Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
KCE

Endovasculaire behandeling van Carotisstenose

KCE reports vol. 13 A

Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
2005

Het Federaal Kenniscentrum voor de Gezondheidszorg

Voorstelling : Het Federaal Kenniscentrum voor de Gezondheidszorg is een parastatale, opgericht door de programma-wet van 24 december 2002 (artikelen 262 tot 266) die onder de bevoegdheid valt van de Minister van Volksgezondheid en Sociale Zaken. Het centrum is belast met het realiseren van beleidsondersteunende studies met binnen de sector van de gezondheidszorg en de ziekteverzekering.

Raad van Bestuur

Effectieve leden : Gillet Pierre (Président), Cuypers Dirk (Vice-Président), Avontroodt Yolande, Beeckmans Jan, Bovy Laurence, De Cock Jo (Vice-Président), Demaeseneer Jan, Dercq Jean-Paul, Ferette Daniel, Gailly Jean-Paul, Goyens Floris, Keirse Manu, Kesteloot Katrien, Maes Jef, Mariage Olivier, Mertens Pascal, Mertens Raf, Moens Marc, Ponce Annick, Smiets Pierre, Van Ermen Lieve, Van Massenhove Frank, Vandermeeren Philippe, Verertbruggen Patrick, Vranckx Charles

Vervangers : Baland Brigitte, Boonen Carine, Cuypers Rita, De Ridder Henri, Decoster Christiaan, Deman Esther, Désir Daniel, Heyerick Paul, Kips Johan, Legrand Jean, Lemye Roland, Lombaerts Rita, Maes André, Palsterman Paul, Pirlot Viviane, Praet François, Praet Jean-Claude, Remacle Anne, Schoonjans Chris, Servotte Joseph, Van Emelen Jan, Vanderstappen Anne

Regeringscommissaris : Roger Yves

Directie

Algemeen Directeur : Dirk Ramaekers

Algemeen Directeur adjunct : Jean-Pierre Closon

Endovasculaire behandeling van Carotisstenose

KCE reports vol. 13A

BONNEUX LUC
CLEEMPUT IRINA
RAMAEKERS DIRK

Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
2005

KCE reports vol. 13A

Titel: Endovasculaire behandeling van Carotisstenose

Auteurs: Luc Bonneux, Irina Cleemput, Dirk Ramaekers

Externe experten: Jaap Buth, Etienne Creemers, Jean-François De Wispelaere, Patrick Galloo, Luc Stockx, Frank Vermassen

Externe validatoren: Peter Gaines (UK), Luc Stockx, Frank Vermassen

Conflict of interest: None declared. De experts en validatoren werkten mee aan het wetenschappelijke rapport. Dit betrof enkel de zeven eerste hoofdstukken. Experts en validatoren werden niet betrokken in de aanbevelingen voor het beleid. Deze aanbevelingen vallen onder de volledige verantwoordelijkheid van het KCE.

Layout: Dimitri Bogaerts, Nadia Bonnouh

Brussel, April 2005

MeSH: Carotid Stenosis; Cerebrovascular Accident/prevention & control; Endarterectomy, Carotid; Stents; Technology Assessment, Biomedical.
NLM classification: W74

Taal: Nederlands, Engels
Format: Adobe® PDF™ (A4)

Wettelijk depot: D/2004/10.273/09

Dit document is beschikbaar vanop de website van het Fedeaal Kenniscentrum voor de Gezondheidszorg.

Hoe refereren naar dit document?
Bonneux L, Cleemput I, Ramaekers D. Endovasculaire behandeling van Carotisstenose. Brussel: Federaal Kenniscentrum voor de Gezondheidszorg (KCE); April 2005. KCE Reports vol. 13A. Ref. D/2005/10.273/09.

Federaal Kenniscentrum voor de Gezondheidszorg - Centre Fédéral d'Expertise des Soins de Santé.

Résidence Palace (10de verdieping-10ème étage)
Wetstraat 155 Rue de la Loi
B-1040 Brussel-Bruxelles
Belgium

Tel: +32 [0]2 287 33 88
Fax: +32 [0]2 287 33 85

Email: info@kenniscentrum.fgov.be , info@centredexpertise.fgov.be
Web: http://www.kenniscentrum.fgov.be , http://www.centredexpertise.fgov.be

Voorwoord

Geconfronteerd met de toenemende kosten van de gezondheidszorg hebben de afgelopen twintig jaar bijna alle Westerse landen Health Technology Assessment (HTA) ingevoerd. Een HTA onderzoekt of een nieuwe technologie doeltreffend en doelmatig is. Doeltreffend betekent dat ze werkt, doelmatig dat ze werkt tegen aanvaardbare kosten. Recent voegde ook België zich bij deze moderne landen. Het Federaal Kenniscentrum voor de Gezondheidszorg (KCE) presenteert hiermee zijn eerste HTA-rapport.

Een door aderverkalking vernauwde halsslagader is een frequente aandoening die een beroerte kan veroorzaken. Sinds de jaren '50 bestaat er een heelkundige ingreep die deze vernauwing verwijdert, een "carotis endarterectomie" (CEA), maar deze ingreep veroorzaakt ook beroerte als complicatie en stond daarom in een slecht daglicht. In de vroege jaren '90 toonde hoogstaand empirisch onderzoek onomstootbaar aan dat - bij gepaste indicaties – CEA bijzonder doelmatig was. Vervolgens werd er ook voorzichtig geëxperimenteerd met angioplastiek en stenting van de vernauwde halsslagader. De resultaten bleven slecht tot beschermende systemen werden ontwikkeld die brokstukjes, afgerukt tijdens de interventie, opvingen. "Protected carotid artery stenting" (PCAS) verscheen op de markt. Dit rapport presenteert een HTA van PCAS vergeleken met CEA.

PCAS is momenteel niet bewezen doeltreffender en zeker niet doelmatiger dan CEA. Er zijn geen bewijzen dat PCAS beter werkt dan CEA, en PCAS is duurder door de hoge prijs van de stent en het beschermingsmateriaal. Het HTA rapport pleit dus tegen een veralgemeende introductie van PCAS in de Belgische gezondheidszorg. De evaluatie toont echter ook dat PCAS een veelbelovende technologie is. Dat stelt ethische vragen: verdere ontwikkeling eist experimenten op patiënten. De tientallen jaren durende ongecontroleerde experimenten met CEA leverden niets op tenzij verhitte redactionelen in de vakpers, tot de eerste gecontroleerde experimenten de discussie snel naar de vuilbak der geschiedenis verwezen. Het rapport suggereert daarom advies te vragen over de ethische introductie van dure, experimentele maar veelbelovende medische technologie aan het Raadgevend Comité voor Bio-ethiek van België.

Voor uitzonderlijke patiënten is er geen beter alternatief dan PCAS. Het rapport suggereert dat minstens één Belgisch ziekenhuis deze techniek (terugbetaald) toepast. Verder breekt het rapport een lans om de ongecontroleerde invoering van experimentele technologie te vervangen door gecontroleerde experimenten, en te leren uit ervaring. We suggereren dat een deel van het geld, dat vroeger verloren ging in ongecontroleerde experimenten, te investeren in een beperkt aantal centra dat deelneemt aan lopend internationaal wetenschappelijk onderzoek. Zo komt PCAS ter beschikking van de huidige bevolking, ontwikkelen de Belgische vasculaire teams ervaring, en leren ze hoe PCAS optimaal aan te wenden voor de toekomstige bevolking.

Geneeskunst zal altijd een kunst blijven, maar wordt meer kunde. De moderne medische technologie is een zegen maar ook een vloek. De tijd is voorbij dat alles wat kon, moest. De burger heeft er recht op dat het vele geld dat naar de gezondheidszorg gaat, optimaal wordt gebruikt. Dat betekent ontmoedigen van wat niet doelmatig is, aanmoedigen van wat wel doelmatig is, en verstandig experimenteren met wat onbekend maar veelbelovend is. Als zodanig betekent dit korte, bescheiden rapport mogelijks een trendbreuk.

Jean-Pierre Closon
Adjunct algemeen directeur

Dirk Ramaekers
Algemeen directeur

Een kort Health Technology Assessment rapport

Achtergrond en vraagstellingen

Carotisstenose ontstaat meestal door atherosclerose. Atherosclerose tast de vaatwand aan. Een stukje van die zieke vaatwand kan afbreken en meegenomen worden door de bloedstroom en daar een vat verstoppen. Gezien de bloedstroom naar de hersenen gaat, is een carotisstenose een belangrijke oorzaak van beroerte.

Het voorkomen en behandelen van carotisstenose is gebaseerd op goed cardiovasculair risicomanagement: stoppen met roken, behandelen van een te hoge bloeddruk of van een hoog LDL-cholesterol met statines (HMG-CoA inhibitoren), goed opvolgen van diabetes mellitus, lage dosis aspirine bij bekende hartpatiënten. Naast dit goed cardiovasculair risicomanagement kan het soms nuttig of zelfs noodzakelijk zijn om de atherosclerotische plaque te behandelen. Hierbij zijn twee keuzen mogelijk. De nu traditionele wijze opent de arterie tijdens een heelkundige ingreep en verwijdert de plaque. Dit heet een Carotisendarterectomie (CEA). Bij de alternatieve ingreep wordt een catheter opgevoerd langs een slagader tot in de Carotis, wordt deze opengeduwd met een ballon en opengehouden met een « stent », een stut in metaal. Een mogelijke complicatie van deze endovasculaire ingreep is beroerte door klontertjes die vrijkomen tijdens de interventie. Recent werden protectiemiddelen ontwikkeld, een filter of ballon die boven de lesie wordt opengevouwen of opgeblazen en die afgescheurde klontertjes afvangt voor ze in de hersenen terecht kunnen komen. Deze nieuwe techniek, PCAS (van "protected carotid artery stenting") is een ernstig alternatief geworden.

Er moeten dus behandelkeuzes gemaakt worden tussen drie alternatieven (een optimaal cardiovasculair risicomanagement is noodzakelijk bij iedere keuze): behoedzaam afwachten, CEA of PCAS. Zowel CEA als PCAS gaan met enig risico gepaard. In geval van complicaties veroorzaken ze wat ze willen voorkomen: beroerte of sterfte. Om baat te hebben bij een invasieve ingreep moet de patiënt een extra hoog risico lopen op beroerte of sterfte dat kan opwegen tegen het risico eigen aan de ingreep. PCAS is momenteel niet terugbetaald in België. Dit rapport formuleert daarom antwoorden op de volgende vragen:

- In welke condities is PCAS zeker beter dan CEA, en moet de technologie ter beschikking komen van de patiënt?
- In welke condities is PCAS mogelijk beter dan CEA, en is verder vergelijkend onderzoek tussen PCAS en CEA aangewezen ?
- Hoe kan PCAS op een verantwoorde manier ingevoerd worden in België, gezien de ingreep niet zonder gevaar is en een hoge graad van zowel competentie als ervaring vereist.

De klinische effectiviteit van PCAS

We onderzochten de literatuur op een systematische wijze. Vergelijkende methoden gebaseerd op technieken uit het geneesmiddelonderzoek zijn hier minder gepast. Chirurgische interventies zijn geen medicijnen. De hoogtechnologische middelen (stentjes met bescherming) verbeteren snel. De resultaten hangen mee af van de ervaring en de deskundigheid van de uitvoerder, de kwaliteit van de beschikbare beeldvorming en het gehele functioneren van het cardiovasculair team. Bij de interpretatie van resultaten van gerandomiseerde gecontroleerde trials (RCT's) van heelkunde en interventionele radiologie moet steeds overwogen worden dat het hier doorgaans de beste patiëntenselectie betreft, behandeld door de deskundigste teams in de meest hoogstaande centra. Vertaling naar de dagelijkse praktijk vergt voorzichtige interpretatie.

Voor CEA zijn meerdere gepoolde analysen van grote trials bij patiënten met symptomatische carotisstenose beschikbaar. Indien de patiënt een hoog risico loopt op een beroerte, is CEA buitengewoon effectief en kan het volstaan om zes patiënten te behandelen om één beroerte te voorkomen. Naarmate risico's op beroerte lager worden, wordt behoedzaam afwachten een beter alternatief omdat CEA ook beroerten veroorzaakt.

Over PCAS zijn nog nauwelijks gegevens bekend. Deze technologie is nog zeer recent. Observationeel bewijs uit registers en voorlopige resultaten van trials heeft de clinici overtuigd van de superioriteit van PCAS ten opzichte van onbeschermde CAS, zodat onbeschermde CAS niet meer te verantwoorden valt, behalve wanneer er contra-indicaties zijn voor het gebruik van de beschermende filter, bijvoorbeeld moeilijk bereikbare vernauwingen of intolerantie tegenover de filter. Oudere systematische literatuuroverzichten van CAS bevatten nauwelijks evaluaties van PCAS-interventies en zijn daarom ongeschikt.

De bewijzen van klinische effectiviteit van PCAS zijn (nog) niet overtuigend. De enige afgeronde RCT is slecht interpreteerbaar. De verschillende studies en registers suggereren dat PCAS een aanvaardbaar alternatief ("non-inferiority") is voor CEA. Er zijn verscheidene grote RCTs die momenteel patiënten rekruteren voor vergelijkende studie van CEA en PCAS (EVA-3S, SPACE, ICSS-2, CREST). Bij publicatie van deze resultaten, vervalt dit rapport.

Doelgroep

Indien te ruim toegepast, veroorzaken carotis-interventies meer beroerten dan ze voorkomen. Dokters moeten zich bewust zijn dat de standaardbehandeling van een carotisstenose medisch en afwachtend is. Carotis-interventies zijn een noodgreep in die groepen die een zeer hoog risico op beroerte lopen. Het risico neemt toe met de graad van stenose, en met de aanwezigheid van recente symptomen. Het "number needed to treat" loopt snel op bij afwezigheid van symptomen en minder enstige stenoses, en kan snel omslaan in een "number needed to harm" door de intrinsieke operatierisico's.

Carotis interventies hebben buitengewoon goede resultaten bij hooggradige stenosen (> 70%) bij patiënten met recente symptomen (< 2 weken). Stenoses onder 50% vormen geen indicatie voor een interventie. Ingrepen bij asymptomatische carotisstenose blijven discutabel.

Carotis-interventies bij personen zonder recente symptomen is een investering op langere termijn. In principe moet de levensverwachting van de asymptomatische stenose-patiënt minstens nog vijf jaar zijn om te kunnen profiteren van een interventie. De kansen op peri-procedurele beroertes zijn te hoog bij oudere patiënten, en deze vormen dus geen goede doelgroep. De operatieresultaten moeten uitstekend zijn. Om goed geïnformeerde beslissingen te kunnen nemen, moeten de operatieresultaten van carotis-ingrepen in België beter bekend worden.

Indien een carotis-ingreep aangewezen is, blijft de eerste keuze een open ingreep (CEA). PCAS is mogelijk aangewezen indien de patiënt een hoog risico loopt op beroerte, én een hoog risico op complicaties tijdens een open ingreep. Deze groep blijft voorlopig onvoldoende goed omschreven, en het is onbekend of PCAS veiliger is bij deze patiënten.

De kosten-effectiviteit van PCAS

We onderzochten de literatuur op een systematische wijze. De economische literatuur over PCAS is nog uiterst beperkt. Dat is een onvermijdelijk gevolg van de nog uiterst beperkte kennis over de effectiviteit. We beperken de discussie daarom tot een kwalitatieve samenvatting.

CEA zonder complicaties zijn ingrepen die niet gepaard gaan met een lange ziekenhuisduur of een sterke aantasting van de kwaliteit van leven. Dat maakt dat - bij gelijke complicatiekansen - er weinig te besparen valt met PCAS. Integendeel, de hoge kosten van stents en beschermingsfilters maken PCAS doorgaans duurder. Bij complicaties worden de kosten van beide ingrepen gedomineerd door de zeer hoge financiële kosten van een beroerte (door de hoge zorgkosten één van de "duurste" aandoeningen in de geneeskunde). Lagere aantallen peri-procedurele beroertes betekenen dus niet alleen een menselijk maar ook een financieel voordeel.

Bij gebrek aan vergelijkende gegevens over effectiviteit, en zeker over effectiviteit over langere termijn moeten we zeer voorzichtig blijven in eender welke uitspraak. Bij historisch vergelijkbare ingrepen (percutane coronaire interventies) haalde een snel evoluerende technologie de chirurgische ingreep snel in.

De introductie van een opkomende technologie

De bestaande praktijk

In de door ons bestudeerde landen (VS, VK, Duitsland, Frankrijk) wordt PCAS enkel aanbevolen onder de voorwaarde van wetenschappelijk verantwoorde opvolging van de resultaten. Frankrijk en het Verenigd Koninkrijk bevelen PCAS aan als een te onderzoeken experimentele technologie in wetenschappelijk vergelijkend onderzoek. De VS en Duitsland bevelen aan om alle patiënten die PCAS ondergaan op te nemen in prospectieve registers.

In België is momenteel nog geen terugbetaling voorzien. Het relatief zeer hoge aantal open interventies (CEA) is opvallend. Dat wil niet zeggen dat de Belgische klinische praktijk goed of slecht is. Een zeer hoog interventiecijfer kan ook wijzen op veel ondergebruik elders. De afwezigheid van goede gegevens over de patiëntenpopulatie en opvolging van de resultaten van deze gevaarlijke ingreep is echter zeker een indicator van onvoldoende organisatorische kwaliteit. Zonder gegevens over de behaalde kwaliteit kunnen zowel arts als patiënt niet geïnformeerd worden over de te behalen baten van de interventie, en kunnen ze geen goed geïnformeerde keuzen maken. De patiënt heeft, zeker bij deze risicovolle ingreep, recht op de best haalbare kwaliteit. Het gebrek aan degelijke informatie over deze risicovolle ingreep toont een medisch-ethisch deficit.

De wenselijke toekomst

Bij de introductie van experimentele dure “emerging technology” zijn beleidskeuzen noodzakelijk. Als absolute principes zijn de vrijheid van therapeutisch handelen, de beste belangen van de patiënt, een optimale verdeling van middelen in de gezondheidszorg en de hoogste toegankelijkheid van deze zorg voor iedereen niet altijd met elkaar te verzoenen. Een ethisch advies is noodzakelijk om de lijnen uit te zetten waarbinnen politieke keuzen ethisch verantwoord blijven. Wij stellen voor om voor introductie van dure “emerging” technologie onpartijdig advies in te winnen bij het Raadgevend Comité voor Bio-ethiek van België.

De uiteindelijke beslissing tot behandeling hoort in de handen van de patiënt te liggen, maar dat gaat niet zonder goede informatie. Deze informatieverstrekking dient te gebeuren door een onpartijdige bron. De vraag naar de rol van de huisarts in dit formele informed consent voor een therapeutisch proces dient gesteld te worden.

Gezien de mogelijke ethische implicaties suggereren wij om advies in te winnen bij het Raadgevend Comité voor Bio-ethiek van België over inhoud en vorm van informed consent procedures.

Adequate regulering eist een helder beeld van een wenselijke toekomst. In deze toekomst staat het recht van de patiënt op de best haalbare kwaliteit in de klinische praktijk centraal. Uit deze rechten kunnen organisatorische principes gedistilleerd worden.

Er heerst bij de betrokken klinische vakgroep de overtuiging dat PCAS een waardevol alternatief kan zijn voor CEA. Deze overtuiging wordt nog onvoldoende ondersteund door empirische gegevens uit betrouwbare studies. PCAS lijkt wel, na een lange en redelijk ontgoochelende periode van experimenten met angioplastiek en stenting zonder bescherming, veelbelovend. Daaruit volgen drie principes.

- PCAS moet beschikbaar worden gesteld voor die patiëntenpopulatie die baat heeft bij een ingreep, maar waarbij open heelkunde geen optie is.
- Er moet door middel van klinische studies meer kennis over de indicatiestellingen vergaard worden.
- De patiënt heeft recht op de hoogste kwaliteit van deze risicovolle ingreep. Dat vergt dat centra voldoende ervaring hebben (voldoende aantallen carotis ingrepen gedaan hebben) en voldoende ervaring onderhouden (voldoende aantallen ingrepen per jaar hebben). De kwaliteit van de ingreep moet routinematig opgevolgd worden. Dit kan in principe reeds vanuit bestaande klinische en facturatiegegevens waaruit complicaties zoals beroerte, heropnames en mortaliteit kunnen bepaald worden.

Momenteel is PCAS een experimentele ingreep met nog weinig bekende effectiviteit. Bij klinische non-inferiority, vergeleken met CEA, maken de hogere kosten PCAS tot een slechter alternatief. De ruimte voor PCAS moet dus beperkt blijven tot klinisch wetenschappelijk onderzoek, en enige interventies bij de schaarse onbetwiste indicaties. Principes van selectie moeten op de volgende principes gebaseerd zijn:

- Het centrum moet een hoog volume en acceptabele kwaliteit kunnen aantonen van carotis-ingrepen. We suggereren minstens 625 carotis ingrepen (PCAS of CEA) in 5 jaar tijd (dat is minimaal 3% van het nationale volume), met hoogstens 15 doden binnen de dertig dagen na interventie (2.4%).
- Het centrum moet bereidheid tonen mee te werken aan streng geprotocolleerd hoogwaardig klinisch onderzoek in het kader van een multi-center trial zoals bijvoorbeeld de ICSS-trial. Het centrum moet bereid zijn om auditing te ontvangen van hun team.
- Een multidisciplinair team, bestaande uit minimaal een neuroloog of internist-geriater, een radioloog en een vasculair chirurg, nemen in het centrum de behandelbeslissingen.

Kernpunten

Achtergrond

- Carotisstenose is meestal een gevolg van atherosclerose en een belangrijke, maar ver van een unieke oorzaak van een beroerte.
- Medische behandeling is gebaseerd op adequaat cardiovasculair risico-management: stoppen met roken, controle van de bloeddruk en diabetes, behandeling met statines, plaatjesremmers (aspirine) bij patiënten met een bekende hartziekte (bewijzen van het krachtigste type, niveau 1).
- Naast een behoedzaam afwachtend beleid kan een interventie aangewezen zijn: een open ingreep (carotisendarterectomie, CEA) of het langs endovasculaire weg plaatsen van een stent (protected carotid artery stenting, PCAS)

Doelstelling

- Dit kort rapport vat de bestaande bewijzen over de effectiviteit en de kosten-effectiviteit van PCAS in vergelijking met CEA samen, en suggereert methoden om PCAS op een verantwoorde manier te introduceren.

Klinische effectiviteit

- PCAS heeft de clinici kunnen overtuigen veiliger te zijn dan onbeschermde CAS (bewijs van niveau 2).
- Er is geen bewijs dat PCAS beter of slechter is dan CEA.
- Momenteel lopen er verscheidene grote studies die PCAS willen vergelijken met CEA.
- Er zijn nog geen studies die asymptomatische patiënten recruteren. De eerste dergelijke studies worden nu opgezet.
- CEA is de beste behandeling voor een specifieke doelgroep met een hoog risico voor beroerte. Dit geldt zeker voor oudere personen.
- Hoe recenter de symptomen (< 2 weken) en hoe groter de stenose is (> 70%), hoe meer de patiënt baat heeft bij een interventie.
- Een ingreep bij een carotisstenose zonder symptomen is discutabel. Een ingreep is mogelijk geïndiceerd bij patiënten onder de 75 jaar, met voldoende levensverwachting, en in centra die een uitstekende kwaliteit kunnen bieden (risico op beroerte of dood door de ingreep kleiner dan 4%).
- PCAS is een mogelijk alternatief voor CEA indien de patiënt een hoog risico loopt voor beroerte en een slechte kandidaat is voor een open ingreep. Deze patiëntengroep is slecht omschreven en het blijft onbekend of een slechte kandidaat voor een open ingreep een betere kandidaat is voor PCAS.

Kosten-effectiviteit

- Gegeven de nog geringe kennis over effectiviteit, ontbreken betrouwbare gegevens over de kosten-effectiviteit van PCAS. De kosten van een beroerte zijn zo hoog, dat lagere kansen op een beroerte héél snel besparingen betekenen. Naast korte termijnsgegevens zijn daarom ook gegevens over langere termijn onmisbaar om een valiede schatting van de kosten-effectiviteit te maken.
- PCAS biedt weinig directe financiële voordelen over CEA. De hoge kosten van de stents en het beschermingsmateriaal maken PCAS daarom de minder kosten-effectieve keuze.
- Snelle technologische ontwikkeling en dalende kostprijzen van stents en filters kunnen de kosten-effectiviteit van PCAS echter verbeteren.

Aanbevelingen voor kwaliteitsbewaking en –verbetering

- In België zijn er zeer hoge interventiecijfers voor CEA, zonder gegevens over de kwaliteit van de behaalde resultaten. Gebrek aan kennis is zeker geen kenmerk van kwaliteit. De registratie moet sterk verbeteren, met strikt omschreven procedures bij slechte resultaten.
- Gezien het risicovolle van iedere carotisingreep heeft de patiënt recht op uitstekende en onpartijdige informatie. Wij stellen voor om advies aan te vragen aan het Raadgevend Comité voor Bio-ethiek van België, over inhoud en vorm van informed consent procedures, te volgen bij iedere experimentele ingreep met mogelijk ernstige gevolgen.
- Bij introductie van een experimentele, dure "emerging" technologie stellen zich in toenemende mate ernstige keuze-problemen met complexe ethische consequenties. Wij stellen voor om systematisch advies aan te vragen aan het Raadgevend Comité voor Bio-ethiek van België over de ethische randvoorwaarden bij introductie van dure "emerging" technologie.

Aanbevelingen voor practische organisatie en implementatie

- In andere landen wordt PCAS gereguleerd door de interventie op te nemen in experimenteel wetenschappelijk patiënt-onderzoek en/of door de resultaten op te volgen in prospectieve registers.
- PCAS moet beschikbaar worden gesteld aan die patiëntenpopulatie die onbetwistbaar baat heeft bij een ingreep, maar waarbij open heelkunde geen optie is. Dat is een onbekend, maar zeer klein aantal.
- Er moet meer klinische kennis van hoge kwaliteit over de indicatiestellingen van deze veelbelovende technologie worden vergaard.
    - Waar er twijfel bestaat over de keuze tussen een open ingreep en PCAS, gebeurt informatievergaring in het kader van uitstekend klinisch onderzoek van een grote multicenter-trial zoals ICSS.
    - Waar een behandeling geïndiceerd is maar een heelkundige behandeling geen goede optie is, gebeurt informatievergaring in het kader van een prospectief register.
- De patiënt heeft recht op de hoogste kwaliteit van deze risicovolle ingreep.
    - Centra moeten voldoende ervaring hebben (voldoende aantallen carotis ingrepen gedaan hebben) en voldoende ervaring onderhouden (een voldoende groot aantal ingrepen per jaar hebben).
    - Gegevens over de kwaliteit moeten routinematig beschikbaar worden.

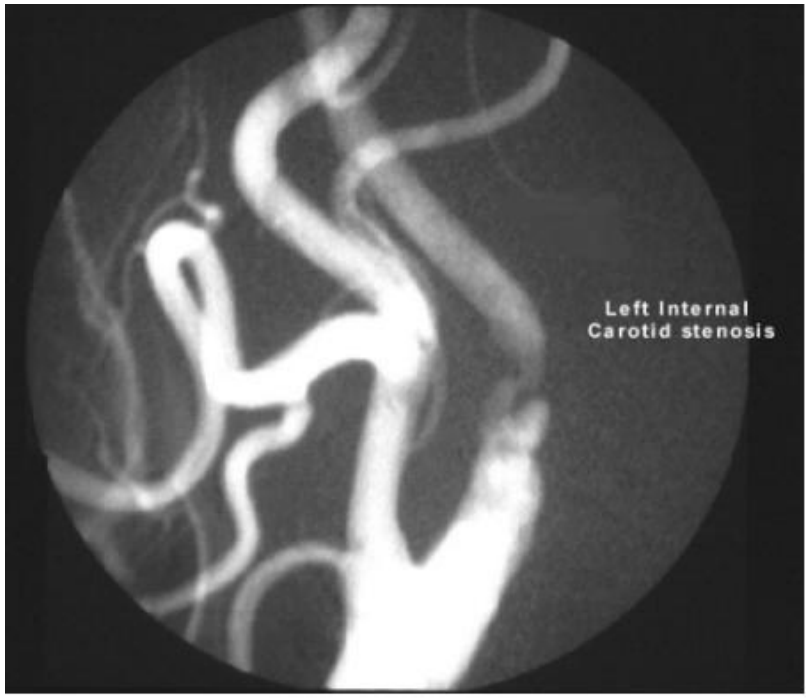
- Er is in België ruimte voor minimaal één en maximaal enige centra die PCAS kunnen toepassen binnen het kader van de Belgische gezondheidszorg. De minimale randvoorwaarden zijn:
    - Minimaal 625 carotis-ingrepen (alle) gedaan hebben in de afgelopen vijf jaar, met maximaal 15 doden binnen de 30 dagen na ingreep.
    - De bereidheid tonen om mee te werken aan hoogstaand geprotocolleerd klinisch onderzoek in het kader van een multicenter trial en auditing door hun team accepteren.
    - Behandelbeslissingen nemen in het kader van een geïntegreerd vasculair team, met minimaal een radioloog, neuroloog of internist-geriater en vasculair chirurg.
- CEA blijft de standaardbehandeling; uitzonderingen dienen specifiek gemotiveerd te worden.

Scientific report: table of contents

1. BACKGROUND

Carotid stenosis is an important cause of transient ischemic attacks, stroke, disability, retinal infarctions, and death. The cause of carotid stenosis itself is most often atherosclerosis. Atherosclerosis comes from the Greek words athero (meaning gruel or paste) and sclerosis (hardness). It's the name of the process in which deposits of fatty substances -cholesterol, cellular waste products, calcium and other substances- build up in the inner lining of an artery. This build-up is called plaque. It usually affects large and medium-sized arteries (such as the carotid artery). Some hardening of arteries always occurs when people grow older.

Figure 1: Angiogram of the carotid of a 73 year-old ex-smoker who presented with intermittent right-sided weakness lasting for approximately 30 minutes. The patient made a complete recovery between these episodes. The carotid colour-flow Doppler and carotid angiogram showed a 60% stenosis of the left internal carotid artery. The patient proceeded to a left carotid endarterectomy and made an uncomplicated recovery (reproduced with permission from http://www.surgical-tutor.org.uk/default-home.htm?xray/radiology12.htm)



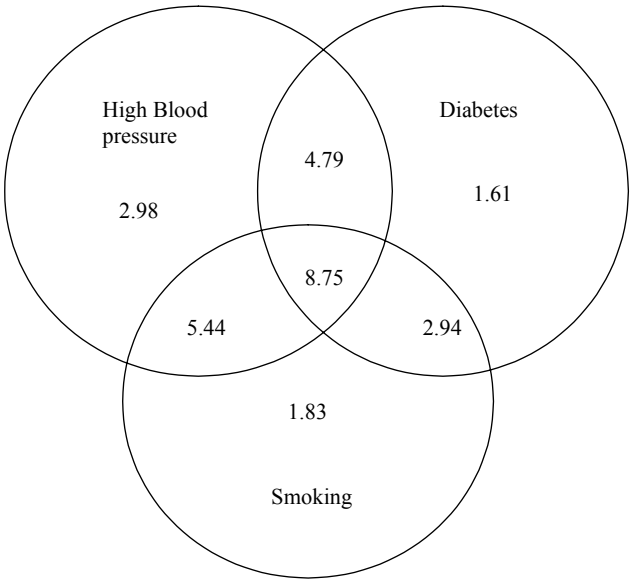
Plaques can grow large enough to significantly reduce the bloodflow through an artery (see Figure 1). But most of the damage occurs when they become fragile and rupture. Plaques that rupture cause blood clots to form that can block blood flow or break off and travel to another part of the body. If either happens and blocks a blood vessel that feeds the heart, it causes a heart attack. If it blocks a blood vessel originating from the carotid artery, it often causes a stroke. If blood supply to the arms or legs is reduced, it can cause difficulty walking and eventually gangrene.

Males, old age and people with a family history of premature cardiovascular disease have an increased risk of atherosclerosis. These risk factors cannot be controlled. Research shows the benefits of reducing the controllable risk factors for atherosclerosis (Evidence level 1, see Appendix 1 for levels of evidence). For primary prevention of stroke, adequate blood pressure reduction, and treatment of hyperlipidemia, use of antithrombotic therapy in patients with atrial fibrillation and of antiplatelet therapy in patients with myocardial infarction are effective and supported by evidence from several randomized trials.1 Effective strategies for the secondary prevention of stroke include

treatment of hypertension and hyperlipidemia, antithrombotic therapy for patients with atrial fibrillation, and antiplatelet therapy (Evidence level 1).1 Statins are effective in the prevention of stroke, although evidence remains limited to heart disease patients (Evidence level 1).2, 3

Smoking cessation is the most important lifestyle target for the prevention of stroke.4-6 All smokers should receive the urgent advice to stop smoking, and help in doing so is to be offered (Evidence level 1, see KCE report Vol. 1A).7, 8 shows the danger of combined risk factors, as these tend to interact: all three for stroke important risk factors give you the stroke risk of a person that is not less than 32 years older. The data are from the Framingham Heart Study and Framingham Offspring Study, showing relative risks for stroke.9, 10 Diabetes and smoking means presence of that risk factor, high blood pressure refers to a systolic blood pressure of 160 compared to 120 mm Hg. In the Framingham Heart Study, cholesterol levels are no determinant of all strokes, but they are for atherosclerotic stroke. Statin therapy decreases risks. For comparison: the relative risk for stroke of a 60, 70 and 80 year old compared to a 50 year old is respectively 2.21, 4.13 and 7.66. Having a single risk factor confers you a risk of a same person that is in average between 6 (diabetes) and 14 year (high blood pressure) older. A smoker with diabetes and high blood pressure has at age 50 the same stroke risk as a person without these risks at age 82 year. Because of inevitable ageing, adequate cardiovascular risk management will never prevent the needs for carotid interventions, but it will postpone them.

Figure 2: Risk factors for stroke: importance and combinations



People with declared atherosclerotic disease, such as angina pectoris, a history of a myocardial infarction or peripheral arterial disease (claudicatio intermittens) have an increased risk of carotid stenosis.

Key messages

- Carotid stenosis is a consequence of atherosclerosis and an important, but not the sole risk factor for stroke.
- Male sex, old age and a family history or premature cardiovascular disease increase the risks of carotid stenosis and stroke but cannot be modified.
- Medical treatment of carotid stenosis is based on optimal cardiovascular risk factor management to lower the risk of stroke. Risks of stroke can be lowered by adequate blood pressure reduction, LDL-cholesterol reduction with statins, use of antithrombotic therapy in patients with atrial fibrillation and of antiplatelet therapy in patients with myocardial infarction (Evidence level 1).
- All smokers should receive the urgent advice to stop smoking, and help in doing so is to be offered (Evidence level 1 for prevention of stroke).

2. OBJECTIVES: CHOICE OF INTERVENTIONS FOR CAROTID STENOSIS

The first choice in the therapy for carotid stenosis is optimal medical therapy (optimal cardiovascular risk management). In addition to optimal medical therapy, stenotic plaques may be treated by removing the plaque by surgery (carotid endarterectomy, CEA) or by treating the stenotic lesion by angioplasty and stenting (CAS). The current issue is whether and how carotid stenting should be implemented in Belgium as an alternative to carotid endarterectomy, given the existing evidence on effectiveness of this technology and its cost-effectiveness.

Specific questions are:

- Should CAS be introduced in 2005 in Belgian health care? This question may be phrased as "Is CAS superior to all other available strategies in certain well specified indications?" An ancillary question is whether CAS with embolic protection (see further) is safer than CAS without embolic protection.
- For which patient-groups exists sufficient clinical equipoise[1] between alternative strategies, including CAS, to support randomised clinical trials? This question may be phrased as "Is there clinical equipoise between CAS and other available strategies in certain well specified indications, to warrant further experimentation?"
- As CAS is a demanding technology with high risks of considerable morbidity and mortality, introduction should be safe for the patient. The question may be phrased as "What are the conditions that are needed for a safe use of CAS?" Ancillary questions address monitoring and auditing.

[1] Equipoise implies that a doctor can not decide which of two competing treatments is best for the patient: the best standard treatment, or a new alternative. That alternative may be better, but might be worse. Clinical equipoise extends this indecision to the community of treating clinicians. The ethical underpinning of a randomised trial is that lack of consensus among treating physicians, called "equipoise". Participation to the trial is always in the best interest of the patient, as either he receives the best treatment available, or a potentially better one.

3. TECHNOLOGY DESCRIPTION

3.1. CAROTID ENDARTERECTOMY (CEA)

Carotid endarterectomy removes harmful plaque from the carotid arteries. The best indications are non-disabling ischemic events (transient ischemic attacks, TIA), associated with important stenosis in the ipsilateral carotid artery. The level of stenosis can be quantified in several ways; two major CEA trials used different methods for quantifying stenosis, with different measures (ECST and NASCET). These methods are now calibrated against each other, showing consistent results in both trials. If it is not mentioned differently, we refer to the NASCET methodology (as in most of the current literature on carotid stenosis). In the NASCET-quantification, important stenosis is between 70% and 99% (higher means near occlusion of the carotid artery). Moderate stenosis is between 50 and 70%. Operating on lower levels of stenosis confers no benefit.

Transient ischemic attacks (TIAs) are one of the most important warning signs of an impending stroke. Sometimes called "mini-strokes," TIAs are temporary episodes of tingling, numbness, blurred vision, or paralysis that can last anywhere from a few minutes to a couple of hours. The operation can stop TIAs from happening and reduces the risk for stroke. While the patient is under anesthesia, surgeons make an incision in the neck, at the location of the blockage. A tube is inserted above and below the blockage to reroute blood flow. Surgeons can then open up the carotid artery and remove the plaque. Once the artery is closed, the tube is removed. In an alternative procedure, the surgeon does not reroute the blood flow but stops the blood flow just long enough to peel the blockage away from the artery.

The most important complication of a CEA is a non-disabling or disabling, fatal or non-fatal stroke. Published studies show the 30-day risks of stroke and death to be around 7% in symptomatic patients.[11-13] Risks of disabling stroke or death were around 2.1%.[11-13] Noteworthy is the difference between publications of the control arms of the trials (7.0% in ECST and NASCET), publications of neurologists (6.5%) and publications of surgeons (4.2% and significantly smaller).[14] Uncontrolled observational series tend to be biased to better outcomes, as surgeons (understandably) will not publish poor results. This shows an imminent danger of underestimation of the risks. Other risks of surgery are wound haematoma or cranial nerve damage, but these rarely lead to disability.15 Occlusion of the internal carotid artery occurred in 1.3% of the NASCET patients, 0.3% had an ipsilateral stroke after occlusion. [15]

3.2. CAROTID ARTERY STENTING (CAS)

Carotid artery stenting (CAS) is comparable to percutaneous transluminal coronary angioplasty (PTCA), a technique dilating or stenting the coronary arteries of the heart to treat or prevent myocardial ischemia or infarction. CAS is a minimally invasive procedure in which a physician uses a combination of balloon angioplasty and a stent implant to unblock and reopen the carotid artery. A catheter is inserted through a puncture in the groin into the femoral artery. The catheter is under fluoroscopic control navigated to the site of the blockage via the circulatory system (the carotid artery bifurcation). Nowadays CAS is mostly performed under cerebral protection, thereby avoiding embolisation of loose material to the brain.

There are 3 different philosophies of performing cerebral protection: a) distal balloon occlusion, b) proximal balloon occlusion c) distal filtration. In distal balloon occlusion, the flow to the brain is blocked with a balloon distal to the lesion, thereby preventing that during the manipulation of the diseased vessel (stent placement and balloon dilatation) debris will flow into the cerebral vessels. After the intervention, the debris is aspirated and the flow is restored by deflating the balloon. Patients who have an incomplete circle of Willis don't tolerate this method. Proximal balloon occlusion consist of blocking the flow with a balloon mounted on a special guiding catheter in the common carotid artery, proximal of the diseased area, thereby creating inversion of the

flow in the internal carotid artery. The debris created during the manipulation of stenting and dilatation of the lesion will thereby be flushed away from the brain. This method of cerebral protection is also not tolerated by patients who have an incomplete circle of Willis. In cerebral protection with distal filtration, the lesion is first passed with the filter, who will then be deployed distal from the lesion. The dislodged debris will be captured in the filter and removed after the intervention. During this procedure, the flow to the brain is maintained. Several devices are commercially available. Because of the stiffness of most of these devices, they can cause some problems in passing very tortuous arteries. Each of these described methods have clear advantages and disadvantages. A knowledge of these and the availability of the different types are mandatory to allow the best choice in every single patient.

The treatment of the lesion itself consist of the delivery and dilatation of a stent at the diseased area. A carotid artery stent is a tiny, metal mesh tube designed to open the stenosed vessel wall and to compress the plaque against the arterial wall and hold it in place. Several carotid artery stents are commercially available; all are self-expanding systems, most are made of nitinol.

As in CEA, CAS carries a considerable risk of stroke during or immediately after the intervention. Older trials showed poor outcomes, and two randomised trials of carotid stenting were stopped early after these poor outcomes in stented patients.[16] These early trials used techniques which have now been superseded, but the safety of endovascular treatment remains as yet insufficiently known.

Key message

- **This assessment summarises the evidence of effectiveness and cost-effectiveness of carotid stents relative to endarterectomy in patients suitable for surgery. A considerably evolving minimal invasive procedure is compared with a vested surgical intervention.**

4. REVIEW OF CLINICAL EFFECTIVENESS

The details of the methodology used for the review of the clinical literature are presented in Appendix 2. Emerging interventional technology is less amenable to the standard methodology of systematic reviews, as the technology evolves considerably and the quality of execution determines the outcome.[17] The aim of this review was not a full systematic review, but a standard assessment of the available evidence.

We searched iteratively, determining the eligible populations for carotid interventions, the evolved technology and the efficacy of that technology. To determine the eligibility, we used high quality trials on CEA only.[11, 12, 18-22]

We based interpretation of the findings on the methodological considerations, put forward in a series of reviews published recently, based largely on the experience from carotid interventions.[22-24] These excellent papers are freely available from the Lancet website (www.thelancet.com), and contain a wealth of information. Devices and surgical interventions are not drugs, which can be used in broad patient indications, where the doctor involvement is limited and placebo effects can be controlled for by a true placebo-arm. Summarizing effect estimates without taking into account the clinical conditions in which these effects occur, is poor methodology in surgical and endovascular interventions, where excellence of the centre, personal skill of the interventionist, preference of surgeon and radiologist for the one or the other intervention and choice of the device are important. In the reviews of CEA, it is shown that the posterior risk tends to be more constant, not the relative risk (the posterior risk divided by the prior risk) (see figure 4 in cited reference)23. Summarizing relative risks over studies with heterogeneous prior risks is wrong, as the observed relative and absolute risk reduction is conditioned by the prior risk.

To determine the efficacy of CAS, we first searched for systematic reviews and guidelines. We found a systematic review of CAS in the Cochrane database and a Interventional Procedures Overview of the National Institute of Clinical Excellence (NICE).[25, 26] The latter was a short overview of an HTA that is currently being performed. Additional studies that updated the reviews were sought in Medline and Embase. The search strings are presented in appendix 2.

We found three more recent papers on randomised controlled trials (see Appendix 2). Two were added as relevant for evaluating PCAS.27, [28] We added four more recent observational studies and one paper from a registry.[29-34] Data extraction sheets are in appendix 2.

4.1. PROTECTED CAROTID ARTERY STENTING (PCAS) VERSUS UNPROTECTED STENTING

CAS is a technology in full development. It changed from angioplasty to angioplasty with stenting to angioplasty with stenting and embolic protection. Embolic protection devices are designed to protect the brain from embolisation during stenting. While there is no unambiguous direct evidence of head to head trials comparing stenting with embolic protection and without embolic protection, stenting with embolic protection is now becoming the clinical standard. This is supported by indirect evidence of observational studies.[32, 34-37] The EVA-3S trial stopped unprotected stenting, sending a clinical alert that protected stenting prevented peri-procedural strokes.[27] Overviews of observational studies suggest a number needed to treat with embolic protection of 27, 30 or 45 to prevent one additional case of stroke or death (see table).[34-36] If there is insufficient clinical equipoise, experiments with unprotected stenting soon become unethical, unless there is no alternative (e.g. for patients who do not tolerate the protection device or in whom the protection device cannot be safely introduced). This is also shown by the gradual increase of embolic protection to 100% of all users in the prospective Carotid Artery Stent (CAS) Registry of the German Arbeitsgemeinschaft Leitende Kardiologische Krankenhausärzte (ALKK).37 Reviews including older technologies including unprotected stenting or angioplasty may underestimate the current 'state of the art' of CAS. Due to absence of unbiased evidence from randomised

trials and heterogeneity, missing information and potential patient, surgeon and centre selection bias, the statement that PCAS is superior to unprotected CAS can not be made at the highest level of evidence. However, worldwide clinical consensus and current clinical practice do not support further use of unprotected CAS (except in those conditions where embolic protection can not be deployed safely).

4.2. PCAS VERSUS CEA

4.2.1. Evidence from finalised RCT

The evidence table shows that only one RCT, the SAPPHIRE trial, has been finalised and published.28 The other two ongoing trials describe safety profiles of the competing interventions, with the EVA-3S trial alerting clinicians for the better outcomes with PCAS over unprotected stenting. There are many problems in the SAPPHIRE trial (for a fuller discussion, see Appendix 2). Power to detect clinically meaningful differences in outcomes was too small; the trial ended prematurely after a change in legislation allowed recruiting patients for PCAS in non-randomised registers. 54% of referred patients were excluded from the trial and sent directly forward to PCAS because they had a "prohibitive high risk".38 It is unclear who this population might conceivably be, as the risk in the SAPPHIRE trial is low compared to the NASCET and ACE (CEA-) trials. This obvious selection bias favouring PCAS in recruitment may be explained by conflict of interests of the authors: the main author invented the protection device and was shareholder of the society who owned that device. Further, the authors claim that the high AMI rates are a significant primary endpoint. A one-year risk of 12.2% - 20.1% of stroke, death or AMI (only first month) in asymptomatic carotid artery stenosis patients is extremely high. With such high procedural risks, patients should fare better with optimal medical treatment. External validity of this trial is impossible to assess.[22] SAPPHIRE adds to observational evidence that PCAS in selected patient populations and in selected surgeon and hospital centres is not inferior to CEA. The trial is too flawed to be considered as experimental evidence.

4.2.2. Evidence from prospective cohort studies, registries or ongoing trials

Registers and prospective studies give useful information of outcomes of interventions in clinical practice. However, direct comparisons between outcomes of different interventions in different populations and centres are fraught with danger, as many confounding factors, known and unknown, can not be controlled for outside randomised designs. We tried to avoid selection bias (results that don't get published because they are poor, compared to other centres) by selecting only prospective studies and registries. These results are the results obtained in patient populations, treated by interventionists in hospitals that do not reflect the results in all populations in all hospitals, let alone in Belgian hospitals. Taking all these caveats into account, the results inform about the outcomes of the better clinical practice.

PCAS in asymptomatic and symptomatic patients show 30 day rates of stroke and death of 1.8% (N=896, 63% symptomatic)35, 2.2% (K-M estimate, N=143 of which 37.1% symptomatic) 39, 3.2% (N=2111 symptomatic patients)34, 2.5% (N=2110 asymptomatic patients) 34, 5.2% (N=97 symptomatic)36, 11.3%(N=53, 57% symptomatic > 75 year old)32, 3.8% (N=213 symptomatic)33, 3.2% (N=602 asymptomatic)33, 2% (N=86>79 years old)33, 3.7% (N=159 29.9% symptomatic)28. Stroke and death rates are around 3% in asymptomatic patients and higher in symptomatic patients.

Two reports show an increased risk of PCAS among older patients (>75 or 80 years),[30, 32] a third showed no increase of risk.[33] Samples are small, but old age seems not a good indication for PCAS.

4.2.3. Ongoing studies

Randomised controlled trials comparing PCAS and CEA are recruiting patients. More details are in Appendix 2. The Endarterectomy Versus Angioplasty in Patients With Symptomatic Severe Carotid Stenosis study (EVA-3S) recruits symptomatic patients with > 60% stenosis.27 Surgeons need to have performed at least 25 CAS, interventional radiologists at least 12 CAS. International carotid stenting study (ICSS, called previously CAVATAS-2) recruits symptomatic patients with >50% stenosis.40 Surgeons are expected to have performed a minimum of 50 carotid operations with an annual rate of at least 10 cases per year. Radiologists are expected to have performed a minimum of 50 stenting procedures, of which at least 10 should be in the carotid artery. The Stent-Supported Percutaneous Angioplasty of the Carotid Artery vs. Endarterectomy Trial (SPACE) recruits symptomatic patients with >50% stenosis.41 Surgeons and interventionists need to show their expertise, but requirements are not specified. EVA-3S, SPACE and ICSS (CAVATAS-2), have prospectively agreed to combine individual patient data after completion of follow-up. This meta-analysis will provide results similar to a mega-trial and should also allow informative subgroup analyses. Carotid Revascularization Endarterectomy versus Stent Trial (CREST) recruits symptomatic patients with >50 % stenosis.[42, 43] Surgeons need to have performed more than 20 interventions.

All ongoing trials recruit symptomatic patients. In 2007, trials should show firm evidence of the clinical effectiveness of PCAS, and the conditions of use in symptomatic patients. A first trial targeting asymptomatic patients (ACST-II) has been planned and financed and might start recruiting (Halliday 2005, personal communication).

Key messages:

- **PCAS has lower peri-procedural rates of stroke and death than unprotected CAS (Evidence level 2). This statement is based on evidence of observational studies from heterogeneous sources and worldwide clinical expert consensus.**
- **There is no convincing evidence that PCAS is superior, inferior or non-inferior to CEA in well defined patient populations (absence of evidence).**
- **Four major randomised controlled trials (of which three cooperate) are recruiting symptomatic patients for PCAS. Introduction of PCAS in routine medical care must wait till final results are peer reviewed, published and found valid.**
- **No randomised trials are recruiting for asymptomatic patients. There is as yet no clinical equipoise of treatment of asymptomatic patients among opinion leaders.**
- **CEA is the standard of treatment of carotid artery stenosis in well defined populations at high risk for stroke. This holds particularly for older patients.**
- **Where CEA is no treatment option and the patient is at high risk of a stroke, PCAS is a useful treatment option.**

5. POPULATION ELIGIBLE FOR A CAROTID INTERVENTION

A full discussion of indications for carotid interventions is beyond the scope of this report. But inappropriate use of CAS as of CEA can cause more strokes than appropriate use may prevent. Risk stratification is paramount, as either CAS or CEA have important adverse event rates. To obtain benefit, the prior risk has to be high 'enough' to balance procedural risks. Prior risk is primarily defined by the presence or absence of symptoms, the duration since the onset of symptoms and the level of the stenosis. Persons with the highest risks of stroke without intervention will benefit most.

5.1. SYMPTOMATIC CAROTID STENOSIS

The first and most important indication for carotid interventions is symptomatic important carotid stenosis.[11, 12, 15, 20, 21, 44]

A pooled analysis of prior and posterior risks of the European Carotid Surgery Trial (ECST) and North American Symptomatic Carotid Endarterectomy Trial (NASCET) trial populations has recently been published.[11, 12, 45] Both trials included recently symptomatic internal carotid stenosis.

The medical risk of any stroke or death in the forthcoming five years in symptomatic persons of the NASCET/ECST trials with a stenosis of ? 50% (according to the NASCET method) was 21%.[14] That risk was further increased by male sex (23%), old age (? 75 y, 31%), time since last event (< 2 weeks, 32%) and diabetes. Other reasons for increased risk (post hoc) were previous events with higher symptoms, (stroke, TIA>1 h), MI or treated hypertension. The one month surgical risk was, in these highly selected patients and surgeons, still 7.4%. Treating patients at low risk is always a strategy at high risk.

An earlier pooled analysis showed the influence of stenosis. In the group with 70-99% stenosis, the benefit was high, and 6.4 persons needed to be treated to save one person from a stroke or death in the next five year risk. In the group with stenosis between 50% and 70%, you needed to treat 12.8 persons. In the group with stenosis 30-49%, you needed to treat 40 persons, but more harm than benefit by treatment was not excluded. In the group with stenosis < 30%, more harm than benefit was caused.

The authors concluded that surgery is of some benefit for patients with 50-69% symptomatic stenosis, and highly beneficial for those with 70% symptomatic stenosis or greater but without near-occlusion.

A recent Cochrane review of the existing randomised trial data concluded that the current evidence does not yet support a shift away from recommending CEA as the standard treatment for carotid stenosis.[25] Currently, patients who are considered to be high risk for conventional surgery are eligible for carotid artery stenting with embolic protection. There are no hard rules for what is high risk: it depends on the clinical experience of the available surgeon or interventional radiologist. Two populations of patients may be considered at high risk for CEA. The first population are those patients where surgery causes anatomical or technical problems: prior carotid artery surgery, previous neck surgery, previous radiation treatment to the neck, or difficult lesions for the surgeon to reach. The second population are those patients with severe co-morbidity that makes open surgery more risky: heart failure, severe lung disease, high bifurcation, morbus Bechterew, contralateral recurrent nerve palsy and contralateral carotid artery occlusion. Although it has been shown that these patients are at high risk for surgery, it is not shown that these patients are not also at high risk for PCAS.

Key messages

- **CEA is beneficial for symptomatic patients with recent non-disabling carotid ischemic events and ipsilateral 70-99% stenosis (Level of evidence 1). This includes elderly patients and women (Level of evidence 1).**
- **CEA is not beneficial for symptomatic patients with recent non-disabling carotid ischemic events and ipsilateral stenosis of less than 50% and more than 99% (near occlusion) (Level of evidence 1).**
- **CEA may have benefit in symptomatic patients with recent non-disabling carotid ischemic events and ipsilateral stenosis of 50-69%. Women with few risk factors and patients with ocular symptoms only and few risk factors have too low risks to benefit sufficiently.**
- **CEA is the first treatment option. Pending further trial evidence, PCAS is to be limited to patients both at high risk for stroke and at high risk for surgery.**

5.2. ASYMPTOMATIC CAROTID STENOSIS

The dilemma of operating in people with asymptomatic carotid stenosis of substantial severity (> 60% stenosis) involves choosing between the increased long term risks of optimal medical intervention and the increased short term risks of surgical intervention. That is problematic, as doctors are not good in estimating risk and there is, as yet, no clear definition of an asymptomatic patient at high risk for stroke. Prognostic models predicting the risk for stroke in asymptomatic patients are being developed in the UK (P. Rothwell, personal communication), but are not yet available. Doctors tend to have inflated perceptions of risk without treatment and tend to overestimate the benefit of treatments with preventive intent, such as carotid interventions.[46] Carotid interventions must not "treat" a stenosis, but should prevent a stroke. Overall, doctors who would not recommend preventive therapy appeared to give more accurate estimates than did doctors who would recommend such therapy.46 In carotid artery surgery, this may generate more strokes that are caused by interventions than that are saved. Five year risks of stroke and death are halved, but at the cost of increased morbidity and mortality the first two years. These benefits are obtained in carefully selected patients by centres of excellence that participate in trials. The mean age at intervention is 72 years in a predominantly male population: life expectancy is limited and competing risks of mortality reduce long term benefits.

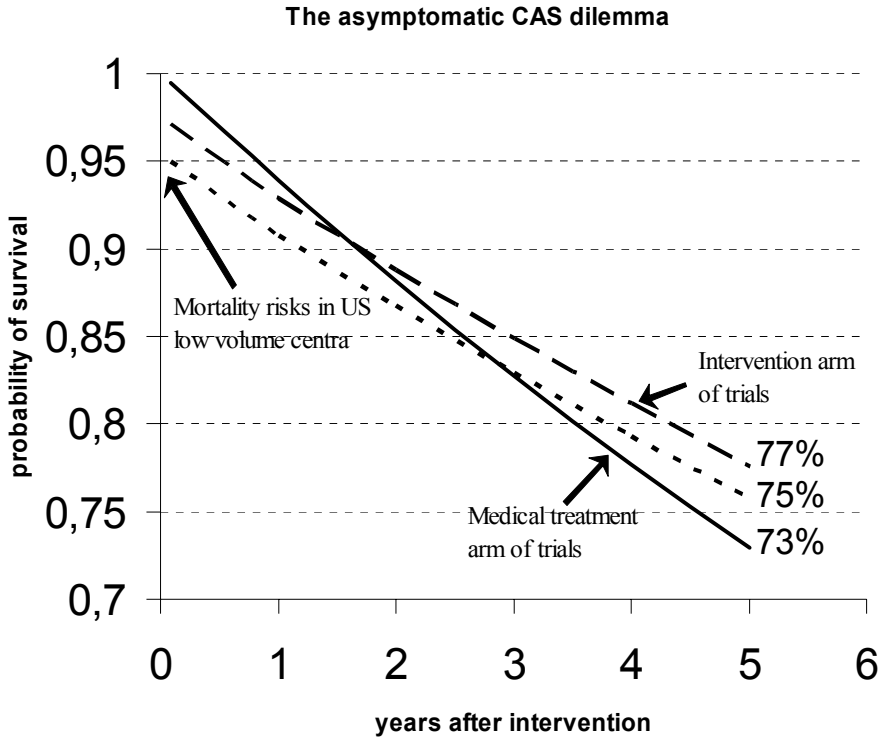
The enthusiasm of institutes to endorse CEA for asymptomatic subjects suggests therefore more problems than solutions, particularly if income is proportional to number of interventions. Five trials have been published, two were flawed and yielded negative results, the third had negative results.[18, 19, 47-49] Two were positive, the ACAS and recently published ACST-trials.[18, 19] They provided the rationale for increasing CEA activity, while the intervention among asymptomatic persons remains of sufficiently dubious benefits to merit great caution.

First and most important, for symptomatic stenosis patients, the number needed to treat to benefit within two years is between 3 to 19, depending on degree of stenosis and age.15 For asymptomatic stenosis, as the Kaplan Mayer-curve suggests, at least five years of follow-up are needed to recoup the lost life years by increased morbidity and mortality (see further).

Second, there is little information about how scrupulous and compliant cardiovascular risk management was in the "medical" arms of both trials: control of blood pressure, lipids, cigarette smoking and platelet inhibition. The population of the ACAS trial was treated largely before the advent of modern risk lowering therapy with statins. Barnett, leader of the NASCET trialists, suggested in his comment in the Lancet that the medical-surgical gap could have been smaller by optimal risk management in the ACST than suggested by the trialists.[50] Better medical treatment will further increase the surgical numbers needed to treat.

Third, the benefits are gained by the very low surgical and angiography complication rates in the participating centres of the ACST trial. Only experienced surgeons with a past record of excellent results were recruited. Compelling results show worse outcomes in non-trial centres, worsening with decreasing volumes.[51] The peri-operative mortality rate was 1.4% (95% CI, 1.2%-1.7%) at trial hospitals; mortality in non-trial hospitals was 1.7% (1.6%-1.8%) (high volume); 1.9% (1.7%-2.1 %) (average volume) and 2.5% (2.0%-2.9%) (low volume); (P for trend, <.001).51 The peri-procedural mortality in the ACST en ACAS trial was 0.6% and 0.1% respectively. These data suggest that the trial centres are centres of excellence, and the trial populations patients of excellence. 40% of the candidate surgeons were excluded from the ACST trial, while they probably did not stop treating patients.50 To be eligible, participating surgeons had to show evidence of their last 50 CEAs. The adverse event rate of stroke or death had to be less than 3 (6%).19 As most previous CEAs would have been for symptomatic patients, this is a low threshold. Surgeons were actively monitored during the trial and potentially excluded of further participation if they had poor results, although this did not happen. In day-to-day clinical practice, the rates of operative complications are 1% to 2% higher than the low rates achieved by trial surgeons. High risk may include other determinants of cardiovascular risk and should be defined and identified objectively.

Studies in the US and Canada show high levels of inappropriate or uncertain use of CEA, with nearly half of CEAs performed in asymptomatic patients.[52, 53] In the SAPPHIRE trial comparing PCAS to CEA, 70 percent of patients were asymptomatic.[28] With a one year major event rate (stroke, myocardial infarction or death) of 12.2%, in surgical and stented patients at rather low risk, it is rather certain that patients would have fared better on medical therapy, certainly in that year.[38] The rebuttal of the authors suggested again more problems than solutions: ‘Most practitioners … refer patients with severe asymptomatic disease for endarterectomy’.[38] Historical examples where most practitioners were wrong abound. Appropriate indications for interventions among asymptomatic patients are rare, while many more patients are at the margins of benefits, were the balance between harms and benefits is not obvious. This conflict may cause treatment decisions a well informed patient might not support.



This picture illustrates the trade offs of operating asymptomatic carotid interventions (spreadsheet available at request). The graphs "Medical treatment" and "trial centres" show the results of the ACST/ACAS trials (expressed as constant hazards of stroke or death from the trials and age dependent hazards of all other cause mortality from the Flemish male life table at age 70 in the year 2000).[18] Intervention starts with a short period of high (peri-procedural) mortality, but the lower post-procedural hazard of death will overtake the higher hazard of medical treatment. One in four will die or have a stroke anyway, mainly because of old age.

To asses the effects of poorer outcomes, we added the peri-procedural mortality of low volume centres in the US, using the observed risk ratio of death to the risks of stroke or death; low volume centres showed a 1.8 times higher peri-procedural mortality.[50]

The balance between benefits and harms depends on the assumption of the residual life expectancy of the survivors (after five years of treatment). In the Flemish male life table, residual life expectancy at age 75 is 9.7 years. By varying that assumption, we can verify that, if the residual life expectancy decreases under 5 years, the balance of harms and benefits starts to be negative at an average performance (risk of peri-operative stroke and death of 4%) at intervention. For CAS to be beneficial for an asymptomatic carotid stenosis, the risk of peri-operative stroke and death should be lower than 4% and the life expectancy sufficiently high (at intervention).

The following table summarises the benefits of carotid interventions compared to medical treatment, assuming relative differences of treatment outcomes according to volume. It will take the best centres still more than three years before patients start to benefit. Peri-procedural risks of stroke or death should be lower than 4%, and life expectancy should be higher than five years.

	relative risk of death	Absolute risk of stroke or death	saved life years†	time to benefit‡	NNT 3 jr	NNT 5 jr
Trialcentra	1,00	2,8%	0,52	> 3 yr	142	28
High volume	1,21	3,5%	0,45	> 3 yr	709	33
Average	1,36	3,9%	0,40	> 4 yr	harm	37
Low volume	1,47	5,1%	0,25	> 5 yr	harm	59

† Sum of life years free of stroke or death during trial period (5 years) and residual life expectancy of survivors at age 75 (independent of treatment).

‡ Duration between intervention and that point in time when the balance of saved and lost life years becomes positive. Note that the assumption of "equal life expectancy" after five years does not take into account improved prognosis by the intervention after that period of five year, but neither does it take into account the shortened survival because of the compromised atherosclerotic cardiovascular system in survivors.

Key messages

- **Asymptomatic patients with carotid stenosis are at lower risk of stroke, and hence at higher risks of harm by peri-operative morbidity.**
- **Treatment of asymptomatic carotid stenosis is poor clinical practice if the stenosis is less than 60%, risks of peri-procedural stroke and death are >= 4% in the operating centre or the residual life expectancy is low (level of evidence 1). In clinical practice, interventions for asymptomatic stenosis among patients older than 75 years will rarely benefit the patient.**
- **Carotid interventions among asymptomatic patients with a carotid stenosis of > 60% may be a treatment option in well specified conditions (level of evidence 1).**
  - **These conditions should be identified in unambiguous guidelines.**
  - **Asymptomatic patients must be informed that the gap between optimal surgical treatment and optimal medical treatment with deferred treatment over the next five years is small.**
  - **Peri-procedural rates of stroke and death must be lower than 4% and life expectancy should be (level of evidence 1). PCAS or CEA should not be performed in asymptomatic persons aged 75 and older.**

6. REVIEW OF COST-EFFECTIVENESS

We searched literature on the cost-effectiveness of CAS versus CEA in Medline, the Cochrane Library, Embase and CRD (DARE, NHS EED, HTA) with the keywords "carotid" and "stenosis" and "stent*" in combination with the keyword "cost*" or "economic*". For Medline and Embase, we used the thesaurus to retrieve the relevant subject headings. We limited our search to papers published between January 1998 and December 2004. Articles written in English, Dutch, French or German were considered for review.

We first selected articles based on abstracts. Studies that did not have economic evaluation or cost evaluation as their main objective or one of their main objectives were excluded. Full economic evaluations as well as partial evaluation (cost descriptions, cost-outcome descriptions and cost analyses) were retained as appropriate study designs. We included only studies that compared CAS with CEA in the review. We placed no restrictions on the patient population studied. Data were extracted using a structured data extraction form, including the year of data collection, design, patient population, measure of costs or proxies for costs, effectiveness measure and results (see Appendix 2). We assessed quality by a quality assessment checklist.[54] As there is currently no scoring system available for economic studies, we discuss the quality of the studies narratively.

6.1. RESULTS

The economic literature on carotid stenting is limited. This is likely caused by the lack of evidence of clinical effectiveness. Five studies examined (an) economic aspect(s) of CAS and CEA. Four studies were cost-outcome descriptions.[55-58] Cost-outcome descriptions are partial economic evaluations that separately compare costs and outcomes of CEAE and CAS, without explicitly calculating an incremental cost-effectiveness ratio. One was a cost-effectiveness analysis[59]. The quality of all but one of the economic studies was poor. The four poor studies studied unprotected CAS as the intervention of interest. With the current state-of-the art knowledge on PCAS versus unprotected CAS, the figures become less relevant. We will therefore focus on the qualitative results rather than on the quantitative results.

6.1.1. Initial hospital costs

Gray et al.55 reviewed two consecutive cohorts of patients undergoing either CEA or CAS in one single hospital. The total adverse outcomes for the two treatment groups were similar, although the baseline characteristics of the patients were not identical: CEA patients were more often symptomatic and PCAS patients more often had co-morbidities that made them at high risk for CEA. Procedural costs were similar in both groups. Non-procedural costs, such as intensive care nursing, pharmacy, radiology, respiratory therapy and central supply costs, were significantly higher in the CEA group than in the CAS group. Length of stay was significantly different, with the surgical group staying on average 3 days in hospital and the CAS group staying on average 1.4 days. The median length of stay was 2 and 1 day(s) respectively.[55]

Another cohort study of CAS and CEA procedures in one hospital, found that hospital charges were about 25% higher for the initial hospitalisation for CAS than for CEA.56 Significant higher charges were found for CAS than for CEA for use of operating or cardiac catheterisation room and radiology. The cost of the implants and monitoring equipment was the decisive factor for the cost of CAS. [56] Post-operative length of stay was shorter in CAS than in CEA, although not significantly (mean 2.9 versus 3.1 days). The incidence of stroke was lower in the CEA group than in the CAS group (1.5% (n=2) versus 7.7% (n=8)). The CEA group, however, had a higher incidence of deaths (1.5% (n=2) versus 0.9% (n=1)).56

A small RCT on CAS in symptomatic patients found significantly higher hospital charges for patients undergoing CAS than for patients undergoing CEA.[57] Variable hospital costs, including operating room or catheterisation laboratory, nursing, pharmacy, laboratory and radiology, were not significantly different between CAS and CEA. Length of stay was shorter for CAS than for CEA with no complications: 1.8 versus 2.7 days. Complications extended length of stay more in the CAS group than in the CEA group. In the group of patients with complications, the average length of stay was 3.8 days for CEA and 13.3 days for CAS. Statistical significance of this difference was not tested.

The same research group performed a similar study on the hospital charges associated with CAS and CEA in asymptomatic patients. Similar conclusions were reached, although length of stay was shorter in asymptomatic patients than in symptomatic patients, both in case of CEA and in case of CAS.[58]

6.1.2. Long term cost-effectiveness

One study simulated the long-term costs and outcomes of CAS versus CEA using a Markov model.[59]. Input data for the model for CEA were obtained from a retrospective review of 447 patients undergoing CEA in a hospital in New York, data for CAS were derived from literature. Thirty-day probability of major stroke was assumed to be 0.45% for CEA and 1.8% for CAS. Thirty-day probability of death was assumed to be 0% and 1.2% respectively. According to the model CEA was less costly and more effective in terms of quality adjusted survival than CAS. Lifetime costs for CAS and CEA were $35 789 and $28 772 respectively (1997 US dollars), lifetime outcomes 8.20 and 8.36 QALYs respectively. Major stroke and mortality were the determining factors for this result. If the major and minor stroke rates and the mortality rate of CAS were set equal to the levels of CEA, an incremental cost-effectiveness ratio of CAS relative to CEA of $68 800 is obtained.

The procedural cost of CAS was about 25% higher than that of CEA. The cost of a carotid stent and protection device was $3 200 in the US in 1997. The most important factors contributing to this cost difference were the stents and the protection devices. The authors concluded from their model that CAS can only become economically competitive with CEA if, either its level of major stroke and mortality significantly decreases below the level of major stroke and mortality of CEA or its procedural cost significantly decreases below the cost of CEA.[59]

Unlike in endovascular interventions of the aorta, where the length of stay of the open intervention is long, the high incremental cost of the stent and the protection device for CAS is not offset by cost savings resulting from a decrease in length of stay. The length of stay in case of CEA is not very long, and the length of stay in case of CAS is only modestly shorter. [59]

6.2. APPRECIATION OF ECONOMIC EVIDENCE

The literature review revealed that the economic benefits of CAS, in terms of shorter hospital stay and avoided complications, do not outweigh the additional costs of the devices in the USA. The carotid stents as well as the cerebral protection devices are still expensive and are not compensated by the savings obtained elsewhere in the treatment process for carotid stenosis.

However, the economic evidence base is weak. First, there is insufficient clinical evidence on the incremental effectiveness of CAS relative to CEA. Lacking comparative effectiveness data on stroke and death, economic evaluations are not very meaningful. Second, the current economic literature on CAS versus CEA is from the USA. It is unlikely that the costs presented in these studies are relevant for the Belgian situation. Third, true costs are rarely presented, but a poor proxy of costs, for example hospital charges.

It is yet uncertain how the technology of CAS will evolve. CAS is still in its developmental phase. As experience with the technology increases, the device may be improved by the manufacturer and operators become more experienced with the procedure of stenting, which both has consequences for outcomes as well as for costs. This evolution has also been observed in CEA. The costs of CEA reduced drastically over the last few year as a consequence of simplified procedures 60, 61, while the outcome has improved; the latter mainly as a consequence of increased experience with the procedure. Decreasing costs in combination with improved outcomes implies an improvement in efficiency.

As CAS would be more widely diffused in clinical practice, the turnover of the industry increases and the competition among manufacturers may increase. Both dynamics may force the price of the device downwards, although such evolutions are difficult to predict. Innovations in technology are rarely cheaper than the existing technology. Given that manufacturers of carotid stents are still trying to improve the device, it is uncertain how the long term price will evolve.

In conclusion, at equal effectiveness, CAS will not be cost-effective. The relative cost-effectiveness may improve by increased competition between stent manufacturers and increasing output volumes. Outcomes may improve, and costs of complications decrease, as operators gain more experience with the procedure. However, if more and more inexperienced operators are performing PCAS, effectiveness may decrease and complication rates increase. The relative cost-effectiveness of CAS may further decrease by inappropriate use of PCAS in dubious indications. It is therefore important to organise the diffusion of CAS carefully in order to allow a safe and cost-effective implementation of this emerging technology (see chapter 10).

Key messages

- **Studies from the USA found that initial hospital costs or charges for CAS (without cerebral protection) are higher than for CEA.**
- **To assess the relative cost-effectiveness of PCAS, long-term results of clinical trials are needed.**
- **At equal effectiveness, the additional costs of devices make PCAS less cost-effective compared to CEA. Stroke rate is the major determinant for the relative cost-effectiveness of PCAS.**
- **The further development of carotid stenting technology and (controlled) diffusion in clinical practice may change the costs and outcomes of the technology and the relative cost-effectiveness of the intervention.**

7. EXPERIENCE WITH THE INTRODUCTION OF CAROTID STENTS IN SELECTED COUNTRIES AND BELGIUM

The limited evidence about the effectiveness of CAS and the potential high risk of carotid interventions calls for a policy of phased introduction of CAS. PCAS is a emerging but promising technology, where randomised trials are still running. The long-term effectiveness of PCAS relative to CEA is insufficiently established to allow use in routine medical care. Premature introduction of new or emerging technologies may cause more harm than the best existing traditional treatment, at additional costs. To guarantee safety and efficiency in the treatment of carotid stenosis, the introduction of the technology must be phased and guided.

A number of delicate questions remain: what are the long-term outcomes of carotid stents, what are the potential future technological improvements to the stents, who are the patients who are most likely to benefit from this procedure and what are the desired requirements of an interventionist in terms of expertise?

UK. Every operator is asked to report his data to the national registry of the British Society Interventional Radiology, but this registration is not compulsory. The National Institute of Clinical Excellence in the U.K. recommended surgeons to include carotid stents patients in the ICSS trial. The Royal College of Physicians of Edinburgh has followed this guidance. Most patients treated with CAS in the UK are included in the ICSS trial, unless they are at high risk patients for CEA. There is an average of 4000 CEA or PCAS in the UK (population of 50 million) [Rothwell, personal communication by e-mail]

USA. Medicare has made the reimbursement of carotid stents conditional upon registration of the patients in a national register to allow long term follow up of outcomes in September 2004.(New York Times, November 5, 2004) Medicare limits reimbursement to symptomatic patients – scientific organisations have appealed this decision.

France. In 2002, the ANAES recommended that carotid angioplasty should not be performed outside the context of a clinical trial.[39]

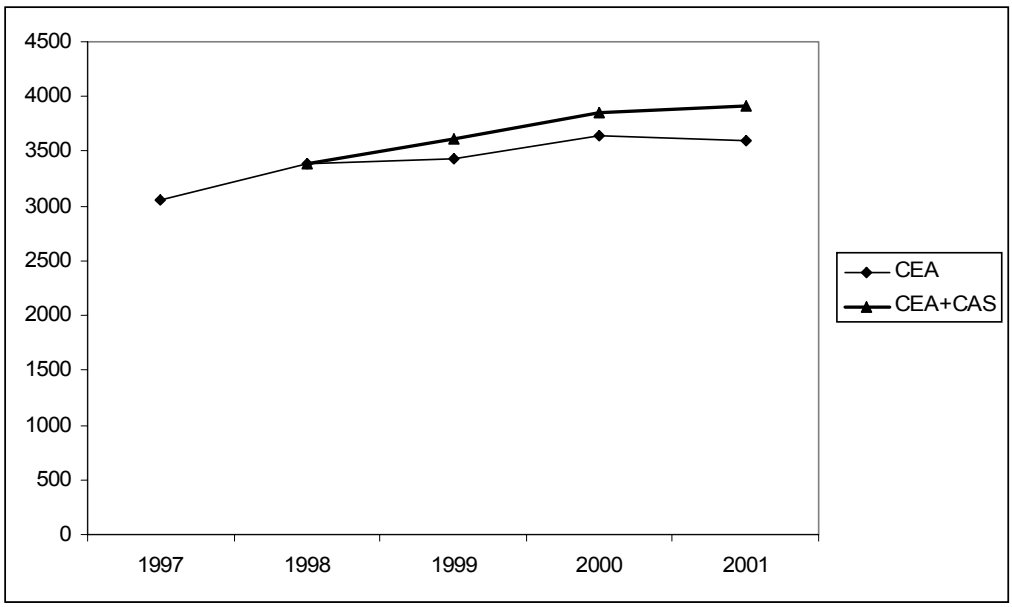
Germany. The German Societies of Angiology and Radiology have instituted a prospective registry of CAS to limit uncontrolled use of CAS and to collect data about technique and results of CAS outside clinical trials.[62]

Belgium. Carotid stents are currently not reimbursed in Belgium. There are no regulatory conditions for carotid stenting.

No specific ICD-9 code exists for CAS. Therefore, the number of carotid stents placed between 1999 and 2001 is estimated based on the ICD-9 code description "stenting of a non-coronary vessel". It is obvious that this is only a crude proxy for the real number of carotid stent interventions, as this code also includes placement of iliac, renal and other non-coronary stents. How many interventions are needed is unknown, as it is not known how many of the performed interventions are appropriate, neither is it known if carotid interventions are underused in symptomatic patients that would have been eligible for CEA or PCAS.

Figure 3 presents the evolution of the estimated number of CEAs and CAS between 1997 and 2001 (aggregated national data RIZIV/INAMI, billing code 235082 for CEA, ICD-9 code 39.90). No non-coronary stents were registered before 1999. The total number of cases steadily increased over time. The benefit of chaotic introduction of emerging technologies is unknown, but may easily be balanced by the harms.

Figure 3: Estimated number of CEA and CAS between 1997 and 2001



The number of CEA and PCAS is in the UK and in the Netherlands were recently less than 1 per 10 000 63, 64. The observed rates in California, Ontario and New York were less than 2 per 10.000 in 1995.65 With close to 4 per 10 000 interventions, intervention rates in Belgium are extremely high compared to the Netherlands and the UK, and higher than in the US.

Key message

- **Rates of carotid interventions in Belgium are extremely high, compared to the UK and the Netherlands, and very high compared to California, Ontario and New York.**

8. PATIENT ISSUES

In the ideal world, the best choice between PCAS and CEA is made by the perfectly informed patient and his treating physician. This poses the problem of competent, impartial information that now will be handled in the chapter of ethical issues. Warren et al. examined patient preferences for treatment of extracranial carotid artery stenosis.66 While the information of risks and benefits of PCAS and CEA is obsolete, their model can easily be updated.

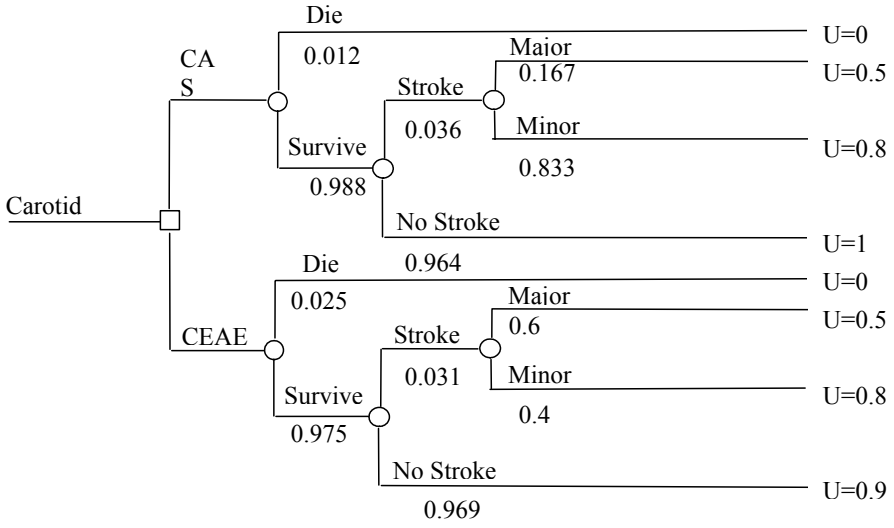
Figure 4 presents a simple decision model that allows the calculation of the expected utility with CAS and with CEA (Figure 4). A rational patient will prefer the treatment with the highest expected utility.

The model uses the utility values collected for the different end points in the study of Warren et al. to re-calculate the expected utility values for CAS and CEA with the information from the SAPPHIRE trial. [66] While the original study concluded that patients prefer CEA over CAS, the current calculations find a preference for CAS. The expected utility for CAS is found to be 0.98 on a scale from 0 (=death) to 1 (=optimal health). The expected utility for CEA is found to be 0.96, so, ceteris paribus, patients would prefer PCAS over CEA.

However, the limitations of this simple exercise have to be understood. The data used are from the SAPPHIRE study, and apply to the population of the SAPPHIRE study, with uncertain external validity and relevancy. The power of SAPPHIRE was too small to estimate reliably a difference in survival of 1%. The probabilities imputed in the decision tree are limited to 30-day outcomes. In the short term, patients might prefer PCAS, but the long-term results remain unknown. If medium term restenosis rates are high in the PCAS group, preference might switch back to CEA.

In short, this little exercise shows eloquently we need more powered trials with longer term results before we are able decide if PCAS is a useful alternative.

Figure 4: Decision tree for the choice between CAS and CEA from the patient's perspective



Key messages

- Patient preferences for PCAS or CEA cannot be established before more information on the long term outcomes of both procedures becomes available.
- According to a simple decision model, based on debatable clinical data of one short term RCT, patients show a slight preference for the endovascular procedure.

9. ETHICAL ISSUES

The question of introduction of new health technology such as stenting devices has been discussed in terms of the technology diffusion cycle. Banta and Luce give a five-stage classification:[67]

1. future technology (not yet developed).
2. emerging technology (prior to adoption).
3. new technology (in the phase of adoption).
4. accepted technology (in general use).
5. obsolete technology (should be taken out of use).

PCAS is an emerging technology for patients eligible for an intervention opening a carotid artery stenosis, and a new technology for patients ineligible for open surgery. The boundaries between categories are separated by these elements:

- the populations and conditions for which use is helpful;
- the expected outcomes of care;
- the skill, personnel, and site requirements;
- the economic, ethical, and legal understandings essential for use, and
- the level of knowledge needed to certify that prospective users can apply it well.

Health technologies of various types, including devices, are continually being developed. As new innovations emerge, authorities are faced with decisions whether to fund them and, if so, to what extent and under what conditions. There are crucial distinctions between drugs and devices.[17] The most crucial differences are the high rate of technological change, the high influence of the treating doctor and the important effect of the hospital environment in which the doctor is working. This is shown by carotid stenting by the comparatively very rapid evolution from angioplasty to angioplasty with stenting (CAS) to stenting with embolic protection (PCAS). The experience of the operator and the quality of his team and his imaging technology are of paramount importance.

Emerging technology creates wholly new ethical problems (see Appendix 3). These problems pertain not only to the appropriate use of experimental medical devices, but also to a fair use of scarce resources. Our ageing society will be confronted with (far) more technology than she can afford, particularly for the increasing "markets" of elderly people – choices in health care should therefore be made transparent and debatable. We therefore suggest that, before introduction of a new emerging but still experimental technology where the benefits for the patient are not clear, the Belgian Advisory Committee on Bioethics (Raadgevend Comité voor Bio-ethiek van België/Comité Consultatif de Bioéthique de Belgique) should advise about the modalities of the implementation of such technology. The recommendations should assist politicians to make hard political choices that are ethically justified.

Patients are facing a bewildering choice of therapies. Particularly in carotid interventions, there is a conflict between high short term risks (death and stroke caused by the intervention) and high long term risks (death and stroke caused by abstinence of intervention). In appropriate indications, this balance is certainly in favour of an intervention. But as indications tend to get glide to lower long term risks among more elderly patients, the high short term risks of interventions may easily cause more strokes than they prevent. Patient preferences regarding risk behaviour are very different. For identical indications, the "gambler" may choose the high short term risk, "the risk averse" may choose the high long term risk. Gentle provoking of risk preferences should lead the patient to the therapy he prefers. Decisions should be shared, not imposed by one party.

Impartial patient information is in all conditions an ethical imperative, but how should this be organised? We suggest asking advice to the Belgian Advisory Committee on Bioethics, who can advice on the conditions, contents and organisation of informed consent for shared decision making, and the role the general practitioner has to play.

Key messages

- **The use of PCAS raises a number of ethical issues:**

  - Scarce resources are used for a technology that has not (yet) proven superiority relative to its alternative.

  - Improving knowledge about the effectiveness of PCAS requires experiments with human beings as subjects.

  - Patients and providers have unequal information about the risks of the procedure.

- **Informed consent from the patient is imperative when using PCAS.**

- **The Belgian Advisory Committee on Bioethics can advise how to organise the required informed consent procedure.**

10. PLANNING, IMPLEMENTATION, UTILIZATION AND LEGAL/REGULATORY ISSUES

Without follow-up of the outcomes, the health care system cannot learn from the experience of others. Actual patients may be harmed, future patients may not benefit from accrued knowledge. Chaotic introduction of emerging technologies is a marker of poor quality of care, and must be avoided. This asks for scientifically controlled experimenting of the medical society. From the regulating authorities, this asks for a more flexible response to emerging technologies, inclusive earmarking funds for researching the clinical effectiveness and cost-effectiveness of these technologies. Emerging technologies should only be introduced after a phase of carefully controlled experiments, either in randomised controlled trials (for comparative studies) or in observational registers and prospective cohort studies (for studies of feasibility). Use of emerging technologies with uncertain balances of harms and benefits outside controlled experiments are futile experiments with human beings. The increased funding in clinical research is a cost-effective investment in health, as it avoids both a waste of life and of money.

Introducing an emerging technology asks for careful and supervised experimentation. First, the technology should be made available for those patients who truly need it, and where there is no equipoise about appropriate use. These are only limited numbers of patients. Second, the technology could be made available to those centres of clinical excellence that wish to resolve the equipoise between the competing choices "CEA or PCAS". As long as PCAS is not "evidence based" superior to CEA, there can be no justified equipoise of "PCAS or watchful waiting". PCAS would be unjustified and unethical experimentation and a waste of health care resources (as PCAS is –at the same effectiveness- more expensive). In other words, there are few undebatable clinical indications for PCAS, and many open scientific issues. PCAS for undebatable indications should be made available in health care; PCAS for scientific use should be researched in clinical studies.

There are no data on the needs for PCAS in undebatable clinical indications. There is no clinical evidence that PCAS performs better than CEA in any indication. Lacking data and lacking evidence, a prudent approach suggests that the number of centres supported to do PCAS should be very limited.

The minimum is one. In Belgium, at least one centre should be allowed to offer PCAS in appropriate indications, covered by health care insurance. Indications exist, but are poorly specified and the real number of patients answering to these indications is unknown. This estimate is pending further empirical evidence. The involved medical groups (interventional radiology, vascular surgery, neurology) are invited to identify medical criteria for PCAS and numbers of patients answering to these.

The vast numbers of indications cover hypotheses of superiority of PCAS over CEA. However, these hypotheses are as yet unfounded in clinical evidence. Further research is needed, and should be defined as such. Experiments with PCAS outside clinical studies are unethical, as they offer increased risks to the patient without increased benefits to the future patients.

PCAS should therefore be limited to a few centres of excellence interested in engaging into medical research. The restriction of PCAS to a limited number of centres of excellence will be a major point of discussion in the Belgian health care system. The following arguments should be taken into consideration: the required skills, the need for multidisciplinary assessment of the appropriateness of an intervention, the clinical and technological environment of the centre, the estimated number of patients eligible for PCAS, the ethical obligation to participate in a trial and/or registry and the unknown volume-outcome relationship for carotid endovascular interventions.

The centres should possess a "vascular team". Treatment decisions should be taken and signed by the team in consensus, and after informed consent of the patient. The team involves at least a radiologist experienced in neuro-radiology, a vascular surgeon

experienced in carotid interventions, and a neurologist or internist-geriatrician. The team should be accredited by an experienced proctor, and should accept external auditing. Informed consent of the patient should stimulate a face to face dialogue of patient and GP. The patient should be clearly informed that the treatment is experimental, and should be clearly informed about the treatment choices.

The potential maximal number of centres participating in the RCT can be back-calculated. To maintain experience and best quality, an average of 25 interventions per year is a minimum. If 20% of all the CEA patients are recruited in the trial, the hospital needs to perform at least 125 CEA interventions a year in the past, or 625 interventions between 1999 and 2003. That is 3% of the national average. That should make more than five and less than ten eligible centres. Mortality in the better centres is 1.4%. In 625 interventions, 9 deaths are expected, with an upper 95% confidence limit of less than 15. To claim excellence, vascular centres need less 15 deaths in 625 patients.

These centres should be invited to participate to the ICSS trial and be audited by e.g. the international team of ICSS. The number of PCAS stents and protection devices should be discussed with the vascular team and can be purchased nationally by the RIZIV/INAMI.

At this moment no formal procedures exist for the selection of hospital services or hospitals as 'vascular centres'. Several strategies are available.

- Instauration of 'care programs' for vascular interventions. However, this is not well adapted to the rapidly changing and experimental nature of emerging technology, as it is asks for long discussions and changes within legislation.
- A RIZIV/INAMI convention with a predetermined limited number of vascular centres of excellence for which the funding is conditional upon participation in a large multi-centre trial and registry with long term follow-up and audit.
- Restrictive use of PCAS in a limited number of centres by physicians who satisfy a number of retrospective and prospective criteria and who participate in trials and registries. Financing occurs through a specific billing code for PCAS as experimental procedure. So far, the 'nomenclature' has not been used for this type of restrictive reimbursement of experimental technology, however, and it is likely to be more resistant to changes or abandonment.

The use of a RIZIV/INAMI convention looks the most appealing for this specific topic. We suggest a new type of convention, a "research convention" covering the phased introduction of emerging technologies by selected centres of excellence participating in international clinical research. Financing of these studies should be by a shared partnership of industry, government, health insurance and hospital or interventionist.

Finally, the question remains whether the use of emerging technology outside research conventions, at the cost of the patient, can be ethically justified. We will forward this question the Belgian Advisory Committee on Bioethics. After advice of the Belgian Advisory Committee on Bioethics, the chapters 7 and subsequent of this report will be updated in partnership with this committee. This research convention stops automatically when research needs stop, at the publication of the RCT results. Then this short report needs a full TA update, assessing the new situation.

Key messages

- PCAS should be made available to patients that are at high risk of stroke, but are poor candidates for surgery.
- Pending further evidence on patients satisfying these criteria (characteristics and numbers), one centre offering PCAS should be sufficient to cover the Belgian population.
- The experimental use of PCAS in other patients should be limited to ongoing randomized clinical trials comparing PCAS with CEA. The reasonable potential space in Belgium for centres participating in a trial on PCAS and CEA is between 5 and 10 centres.
- Experimentation with PCAS outside clinical trials is both ethically and economically hard to justify.
- Financing of participation in the trials should be a joint effort of the government, the hospital or interventionist and the industry. Investing in independent clinical research of promising technology likely saves money to the future society.

11. DISCUSSION AND CONCLUSIONS

First angioplasty, then angioplasty with stenting (CAS) and now stenting with embolic protection (PCAS) emerged as alternative interventions for open surgery. Until the introduction of embolic protection, carotid artery stenting seemed inferior to CEA. CAS was only an alternative for patients with a carotid artery stenosis, at very high risk of stroke and at very high risk of surgical complications when performing a CEA. Although no direct evidence is available, indirect evidence is sufficiently strong to support the conclusion that PCAS is superior to unprotected CAS. This brings PCAS forward as a potential alternative to CEA.

However, for the time being, evidence of the performance of PCAS over short term and long term is insufficient to make any other statement than that PCAS is a promising emerging technology, for the time being more expensive than CEA. The ongoing recruitment of patients in large randomised controlled trials promises that sufficient information will be available to support well informed decisions in 2007.

Both PCAS and CEA are interventions at high risk of stroke and death. For the time being, it is not clear why in Belgium so many CEA are performed. To improve clinical practice, evidence based guidelines for the use of carotid interventions would mean an important progress. The use of objective information about the risks and perils of alternative actions (watchful waiting, PCAS or CEA) would improve informed consent of the patient. In risk management, the use of absolute risk charts informs patients about their absolute risk of stroke or death within two and five years. The absolute risks of stroke or death of carotid interventions in Belgian hospitals could be extracted from the future carotid intervention register.

The economic literature review showed that CAS is, as yet, not cost-effective relative to CEA. The additional costs of CAS, mainly associated with the stents and cerebral protection devices, do not outweigh the short term savings associated with shorter length of stay nor the slightly fewer short term complications.

It is unlikely that these findings will be robust in the future and in different settings. Changes in outcomes and costs will inevitably occur if the technology becomes more widely used. CAS is an emerging technology and, as such, subject to rapid changes over time, both technically and operationally. Technical improvements are made by the manufacturer, based on early experiences with the technology. Operational changes occur at the operator table, as operators become more experienced with the procedure.

Both changes have implications for the effectiveness of the technology as well as its costs.

Published literature is usually based on clinical trials or observational studies in centres of clinical excellence. Surgeons in clinical trials are usually rigorously screened before they can participate in the trial and most often have a higher than average level of experience with the procedure. Besides selection of surgeons, patients are selected too for RCTs. Trial patients are generally not representative for the general patient population for whom the technology is likely to be used in the future. Once a technology becomes widely available without clear guidance or conditions for its use, the outcomes will deteriorate and costs increase.

Regulation of the diffusion of an emerging technology is necessary to avoid harm to patients and uncontrolled expenditures for a technology with unproven long term effectiveness.

In conclusion, carotid artery stenting is an extremely interesting subject for the study of an emerging new technology, as it has all the features of such technology in a most challenging way.

- Carotid artery stenosis is a frequent finding; stroke is a first order public health problem and a tragedy for the patient. Elderly will often fear a disabling stroke more than death.
- Any carotid intervention may decrease the risk of a stroke after a recently symptomatic stenosis, but at the prize of stroke or death caused by the intervention. In asymptomatic stenosis, the balance between harms and benefits becomes easily more negative.
- The very high rates of carotid interventions in Belgium need monitoring and auditing. The authors feel that this holds for all carotid interventions.
- For any carotid intervention, the skill of the interventionist (be it the surgeon or endovascular radiologist), the excellence of his team and the standards of his equipment are very important.
- In case of stenting, the importance of the standards of equipment holds for the used stenting procedures, too. The techniques evolved very rapidly, from angioplasty without stenting over angioplasty with stenting but without embolic protection, to angioplasty with stenting and embolic protection. That evolution made older techniques obsolete. The technology evolved more rapidly than the required time to set up studies, recruit patients and follow these up over a sufficiently long period. Evidence is to be stitched together, hoping that the stitching is valid. For the time being, there is indirect evidence that protected CAS is superior than CAS without embolic protection for the majority of patients tolerate the protection devices
- The endovascular procedure is very different from the traditional surgical technique. While vascular CEA is the traditional domain of the vascular surgeon, CAS is not. This is a potential source of conflicts between medical specialist professions. However, this conflict should be mitigated by shared decision making in multidisciplinary teams.
- Compared to the classical intervention, CEA, PCAS is expensive. The additional costs of device and protection are high and it is very unlikely that PCAS will be soon cost-effective, compared to CEA. In some conditions the patient is inoperable, PCAS is the only alternative and it seems acceptable to make PCAS available.

12. POLICY RECOMMENDATIONS

This report is a first report making recommendations for the prudent introduction of emergent experimental technology. It may serve as a first canvas for similar problems.

1. We recommend asking advice about the introduction of expensive emergent experimental technology to the Belgian Advisory Committee on Bioethics. As experimental technology in health care implies "hands on" experimentation on the patient population, ethical advice is no luxury item.
2. The patient needs to be clearly informed about the experimental nature of PCAS, and alternative choices. Such unpartial, transparent and intelligible information of the patient, nearly by definition an elderly person with vascular disease, is not evident. We recommend asking advice about the content and process of informed consent procedures to the Belgian Advisory Committee on Bioethics. In that advice, the role of the general practitioner as impartial and competent adviser should be specified.
3. We recommend against the uncontrolled introduction of PCAS. CEA is the treatment of choice. The effectiveness of PCAS is unknown; at equal effectiveness PCAS is still not cost-effective. To be an alternative, empirical evidence of superiority of PCAS is needed. Evidence of superiority or inferiority may be expected in 2007.
4. PCAS may be better then CEA if the patient is at high risk for surgical related complications (re-intervention, difficult location, a-specific non-atherosclerotic disease). However, strict indications are unknown, and it is unknown if PCAS performs better than CEA in these groups. Lacking clear indications, it is necessarily a small number. One Belgian centre would be sufficient to cover all unavoidably necessary PCAS. All PCAS outside RCT-protocols need to be entered in a prospective register.
5. PCAS is an experimental technology that may be a promising alternative for CEA. However, where PCAS is used as an alternative for CEA, its use is experimental and should be part of excellent experimental clinical research. We recommend a new type of convention that supports this type of experimental use of promising new technology.
6. Larger centres showing good outcomes should be invited to participate to large multi-centre trials comparing CEA to PCAS. The Belgian Advisory Committee on Bioethics will be asked to give advice if the use of experimental interventions outside excellent clinical research can find ethical justification.
7. Large centres with good outcomes are defined as having had 625 CEA the last five years, with less than 15 peri-procedurals deaths. Treatment decisions should be taken by vascular teams, consisting of at least one surgeon, radiologist or neurologist (or a geriatrician replacing the neurologist).
8. We recommend improved registration of all carotid interventions and their outcomes.
9. We recommend the development of evidence based guidelines for the treatment of carotid artery stenosis.
10. This report needs to be temporally updated after receiving advice of the Belgian Advisory Committee on Bioethics. This report needs to be updated after publication of the results of the major RCT comparing CEA to PCAS.

13. SUMMARY OF KEY MESSAGES AND POLICY RECOMMENDATIONS

13.1. KEY MESSAGES

13.1.1. Background

- Carotid stenosis is a consequence of atherosclerosis and an important, but not the sole risk factor for stroke.
- Male sex, old age and a family history or premature cardiovascular disease increase the risks of carotid stenosis and stroke but cannot be modified.
- Medical treatment of carotid stenosis is based on optimal cardiovascular risk factor management to lower the risk of stroke. Risks of stroke can be lowered by adequate blood pressure reduction, LDL-cholesterol reduction with statins, use of antithrombotic therapy in patients with atrial fibrillation and of antiplatelet therapy in patients with myocardial infarction (Evidence level 1)
- All smokers should receive the urgent advice to stop smoking, and help in doing so is to be offered (Evidence level 1 for prevention of stroke)

13.1.2. Research questions

- Is carotid artery stenting with embolic protection (PCAS) safer than CAS without embolic protection? Should PCAS be introduced in 2005 in Belgian health care? Under which conditions should PCAS be introduced?
- This assessment summarises the evidence of effectiveness and cost-effectiveness of carotid stents relative to endarterectomy in patients suitable for surgery.

13.1.3. Clinical effectiveness

- PCAS has lower peri-procedural rates of stroke and death than unprotected CAS (Evidence level 2). This statement is based on evidence of observational studies from heterogeneous sources and worldwide clinical expert consensus.
- There is no convincing evidence that PCAS is superior, inferior or non-inferior to CEA in well defined patient populations (absence of evidence).
- Four major randomised controlled trials (of which three cooperate) are recruiting symptomatic patients for PCAS. Introduction of PCAS in routine medical care must wait till final results are peer reviewed, published and found valid.
- No randomised trials are recruiting for asymptomatic patients. There is as yet no clinical equipoise of treatment of asymptomatic patients among opinion leaders.
- CEA is the standard of treatment of carotid artery stenosis in well defined populations at high risk for stroke. This holds particularly for older patients.
- Where CEA is no treatment option and the patient is at high risk of a stroke, PCAS may be a useful alternative treatment option. It is unkown if in these conditions, PCAS performs better.
- Asymptomatic patients with carotid stenosis are at lower risk of stroke, and hence at higher risks of harm by peri-operative morbidity. There are as yet no RCT trials recruiting for use of PCAS in asymptomatic patients. PCAS in asymptomatic patients should be discouraged.

13.1.4. Cost-effectiveness

- Studies from the USA found that initial hospital costs or charges for CAS (without cerebral protection) are higher than for CEA.
- To assess the relative cost-effectiveness of CAS, long-term effectiveness results are needed.
- At equal effectiveness, the additional costs of devices make PCAS less cost-effective compared to CEA. Stroke rate is the major determinant for the relative cost-effectiveness of PCAS.
- The further development of carotid stenting technology and (controlled) diffusion in clinical practice may change the costs and outcomes of the technology and the relative cost-effectiveness of the intervention.
- Issues of implementation on patient level
- Rates of carotid interventions in Belgium are extremely high, compared to the UK and the Netherlands, and very high compared to California, Ontario and New York.
- Patient preferences for PCAS or CEA cannot be established before more information on the long term outcomes of both procedures becomes available.
- Scarce resources are used for a technology that has not (yet) proven superiority relative to its alternative.
- Improving knowledge about the effectiveness of PCAS requires experiments with human beings as subjects.
- Patients and providers have unequal information about the risks of the procedure. Informed consent from the patient is imperative when using PCAS.
- The Belgian Advisory Committee on Bioethics can advise how to organise the required informed consent procedure.

13.1.5. Issues of implementation on societal level

- PCAS should be made available to patients that are at high risk of stroke, but are poor candidates for surgery.
- Pending further evidence on patients satisfying these criteria (characteristics and numbers), one centre offering PCAS should be sufficient to cover the Belgian population.
- The experimental use of PCAS in other patients should be limited to ongoing randomized clinical trials comparing PCAS with CEA. The reasonable potential space in Belgium for centres participating in a trial on PCAS and CEA is between 5 and 10 centres.
- Experimentation with PCAS outside clinical trials is both ethically and economically hard to justify.
- Financing of participation in the trials should be a joint effort of the government, the hospital or interventionist and the industry. Investing in independent clinical research of promising technology likely saves money to the future society.

14. REFERENCES

1. Straus SE, Majumdar SR, McAlister FA. New evidence for stroke prevention: scientific review. Jama. 2002;288(11):1388-95.
2. Amarenco P, Tonkin AM. Statins for stroke prevention: disappointment and hope. Circulation. 2004;109(23 Suppl 1):III44-9.
3. Cheung BM, Lauder IJ, Lau CP, Kumana CR. Meta-analysis of large randomized controlled trials to evaluate the impact of statins on cardiovascular outcomes. Br J Clin Pharmacol. 2004;57(5):640-51.
4. Doll R, Peto R, Boreham J, Sutherland I. Mortality in relation to smoking: 50 years' observations on male British doctors. Bmj. 2004;328(7455):1519.
5. Doll R, Hill AB. The mortality of doctors in relation to their smoking habits: a preliminary report. 1954. Bmj. 2004;328(7455):1529-33; discussion 1533.
6. Doll R, Peto R, Wheatley K, Gray R, Sutherland I. Mortality in relation to smoking: 40 years' observations on male British doctors. Bmj. 1994;309(6959):901-11.
7. Lightwood JM, Glantz SA. Short-term economic and health benefits of smoking cessation: myocardial infarction and stroke [see comments]. Circulation. 1997;96(4):1089-96.
8. Van Den Bruel A, Cleemput I, Van Linden A, Schoefs D, Ramaekers D, Bonneux L. Effectiveness and cost-effectiveness of smoking cessation strategies. Brussel: Belgian Health Care Knowledge Center; 2004. Available from:
9. O'Leary DH, Anderson KM, Wolf PA, Evans JC, Poehlman HW. Cholesterol and carotid atherosclerosis in older persons: the Framingham Study. Ann Epidemiol. 1992;2(1-2):147-53.
10. Anderson KM, Odell PM, Wilson PW, Kannel WB. Cardiovascular disease risk profiles. Am Heart J. 1991;121(1 Pt 2):293-8.
11. European Carotid Surgery Trialists Group. Randomised trial of endarterectomy for recently symptomatic carotid stenosis: final results of the MRC European Carotid Surgery Trial (ECST). Lancet. 1998;351(9113):1379-87.
12. 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. North American Symptomatic Carotid Endarterectomy Trial Collaborators. N Engl J Med. 1998;339(20):1415-25.
13. Taylor SM, Robison JG, Langan EM, 3rd, Crane MM. The pitfalls of establishing a statewide vascular registry: the South Carolina experience. Am Surg. 1999;65(6):513-8; discussion 518-9.
14. Bond R, Rerkasem K, Shearman CP, Rothwell PM. Time trends in the published risks of stroke and death due to endarterectomy for symptomatic carotid stenosis. Cerebrovasc Dis. 2004;18(1):37-46.
15. Barnett HJ, Meldrum HE, Eliasziw M. The appropriate use of carotid endarterectomy. Cmaj. 2002;166(9):1169-79.
16. Brown MM, Hacke W. Carotid artery stenting:the need for randomised trials. Cerebrovasc Dis. 2004;18(1):57-61.
17. Forrester JS, Topol EJ, Abele JE, Holmes DR, Jr., Skorton DJ. 28th Bethesda Conference. Task Force 5: Assessment, approval, and regulation of new technology. J Am Coll Cardiol. 1997;29(6):1171-9.
18. Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. Endarterectomy for asymptomatic carotid artery stenosis. JAMA. 1995;273(18):1421-8.
19. Halliday A, Mansfield A, Marro J, Peto C, Peto R, Potter J, et al. Prevention of disabling and fatal strokes by successful carotid endarterectomy in patients without recent neurological symptoms: randomised controlled trial. Lancet. 2004;363(9420):1491-502.

20. Rothwell PM, Eliasziw M, Gutnikov SA, Warlow CP, Barnett HJ. Endarterectomy for symptomatic carotid stenosis in relation to clinical subgroups and timing of surgery. Lancet. 2004;363(9413):915-24.
21. 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(9352):107-16.
22. Rothwell PM. External validity of randomised controlled trials: "to whom do the results of this trial apply?" Lancet. 2005;365(9453):82-93.
23. Rothwell PM, Mehta Z, Howard SC, Gutnikov SA, Warlow CP. Treating Individuals 3: From subgroups to individuals: general principles and the example of carotid endarterectomy. Lancet. 2005;365(9455):256-265.
24. Rothwell PM. Treating individuals 2. Subgroup analysis in randomised controlled trials: importance, indications, and interpretation. Lancet. 2005;365(9454):176-86.
25. Coward LJ, Featherstone RL, Brown MM. Percutaneous transluminal angioplasty and stenting for carotid artery stenosis. In; 2004.
26. Anonymous. Interventional procedures overview of carotid artery stent placement for carotid stenosis. 2004. Available from: http://www.nice.org.uk/pdf/ip/ip008overview.pdf
27. Mas JL, Chatellier G, Beyssen B. Carotid angioplasty and stenting with and without cerebral protection: clinical alert from the Endarterectomy Versus Angioplasty in Patients With Symptomatic Severe Carotid Stenosis (EVA-3S) trial. Stroke. 2004;35(1):e18-20.
28. 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(15):1493-501.
29. Becquemin J, El Kadi HB, Desgranges P, Kobeiter H. Carotid stenting versus carotid surgery: a prospective cohort study. Journal of Endovascular Therapy. 2003;10(4):687-94.
30. Hobson RW, 2nd, Howard VJ, Roubin GS, Brott TG, Ferguson RD, Popma JJ, et al. Carotid artery stenting is associated with increased complications in octogenarians: 30-day stroke and death rates in the CREST lead-in phase. Journal of Vascular Surgery. 2004;40(6):1106-11.
31. McKinlay S, White RA, Diethrich EB, Fogarty TJ, Zarins CK, Hopkins LN, et al. Carotid Revascularization Using Endarterectomy or Stenting Systems (CARESS): Phase I Clinical Trial. Journal of Endovascular Therapy. 2003;10(6):1021-1030.
32. Kastrup A, Schulz JB, Raygrotzki S, Groschel K, Ernemann U. Comparison of angioplasty and stenting with cerebral protection versus endarterectomy for treatment of internal carotid artery stenosis in elderly patients. Journal of Vascular Surgery. 2004;40(5):945-51.
33. Reimers B, Schluter M, Castriota F, Tubler T, Corvaja N, Cernetti C, et al. Routine use of cerebral protection during carotid artery stenting: results of a multicenter registry of 753 patients. Am J Med. 2004;116(4):217-22.
34. Wholey MH, Al-Mubarek N. Updated review of the global carotid artery stent registry. Catheter Cardiovasc Interv. 2003;60(2):259-66.
35. Kastrup A, Groschel K, Krapf H, Brehm BR, Dichgans J, Schulz JB. Early outcome of carotid angioplasty and stenting with and without cerebral protection devices: a systematic review of the literature. see comment . Review 71 refs. Stroke. 2003;34(3):813-9.
36. McKevitt FM, Macdonald S, Venables GS, Cleveland TJ, Gaines PA. Complications following carotid angioplasty and carotid stenting in patients with symptomatic carotid artery disease. Cerebrovasc Dis. 2004;17(1):28-34.
37. Zahn R, Mark B, Niedermaier N, Zeymer U, Limbourg P, Ischinger T, et al. Embolic protection devices for carotid artery stenting: better results than stenting without protection? Eur Heart J. 2004;25(17):1550-8.

38. Friedman HS, Eliasziw M, Barnett HJM, Killestein J, Tonarelli SB, Hart RG, et al. Carotid-Artery Stenting versus Endarterectomy. N Engl J Med. 2005;352(6):624-627.

39. CARESS steering committee. Carotid revascularization using endarterectomy or stenting systems (CARESS): phase I clinical trial. J Endovasc Ther. 2003;10(6):1021-30.

40. Featherstone RL, Brown MM, Coward LJ. International carotid stenting study: protocol for a randomised clinical trial comparing carotid stenting with endarterectomy in symptomatic carotid artery stenosis. Cerebrovasc Dis. 2004;18(1):69-74.

41. Ringleb PA, Kunze A, Allenberg JR, Hennerici MG, Jansen O, Maurer PC, et al. The Stent-Supported Percutaneous Angioplasty of the Carotid Artery vs. Endarterectomy Trial. Cerebrovascular-Diseases. 2004;18(1):66-68.

42. Hobson RW, 2nd. CREST (Carotid Revascularization Endarterectomy versus Stent Trial): background, design, and current status. Semin Vasc Surg. 2000;13(2):139-43.

43. Hobson RW, 2nd, Brott T, Ferguson R, Roubin G, Moore W, Kuntz R, et al. CREST: carotid revascularization endarterectomy versus stent trial. Cardiovasc Surg. 1997;5(5):457-8.

44. Rothwell PM. ACST: which subgroups will benefit most from carotid endarterectomy? Lancet. 2004;364(9440):1122-3; author reply 1125-6.

45. Rothwell PM. Effective stroke prevention in patients with symptomatic carotid stenosis. Cerebrovasc Dis. 2004;17 Suppl 1:89-104.

46. Friedmann PD, Brett AS, Mayo-Smith MF. Differences in generalists' and cardiologists' perceptions of cardiovascular risk and the outcomes of preventive therapy in cardiovascular disease. Ann Intern Med. 1996;124(4):414-21.

47. The CASANOVA Study Group. Carotid surgery versus medical therapy in asymptomatic carotid stenosis. Stroke. 1991;22(10):1229-35.

48. Mayo Asymptomatic Carotid Endarterectomy Study Group. Results of a randomized controlled trial of carotid endarterectomy for asymptomatic carotid stenosis. Mayo Clin Proc. 1992;67(6):513-8.

49. Hobson RW, 2nd, Weiss DG, Fields WS, Goldstone J, Moore WS, Towne JB, et al. Efficacy of carotid endarterectomy for asymptomatic carotid stenosis. The Veterans Affairs Cooperative Study Group. N Engl J Med. 1993;328(4):221-7.

50. Barnett HJ. Carotid endarterectomy. Lancet. 2004;363(9420):1486-7.

51. Wennberg DE, Lucas FL, Birkmeyer JD, Bredenberg CE, Fisher ES. Variation in carotid endarterectomy mortality in the Medicare population: trial hospitals, volume, and patient characteristics. Jama. 1998;279(16):1278-81.

52. Cebul RD, Snow RJ, Pine R, Hertzer NR, Norris DG. Indications, outcomes, and provider volumes for carotid endarterectomy. Jama. 1998;279(16):1282-7.

53. Kennedy J, Quan H, Ghali WA, Feasby TE. Variations in rates of appropriate and inappropriate carotid endarterectomy for stroke prevention in 4 Canadian provinces. Cmaj. 2004;171(5):455-9.

54. Drummond MF, Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. Bmj. 1996;313(7052):275-83.

55. Gray WA, White HJ, Jr., Barrett DM, Chandran G, Turner R, Reisman M. Carotid stenting and endarterectomy: a clinical and cost comparison of revascularization strategies. Stroke; a journal of cerebral circulation. 2002;33(4):1063-70.

56. Jordan WD, Roye GD, Fisher WS, III, Redden D, McDowell HA. A cost comparison of balloon angioplasty and stenting versus endarterectomy for the treatment of carotid artery stenosis. Journal of Vascular Surgery. 1998;27(1):16-22.

57. 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(6):1589-95.

58. 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(2):318-324.

59. Kilaru S, Korn P, Kasirajan K, Lee TY, Beavers FP, Lyon RT, et al. Is carotid angioplasty and stenting more cost effective than carotid endarterectomy? J Vasc Surg. 2003;37(2):331-9.

60. Calton WC, Jr., Franklin DP, Elmore JR, Han DC. Carotid endarterectomy: the financial impact of practice changes. J Vasc Surg. 2000;32(4):643-8.

61. Hodby D. Dollars and sense: the economics and outcomes of patients undergoing carotid endarterectomy at Royal Adelaide Hospital. J Vasc Nurs. 2002;20(1):6-11; quiz 12-3.

62. Theiss W, Hermanek P, Mathias K, Ahmadi R, Heuser L, Hoffmann FJ, et al. Pro-CAS: a prospective registry of carotid angioplasty and stenting. Stroke. 2004;35(9):2134-9.

63. Rothwell PM. Personal communication. In; 2005.

64. Blankensteijn JD. Vaatchirurgie terecht.: K.U. Nijmegen; July 2, 2004.

65. Tu JV, Hannan EL, Anderson GM, Iron K, Wu K, Vranizan K, et al. The fall and rise of carotid endarterectomy in the United States and Canada. N Engl J Med. 1998;339(20):1441-7.

66. Warren JA, Jordan WD, Jr., Heudebert GR, Whitley D, Wirthlin DJ. Determining patient preference for treatment of extracranial carotid artery stenosis: carotid angioplasty and stenting versus carotid endarterectomy. Ann Vasc Surg. 2003;17(1):15-21.

67. Banta HD, Luce BR. Health technology and it's assesment. Oxford: Oxford University Press; 1993.

15. APPENDICES

APPENDIX 1: LEVELS OF EVIDENCE

In Evidence Based Medicine, systems of levels of evidence and grades of recommendation have been developed. The intrinsically positivist inductive logic behind these systems is inconsistent with the modern philosophical concepts of deductive logic and Bayesian argumentation. Categorisation of evidence in levels is unscientific. The fallacy states that in order to be scientific we are forced to draw a definite line somewhere in an infinite series - ranging from the absolute black of clear wrong, through all possible gray shades of doubt, down to the absolute white of unmovable right - at the precise point where black changes to white and wrong changes to right. As the impossibility of this fallacy jumps up at every evaluation, the answer is a flight forward in always more complex systems, reiterating the fallacy of making categorical distinctions, now between infinite shades of grey.

The ranking of level of evidence according to study design is scientifically worse and ludicrous. It should be abandoned, as it discredits evidence based medicine as a logical mess. There are small case series that successfully ended a scientific debate and large randomised controlled trials that succeeded in confusing all the issues. Levels of evidence of effectiveness ought to include considerations of biological plausibility, consistency, strength of the measured effect, potential for bias and confounding, consensus or dissensus of opinion leaders. Study design is a very ancillary consideration, if it ought to be a consideration at all. The point is that randomised controlled trials are in general less liable to bias, not that RCT are a priori a superior design.

"Grades of recommendation" suggest that recommendations are to be made on a scientific basis. That posits the tyranny of the technocrat as a Platonic "Philosopher King". A recommendation is a policy advice that should include other considerations than mere scientific evidence of effectiveness, such as available human and financial resources, patient preference, ethical considerations of equity, and many more.

But, while linking "level of evidence" to a particular study design is invalid, we value the available empirical evidence supporting a statement differently depending on the context, the source of the study and the consistency of the findings. This valuing should be considered a pragmatic help for the reader to understand our personal and subjective assessment of the strength of the available evidence. For aiding the reader and for comparability, we took over the simple system used by the Wetenschappelijke Vereniging voor Vlaamse Huisartsen (WVVH) with some minor modifications (http://www.wvvh.be/files/niveaus_bewijskracht.pdf). The minor modifications stress the importance of ancillary evidence and supporting debate.

1. Convincing evidence from empirical studies. Evidence is considered convincing if it is collected in well designed studies, consistently reproduced and not highly debatable or debated.

   In the context of carotid artery interventions, a statement supported by evidence of level I is "CEA in patients with a recent cerebrovascular adverse event and a carotis stenosis of 70-99% (NASCET criteria) is effective." That finding is biological plausible, reproduced in major trials and supported by all editorials of all major scientific journals.

2. Debatable evidence from empirical studies. Evidence is considered debatable if it includes smaller studies, less quality, more heterogeneity in the results. RCT may be perfect, but the recruited population of either patients or doctors (in the case of interventions requiring considerable expertise) may not be representative of day-to-day practice. Experts disagree on the interpretation of the findings.

In the context of carotid artery interventions, a statement supported by evidence of level 2 is "CEA in patients without symptoms and a carotid stenosis of > 60% (NASCET criteria) may be effective." That finding is consistently reproduced in major trials but not widely supported as externally valid. As the risks of a stroke in the asymptomatic patient decrease sharply, the benefits of an intervention that can cause a stroke decrease. In day-to-day practice, selection of patients at even lower risks and lower quality of surgical outcome may reverse the balance and cause more harm than benefit.

3. Lack of convincing or debatable empirical evidence. Studies are poor, inconsistent or contradictory. However, expert consensus based on clinical experience and informed opinions tend to agree on the main conclusion.

   In the context of carotid artery interventions, a statement supported by evidence of level 3 is "PCAS is a treatment option in patients eligible for a CEA but at high risk for surgical morbidity." Available studies do suggest acceptable outcomes with PCAS, but it is not clear that PCAS is a safe alternative, if CEA is unsafe.

APPENDIX 2: LITERATURE SEARCH STRATEGIES

CLINICAL REVIEW

Literature search strategy

We performed an iterative literature search. First, systematic reviews and meta-analyses were searched. Second, we looked for original research published after the systematic reviews and meta-analyses.

We searched for systematic reviews and original research in the CRD database, Medline, Embase and Cinahl databases and in the Cochrane Library. In addition, the Controlled Trials Register was consulted to check for running or finalised RCTs. The search was performed on 10 January 2004.

In addition to a literature search in the different scientific literature databases, the different stakeholders, including manufacturers and patient groups, were contacted for additional information. External experts in the field of carotid stenting were consulted.

A Cochrane review was published in 2004, reviewing all randomised clinical trials up till 2003. Hence, we limited our search to articles published between January 2003 and 10 January 2005.

Limits:

Years: January 1998 – December 2004

Search strategy:

Medline (Ovid)

((exp endarterectomy, carotid/ or endarterectomy.tw) AND ((angioplasty adj2 stent$).tw. or stents/ae or (stent$.tw. and angioplasty.mp) or (stent$ adj3 endovascular).mp)) AND (carotid stenosis/su,th or carotid arteries/su or carotid artery diseases/su,th) OR (CAS adj5 CEA).mp OR (endarterectomy adj2 stent$).ti OR ((carotid adj2 stent$) and (carotid adj2 stenosis).ti) AND limit to yr=2003-2005

Filters were used to retain systematic reviews, meta-analyses and randomised clinical trials (Haynes).

Embase

Carotid artery obstruction (all subheadings) and endoprosthesis (all subheadings) and (clinical trial or longitudinal study or prospective study) or systematic review)

Selection criteria

Studies selected for review were randomized controlled trials (RCTs), prospective case series with at least 100 patients or large registries.

The population we focused on were symptomatic or asymptomatic patients with carotid stenosis at high or low risk for endarterectomy. The intervention of interest was carotid angioplasty with or without stenting and the relevant comparator was carotid endarterectomy or medical treatment. Medical treatment was used as a comparator for patients at high risk for endarterectomy.

The major outcomes of interest were: peri-procedure stroke and death, 30 day stroke (major/minor) and mortality, 1-year stroke (major/minor) and mortality, non-neurologic complications and re-stenosis.

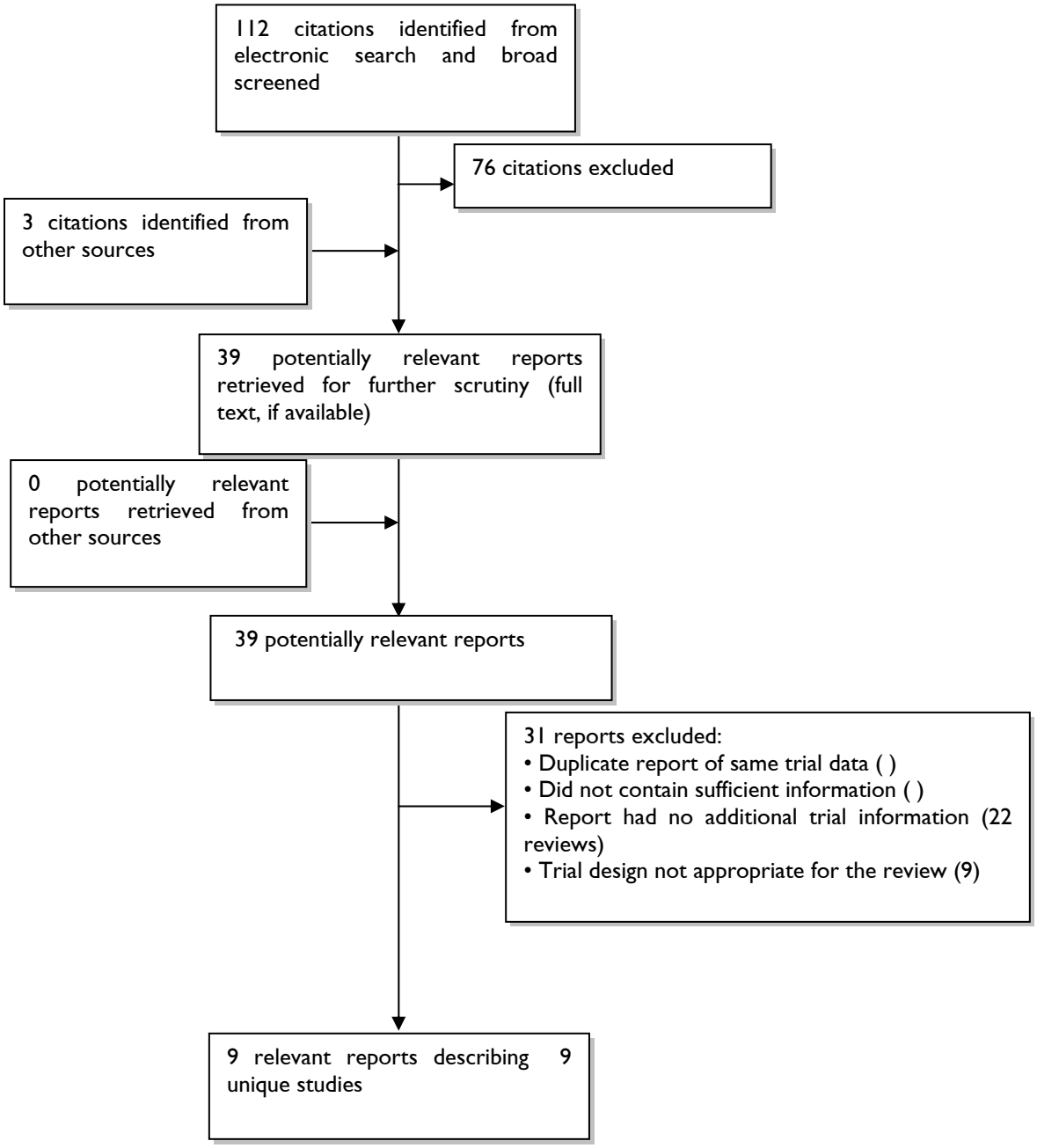
Anything that was not a clinical study of single first therapeutic interventions for stenotic lesions was excluded from the review as well as re-interventions, combinations

with coronary procedures, interventions for trauma and articles in other languages than English, Dutch, French or German.

Data extraction strategy

We used a structured form to extract the data. Information was captured about the study design, number and type of patients included, intervention, comparator, outcome variables and results.

Search results (flow diagram)



DATA EXTRACTION

Randomised controlled trials

<table>
<tr><th>Study details</th><th>Patients</th><th>Intervention/comparator</th><th>Outcomes</th></tr>
<tr><td>Mas 2004 (EVA-3S clinical alert)</td><td>Symptomatic patients >70% stenosis according to NASCET</td><td>- CAS without protection (n=15)
- CAS with protection (n=58)</td><td>Risk of any stroke within 30 days of unprotected CAS was about 3 times that of patients treated with cerebral protection (26.7% versus 8.6%): number needed to harm was 6.</td></tr>
<tr><td>Yadav 2004 SAPPHIRE</td><td>Symptomatic >50% diameter stenosis
Asymptomatic >80% diameter stenosis</td><td>Carotid stenting with protection device (n=167)
CEA (n=167)</td><td>Outcomes at 1 year:
<table>
<tr><th></th><th>CEA</th><th>Stenting</th><th>P-value</th></tr>
<tr><td>Death</td><td>13.5%</td><td>7.4%</td><td>0.08</td></tr>
<tr><td>Stroke</td><td>7.9%</td><td>6.2%</td><td>0.52</td></tr>
<tr><td>M.I.</td><td>7.5%</td><td>3.0%</td><td>0.03</td></tr>
<tr><td>Primary end point*</td><td>8.4%</td><td>5.5%</td><td>0.05</td></tr>
</table>
* death, stroke or M.I. at 30 days plus ipsilateral stroke or death from neurologic causes within 31 days to 1 year</td></tr>
<tr><td>McKevitt 2003</td><td>Symptomatic or asymptomatic patients, any degree of stenosis, suitable for both CEA and CAS</td><td>CEA (n=49)
Carotid angioplasty (n=31)
Self-expandable stent (n=11)
Balloon expandable stent (n=13)</td><td>The occurrence of episodes of hypotension or hypertension does not differ between CEA and CA, but the pattern of change in blood pressure is different. CEA: reduction in blood pressure at 1 hour, but then recovered quickly; by 1 month fall in blood pressure that was sustained at 6 months. CA: sustained fall in blood pressure in the immediate post-procedural period that recovered to pre-procedure levels by 1 month and was unchanged at 6 months.</td></tr>
</table>

Observational studies

<table>
<tr><th>Study details</th><th>Patients</th><th>Intervention/comparator</th><th>Outcomes</th><th>Comments</th></tr>
<tr><td>Becquemin 2003</td><td>Symptomatic >70% stenosis (n=182)
Asymptomatic >80% stenosis (n=273)
(total=455)</td><td>CAS with (n=46) or without embolic protection (n=68), of which 35 (32.7%) symptomatic
CEA (n=348), of which 147 (42.2%) symptomatic</td><td>30-day outcomes
<table>
<tr><th></th><th>CAS (n=114)</th><th>CEA (n=368)</th></tr>
<tr><td>TIA</td><td>4 (3.5%)</td><td>6 (1.6%)</td></tr>
<tr><td>Temporary minor stroke</td><td>5 (4.4%)</td><td>0</td></tr>
<tr><td>Persistent minor stroke</td><td>2 (1.8%)</td><td>1 (0.3%)</td></tr>
<tr><td>Major stroke</td><td>1 (0.9%)</td><td>0</td></tr>
<tr><td>Total neurological events</td><td>12 (10.5%)</td><td>7 (1.9%)</td></tr>
<tr><td>Deaths</td><td>0</td><td>3 (0.8%)</td></tr>
<tr><td>Total neuro events/deaths</td><td>12 (10.5%)</td><td>10 (2.7%)</td></tr>
<tr><td>Permanent neuro events/deaths</td><td>3 (2.6%)</td><td>4 (1.1%)</td></tr>
</table>
Overall neurological event rate for protected CAS: 6.5%
Overall neurological event rate for unprotected CAS: 13.2%
Follow-up data were presented but not useful due to large variation in length of follow up (1-68 months)</td><td>Years of inclusion: January 1995-2002
Minor stroke defined as neurological deficit that resolved completely within 30 days or increased NIH Stroke Scale by <4. Temporary minor stroke: symptoms last for <21 days. Permanent: symptoms last for >21 days.
Patients selected for CAS had a higher incidence of comorbid conditions, were more frequently asymptomatic.</td></tr>
</table>

<table>
<tr><th>Study details</th><th>Patients</th><th>Intervention/comparator</th><th>Outcomes</th><th>Comments</th></tr>
<tr><td>Hobson 2004
Lead-in phase analysis CREST</td><td>Symptomatic >50% stenosis (n=230)
Asymptomatic >70% stenosis (n=519)</td><td>CAS with embolic protection in octogenarians
CAS with embolic protection in non-octogenarians</td><td>30-day stroke and death
<table>
<tr><th>Age</th><th>N</th><th>Events N (%)</th><th>Odds ratio (95% CI)</th></tr>
<tr><td><60</td><td>120</td><td>2 (1.7%)</td><td>1.0 (ref)</td></tr>
<tr><td>60-69</td><td>229</td><td>3 (1.3%)</td><td>0.78 (0.13-4.75)</td></tr>
<tr><td>70-79</td><td>301</td><td>16 (5.3%)</td><td>3.31 (0.75-14.63)</td></tr>
<tr><td>80+</td><td>99</td><td>12 (12.1%)</td><td>8.14 (1.78-37.30)</td></tr>
</table>
Conclusion: Octogenarians should be considered high-risk patients for CAS stenting.</td><td>Adjustment of Odds ratios for symptomatic status, use of protection device, gender and percent stenosis did not change the conclusion.</td></tr>
<tr><td>Kastrup 2004</td><td>Elderly patients (>75 years)
Symptomatic
Asymptomatic</td><td>CAS with embolic protection (n=53 of which 57% symptomatic)
CEA (n=110 of which 63% symptomatic)</td><td>30 day outcomes
<table>
<tr><th></th><th>CEA</th><th>Stenting</th></tr>
<tr><td>Death</td><td>0</td><td>0</td></tr>
<tr><td>Minor stroke</td><td>0</td><td>7.5%</td></tr>
<tr><td>Major stroke</td><td>1.8%</td><td>3.8%</td></tr>
<tr><td>All Stroke</td><td>1.8%</td><td>11.3%</td></tr>
</table>
Conclusion: complication rates associated with CAS are significantly higher than with CEA in patients 75 years of age or older.</td><td>Data for CAS gathered prospectively. Data for CEA obtained retrospectively.</td></tr>
<tr><td>McKinlay 2003
CARESS</td><td>Symptomatic >50% stenosis (n=127)
Asymptomatic >75% stenosis (n=270)</td><td>- CAS with embolic protection (n=143 of which 30.8% symptomatic)
- CEA (n=254 of which 32.7% symptomatic)</td><td>30 day outcomes
<table>
<tr><th></th><th>CEA</th><th>Stenting</th></tr>
<tr><td>Death</td><td>0.4%</td><td>0%</td></tr>
<tr><td>Stroke</td><td>2.4%</td><td>2.1%</td></tr>
<tr><td>Combined stroke+death</td><td>2.4%</td><td>2.1%</td></tr>
</table></td><td>Prospective non-randomised trial</td></tr>
</table>

Registries

<table>
<tr><th>Study details</th><th>Patients</th><th>Intervention/comparator</th><th>Outcomes</th><th>Comments</th></tr>
<tr><td>Wholey 2003</td><td>N=11,243
Symptomatic patients (53.2%)
Asymptomatic patients (46.8%)</td><td>- CAS without embolic protection (60%)
- CAS with embolic protection</td><td>30 day event rate (see separate table below)
12-24-36-48 months after stent placement:
<table>
<tr><th></th><th>Restenosis >50%</th><th>Ipsilateral neurologic events (incl. TIAs, major and minor strokes and deaths)</th></tr>
<tr><td>12 months FU</td><td>2.7%</td><td>1.2%</td></tr>
<tr><td>24 months FU</td><td>2.6%</td><td>1.3%</td></tr>
<tr><td>36 months FU</td><td>2.4%</td><td>1.7%</td></tr>
<tr><td>48 months FU</td><td>5.6%</td><td>4.5%</td></tr>
</table></td><td></td></tr>
<tr><td>Reimers 2004</td><td></td><td>Carotid artery stenting with protection device (n=815 lesions in 753 consecutive patients; >70% diameter stenosis)</td><td>Procedural success protection device: 98%
Procedural success stent: 99%
Outcomes within 30 days:
TIA: 2.7%
Minor stroke: 2%
Major non-fatal stroke: 0.7%
Major fatal stroke: 0.1%
Deaths: 0.5%
Fatal M.I.: 0.4%
Nonfatal M.I.: 0.4%</td><td>Only about one quarter of the lesions were associated with neurologic symptoms within 6 months before the procedure</td></tr>
</table>

Wholey 2003

	N (%)	Symptomatic patients (n=6,392)	Asymptomatic patients (n=4,581)	Unprotected CAS (n=6,753)	Protected CAS (n=4,221)
TIA	381 (3.07%)				
Minor stroke	265 (2.14%)	2.53%	1.66%	2.86%	1.08%
Major stroke	149 (1.20%)	1.56%	0.87%	1.61%	0.72%
Procedure related death	79 (0.64%)	0.85%	0.42%	0.81%	0.43%
Stroke+procedure related death	493 (3.98%)	4.94%	2.95%	5.29%	2.23%
Total stroke+death	589 (4.75%)				

CHARACTERISTICS OF A FINISHED RANDOMISED CONTROLLED TRIAL

SAPPHIRE

Patients included

29% symptoms and > 50% stenosis

71% asymptomatic and > 80% stenosis

Mean age 72.5

Surgeons included

Range of experience between 20-700 interventions

Previous complication rate (stroke and death) < 6%

Exclusions, loss fo fu, total allocated

747 patients recruited, 334 randomised for CAS or CEAE, 406 referred for CAS, 7 referred for CEAE. 159/167 received CAS, 151/167 received CEAE (difference explained by withdrawal of consent

"Redo intervention" after previous intervention was NOT a reason to be excluded from CEAE and sent to register.

Considerable imbalances between allocated groups, with more CHD patients in CAS-group, but more patients with MI

Intervention

Techniques used

Aspirine 81mgr/325 mgr and heparine (all), clopidogrel (stent)

Stent with embolic protection (CORDIS)

Comparator

Surgical outcome related to trials (NASCET, ECST) and non trial hospitals

Outcome

Ascertainment

30 day, 6 month and 12 month..Not blinded.

Primary endpoint stoke, death or MI after 30 day, death or stroke after 1 year

Stroke defined as ischemic neurologic deficit > 24 h

MI: defined as increase of creatinine kinase higher than two times the upper limit with a positive MB fraction

Conventional endpoints:

stroke or death within 1 year: 9/167 (5.5%) (CAS) versus 13/167 (8.4%) (CEA) intention to treat.

stroke or death within 1 year: 8/159 (5.1%) (CAS) versus 11/151 (7.5%) (CEA) actually treated.

Conflict of interest: trial funded by Cordis, First author is inventor of Angiocard protection device and shareholder of angiocard.

Comments

High exclusion rates suggest bias for CAS.

Inclusion of > 20% 'redo' interventions is strange, compared to the over all > 50% exclusion rate. As there is less clinical equipoise about 'redo' interventions as indication for CAS, this flaws the trial.

Power is too small to make conclusions.

Inclusion of MI as primary endpoint is unusual. Such high rates of complications might make medical treatment and watchful waiting a more attractive option.

High conflicts of interest, severe bias in favour of CAS and low power to detect meaningful differences endangers interpretation of this trial.

CHARACTERISTICS OF ONGOING RANDOMISED CONTROLLED TRIALS

EVA-3S

Design

RCT

Patients included

Symptomatic patients: TIA or non-disabling stroke within 4 months before randomisation.

Degree of stenosis: >60% according to the NASCET method.

Surgeons and interventionalists included

Surgeon: required experience at least 25 interventions

Interventionalist: at least 12 cases of CAS or 5 cases of CAS and 30 cases of endovascular treatment of other supra-aortic trunks

Sample size

Envisaged number of patients: 900. In April 2004; 300 patients were included.

Intervention

Techniques used

Aspirin (100-300 mg) and clopidogrel (75 mg) or ticlopidine (500 mg) for at least

Stent with embolic protection since January 2003

Comparator

Carotid endarterectomy performed using standard operative techniques.

Outcome

Ascertainment

30 day, 6 months, and every 6 months thereafter for 2-4 years

Primary endpoint:

within 30 days: (a) any stroke or death, (b) any stroke of death

during follow-up: ipsilateral stroke

Major stroke defined as a stroke that increases the modified Rankin scale score to 3 or more, 1 month after the event

Secondary endpoints:

Within 30 days (a) MI, TIA, loco-regional complications (e.g. cranial nerve palsy or complications at the site of punction) or general complications; (b) any disabling stroke or death, any stroke or death

During follow-up: disabling or fatal ipsilateral stroke, any stroke, TIA

2 years after the procedure: carotid re-stenosis

Comments

Clinical alert on CAS with and without cerebral protection published in 2004 (EVA-3S, Stroke 35:e18-e21):

Population

80 patients randomised to CAS, 73 treated with CAS

58 (79.5%) with cerebral protection

100% symptomatic, severe (>70% stenosis according to NASCET)

Results

Risk of any stroke within 30 days of unprotected CAS was about 3 times that of patients treated with cerebral protection (26.7% versus 8.6%): number needed to harm was 6.

ICSS

Design

RCT

Patients included

Symptomatic patients with >50% stenosis according to NASCET method, >40 years of age.

Surgeons and interventionalists included

Surgeon: required experience at least 50 carotid interventions, with annual rate of at least 10 cases per year.

Radiologists: at least 50 stenting procedures, of which at least 10 in the carotid artery.

Both surgeons and radiologists are expected to show a stroke and death rate within 30 days of 6% or less.

Sample size

Envisaged number of patients by the end of 2007: 1,500.

Intervention

Techniques used

Aspirin + clopidogrel recommended. Intraprocedural heparin mandatory

Stent with embolic protection whenever the operator thinks one can be safely deployed

Comparator

Carotid endarterectomy performed using operative procedures that are standard in the centre.

Outcome

Ascertainment

30 day, 6 months after randomisation, annually up to 5 years after randomisation.

any stroke or death, TIA, MI, cranial nerve palsy, transient monocular blindness, haematoma, disabling outcome events, recovered stroke.

Comments

Conflict of interest: ICSS has been funded by grants from the Stroke Association, Sanofi-Synthelabo and the European Commission.

CREST

Design

RCT

Patients included

Symptomatic patients with >50% stenosis.

Surgeons and radiologists included

Surgeon: >20 CAS procedures. 30-day stroke and death rate in last 10 to 30 CAS procedures should be below 6% to 8%.

Sample size

Envisaged number of patients by the end of 2007: 2,500.

Intervention

Techniques used

CAS with cerebral protection (ACCULINK carotid stent system and ACCUNET embolic protection system); cerebral protection since September 2001.

Comparator

Carotid endarterectomy

Outcome

Ascertainment

Stroke, MI, death within 30 days.

Ipsilateral stroke during follow-up.

Comments

Analysis of the data resulting from the lead-in phase of CREST showed that vascular surgeons with basic catheter and guidewire skills can be credentialed to perform CAS.

Included credentialed interventionalists: vascular surgeons (22), neurosurgeons (10), cardiologists (52), interventional neuroradiologists (31), interventional radiologists (15) and neurologists (4).

Vascular surgeons have performed 131 of 789 lead-in procedures.

Outcome: 30-day stroke and death for vascular surgeons and neurosurgeons: 5.3%; 30-day stroke and death for all other specialists: 4.4%

SPACE

Design

RCT

Patients included

Symptomatic patients with >50% stenosis according to the NASCET method.

Surgeons and interventionalists included

Neurologists, vascular surgeons and interventionalists must demonstrate their expertise. Requirements not specified.

Sample size

Envisaged number of patients by the end of 2007: 1,900. Up to 18 february 2004, 667 patients have been recruited.

Intervention

Techniques used

CAS with or without protection. Only requirement: stent systems must have CE certification.

Outcome

Ascertainment

30 days, 6 months, 12 months, 24 months.

- stroke and death

- restenosis >70% (equivalent to >50% according to NASCET method) after 6, 12 and 24 months

- procedural technical failure

Comments

Study financially supported by two companies, the German Research Foundation and the Federal Ministry of Education and Research.

ECONOMIC REVIEW

LITERATURE SEARCH STRATEGY

The following databases were searched: Medline, Cochrane Library, Embase, CRD (DARE, NHS EED, HTA), CINAHL. The keywords "carotid" and "stenosis" and "stent*" were used in combination with the keyword "cost*" or "economic*". For Medline, Cinahl and Embase, the thesaurus was used to retrieve the relevant subject headings. The search was limited to papers published between January 1998 and December 2004. Articles written in English, Dutch, French or German were considered for review.

Limits:

Years: January 1998 - December 2004

Search strategy:

Medline (PubMed)

Carotid stenosis (MeSH) and Stents (MeSH) and Economics

Embase

Carotid artery obstruction (all subheadings) and endoprosthesis (all subheadings) and economic aspect (all subheadings)

Cinahl

Carotid stenosis and stents and (economics or (costs and cost analysis))

CRD

Carotid stenosis and cost and stents

Cochrane Library

Carotid stenosis and stent$ and (econom$ or cost$)

SELECTION CRITERIA

A first selection of articles was done on the basis of the abstracts. Studies that did not have economic evaluation or cost evaluation as their main objective or one of their main objectives were excluded. Full economic evaluations as well as partial evaluation (cost descriptions, cost-outcome descriptions, cost analyses) were retained as appropriate study designs.(definitions according Drummond et al.[16] Only studies that compared carotid stenting with carotid endarterectomy were included in the review. No restrictions were placed on the characteristics of the patient population studied.

DATA EXTRACTION/ABSTRACTION STRATEGY

A structured form was developed, including information on the year of data collection, design, patient population, measure of costs or proxies for costs, effectiveness measure and results. The results of the studies were extracted in a separate tabulated form, differentiating between CAS and CEAE and including the following outcome parameters: length of stay, costs and effectiveness. Data extraction was done by one reviewer.

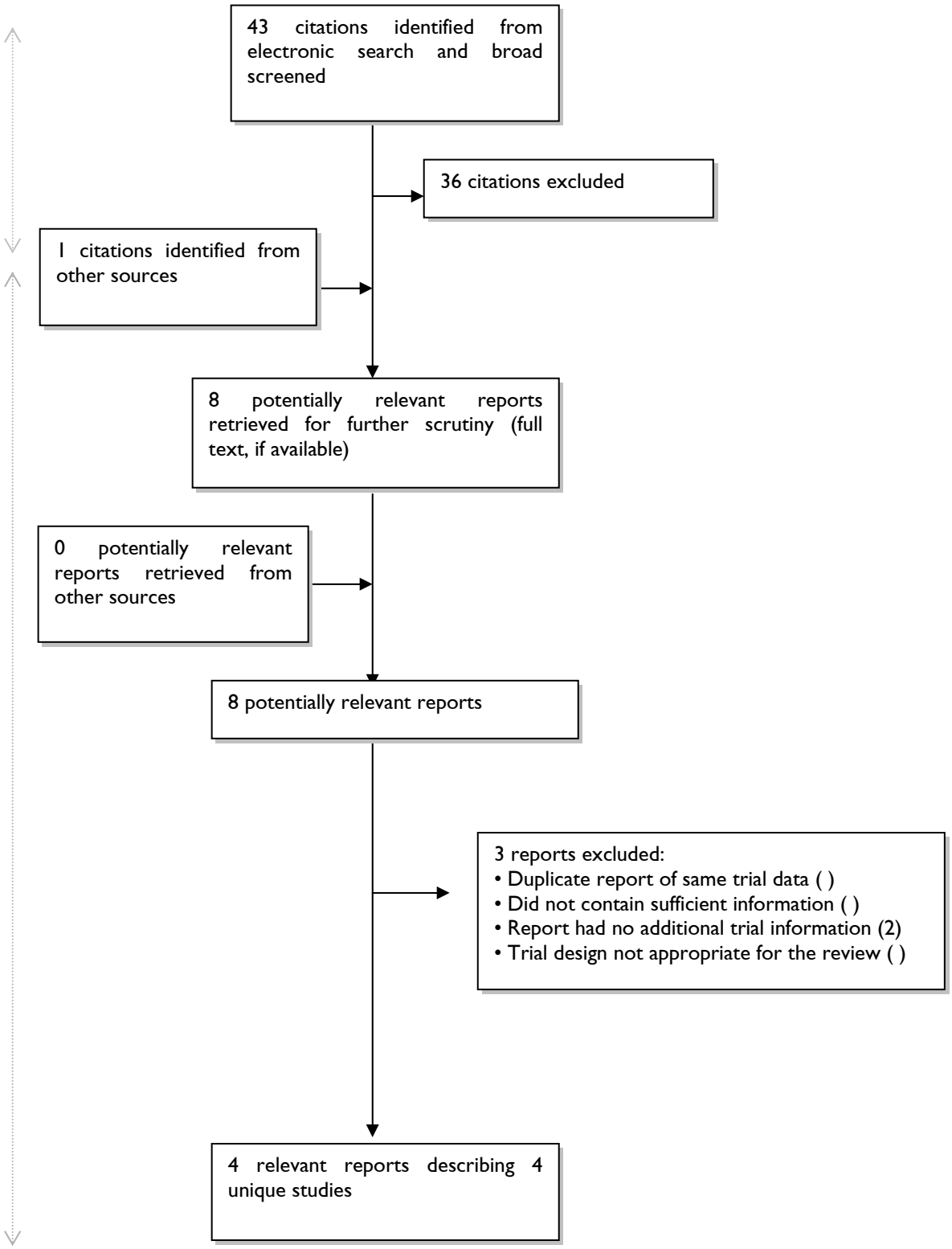
STRATEGY FOR QUALITY ASSESSMENT OF THE STUDIES

Quality assessment was done on the basis of a quality assessment checklist.[17] As there is currently no scoring system available for economic studies, the quality of the studies could only be presented in a decomposed way.

DATA ANALYSIS METHODS

The results of the study were summarized in a table. We performed a narrative review of the included studies.

Flow diagram



Data extraction sheet Economic studies

STUDY IDENTIFIER		
Author, year		
Journal		
Design	☐	cost description
	☐	cost-outcome description
	☐	cost analysis
	☐	cost minimisation analysis
	☐	cost-effectiveness (-benefit, -utility) analysis
Method	☐	Observational data
	☐	Model
	☐	Simulation
Year of data collection		
Currency year		
Population	☐	symtomatic
	☐	asymptomatic
	☐	suitable for surgery
	☐	not suitable for surgery
Intervention	☐	carotid angioplasty
	☐	carotid stenting without protection
	☐	carotid stenting with protection
Comparison	☐	carotid endarterectomy
	☐	medical treatment
Outcomes		
Clinical	☐	in-hospital outcomes
	☐	30 day outcomes
	☐	long term outcomes
	☐	non-disabling stroke
	☐	disabling stroke
	☐	fatal stroke
	☐	all stroke
	☐	death
	☐	stroke+death combined
	☐	nonneurologic complications
Economic	☐	hospital costs
	☐	costs (all)
	☐	hospital charges
	☐	charges (all)
	☐	length of stay
	☐	cost-effectiveness

Quality assessment economic studies

	Brooks et al. 2004	Brooks et al. 2001	Gray et al. 2002	Jordan et al. 1998	Kilaru et al. 2003
Study design					
The research question is stated	Y	Y	Y	Y	Y
The economic importance of the research question is stated	Y	Y	Y	Y	Y
The viewpoints of the analysis are clearly stated and justified	N	N	N	N	N
The rationale for choosing the alternative programmes or interventions compared is stated	Y	Y	Y	Y	Y
The alternatives being compared are clearly described	Y	Y	Y	Y	Y
The form of economic evaluation used is stated	N	N	N	N	Y
The choice of form of economic evaluation is justified in relation to the questions addressed	N	N	N	N	Y
Data collection					
The sources of effectiveness estimates used are stated	Y	Y	Y	Y	Y
Details of the design and results of effectiveness study are given (if based on a single study)	Y	Y	Y	Y	Y
Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)	NA	NA	NA	NA	N
The primary outcome measure(s) for the economic evaluation are clearly stated	Y	Y	Y	Y	Y
Methods to value health states and other benefits are stated	Y	Y	Y	Y	Y
Details of the subjects from whom valuations were obtained are given	Y	Y	Y	Y	N
Productivity changes (if included) are reported separately	Y	Y	NA	NA	NA
The relevance of productivity changes to the study question is discussed	Y	Y	NA	NA	NA
Quantities of resources are reported separately from their unit costs	N	N	N	N	Y
Methods for the estimation of quantities and unit costs are described	Y	Y	Y	Y	Y
Currency and price data are recorded	N	N	N	N	Y
Details of currency or price adjustments for inflation or currency conversion are given	N	N	N	N	N
Details of any model used are given	NA	NA	NA	NA	N
The choice of model used and the key parameters on which it is based are justified	NA	NA	NA	NA	Y

	Brooks et al. 2004	Brooks et al. 2001	Gray et al. 2002	Jordan et al. 1998	Kilaru et al. 2003
Analysis and interpretation of results					
Time horizon of costs and benefits is stated	Y	Y	Y	Y	Y
The discount rate(s) is stated	NA	NA	NA	NA	Y
The choice of rate(s) is justified	NA	NA	NA	NA	Y
An explanation is given if costs or benefits are not discounted	N	N	N	N	NA
Details of statistical tests and confidence intervals are given for stochastic data	Y	Y	Y	N	N
The approach to sensitivity analysis is given	NA	NA	NA	NA	Y
The choice of variables for sensitivity analysis is justified	NA	NA	NA	NA	Y
The ranges over which the variables are varied are stated	NA	NA	NA	NA	Y
Relevant alternatives are compared	Y	Y	Y	Y	Y
Incremental analysis is reported	N	N	N	N	Y
Major outcomes are presented in a disaggregated as well as aggregated form	N	N	Y	N	N
The answer to the study question is given	Y	Y	Y	Y	Y
Concusions follow from the data reported	Y	Y	Y	Y	Y
Conclusions are accompanied by the appropriate caveats	Y	Y	Y	N	N

NA=Not applicable

Characteristics and results of reviewed economic studies

	Brooks et al. 2004	Brooks et al. 2001	Gray et al. 2002	Jordan et al. 1998	Kilaru et al. 2003
Design	**Cost-outcome description**	**Cost-outcome description**	**Cost-outcome description**	**Cost-outcome description**	**Cost-effectiveness analysis**
Method	Observational data from prospective RCT	Observational data from prospective RCT	Observational data	Observational data	Markov model
Year of data collection	Not specified	Not specified	1996-1997	1994-1995	1997
Currency year	Not specified	Not specified	1997	1995	1997
Population	Asymptomatic patients Suitable for surgery	Symptomatic patients Suitable for surgery	all patients with carotid stenosis >60% symptomatic/asymptomatic suitable for surgery/not suitable for surgery	all patients referred to CAS or CEA, no randomisation symptomatic/asymptomatic suitable for surgery/not suitable for surgery	hypothetical cohort of 70-year old patients with carotid
Intervention	CAS without distal protection	CAS without distal protection	CAS without distal protection	symptomatic/asymptomatic suitable for surgery/not suitable for surgery	
Comparison	CEA	CEA	CEA	CEA	CEA
Clinical outcomes	in-hospital outcomes major stroke minor stroke death Non-neurologic complications	in-hospital outcomes major stroke minor stroke death non-neurologic complications	in-hospital outcomes major stroke minor stroke death non-neurologic complications	in-hospital outcomes major stroke minor stroke death non-neurologic complications	QALYs
	hospital costs hospital charges length of stay return to full activity	hospital costs hospital charges length of stay return to full activity	hospital costs length of stay	hospital charges length of stay	lifetime costs

Study	Cost ($)			Length of stay (days)			Outcome			Cost-effectiveness ratio
		CEA	CAS		CEA	CAS		CEA	CAS	CAS relative to CEA
Jordan et al. 1998	Hospitalisation:	21 670	30 140	Mean:	3,1	2,9	Stroke (all):	3,10%	7,70%	
				Median:	3	2	Death:	1,50%	0,90%	
Kilaru et al. 2003	Procedure:	7 871	10 133	Mean:	?	1,9	QALYs:	8,36	8,2	CEAE dominates CAS in base-case analysis
	Lifetime:	28 772	35 789				Stroke (all):	0,90%	5%	
							Death:	0%	1,2%	
Brooks et al. 2001	Variable cost#:	3 415	4 077	Mean (all):	3,7	5,2	Stroke:	0%	0%	
	Patient charges:	5 594	6 653	Mean (without complications):	2,7	1,8	Death:	1,90%	0%	
Gray et al. 2002	Hospitalisation:	5 409	3 417	Mean:	3	1,4	Major stroke:	1,50%	0%	
	Procedure:	2 542	2 862	Median:	2	1	Minor stroke:	2,20%	3,6%	
							Death:	1,50%	0%	
Broosk et al. 2004	Variable cost#:	3 600	3 600	Mean (all):	1,7	1,5	Stroke:	0%	0%	
	Patient charges:	5 371	6 447	Mean (without complications):	1,2	1,1	Death:	0%	0%	

* ICER=Incremental Cost-Effectiveness Ratio
# Variable cost=actual hospital expenditure

APPENDIX 3: ETHICAL CONSIDERATIONS IN THE ASSESSMENT OF EMERGING HEALTH TECHNOLOGY

Ethical issues in the diffusion and implementation of new or emerging medical technology have, up till now, not systematically been included in the health care policy making process. Only for specific, heavily morally loaded technologies, such as IVF, ethical discussions have taken place in the context of policy making. In general, ethical considerations are only raised when a technology is already close to implementation.

The problem with emerging technologies is that the evidence base is still very poor or non-existing. Ethical issues already arise before the technology is ready for diffusion. The problems we will discuss here are different from the ethical issues raised in the context of clinical trials. We will discuss the ethical problems on the level of policy making. Ethical dilemmas faced by policy makers and stakeholders relate to the diffusion of emerging technology with unproven effectiveness, the appropriateness of public financing of studies of emerging technologies and clinical freedom.

Diffusion of a technology with lack of evidence

Even though the evidence base for emerging technologies is weak or non-existing, policy makers are often confronted with a threatening uncontrolled diffusion of such technology.

The debate on the acceptability of the diffusion of an emerging medical technology depends first on whether there are reasonable expectations of superior benefits of the new technology relative to an alternative (e.g. on the basis of RCTs). If the risks and benefits are uncertain and there is clinical equipoise, case studies can be performed in patients for whom no alternative treatment exists. The crucial ethical element is "adequate" information and patients' informed consent for being subject to an experimental intervention. Patients should be fully informed about the uncertainty surrounding the technology.

Second, the full implications of the diffusion of an emerging and still experimental technology should be assessed in an HTA. An HTA can serve the health care policy making process by showing the clinical, economic, social and organisational consequences of a technology. An ethical committee, for example the Raadgevend Comité voor Bio-ethiek or another competent organ, should review the HTA report and assess the ethical justification of the recommendations. Any subsequent decision about the reimbursement and associated accreditation criteria for centres and interventionists should be in line with the advice of the ethical committee to be ethically justified. More transparency and independency from direct stakeholders is a key issue in all decision making processes. The further follow-up and evaluation of the effectiveness of the emerging technology should be publicly available.

Third, the application of an emerging technology should be subject to accreditation of centres and interventionists. Interventionists who perform the procedure without formal accreditation should be sanctioned. It is ethically not defendable to allow uncontrolled diffusion, as this will influence patients' outcomes. Moreover, uncontrolled diffusion precludes collection of data needed to evaluate the effectiveness of the technology.

Public financing of research

The appropriateness of public financing of research for emerging technologies depends on (1) the relative importance of the expected benefits of the technology and (2) the availability of alternative sources of financing.

Health is not only an individual, but also a public, a collective good. This raises particular equity concerns. The relative importance of the expected benefits is one element in the decision making process for the investment in research on emerging technology. Investments in research must be weighted against alternative uses of scarce health care resources. This is obviously a very difficult exercise as it involves the weighting of preferences for clinical, economic and societal outcomes of a diversity of established and emerging technologies. Nevertheless, it is better to be explicit about these choices than to be implicit. Transparency of the decision making process is crucial for the ethical justification of the decision. The general public should be informed about the elements that are taken into account in the decision making process and about the concerns that were raised.

This does not mean that health policy makers should limit technological innovations in situations of limited public money. When alternative sources of financing are available, public financing may not be needed. This does not imply, however, that there should be no control and restrictions on the use of the technology. Uncontrolled diffusion leads to worse outcomes and is not to the best interest of the patient. Access to the experimental technology is not the main ethical issue at this stage, but rather ensuring the quality of care to patients who participate in clinical trials.

Therapeutic freedom

Therapeutic freedom can be defended as long as it is used to serve the best interest of the individual patient. From a policy point of view, collective interests must be pursued. This can often only be obtained by limiting the therapeutic freedom of individual providers. Unlimited therapeutic freedom contrasts sharply with efficient allocation of scarce resources in health care. Therefore, therapeutic freedom is no argument for the uncontrolled diffusion of emerging technologies that have not yet proven their effectiveness.

A final point of discussion is the weighting of different perspectives in HTA. Patients, providers, policy makers and the general public may have different viewpoints regarding a technology, its usefulness, importance and its desired implementation strategy. An HTA report should clarify the different perspectives. Participation of patient groups in the HTA process is considered problematic in Belgium. Unlike many other countries, Belgium does not have a tradition of a pluralistic patient organisation that can represent the patient perspective in HTA. Time-consuming participative HTA, is one (out of other ways) to incorporate the patient perspective in a systematic way.

Although the final decision on an emerging technology will be political, it should at least be an informed decision.

This page is left intentionaly blank.

Wettelijk depot : D/2005/10.273/09

KCE reports

1. Effectiviteit en kosten-effectiviteit van behandelingen voor rookstop. D/2004/10.273/1.
2. Studie naar de mogelijke kosten van een eventuele wijziging van de rechtsregels inzake medische aansprakelijkheid (fase 1). D/2004/10.273/2.
3. Antibioticagebruik in ziekenhuizen bij acute pyelonefritis. D/2004/10.273/5.
4. Leukoreductie. Een mogelijke maatregel in het kader van een nationaal beleid voor bloedtransfusieveiligheid. D/2004/10.273/7.
5. Het preoperatief onderzoek. D/2004/10.273/9.
6. Validatie van het rapport van de Onderzoekscommissie over de onderfinanciering van de ziekenhuizen. D/2004/10.273/11.
7. Nationale richtlijn prenatale zorg. Een basis voor een klinisch pad voor de opvolging van zwangerschappen. D/2004/10.273/13.
8. Financieringssystemen van ziekenhuisgeneesmiddelen: een beschrijvende studie van een aantal Europese landen en Canada. D/2004/10.273/15.
9. Feedback: onderzoek naar de impact en barrières bij implementatie – Onderzoeksrapport: deel 1. D/2005/10.273/01.
10. De kost van tandprothesen. D/2005/10.273/03.
11. Borstkankerscreening. D/2005/10.273/05.
12. Studie naar een alternatieve financiering van bloed en labiele bloedderivaten in de ziekenhuizen. D/2005/10.273/07.
13. Endovasculaire behandeling van Carotisstenose. D/2005/10.273/09.

Inlichtingen

Federaal Kenniscentrum voor de Gezondheidszorg - Centre Fédéral d'Expertise des Soins de Santé.
Résidence Palace (10de verdieping-10ème étage)
Wetstraat 155 Rue de la Loi
B-1040 Brussel-Bruxelles
Belgium
Tel: +32 [0]2 287 33 88
Fax: +32 [0]2 287 33 85
Email : info@kenniscentrum.fgov.be , info@centredexpertise.fgov.be
Web : http://www.kenniscentrum.fgov.be , http://www.centredexpertise.fgov.be