

Traitement endovasculaire de la sténose carotidienne

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Le Centre Fédéral d'Expertise des Soins de Santé

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Titre: Traitement endovasculaire de la sténose carotidienne

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Préface

Confrontés à l'augmentation du coût des soins de santé, presque tous les pays occidentaux mènent, depuis une vingtaine d'années, des évaluations des nouvelles technologies disponibles dans le domaine de la santé (*Health Technology Assessment*, HTA). L'objectif de telles évaluations est d'établir si la technologie en question est efficace (est-ce que ça marche?), mais aussi efficiente (est-ce que ça marche, à un coût raisonnable ?)

La Belgique s'est jointe depuis peu aux pays menant des évaluations technologiques et le Centre Fédéral d'Expertise des Soins de Santé (KCE) présente ici son premier rapport HTA.

La sténose (rétrécissement) de l'artère carotidienne est une affection fréquente pouvant occasionner une thrombose cérébrale. Jusqu'il y a peu, le traitement de choix de la sténose carotidienne était l'endartérectomie carotidienne (EC), une intervention développée dans les années '50. Un inconvénient majeur de l'EC est le risque de thrombose cérébrale lié à l'intervention, qui explique aussi sa mauvaise réputation. Cependant des recherches empiriques menées dans les années '90 ont démontré l'efficience de l'EC pour certaines indications bien précises.

De nouvelles techniques pour le traitement de la sténose carotidienne ont été expérimentées ces dernières années, telles que l'angioplastie et le 'stent', (sorte de manchon rigide maintenant la carotide dilatée), mais avec des résultats décevants. Cependant un récent perfectionnement de la méthode du 'stent' semble très prometteur: il s'agit de systèmes de protection qui retiennent les débris arrachés à la paroi artérielle au cours de l'intervention, prévenant ainsi la thrombose cérébrale. Le Stent Carotidien Protégé (SCP) ("*Protected carotid artery stenting*", PCAS) est apparu sur le marché.

Ce rapport présente une évaluation technologique comparant le stent carotidien protégé à l'endartérectomie pour le traitement de la sténose carotidienne. L'efficacité du SCP n'a pas été prouvée, ni son efficience. Il n'y a pas de preuves que le SCP fonctionne mieux que l'EC, par contre il est plus cher car le stent lui-même est extrêmement coûteux. Cette évaluation technologique plaide donc contre une introduction généralisée du SCP dans les services de santé belges.

Cependant l'évaluation montre aussi que le SCP est une technologie prometteuse, en pleine évolution. Cela pose des questions éthiques: son développement ultérieur nécessite de conduire des expériences utilisant des patients. L'EC a été, pendant des dizaines d'années, le sujet d'expériences non contrôlées qui n'ont servi à rien si ce n'est nourrir des discussions passionnées dans la littérature médicale spécialisée, jusqu'à ce que les premières études contrôlées apportent des réponses sans équivoque et relèguent le débat dans les poubelles de l'histoire.

Le rapport suggère donc de prendre l'avis du « Comité Consultatif de Bioéthique de Belgique » quant aux aspects éthiques de l'introduction en Belgique d'une technologie médicale chère, encore expérimentale, mais prometteuse.

Pour un nombre limité de patients présentant des caractéristiques particulières, le SCP est la seule option thérapeutique. Le rapport suggère qu'au moins un hôpital belge puisse mettre en pratique l'utilisation de SCP (avec remboursement). Il suggère aussi de remplacer l'introduction non contrôlée de cette technologie expérimentale par une approche contrôlée. Nous suggérons qu'une partie de l'argent qui aurait servi auparavant à financer d'inutiles expériences non contrôlées, permette de soutenir un nombre restreint de centres afin qu'ils participent à la recherche scientifique internationale dans le cadre d'étude multicentrique. Cette approche devrait permettre de rendre le SCP accessible à ceux qui en ont besoin en Belgique et favoriserait le développement de l'expérience des équipes belges vasculaires, afin de garantir une utilisation optimale de cette technologie dans le futur.

La médecine restera toujours un art, mais devient de plus en plus une science. La technologie médicale moderne représente à la fois une bénédiction et une malédiction. Les temps ne sont plus, où tout ce qui 'pouvait' être possible, 'devait' être possible. C'est un droit du citoyen, que les sommes d'argent importantes qu'il investit dans les soins de santé, soient utilisées d'une façon optimale. Cela implique de décourager l'utilisation de technologies inefficaces, d'encourager l'utilisation de technologies efficaces et d'expérimenter de manière réfléchie les nouvelles technologies prometteuses. S'il en est ainsi, ce rapport, même court et modeste, pourrait représenter une rupture avec le passé.

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Résumé du rapport d'évaluation technologique

Contexte et problèmes posés

La sténose carotidienne est le plus souvent la conséquence de l'athérosclérose. L'athérosclérose altère la paroi vasculaire. Un morceau de cette paroi malade peut se détacher, être entraîné dans la circulation et obstruer un vaisseau. Comme la carotide irrigue le cerveau, la sténose carotidienne est une cause importante de thrombose cérébrale.

La prévention et le traitement de la sténose carotidienne reposent sur une bonne gestion du risque cardio-vasculaire: arrêt de la consommation de tabac, traitement de l'hypertension ou d'un taux de cholestérol LDL trop élevé avec des statines (inhibiteurs HMG-CoA), suivi correct du diabète sucré, traitement à l'aspirine faiblement dosée pour les patients cardiaques connus. Outre cette bonne gestion du risque cardio-vasculaire, il est parfois utile voire indispensable de traiter la plaque athérosclérotique. Deux possibilités existent. La méthode classique consiste à ouvrir l'artère au cours d'une intervention chirurgicale et à enlever la plaque. Cette opération s'appelle une endartérectomie carotidienne (EC). Dans une méthode développée plus récemment, un cathéter est introduit le long d'une artère jusque dans la carotide au niveau de la sténose, laquelle est dilatée à l'aide d'un ballon ; la dilatation est maintenue en position au moyen d'un « stent », sorte de tuteur cylindrique en métal. Autrefois, cette intervention endovasculaire entraînait souvent des complications, en particulier une thrombose cérébrale due à des caillots qui se libéraient pendant l'intervention. Afin de prévenir cette complication on utilise depuis peu un système de protection –un filtre qui se déploie ou un ballon qui se gonfle- au-dessus de la lésion et qui bloque les petits caillots désagrégés avant qu'ils ne puissent arriver au cerveau. Cette nouvelle technique, SCP (“protected carotid artery stenting”, stenting carotidien protégé) est en train de concurrencer sérieusement la méthode classique.

Il existe donc 3 options possibles pour le traitement de la sténose carotidienne (toutes incluant gestion optimale du risque cardio-vasculaire): l'expectative armée, l'EC ou le SCP. L'EC et le SCP sont des techniques qui présentent un certain risque. En cas de complications, ces techniques entraînent ce qu'elles veulent éviter: une thrombose cérébrale pouvant même mener au décès du patient. Il convient donc de peser le risque de thrombose du patient sans intervention, par rapport au risque inhérent à l'intervention. Actuellement, le SCP n'est pas remboursé en Belgique. Le présent rapport formule dès lors des réponses aux questions suivantes :

- Quelles sont les indications pour lesquelles le SCP présente un avantage certain par rapport à l'EC, et qui imposent que la technologie soit mise à la disposition du patient ?
- Quelles sont les indications pour lesquelles un SCP présente probablement un avantage par rapport à une EC, et pour lesquelles des recherches supplémentaires sont nécessaires, afin de confirmer cet avantage ?
- Comment introduire le SCP en Belgique de manière responsable, étant donné que l'intervention n'est pas sans risque et requiert un degré élevé de compétence et d'expérience ?

L'efficacité clinique du SCP

Nous avons mené une recherche systématique de la littérature scientifique sur le sujet. Les méthodes utilisées pour l'évaluation de médicaments - comme les essais cliniques randomisés - présentent certaines limitations quand elles sont appliquées à l'évaluation de nouvelles technologies. Les technologies de pointe (stents avec protection) évoluent rapidement. Les résultats sont fonction de l'expérience et du savoir-faire du praticien, de la qualité de l'imagerie disponible et du fonctionnement de toute l'équipe cardio-vasculaire. Lors de l'interprétation des résultats des essais cliniques randomisés comparant la chirurgie (EC) et la radiologie interventionnelle (SCP), il ne faut pas perdre

de vue qu'il s'agit bien souvent de patients hautement sélectionnés, traités par les équipes les plus compétentes dans les centres les plus performants en la matière. Il faut être prudent avant d'attendre des résultats similaires dans la pratique quotidienne.

Plusieurs meta-analyses de grandes études cliniques impliquant des patients atteints de sténose carotidienne symptomatique sont disponibles pour l'EC. Pour les patients à haut risque de thrombose cérébrale, l'EC s'avère particulièrement efficace et il peut suffire de traiter six patients pour prévenir une thrombose cérébrale. Plus le risque de thrombose cérébrale diminue, plus l'«expectative armée» est indiquée car l'EC entraîne également des thromboses cérébrales.

Il n'y a que très peu de données disponibles sur le SCP, car cette technologie est encore très récente. Des études observationnelles (analyse des registres des interventions), et les résultats préliminaires d'essais cliniques ont cependant convaincu les cliniciens de la supériorité du SCP par rapport au SC non protégé, et le SC non protégé n'est actuellement plus justifié, sauf en cas de contre-indications à l'utilisation du filtre protecteur, par exemple en cas de sténoses difficiles d'accès ou d'intolérance au filtre. Les revues de littérature plus anciennes sur le SC ne comportent pratiquement pas d'évaluation des interventions SCP et ne sont donc plus guère utiles.

Les preuves de l'efficacité clinique du SCP ne sont pas (encore) convaincantes. Le seul essai clinique randomisé mené à bien est difficilement interprétable. Les données disponibles (différentes études et analyse de registres) suggèrent que le SCP est une solution alternative acceptable (c'est-à-dire «non-inférieure») pour l'EC. Plusieurs grands essais cliniques visant à comparer EC et SCP sont actuellement en cours (EVA-3S, SPACE, ICSS-2, CREST). Le présent rapport deviendra obsolète à la publication de leurs résultats.

Groupe cible

Utilisées pour des indications trop larges, les interventions sur la carotide occasionnent plus de thromboses cérébrales qu'elles n'en préviennent. Les médecins doivent être conscients du fait que la prise en charge standard d'une sténose carotidienne est le traitement médical et l'expectative. L'intervention est un pis-aller réservé aux groupes à risque particulièrement élevé de thrombose cérébrale. Ce risque augmente avec le degré de sténose, ainsi qu'avec la présence de symptômes récents. Le «nombre de sujets à traiter» ('number needed to treat') augmente rapidement en l'absence de symptômes et dans les sténoses moins graves, et peut rapidement se transformer en «number needed to harm» (nombre de personnes traitées présentant un effet négatif) en raison des risques liés à de l'opération.

Les résultats les meilleurs sont obtenus dans le cas de sténoses importantes (> 70 %) sur des patients présentant des symptômes récents (< 2 semaines). Les sténoses de moins de 50 % ne constituent pas une indication pour une intervention. Les interventions en cas de sténose carotidienne asymptomatique demeurent controversées.

Les interventions sur des personnes sans symptômes récents sont un investissement à plus long terme. En principe, l'espérance de vie d'un patient atteint de sténose asymptomatique doit être de cinq ans pour pouvoir profiter d'une intervention. La probabilité de thrombose cérébrale péri-opératoire est trop élevée chez les patients plus âgés, de sorte que ceux-ci ne constituent pas un bon groupe cible. Les résultats de l'opération doivent être excellents. Pour pouvoir prendre des décisions en parfaite connaissance de cause, les résultats des interventions sur la carotide doivent être mieux connus en Belgique.

Au cas où une intervention sur la carotide serait indiquée, l'EC reste le premier choix ; le SCP peut être indiqué si le patient court un risque élevé de thrombose cérébrale, et 'un risque élevé de complication après l'intervention ouverte. Ce groupe n'est pas encore suffisamment bien décrit et rien ne permet d'affirmer que le SCP est plus sûr chez ces patients.

Coût-Efficacité du SCP

Nous avons mené une recherche systématique de la littérature scientifique sur le sujet. La littérature économique sur le SCP est encore extrêmement limitée. C'est la conséquence des connaissances encore très limitées quant à l'efficacité. C'est la raison pour laquelle nous nous limiterons à une discussion qualitative.

Les EC sans complications sont des interventions qui ne s'accompagnent pas d'une longue hospitalisation, ni d'une altération marquée de la qualité de vie. A risque de complication égal, la technique non-invasive qu'est le stent ne permettra que peu d'économies à cet égard. Par contre le coût élevé des stents et des filtres de protection rend généralement le SCP plus onéreux.

Le coût de ces deux interventions est dominé par le coût extrêmement élevé de la prise en charge des complications (thromboses cérébrales). Une différence de risque de complications entre les 2 interventions aura donc un impact important, non seulement sur le plan humain mais aussi financier.

En l'absence de données comparatives sur l'efficacité, et surtout sur l'efficacité à long terme, il n'est pas possible de prendre aujourd'hui position de façon catégorique. Il est possible que, comme cela s'est passé pour les interventions coronaires percutanées, l'évolution rapide de la technologie aboutisse finalement à une supériorité incontestable des techniques non-invasives.

L'introduction d'une technologie en plein développement

La pratique existante

Dans les pays que nous avons étudiés (USA, R-U, Allemagne, France), l'utilisation du SCP est conditionnée à un suivi scientifique des résultats. La France et le Royaume-Uni recommandent le SCP comme une technique expérimentale qu'il faut encore explorer dans le cadre d'études comparatives. Les USA et l'Allemagne recommandent d'inclure tous les patients recevant un SCP dans des registres permettant une évaluation prospective.

En Belgique, aucun remboursement n'est prévu pour l'instant. Le taux d'utilisation très élevé des interventions ouvertes (EC) (par rapport à d'autres pays) est frappant. Cela ne signifie pas que la pratique clinique belge soit bonne ou mauvaise. Un taux d'utilisation comparativement élevé pourrait également indiquer une sous-utilisation ailleurs. Cependant, l'absence de données correctes sur la population de patients, et le suivi des résultats de cette intervention dangereuse, constituent un indicateur certain d'une faiblesse dans l'organisation. Sans données sur les résultats de l'intervention, ni le patient ni le médecin ne peuvent être suffisamment informés des avantages à en attendre et ne peuvent donc opérer un choix éclairé. Le patient a droit à la meilleure qualité possible, d'autant plus qu'il s'agit d'une intervention à risque. L'absence de données fiables dans notre pays sur cette intervention à risque représente une carence médico-éthique.

Que souhaite-t-on pour l'avenir ?

L'introduction d'une "technologie émergente" coûteuse impose des choix politiques. Il n'est pas toujours possible de réconcilier les principes absolus de liberté du traitement thérapeutique, de l'intérêt du patient, de la répartition optimale des moyens dans le secteur des soins de santé, et de la plus grande accessibilité de ces soins. Il est nécessaire de définir un cadre à l'intérieur duquel faire des choix éthiquement responsables. Nous suggérons, avant de considérer l'introduction d'une technologie "émergente" coûteuse, de demander un avis impartial au Comité Consultatif de Bioéthique de Belgique.

La décision finale relative au traitement incombe au patient, mais nécessite qu'il soit correctement informé. Cette information doit émaner d'une source impartiale. La question du rôle du médecin généraliste dans le processus de consentement informé du patient doit donc être posée. En raison des implications éthiques possibles, nous suggérons d'obtenir l'avis du Comité consultatif de Bioéthique de Belgique quant au contenu et à la forme des procédures de consentement éclairé.

Une réglementation adéquate requiert une image très claire de ce que l'on souhaite pour l'avenir. Dans cet avenir, le droit du patient à la meilleure qualité possible de pratique clinique occupe une place centrale. Nous pouvons en déduire certains principes.

Le groupe clinique concerné est convaincu que le SCP peut constituer une alternative à l'EC, mais cette conviction est encore insuffisamment étayée par des données empiriques. Le SCP semble néanmoins très prometteur, après une longue période d'expérimentations relativement décevantes avec l'angioplastie et le stenting non protégé. Trois principes en ressortent.

- Le SCP doit être mis à la disposition de populations de patients ayant intérêt à subir une intervention, mais pour lesquels une chirurgie ouverte ne constitue pas une option.
- Il est nécessaires de récolter des données permettant de mieux préciser les indications cliniques.
- Le patient a droit à la qualité la plus élevée dans l'exécution de cette intervention à risque. Cela requiert une expérience suffisante de la part des centres (nombre suffisant d'interventions effectuées sur la carotide) et un maintien suffisant de l'expérience accumulée (un nombre suffisamment élevé d'interventions par an). La qualité de cette intervention doit être suivie en routine. En principe cela est déjà possible à partir de données existantes – cliniques, et de facturation – qui devraient permettre de connaître les complications telles que thromboses, réhospitalisations, et mortalité.

À l'heure actuelle, le SCP est une intervention expérimentale dont l'efficacité est encore trop peu connue. Si son efficacité clinique est comparable à l'EC ('non-infériorité'), son coût élevé en fait une alternative moins avantageuse. L'utilisation du SCP doit donc être se faire uniquement dans le cadre d'une recherche scientifique, ainsi que pour quelques rares indications dans lesquelles sa supériorité n'est pas contestée. On peut formuler les principes suivants en ce qui concerne le choix des centres et des patients.

- Le centre doit pouvoir faire état d'un volume élevé et d'une qualité acceptable en matière d'interventions sur la carotide. Nous suggérons au moins 625 interventions sur la carotide (SCP ou EC) en 5 ans (cela correspond à 3 % minimum du volume national), avec tout au plus 15 décès dans les trente jours suivant l'intervention.
- Le centre doit se montrer disposé à participer à une recherche clinique dans le cadre d'un essai multicentrique (comme par exemple l'essai ICSS) dont le protocole sera rigoureusement respecté. Le centre doit être disposé à se soumettre aux audits requis par cette étude.
- La décision de traitement sera prise dans ce centre par une équipe pluridisciplinaire, composée au minimum d'un neurologue ou internist-gériâtre, d'un radiologue et d'un chirurgien vasculaire.

Messages clés

Contexte

- La sténose carotidienne est généralement une conséquence de l'athérosclérose et une cause importante - mais non la seule - de thrombose cérébrale.
- Le traitement médical repose sur une gestion adéquate du risque cardiovasculaire: arrêt de la consommation de tabac, contrôle de la pression sanguine et du diabète, traitement aux statines, inhibiteurs plaquettaires (aspirine) chez les patients atteints d'une maladie coronarienne connue (évidence de type I, soit la plus forte).
- A côté de l' 'expectative armée', on peut parfois conseiller une intervention: intervention ouverte (endartérectomie carotidienne, EC), ou le placement d'un stent par voie endovasculaire (stenting carotidien protégé, SCP)

Objectif

- La présente synthèse résume l'évidence existante sur l'efficacité et le coût-efficacité du SCP par rapport à l'EC, et suggère des méthodes visant à introduire le SCP de manière responsable.

Efficacité clinique

- Le SCP est parvenu à convaincre les cliniciens qu'il était plus sûr que le SC non protégé (niveau d'évidence I).
- Il n'existe aucune preuve que le SCP soit plus ou moins efficace que l'EC.
- Plusieurs grandes études visant à comparer le SCP à l'EC sont actuellement en cours.
- Aucune étude ne recrute pour l'instant des patients asymptomatiques. Les premières études du genre sont mises sur pied en ce moment.
- L'EC est le meilleur traitement pour les patients présentant un risque élevé de thrombose cérébrale. Ce groupe inclut les personnes plus âgées.
- Plus les symptômes sont récents (< 2 semaines) et plus la sténose est importante (> 70 %), plus le patient a intérêt à subir une intervention.
- Une intervention pour une sténose carotidienne asymptomatique est discutable. Pour l'instant, une telle intervention est peut-être indiquée chez les patients de moins de 75 ans, ayant une espérance de vie suffisante, et dans des centres de très haute qualité (risque de thrombose cérébrale ou de décès suite à l'intervention inférieur à 4 %).
- Le SCP est une solution alternative possible pour l'EC pour les patients à haut risque de thrombose cérébrale, mais pour lesquels une intervention ouverte n'est pas indiquée. Ce groupe de patients n'est pas très bien décrit, et rien ne permet de déterminer si un mauvais candidat pour une intervention ouverte est un meilleur candidat pour le SCP.

Coût-Efficacité

- En raison des connaissances encore limitées quant à l'efficacité du SCP, les données fiables de coût-efficacité font encore défaut. Le coût d'une thrombose cérébrale est à ce point élevé qu'un risque plus faible de thrombose cérébrale avec le SCP représenterait des économies importantes. Il est indispensable de compléter les données de suivi à court terme disponibles, par des données de suivi à plus long terme, pour réaliser une évaluation valable de son rapport coût/efficacité.
- Le SCP offre peu d'avantages financiers directs par rapport à l'EC. Le SCP est un choix moins 'coût-efficace' que l'EC, en raison du coût élevé du stent et du matériel de protection.
- Le développement rapide de la technologie et la baisse du prix de revient des stents et des filtres pourraient améliorer rapidement le rapport coût-efficacité du SCP par rapport à l'EC.

Recommandations pour le contrôle et l'amélioration de la qualité

- Le taux d'utilisation des EC en Belgique est très élevé (par rapport à d'autres pays), pourtant on ne dispose pas de données sur la qualité des résultats obtenus, ce qui est en soi un signe de qualité insuffisante. Le recueil de données doit être sensiblement amélioré, et suivre un protocole clairement et strictement défini.
- En raison des risques inhérents à chaque intervention sur la carotide, le patient a le droit de recevoir des informations d'excellente qualité et impartiales. Nous suggérons de demander l'avis au Comité Consultatif de Bioéthique de Belgique, quant au contenu et à la forme des procédures de consentement éclairé, à suivre dans toute intervention majeure pouvant avoir des conséquences graves.
- L'apparition d'une technologie "émergente" coûteuse, nécessite de faire des choix importants dont les implications éthiques sont souvent complexes. Nous suggérons de solliciter dans ce cas, et de manière systématique, l'avis du Comité Consultatif de Bioéthique de Belgique.

Recommandations pour l'organisation et la mise en œuvre pratiques

- Dans les autres pays, l'usage du SCP est réglementé et doit s'intégrer dans un protocole de recherche scientifique incluant un suivi prospectif des résultats.
- Le SCP doit être mis à la disposition des patients ayant incontestablement intérêt à subir une telle intervention, mais pour lesquels la chirurgie ouverte n'est pas une option. Leur nombre est inconnu mais certainement très réduit.
- Il est nécessaire de récolter plus de données afin de préciser les indications cliniques de cette technologie prometteuse.
 - Les données permettant d'analyser le choix de l'une ou l'autre approche thérapeutique, ainsi que ses résultats, doivent être récoltées suivant des protocoles bien définis, en participant aux grandes études multicentriques en cours, comme l'ICSS.
 - Lorsqu'un traitement est indiqué mais qu'un traitement chirurgical n'est pas une bonne option, la collecte d'informations se fait dans le cadre d'un registre prospectif.

- Le patient a droit à la meilleure qualité pour cette intervention à risque.
 - Les centres doivent pouvoir se prévaloir d'une expérience suffisante (nombre suffisant d'interventions effectuées sur la carotide) et d'un maintien suffisant de l'expérience accumulée (un nombre suffisamment élevé d'interventions par an).
 - Les données relatives à la qualité doivent être récoltées en routine.
- Il serait justifié en Belgique d'accueillir au minimum un, et au maximum quelques, centres pouvant réaliser l'intervention de SCP dans le cadre des soins de santé belges. Les conditions nécessaires minimales sont :
 - Minimum 625 interventions sur la carotide (toutes) effectuées au cours des cinq dernières années, avec 15 décès maximum dans les 30 jours suivant l'intervention.
 - Accepter de travailler suivant un protocole de recherche clinique rigoureux, s'inscrivant dans le cadre d'une étude multicentrique, et accepter l'audit externe régulier requis par la participation à une telle étude.
 - Prendre des décisions de traitement dans le cadre d'une équipe vasculaire multidisciplinaire, constituée au minimum d'un radiologue, un neurologue ou internist-gériâtre et un chirurgien vasculaire.
- L'EC demeure le traitement standard ; les exceptions doivent être spécifiquement motivées.

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I. 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>)



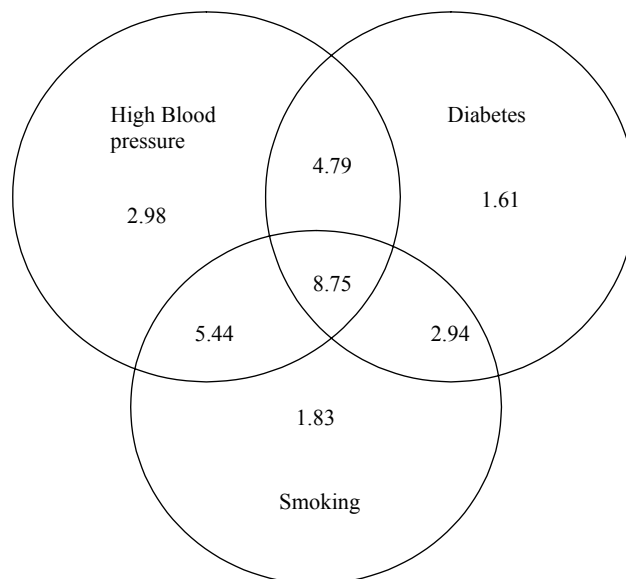
Plaques can grow large enough to significantly reduce the bloodflow through an artery (see Figure 1). But most of the damage occurs when they become fragile and rupture. Plaques that rupture cause blood clots to form that can block blood flow or break off and travel to another part of the body. If either 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 I, see Appendix I 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} Figure 2 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 I).
- All smokers should receive the urgent advice to stop smoking, and help in doing so is to be offered (Evidence level I 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 equipoise¹ 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 $\geq 50\%$ (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 I). This includes elderly patients and women (Level of evidence I).
- 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 I).
- 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.

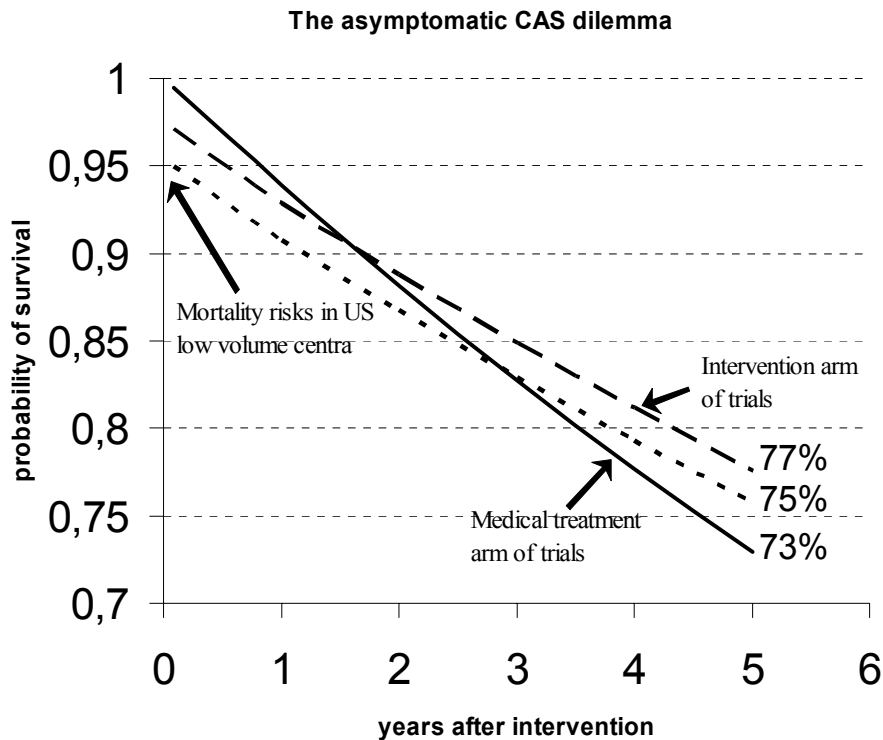
The enthusiasm of institutes to endorse CEA for asymptomatic subjects suggests therefore more problems than solutions, particularly if income is proportional to number of interventions. Five trials have been published, two were flawed and yielded negative results, the third had negative results.^{18, 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 SAPHIRE 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, where 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 assess 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	of 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 $\geq 4\%$ in the operating centre or the residual life expectancy is low (level of evidence I). 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 I).
 - 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 I). 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 CEA and CAS, without explicitly calculating an incremental cost-effectiveness ratio. One was a cost-effectiveness analysis⁵⁹. 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 comorbidities 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 an 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.

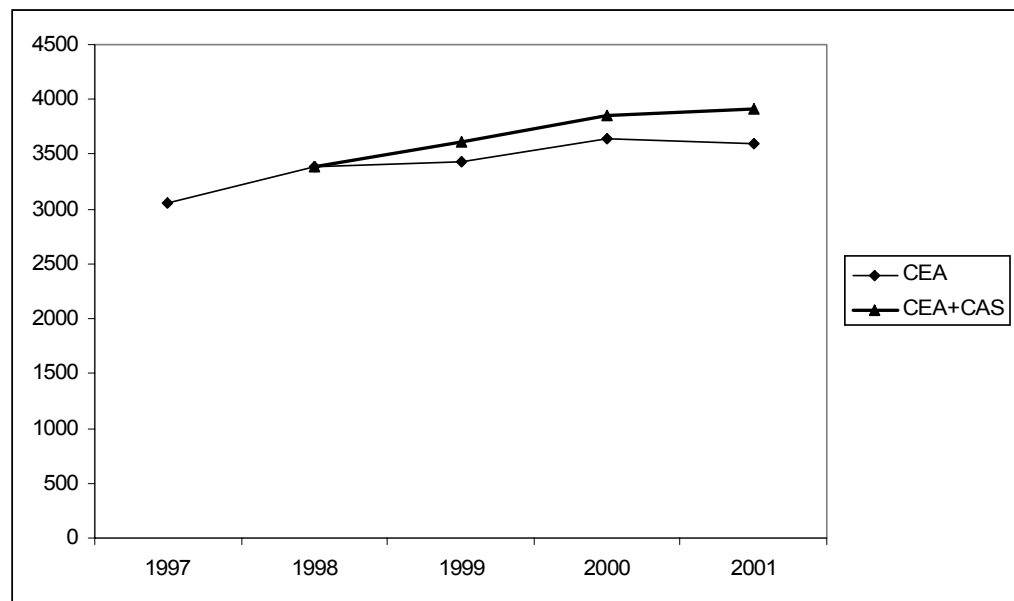
France. In 2002, the ANAES recommended that carotid angioplasty should not be performed outside the context of a clinical trial.³⁹

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 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.

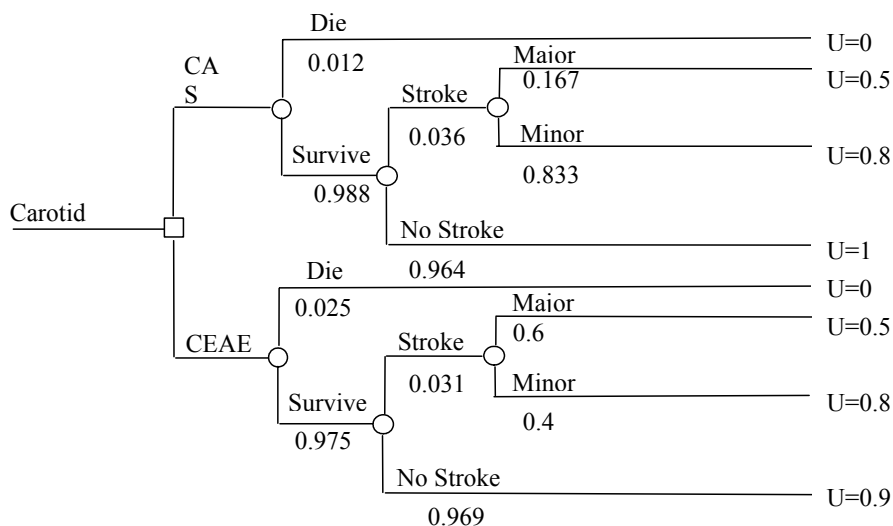
Figure 4 presents a simple decision model that allows the calculation of the expected utility with CAS and with CEA (Figure 4). A rational patient will prefer the treatment with the highest expected utility.

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 SAPHIRE 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 SAPHIRE study, and apply to the population of the SAPHIRE study, with uncertain external validity and relevancy. The power of SAPHIRE 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 to 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 advise 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 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.

II. 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 impartial, 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 than 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-procedural 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 I)
- All smokers should receive the urgent advice to stop smoking, and help in doing so is to be offered (Evidence level I 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 unknown 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.

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15. APPENDICES

APPENDIX I: 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.

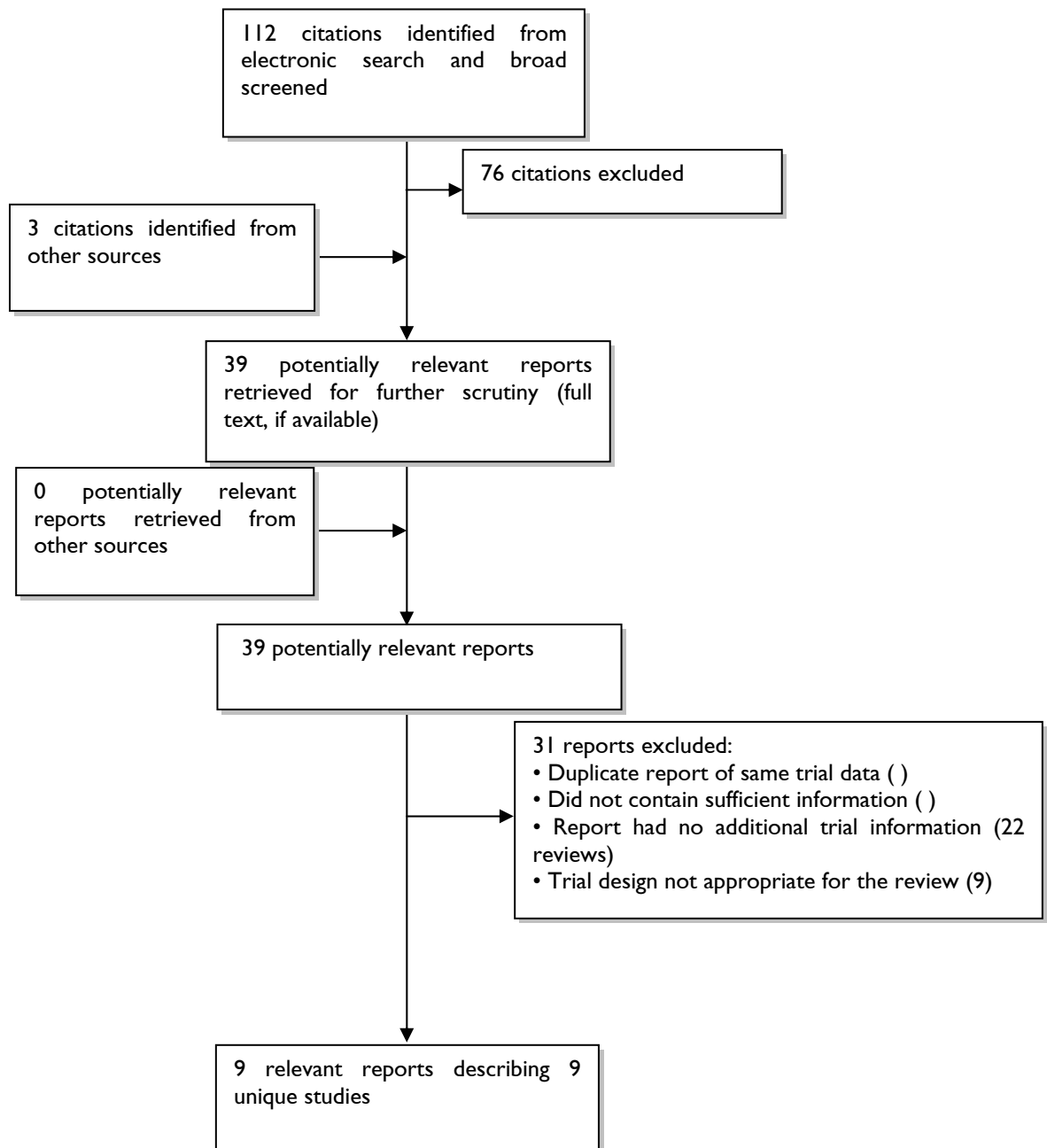
Anything that was not a clinical study of single first therapeutic interventions for stenotic lesions was excluded from the review as well as re-interventions, combinations

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

Study details	Patients	Intervention/comparator	Outcomes																				
Mas 2004 (EVA-3S clinical alert)	Symptomatic patients >70% stenosis according to NASCET	- CAS without protection (n=15) - CAS with protection (n=58)	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.																				
Yadav 2004 SAPHIRE	Symptomatic >50% diameter stenosis Asymptomatic >80% diameter stenosis	Carotid stenting with protection device (n=167) CEA (n=167)	<p>Outcomes at 1 year:</p> <table border="1"> <thead> <tr> <th></th> <th>CEA</th> <th>Stenting</th> <th>P-value</th> </tr> </thead> <tbody> <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> </tbody> </table> <p>* death, stroke or M.I. at 30 days plus ipsilateral stroke or death from neurologic causes within 31 days to 1 year</p>		CEA	Stenting	P-value	Death	13.5%	7.4%	0.08	Stroke	7.9%	6.2%	0.52	M.I.	7.5%	3.0%	0.03	Primary end point*	8.4%	5.5%	0.05
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Primary end point*	8.4%	5.5%	0.05																				
McKevitt 2003	Symptomatic or asymptomatic patients, any degree of stenosis, suitable for both CEA and CAS	CEA (n=49) Carotid angioplasty (n=31) Self-expandable stent (n=11) Balloon expandable stent (n=13)	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.																				

Observational studies

Study details	Patients	Intervention/comparator	Outcomes			Comments
Becquemin 2003	Symptomatic >70% stenosis (n=182) Asymptomatic >80% stenosis (n=273) (total=455)	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	30-day outcomes			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.
			CAS (n=114)	CEA (n=368)		
			TIA	4 (3.5%)	6 (1.6%)	
			Temporary minor stroke	5 (4.4%)	0	
			Persistent minor stroke	2 (1.8%)	1 (0.3%)	
			Major stroke	1 (0.9%)	0	
			Total neurological events	12 (10.5%)	7 (1.9%)	
			Deaths	0	3 (0.8%)	
			Total neuro events/deaths	12 (10.5%)	10 (2.7%)	
			Permanent neuro events/deaths	3 (2.6%)	4 (1.1%)	
			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)			

Study details	Patients	Intervention/comparator	Outcomes	Comments																									
Hobson 2004 Lead-in phase analysis CREST	Symptomatic >50% stenosis (n=230) Asymptomatic >70% stenosis (n=519)	CAS with embolic protection in octogenarians CAS with embolic protection in non-octogenarians	30-day stroke and death <table border="1"> <thead> <tr> <th>Age</th> <th>N</th> <th>Events (%)</th> <th>N</th> <th>Odds ratio (95% CI)</th> </tr> </thead> <tbody> <tr> <td><60</td> <td>120</td> <td>2 (1.7%)</td> <td></td> <td>1.0 (ref)</td> </tr> <tr> <td>60-69</td> <td>229</td> <td>3 (1.3%)</td> <td></td> <td>0.78 (0.13-4.75)</td> </tr> <tr> <td>70-79</td> <td>301</td> <td>16 (5.3%)</td> <td></td> <td>3.31 (0.75-14.63)</td> </tr> <tr> <td>80+</td> <td>99</td> <td>12 (12.1%)</td> <td></td> <td>8.14 (1.78-37.30)</td> </tr> </tbody> </table> <p>Conclusion: Octogenarians should be considered high-risk patients for CAS stenting.</p>	Age	N	Events (%)	N	Odds ratio (95% CI)	<60	120	2 (1.7%)		1.0 (ref)	60-69	229	3 (1.3%)		0.78 (0.13-4.75)	70-79	301	16 (5.3%)		3.31 (0.75-14.63)	80+	99	12 (12.1%)		8.14 (1.78-37.30)	Adjustment of Odds ratios for symptomatic status, use of protection device, gender and percent stenosis did not change the conclusion.
Age	N	Events (%)	N	Odds ratio (95% CI)																									
<60	120	2 (1.7%)		1.0 (ref)																									
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Kastrup 2004	Elderly patients (>75 years) Symptomatic Asymptomatic	CAS with embolic protection (n=53 of which 57% symptomatic) CEA (n=110 of which 63% symptomatic)	30 day outcomes <table border="1"> <thead> <tr> <th></th> <th>CEA</th> <th>Stenting</th> </tr> </thead> <tbody> <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> </tbody> </table> <p>Conclusion: complication rates associated with CAS are significantly higher than with CEA in patients 75 years of age or older.</p>		CEA	Stenting	Death	0	0	Minor stroke	0	7.5%	Major stroke	1.8%	3.8%	All Stroke	1.8%	11.3%	Data for CAS gathered prospectively. Data for CEA obtained retrospectively.										
	CEA	Stenting																											
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McKinlay 2003 CARESS	Symptomatic >50% stenosis (n=127) Asymptomatic >75% stenosis (n=270)	- CAS with embolic protection (n=143 of which 30.8% symptomatic) - CEA (n=254 of which 32.7% symptomatic)	30 day outcomes <table border="1"> <thead> <tr> <th></th> <th>CEA</th> <th>Stenting</th> </tr> </thead> <tbody> <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> </tbody> </table>		CEA	Stenting	Death	0.4%	0%	Stroke	2.4%	2.1%	Combined stroke+death	2.4%	2.1%	Prospective non-randomised trial													
	CEA	Stenting																											
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Combined stroke+death	2.4%	2.1%																											

Registries

Study details	Patients	Intervention/comparator	Outcomes	Comments															
Wholey 2003	N=11,243 Symptomatic patients (53.2%) Asymptomatic patients (46.8%)	- CAS without embolic protection (60%) - CAS with embolic protection	30 day event rate (see separate table below) 12-24-36-48 months after stent placement: <table border="1"> <thead> <tr> <th></th> <th>Restenosis >50%</th> <th>Ipsilateral neurologic events (incl. TIAs, major and minor strokes and deaths)</th> </tr> </thead> <tbody> <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> </tbody> </table>		Restenosis >50%	Ipsilateral neurologic events (incl. TIAs, major and minor strokes and deaths)	12 months FU	2.7%	1.2%	24 months FU	2.6%	1.3%	36 months FU	2.4%	1.7%	48 months FU	5.6%	4.5%	
	Restenosis >50%	Ipsilateral neurologic events (incl. TIAs, major and minor strokes and deaths)																	
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24 months FU	2.6%	1.3%																	
36 months FU	2.4%	1.7%																	
48 months FU	5.6%	4.5%																	
Reimers 2004		Carotid artery stenting with protection device (n=815 lesions in 753 consecutive patients; >70% diameter stenosis)	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%	Only about one quarter of the lesions were associated with neurologic symptoms within 6 months before the procedure															

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 to follow up, 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 81 mgr/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 stroke, 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 puncture) 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.

<p>Limits:</p> <p>Years: January 1998 - December 2004</p> <p>Search strategy:</p> <p>Medline (PubMed)</p> <p>Carotid stenosis (MeSH) and Stents (MeSH) and Economics</p> <p>Embase</p> <p>Carotid artery obstruction (all subheadings) and endoprosthesis (all subheadings) and economic aspect (all subheadings)</p> <p>Cinahl</p> <p>Carotid stenosis and stents and (economics or (costs and cost analysis))</p> <p>CRD</p> <p>Carotid stenosis and cost and stents</p> <p>Cochrane Library</p> <p>Carotid stenosis and stent\$ and (econom\$ or cost\$)</p>

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

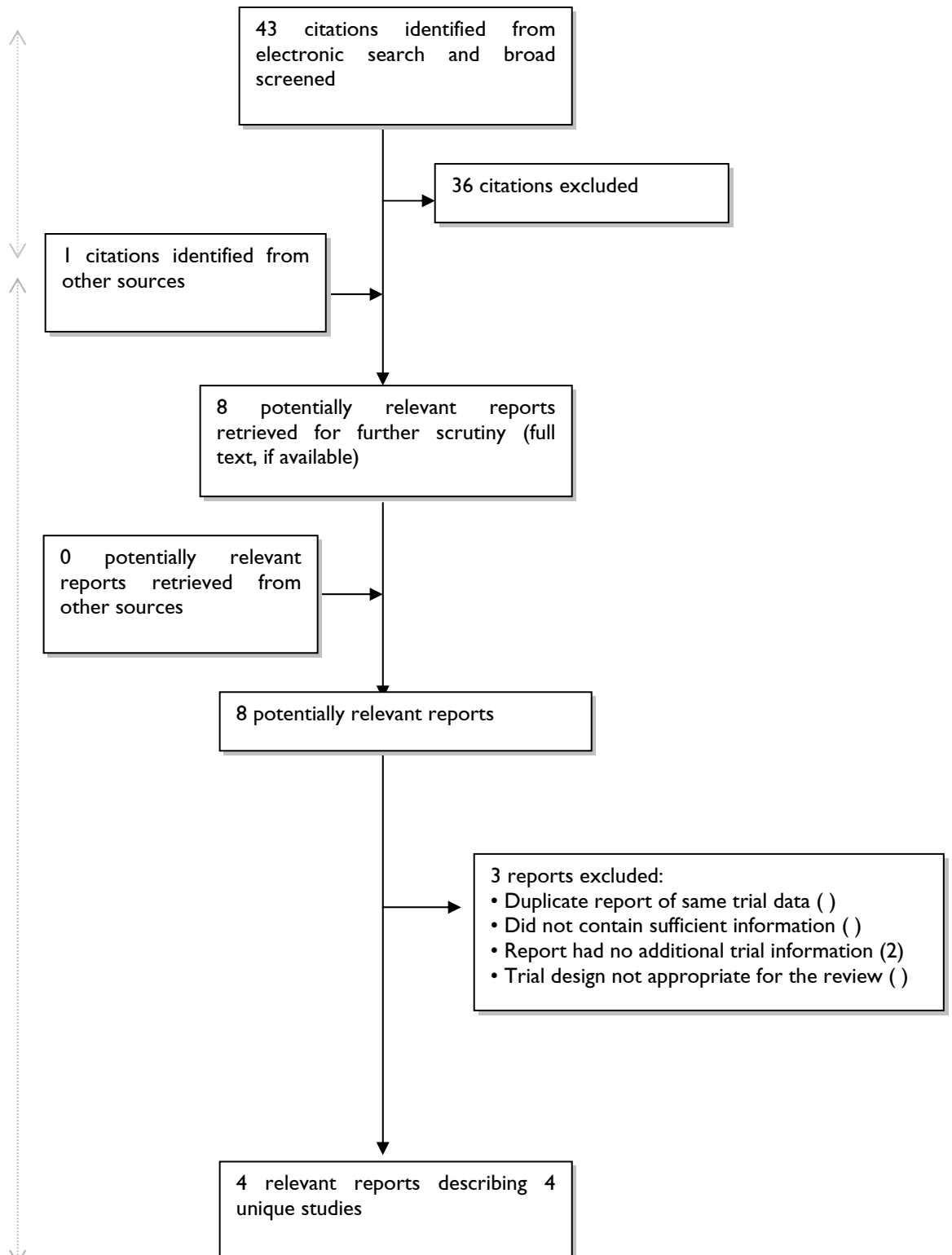
A structured form was developed, including information on the year of data collection, design, patient population, measure of costs or proxies for costs, effectiveness measure and results. The results of the studies were extracted in a separate tabulated form, differentiating between CAS and CEAE and 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	<input type="checkbox"/>	cost description
	<input type="checkbox"/>	cost-outcome description
	<input type="checkbox"/>	cost analysis
	<input type="checkbox"/>	cost minimisation analysis
	<input type="checkbox"/>	cost-effectiveness (-benefit, -utility) analysis
Method	<input type="checkbox"/>	Observational data
	<input type="checkbox"/>	Model
	<input type="checkbox"/>	Simulation
Year of data collection		
Currency year		
Population	<input type="checkbox"/>	symptomatic
	<input type="checkbox"/>	asymptomatic
	<input type="checkbox"/>	suitable for surgery
	<input type="checkbox"/>	not suitable for surgery
Intervention	<input type="checkbox"/>	carotid angioplasty
	<input type="checkbox"/>	carotid stenting without protection
	<input type="checkbox"/>	carotid stenting with protection
Comparison	<input type="checkbox"/>	carotid endarterectomy
	<input type="checkbox"/>	medical treatment
Outcomes		
Clinical	<input type="checkbox"/>	in-hospital outcomes
	<input type="checkbox"/>	30 day outcomes
	<input type="checkbox"/>	long term outcomes
	<input type="checkbox"/>	non-disabling stroke
	<input type="checkbox"/>	disabling stroke
	<input type="checkbox"/>	fatal stroke
	<input type="checkbox"/>	all stroke
	<input type="checkbox"/>	death
	<input type="checkbox"/>	stroke+death combined
	<input type="checkbox"/>	nonneurologic complications
Economic	<input type="checkbox"/>	hospital costs
	<input type="checkbox"/>	costs (all)
	<input type="checkbox"/>	hospital charges
	<input type="checkbox"/>	charges (all)
	<input type="checkbox"/>	length of stay
	<input type="checkbox"/>	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
Conclusions 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 defensible 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.

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Dépôt légal : D/2005/10.273/10

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1. Efficacité et rentabilité des thérapies de sevrage tabagique. D/2004/10.273/2.
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Renseignements

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