*. N Engl J Med 1998;339:1415-1425.
Baker WH *et al*. Stroke 2000;31:2330-2334.
Allcutt DA *et al*. Br J Neurosurg 1991;5:257-264.
AbuRahma AF *et al* .Stroke 2000;31:1566-1571.

Coronary artery disease
CAS

Randall MS *et al*. Circ Cardiovasc Interv 2010;3:50-56.
De Rango P *et al*. J Vasc Surg 2010;51:337-344.
Cremonesi A *et al*. EuroIntervention 2009;5:589-598.
Lanzer P *et al*. Clin Res Cardiol 2006;95:4-12.
Gupta AK *et al*. Neurol India 2006;54:68-72.
Hofmann R *et al*. Stroke 2006;37:2557-2561.
Topakian R *et al*. Eur J Neurol 2007;14:672-678.
Aydiner O *et al*. Anadolu Kardiyol Derg 2007;7:152-157.

CEA

Wong JH *et al*. Stroke 1997;28:891-898.
Tu JV *et al*. Stroke 2003;34:2568-2573.
Magnan PE *et al.* Ann Vasc Surg 1993;7:521-529.
Magnadottir HB *et al*.Neurosurgery 1999;45:786-791.
Kucey DS *et al*.J Vasc Surg 1998;28:1051-1058.
Kerdiles Y *et al*. J Cardiovasc Surg (Torino) 1997;38:327-334.
Jordan WD *et al*. J Vasc Surg 2002;35:16-21.
Hannan EL *et al*. Stroke 2001;32:2890-2897.
Halm EA *et al*. Stroke 2009;40:221-229.
Goodney PP *et al*. J Vasc Surg 2008;48:1139-1145.
Furst H *et al*. World J Surg 2001;25:969-974.
Lancet 1998;351:1379-1387.
Dorigo W *et al*. J Vasc Surg 2011;53:44-52.
Barnett HJ *et al*. N Engl J Med 1998;339:1415-1425.
Allcutt DA *et al*. Br J Neurosurg 1991;5:257-264.

Diabetes
CAS

Schluter M *et al*. J Endovasc Ther 2007;14:271-278.
Randall MS *et al*. Circ Cardiovasc Interv 2010;3:50-56.
Kawabata Y *et al*. J Vasc Interv Radiol 2009;20:9-16.
Karkos CD *et al*. Cardiovasc Intervent Radiol 2010;33:34-40.
De Rango P *et al*. J Vasc Surg 2010;51:337-344.
Cremonesi A *et al*. EuroIntervention 2009;5:589-598.
Criado E *et al*. Am J Cardiol 2006;98(suppl 1):243M.
Setacci C *et al*. Am J Cardiol 2006;98(suppl 1):12M.
Lanzer P *et al*. Clin Res Cardiol 2006;95:4-12.
Hofmann R *et al*. Stroke 2006;37:2557-2561.
Topakian R *et al*. Eur J Neurol 2007;14:672-678.
Aydiner O. *et al*. Anadolu Kardiyol Derg 2007;7:152-157.

CEA

Young B *et al*. Stroke 1996;27:2216-2224.
Tu JV *et al*. Stroke 2003;34:2568-2573.
Tretter MJ *et al*. J Vasc Surg 1999;30:618-631.
Stoner MC *et al*. J Vasc Surg 2006;43:285-295.
Pistolese GR *et al*. J Vasc Surg 2001;33:148-154.
Magnan PE *et al*. Ann Vasc Surg 1993;7:521-529.
Magnadottir HB *et al*. Neurosurgery 1999;45:786-791.

Kucey DS *et al*. J Vasc Surg 1998;28:1051-1058.
Kerdiles Y *et al*. J Cardiovasc Surg (Torino) 1997;38:327-334.
Hannan EL *et al*. Stroke 2001;32:2890-2897.
Halm EA *et al*. Stroke 2009;40:221-229.
Halliday A *et al*. Lancet 2004;363:1491-1502.
Goodney PP *et al*. J Vasc Surg 2008;48:1139-1145.
Furst H *et al*. World J Surg 2001;25:969-974.
ECST. Lancet 1998;351:1379-1387.
Dorigo W *et al*. J Vasc Surg 2011;53:44-52.
Debing E *et al*. Vasc Endovasc Surg 2011;45:28-32.
Cebul RD *et al*. JAMA 1998;279:1282-1287.
Barnett HJ *et al*. N Engl J Med 1998;339:1415-1425.
Ballotta E *et al*. Surgery 2001;129:146-152.
Allcutt DA *et al*. Br J Neurosurg 1991;5:257-264.
Aguiar ET *et al*. Sao Paulo Medical Journal 2001;119:206-211.

Gender
CAS

Tietke MW *et al*. Neuroradiology 2010;52:611-618.
Takayama K *et al*. Radiat Med 2008;26:348-354.
Randall MS *et al*. Circ Cardiovasc Interv 2010;3:50-56.
Perona F *et al*. Radiology 2009;250:178-183.
Park B *et al*. Vasc Endovasc Surg 2008;42:321-328.
Karkos CD *et al*. Cardiovasc Intervent Radiol 2010;33:34-40.
Howard VJ *et al*. Lancet Neurol 2011;10:530-537.
Howard VJ *et al*. Stroke 2009;40:1140-1147.
Goldstein LJ *et al*. J Vasc Surg 2009;49:315-323.
De Rango P *et al*. J Vasc Surg 2010;51:337-344.
Cremonesi A *et al*. EuroIntervention 2009;5:589-598.
Kypta A *et al*. Am J Cardiol 2006;98(suppl 1):244M.
Gonzalez-Marcos JR *et al*. Int J Stroke 2006;1(suppl 1):65.
Arjomand H *et al*. J Am Coll Cardiol 2008;52:B78 (abstract)
Iihara K *et al*. J Neurosurg 2006;105:546-554.
Theiss W *et al*. Stroke 2008;39:2325-2330.
Teitelbaum GP *et al*. Surgical Neurology 1998;50:300-311.
Reimers B *et al*. Am J Med 2004;116:217-222.
Biasi GM *et al*. Circulation 2004;110:756-762.
Gupta AK *et al*. Neurol India 2006;54:68-72.
Aydiner O *et al*. Anadolu Kardiyol Derg 2007;7:152-157.

CEA

Vigo J *et al*. Bol Asoc Med P R 1992;84:128-131.
JAMA 1995;273:1421-1428.
Taylor DW *et al*. Lancet 1999;353:2179-2184.
Syrek JR *et al*. Surgery 1999;125:96-101.
Stoner MC *et al*. J Vasc Surg 2006;43:285-295.
Sternbach Y *et al*. Surgery 2000;127:272-275.
Sokol D *et al*. Acta Neurochir (Wien) 2011;153:363-369.
Schneider JR *et al*. J Vasc Surg 1997;25:890-896.
Sarac TP *et al*. J Vasc Surg 2002;35:748-753.
Perler BA *et al*. Cardiovasc Surg 1995;3:631-636.
Park B *et al*. Vasc Endovasc Surg 2008;42:321-328.
Organ N *et al*. Eur J Vasc Endovasc Surg 2008;35:273-279.
Naylor AR *et al*. J Vasc Surg 2000;32:750-759.
Magnan PE *et al*. Ann Vasc Surg 1993;7:521-529.
Lane JS *et al*. J Vasc Surg 2003;37:568-574.
Kucey DS *et al*. J Vasc Surg 1998;28:1051-1058.
Kerdiles Y *et al*. J Cardiovasc Surg (Torino) 1997;38:327-334.
Kapral MK *et al*. Stroke 2003;34:1120-1124.
Kapral MK *et al*. J Women's Health Gender Med 2000;9:987-994.
Jordan WD *et al*. J Vasc Surg 2002;35:16-21.
James DC *et al*. Am J Surg 2001;182:654-657.

Hugl B *et al*. Ann Vasc Surg 2006;20:602-608.
Howard VJ *et al*. Lancet Neurol 2011;10:530-537.
Hartmann A *et al*. Cerebrovasc Dis 1999;9:152-156.
Hannan EL *et al*. Stroke 2001;32:2890-2897.
Halm EA *et al*. Stroke 2009;40:221-229.
Halliday A *et al*. Lancet 2004;363:1491-1502.
Goodney PP *et al*. J Vasc Surg 2008;48:1139-1145.
Furst H *et al*. World J Surg 2001;25:969-974.
ECST. Lancet 1998;351:1379-1387.
Eckstein HH *et al*. J Vasc Surg 2002;36:997-1004.
Dorigo W *et al*. J Vasc Surg 2009;50:1301-1306.
De Rango P *et al*. J Vasc Surg 2010;51:337-344.
Chang JB *et al*. Vasc Endovasc Surg 2002;36:21-27.
Cebul RD *et al*. JAMA 1998;279(16):1282-1287.
Blohme L *et al*. Eur J Vasc Endovasc Surg 1999;17:213-218.
Barnett HJ *et al*. N Engl J Med 1998;339:1415-1425.
Ballotta E *et al*. Ann Surg 2000;232:119-125.
Archie JP *et al*. J Vasc Surg 1999;29:654-664.
Akbari CM *et al*. J Vasc Surg 2000;31:1103-1109.
Aguiar ET *et al*. Sao Paulo Medical Journal 2001;119:206-211.

Hypertension
CAS
Randall MS *et al*. Circ Cardiovasc Interv 2010;3:50-56.
Kawabata Y *et al*. J Vasc Interv Radiol 2009;20:9-16.
Karkos CD *et al*. Cardiovasc Intervent Radiol 2010;33:34-40.
De Rango P *et al*. J Vasc Surg 2010;51:337-344.
Cremonesi A *et al*. EuroIntervention 2009;5:589-598.
Gupta AK *et al*. Neurol India 2006;54:68-72.
Hofmann R *et al*. Stroke 2006;37:2557-2561.
Topakian R *et al*. Eur J Neurol 2007;14:672-678.
Aydiner O *et al*. Anadolu Kardiyol Derg 2007;7:152-157.

CEA
Young B *et al*. Stroke 1996;27:2216-2224.
Wong JH *et al*. Stroke 1997;28:891-898.
Tu JV *et al*. Stroke 2003;34:2568-2573.
Tretter MJ *et al*. J Vasc Surg 1999;30:618-631.
Taylor DW *et al* .Lancet 1999;353:2179-2184.
Magnan PE *et al*. Ann Vasc Surg 1993;7:521-529.
Kucey DS *et al*. J Vasc Surg 1998;28:1051-1058.
Kerdiles Y *et al*. J Cardiovasc Surg (Torino) 1997;38:327-334.
Hannan EL *et al*. Stroke 2001;32:2890-2897.
Halm EA *et al*. Stroke 2009;40:221-229.
Goodney PP *et al*. J Vasc Surg 2008;48:1139-1145.
Furst H *et al*. World J Surg 2001;25:969-974.
Lancet 1998;351:1379-1387.
Dorigo W *et al*. J Vasc Surg 2011;53:44-52.
Cebul RD *et al*. JAMA 1998;279:1282-1287.
Barnett HJ *et al*. N Engl J Med 1998;339:1415-1425.

Peripheral artery disease Intervention
CAS
Karkos CD *et al*. Cardiovasc Intervent Radiol 2010;33:34-40.
De Rango P *et al*. J Vasc Surg 2010;51:337-344.
Cremonesi A *et al*. EuroIntervention 2009;5:589-598.
Lanzer P *et al*. Clin Res Cardiol 2006;95:4-12.
Hofmann R *et al*. Stroke 2006;37:2557-2561.
Aydiner O *et al*. Anadolu Kardiyol Derg 2007;7:152-157.

CEA
Tu JV *et al*. Stroke 2003;34:2568-2573.
Kucey DS *et al*. J Vasc Surg 1998;28:1051-1058.
Halm EA *et al*. Stroke 2009;40:221-229.
ECST. Lancet 1998;351:1379-1387.
Dorigo W *et al*. J Vasc Surg 2011;53:44-52.
Barnett HJ *et al*. N Engl J Med 1998;339:1415-1425.
Allcutt DA *et al*. Br J Neurosurg 1991;5:257-264.

Restenosis
CAS
Vos JA *et al*. J Vasc Surg 2009;50:755-761.
Massop D *et al*. Catheter Cardiovasc Interv 2009;73:129-136.
Cuadra S *et al*. Ann Vasc Surg 2009;23:330-334.
AbuRahma AF *et al*. J Vasc Surg 2009;50:1031-1039.
Theiss W *et al*. Stroke 2008;39:2325-2330.
Biasi GM *et al*. Circulation 2004;110:756-762.
Kasirajan K *et al*. Int J Angiol 2006;15:20-24.
Gupta AK *et al*. Neurol India 2006;54:68-72.
Halabi M *et al*. Catheter Cardiovasc Interv 2006;67:513-518.
Safian RD *et al*. J Am Coll Cardiol 2006;47:2384-2389.
Mehta RH *et al*. Am J Cardiol 2007;99:1288-1293.

CEA
Tu JV *et al*. Stroke 2003;34:2568-2573.
Pulli R *et al*. Am J Surg 2005;189:714-719.
Organ N *et al*. Eur J Vasc Endovasc Surg 2008;35:273-279.
Maxwell BG *et al*. Am Surg 2000;66:793-796.
Magnadottir HB *et al*. Neurosurgery 1999;45:786-791.
Kresowik TF *et al*. J Vasc Surg 2004;39:372-380.
Jordan WD *et al*. J Vasc Surg 2002;35:16-21.
Hill BB *et al*. J Vasc Surg 1999;30:26-35.
Hertzer NR *et al*. J Vasc Surg 1997;26:1-10.
Domenig C *et al*. Ann Vasc Surg 2003;17:622-628.
Coyle KA *et al*. Ann Surg 1995;221:517-521.
Cho JS *et al*. J Vasc Surg 2004;39:155-161.
AbuRahma AF *et al*. Vasc Surg 2001;35:167-174.

Stenosis side
CAS
Zahn R *et al*. Catheter Cardiovasc Interv 2009;74:1-8.
Randall MS *et al*. Circ Cardiovasc Interv 2010;3:50-56.
Theiss W *et al*. Stroke 2008;39:2325-2330.
Topakian R *et al*. Eur J Neurol 2007;14:672-678.

CEA
Tu JV *et al*. Stroke 2003;34:2568-2573.
Tretter MJ *et al*. J Vasc Surg 1999;30:618-631.
Kucey DS *et al*. J Vasc Surg 1998;28:1051-1058.
Halm EA *et al*. Stroke 2009;40:221-229.
Girard LP *et al*. Circ Cardiovasc Qual Outcomes 2009;2:642-647.
ECST. Lancet 1998;351:1379-1387.
Barnett HJ *et al*. N Engl J Med 1998;339:1415-1425.
Allcutt DA *et al*. Br J Neurosurg 1991;5:257-264.

PRISMA Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3-4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5-6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5-6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5-6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5

PRISMA Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	NA
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6-8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9 & Suppl
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	NA
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	9, 22, Suppl
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	9, 22, Suppl
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	NA
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	9, Suppl
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	12
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	12-15
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	12-15
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	8

RESEARCH ARTICLE

Higher Alu Methylation Levels in Catch-Up Growth in Twenty-Year-Old Offsprings

Kittipan Rerkasem[1,2]*, Prakasit Rattanatanyong[3], Amarapron Rerkasem[1], Antika Wongthanee[2], Kittipong Rungruengthanakit[2], Ampica Mangklabruks[2,4], Apiwat Mutirangura[3]

1 Department of Surgery, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand, **2** The Research Institute for Health Sciences, Chiang Mai University, Chiang Mai, Thailand, **3** Center of Excellence of Molecular Genetics of Cancer and Human Diseases, Department of Anatomy, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand, **4** Department of Internal Medicine, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand

* rerkase@gmail.com

Citation: Rerkasem K, Rattanatanyong P, Rerkasem A, Wongthanee A, Rungruengthanakit K, Mangklabruks A, et al. (2015) Higher Alu Methylation Levels in Catch-Up Growth in Twenty-Year-Old Offsprings. PLoS ONE 10(3): e0120032. doi:10.1371/journal.pone.0120032

Academic Editor: Umberto Simeoni, Centre Hospitalier Universitaire Vaudois, FRANCE

Received: July 8, 2014

Accepted: January 31, 2015

Published: March 25, 2015

Data Availability Statement: All relevant data are within the paper.

Funding: This work was supported by joint funding from the Thailand Research Fund (MRG 5280229) and the National Research University Project under Thailand's office of The Commission of Higher Education. This research was also funded by the Endocrine Unit of Maharaj Nakorn Chiang Mai Hospital and the Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand. The methylation analysis was funded by Research Chair Grant 2011 from the National Science and Technology

Abstract

Alu elements and long interspersed element-1 (LINE-1 or L1) are two major human intersperse repetitive sequences. Lower Alu methylation, but not LINE-1, has been observed in blood cells of people in old age, and in menopausal women having lower bone mass and osteoporosis. Nevertheless, Alu methylation levels also vary among young individuals. Here, we explored phenotypes at birth that are associated with Alu methylation levels in young people. In 2010, 249 twenty-years-old volunteers whose mothers had participated in a study association between birth weight (BW) and nutrition during pregnancy in 1990, were invited to take part in our present study. In this study, the LINE-1 and Alu methylation levels and patterns were measured in peripheral mononuclear cells and correlated with various nutritional parameters during intrauterine and postnatal period of offspring. This included the amount of maternal intake during pregnancy, the mother's weight gain during pregnancy, birth weight, birth length, and the rate of weight gain in the first year of life. Catch-up growth (CUG) was defined when weight during the first year was $>$0.67 of the standard score, according to WHO data. No association with LINE-1 methylation was identified. The mean level of Alu methylation in the CUG group was significantly higher than those non-CUG (39.61% and 33.66 % respectively, $P < 0.0001$). The positive correlation between the history of CUG in the first year and higher Alu methylation indicates the role of Alu methylation, not only in aging cells, but also in the human growth process. Moreover, here is the first study that demonstrated the association between a phenotype during the newborn period and intersperse repetitive sequences methylation during young adulthood.

Introduction

DNA methylation is an epigenetic mark directly on CpG dinucleotide sequences [1]. The majority of DNA methylation in the human genome is on intersperse repetitive sequences (IRS).

Development Agency (NSTDA), Thailand. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: The authors have declared that no competing interests exist.

IRS methylation plays a crucial role in cellular phenotypes, controlling genomic integrity as well as gene expression [2]. Reduction of genomic methylation can lead to genomic instability [1], relating to endogenous DNA double strand break repair [3]. Genomic instability is one of the hallmark characteristics of cancer and aging cells. Global hypomethylation also alters gene expression. For example, long interspersed element-1 (LINE-1 or L1) can regulate the degree of gene expression by adjusting intragenic LINE-1 methylation level [4,5]. Here in this study we evaluated whether IRS methylation during young adulthood would be associated with phenotypes during the new born period.

Alu elements are human abundant IRS, presenting up to 300,000 copies in the human genome [1]. Lower Alu methylation has been observed in blood cells of people during old age [6], and in menopausal women having lower bone mass and osteoporosis [7], familial breast cancer [8], gastric cancer [9], and chronic lymphocytic leukemia [10]. On the other hand, higher Alu methylation has been reported in various conditions such as colorectal cancer [11], insulin resistance [12], cardiovascular risk, including hypertension/diabetes [13], and systemic lupus erythematosus [14]. No change was found in many conditions, such as exposure to pollutants, including metals and particulate air pollution [15], breast cancer [16], and prenatal arsenic exposure [17].

Most of LINE-1s are truncated. Only approximately 2 thousand copies contain 5'UTR, where methylated CpG were studied [1]. Many studies of blood cells reported lower methylation of LINE-1 in pollution exposure [9,18–20], smoking in patients with Parkinson's disease [21], increased oxidative stress [22], and several cancers [23], whereas higher methylation of LINE-1 was detected in early colorectal cancer [11], malignant melanoma [24]. Recently some studies reported the association between intrauterine and early life insult and epigenetic with the levels of line-1 methylation [17]. For example intrauterine exposure to higher levels of arsenic was positively associated with DNA methylation in LINE-1 in umbilical cord blood [17]. Also lower LINE-1 methylation is related to development of adiposity in 553 boys, aged 5–12 years [25].

Here we investigated the correlation between phenotypes of the perinatal period with IRS methylation during young adulthood. In 2010, we invited volunteers who had participated as newborns for birth weight and nutrition during a pregnancy study in 1990 (Chiang Mai Low Birth Weight Study-CMLBWS) [26]. We found that offsprings with history of intrauterine growth retardation (IUGR) such as poor intrauterine nutrition, mother with pregnancy induced hypertension (PIH) were associated significantly with rapid weight gain (catch-up growths) in the first year of life than those offsprings without IUGR [27]. Also these IUGR offsprings with abundant postnatal nutrition were significantly associated with catch-up growths (CUG) during the first year of life. These CUG had been reported previously, but was associated with metabolic and non-communicable diseases, such as high body fat deposition [28], increased blood pressure [29], and diabetes [30]. However, the precise mechanism of this association is still unknown. The epigenetic memory was proposed to be a molecular mechanism [31]. During in utero, or early postnatal development, short term changes through environmental affect could permanently change gene expression, and consequently organ development at a time of extreme vulnerability.

We chose to evaluate DNA methylation, not only its levels, but also its patterns. Changes in DNA methylation of IRS is not homogenous. Previously, we demonstrated not only a general, but also locus specific influence of LINE-1 methylation [32]. Therefore, in some situations methylation of different IRS loci were not harmoniously changed. For example, both hypo and hypermethylated LINE-1 loci can be discovered in smoke-exposed oral epithelial [33]. Currently, there are two commonly used techniques: pyrosequencing [1], and Combine Bisulfite Restriction Analysis (COBRA) [34].Both techniques precisely measure methylation levels.

Unfortunately, pyrosequencing can only measure DNA methylation levels. Therefore, herein this study, we chose to evaluate LINE-1 and Alu methylation levels and patterns by COBRA.

Materials and Methods

In 2010, we invited adolescents whose mothers had participated in a birth weight and nutrition during pregnancy study in 1990 [26]. In brief, the 1990 study recruited 2184 pregnant women with gestational age $<$ 24 weeks. Researchers followed up every subject's antenatal care up to delivery. The study recorded demographic data, anthropometric data, socioeconomic data. During delivery, the birth weight, birth length, and placental weight were also recorded. As a follow-up, every three months in the first year of the child's life, their weight was also recorded. Maternal diet intake was assessed by two methods. First, the 24-hour food recall method was used during the initial interview. Each mother was asked to recall all food consumed during the previous day and to estimate quantities in ordinary measures or servings. Then all details were calculated by using Thai Food Tables [35]. The amount of food was calculated as energy, protein, fat and carbohydrate at each of the three trimesters: weeks 10–12 (first trimester), weeks 22–24 (second trimester), and weeks 32–34 (third trimester).The food frequency questionnaire (FFQ) was used to assess the frequency of consumption of 34 foods in the previous month. Nutrient intakes in the FFQ were validated against the 24-hour food recall method.

In 2010, all 2184 offspring were invited to participate in the study. Their histories, physical exams, and blood samples were collected to determine their current general condition. The test consisted of the participants sitting quietly in a room at the clinic for at least 20 minutes. Twice, at intervals of 5–10 minutes, their blood pressure was measured on the left arm at heart level. Anthropometric measurements were performed. While wearing indoor clothes, the participant's height, weight, and waist circumference measurement were taken. Each participant filled out questionnaires on various cardiovascular risk factors, smoking experience, and past medical history. The participants fasted at least 12 hours before attending the study, and then venous blood samples were collected. Total cholesterol and plasma glucose were measured using the Beckman Coulter analyzer (UnicelDxc 800, Fullerton, California, USA).

COBRA LINE-1 and COBRA Alu

Also blood samples were collected and extracted to measure the level of LINE-1 and Alu methylation [36]. DNA extraction was performed by standard phenol chloroform extraction protocol. All DNA samples were treated with sodium bisulfite essentially following guidelines provided (EZ DNA Methylation-Gold Kit, Zymo research corp, Orange, CA, USA). For COBRA LINE-1, the bisulfate-treated DNA was subjected to 40 PCR cycles with LINE-1-F (5'-CGTAAGGGGTTAGGGAGTTTTT-3') and LINE-1-R (5'-RTAAAACCCTCCRAACCAAATATAAA-3') primers at an annealing temperature of 50°C. For COBRA Alu, the bisulfite-treated DNA was subjected to 40 cycles of PCR with two primers, Alu-F (5'-GGCGCGGTGGTTTACGTTTGTAA-3') and Alu-R (5'TTAATAAAAACGAAAT TTCACCATATTA ACCAAAC-3') at an annealing temperature of 53°C. After PCR amplification, the LINE-1 amplicons (160 bp) were digested with *TaqI* and *TasI* in NEB buffer 3 (New England Biolabs, Ontario, Canada), while the Aluamplicons (117 bp) were digested with *TaqI* in *TaqI* buffer (MBI Fermentas, Burlington, Canada). Both digestion reactions were incubated at 65°C overnight. The LINE-1 and Alu element digested products were then electrophoresed on an 8% non-denaturing polyacrylamide gel and stained with the SYBR green nucleic acid gel stain (Gelstar, Lonza, Rockland, ME, USA). Distilled water was used as negative control. All experiments were performed in duplicate. DNA samples from HeLa, Jurkat and Daudi cell lines were used as positive controls in every experiment and to standardize interassay variation [1].

Both COBRA LINE-1 and COBRA Alu detected methylation status of two CpG dinucleotides [36]. Therefore, COBRA can report four IRS methylation patterns, hypermethylation ($^{m}C^{m}C$) when both of the CpGs of the same locus were methylated. Hypomethylation ($^{u}C^{u}C$) when both of the CpGs of the same locus were unmethylated. We also reported two partial methylation pattern ($^{m}C^{u}C$ and $^{u}C^{m}C$). Both methylation level and pattern were reported in percentage number. For methylation levels we reported the percentage of methylated CpG. For methylation pattern, percentage numbers of loci of each pattern were determine. Detail analysis of LINE-1 and Alu methylation levels and patterns were the same as recently reported [36].

Statistical analysis

We analyzed the association between the level of LINE-1 and Alu methylation with various nutritional parameters, both intrauterine factors and early postnatal period. Since our study in LINE-1 and Alu methylation was conducted in blood sampling 20 years later, we therefore analyzed current parameters and epigenetic levels to see the difference between perinatal risk factors and current risk factors. The small for gestational age (SGA) defined as weight <10 percentile of gestational age [37], and the history of CUG in weight during the first year of life, defined the weight >0.67 standard score according to WHO data [38]. For the dichotomous data, an independent sample *t*-test was performed to determine differences between LINE-1 and Alu element methylation patterns. The continuous data were analyzed for the correlation with Pearson method. All P value was corrected for multiple comparisons (fault discovery rate —Simmes method). The data was presented in mean and standard deviation. Analysis was performed by STATA for Windows version 13.0. The significant levels quoted were two-sided and $P < 0.05$ was considered statistically significant.

Table 1. Baseline data of participants during pregnancy and delivery period (in 1990) and during follow up period in 2010 study.

Baseline item	Mean ± standard deviation
Pregnancy and delivery period	
Mothers age (yr) during pregnancy	26 ± 4.63
Body mass index at recruitment in study	21.26 ± 2.50
Birth weight (gram)	2814.54 ± 452.07
Birth length (cm)	47.89 ± 4.61
Gestational age (months)	38.90 ± 1.98
Age of mother during delivery (years)	26.20 ± 4.69
Placental weight (gm)	556 ± 111.57
Placental diameter (cm)	19.20 ± 2.64
Follow up period	
Age of offsprings (months)	246.06 ± 5.63
Waist circumference (cm)	77.25 ± 1.30
Body mass index	21.71 ± 4.80
Plasma cholesterol (mg/dl)	167.13 ± 31.93
Fasting blood sugar (mg/dl)	83.66 ± 13.27
Systolic blood pressure (mmHg)	115.23 ± 12.93
Diastolic blood pressure (mmHg	73.71 ± 10.80

doi:10.1371/journal.pone.0120032.t001

Table 2. The comparison of percentage of Alu (above panel) methylation and the percentage of LINE-1 methylation (below panel) in participants who are absence or presence the following risk factors: catch up growth, small for gestational age, male and smoking history.

Type of methylation	Total Alu		Alu_UU		Alu_MM		Alu_UM		Alu_MU	
Intrauterine factor/early postnatal factors										
Catch up growth history	Absence	Presence	Absence	Presence	Absence	Presence	Absence	Presence	Absence	Presence
Mean	33.66	39.61	44.85	37.39	12.16	16.60	23.75	26.04	19.23	19.97
SD	6.99	7.22	8.76	8.71	9.07	8.58	6.95	7.11	6.06	6.55
p-values control the FDR(simes)	<0.00001		<0.00001		0.0233		0.1858		0.7849	
Small for gestational age history	Absence	Presence	Absence	Presence	Absence	Presence	Absence	Presence	Absence	Presence
Mean	36.32	33.91	40.50	44.61	13.14	12.44	25.56	24.06	20.80	18.90
SD	7.67	7.72	8.78	9.36	11.00	8.31	7.89	6.73	6.89	5.54
p-values control the FDR(simes)	0.1428		0.0700		0.6999		0.3723		0.1428	
Gender of off spring	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male
Mean	34.63	34.06	43.20	44.62	12.47	12.74	25.04	23.38	19.30	19.26
SD	7.92	7.53	9.66	8.93	8.89	8.95	7.30	6.43	5.56	6.32
p-values control the FDR(simes)	0.8233		0.6373		0.9136		0.3820		0.9574	
Smoking history	Absence	Presence	Absence	Presence	Absence	Presence	Absence	Presence	Absence	Presence
Mean	34.07	35.27	44.07	42.99	12.21	13.53	24.30	23.49	19.42	19.99
SD	7.55	7.75	9.37	8.72	8.53	9.79	6.85	5.50	5.68	6.77
p-values control the FDR(simes)	0.6251		0.6251		0.6251		0.6251		0.6251	
Type of methylation	**Total LINE- 1**		**LINE- 1_MM**		**LINE- 1_UU**		**LINE- 1_MU**		**LINE- 1_UM**	
Intrauterine factor/early postnatal factors										
Catch up growth history	Absence	Presence	Absence	Presence	Absence	Presence	Absence	Presence	Absence	Presence
Mean	79.87	79.74	49.09	50.49	7.86	8.35	22.28	20.19	20.78	20.98
SD	5.52	8.95	12.20	18.26	5.40	6.21	9.35	10.10	14.19	15.46
p-values control the FDR(simes)	0.9410		0.7849		0.7849		0.4542		0.9410	
Small for gestational age history	Absence	Presence	Absence	Presence	Absence	Presence	Absence	Presence	Absence	Presence
Mean	79.24	80.21	48.95	49.53	9.27	7.31	23.11	21.90	18.67	21.26
SD	6.23	5.96	13.14	12.42	6.22	4.99	9.03	9.02	13.63	13.25
p-values control the FDR(simes)	0.4470		0.7718		0.0990		0.5007		0.3723	
Gender of off spring	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male
Mean	80.11	79.88	49.91	48.72	8.24	6.93	21.54	22.98	20.31	21.37
SD	5.73	6.42	12.09	13.18	5.69	4.61	8.39	9.81	13.14	13.65
p-values control the FDR(simes)	0.9136		0.8233		0.3820		0.6373		0.8233	
Smoking history	Absence	Presence	Absence	Presence	Absence	Presence	Absence	Presence	Absence	Presence
Mean	79.69	80.48	48.82	49.94	7.86	6.61	21.57	23.38	21.76	20.06
SD	5.98	6.96	12.46	14.23	5.54	3.60	8.92	9.50	13.54	12.72
p-values control the FDR(simes)	0.6251		0.6251		0.6251		0.6251		0.6251	

doi:10.1371/journal.pone.0120032.t002

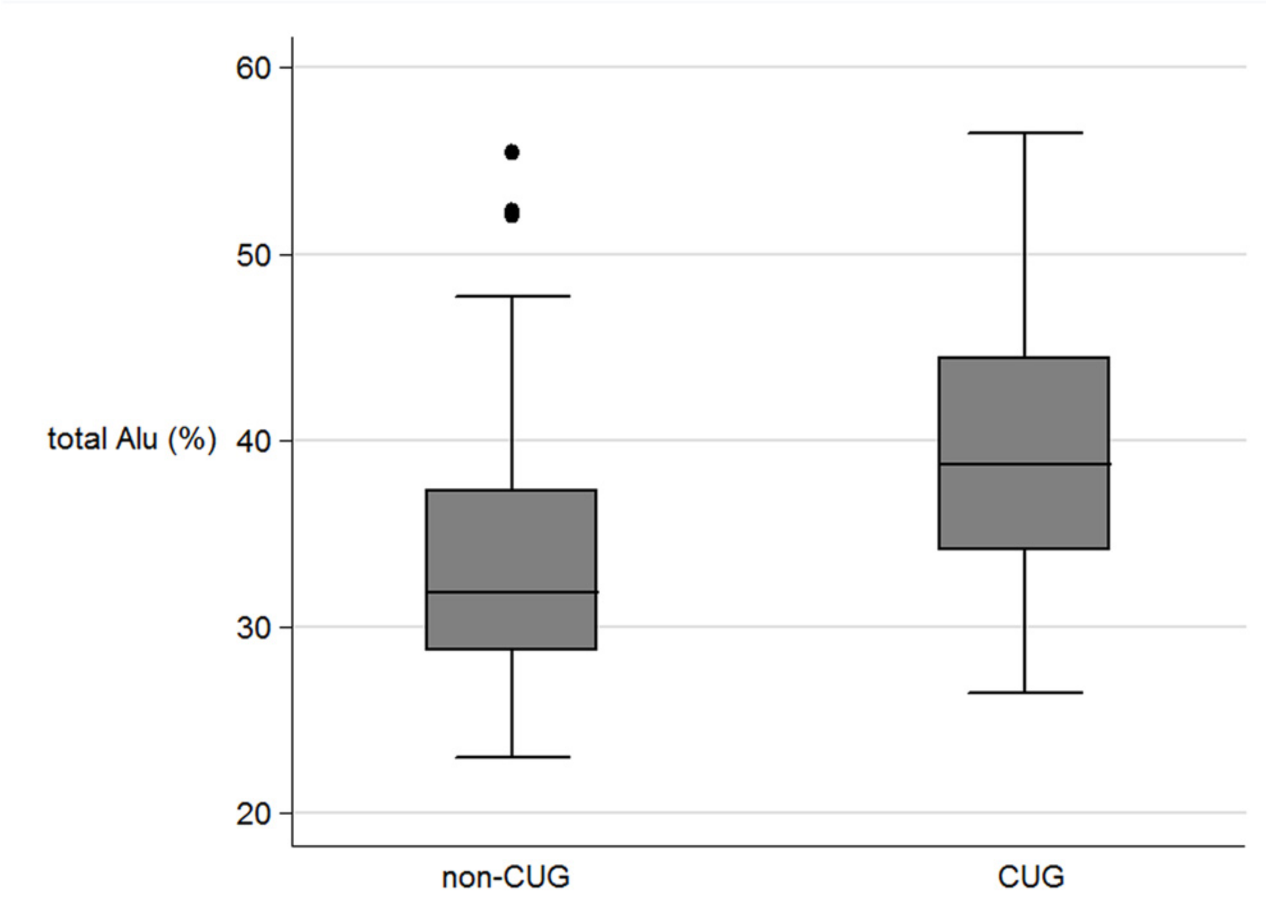


Fig 1. The boxplots of the total Alu methylation (%) between non catch up growth group (non-CUG) and catch up growth (CUG).

doi:10.1371/journal.pone.0120032.g001

Ethics statement

This study was conducted according to the guidelines laid down in the Declaration of Helsinki, and all procedures involving human subjects were approved by the Human Experimentation Committee, Research Institute for Health Sciences, Chiang Mai University, Chiang Mai, Thailand (Project Number 17/52). Written informed consent was obtained from all subjects together with their mothers and participants' anonymity was preserved.

Results

249 participants, who were offspring in CMLBWS, were recruited in this study. There were 103 males (41.4%), 27 current smokers (10.8%), 49 SGA, and 45 CUG. Mothers in CMLBWS, on average, had a normal range of BMI (Table 1). During delivery phase, the mean birth weight of offspring was 2814.54 grams, which was not in a low birth weight range.

In the perinatal parameters, there were significant correlations only between CUG and non-CUG in the levels of methylation in the percentage of total Alu, Alu_UU, and Alu_MM (Table 2). The mean level of total Alu_methylation in the CUG group was marked higher than

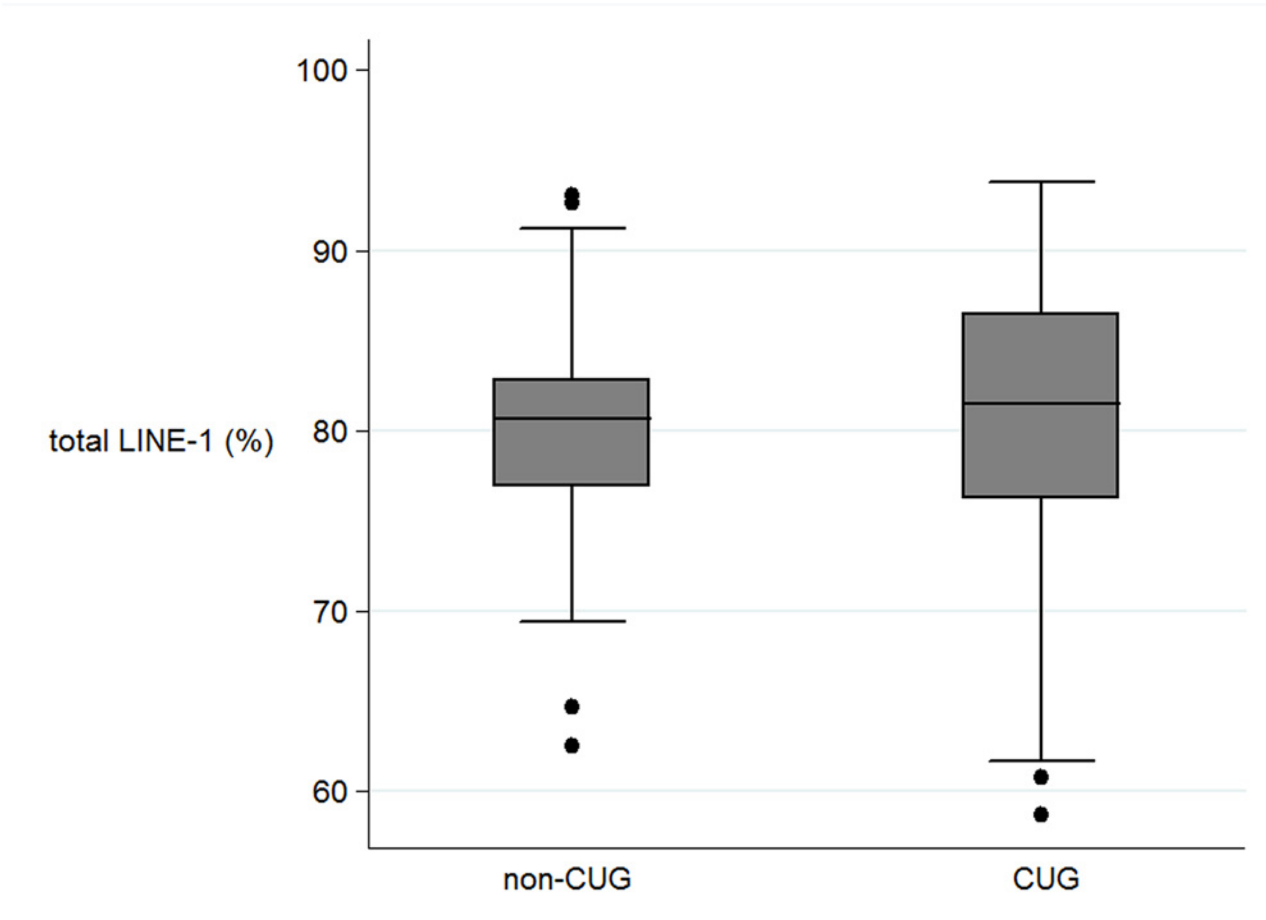


Fig 2. The boxplots of the LINE-1 methylation (%) between non catch up growth group (non-CUG) and catch up growth (CUG).

doi:10.1371/journal.pone.0120032.g002

those not in CUG (39.61% and 33.66% respectively, $P < 0.0001$) (Fig. 1). In contrast, the mean level of unmethylated loci (Alu_UU) in the CUG group was considerably lower than those in non-CUG group (37.39% and 44.85%, $P<.0001$ respectively). In contrast, there was no significant association between the levels of Alu_methylation with other perinatal parameters. The LINE-1 methylation levels were not correlated with any perinatal parameters (Fig. 2).

There was no significant correlation between the levels of Alu_methylation and LINE-1 methylation with various intrauterine parameters (during pregnancy), including maternal intake during 3 trimesters (carbohydrate, protein, fat, energy, weight gain), birth weight and placental weight (Table 3). Similarly no correlation was found between Alu_methylation and LINE-1 methylation with early postnatal factors.

There was no significant correlation between Alu_methylation and LINE-1 methylation with current factors such as gender, age, BMI, waist circumference, plasma cholesterol, fasting glucose and blood pressure (Table 4) (Figs. 3, 4). When authors analysed the association between CUG and non-CUG with the perinatal data, CUG group had higher incidence of pregnancy induce hypertension of mother during pregnancy than those in non-CUG (9.8% and 0.3% respectively, $P = 0.04$). Also maternal fat intake in the first trimester in CUG group was significant lower than those in non-CUG group ($P = 0.03$). When authors explored further on the association between CUG and non-CUG with current factors, waist circumference in CUG

Table 3. The correlation analysis between the percentage of Alu and LINE-1 methylation in various nutritional factors during pregnancy and delivery.

Type of methylation	Total Alu	Alu_UU	Alu_MM	Alu_UM	Alu_MU	Total LINE-1	LINE-1_MM	LINE-1_UU	LINE-1_MU	LINE-1_UM
Intrauterine factor/early postnatal factors										
bmi in first visit of mothers										
Correlation, r	0.0868	-0.1361	0.0079	0.1834	-0.0131	0.0025	0.0165	0.0588	-0.0620	0.0031
p-values control the FDR(simes)	0.6217	0.1895	0.9687	0.0500	0.9687	0.9687	0.9687	0.7134	0.7134	0.9687
Gestational age at delievery										
Correlation, r	0.0061	0.0307	0.0430	-0.0218	-0.0883	0.0797	0.0437	-0.1459	-0.1139	0.0938
p-values control the FDR(simes)	0.9260	0.8015	0.7340	0.8233	0.4222	0.4222	0.7340	0.2150	0.3675	0.4222
Mother age when pregnancy										
Correlation, r	0.1340	-0.1308	0.0956	0.0357	0.0215	-0.0758	-0.0496	0.0675	0.0603	-0.0209
p-values control the FDR(simes)	0.2300	0.2300	0.4853	0.7341	0.7446	0.5737	0.6236	0.5737	0.5737	0.7446
Mother weight gain in 1st trim										
Correlation, r	-0.2221	0.1445	-0.2911	0.0495	0.0008	-0.0719	-0.0911	-0.0730	0.0495	0.0809
p-values control the FDR(simes)	0.9188	0.9188	0.9188	0.9188	0.9972	0.9188	0.9188	0.9188	0.9188	0.9188
Mother weight gain in 2nd trim										
Correlation, r	0.0359	0.0313	0.0939	-0.0664	-0.1127	0.0282	0.0194	-0.0134	-0.0977	0.0543
p-values control the FDR(simes)	0.8295	0.8295	0.5313	0.8012	0.5313	0.8295	0.8364	0.8364	0.5313	0.8030
Mother weight gain in 3rd trim										
Correlation, r	0.0069	-0.0298	-0.0191	0.0597	0.0054	-0.0026	0.0399	0.1415	-0.1234	-0.0075
p-values control the FDR(simes)	0.9681	0.9681	0.9681	0.9681	0.9681	0.9681	0.9681	0.2835	0.2835	0.9681
maternal protein intake in 1st trim										
Correlation, r	0.1792	-0.3042	-0.0243	0.3200	0.2015	-0.1120	-0.0679	0.0569	0.1524	-0.0596
p-values control the FDR(simes)	0.4560	0.1070	0.8576	0.1070	0.4427	0.6782	0.7490	0.7490	0.5154	0.7490
maternal protein intake in 2nd trim										
Correlation, r	-0.0781	0.0889	-0.0426	-0.0523	-0.0090	0.0771	0.1000	0.0220	-0.0971	-0.0347
p-values control the FDR(simes)	0.6140	0.6140	0.8016	0.8016	0.9062	0.6140	0.6140	0.8533	0.6140	0.8016
maternal protein intake in 3rd trim										
Correlation, r	0.0351	0.0047	0.0662	-0.0471	-0.0516	0.0649	0.0316	-0.0599	-0.0524	0.0277
p-values control the FDR(simes)	0.7752	0.9494	0.7752	0.7752	0.7752	0.7752	0.7752	0.7752	0.7752	0.7752
maternal carbohydrate intake in 1st trim										
Correlation, r	0.0455	-0.1566	-0.1002	0.2867	0.0863	-0.0482	-0.0179	0.0986	0.1776	-0.1482
p-values control the FDR(simes)	0.8188	0.6780	0.7476	0.3060	0.7476	0.8188	0.8950	0.7476	0.6780	0.6780
maternal carbohydrate intake in 2nd trim										
Correlation, r	0.0130	-0.0545	-0.0335	0.0541	0.0717	-0.0548	-0.0362	0.0292	-0.0124	0.0326
p-values control the FDR(simes)	0.8679	0.8679	0.8679	0.8679	0.8679	0.8679	0.8679	0.8679	0.8679	0.8679
maternal carbohydrate intake in 3rd trim										
Correlation, r	0.0667	-0.0562	0.0586	0.0261	-0.0319	0.0584	0.0239	-0.0744	-0.0437	0.0346
p-values control the FDR(simes)	0.7371	0.7371	0.7371	0.7371	0.7371	0.7371	0.7371	0.7371	0.7371	0.7371
maternal fat intake in 1st trim										
Correlation, r	-0.1108	-0.0070	-0.2159	0.1875	0.1165	-0.2166	-0.1785	0.1022	0.0731	0.0820
p-values control the FDR(simes)	0.6420	0.9589	0.4600	0.4600	0.6420	0.4600	0.4600	0.6420	0.6543	0.6543

(*Continued*)

Table 3. (*Continued*)

Type of methylation	Total Alu	Alu_UU	Alu_MM	Alu_UM	Alu_MU	Total LINE-1	LINE-1_MM	LINE-1_UU	LINE-1_MU	LINE-1_UM
maternal fat intake in 2nd trim										
Correlation, r	-0.0856	0.0317	-0.1138	0.0983	0.0020	-0.0075	-0.0097	-0.0065	0.0657	-0.0357
p-values control the FDR(simes)	0.8757	0.9797	0.8757	0.8757	0.9797	0.9797	0.9797	0.9797	0.9422	0.9797
maternal fat intake in 3rd trim										
Correlation, r	-0.1703	0.2038	-0.0872	-0.1354	-0.0260	0.0059	-0.0040	-0.0109	-0.0217	0.0223
p-values control the FDR(simes)	0.0975	0.0500	0.5855	0.2130	0.9557	0.9557	0.9557	0.9557	0.9557	0.9557
Amount of energy intake in 1st trim										
Correlation, r	0.0310	-0.1641	-0.1361	0.3124	0.1248	-0.1082	-0.0672	0.1172	0.1745	-0.1053
p-values control the FDR(simes)	0.8189	0.5444	0.5444	0.1800	0.5444	0.5444	0.6880	0.5444	0.5444	0.5444
Amount of energy intake in 2nd trim										
Correlation, r	-0.0230	-0.0237	-0.0635	0.0658	0.0541	-0.0340	-0.0152	0.0283	-0.0078	0.0094
p-values control the FDR(simes)	0.9169	0.9169	0.9169	0.9169	0.9169	0.9169	0.9169	0.9169	0.9169	0.9169
Amount of energy intake in 3rd trim										
Correlation, r	-0.0078	0.0339	0.0214	-0.0367	-0.0421	0.0534	0.0186	-0.0692	-0.0468	0.0398
p-values control the FDR(simes)	0.9152	0.8831	0.8831	0.8831	0.8831	0.8831	0.8831	0.8831	0.8831	0.8831
brithweight										
Correlation, r	-0.0985	0.1054	-0.0604	0.0283	-0.1105	0.1267	0.0767	-0.1694	-0.1095	0.0693
p-values control the FDR(simes)	0.2233	0.2170	0.3984	0.6673	0.2170	0.2170	0.3270	0.0750	0.2170	0.3466
birthlegth										
Correlation, r	-0.1064	0.0905	-0.0887	0.0533	-0.0713	0.0487	0.0102	-0.1007	-0.0204	0.0438
p-values control the FDR(simes)	0.5120	0.5120	0.5120	0.6491	0.6170	0.6491	08809	0.5120	0.8487	0.6491
Placental weight										
Correlation, r	-0.0935	0.0415	-0.1196	0.0860	0.0118	-0.0427	-0.0417	-0.0056	-0.0587	0.0809
p-values control the FDR(simes)	0.5340	0.6724	0.5340	0.5340	0.9320	0.6724	0.6724	0.9320	0.6724	0.5340

trim = trimester

doi:10.1371/journal.pone.0120032.t003

group was significantly higher than those in non-CUG group (78.6 cm and 74.9 cm respectively, P = 0.04). The mean BMI in CUG group was higher than those in non- CUG group (22.5 cm and 20.7 cm respectively, P = 0.05).

Discussion

This study evaluated the association between Alu and LINE-1 methylation of 20-year-old individuals with various phenotypes during their babies period (intrauterine and early postnatal period). Whereas no association with LINE-1 methylation was identified, the correlation between the history of CUG in the first year, and higher Alu methylation,was demonstrated. Interestingly, Alu, but not LINE-1 hypomethylation, is associated with aging, and also disease phenotype due to aging, such as osteoporosis [6][7]. These two evidences suggest that methylation of different IRSs possess different functions. Alu methylation plays a role in cell growth and prevents cellular aging[6][7]. The role of IRS methylation is to control genome stability. Loss of Alu methylation in aging cells may lead to genomic instability, one of the hallmarks of aging cells. Cells of individuals with CUG may require higher levels of genome stability. Our

Table 4. The correlation analysis between the percentage of Alu and LINE-1 methylation in various current risk factors during follow up study (2010).

Type of methylation	Total Alu	Alu_uu	Alu_MM	Alu_UM	Alu_MU	Total LINE-1	LINE-1_MM	LINE-1_UU	LINE-1_MU	LINE-1_UM
Factors in follow up study 2010										
Age at recent study										
Correlation, r	0.0503	-0.0050	0.0815	-0.0294	-0.0805	0.0056	-0.0010	-0.0492	-0.0083	0.0261
p-values control the FDR(simes)	0.9881	0.9881	0.9881	0.9881	0.9881	0.9881	0.9881	0.9881	0.9881	0.9881
Body mass index in recent study										
Correlation, r	0.0307	-0.0788	-0.0295	0.0497	0.1114	-0.0459	-0.0716	-0.1211	-0.0350	0.1391
p-values control the FDR(simes)	0.6541	0.5224	0.6541	0.6541	0.2997	0.6541	0.5224	0.2845	0.6541	0.2845
Waist circumference in recent study										
Correlation, r	-0.0013	-0.0324	-0.0364	0.0155	0.0885	-0.0536	-0.0819	-0.1282	-0.0360	0.1532
p-values control the FDR(simes)	0.9839	0.7789	0.7789	0.9049	0.5010	0.7789	0.5010	0.2230	0.7789	0.1620
Plasma cholesterol in recent study										
Correlation, r	-0.0063	-0.0361	-0.0498	0.0482	0.0755	-0.0183	-0.0035	0.0604	-0.0228	-0.0034
p-values control the FDR(simes)	0.9589	0.9589	0.9589	0.9589	0.9589	0.9589	0.9589	0.9589	0.9589	0.9589
Fasting glucose in recent study										
Correlation, r	-0.0478	0.0655	-0.0145	-0.0858	0.0186	0.0545	0.0671	0.0758	-0.0958	-0.0287
p-values control the FDR(simes)	0.6713	0.6428	0.8270	0.6428	0.8270	0.6582	0.6428	0.6428	0.6428	0.8174
Systolic blood pressure in recent study										
Correlation, r	0.0679	-0.0244	0.0925	-0.0917	0.0077	-0.0123	-0.0162	-0.0653	-0.0523	0.0766
p-values control the FDR(simes)	0.6138	0.9072	0.6138	0.6138	0.9072	0.9072	0.9072	0.6138	0.6892	0.6138
Diastolic blood pressure in recent study										
Correlation, r	0.0773	-0.0369	0.0959	-0.0158	-0.0677	-0.0465	-0.0463	0.0155	-0.1551	0.1423
p-values control the FDR(simes)	0.6015	0.7194	0.4850	0.8133	0.6084	0.6697	0.6697	0.8133	0.1270	0.1270

trim = trimester

doi:10.1371/journal.pone.0120032.t004

PCR evaluated overall methylation statuses of a hundred thousand copies of Alu, but only a few thousand copies of LINE-1. Although there are hundreds of thousands of copies of Alu and LINE-1, most of LINE-1 are truncated and missing CpG dinucleotide containing 5'UTR. Therefore, Alu methylation represents genomic methylation more than LINE-1, consequently genomic stability.

This study is the first to show the correlation of IRS methylation in young adults with that of new born phenotypes. Therefore, it is highly likely that IRS methylation is quite stable. There are a number of studies that show differences in IRS methylation in WBC of many diseases [8–14]. Therefore, IRS methylation is a potential marker for disease risk prediction.

An additional study to evaluate Alu methylation levels at birth is useful to prove that Alu hypermethylation is discoverable at birth. Moreover, Alu methylation level may be useful in predict in growth rates of new born infants and better nutritional management. This is particularly important because many previous studies found CUG in early life is associated with metabolic syndrome [39][40] and future coronary artery disease [41][42]. Guenard and colleagues conduct a study to analyse the effect of maternal weight loss surgery (bariatric surgery) on

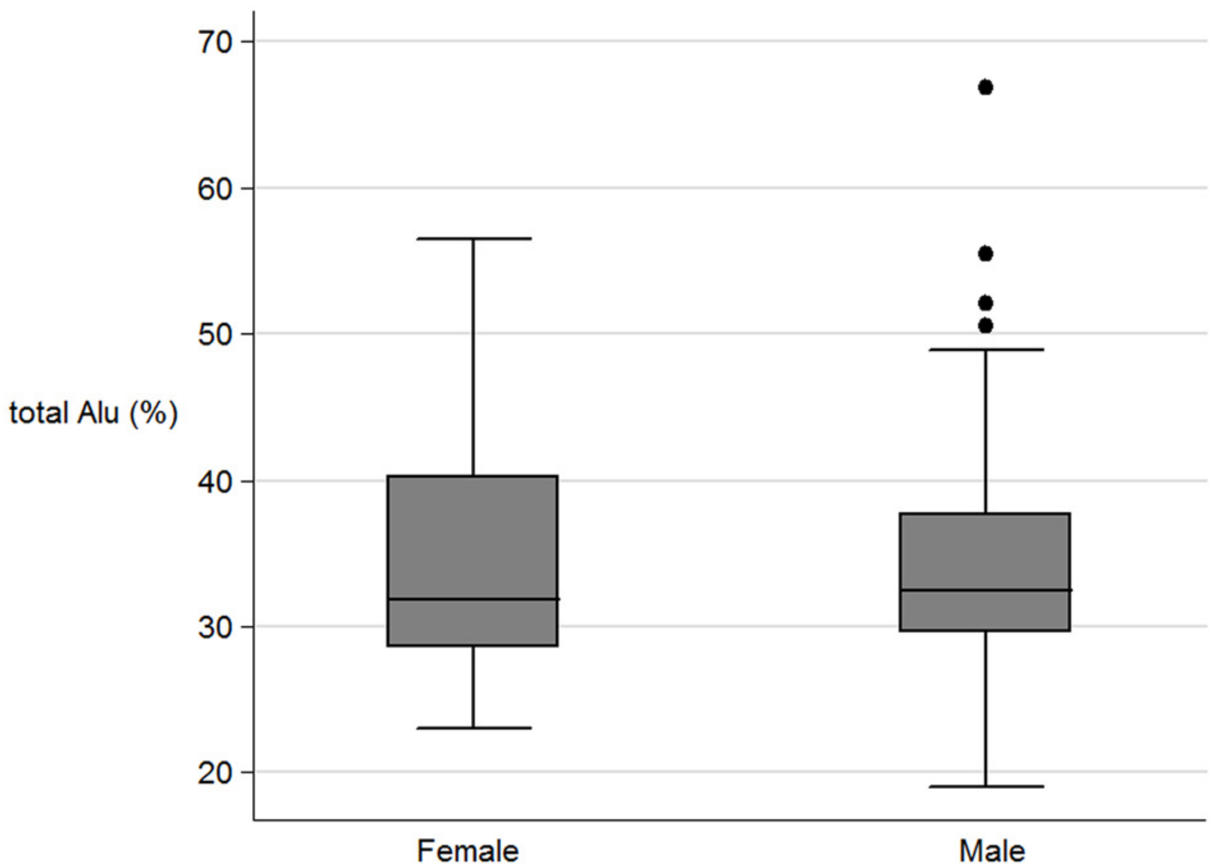


Fig 3. The boxplots of the total Alu methylation (%) between female and male.

doi:10.1371/journal.pone.0120032.g003

methylation levels of genes involved in cardiometabolic pathway in before surgery and after surgery [43]. Based on 5,698 genes, the methylation level was differentiated between before surgery and after surgery sibling, indicating a preponderance of glucoregulatory, inflammatory and vascular disease genes. They also demonstrated previously that the prevalence of obesity, adiposity, hypertension, dyslipidemia in children born after bariatric surgery was markedly lower than in sibling born before maternal bariatric surgery[44]. They suggest that these improvements in cardiometabolic indicators may be attributable to an improvement intrauterine environment. Similarly our study found the mean level of Alu methylation was higher in CUG group than those non-CUG. Maternal in CUG had higher incidence of pregnancy induced hypertension and lower maternal diet of fat in first trimester than those in non-CUG group. Also CUG group was associated with higher waist circumference and BMI than those in non-CUG group in adult. These stressed the importance of the intrauterine environment such as nutritional factors and maternal stress in fetal programming [45]. Epigenetics is a potential mechanism of this association.

Conclusions

This study showed the positive correlation between the history of CUG in the first year, and that higher Alu methylation indicates the role of Alu methylation in the human growth

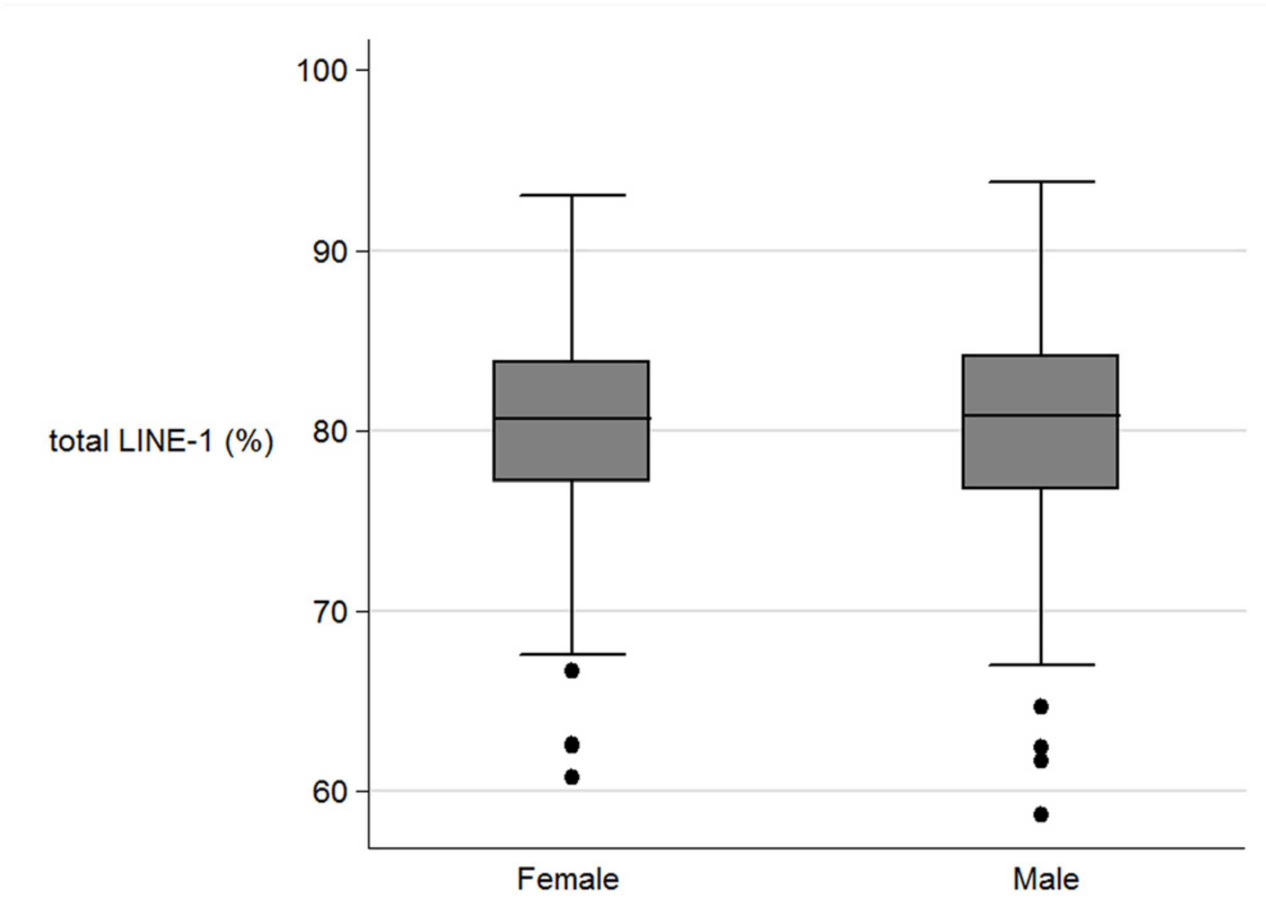


Fig 4. The boxplots of the LINE-1 methylation (%) between female and male.

doi:10.1371/journal.pone.0120032.g004

process. To our knowledge, this is the first study which demonstrated the association between a phenotype during the newborn period and IRS methylation during young adulthood. Knowing Alu methylation levels at birth may be useful in predicting the growth rate of newborns, and better nutritional management to prevent metabolic syndrome and coronary artery disease in adults.

Acknowledgments

We are grateful for the willing cooperation of all participants. We also would like to thank Drs. Pien Chiowanich, Jutamas Sudasna, Sakda Pruenglampoo, Somchai Laohawattana, Piyamitr Sritara, and all investigators in the 1990 study. The clinical data files and blood specimens of this project have been processed and stored with the help of the members in the Specimen Processing Unit and the Nutritional Research Unit of The Research Institute of Health Sciences.

Author Contributions

Conceived and designed the experiments: K. Rerkasem A. Mangklabruks A. Mutirangura. Performed the experiments: K. Rerkasem PR AR K. Rungruengthanakit A. Mangklabruks. Analyzed the data: AW K. Rerkasem A. Mangklabruks. Contributed reagents/materials/analysis tools: AW K. Rungruengthanakit A. Mutirangura. Wrote the paper: K. Rerkasem PR AR AW K. Rungruengthanakit A. Mangklabruks A. Mutirangura.

References

1. Chalitchagorn K, Shuangshoti S, Hourpai N, Kongruttanachok N, Tangkijvanich P, Thong-ngam D, et al. Distinctive pattern of LINE-1 methylation level in normal tissues and the association with carcinogenesis. Oncogene. 2004; 23: 8841–8846. PMID: 15480421
2. Kitkumthorn N, Mutirangura A. Long interspersed nuclear element-1 hypomethylation in cancer: biology and clinical applications. Clin Epigenetics. 2011; 2: 315–330 doi: 10.1007/s13148-011-0032-8 PMID: 22704344
3. Kongruttanachok N, Phuangphairoj C, Thongnak A, Ponyeam W, Rattanatanyong P, Pornthanakasem W, et al. Replication independent DNA double-strand break retention may prevent genomic instability. Mol Cancer. 2010 Mar 31; 9:70. doi: 10.1186/1476-4598-9-70 PMID: 20356374
4. Aporntewan C, Phokaew C, Piriyapongsa J, Ngamphiw C, Ittiwut C, Tongsima S, et al. Hypomethylation of intragenic LINE-1 represses transcription in cancer cells through AGO2. PLoS One. 2011; 6: e17934. doi: 10.1371/journal.pone.0017934 PMID: 21423624
5. Wanichnopparat W1, Suwanwongse K, Pin-On P, Aporntewan C, Mutirangura A. Genes associated with the cis-regulatory functions of intragenic LINE-1 elements. BMC Genomics. 2013 Mar 27; 14:205. doi: 10.1186/1471–2164–14–205 PMID: 23530910
6. Jintaridth P, Mutirangura A. Distinctive patterns of age-dependent hypomethylation in interspersed repetitive sequences. Physiol Genomics. 2010; 41: 194–200. doi: 10.1152/physiolgenomics.00146.2009 PMID: 20145203
7. Jintaridth P, Tungtrongchitr R, Preutthipan S, Mutirangura A. Hypomethylation of Alu elements in postmenopausal women with osteoporosis. PLoS One. 2013; 8: e70386. doi: 10.1371/journal.pone.0070386 PMID: 23990903
8. Wu HC, John EM, Ferris JS, Keegan TH, Chung WK, Andrulis I, et al. Global DNA methylation levels in girls with and without a family history of breast cancer. Epigenetics. 2011; 6: 29–33. doi: 10.4161/epi.6.1.13393 PMID: 20930546
9. Hou L, Wang H, Sartori S, Gawron A, Lissowska J, Bollati V, et al. Blood leukocyte DNA hypomethylation and gastric cancer risk in a high-risk Polish population. Int J Cancer. 2010; 127: 1866–1874. doi: 10.1002/ijc.25190 PMID: 20099281
10. Fabris S, Bollati V, Agnelli L, Morabito F, Motta V, Cutrona G, et al. Biological and clinical relevance of quantitative global methylation of repetitive DNA sequences in chronic lymphocytic leukemia. Epigenetics. 2011; 6: 188–194. PMID: 20930513
11. Walters RJ, Williamson EJ, English DR, Young JP, Rosty C, Clendenning M, et al. Association between hypermethylation of DNA repetitive elements in white blood cell DNA and early-onset colorectal cancer. Epigenetics. 2013; 8: 748–755. doi: 10.4161/epi.25178 PMID: 23804018
12. Zhao J, Goldberg J, Bremner JD, Vaccarino V. Global DNA methylation is associated with insulin resistance: a monozygotic twin study. Diabetes. 2012; 61: 542–546. doi: 10.2337/db11-1048 PMID: 22210312
13. Kim M, Long TI, Arakawa K, Wang R, Yu MC, Laird PW. DNA methylation as a biomarker for cardiovascular disease risk. PLoS One. 2010; 5: e9692. doi: 10.1371/journal.pone.0009692 PMID: 20300621
14. Nakkuntod J, Avihingsanon Y, Mutirangura A, Hirankarn N. Hypomethylation of LINE-1 but not Alu in lymphocyte subsets of systemic lupus erythematosus patients. Clin Chim Acta. 2011; 412: 1457–1461. doi: 10.1016/j.cca.2011.04.002 PMID: 21496453
15. Kile ML, Fang S, Baccarelli AA, Tarantini L, Cavallari J, Christiani DC. A panel study of occupational exposure to fine particulate matter and changes in DNA methylation over a single workday and years worked in boilermaker welders. Environ Health. 2013; 12: 47. doi: 10.1186/1476-069X-12-47 PMID: 23758843
16. Wu HC, Delagado-Cruzata L, Flom JD, Perrin M, Liao Y, Ferris JS, et al. Repetitive element DNA methylation levels in white blood cell DNA from sisters discordant for breast cancer from the New York site of the Breast Cancer Family Registry. Carcinogenesis. 2012; 33: 1946–1952. doi: 10.1093/carcin/bgs201 PMID: 22678115
17. Kile ML, Baccarelli A, Hoffman E, Tarantini L, Quamruzzaman Q, Rahman M, et al. Prenatal arsenic exposure and DNA methylation in maternal and umbilical cord blood leukocytes. Environ Health Perspect. 2012; 120: 1061–1066. doi: 10.1289/ehp.1104173 PMID: 22466225

18. Peluso M, Bollati V, Munnia A, Srivatanakul P, Jedpiyawongse A, Sangrajrang S, et al. DNA methylation differences in exposed workers and nearby residents of the Ma Ta Phut industrial estate, Rayong, Thailand. Int J Epidemiol. 2012; 41: 1753–1760. doi: 10.1093/ije/dys129 PMID: 23064502

19. Intarasunanont P, Navasumrit P, Waraprasit S, Chaisatra K, Suk WA, Mahidol C, et al. Effects of arsenic exposure on DNA methylation in cord blood samples from newborn babies and in a human lymphoblast cell line. Environ Health. 2012; 11: 31. doi: 10.1186/1476-069X-11-31 PMID: 22551203

20. Ogino S, Nosho K, Irahara N, Meyerhardt JA, Baba Y, Shima K, et al. Lymphocytic reaction to colorectal cancer is associated with longer survival, independent of lymph node count, microsatellite instability, and CpG island methylator phenotype. Clin Cancer Res. 2009; 15: 6412–6420. doi: 10.1158/1078-0432.CCR-09-1438 PMID: 19825961

21. Searles NS, Checkoway H, Butler RA, Nelson HH, Farin FM, Longstreth WT Jr, et al. LINE-1 DNA methylation, smoking and risk of Parkinson's disease. J Parkinsons Dis. 2012; 2: 303–308. doi: 10.3233/JPD-012129 PMID: 23938260

22. Wongpaiboonwattana W1, Tosukhowong P, Dissayabutra T, Mutirangura A, Boonla C. Oxidative stress induces hypomethylation of LINE-1 and hypermethylation of the RUNX3 promoter in a bladder cancer cell line. Asian Pac J Cancer Prev. 2013; 14: 3773–3778. PMID: 23886181

23. Kitkumthorn N1, Tuangsintanakul T, Rattanatanyong P, Tiwawech D, Mutirangura A. LINE-1 methylation in the peripheral blood mononuclear cells of cancer patients. Clin Chim Acta. 2012; 413: 869–874. doi: 10.1016/j.cca.2012.01.024 PMID: 22326975

24. Hyland PL, Burke LS, Pfeiffer RM, Mirabello L, Tucker MA, Goldstein AM, et al. LINE-1 methylation in peripheral blood and the risk of melanoma in melanoma-prone families with and without CDKN2A mutations. Melanoma Res. 2013; 23: 55–60. doi: 10.1097/CMR.0b013e32835adc51 PMID: 23222549

25. Perng W, Mora-Plazas M, Marin C, Rozek LS, Baylin A, Villamor E. A prospective study of LINE-1DNA methylation and development of adiposity in school-age children. PLoS One. 2013; 8: e62587. doi: 10.1371/journal.pone.0062587 PMID: 23638120

26. Chiang Mai Low Birth weight Study Group. The risk factor of low birth weight infant in the Northern part of Thailand. J Med Assoc Thai. 2012; 95:358–365. PMID: 22550834

27. Rerkasem K, Wongthanee A, Rerkasem A, Chiowanich P, Sritara P, Pruenglampoo S, et al. Intrauterine nutrition and carotid intimal media thickness in young Thai adults. Asia Pac J Clin Nutr. 2012; 21: 247–52. PMID: 22507612

28. Toschke AM, Grote V, Koletzko B, von KR. Identifying children at high risk for overweight at school entry by weight gain during the first 2 years. Arch Pediatr Adolesc Med. 2004; 158: 449–452. PMID: 15123477

29. Bansal N, Ayoola OO, Gemmell I, Vyas A, Koudsi A, Oldroyd J, et al. Effects of early growth on blood pressure of infants of British European and South Asian origin at one year of age: the Manchester children's growth and vascular health study. J Hypertens. 2008; 26: 412–418. doi: 10.1097/HJH.0b013e3282f3168e PMID: 18300849

30. Dunger DB, Salgin B, Ong KK. Session 7: Early nutrition and later health early developmental pathways of obesity and diabetes risk. Proc Nutr Soc. 2007; 66: 451–457. PMID: 17637098

31. Koletzko B, Beyer J, Brands B, Demmelmair H, Grote V, Haile G, et al. Early influences of nutrition on postnatal growth. Nestle Nutr Inst Workshop Ser. 2013; 71: 11–27. doi: 10.1159/000342533 PMID: 23502135

32. Phokaew C, Kowudtitham S, Subbalekha K, Shuangshoti S, Mutirangura A. LINE-1 methylation patterns of different loci in normal and cancerous cells. Nucleic Acids Res. 2008; 36: 5704–5712. doi: 10.1093/nar/gkn571 PMID: 18776216

33. Wangsri S, Subbalekha K, Kitkumthorn N, Mutirangura A. Patterns and possible roles of LINE-1 methylation changes in smoke-exposed epithelia. PLoS One. 2012; 7: e45292. doi: 10.1371/journal.pone.0045292 PMID: 23028911

34. Pobsook T, Subbalekha K, Sannikorn P, Mutirangura A. Improved measurement of LINE-1 sequence methylation for cancer detection. Clin Chim Acta. 2011; 412: 314–321. doi: 10.1016/j.cca.2010.10.030 PMID: 21078311

35. Nutrition Division, Department of Health. Nutritive value of Thai food. 1st ed. Bangkok: Veterans Organisation Press; 1992.

36. Sirivanichsuntorn P, Keelawat S, Danuthai K, Mutirangura A, Subbalekha K, Kitkumthorn N. LINE-1 and Alu hypomethylation in mucoepidermoid carcinoma. BMC Clin Pathol. 2013 Mar 19; 13:10. doi: 10.1186/1472–6890–13–10 PMID: 23510117

37. Lo Lubchenco, Hansman C, Dressler M, Boyd E. Intrauterine growth as estimated from liveborn birthweight data at 24 to 42 weeks of gestation. Pediatrics. 1963; 32: 793–800. PMID: 14075621

38. Leunissen RW, Kerkhof GF, Stijnen T, Hokken-Koelega A. Timing and tempo of first-year rapid growth in relation to cardiovascular and metabolic risk profile in early adulthood. JAMA. 2009; 301: 2234–2242. doi: 10.1001/jama.2009.761 PMID: 19491185

39. Dulloo AG. Adipose tissue plasticity in catch-up-growth trajectories to metabolic syndrome: hyperplastic versus hypertrophic catch-up fat. Diabetes. 2009; 58:1037–1039. doi: 10.2337/db09-0290 PMID: 19401433

40. Nobili V, Alisi A, Panera N, Agostoni C. Low birth weight and catch-up-growth associated with metabolic syndrome: a ten year systematic review. Pediatr Endocrinol Rev. 2008; 6:241–247. PMID: 19202511

41. Eriksson JG, Forsén T, Tuomilehto J, Winter PD, Osmond C, Barker DJ. Catch-up growth in childhood and death from coronary heart disease: longitudinal study. BMJ. 1999; 318: 427–431. PMID: 9974455

42. Eriksson JG, Forsén T, Tuomilehto J, Osmond C, Barker DJ. Early growth and coronary heart disease in later life: longitudinal study. BMJ. 2001; 322: 949–953. PMID: 11312225

43. Guénard F, Tchernof A, Deshaies Y, Cianflone K, Kral JG, Marceau P, et al. Methylation and expression of immune and inflammatory genes in the offspring of bariatric bypass surgery patients. J Obes. 2013 Jun 11. 492170. doi: 10.1155/2013/492170 PMID: 23840945

44. Kral JG, Biron S, Simard S, Hould FS, Lebel S, Marceau S, et al. Large maternal weight loss from obesity surgery prevents transmission of obesity to children who were followed for 2 to 18 years. Pediatrics. 2006; 118: e1644–9. PMID: 17142494

45. Phillips DI, Matthews SG. Is perinatal neuroendocrine programming involved in the developmental origins of metabolic disorders? World J Diabetes. 2011; 2: 211–6. doi: 10.4239/wjd.v2.i12.211 PMID: 22174956

Kittipan Rerkasem <rerkase@gmail.com>

STROKE/2015/010052 Decision Letter

4 messages

stroke@strokeahajournal.org <stroke@strokeahajournal.org> Mon, Jun 1, 2015 at 8:17 PM

Reply-To: stroke@strokeahajournal.org
To: touze-e@chu-caen.fr
Cc: marion.boulanger@club-internet.fr, lcameliere@gmail.com, rjrfelgueiras@gmail.com, berger-l@chu-caen.fr, rerkase@gmail.com, peter.rothwell@ndcn.ox.ac.uk

June 1, 2015

Prof. Emmanuel Touzé
CHU Caen
Neurology
Avenue de la Cote de Nacre
CAEN 14000
FRANCE

MS ID#: STROKE/2015/010052
MS TITLE: Periprocedural Myocardial Infarction after Carotid Endarterectomy and Stenting: systematic review and meta-analysis

Dear Prof. Touzé:

Your manuscript is of interest to the readers of Stroke. However, the reviewers have raised points that require your consideration before a final decision can be made.

Please respond to the concerns by making those alterations that have been indicated. When resubmitting the manuscript, respond to each of the criticisms, point-by-point in an uploaded document. In this document, please provide each comment verbatim in bold followed by your response. If substantive changes have been made to the manuscript, please provide a clear description of what you did and where. If you insert important sentences, paragraphs or sections in response to the comments, please include them in this response. Please also be clear about any deletions. Please make all additions to the manuscript obvious by putting them in bold or another obvious iteration. You may consider some of the suggestions inappropriate and, if that is the case, please give the reasons in your response.

In addition to replying to comments, please review your manuscript for the following items.

1. References: Please ensure that your references are listed sequentially within the text of the manuscript. There are 31 citations to references in the manuscript text; however the reference section lists 51 references. If there are 51 references, all 51 must be cited in the text.

2. Please cite all supplemental tables in order in the manuscript text. Currently, supplemental table III is cited before tables I and II.

3. All sources of funding must appear under the heading, Funding Sources, not in the Acknowledgments.

4. Original source files for the text and figures are required. The acceptable format for your manuscript text and tables is Microsoft Word. Acceptable figure formats are TIFF, EPS, or PPT.

5. Online Supplemental Data: A combined, single-spaced PDF of your supplemental data must be provided. The first page of this PDF should include the heading, "SUPPLEMENTAL MATERIAL." Online supplemental data is NOT copy edited or typeset. It will be uploaded to the journal website as is.

6. All authors must submit electronic disclosure and copyright forms PRIOR to resubmission. We strongly suggest that you start collecting the forms as soon as possible; you have the 60 days of the revision period to complete the forms. Do not wait until you are ready to upload the revised paper. The corresponding author may start the revision and go to Step 2, Electronic forms tab, to contact coauthor (s) and send reminders. You may not submit the manuscript until all forms have been submitted; there will be no exceptions. Please note that disclosures stated in the text must match the online disclosures.

7. Please note that the manuscript is over the word limit. An excess word fee will apply if accepted. If you wish to avoid a fee, please shorten the manuscript.

It is the author's responsibility to read the instructions prior to submission. The instructions to authors can be found at http://stroke.ahajournals.org/misc/ifora.shtml. Log on to http://stroke-submit.aha-journals.org and follow the instructions for electronic submission.

Before submitting your revised manuscript, please review the costs to author in the instructions for authors. To defray costs of publication, authors are charged $70 per printed page. Authors of papers exceeding 4,500 words (1,800 words for Brief Reports) will be charged a minimum fee of $425 per additional 1,000 words. Thus, a 5000 word manuscript would carry the $425 fee. This is in addition to the standard $70 per page charge ($35 per page for online-only articles). Word count will be calculated by the editorial office, using the Microsoft Word Count tool. Title page, abstract, main body of text, acknowledgments, sources of funding, disclosures, references, figure legends, tables, and appendices intended for the print version are included in the total word count. Color charges are $653.00 per color page. This is in addition to the page charges. Estimate of color costs will be provided for author's approval by the publisher. No estimate of the total publication cost is provided,
but authors may estimate the total cost upon receipt of page proofs should the paper be accepted. For all costs to authors, please refer to the Instructions for Authors.

So that our published articles are as up to date as possible, we would like to receive all revisions within 60 days. If we do not receive your revision within that time frame, we will drop the manuscript from our active files. If you decide not to submit a revised manuscript, please let us know.

We thank you for giving us the opportunity to consider your paper and we look forward to seeing your manuscript back within 60 days.

Sincerely,

Jeffrey L. Saver, MD
Handling Editor
Stroke

==
Reviewer Comments
==

Reviewer #1:

The paper would be improved by the following:

1. Introduction: Please add "In older clinical trials, CEA reduces the absolute risk..." since the risk reduction relative to modern medical therapy is unknown.
2. P 11. The comment that the "periprocedural risk of MI" has not been compared for other atherosclerotic arteries is hard to believe. Are the authors saying that these rates have never been evaluated in procedures done for PAD?
3. Would add as a limitation that periprocedural medication use was not assessed. This could impact the rate of MI.
4. Would add that the rate of MI may be higher in women due to lower use of antiplatelets and/or statins, which has been shown in other stroke prevention studies.

Reviewer #2:

As mentioned by the authors themselves this metaanalysis has the severe limitation of the small numbers of events reported in the analysed studies and because of the population case-mix in these

studies, the results on absolute risks of MI were heterogeneous.
In comparison to the available randomized studies this metaanalysis
does not enhance the knowledge about rate and riskfactors of MI after CEA or CAS.

Reviewer #3:

This is a very well-analysed systemic review on the periprocedural risks of MI after CEA an CAS.

The authors state that cervical incision provokes local inflammation, stress and liberation of pro inflammatory cytokines that causes prothrombotic state. This prothrombotic state could favor the periprocedural risk of MI after CEA. A reference to this statement is missing and should be included.

Peter Rothwell <peter.rothwell@ndcn.ox.ac.uk> Mon, Jun 1, 2015 at 8:19 PM
To: "stroke@strokeahajournal.org" <stroke@strokeahajournal.org>, "touze-e@chu-caen.fr" <touze-e@chu-caen.fr>
Cc: "marion.boulanger@club-internet.fr" <marion.boulanger@club-internet.fr>, "lcameliere@gmail.com" <lcameliere@gmail.com>, "rjrfelgueiras@gmail.com" <rjrfelgueiras@gmail.com>, "berger-l@chu-caen.fr" <berger-l@chu-caen.fr>, "rerkase@gmail.com" <rerkase@gmail.com>

Well done!

Peter

From: stroke@strokeahajournal.org [mailto:stroke@strokeahajournal.org]
Sent: 01 June 2015 14:18
To: touze-e@chu-caen.fr
Cc: marion.boulanger@club-internet.fr; lcameliere@gmail.com; rjrfelgueiras@gmail.com; berger-l@chu-caen.fr; rerkase@gmail.com; Peter Rothwell
Subject: STROKE/2015/010052 Decision Letter

[Quoted text hidden]

TOUZE EMMANUEL <touze-e@chu-caen.fr> Tue, Jun 2, 2015 at 3:06 PM
To: "lcameliere@gmail.com" <lcameliere@gmail.com>, "rjrfelgueiras@gmail.com" <rjrfelgueiras@gmail.com>, BERGER LUDOVIC <berger-l@chu-caen.fr>, "rerkase@gmail.com" <rerkase@gmail.com>, "peter.rothwell@ndcn.ox.ac.uk" <peter.rothwell@ndcn.ox.ac.uk>
Cc: "marion.boulanger@club-internet.fr" <marion.boulanger@club-internet.fr>

Dear all,

As you already know, we got good news from Stroke. The paper requires minor revisions. Well done to all.

May I ask you to submit electronic disclosure and copyright forms on the website as soon as you can.

Thanks in advance,

Best wishes

Emmanuel

De : stroke@strokeahajournal.org [mailto:stroke@strokeahajournal.org]
Envoyé : lundi 1 juin 2015 15:18
À : TOUZE EMMANUEL
Cc : marion.boulanger@club-internet.fr; lcameliere@gmail.com; rjrfelgueiras@gmail.com; BERGER LUDOVIC; rerkase@gmail.com; peter.rothwell@ndcn.ox.ac.uk
Objet : STROKE/2015/010052 Decision Letter

[Quoted text hidden]

Kittipan Rerkasem <rerkase@gmail.com> Thu, Jun 4, 2015 at 5:17 PM
To: TOUZE EMMANUEL <touze-e@chu-caen.fr>

Emmanuel

I have submitted these two documents as your previous mail indicated.

Kittipan
[Quoted text hidden]
--
ขอแสดงความนับถือ Best Wishes

กิตติพันธุ์- Kittipan

ศาสตราจารย์ (เชี่ยวชาญพิเศษ) กิตติพันธุ์ ฤกษ์เกษม
Professor Kittipan Rerkasem, MD, PhD
Chief, Division of Vascular Surgery
Department of Surgery, Faculty of Medicine,
Chiang Mai University, Chiang Mai, Thailand 50200
Tel +66 (0)53 945532, Fax +66 (0)53 946139 or +66 (0)53 894780
Email: rerkase@gmail.com or krerkase@med.cmu.ac.th

Head, Center for Applied Sciences, Research Institute of Health Sciences, P.O.Box 80, Chiang Mai University, Chiang Mai, Thailand 50202
Tel +66 (0)53 945055 ext 352 Fax +66 (0)53 894780

Risk and risk factors of periprocedural myocardial infarction after Carotid Endarterectomy and Carotid Angioplasty and Stenting: systematic review and meta-analysis

Marion Boulanger, MD; Lucie Camelière, MD; Rui Felgueiras, MD; Ludovic Berger, MD, PhD; Kittipan Rerkasem, MD, PhD; Peter M Rothwell, MD, PhD, FRCP, FMedSci; Emmanuel Touzé, MD, PhD

Université de Caen Basse Normandie, Service de Neurologie, CHU Côte de Nacre, Caen (M.B. E.T.)

INSERM UMR U919, Caen (E.T.)

Université de Caen Basse Normandie, Service de Chirurgie Vasculaire, CHU Côte de Nacre, Caen (L.C., L.B.)

Neurology Department, Hospital Santo António, Centro Hospitalar do Porto, Largo Professor Abel Salazar, Porto, Portugal (R.F.);

Department of Surgery, Faculty of Medicine and Research Institute for Health Science, Chiang Mai University, Chiang Mai, Thailand (K.R.)

Stroke Prevention Research Unit, Nuffield Department of Clinical Neuroscience, University of Oxford, Oxford, UK (PM.R.)

Correspondence

Prof. Emmanuel Touzé
Université de Caen Basse Normandie
Service de Neurologie, CHU Côte de Nacre, Caen
E-mail: emmanuel.touze@unicaen.fr

Short title: Myocardial infarction after carotid revascularization

Key words: carotid stenosis – atherosclerosis – carotid endarterectomy – carotid stenting – myocardial infarction – prevention – meta-analysis – systematic review.

Abstract

Background and Purpose – Carotid Angioplasty and Stenting (CAS) is associated with higher risk of periprocedural stroke and death compared with carotid endarterectomy (CEA). By contrast, the risk of myocardial infarction (MI) was higher after CEA than after CAS in randomized trials. However, numbers were small and risk factors are unknown. We aimed to estimate the 30-day absolute risk of MI after CAS and CEA and to determine subgroups at higher risk.

Methods – We performed a systematic review and a meta-analysis of studies published from 01/1980 to 06/2014 and collected unpublished data. We extracted data on 9 predefined risk factors (age, contralateral carotid occlusion, coronary artery disease, diabetes mellitus, sex, hypertension, peripheral artery disease, type stenosis, and clinical presentation). We selected studies with data available on MI in at least one subgroup, calculated absolute and relative risks and identified differential effects on risks of MI.

Results **–** The 30-day absolute risk of MI was 0.87% (95%CI, 0.69-1.07) after CEA and 0.70% (95%CI, 0.54-0.88) after CAS (Pint=0.07). After CAS, patients with symptomatic stenosis, restenosis were at higher risk of MI whereas males were at lower risk. After CEA, age, history of coronary artery disease, peripheral artery disease, and restenosis increased the risk of MI. Only the effect of sex differed between CAS and CEA with males being at lower risk of MI than females after CAS whereas there was no difference between after CEA (Pint=0.01).

Conclusions **–** The risk of MI is slightly higher after CEA than after CAS. Risk factors for MI are overall similar in both techniques except that males are at lower risk of MI after CAS but not after CEA.

Introduction

Carotid artery stenosis accounts for 15-20% of patients with ischemic stroke (IS) or transient ischemic attack (TIA). Carotid endarterectomy (CEA) reduces the absolute risk of IS by about 50% in patients with symptomatic or asymptomatic carotid stenosis compared with medical treatment.[1,2,3] Carotid angioplasty and stenting (CAS) has been evaluated as an alternative to CEA for several years. In the 3 European trials conducted in patients with symptomatic carotid stenosis, the 30-day risk of stroke or death was higher after CAS than after CEA.[4] In CREST, a similar higher risk of periprocedural stroke or death was observed in symptomatic and asymptomatic carotid stenosis.[5] Nevertheless, CEA and CAS have a similar long-term beneficial effect.[4,5,6,7]

An excess risk of periprocedural MI after CEA was observed in all randomized trials (pooled OR=2.23; 95%CI 1.37-3.63, 6 studies, 5725 patients, I^2=0%; supplementary figure I). Thus, in CREST, the 4-year composite outcome (stroke, MI, death) did not differ between CEA and CAS. This excess of MI after CEA is not well understood and the clinical importance of these coronary events has been questioned, mainly because small elevations of cardiac enzymes were considered in CREST.[8,9] On the other hand, it has been shown that small elevations of cardiac enzymes after a variety of vascular non cardiac and cardiac procedures are associated with increased future mortality and this has also been shown in CREST.[5,9-17] Thus, while stroke is correlated with functional impairment, MI could be an important cause of periprocedural death. Although this finding is consistent across all trials, the number of events observed in these trials was small (<100 MI in total) and risk factors for periprocedural MI remains unknown. We have recently shown that using a simple rule (SCAR rule) could help selecting patients with a similar risk of periprocedural stroke or death after CAS as after CEA,[18] but it is unknown whether this applies for MI. We therefore performed a systematic review of observational and randomized studies of the risk of periprocedural MI after CAS and CEA in order (1) to assess the absolute risk of periprocedural MI and the absolute risk of periprocedural death after CAS and CEA, and (2) to identify which risk factors may differ between the 2 interventions.

Methods

We updated our previous systematic reviews,[18,19] from October 1st, 2011 until June 30th, 2014, following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations for reporting.[20]

Selection criteria – Eligible studies were those which enrolled patients with symptomatic or asymptomatic stenosis located in the region of the carotid bifurcation, treated by CAS or CEA, and in which the numbers of MI or death could be extracted for any subgroup among a predefined list of 9 risk factors: age (≥ 75-80 years *vs.* <75-80 years, corresponding to the most common cutoffs used to separate elderly from nonelderly patients), contralateral carotid occlusion, coronary artery disease, diabetes mellitus, sex (male *vs.* female), hypertension, peripheral artery disease, type of stenosis (restenosis after CEA *vs.* primary atherosclerotic disease) and clinical presentation (symptomatic *vs.* asymptomatic stenosis). Studies were considered irrespective of setting and language. We excluded studies that enrolled only specific populations (*e.g.* postradiation stenosis, restenosis after CEA, and patients treated in an emergency context) and case reports.

For estimation of the absolute risks, we included studies that reported the risks at 30 days only. For the relative risks analysis, we included all studies that reported periprocedural risk (that could be periprocedural, intra-hospital or within 30 days after intervention).

Search strategy – The search strategy was based primarily on electronic searches of 3 databases (Medline, Embase and Cochrane Library database) from 1980 until 30th June 2014.

(supplementary table III). We hand-searched the references of all included studies and any relevant reviews. We also searched books of abstracts from recent conferences that were available online, the US Food and Drug Administration (http://fda.gov) and the European Medicines Agency (http://emea.europa.eu) databases. We contacted 17 authors of studies published after 2003 with data on the risk of periprocedural MI but with no data available on subgroups. We also added a retrospective registry from the vascular surgery department of our hospital (Caen University Hospital, France) of all patients treated by CEA from 2000 until 2013. In case of multiple publications referred to the same population, we retained one with data of the most important number of patients or the most relevant for the studied subgroup.

Analysis

Absolute risk – Proportion of MI and death were calculated after CAS and CEA. Each individual proportion was first transformed into a quantity with the Freeman-Tukey variance stabilizing transformation.[21] A weighted mean of the transformed proportions was computed by using a DerSimonian-Laird random effects model.[22] The combined proportion was calculated as the back-transform of this weighted mean.[23] We estimated the median year of the period of inclusion (mid-cohort year) and analyzed the evolution of the absolute risks over time by meta-regressions.

Relative risks – For each of the 9 potential risk factors and separately for studies of CAS and CEA, we calculated the relative risks (RR) of a periprocedural event in patients versus those without the risk factor. Because of differences between studies in which the risk factor data were reported, the numbers of studies (and patients) included in each meta-analysis differed. When zero cell count was observed in 1 group or both groups (*i.e.*, patients with and without the risk factor) we used a continuity correction, by adding a factor proportional to the reciprocal of the size of the contrasting study group to all cells.[24] Homogeneity of RR across studies in each meta-analysis was assessed using the I^2 statistic. I^2 >30% represents moderate heterogeneity, $I^2>50\%$ substantial heterogeneity and $I^2>70\%$ considerable heterogeneity. For each risk factor, we assessed whether the effect on the periprocedural risk of event differed between CAS and CEA by performing an interaction test using random effects meta-regressions. As recommended for such analyses, we considered a probability value of ≤ 0.10 as evidence of statistically significant interaction.[25] Statistical analyses were performed with SAS 9.2 and STATA 11.0.

Results

Of the 1584 articles identified from our update of the electronic searches, 147 abstracts were screened, 140 references were retrieved for assessment in full text and 96 references were finally eligible for the systematic review (supplementary figure II).

In addition, we added 202 references obtained from other sources: (1) 200 references from our previous systematic review;[18] (2) one reference from our own registry from the department of vascular surgery (2000 to 2013); (3) one reference for which unpublished data was obtained (*i.e.*, the only author who replied).[26] These 202 references and the 96 references obtained from electronic searches were screened and we secondly excluded 25 references corresponding to multiple publications referring to same population. Therefore, 273 references were included corresponding to 120 independent populations (studies). The list of all references included in the systematic review is available in the supplementary data.

30-day absolute risk of MI

We included 52 independent studies of CEA (62,336 patients) and 68 independent studies of CAS (31,843 patients) for the calculation of the absolute risk of MI. The characteristics of these studies and those of the 1,609 patients from our own registry, the list of references and the list of all references included in the systematic review are shown in supplementary tables I and II.

Only 29 (56%) out of 52 CEA studies and 13 (19%) out of the 68 CAS studies provided an explicit definition of MI. Table 1 shows that MI definitions varied across studies, being based on clinical parameters (chest pain suggestive of coronary ischemia), and/or biology (elevation of myocardial necrosis enzymes levels such as creatine kinase (CK), CK-MB or troponin), and/or ECG changes (development of pathological Q waves, new significant ST segment changes or T waves changes or new left bundle branch block). In our registry, MI was defined as a chest pain associated with ECG changes (development of pathological Q waves, new significant ST segment changes or T waves changes or new left bundle branch block) or/and elevation of troponin higher than the laboratory limit.

The pooled 30-day absolute risk of MI was 0.87% (95%CI, 0.69-1.07, I^2=81%) after CEA and 0.70% (95%CI, 0.54-0.88, I^2=59%) after CAS (Pint=0.07). In meta-regressions analyses using the mid-cohort year as covariate, the absolute risk of MI did not vary over time neither in CAS studies (since 1990, p=0.82) nor in CEA studies (since 1980, p=0.54) (supplementary figure III).

30-day absolute risk of death

We included 101 independent studies of CEA (30,553 patients) and 83 independent studies of CAS (39,184 patients) for the calculation of the 30-day absolute risk of death. The pooled 30-day absolute risk of death was 0.64% (95%CI, 0.53-0.75; I^2=88%) after CEA and 1.03% (95%CI, 0.83-1.26; I^2=70%) after CAS (Pint=0.25). In metaregression analyses, the risk of death slightly decreased over time in CEA studies (p<0.001) but did not changed in CAS studies (Pint=0.80). There was no interaction between CAS and CEA (Pint=0.17) (figure not shown)

30-day proportion of death related to stroke and MI

Afterwards, we retained only studies that had recorded the 30-day proportions of death attributable to stroke (stroke-death) and/or death attributable to MI (MI-death). We included 35 independent studies of CEA (24,690 patients) and 21 independent studies of CAS (7,321 patients) in this analysis. The proportion of stroke-death was 35% (95%CI, 25-46, I^2=53%) after CEA and 42% (95%CI, 25-60, I^2=67%) after CAS. The proportion of MI-death was 24% (95%CI, 17-31, I^2=30%) after CEA and 18% (95%CI, 8-29, I^2=47%) after CAS.

Risk factors for periprocedural MI

Figure 1 shows the relative risks of periprocedural MI according to the 9 potential risk factors. Patients with symptomatic stenosis, restenosis were at higher risk of MI whereas males were at lower risk of MI after CAS. Older age, coronary artery disease, peripheral artery disease, and restenosis increased the risk of MI after CEA. Only the effect of sex differed between CAS and CEA with males being at lower risk of MI than females after CAS whereas there was no difference after CEA (Pint=0.01).

Risk factors for periprocedural death

Figure 2 shows the relative risks of periprocedural death according to the 9 potential risk factors. Older age and symptomatic stenosis were associated with a higher risk of death after CAS. Older age, contralateral occlusion, coronary heart disease, diabetes, peripheral artery disease, and symptomatic stenosis were associated with a higher risk of death after CAS. We did not found any differential effect on death between CAS and CEA.

Discussion

We have shown that the 30-day absolute risk of MI is slightly higher after CEA than after CAS, but with a small absolute difference (0.87% *vs.* 0.70%) and that there was no major factors that could help to identify patients with a differential risk of MI after CEA compared to CAS.

The absolute risk of MI we found after CEA was lower than the one found in a pooled analysis restricted to randomized trials only (1.87%). By contrast, the absolute risk of MI after CAS was comparable to that observed in randomized trials (0.75%). The risk of MI after CEA could have been underestimated because we included retrospective registries, but a similar underestimation should have been found for CAS. As overall, CEA registries were carried out earlier than CAS registries and because definition of MI has changed over time, there is a possibility that MI was less likely to be diagnosed in the past. If this excess of periprocedural MI after CEA compared to CAS is true, the reasons remain unclear. First, the use of combined antiplatelet therapy (aspirin/clopidogrel for at least 1 month) in CAS but not in CEA might explain the absolute difference between CAS and CEA. Combined antiplatelet therapy is not commonly used in patients scheduled for CEA as it seems to increase the risk of bleeding and to slow down healing. Second, the type of anesthesia differs between CEA and CAS. CAS is performed under local anesthesia while, depending on centers, CEA is performed under general or locoregional anesthesia. Although the periprocedural risk of stroke and death at 30 days does not differ between the two types of anesthetic techniques after CEA,[27] there is no data on the risk of MI. One randomized controlled trial reported a two-fold higher risk of MI at 30 days after general anesthesia compared with local anesthesia, but the number of events was small (3/52 vs 1/55) and all cases had known coronary artery disease.[28] Thus, considering the few number of studies it remains difficult to know the exact influence of anesthesia technique on the risk of MI after CEA and CAS. Third, cervical incision provokes local inflammation, stress and liberation of pro-inflammatory cytokines that causes pro-thrombotic state. This pro-thrombotic state could favor the periprocedural risk of MI after CEA.

Non-cardiac vascular surgery (carotid artery, lower extremity artery, abdominal aortic aneurysm) is associated with a periprocedural risk of MI, mainly because atherosclerosis is a systematic disease. In a meta-analysis, this risk has been estimated to vary between 1 and 26%.[16] As expected, in our study, the main risk factor for periprocedural MI was a history of coronary artery disease. The periprocedural risk of MI after surgery and angioplasty/stenting has never been compared in other atherosclerotic arteries. Thus uncertainty remains on whether our results are specific or not of the carotid artery.

Sex had a differential effect on the risk of MI between CAS and CEA. As compared to what we found for stroke and death, sex was the only factor that differed between the 2 techniques.[18] Males were at lower risk of MI than females after CAS. On the contrary, in our previous meta-analysis, male sex was associated with a lower risk of periprocedural stroke or death after CEA whereas sex had no significant influence on the risk after CAS. Considering the huge number of studies included for this subgroup and the absence of heterogeneity in our analyses on MI, the effect is likely to be true. However, it remains difficult to explain. No data is available on the influence of sex on the periprocedural risk of MI after angioplasty/stenting and surgery in other atherosclerotic arteries.

Our analysis has several potential limitations. First, the numbers of events were sometimes small and because of the population case-mix, our results on absolute risks were heterogeneous (I^2=81% for CEA and 59% for CAS). However, this heterogeneity is common in the combination of absolute risks. We consequently used random effects models. In opposite, there was no or little heterogeneity in analyses dedicated to risk factors. Second, MI definitions have varied over time and between studies, especially the use of cardiac biomarkers has changed (CK appeared first then CK-MB and troponin is now used since a decade). However, this has probably not affected the estimate of the risk of MI. Diagnosis of MI in studies was based, when available, on the presence of several parameters (clinical symptoms and at least one parameter among biology or ECG). It is common knowledge that elevation of cardiac biomarkers can occur after vascular carotid procedure. For this reason, biomarkers elevation without symptoms suggestive of coronary ischemia or ECG changes were not included in the calculation of the absolute risk of MI. Furthermore, in spite of changes in MI definition over time, the absolute risk of MI has not changed over time. Third, we were not able to validate our results on sex in randomized controlled trials. Few randomized controlled trials have recorded data on MI for sex subgroup. Moreover, the total number of events in these randomized trials was too small to assess the reproducibility of our results. Fourth, we only included studies that reported events in at least one of the 9 predefined subgroups for the calculation of the absolute risk of MI and death. However, this should not have introduced selection bias. On the one hand, we excluded most of the randomized controlled trials; on the other hand, the ones retained were the randomized controlled trials with larger sample size than those excluded and had therefore more precise estimations of absolute risks. Additionally, 8% of total of references eligible (from our previous systematic review and update) were excluded due to absence of data on subgroup that represents a negligible proportion.

Randomized controlled trials have shown that stroke is the main cause of periprocedural death after carotid revascularization.[2,29-31] Our results do not support that MI is an important cause of periprocedural death. Therefore, it appears more relevant to focus on the risk factors for periprocedural stroke to better understand the risk factors for periprocedural death. Although we found that male sex is associated with a lower risk of MI compared with female sex after CAS, this should not be considered as a major criteria to select candidates for CAS, because MI is far less common than stroke, MI accounts little for periprocedural death, and male sex is a strong risk factor for periprocedural stroke or death after CAS.

Disclosures: none

Acknowledgement

Dr. Rerkasem has been funded by the Thailand Research Fund (RSA5580008), Faculty of Medicine, Chiang Mai University.

References

1. Rothwell PM, Eliasziw M, Gutnikov SA, Fox AJ, Taylor DW, Mayberg MR, et al. Analysis of pooled data from the randomized controlled trials of endarterectomy for symptomatic carotid stenosis. *Lancet.* 2003;361:107-116.

2. Cavatas Investigators. Endovascular versus surgical treatment in patients with carotid stenosis in the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS): a randomized trial. *Lancet*. 2001;357:1729-1737.

3. Taylor DW, Barnett HJM, Haynes RB, Ferguson GG, Sackett DL,Thorpe KE, et al. Low-dose and high-dose acetylsalicylic acid for patients undergoing carotid endarterectomy: a randomized controlled trial (ACE). *Lancet*. 1999;353:2179-2184.

4. Trialists'collaboration Cs, Bonati LH, Dobson J, Algra A, Branchereau A, Chatellier G, et al. Short-term outcome after stenting versus endarterectomy for symptomatic carotid stenosis: a preplanned meta-analysis of individual patient data. *Lancet.* 2010;376:1062-1073.

5. Brott TG, Hobson RW, Howard G, Roubin GS, Clark WM, Brooks W, et al. Stenting versus Endarterectomy for Treatment of Carotid-Artery Stenosis. *N Engl J Med*. 2010;363:11-23.

6. Eckstein HH, Ringleb P, Allenberg JR, Berger J, Fraedrich G, Hacke W, et al. Results of the Stent-Protected Angioplasty versus Carotid Endarterectomy (SPACE) study to treat symptomatic stenoses at 2 years: a multinational, prospective, randomized trial. *Lancet Neurol*. 2008;7:893-902.

7. Mas JL, Arquizan C, Calvet D, Viguier A, Albucher J-F, Piquet P, et al. Long-Term Follow-Up Study of Endarterectomy Versus Angioplasty in Patients With Symptomatic Severe Carotid Stenosis Trial. *Stroke*. 2014;45:2750-2756.

8. Blackshear JL, Cutlip DE, Roubin GS, Hill MD, Leimgruber PP, Begg RJ, et al. Myocardial Infarction After Carotid Stenting and Endarterectomy: Results From the Carotid Revascularization Endarterectomy Versus Stenting Trial. *Circulation*. 2011;123:2571-2578.

9. Galyfos G, Sigala F, Karanikola E, Loizou C, Toutouzas K, Filis K. J. Postoperative cardiac damage after standardized carotid endarterectomy procedures in low- and high-risk patients. *Anesth*. 2014;28:866-872.

10. Botto F, Alonso-Coello P, Chan MT, Villar JC, Xavier D, Srinathan S, Guyatt G, et al. Myocardial injury after noncardiac surgery: a large, international, prospective cohort study establishing diagnostic criteria, characteristics, predictors, and 30-day outcomes. *Anesthesiology*. 2014;120:564-578.

11. Kim LJ, Martinez EA, Faraday N, Dorman T, Fleisher LA, Perler BA, et al. Cardiac troponin I predicts short-term mortality in vascular surgery patients. *Circulation*. 2002;106:2366-2371.

12. Landesberg G, Shatz V, Akopnik I, Wolf YG, Mayer M, Berlatzky Y, et al. Association of cardiac troponin, CK-MB, and postoperative myocardial ischemia with long-term survival after major vascular surgery. *J Am Coll Cardiol.* 2003;42:1547-1554.

13. Kertai M, Boersma E, Klein J, Van Urk H, Bax J, Poldermans D. Long-term Prognostic Value of Asymptomatic Cardiac Troponin T Elevations in Patients After Major Vascular Surgery. *Eur J Vasc Endovasc Surg*. 2004;28:59-66.

14. Nienhuis MB, Ottervanger JP, Bilo HJG, Dikkeschei BD, Zijlstra F. Prognostic value of troponin after elective percutaneous coronary intervention: A meta-analysis. *Catheter Cardiovasc Interv*. 2008;71:318-324.

15. Kan P, Dumont TM, Abla AA, Siddiqui AH,Levy EI,Hopkins LN. Myocardial Infarction After CAS and CEA:Why Does It Matter? *Endovascular Today*. 2011;71:71-74.

16. Flu W-J, Schouten O, Van Kuijk J-P, Poldermans D. Perioperative Cardiac Damage in Vascular Surgery Patients.*European Journal of Vascular and Endovascular Surgery*. 2010;40:1-8.

17. Oscarsson A, Eintrei C, Anska¨S, Engdahl O, Fagerstro L, Blomavist P, et al. *Acta Anaesthesiol Scand*. 2004; 48:1071-1079.

18. Touze E, Trinquart L, Felgueiras R, Rerkasem K, Bonati Lh, Meliksetyan G, et al. A Clinical Rule (Sex, Contralateral Occlusion, Age, and Restenosis) to Select Patients for Stenting Versus Carotid Endarterectomy: Systematic Review of Observational Studies With Validation in Randomized Trials. *Stroke*. 2013;44:3394-3400.

19. Touze E, Trinquart L, Chatellier G, Mas J-L. Systematic Review of the Perioperative Risks of Stroke or Death After Carotid Angioplasty and Stenting. *Stroke*. 2009;40:e683-e693.

20. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med.* 2009;151:264–269.

21. Freeman M, Tukey J. Transformation related to the angular and the sqaure root. *Ann Math Stat*. 1950;21:607-611.

22. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7:177-188.

23. Trinquart L, Touze E. Pitfalls in Meta-Analysis of Observational Studies: Lessons From a Systematic Review of the Risks of Stenting for Intracranial Atherosclerosis. *Stroke*. 2009;40:e586-e587.

24. J Sweeting M, J Sutton A, C Lambert P. What to add to nothing? Use and avoidance of continuity corrections in meta-analysis of sparse data. *Stat Med*. 2004;23:1351-1375.

25. Fleiss JL. Analysis of data from multiclinic trials. *Control Clin Trials*. 1986;7:267-275.

26. Mazzaccaro D, Steger S, Occhiuto MT, Malacrida G, Caldana M, Tealdi DG, et al. Treatment of significant carotid artery stenosis in 1824 patients. *J Cardiovasc Surg*. 2011;56:107-118.

27. Vaniyapong T, Chongruksut W, Rerkasem K. Local versus general anaesthesia for carotid endarterectomy. *Cochrane Database Syst Rev*. 2013;12.

28. Sbarigia E, Dario Vizza C, Antonini M, Speziale F, Maritti M, Fiorani B, et al. Locoregional versus general anesthesia in carotid surgery: Is there an impact on perioperative myocardial ischemia? Results of a prospective monocentric randomized trial. *J Vasc Surg*. 1999;30:131-138

29. EVA-3S Investigators. Endarterectomy vs. Angioplasty in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S) Trial. *Cerebrovasc Dis*. 2004;18:62-65.

30. Investigators ICSS, Others. Carotid artery stenting compared with endarterectomy in patients with symptomatic carotid stenosis (International Carotid Stenting Study): an interim analysis of a randomised controlled trial. *Lancet*. 2010;375:985.

31. Brooks WH, Mcclure RR, Jones MR, Coleman Tc, Breathitt L. Carotid angioplasty and stenting versus carotid endarterectomy: randomized trial in a community hospital. *J Am Coll Cardiol*. 2001;38:1589-1595.

32. Barnett HJ, Taylor DW, Eliasziw M, Fox AJ, Ferguson GG, Haynes RB, et al. Benefit of carotid endarterectomy in patients with symptomatic moderate or severe stenosis. *N Engl J Med*. 1998;339:1415-1425.

33. European Carotid Surgery Trialists'collaborative Group. Randomised trial of endarterectomy for recently symptomatic carotid stenosis: final results of the MRC European Carotid Surgery Trial (ECST). *Lancet.* 1998; 351:1379-1387.

34. Chaturvedi S, Bruno A, Feasby T, Holloway R, Benavente O, Cohen SN, et al. Carotid endarterectomy--An evidence-based review: Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology*. 2005;65:794-801.

35. Goldstein LB, Adams R, Alberts MJ, Appel LJ, Brass Lm, Bushnell CD, et al. Primary Prevention of Ischemic Stroke: A Guideline From the American Heart Association/American Stroke Association Stroke Council: Cosponsored by the Atherosclerotic Peripheral Vascular Disease Interdisciplinary Working Group; Cardiovascular Nursing Council; Clinical Cardiology Council; Nutrition, Physical Activity, and Metabolism Council; and the Quality of Care and Outcomes Research Interdisciplinary Working Group: The American Academy of Neurology affirms the value of this guideline. *Stroke*. 2006;37:1583-1633.

36. Sacco RL, Adams R, Albers G, Alberts MJ, Benavente O, Furie K, et al. Guidelines for Prevention of Stroke in Patients With Ischemic Stroke or Transient Ischemic Attack: A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association Council on Stroke: Co-Sponsored by the Council on Cardiovascular Radiology and Intervention: The American Academy of Neurology affirms the value of this guideline. *Stroke.* 2006;37:577-617.

37. Abbott AL. Medical (Nonsurgical) Intervention Alone Is Now Best for Prevention of Stroke Associated With Asymptomatic Severe Carotid Stenosis: Results of a Systematic Review and Analysis. *Stroke.* 2009;40:e573-e583.

38. the SPACE Collaborative Group. 30 day results from the SPACE trail of stent-protected angioplasty versus endarterectomy in symptomatic patients: a randomized non-inferiority trial. *Lancet.* 2006;368:1239-1247.

39. Mas JL, Trinquart L, Leys D, Albucher JF, Rousseau H, Viguier A, et al. Endarterectomy Versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S) trial: results up to 4 years from a randomised, multicenter trial. *Lancet Neurol*. 2008;7:885-892.

40. Yadav JS, Wholey MH, Kuntz RE, Fayad P, Katzen BT, Mishkel GJ, et al. Protected carotid-artery stenting versus endarterectomy in high-risk patients. *N Engl J Med*. 2004;351:1493-1501.

41. Committee Cs, Others. Carotid Revascularization using Endarterectomy or Stenting Systems (CARESS): phase I clinical trial. *J Endovasc Ther Off J Int Soc Endovasc Spec*. 2003;10:1021.

42. Naylor AR. Randomized study of carotid angioplasty and stenting versus carotid endarterectomy: a stopped trial. *J Vasc Surg.* 1998;28:326-334.

43. Ling F, Jiao LQ. Preliminary report of trial of endarterectomy versus stenting for the treatment of carotid atherosclerotic stenosis in China (TESCAS-C).*Chinese Journal of Cerebrovascular Diseases*. 2006;3:4-8.

44. Alberts MJ. Results of a Multicenter Prospective Randomized Trial of Carotid Artery Stenting vs. Carotid Endarterectomy: *Stroke*. 2001;32:325-328.

45. Kirschf EC. Carotid artery stenting versus carotid endarterectomy–a prospective randomised controlled single-centre trial with long-term follow-up (BACASS). *Neurol Psychiatr*. 2008;159:84-89.

46. Brooks WH, Mcclure RR, Jones MR, Coleman TL, Breathitt L
Carotid angioplasty and stenting versus carotid endarterectomy for treatment of asymptomatic carotid stenosis: a randomized trial in a community hospital. *Neurosurgery*. 2004;54:318-324

47. Alam M, Huang HD, Shahzad SA, Kar B, Virani SSV, Rogers PA, et al. Percutaneous coronary intervention vs. coronary artery bypass graft surgery for unprotected left main coronary artery disease in the Drug-Eluting Stents Era. *Circ J.* 2013;77:372-382.

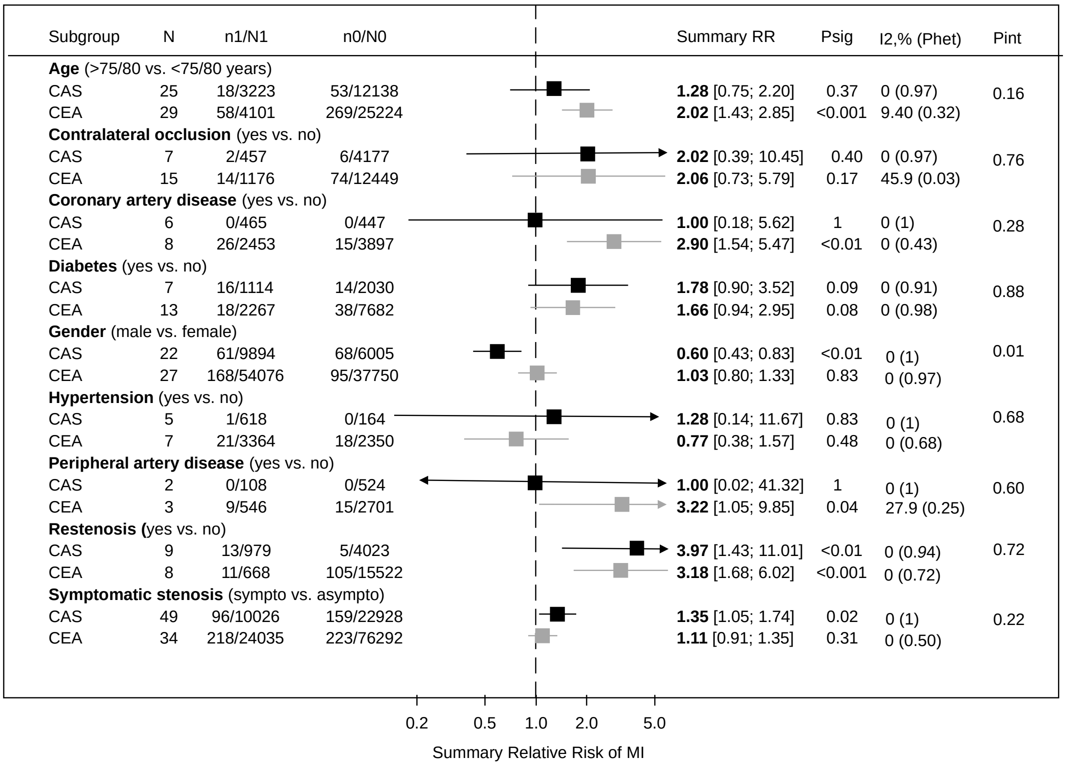
48. Lee MS, Yang T, Dhoot J, Liao H. Meta-analysis of clinical studies comparing coronary artery bypass grafting with percutaneous coronary intervention and drug-eluting stents in patients with unprotected left main coronary artery narrowings. *Am J Cardiol.* 2010;105:1070-1075

49. Howard VJ, Lutsep HL, Mackey A, Demaerschalk BM, Sam Ii Ad, Gonzales NR, et al. Influence of sex on outcomes of stenting versus endarterectomy: a subgroup analysis of the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST). *Lancet Neurol*. 2011;10:530-537.

50. Touze E, Varenne O, Chatellier G, Peyrard S, Rothwell PM, MAS J-L. Risk of Myocardial Infarction and Vascular Death After Transient Ischemic Attack and Ischemic Stroke: A Systematic Review and Meta-Analysis. *Stroke*. 2005;36:2748-2755.

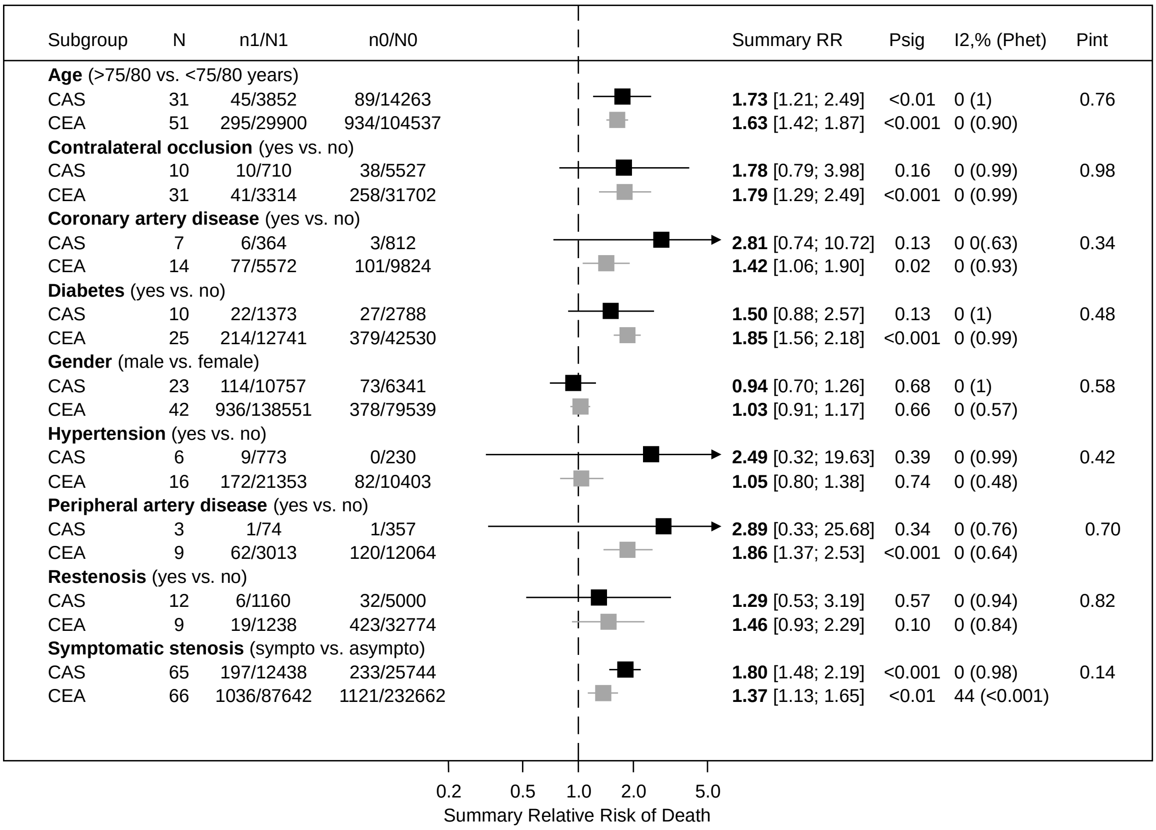
51. Brown MM, Raine R. Should sex influence the choice between carotid stenting and carotid endarterectomy? *Lancet Neurol.* 2011;10(6):494-7.

Figure 1. Meta-analyses of the relative risk of MI after CAS and CEA according to the 9 potential risk factors.



N indicates number of studies; n1, number of events in patients with clinical factor; N1, number of patients with clinical factor; n0, number of events in patients without clinical factor; N0, number of patients without clinical factor; P_{het}, Cochran homogeneity test probability value; P_{int}, P interaction; P_{sig}, P significance; and RR, relative risk.

Figure 2. Meta-analyses of the relative risk of death after CAS and CEA according to the 9 potential risk factors.



N indicates number of studies; n1, number of events in patients with clinical factor; N1, number of patients with clinical factor; n0, number of events in patients without clinical factor; N0, number of patients without clinical factor; P_{het}, Cochran homogeneity test probability value; P_{int} , P interaction; $P_{sig,}$ P significance; and RR, relative risk.

Table 1. MI definitions used in the studies included for the calculation of the 30-day absolute risk of MI

	CAS (N= 68 studies)	CEA (N= 52 studies)
MI definitions	*N (%)*	*N (%)*
Symptoms suggestive of MI and CK-MB or troponin elevation and ECG changes	5 (7)	11 (21)
Symptoms suggestive of MI and CK-MB elevation and ECG changes	4 (6)	15 (29)
Symptoms suggestive of MI and troponin elevation and ECG changes	3 (4)	3 (6)
Symptoms suggestive of MI and ECG changes without biological markers	1 (1)	0
No explicit definition	55 (81)	23 (44)

Supplemental data

Risk and risk factors of periprocedural myocardial infarction and death after Carotid Endarterectomy and Carotid Angioplasty and Stenting: systematic review and meta-analysis

Supplementary table I - Characteristics of studies included for the calculation of the 30-day absolute risk of MI.

	CAS 68 studies (31,843 patients)		CEA 52 studies (62336 patients)	
Characteristics	*Value N (%)**	*N studies with data available*	*Value N (%)**	*N studies with data available*
Mean number of patients per study (min/max)	468 (20/3,737)	68	1,199 (65/9,440)	52
Mean age (years)	71.4	61	69.5	39
Male	18,818 (67)	59	27,473 (60)	40
Symptomatic stenosis	11,066 (46)	60	25,923 (54)	43

*Except where stated otherwise in the table

Supplementary table II - Characteristics of the patients treated by CEA at Caen University Hospital from 2000 to 2013.

	Caen University Hospital registry (N= 1609)
Characteristics	*N (%) **
Mean age (years)	71,8
Minimal /Maximal age (years)	43/97
Age > 80 ans	400 (25)
Males	1170 (73)
Hypertension	1317 (82)
Coronary artery disease	574 (36)
Diabetes	397 (25)
Symptomatic stenosis	578 (36)

*Except where stated otherwise in the table

Supplementary table III - Search Strategy.

(((((((carotid stenosis[MeSH Terms]) AND stenting[MeSH Terms]) OR angioplasty[MeSH Terms]) OR endarterectomy[MeSH Terms]) AND myocardial infarction[MeSH Terms]) AND outcome[MeSH Terms]) OR death[MeSH Terms]) AND humans[MeSH Terms] AND ("2011/10"[Date - Publication] : "2014/07"[Date - Publication])

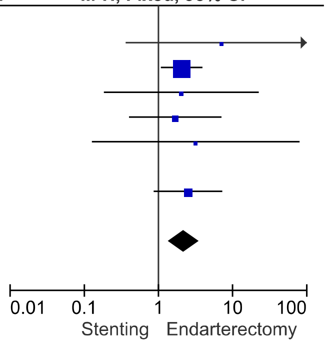
Supplementary figure I - Risk of periprocedural MI in all randomized controlled trials comparing CAS (carotid angioplasty stenting) and CEA (carotid endarterectomy).

	Stenting		Endarterectomy			Odds Ratio (Non-event)
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
BACASS 2008 [45]	0	10	0	10		Not estimable
CAVATAS 2001 [2]	0	251	3	253	2.1%	7.03 [0.36, 136.76]
CREST 2010 [5]	14	1262	28	1240	58.6%	2.06 [1.08, 3.93]
EVA 3 S 2008 [29]	1	265	2	262	4.3%	2.03 [0.18, 22.53]
ICSS 2009 [30]	3	828	5	821	12.8%	1.69 [0.40, 7.07]
KENTUCKY 2001 [31]	0	53	1	51	2.1%	3.18 [0.13, 79.83]
KENTUCKY 2004 [46]	0	43	0	42		Not estimable
SAPPHIRE 2004 [40]	5	167	12	167	20.1%	2.51 [0.86, 7.29]
Total (95% CI)		**2879**		**2846**	**100.0%**	**2.23 [1.37, 3.63]**
Total events	23		51			

Heterogeneity: Chi² = 0.88, df = 5 (P = 0.97); I² = 0%

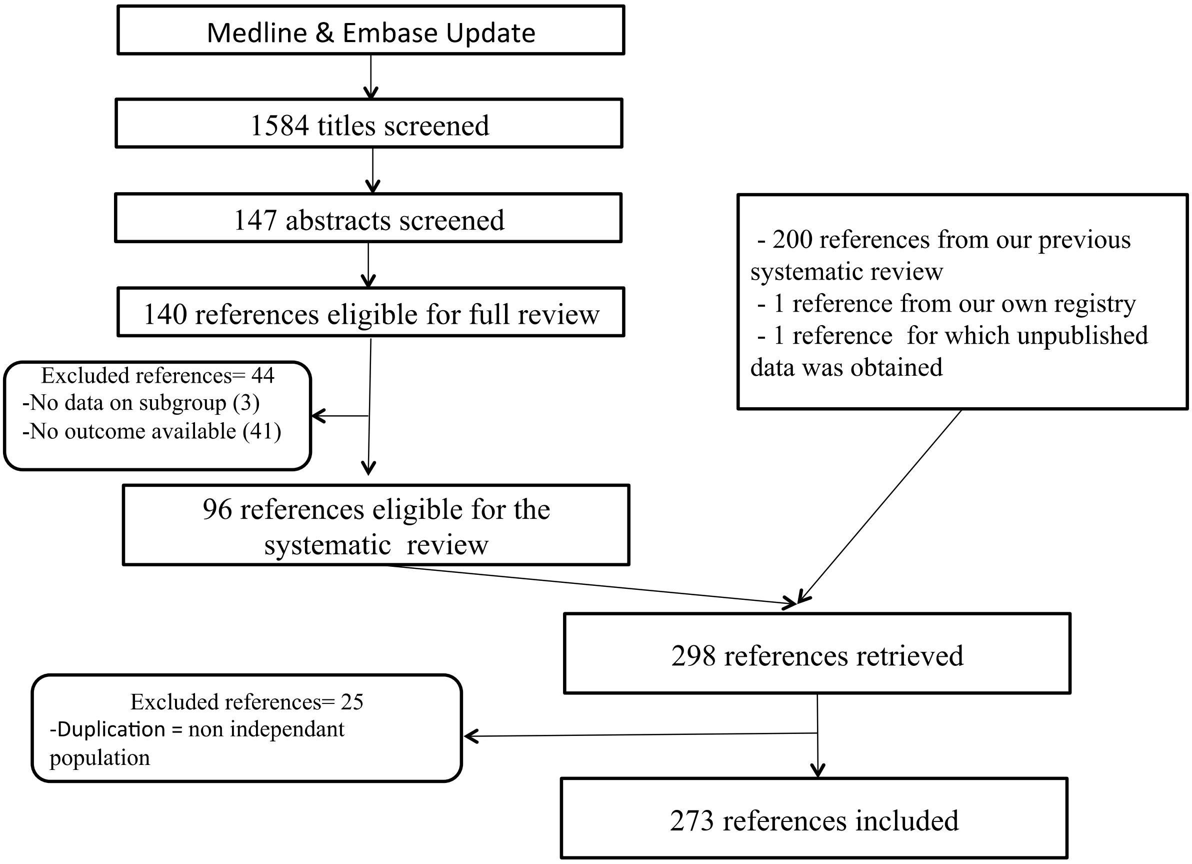
Test for overall effect: Z = 3.22 (P = 0.001)

Odds Ratio (Non-event)
M-H, Fixed, 95% CI

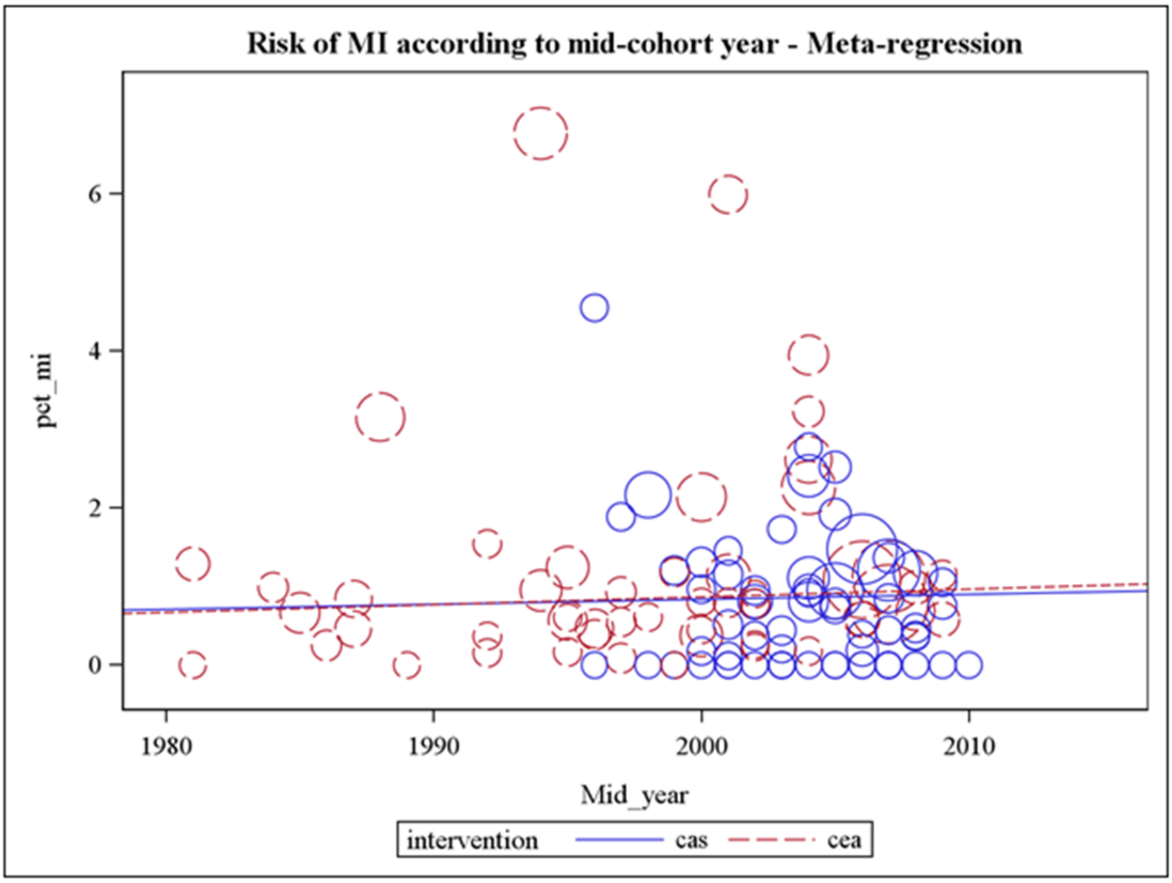


The risk of periprocedural MI was 0.75% (95% CI, 0.31-1.39) after CAS and 1.87% (95% CI,0.84-3.31) after CEA. The following trials CARESS, LEICESTER, SPACE, TESCAS, and WALLSTENT, did not assess periprocedural MI.

Supplementary figure II - Flow chart for selection of studies.



Supplementary figure III - Evolution of the absolute risk of MI at 30 days according to the mid-cohort year in CAS and CEA studies from 1980 à 2014 by meta-regressions.



The size of each circle is inversely proportional to the variance of the absolute risk.

The absolute risk of MI according to mid-cohort year did not vary over time neither in CAS studies (since 1990, p=0.82) nor in CEA studies (since 1980, p=0.54).

List of all references included in the systematic review.

References followed by **(death)** were included for the calculation of the risk of death
References followed by **(MI)** were included for the calculation of the risk of MI
References followed by **(death and MI)** were included for the calculation of the risk of death and MI

Sub-group: Age
CAS
Ahmadi R *et al.* J Endovasc Ther 2002;9:559-565. **(death)**
Alkins R *et al.* Can J Neurol Sci 2012;39:338-342. **(death and MI)**
Allison SK *et al*. J Am Coll Surg 2011;213:173-179. **(MI)**
Almekhafi MA *et al.* Can J Neurol Sci 2011;38:446-451. **(death and MI)**
Arjomand H *et al* J Am Coll Cardiol 2008;52(suppl 2). **(MI)**
Aydiner O *et al*. Anadolu Kardiyol Derg 2007;7:152-157. **(death and MI)**
Bacharach JM *et al*. Ann Vasc Surg 2010; 24:153-159. **(death and MI)**
Brown KE e*t al.* Ann Vasc Surg 2009, 23:439-445. **(death and MI)**
Eskandari MK *et al.* J Vasc Surg 2010; 51:1145-51. **(death and MI)**
Gray WA *et al*. Catheter Cardiovasc Interv 2007;70:1025-1033. **(death and MI)**
Henry M *et al*. Catheter Cardiovasc Interv 2008;72:309-317. **(death and MI)**
Hopkins NL *et al.* Catheter Cradiovasc Interv. 2008;71:950-960. **(death and MI)**
Kadkhodayan Y et *al.* Neuroradiology 2007; 49:933-938. **(death and MI)**
Kastrup A *et al.* Am J Neuroradiol 2008;29:608-612. **(death)**
Katzen B *et al.* Am J Cardiol 2006;98:11M. **(death and MI)**
Kawabata Y *et al*. J Vasc Interv Radiol 2009;20:9-16. **(death)**
Kfoury E *et al.* Vasc Endovascular Surg 2013;47:599-602. **(death and MI)**
Lam RC *et al.* J Vasc Surg. 2007;45:875-880. **(death and MI)**
Langhoff R *et al*. Vasc Endovasc Surg 2014;48:317-324. **(death and MI)**
Mas JL *et al.* N Engl J Med 2006;355:1660-1671. **(death)**
Matsumura JS *et al.* J Vasc Surg 2012;55:968-977. **(death and MI)**
Myla S *et al.* Catheter Cardiovasc Interv 2010;75:817-822. **(death and MI)**
Pinter L *et al.* J Vasc Surg 2011;54:1317-1323. **(death and MI)**
Safian RD *et al.* J Am Coll Cardiol 2006;47:2384-2389. **(death and MI)**
Schlutler M *et al.* J Endovasc Ther 2007;14:271-278. **(death)**
Setacci C *et al.* J Endovasc Ther 2006;13:302-309 **(death and MI)**
Shawl F *et al.* J Am Coll Cardiol 2000;35:1721-1728. **(death and MI)**
Sztriha LK *et al.* Stroke 2004;35:2862-2866. **(MI)**
Takayama K *et al.* Radiat Med 2008; 26:348-354. **(death and MI)**
Tatli E *et al.* Postep Kardiol Inter 2013;9(33): 221–227. **(death and MI)**
Tedesco MM *et al.* J Vasc Surg 2009;49:607-613. **(death)**
Teitelbaum GP *et al.* Surgical Neurology1998;50:300-311. **(death and MI)**
Zahn R e*t al.* Eur Heart J 2007;28:370-375. **(death and MI)**
Zarins CK *et al.* J Endovasc Ther 2009;16:397-409. **(death and MI)**

CEA
Aune S *et al.* Int Angiol. 2003;22:421-425. **(death)**
Allcutt DA *et al.* Br J Neurosurg. 1991;5:257-264. **(death and MI)**
Alozairi O *et al.* Eur J Vasc Endovasc Surg. 2003;26:245-249. **(death)**
Ballotta E *et al.* J Vasc Surg. 2009;50:518-25. **(death and MI)**
Barnett HJM *et al.* N Engl J Med 1998;339:1415-1425. **(death and MI)**
Brott T *et al.* Stroke 1984;15;950-955. **(death)**
Brown KE *et al.* Ann Vas Surg 2009,23:439-445. **(death)**
Cartier B *et al.* Ann Vasc Surg 2002;16:751-725. **(death and MI)**
Coyle KA *et al.* Ann Vasc Surg 1994;8:417-420. **(death and MI)**
Dorafshar AH *et al.* Ann Vasc Surg 2004;18:729-735. **(death and MI)**
Duran Marino JL *et al.* Rev Esp Geriatr Gerontol 2011;46:121-124. **(death)**
ECST Lancet 1998; 351:1379-1387. **(death and MI)**
Faggioli G *et al.* J Vasc Interv Radiol 2013; 24:370-377. **(death and MI)**
Goldmann KA *et al.* Vascular Surgery 1999;33:451-459. **(death and MI)**

Goldstein LB *et al.* Stroke 1994;25:1116-1121. **(death and MI)**
Kang JL *et al.* J Vasc Surg 2009;49:331-339. **(death)**
Kerdiles Y *et al.* J Cardiovasc Surg 1997;38:327-334. **(death and MI)**
Kfoury E *et al.* Vasc Endovascular Surg 2013;47:599-602. **(death and MI)**
Kucey DS *et al.* J Vasc Surg 1998;28:1051-1058. **(death)**
Lau D *et al.* The American Journal of Surgery 2005;190:795-799. **(death and MI)**
Love A *et al.* Cardiovascular Surgery 2000;8:429-435. **(death)**
Magnadottir HB *et al.* Neurosurgery 1999;45:786-791. **(death and MI)**
Mas JL *et al.* N Engl J Med 2006;355:1660-1671. **(death)**
Maxwell JG *et al.* Am Surg 2000;66:773-780. **(death)**
Menyhei G *et al.* Eur J Vasc Endovasc Surg 2011;41:735e740. **(death)**
Middleton S *et al.* J Vasc Surg 2002;36:62-69. **(death and MI)**
Miller MT *et al*. J Vasc Surg 2005;41:231-237. **(death and MI)**
Navas I *et al.* Neurología 2008;23:408-414. **(death)**
Nunnelee JD *et al.* Geriatr Nurs 1995;15:121-123. **(death and MI)**
Ommer A *et al.* Cardiovasc Surg 2001;9:552-558. **(death)**
Organ N *et al.* Eur J Vasc Endovasc Surg 2008;35:273-279. **(death)**
Ouriel K *et al.* Surg Gynecol Obst 1986;162:334-336. **(death and MI)**
Papachristou EA *et al.* Vascular Surgery 1994;28:531-537. **(death and MI)**
Perler BA *et al.* Cardiovasc Surg 1995;3:631-636. **(death and MI)**
Pruner G *et al.* Cardiovasc Surgery 2003;11:105-112. **(death and MI)**
Reed AB *et al.* J Vasc Surg 2003;37:1191-1199. **(death and MI)**
Rockman CB *et al.* Ann Vasc Surg 2003;17:9-14. **(death and MI)**
Salameh JR *et al.* Arch Surg 2002;137:1284-1287. **(death and MI)**
Schneider JR *et al*. J Vasc Surg 2000;31:927-35 **(death and MI)**
Schultz RD *et al.* Surg Gynecol Obstet 1988;166:245-251. **(death)**
Sokol D *et al.* Acta Neurochir 2011;153:363-369. **(death and MI)**
Sternbergh WC *et al.* The Ochsner Journal 2003;5:23-29. **(death)**
Stoner MC *et al.* Vasc Surg 2006;43:285-296. **(death)**
Teso D *et al.* J Am Coll Surg 2005; 200:734-741. **(death)**
Thomas PC *et al.* Aust N Z J Surg 1996;66:231-234. **(death and MI)**
Ting ACW *et al.* Cardiovascular Surgery, 2000;8:441-445. **(death)**
Tu JV *et al.* Stroke 2003;4:2568-2573. **(death)**
Van Damme H *et al.* Acta Chir Belg 1996;96:71-77. (**death and MI)**
Young B *et al.* Stroke. 1996;27:2216-2224. **(death and MI)**
Zarins CK *et al.* J Endovasc Ther 2009;16:397-409. **(death and MI)**

Sub-group: Contralateral occlusion
CAS
Clark DJ *et al.* Catheter Cardiovasc Interv 2004; 63:355-362. **(death)**
Hofmann R *et al.* Stroke 2006;37:2557-2561. **(MI)**
Kao HL *et al*. Cardiology 2002;97:89-93. **(MI)**
Kawabata Y *et al.* J Vasc Interv Radiol 2009;20:9-16. **(death)**
Keldahl ML *et al*. Ann Vasc Surg 2012;26:40-45. **(death and MI)**
Lanzer P *et al.* Clin Res Cardiol 2006;95:4-12. **(death)**
Mas JL *et al*. N Engl J Med 2006;355:1660-1671. (**death)**
Massop D *et al.* Catheter Cardiovasc Interv 2009;73:129-136. **(death)**
Mehta RH *et al.* Am J Cardiol 2009;104:725-731. **(death and MI)**
Pinter L *et al*. J Vasc Surg 2011;54:1317-1323. **(death and MI)**
Stingele R *et al.* Lancet Neurol 2008;7:216-222. **(death)**
Veselka J *et al.* Ann Vasc Surg 2011;25:796-804. **(death and MI)**

CEA

AbuRahma AF *et al.* Stroke 2000;31:1566-1571. **(death and MI)**
Allcutt DA *et al*. Br J Neurosurg 1991;5:257-264. **(death and MI)**
Ballotta E *et al*. Langenbeck's Arch Surg 2002;387:216-221. **(death and MI)**
Barnett HJM *et al.* N Engl J Med 1998; 339:1415-1425. **(death and MI)**
Bunt TJ *et al.* Am Surg 1985;51:61-69. **(death)**
Cao P *et al.* Eur J Vasc Endovasc Surg 1995;10:16-22. **(death and MI)**
da Silva AF *et al*. Br J Surg 1996;83:1370-1372. **(death)**
Domenig C *et al.* Ann Vasc Surg 2003;17:622-628. **(death and MI)**
Deriu GP *et al.* Ann Vasc Surg 1994;8:337-342. **(death)**
ECST Lancet 1998;351:1379-1387. **(death and MI)**
Fitzpatrick CM *et al.* Mil Med 2005;170:1069-1074. **(death and MI)**
Furst H *et al.* World J Surg 2001;25:969-974. **(MI)**
Grego F *et al.* Ann Vasc Surg 2005;19:882-889. **(death)**
Jansen C *et al.* Ann Vasc Surg 1993;7:95-101. **(death)**
Karmeli R *et al.* Cardiovasc Surg 2001;9:334-338. **(death)**
Lacroix H *et al.* Cardiovasc Surg 1994;2:26-31. **(death)**
Mackey WC *et al.* J Vasc Surg 1990;11:778-83 **(death)**
Magnadottir HB *et al.* Neurosurgery 1999;45:786-791. **(death and MI)**
Mas JL *et al*. N Engl J Med 2006;355:1660-1671. **(death)**
Mattos MA *et al.* Surgery 1992;112:670-679. **(death)**
Menyhei G *et al.* Eur J Vasc Endovasc Surg 2011;41:735e740. **(death)**
McCarthy WJ *et al.* Am J Surg 1993;166:168-171. **(death)**
Perler BA *et al.* J Vasc Surg 1992;16:347-352. **(death and MI)**
Plestis KA *et al.* J Vasc Surg 1996;24:109-119. **(death)**
Reed AB *et al.* J Vasc Surg 2003;37:1191-1199. **(death)**
Rockman CB *et al.* Ann Vasc Surg 2003;17:9-14. **(death and MI)**
Samson RH *et al.* Cardiovasc Surg 1998; 6:475-484. **(death and MI)**
Schneider JR *et al.* J Vasc Surg 2002;35:1114-1122. **(death)**
Simo G *et al.* Cardiovasc Surg 2001;9:29-29. **(death)**
Stingele R *et al*. Lancet Neurol 2008;7:216-222. **(death)**
Tu JV *et al.* Stroke 2003;4:2568-2573. **(death)**
Young B *et al.* Stroke 1996;27:2216-24. **(death and MI)**

Sub-group: Coronary artery disease

CAS

Aydiner O *et al.* Anadolu Kardiyol Derg 2007;7:152-157. **(death and MI)**
Balashankar GS *et al.* Indian Heart J. 2008;60:325-329. **(MI)**
Gupta AK *et al.* Neurol India 2006;54:68-72. **(death and MI)**
Hofmann R *et al.* Stroke 2006;37:2557-2561. **(MI)**
Lanzer P *et al.* Clin Res Cardiol 2006;95:4-12. **(death)**
Mas JL *et al*. N Engl J Med 2006;355:1660-1671. **(death)**
Stingele R *et al*. Lancet Neurol 2008;7:216-222. **(death)**
Tatli E *et al*. Postep Kardiol Inter 2013;9:221-227. **(death and MI)**
Tedesco MM *et al*. J Vasc Surg 2009;49:607-613. (**death)**

CEA

Allcutt DA *et al.* Br J Neurosurg 1991;5:257-264. **(death and MI)**
Barnett HJM *et al.* N Engl J Med 1998;339:1415-1425. **(death and MI)**
ECST Lancet 1998; 351:1379-1387. **(death and MI)**
Faggioli G *et al.* J Vasc Interv Radiol 2013;24:370-377. **(death and MI)**
Furst H *et al.* World J Surg 2001;25:969-974. **(death and MI)**

Kucey DS *et al.* J Vasc Surg 1998; 28:1051-1058. **(death)**
Magnadottir HB *et al.* Neurosurgery 1999;45:786-791. **(death and MI)**
Mas JL *et al.* N Engl J Med 2006;355:1660-1671. **(death)**
Radak DJ *et al.* Ann Vasc Surg 2010;24:185-189. **(death)**
Papachristou EA *et al.* Vascular Surgery 1994;28:531-537. **(death)**
Plestis KA *et al.* J Vasc Surg 1996;24:109-119. **(death)**
Posacioglu H *et al.* Tex Heart Inst J 2008;35:395-401. **(death)**
Tu JV *et al.* Stroke 2003;4:2568-2573. **(death)**
Young B *et al*. Stroke. 1996;27:2216-2224. **(death and MI)**

Sub-group: Diabetes
CAS
Aydiner O *et al.* Anadolu Kardiyol Derg 2007;7:152-157. **(death and MI)**
Balashankar GS *et al*. Indian Heart J. 2008;60:325-329. **(MI)**
Clark DJ *et al.* Catheter Cardiovasc Interv 2004;63:355-362. **(MI)**
Criado E *et al.* Am J Cardiol 2006;98(suppl1). **(death and MI)**
Gurm HS *et al.* Catheter Cardiovasc Interv 2007;69:541-545. **(death and MI)**
Hofmann R *et al.* Stroke 2006;37:2557-2561. **(MI)**
Kawabata Y *et al*. J Vasc Interv Radiol 2009;20:9-16. **(death)**
Lanzer P *et al.* Clin Res Cardiol 2006;95:4-12. **(death)**
Pinter L *et al*. J Vasc Surg 2011;54:1317-1323. **(death and MI)**
Mas JL *et al.* N Engl J Med 2006;355:1660-1671. **(death)**
Schlutler M *et al.* J Endovasc Ther 2007;14:271–278. **(death)**
Stingele R *et al.* Lancet Neurol 2008;7:216-222. (**death)**
Tedesco MM *et al.* J Vasc Surg 2009;49:607-613. **(death)**

CEA
Aguiar ET *et al.* Sao Paulo Medical Journal 2001;119:206-211. **(death and MI)**
Allcutt DA *et al.* Br J Neurosurg 1991;5:257-264. **(death and MI)**
Ballotta E *et al*. Langenbeck's Arch Surg 2002;387:216-221. **(death and MI)**
Barnett HJM *et al.* N Engl J Med 1998;339:1415-1425. **(death and MI)**
Dorigo W *et al.* J Vasc Surg 2011;53:44-52. **(death)**
ECST Lancet 1998;351:1379-1387. **(death and MI)**
Debing E *et al.* Vasc Endovasc Surg 2011;45:28-32. **(death)**
Faggioli G *et al.* J Vasc Interv Radiol 2013;24:370-377. **(death and MI)**
Furst H e*t al.* World J Surg 2001;25:969-974. **(death and MI)**
Kang JL *et al.* J Vasc Surg 2009;49:331-339. **(death)**
Kucey DS *et al.* J Vasc Surg 1998;28:1051-1058. **(death)**
Magnadottir HB *et al.* Neurosurgery 1999;45:786-791. **(death and MI)**
Mas JL *et al.* N Engl J Med 2006;355:1660-1671. **(death)**
Mommertz G *et al.* J Cardiovasc Surg 2009;50:665-668. **(death and MI)**
Papacristou EA *et al.* Vascular Surgery 1994;28:531-537. **(MI)**
Pistolese GR *et al.* J Vasc Surg 2001;33:148-154. **(death and MI)**
Plestis KA *et al.* J Vasc Surg 1996;24:109-119. **(death)**
Posacioglu H *et al*. Tex Heart Inst J 2008;35:395-401. **(death)**
Radak DJ *et al.* Ann Vasc Surg 2010;24:185-189. **(death)**
Rigdon EE *et al*. Am Surg 1998;6:527-530. **(death)**
Rockman CB *et al.* Ann Vasc Surg 2003;17: 9-14. **(death and MI)**
Stingele R *et al.* Lancet Neurol 2008;7:216-222. **(death)**
Stoner MC *et al.* J Vasc Surg 2006;43:285-295. **(death)**
Teso D *et al.* J Am Coll Surg 2005;200:734-741. **(death)**
Tu JV *et al.* Stroke 2003;4:2568-2573. **(death)**
Young B *et al.* Stroke. 1996;27:2216-2224. **(death and MI)**

Sub-group: Sex

CAS

Allison SK *et al.* J Am Coll Surg 2011;213:173-179. **(MI)**
Arjomand H *et al.* J Am Coll cardiol 2008;52(suppl2). **(death and MI)**
Aydiner O *et al.* Anadolu Kardiyol Derg 2007;7:152-157. **(death and MI)**
Balashankar GS *et al.* Indian Heart J. 2008;60:325-329. **(MI)**
Bayram N *et al.* Perfusion 2012;27:146-149. **(death and MI)**
Biasi GM *et al*. Circulation 2004;110;756-762. **(death)**
Bisdas T *et al.* European J of Vasc Endovasc Surg 2012;44:244-250. **(death and MI)**
Clark DJ *et al*. Catheter Cardiovasc Interv 2004;63:355-362. **(MI)**
Goldstein LJ *et al*. J Vasc Surg 2009;49:315-324. **(death and MI)**
Gonzales-Marcos JR *et al.* Int J Stroke 2006;1(suppl1). **(MI)**
Gupta AK *et al.* Neurol India 2006;54:68-72. **(death and MI)**
Howard VJ *et al.* Stroke 2009;40:1140-1147. **(death and MI)**
Jim J *et al.* J Vasc Surg 2014;59:742-8 **(death and MI)**
Kawabata Y *et al*. J Vasc Interv Radiol 2009;20:9-16. **(death and MI)**
Kypta A *et al.* Am J Cardiol 2006;98(suppl1):244M. **(death)**
Langhoff R *et al.* Vasc Endovasc Surg 2014;48:317-324. **(death and MI)**
Lihara K *et al.* J Neurosurg 2006;105:546-554. (**death and MI)**
Mas JL *et al.* N Engl J Med 2006;355:1660-1671. **(death)**
Park BD *et al.* J Vasc Surg 2009;50:526-533. **(death and MI)**
Pinter L *et al.* J Vasc Surg 2011;54:1317-1323. (**death and MI)**
Sidawy AN *et al.* J Vasc Surg 2009;49:71-79. **(death and MI)**
Stingele R *et al.* Lancet Neurol 2008;7:216-222. **(death)**
Sztriha LK *et al.* Stroke 2004;35:2862-2866. **(death)**
Takayama K *et al.* Radiat Med 2008;26:348-354. **(death and MI)**
Tatli E et al. Postep Kardiol Inter 2013;9:221-227. **(death and MI)**
Tietke MW *et al.* Neuroradiology 2010;52:611-618. **(death)**
Teitelbaum GP *et al.* Surgical Neurology1998;50:300-311. **(death and MI)**
Tedesco MM *et al*. J Vasc Surg 2009;49:607-613. **(death)**

CEA

Archie JP *et al.* J Vasc Surg 1999;29:654-664. **(death)**
Aguiar ET *et al.* Sao Paulo Medical Journal 2001;119:206-211. **(MI)**
Akbari CM *et al.* J Vasc Surg 2000;31:1103-1109. **(death and MI)**
Ballotta E *et al.* Ann Surg 2000;232:119-125. **(death and MI)**
Barnett HJM *et al.* N Engl J Med 1998;339:1415-1425. **(death and MI)**
Bisdas T *et al.* European J of Vasc Endovasc Surg 2012;44:244-250. **(death and MI)**
Blohme L *et al*. Eur J Vasc Endovasc Surg 1999;17:213-218. **(MI)**
Chang JB *et al.* Vasc Endovasc Surg 2002;36:21-27. **(death and MI)**
Dorigo W *et al*. J Vasc Surg 2009;50:1301-1307. **(death and MI)**
Eckstein HH *et al.* J Vasc Surg 2002;36:997-1004. **(death and MI)**
ECST Lancet 1998; 351:1379-1387. **(death and MI)**
Faggioli G *et al.* J Vasc Interv Radiol 2013;24:370-377. **(death and MI)**
Furst H *et al*. World J Surg 2001;25:969-974. **(death and MI)**
Harthun NL *et al.* J Vasc Surg 2005;41:223-230. **(death)**
Hartmann A *et al.* Cerebrovasc Dis 1999;9:152-156. **(death)**
Howard VJ *et al.* Lancet Neurol 2011;10:530-537. **(death)**
Hugl B *et al.* Ann Vasc Surg 2006;20:602-608. **(death)**
James DC *et al.* Am J Surg 2001;182:654-657. **(death and MI)**
Jim J *et al.* J Vasc Surg 2014;59:742-748. **(death and MI)**
Kapral MK *et al*. Stroke 2003;34:1120-1124. **(death)**

Kapral MK *et al.* J Women's Health Gender Med 2000;9:987-994. **(death)**
Kucey DS *et al.* J Vasc Surg 1998;28:1051-1058. **(death)**
Lane JS *et al.* J Vasc Surg 2003;37:568-574. **(death)**
Magnadottir HB *et al.* Neurosurgery 1999;45:786-791. **(death)**
Mas JL *et al.* N Engl J Med 2006;355:1660-1671. **(death)**
Mattos MA *et al.* Annals of Surgery 2001;234:438-446. **(death and MI)**
Middleton S *et al.* J Vasc Surg 2002;36:62-69. **(death and MI)**
Menyhei G *et al.* Eur J Vasc Endovasc Surg 2011;41:735e740. **(death)**
Mommertz G *et al.* J Cardiovasc Surg 2009;50:665-668. **(death and MI)**
Papachristou EA *et al.* Vascular Surgery 1994;28:531-537. **(death)**
Park BD *et al.* J Vasc Surg 2009;50:526-533. **(death and MI)**
Perler BA *et al.* Cardiovasc Surg 1995;3:631-636. **(death)**
Plestis KA *et al.* J Vasc Surg 1996;24:109-119. **(death)**
Posaciogliu H *et al.* Tex Heart Inst J 2008;35:395-401. **(death)**
Rigdon EE *et al.* Am Surg 1998;6:527-530. **(death)**
Rockman CB *et al.* J Vasc Surg 2001;33:236-241. **(death and MI)**
Sarac TP *et al.* J Vasc Surg 2002;35:748-753. **(death)**
Schneider JR *et al.* J Vasc Surg 1997;25:890-898. **(death and MI)**
Sidawy AN *et al.* J Vasc Surg 2009;49:71-79. **(death and MI)**
Sokol D *et al.* Acta Neurochir 2011;153:363-369. **(death and MI)**
Sternbach Y *et al.* Surgery 2000;127:272-275. (**death and MI)**
Stoner MC *et al.* J Vasc Surg 2006;43:285-295. **(death)**
Syrek JR *et al.* Surgery 1999;125:96-101. **(death)**
Teso D *et al.* J Am Coll Surg 2005;200:734–741. **(death)**
Vigo J *et al.* Bol Assoc Med P R 1992;84:128-131. **(death)**
Zenonos G *et al.* Neurosurgery 2012;70:646-655. **(MI)**
Kang JL *et al.* J Vasc Surg 2009;49:331-339. **(death)**

Sub-group: Hypertension
CAS
Aydiner O *et al.* Anadolu Kardiyol Derg 2007;7:152-157. **(death and MI)**
Balashankar GS *et al.* Indian Heart J. 2008;60:325-329. **(MI)**
Gupta AK *et al.* Neurol India 2006;54:68-72. **(death and MI)**
Hofmann R *et al.* Stroke 2006;37:2557-2561. **(MI)**
Kawabata Y *et al.* J Vasc Interv Radiol 2009;20:9-16. **(death and MI)**
Mas JL *et al.* N Engl J Med 2006;355:1660-1671. **(death)**
Stingele R *et al.* Lancet Neurol 2008;7:216-222. **(death)**
Tedesco MM *et al.* J Vasc Surg 2009;49:607-613. **(death)**

CEA
Barnett HJM *et al.* N Engl J Med 1998;339:1415-1425. **(death and MI)**
ECST Lancet 1998;351:1379-1387. **(death and MI)**
Faggioli G *et al.* J Vasc Interv Radiol 2013;24:370-377. **(death and MI)**
Furst H *et al.* World J Surg 2001;25:969-974. **(death and MI)**
Kang JL *et al.* J Vasc Surg 2009;49:331-339. **(death)**
Kucey DS *et al.* J Vasc Surg 1998;28:1051-1058. **(death)**
Mas JL *et al.* N Engl J Med 2006;355:1660-1671. **(death)**
Mommertz G *et al.* J Cardiovasc Surg 2009;50:665-668. **(death and MI)**
Papachristou EA *et al*. Vascular Surgery 1994;28:531-537. **(MI)**
Plestis KA *et al*. J Vasc Surg 1996;24:109-119. **(death)**
Posaciogliu H *et al.* Tex Heart Inst J 2008;35:395-401. **(death)**
Radak DJ *et al.* Ann Vasc Surg 2010;24:185-189. **(death)**
Rigdon EE *et al*. Am Surg 1998;6:527-530. **(death)**

Stingele R *et al.* Lancet Neurol 2008;7:216-222. **(death)**
Teso D *et al.* J AmColl Surg 2005;200:734-741. **(death)**
Tu JV *et al*. Stroke 2003;4:2568-2573. **(death)**
Young B *et al.* Stroke 1996;27:2216-2224. **(death and MI)**

Sub-group: Peripheral artery disease
CAS
Aydiner O *et al.* Anadolu Kardiyol Derg 2007;7:152-157. **(death and MI)**
Hofmann R *et al.* Stroke 2006;37:2557-2561. **(MI)**
Lanzer P *et al.* Clin Res Cardiol 2006;95:4-12. **(death)**
Mas JL *et al.* N Engl J Med 2006;355:1660-1671. **(death)**

CEA
Allcutt DA *et al.* Br J Neurosurg 1991;5:257-264. **(death and MI)**
Barnett HJM *et al.* N Engl J Med 1998;339:1415-1425. **(death and MI)**
ECST Lancet 1998;351:1379-1387. **(death and MI)**
Kang JL *et al.* J Vasc Surg 2009;49:331-339. **(death)**
Kucey DS *et al.* J Vasc Surg 1998;28:1051-1058. **(death)**
Mas JL *et al.* N Engl J Med 2006;355:1660-1671. **(death)**
Posaciogliu H *et al.* Tex Heart Inst J 2008;35:395-401. **(death)**
Radak DJ *et al.* Ann Vasc Surg 2010;24:185-189. **(death)**
Tu JV *et al.* Stroke 2003;4:2568-2573. **(death)**

Sub-group: Restenosis
CAS
AbuRahma AF *et al.* J Vasc Surg 2009;5:1031-1039. **(death and MI)**
Biasi GM *et al.* Circulation 2004;110;756-762. **(death)**
Clark DJ *et al*. Catheter Cardiovasc Interv 2004;63:355-362. **(MI)**
Eskandari MK *et al.* J Vasc Surg 2010;51:1145-1151. **(death and MI)**
Fokkema M *et al.* J Vasc Surg 2014;59:8-15. **(MI)**
Halabi M *et al.* Catheter Cardiovasc Interv2006;67:513-518. **(death)**
Gupta A *et al.* Catheter Cardiovasc Interv 2000;50:1-8. **(death and MI)**
Gupta AK *et al.* Neurol India 2006;54:68-72. **(MI)**
Kasirajan K *et al*. Int J Angiol 2006;15:20-24. **(death)**
Mehta RH *et al.* Am J Cardiol 2007;99:1288-1293. **(death and MI)**
Nolan BW *et al.* J Vasc Surg 2012;56:990-996. **(death and MI)**
Pinter L *et al.* J Vasc Surg 2011;54:1317-1323. **(death and MI)**
Safian RD *et al*. J Am Coll Cardiol 2006;47:2384-2389. **(death and MI)**
Tedesco MM *et al.* J Vasc Surg 2009;49:607-613. **(death)**
Vos JA *et al.* J Vasc Surg 2009;49:5S. **(death)**

CEA
AbuRahma AF *et al.* Vasc Surg 2001;35:167-174. **(MI)**
Cho JS *et al.* J Vasc Surg 2004;39:155-61. **(death and MI)**
Coyle KA *et al.* Ann Surg 1995;221:517-521. **(death and MI)**
Domenig C *et al.* Ann Vasc Surg 2003;17:622-628. **(death and MI)**
Fokkema M *et al.* J Vasc Surg 2014;59:8-15. **(MI)**
Hill BB *et al*. J Vasc Surg 1999;30:26-35. **(death and MI)**
Kresowik TF *et al.* J Vasc Surg Surg 2004;39:372-380. **(death)**
Magnadottir HB *et al.* Neurosurgery 1999;45:786-791. **(death and MI)**
Nolan BW e*t al*. J Vasc Surg 2012;56:990-996. **(death and MI)**
Maxwell JG *et al.* Am Surg. 2000;66:773-780. **(death and MI)**
Plestis KA *et al.* J Vasc Surg 1996;24:109-119. **(death)**

Tu JV *et al.* Stroke 2003;4:2568-2573. **(death)**

Sub-group: Symptomatic stenosis
CAS

Allison SK *et al.* J Am Coll Surg 2011;213:173-179. **(MI)**
Arjomand H *et al.* J Am Coll cardiol 2008;52(suppl2). **(death and MI)**
Aydiner O *et al.* Anadolu Kardiyol Derg 2007;7:152-157. **(death and MI)**
Bayram N *et al.* Perfusion 2012;27:146-9. **(death and MI)**
Biasi GM *et al.* Circulation 2004;110;756-762. **(death and MI)**
Bisdas T *et al.* European J of Vasc Endovasc Surg 2012;44:244-250. **(death and MI)**
Brown KE *et al.* Ann Vas Surg 2009;23:439-445. **(death and MI)**
Cernetti *et al.* Ital Herat J 2003;4:695-700. **(death and MI)**
Chiam PTL *et al.* Circulation 2009;119:2343-2348. **(death and MI)**
Clark DJ *et al.* Catheter Cardiovasc Interv 2004;63:355-362. **(MI)**
Cremonesi A *et al.* Stroke 2003;34:1936-1941. **(death)**
Criado E *et al.* Am J Cardiol 2006;98(suppl1). **(death and MI)**
Eskandari MK *et al.* J Vasc Surg 2010;51:1145-1151. **(death and MI)**
Fokkema M *et al.* J Vasc Surg 2014;59:8-15. **(MI)**
Grant A *et al.* Catheter Cardiovasc Interv 2010;75:651-655. **(death and MI)**
Gray WA *et al*. Catheter Cardiovasc Interv 2007;70:1025-1033. **(death and MI)**
Gray WA *et al.* J Vasc Surg 2006;44:258-268. **(death and MI)**
Gupta A *et al.* Catheter Cardiovasc Interv 2000;50:1-8. **(death and MI)**
Hammer FD *et al.* J Vasc Surg 2005;42:847-853. **(death)**
Hart JP *et al.* J Vasc Surg 2006;44:725-730. **(death)**
Hong JH *et al.* Cardiovasc Intervent Radiol 2015;38:280-287. **(death and MI)**
Hopkins NL *et al.* Catheter Cardiovasc Interv 2008;71:950-960. **(death and MI)**
Howard VJ *et al.* Lancet Neurol 2011;10:530-537. **(death and MI)**
Ielasi A *et al.* J endovasc Ther 2010;17:298-307. **(death and MI)**
Ikari Y *et al.* Cardiovasc Interv Ther 2013;28:37-44. **(death and MI)**
Jim J et al. J vasc Surg 2014;59:742-748. **(death and MI)**
Kadkhodayan Y *et al.* Neurosurg Focus 2005;18:e1. **(death and MI)**
Kao HL *et al.* Cardiology 2002;97:89-93. **(death and MI)**
Kastrup A *et al.* AJNR Am J Neuroradiol 2008;29:608-612. **(death)**
Katzen BT *et al.* Catheter Cardiovasc Interv 2007;70:316-323. **(death and MI)**
Kasirajan K *et al.* Int j Angiol 2006;15:20-24. **(death)**
Kawabata Y *et al.* J Vasc Interv Radiol 2009;20:9-16. **(death and MI)**
Kirsch EC *et al*. Radiology 2001;220:737-744. **(death and MI)**
Knur R *et al.* Herat Vessels 2011;26:125-130. **(death and MI)**
Koch C *et al.* Rofo 2002;174:1506-1510. **(death and MI)**
Krasniqi N *et al.* PLoS ONE 2012;7:e35300 **(death and MI)**
Langhoff R *et al* Vasc Endovasc Surg 2014;48:317-324. **(death and MI)**
Lanzer P *et al.* Clin Res Cardiol 2006;95:4-12. **(death)**
Lihara K *et al.* J Neurosurg 2006;105:546-554. **(death and MI)**
Mansour OY *et al.* Clin Neuroradiol 2010;21:65-73. **(death and MI)**
Matsumura JS *et al.* J Vasc Surg.2012;55:968-977. **(death and MI)**
Mattos MA *et al*. Surgery 1992;112:670-679. **(death)**
Mazzaccaro D *et al.* J Cardiovasc Surg 2015;56:107-18. Epub 2013 Jun 3. **(death and MI)**
Meyer SA *et al.* Neurosurgery 2010;66:448-454. **(death and MI)**
Middleton S *et al.* J Vasc Surg 2002;36:62-69. **(death and MI)**
Myla S *et al.* Catheter Cardiovasc Interv 2010;75:817-822. **(death and MI)**
Nikas D *et al*. Catheter Cardiovasc Interv 2012;80:1060-1068. **(death and MI)**
Micari A *et al.* Catheter and Cardiovas Interv 2010;76:9-15. **(death)**
Nolan BW *et al.* J Vasc Surg 2012;56:990-996. **(death and MI)**

Nolz R *et al.* Cardiovasc Intervent Radiol.2010;33:251-259. **(death and MI)**
Patel T *et al.* Catheter Cardiovasc interv 2010;75:268-275. **(death and MI)**
Posaciogliu H *et al.* Tex Heart Inst J 2008;35:395-401. **(death)**
Powell RJ *et al.* J Vasc Surg 2004;39:193-119. **(death)**
Sadato A *et al.* Neurol Med Chir 2004;44:337-342. **(death)**
Safian RD *et al.* J Am Coll Cardiol 2006;47:2384-2389. **(death and MI)**
Sanchez A *et al.* Am J Cardiol 2007;100(Suppl1):187L. **(death)**
Schermerhorn ML *et al.* J Vasc Surg 2013;57:1318-1324. **(death and MI)**
Sganzerla P *et al.* J Invasive Cardiol 2004;16:592-595. **(death and MI)**
Sidawy AN *et al.* J Vasc Surg 2009;49:71-79. **(death and MI)**
Silvestro A *et al.* J Cardiovasc Med 2008;9:137-141. **(death)**
Shobha N *et al.* Can J Neurol sci 2010;37:568-573. **(death and MI)**
Spangler EL *et al.* J Vasc Surg. 2014;60:1227-1231. **(death)**
Sztriha LK *et al.* Stroke 2004;35:2862-2866. **(death and MI)**
Takayama K *et al.* Radiat Med 2008;26:348-354. **(death and MI)**
Tatli E *et al.* Postep Kardiol Inter 2013;9:221-227. **(death and MI)**
Tedesco MM *et al.* J Vasc Surg 2009;49:607-613. **(death)**
Tietke MW *et al*. Neuroradiology 2010;52:611-618. **(death)**
Velez CA *et al.* Catheter Cardiovasc Interv 2008;72:303-308. **(death and MI)**
White CJ *et al.* Catheter Cardiovasc Interv 2006;67:503-512. **(death and MI)**
Yen MH *et al.* Am J Cardiol 2005;95:297-300. **(death and MI)**
Zarins CK *et al.* J Endovasc Ther 2009;16:397-409. **(death and MI)**

CEA
Aguiar ET *et al.* Sao Paulo Medical Journal 2001;119:206-211. **(MI)**
Berger L *et al.* 2014 (unpublished). **(death and MI)**
Bernstein EF *et al*. Ann Surg 1983;198:80-86. **(death)**
Bisdas T *et al.* European J of Vasc Endovasc Surg 2012;44:244-250. **(death and MI)**
Boontje AH *et al.* Cardiovasc Surg 1994;5:549-554. **(MI)**
Brinjikji W *et al.* Stroke 2010;41:2186-2190. **(death and MI)**
Brott T *et al.* Stroke 1984;15;950-955. **(death)**
Brott TG *et al.* N Engl J Med 2010;363:11-23. **(MI)**
Brown KE *et al.* Ann Surg 2008,248:110-116. **(death)**
Bunch CT *et al.* Semin Vasc Surg 2004;17:209-213. **(death)**
Bunt TJ *et al.* Am Surg 1985;51:61-69. **(death)**
Burns RJ *et al.* Med J Austr 1991;154:650-653. **(death)**
Carmichael JD *et al.* Ach Surg 1980;115:937-939. **(death)**
Dellagrammaticas D *et al.* Clinical Medicine 2007;7:589-592. **(death and MI)**
Eckstein HH *et al.* J Vasc Surg 2002;36:997-1004. **(death and MI)**
Faggioli G *et al*. J Vasc Interv Radiol 2013;24:370-377. **(death and MI)**
Faggioli GL *et al*. Eur J Vasc Endovasc Surg 2011;41:238-248. **(MI)**
Feasby TE *et al.* Arch Neurol 2007;64:1496-1500. **(death and MI)**
Flanigan DP *et al*. J Vasc Surg 2007;46:876-882. **(death and MI)**
Fode NC *et al*. Stroke 1986;17:370-376. **(death and MI)**
Fokkema M *et al.* J Vasc Surg 2014;59:8-15. **(MI)**
Friedmann P *et al.* Stroke 1988;19:1323-1327. **(death and MI)**
Girard LP *et al.* Circ Cardiovasc Qual Outcomes 2009;2:642-647. **(death)**
Goldstein LB *et al.* Stroke 1994;25:1116-1121. **(death and MI)**
Hafner CD *et al.* J Vasc Surg 1984;1:392-397. **(death)**
Hagmuller GW *et al.* Aust J Cardiol 2004;11:206-211. **(death)**
Hartmann A *et al.* Cerebrovasc Dis 1999;9:152-156. **(death)**
Healy DA *et al.* Stroke 1989;20;1138-1142. **(death)**
Howard VJ *et al.* Lancet Neurol 2011;10:530-537. **(death and MI)**

Hoyne RF *et al*. Surg Gynecol Obstet 1990;170:522-526. **(death)**
Jim J *et al.* J vasc Surg 2014;59:742-748. **(death and MI)**
Kadwa AM *et al.* S Afr Med J 1993;83:248-252. **(death)**
Katz M *et al.* Cardiovasc Surg 2001;S096-2109:2130.**(death)**
Kragsterman B *et al.* J Vasc Surg 2006;44:79-85. **(death)**
Kresowik TF *et al.* J Vasc Surg Surg 2004;39:372-380. **(death)**
Kucey DS *et al.* J Vasc Surg 1998;28:1051-1058. **(death)**
Lepore MR *et al.* J Vasc Surg 2001;34:581-586. **(death and MI)**
Magnadottir HB *et al.* Neurosurgery 1999;45:786-791. **(death)**
Maxwell JG *et al.* Am J Surg 1990;160:598-603. **(death and MI)**
Mazzaccaro D *et al.* J Cardiovasc Surg 2015;56:107-18. Epub 2013 Jun 3. **(death and MI)**
Menyhei G *et al*. Eur J Vasc Endovasc Surg 2011;41:735e740. **(death)**
Middleton S *et al*. J Vasc Surg 2002;36:62-69. **(death and MI)**
Miller MT et al. J Vasc Surg 2005; 41: 231-237. **(death)**
Mommertz G *et al.* J Cardiovasc Surg 2009;50:665-668. **(death and MI)**
Mulaudzi TV *et al.* Cardiovasc J Afr 2009;20:116-118. **(MI)**
Musser DJ *et al.* Ann Vasc Surg 1996;10:143-146. **(death)**
Naik DK *et al.* NZ Med J 1994;407:334-335. **(death)**
Nault P *et al.* J Vasc Surg 2008;47:530-536. **(death and MI)**
Nolan BW *et al*. J Vasc Surg 2012;56:990-996. **(death and MI)**
Perler BA *et al* Cardiovasc Surg 1995;3:631-636. **(death)**
Plestis KA *et al.* J Vasc Surg 1996;24:109-119. **(death)**
Poulias GE *et al.* Cardiovasc Surg 1994;2:586-591. **(death)**
Rantner B *et al.* J stroke Cerebrovasc Dis 2006;15:114-120. **(death and MI)**
Reed AB *et al.* J Vasc Surg 2003;37:1191-1199. **(MI)**
Rigdon EE *et al.* Am Surg 1998;6:527-530. **(death)**
Rinckenbach V *et al*. J Mal Vasc. 2007;32:192-200. **(death)**
Santamaria G *et al.* Minerva Anestesiol 2004;70:771-778. **(death)**
Sarac TP *et al.* J Vasc Surg 2002;35:748-753. **(death)**
Schermerhorn ML *et al.* J Vasc Surg 2013;57:1318-1324. **(death and MI)**
Shah DM *et al.* Ann Of Surgery1998;228:471-478. **(death)**
Sidawy AN *et al.* J Vasc Surg 2009;49:71-79. **(death)**
Sise MJ *et al.* Stroke 1989;20:329-332. **(death)**
Spangler EL *et al.* J Vasc Surg. 2014;60:1227-1231. **(death)**
Spencer MP *et al*. Stroke 1997;28:685-691. **(death)**
Syrek JR *et al.* Surgery 1999;125:96-101. **(death)**
Tan TW *et al.* Ann Vasc Surg 2011;25:87-93. **(death)**
Teso D *et al.* J AmColl Surg 2005;200:734-741. **(death)**
Till JS *et al.* Stroke 1987;18:823-829. **(death and MI)**
Treiman RL *et al.* Ann Vasc Surg 1992;6:321-324. **(death and MI)**
Tsao NW *et al.* Chin Med J 2002;65:69-73. **(death)**
Tu JV *et al.* Stroke 2003;4:2568-2573. **(death)**
White JS *et al.* Arch Surg. 1981;116:409-412. **(death and MI)**
Whitney DG *et al.* Arch Surg 1980;115:1393-1399. **(death)**
Zarins CK *et al.* J Endovasc Ther 2009;16:397-409. **(death and MI)**
Zenonos G *et al.* Neurosurgery 2012;70:646-655. **(MI)**