HTA De electieve endovasculaire behandeling van het abdominale aorta aneurysma (AAA)

KCE reports vol.23 A

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

Bij een *health technology assessment* van een nieuwe medische technologie zijn telkens 3 vragen op hun plaats: "Kan het werken?", "Werkt het in de praktijk?" en "Is het het waard?"[1]. Een leek kan denken dat het vanzelfsprekend is dat op die vragen driemaal "ja" volgt. Het echte leven is echter anders.

Een goed voorbeeld is de endovasculaire behandeling van een aorta-aneurysma (ook EVAR genaamd), geïntroduceerd begin de jaren 1990. Zo'n verwijding van de grote buikslagader is op termijn levensbedreigend: preventief opereren lijkt de boodschap. Maar die open operatie is zwaar, en de doorsnee patënt is de oudere roker met chronische ziekte. Het verschijnen van een nieuwe techniek die deze zware operatie kan vermijden door de operatie uit te voeren via een slagader binnenin de vaten ("endovasculair") lijkt dan ook een geschenk uit de hemel.

Maar is dit wel zo eenvoudig? Zijn er bewijzen dat het endovasculair plaatsen van een stent inderdaad beter is dan de klassieke open chirurgie? Is EVAR beter dan behoedzaam afwachten bij kleine aneurysmata? En als patiënten niet operabel zijn, zijn ze dan geschikt voor EVAR? Leidt de meerkost van 6000 € voor de stent tot besparingen en/of tot aantoonbare gezondheidswinst?

Paradoxaal genoeg zijn pas enkele maanden geleden, in 2005, de eerste klinische studies gepubliceerd die een eerste antwoord bieden op de meeste van bovenstaande vragen. Die klinische studies zijn niet van eigen bodem, ondanks de sinds 5 jaar voorziene financiering uit de ziekteverzekering en de behandeling van meer dan 1500 patiënten. In de Belgische ziekteverzekering bestaat de mogelijkheid om een experimentele techniek geleidelijk in te voeren via een conventie met een beperkt aantal ziekenhuizen. Dat was ook de oplossing die in 2001 werd gekozen, onder meer na druk via de media. De evaluatie van deze implementatie van EVAR in België kan u terugvinden in voorliggend rapport, dat mede tot stand kwam op vraag van het RIZIV en in nauwe samenwerking met het intermutualistisch agentschap. Op de eerste vraag, "Kan het werken", was het antwoord: "Het is lastiger dan oorspronkelijk vermoed." Op de tweede vraag "Werkt het in de praktijk?" luidt het antwoord "Minder dan oorspronkelijk gedacht". Op de derde vraag "Is het het waard?" is het antwoord nu "Nee, niet nu maar misschien wel later.".

Voor aorta-stents blijven dus, anno 2005, meer vragen dan antwoorden. EVAR werd te gauw op de markt gegooid, met meer enthousiasme dan wijsheid. Bij patiënten ook geschikt voor open heelkunde is EVAR mogelijk iets beter dan open heelkunde, maar het is erg duur. Over langere termijn blijft grote onzekerheid heersen. Patiënten niet geschikt voor open heelkunde blijken ook niet geschikt voor EVAR: voorzichtig afwachten is beter. Het minder ingrijpende EVAR bevordert daarbij overbehandeling van kleine aneurysmata, die beter af zijn met een beleid van voorzichtig afwachten.

[1] Effectiveness and Efficiency, Random reflections on Health Services. Cochrane. 1971.

Verstandig experimenteren met nieuwe technologieën is daarom meer dan ooit de boodschap. Vernieuwende technologie mag pas worden geïntroduceerd in de routine zorg na een periode van gecontroleerd experimenteren die wetenschappelijke bewijzen levert dat de technologie veilig en effectief is tegen aanvaardbare kosten. Eens te meer bevestigde EVAR dat het gerandomiseerde klinische onderzoek, waarbij de ene patiënt de nieuwe technologie krijgt en de andere patiënt de best beschikbare standaardbehandeling, de sleutel blijft tot de betere kennis. Medische wetenschapsbeoefening mag niet achterblijven bij medische technologie. Er is dus nog veel werk aan de winkel in België, maar er is geen enkele reden waarom onze goede klinische geneeskunde niet hand in hand kan gaan met goede klinische wetenschap.

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Samenvatting van het rapport: De electieve endovasculaire behandeling van het abdominale aorta aneurysma (AAA)

Achtergrond en doelstelling

Een abdominaal aorta aneurysma (AAA) is een vasculaire aandoening die vooral oudere rokende mannen treft. Het is een verwijding van de buikslagader, die geleidelijk zal toenemen in omvang en onbehandeld kan scheuren. Het scheuren van de buikslagader loopt doorgaans fataal af, vaak nog voordat het ziekenhuis kan bereikt worden. De klassieke electieve behandeling gebeurt met open heelkunde, die gepaard gaat met een hoge sterfte en morbiditeit.

Een AAA komt vrij veel voor: 5 % van de mannen van 65 jaar en ouder blijken een AAA te hebben. De sterfte is toch redelijk gering, omdat oudere rokers aan vele andere doodsoorzaken kunnen overlijden: naast AAA is het risico op hartziekte, beroerte of chronische longziekte erg hoog. Kleine AAA hebben een kleine kans op scheuren, en het risico van de operatie weegt niet op tegen behoedzaam afwachten. Experimenteel onderzoek heeft aangetoond dat opereren bij AAA met een diameter van 5.5 cm en lager weinig voordelen biedt. Bij bepaalde risicogroepen (vrouwen, omdat ze een hoger risico op ruptuur lopen, of jongere patiënten, omdat ze door hun hogere levensverwachting een operatie niet zullen ontlopen) kan deze ondergrens worden doorgeschoven naar 5.0 cm.

Sinds het begin van de jaren '90 is een endovasculaire behandeling ontwikkeld, EVAR (endovasculaire aneurysma reparatie), die veel minder belastend lijkt voor de patiënt. Maar de endovasculaire behandeling van een dergelijk groot bloedvat bleek een zware technologische opgave. Deze nieuwe en aantrekkelijke technologie werd sterk gepropageerd door de medische industrie. Ze werd toegepast op tienduizenden patiënten zonder veel bewijs van effectiviteit. Ook in België werd EVAR geïntroduceerd onder de vorm van een RIZIV-conventie met een aantal ziekenhuizen. Dit rapport beschrijft de effectiviteit en kosten-effectiviteit van de huidige bestaande technologie en doet suggesties voor verdere implementatie.

Klinische effectiviteit en kosten-effectiviteit

Niet gerandomiseerde, maar redelijk gecontroleerde en twee recente gerandomiseerde studies komen tot dezelfde besluiten over patiënten geschikt voor heelkunde: EVAR biedt als belangrijkste voordeel een minder belastende interventie met een lagere onmiddellijke postoperatieve sterfte. Maar het sterfte-voordeel verdwijnt snel over halflange termijn (één à twee jaar). De reden is vermoedelijk de hoge concurrerende sterfte, waarbij open heelkunde die patiënten "wegmaait" die anders ook op korte termijn zouden overlijden. Op langere termijn wegen de nadelen van EVAR zwaar door. Open heelkunde is, na enige maanden, een veilige en duurzame interventie. Dit geldt niet voor EVAR, dat vele complicaties kent en herhaalde interventies vergt. Er kunnen lekken ontstaan (endoleak), waardoor het aneurysma onder druk blijft, en uiteindelijk toch barst. De endostent kan van plaats verschuiven (migration), kan breken of kan op andere manieren beschadigd worden door de grote drukverschillen in de aorta of de sterke krachten van krimpend weefsel bij succesvolle afsluiting van het aneurysma.

EVAR werd oorspronkelijk ontwikkeld om patiënten, ongeschikt voor heelkunde, te behandelen. Dit bleek echter een misrekening: een recente

gerandomiseerde trial naar patiënten niet geschikt voor heelkunde toonde geen baten aan in vergelijking met een afwachtend beleid.

EVAR zorgt voor besparingen in de periode van de ingreep zelf (kortere hospitalisatieduur, kortere ligduur in intensieve zorgen, minder bloedverbruik), maar deze besparingen wegen niet op tegen de hoge kosten van de endoprothese. Belgische gegevens toonde kosten voor EVAR en open heelkunde in de grootte-orde van 11500 € en 7900 €. Deze verhouding is vergelijkbaar met de kosten berekend in de twee trials (het Engelse EVAR en het Nederlandse DREAM). Met toenemende follow-up wegen de hoge kosten van beeldvorming en herïnterventies na EVAR steeds zwaarder door.

EVAR is daarom niet kosten-effectief. Om kosten-effectief te zijn moeten drie kernvoorwaarden vervuld worden. De patiëntenselectie moet verbeteren om te verhinderen dat patiënten met hoge sterftekansen toch nog behandeld worden. De kostprijs van de endostent moet verlagen. De hoge kosten in de follow-up na EVAR moeten verlagen door betere duurzaamheid van de endostent, minder noodzaak tot intensieve na-controles en minder re-interventies.

Ervaringen met EVAR in België

EVAR werd ingevoerd in 2001 via een "conventie" van het RIZIV met een aantal ziekenhuizen. Deze conventie loopt af in 2006. De ingewikkelde in- en exclusiecriteria waren nauwelijks te controleren, en het peer review commitee dat het gebruik van EVAR moest opvolgen bleek feitelijk machteloos. Na 40 maanden waren er niet minder zeventig centra die minstens éénmaal EVAR hadden uitgevoerd, een ingreep die hoge eisen stelt aan behandelteam en beeldvormingscapaciteit. De conventie legde twintig onder supervisie uitgevoerde EVAR op als bewijs van expertise om erkend te worden. In het EUROSTAR register voerden later slechts 20 van de 70 centra over 40 maanden twintig of meer EVAR uit. Het is aan de behandelaars om te verklaren hoe en waar zij deze expertise hebben kunnen opdoen: op basis van de waargenomen aantallen lijkt dit onmogelijk.

De financiering van EVAR leverde daarbij een onbedoelde maar aanzienlijke stimulus ten voordele van deze nieuwe en onbewezen technologie, ten nadele van de vertrouwde open heelkunde. De stent wordt 6 000 € terugbetaald, de vasculair chirurg ontvang hetzelfde bedrag als voor een open ingreep en het ziekenhuis wint door de verminderde ligduur.

De conventie verplichtte deelname aan EUROSTAR, een register dat de resultaten van EVAR opvolgt. De resultaten behaald door de Belgische chirurgen waren behoorlijk, maar de helft van de behandelde patiënten hadden kleinere aneurysma's van < 5.5 cm. Van de 1437 geopereerde personen was 17% van de patiënten boven de 80 jaar, en 29% was ongeschikt voor heelkunde. De minder invasieve interventie, EVAR, bleek een sterke stimulans naar het uitbreiden van de behandelindicaties. Deze trend werd ook in andere landen (USA, Frankrijk) gezien. 25% van de patiënten bleek een aneurysma van 5.0 cm te vertonen. Zeldzame harde behandelindicaties van dergelijke kleine aneurysma's en de lage ruptuurkansen suggeren overbehandeling die niet in het belang van de patiënten was, in meerderheid oudere rokers met uitgebreide vaataantasting, hartziekte en longlijden. Het zeer lage behandelingspercentage (18%) met statines toont daarbij ook medische onderbehandeling.

De aantallen waren te klein om de effecten van een leercurve hard te maken. In de 50 kleine centra (met 20 patiënten of minder patiënten) die samen 482 patiënten behandelden was de vielen 18 doden door operatiesterfte (3.7%), In

de grotere centra was deze operatiesterfte 2.5%. Deze hogere sterfte (+49%) is statistisch niet significant, maar is wel consistent met de EUROSTAR gegevens uit geheel Europa.

Besluiten en aanbevelingen

Gecontroleerde introductie van emergeing technologie

De introductie van EVAR in België was een mislukking, maar België staat hier niet bepaald alleen. De combinatie van grote financiële belangen van de medische industrie, een aantrekkelijke nieuwe technologie en de belastende traditionele open ingreep leverde een nauwelijks weerstaanbaar cocktail. EVAR werd te gauw geïntroduceerd en te aggressief gepropageerd. De wetenschappelijke kwaliteit van de door het FDA goedgekeurde "pivotal trials" was belabberd. We moeten Nederland en Groot-Brittanië dankbaar zijn voor de moed die ze hebben betoond om deugdelijk gerandomiseerd onderzoek op te starten. De Nederlandse RCT was echter te klein, mede omdat Nederland een te kleine bevolking heeft. Het KCE beveelt daarom aan om de introductie van "emerging technology" grondiger aan te pakken op een wetenschappelijke basis in internationale samenwerkingsverbanden. Het KCE beveelt aan dat ook implantaten systematisch het vuur van goed wetenschappelijk gecontroleerd experimenteel onderzoek en toegevoegde economische analyse moeten weerstaan voor ze breed worden ingevoerd in de routine zorg, net zoals dat in toenemende mate van geneesmiddelen wordt geëist. De financiële input die dit vergt is niet gering, maar blijft slecht een kleine fractie van de middelen die nu werden besteed aan ongecontroleerde en dure experimenten zonder bekende opbrengst.

Regeling van te dure technologie

EVAR is effectief maar niet kosten-effectief in de electieve behandeling van AAA in patiënten geschikt voor een open ingreep en met een voldoende groot aneurysma (5.5 cm). Het invoeren van EVAR betekent een financiële belasting van het gezondheidszorgbudget met onvoldoende opbrengst. Wij bevelen daarom aan de conventie en de terugbetaling van endostents in een groot aantal centra zonder enige kwaliteitsgarantie stop te zetten, en EVAR enkel gelimiteerd beschikbaar te maken in een beperkt aantal centra (zie verder).

De patiënt-consument kan EVAR opeisen als effectieve technologie, door beroep te doen op het recht op individuele autonomie. Hij kan daarbij de extra-kosten op zich nemen, zoals hij ook de kosten van een dure wagen op zich neemt. Een eerste probleem is dat dit volledige informatie vergt, gegeven door een objectieve informatiebron zonder financiële of andere belangen bij de ingreep. Vervolgens komt de individuele autonomie van de patiënt-consument in botsing met sociale rechtvaardigheid: enkel wie voldoende rijk is kan zich deze dure technologie permitteren. In België komt deze praktijk van individuele financiering echter al voor, zonder dat deze systematisch in vraag wordt gesteld. In de toekomst zal dit dilemma tussen individuele autonomie en sociale rechtvaardigheid nog meer aan de orde komen. EVAR vormt een interessante case study, want EVAR is zowel zeer duur als een aantrekkelijk alternatief voor een belastende ingreep. Wij bevelen verdere studie aan naar het principe van individuele financiering van de kosten van effectieve maar te dure technologie.

Toekomstige regelingen voor terugbetaling van EVAR vergen het zoeken naar een beter evenwicht tussen de (totale) terugbetaling van een open ingreep en de (totale) terugbetaling van EVAR, waarbij het onderhandelen met de industrie over de kostprijs van de stent cruciaal is.

Betere kwaliteitsborging door registratie en centralisatie

Vasculaire chirurgie stelt hoge eisen aan behandelteam en technologische structuur, en legt desondanks een hoog risico op aan de patiënt. De overheid is verplicht de kwaliteit en de veiligheid van deze toch veel voorkomende ingrepen te borgen. Registratiegegevens moeten routinematig een minimum aantal betrouwbare klinische gegevens verzamelen over indicaties en behandelresultaten. Deze registers kunnen in de plaats treden van EUROSTAR, waarbij naast AAA ook carotisstenose gevolgd wordt, zowel voor endovasculaire behandeling als voor open heelkunde.

EVAR stelt de vraag naar de verdere toekomst van de vasculaire chirurgie. Endovasculaire behandeling is een in toenemende mate aantrekkelijk alternatief voor de "core-business" van de vasculaire chirurg (zie ook het KCE rapport over protected carotid artery stenting). Het vergt een zeer nauwe samenwerking met de radioloog en stelt hoge eisen aan de beeldvorming. Tegelijkertijd blijft de typisch heelkundige competentie onmisbaar, omdat endovasculaire behandeling vaak onmogelijk is. De noodzakelijke ervaring en technologie vergt een minimaal volume van investeringen en ingrepen om deze investeringen terug te verdienen. De huidige dilutie van majeure vasculaire chirurgie in België leidt daarom tot overbehandeling en tot minder goede resultaten in te kleine centra. Het is numeriek onmogelijk om veeleisende technologie, ervaren behandelteams en een kostenbewuste organisatie aan te bieden in zeventig centra. Het KCE beveelt centralisatie van de electieve endovasculaire behandeling van AAA aan in tertiaire vasculaire centra. Op basis van internationale vergelijkingen biedt een bevolking van tien miljoen ruimte voor minimum 20 en maximum 30 dergelijke tertiaire centra die de grote vasculaire heelkundige ingrepen centraliseren. In principe zijn criteria van erkenning voor tertiaire ziekenhuisdiensten gebaseerd op een goede geografische spreiding van het tertiaire aanbod, een netwerk van samenwerking met secundaire ziekenhuizen om een voldoende volume van vasculaire ingrepen te garanderen, goede multi-disciplinaire samenwerking, voldoende uitrusting en capaciteit en goede samenwerking met bestaande registers (hier EUROSTAR). Het is daarbij niet wenselijk om één enkele techniek (hier EVAR) te reguleren los van dit meer omvattende kader: EVAR is één van de strategieën van behandeling van aorta-aneurysmata. Het hanteren van aantallen ingrepen als selectiecriteria bevordert en beloont ongepaste en mogelijk gevaarlijke overbehandeling. De specifieke criteria voor erkenning van deze centra voor tertiaire vasculaire chirurgie vallen echter buiten het bestek van dit rapport.

Kernboodschappen

Epidemiologie

- In België leven 50 000 mannen en 10 000 vrouwen met een abdominaal aorta aneurysma (AAA). Het meerendeel heeft geen symptomen.
- De voornaamste oorzaken van AAA zijn de toenemende leeftijd, het geslacht, een familiale voorgeschiedenis, het bestaan van vasculair lijden en roken. De typische patiënt is een rokende oudere man met vaatlijden.
- Onbehandeld groeit een AAA. De groeisnelheid is variabel maar neemt toe met de omvang van het aneurysma: hoe groter het aneurysma, hoe sneller de groei. Het is niet bewezen dat enige medische behandeling invloed heeft op de groeisnelheid van AAA, buiten stoppen met roken.
- In België overlijden ongeveer 700 mensen jaarlijks aan een gesprongen AAA. De ruptuurkans is klein bij kleine AAA, maar neemt snel toe met de omvang van het AAA tot hoge waarden bij grote AAA. Het risico is groter bij vrouwen.
- Concurrerende sterfterisico's zijn hoog bij deze oudere, vasculair aangetaste patiënten. Relatief weinig mensen met een AAA zullen er ook aan overlijden; twee derden overlijdt door andere hart- en vaatziekten (hartinfarct, beroerte, ...).

Onderzoeksvragen

- Wat is de huidige bewijskracht over de effectiviteit en de kosten-effectiviteit van de electieve endovasculaire behandeling van AAA (EVAR), vergeleken met behoedzaam afwachten en open heelkunde?
- Voor welke indicaties is EVAR een betere keuze dan open heelkunde of behoedzaam afwachten?
- Wat zijn goede voorwaarden voor een veilig gebruik van EVAR?

Beschrijving van de technologie

Behoedzaam afwachten

- Voor kleinere AAA (< 5.5 cm) is behoedzaam afwachten de betere behandeling. Screeningsintervals van 36, 24, 12 en 3 maanden voor mannelijke patiënten met AAA van 35, 40, 45 en 50 mm verkleinen het ruptuurrisico tot minder dan 1% per jaar. Met dit schema, zullen jaarlijks ongeveer 5% van de patiënten met een AAA in aanmerking komen voor behandeling.
- Voor vrouwen is de drempel van 5.5 cm misschien te hoog, omdat hun ruptuurkansen hoger zijn. Studiegegevens staan niet toe om een lagere drempel te specificeren, gedeeltelijk omdat AAA redelijk zeldzaam zijn bij vrouwen. Bij vrouwen is de ruptuurkans hoger, maar ook de operatiesterfte.

- Sterfte door hartziekte of beroerte is een belangrijker doodsoorzaak bij patiënten met een klein AAA dan een fatale aortaruptuur. Gepast cardiovasculair risicomanagement verlengt het leven meer dan herstel van kleine AAA.

Open heelkunde

- Open heelkunde van AAA kent een aanzienlijke sterfte en morbiditeit. In niet geselecteerde gegevens is de sterfte rond 7% en cardiale, pulmonaire en renale complicates zijn rond 11%, 8% en 8%. In US gegevens varieerde de sterfte van 3.6 tot 6.4%, afhankelijk van de ervaring van het ziekenhuis en de chirurg.
- In de Verenigde Staten zijn de ervaring van de chirurg en het volume ingrepen van het ziekenhuis belangrijke voorspellers van de operatiesterfte. In België zijn er hierover geen gegevens.
- Buiten impotentie en ejaculatiestoornissen is de lange termijnsprognose na een open ingreep uitstekend. Hartziekte, beroerte en longaandoeningen bij de (ex-)roker veroorzaken veroorzaken de meeste van de sterfgevallen.

EVAR

- Vergeleken met open heelkunde, is EVAR een minder ingrijpende operatie. Operatiesterfte, operatieduur, morbiditeit en ligduur in het ziekenhuis is geringer. Over de langere termijn heeft EVAR meer complicaties dan open heelkunde. Dit noodzaakt een intensievere follow-up en veroorzaakt meer her-ingrepen.
- De voornaamste complicaties van EVAR zijn migratie van de endoprothese, stuk gaan van de endoprothese en lekken ("endoleak"), die het aneurysma onder druk kunnen houden. Migratie en endoleaks type 1 en 3 noodzaken her-ingrepen, endoleaks type 2 noodzaken surveillance.
- Stuk gaan van de stent was een probleem van oudere endostents. De nieuwere generaties van endostents tonen betere resultaten, maar tot nog toe zijn er weinig gegevens over de duurzaamheid over langere termijn van deze nieuwe endostents.

Klinische effectiviteit

Beschrijving van de studies

- Twee klinische multicentre studies hebben gerandomiseerde patiënten, geschikt voor open heelkunde, en behandeld met EVAR of open heelkunde, over twee en vier jaar opgevolgd. De Britse EVAR-1 was een goede studie, de Nederlandse DREAM was een matig goede studie.
- Zeven "pivotal" multicentre studies hebben één tot zes jaar follow-up beschreven van niet gerandomiseerde patiënten behandeld met EVAR of open heelkunde. "Pivotal" studies dienen om erkenning van de Food and Drug Administration (FDA, USA) te verkrijgen. De vergelijkbaarheid tussen beide patiëntgroepen was gering, waarom deze studies als slecht beoordeeld werden.
- Vele studies uit één enkel centrum die AAA patiënten na EVAR of open heelkunde vergelijken zijn gepubliceerd. Deze studies zijn zelden interpreteerbaar, omdat de verschillende criteria voor het uitvoeren van EVAR of heelkunde beide patiëntgroepen onvergelijkbaar maken.

Effectiviteit bij patiënten geschikt voor open heelkunde

- De behoefte tot open heelkunde verdwijnt niet met het beschikbaar stellen van EVAR: er blijken meer mensen niet in aanmerking te komen voor EVAR dan wel.
- In beide patiëntgroepen (EVAR of open heelkunde) was de kwaliteit van leven vóór de ingreep geringer dan in een vergelijkbare bevolking zonder AAA. De kennis over een potentieel fatale aandoening vermindert de levenskwaliteit.
- EVAR is minder invasief. Over korte termijn biedt EVAR belangrijke voordelen over open heelkunde.
- Na één tot twéé jaar verdwijnt het sterfte-voordeel van EVAR. De hogere operatiesterfte van open heelkunde vervroegt het moment van overlijden in vasculair aangetaste patiënten, maar niet zo veel. EVAR kent drie tot vijfmaal meer heringrepen en complicaties dan open heelkunde over de langere termijn.
- DREAM en EVAR-1 zijn het niet eens over de lange termijnsresultaten van kwaliteit van leven. In DREAM zijn deze lager in de EVAR groep, in EVAR-1 is er geen verschil.
- Om samen te vatten, EVAR biedt betere resultaten over de korte termijn, maar minder goede resultaten over de lange termijn. Het sterftevoordeel dat EVAR aanvankelijk biedt, verdwijnt binnen de 2 jaar na de interventie.

Effectiviteit bij patiënten niet geschikt voor open heelkunde.

- Terwijl EVAR ontwikkeld werd voor patiënten die niet geschikt waren voor open heelkunde en EVAR ook als dusdanig verkocht werd aan het publiek, werd dit voordien nooit onderzocht. De eerste resultaten van een gerandomiseerde studie die EVAR vergeleek met afwachten verschenen pas in 2005, EVAR-2. EVAR-2 werd matig goed bevonden: de aantallen waren klein en er trad veel "cross-over" op van afwachten naar EVAR.
- In EVAR-2 was er geen statistisch significant verschil tussen behandelen met EVAR of afwachten: de sterfte was 21% hoger in de behandelde groep, maar kon ook 13% lager of 96% hoger zijn dan in de onbehandelde groep.
- Morbiditeit en heringrepen waren vijf tot zesmaal hoger in de behandelde groep dan in de onbehandelde groep. Deze cijfers waren statistisch significant.
- Er waren geen duidelijke verschillen in levenskwaliteit tussen de behandelde en de onbehandelde groep.
- In afwachting van meer en betere gegevens stellen we dat EVAR bij patiënten ongeschikt voor heelkunde het risico op complicaties en heringrepen verhoogt zonder de sterfte te verminderen.

Kosten-effectiviteit

Kosten van EVAR en mogelijke evolutie

- EVAR is duurder dan open heelkunde
- De voornaamste kostencomponent die EVAR duurder maakt is de kostprijs van de endoprothese, die ongeveer 57% van de initiële hospitalisatiekosten uitmaakt. De kosten van follow-up zijn hoger na EVAR, door de verhoogde nood tot surveillance en beeldvorming.
- Bij de huidige kostprijs van de endoprothese is het onwaarschijnlijk dat EVAR ooit de kostprijs van open heelkunde benadert, zelfs als de andere kosten zouden verminderen door toegenomen ervaring van de operator.
- De evolutie van kostprijs van de endoprothese en de te verwachten minder intensieve opvolging na EVAR blijven onzeker, want ze zijn sterk afhankelijk van de industriële dynamiek en de technologische ontwikkelingen.

De kosten-effectiviteit van EVAR

- De bestaande evaluaties van de kosten-effectiviteit van EVAR, vergeleken met open heelkunde, staan geen brede implementatie van EVAR toe.
- Onzekerheid over de kosten effectiviteit van EVAR is nog zeer groot.
- Belangrijke determinanten van de kosten-effectiviteit zijn het aantal door EVAR gewonnen levensjaren, het aantal gewonnen levensjaren vrij van belangrijke complicaties en het verschil tussen de kostprijs van EVAR en open heelkunde.

Het invoeren van EVAR in België

De conventie

- In België werd in 2001 een conventie afgesloten voor de duur van vijf jaar, houdende de terugbetaling van de endoprothese bij het vervullen van een aantal condities. Inclusie van de patiënten in het internationaal EUROSTAR register maakte deel uit van deze conventie. De ons beschikbare EUROSTAR gegevens beschrijven 1437 Belgische patiënten, opgenomen in het register tussen april 2001 en oktober 2004.

De klinische resultaten

- Veel meer centra (70) dan voorzien recruteerden patiënten, met kleine volumes per centrum als gevolg. Gedurende 40 maanden recruteerden 50 centra minder dan 20 patiënten per centrum.
- De leeftijd was gemiddeld 72.7 jaar, met 17% van de patiënten die ouder dan 80 waren. 29% van de patiënten waren ongeschikt voor heelkunde. De gemiddelde diameter van het AAA was 56.6 mm, waarbij 25 % van de patiënten een AAA hadden van ≤ 5.0 cm en 50 % van de patiënten AAA hadden van ≤ 5.5 cm.
- Na EVAR was de korte termijnssterfte (30 dagen of tijdens hospitalisatie) 2.6%. Twee jaar na de ingreep was de sterfte 13.4% en de gecumuleerde kans op heringrepen 7.8%.
- In de 50 ziekenhuizen met 20 patiënten of minder, was de korte termijnssterfte 3.6%. In de 20 ziekenhuizen met meer dan 20 patiënten, was de korte termijnssterfte 2.1%. De sterfte was 49% hoger in de kleinere ziekenhuizen, maar de betrouwbaarheidsintervallen lagen tussen -29% en +213%: het verschil was statistisch niet significant. Maar dit verschil in sterfte tussen ervaren en minder ervaren centra is wel vergelijkbaar met de Europese resultaten van EUROSTAR en is te verklaren door een leercurve.
- De twee-jaarsresultaten van EVAR in EUROSTAR zijn observationeel vergeleken met vier belangrijke gerandomiseerde klinische studies. Voor de kleine AAA in EUROSTAR waren de resultaten vergelijkbaar met de resultaten van behoedzaam afwachten in UKSAT (één van de grote trials die heeft aangetoond dat heelkundig behandelen van kleine AAA niet beter is dan behoedzaam afwachten). Voor de grote AAA zijn de resultaten van EUROSTAR vergelijkbaar met EVAR-1 en DREAM. Voor de grote AAA in patiënten ongeschikt voor heelkunde zijn de resultaten van EUROSTAR beter dan EVAR-2.
- EVAR werd ook geïdentificeerd in de gegevensbanken van het intermutualistisch agentschap (IMA). De gegevens van EUROSTAR en IMA werden gekoppeld.
    - Veel EVAR die opgenomen werden in EUROSTAR werden niet weergevonden in IMA. Dit suggereert dat voor deze interventies geen terugbetaling werd aangevraagd.
    - Na twee jaar was de waargenomen sterfte in IMA hoger dan in EUROSTAR. Dit toont dat de sterfte in EUROSTAR

onderschat wordt (wanneer de patiënt overlijdt, wordt dit automatisch doorgegeven aan IMA). Dit kan mee verklaard worden door de trage overdracht van de gegevens naar EUROSTAR.

De kosten

- De kosten van EVAR voor AAA in België zijn gemiddeld 11500 € (mediaan 10400 €). De kosten van open heelkunde voor AAA in België zijn gemiddeld 7900 € (mediaan 6200 €).
- De relatieve en absolute kostenverschillen tussen EVAR en open heelkunde zijn vergelijkbaar met deze waargenomen in de gerandomiseerde studies (EVAR en DREAM).

Ethische overwegingen

Ethische en politieke dilemma's ontstaan door financiering van effectieve maar dure en niet kosten-effectieve medische technologie:

- Keuze 1: EVAR wordt niet gefinancierd door de gemeenschap, en wordt geheel niet ter beschikking gesteld
  - EVAR is niet beschikbaar voor diegenen die een interventie wensen met lagere risico's op kortere termijn
  - De keuzevrijheid van patiënt en arts wordt ingeperkt.
  - Zonder tijdige terugbetaling van haar investeringen kan de medische industrie afzien van verdere technologie-ontwikkeling, en zo toekomstige patiënten superieure medische technologie onthouden
- Keuze 2: EVAR wordt niet gefinancierd door de gemeenschap, maar wel ter beschikking gesteld van de individuele patiënt
  - EVAR is enkel beschikbaar voor diegenen die voldoende financiële middelen hebben om ze te betalen
  - Arm en rijk worden ongelijk behandeld.
  - Informatie-asymmetrie tussen arts en patiënt moedigt behandelbeslissingen aan die meer in het belang van de arts zijn dan in in het belang van de patiënt.
- EVAR wordt gefinancierd door de gemeenschap en breed ter beschikking gesteld
  - Middelen worden gespendeerd die niet meer beschikbaar zijn voor meer kosten-effectieve zorg elders.
  - Sociale onrechtvaardigheid ontstaat met andere patiëntengroepen, die geen toegang hebben tot dergelijke dure zorg. Onrechtvaardigheid ontstaat omdat de stijgende gezondheidszorgkosten middelen wegnemen van andere budgetten (onderwijs, economie, pensioenen, armoedebestrijding, ...)

Discussie en conclusies

- EVAR werd te gauw ingevoerd, op een moment dat het technologische niveau van de endoprothese nog onvoldoende was. Dit heeft wereldwijd geleid tot niet-geïnformeerde experimenten op tienduizenden patiënten voor twijfelachtige indicaties, die achteraf ongepast bleken.
- Goede gerandomiseerde klinische studies met voldoende follow-up verschenen pas in 2005. Ze toonden weinig belangrijke maar tastbare effecten van EVAR aan, aan zeer hoge kosten. Patiënten ongeschikt voor open heelkunde bleken ook ongeschikt voor EVAR.
- Ten overvloede: experimenteel onderzoek zonder degelijke controle-groep levert zelden interpreteerbare resultaten.
- EVAR blijft een veelbelovende technologie, die niet kosten-effectief is. EVAR hoort niet beschikbaar te worden gesteld worden in de standaard gezondheidszorg, omdat het schaarse middelen verspilt die elders beter worden aangewend. Om kosten-effectief te worden moeten nog vele voorwaarden vervuld worden:
  - De kostprijs van de endostent moet dalen
  - De indicatiestelling voor EVAR moet verbeteren.
  - De aantallen heringrepen moeten dalen.
- Indien EVAR wordt gebruikt, is het enkel toepasbaar bij patiënten geschikt voor open heelkunde en met voldoende grote AAA ($\geq$ 5.5 cm, of $\geq$ 5.0 cm met specifieke risicofactoren).
- De keuze tussen EVAR en open heelkunde moet worden gemaakt door een multidisciplinair vasculair team. De beslissing blijft de eindverantwoordelijkheid van de behandelaar (vasculair chirurg of interventioneel radioloog). De gepaste medische behandeling van deze oudere patiënten met meerdere chronische aandoeningen is minstens even belangrijk als de heelkundige ingreep.
- Artsen die doorverwijzen voor deze ingreep hebben behoefte aan aan de nieuwe inzichten aangepaste basiskennis over AAA. De beslissing om in te grijpen is complex, waarbij de kosten en de baten voor oudere en kwetsbare patiënten tegen elkaar moeten worden afgewogen. Een AAA bij deze patiënt is één tijdbom tussen vele andere.

Beleidsaanbevelingen

Wijs (verder) experimenteren met EVAR

- Bij kleine AAA (< 5.5 cm) is behoedzaam afwachten de regel en behandeling met EVAR of open heelkunde de uitzondering. In grote AAA (≥ 5.5 cm) is behandelen de regel en behoedzaam afwachten de uitzondering.
- EVAR is duur en onvoldoende effectief. EVAR mag niet financieel worden aangemoedigd ten nadele van open heelkunde. De extra kosten van EVAR moeten gedragen worden door research budgets, ondersteund door goede wetenschappelijke studie-protols, en niet door gezondheidszorgbudgetten. Deze klinische budgetten zouden gezamenlijke investeringen betreffen van de medische industrie (R&D) en de gemeenschap (klinisch medisch onderzoek).

Vasculaire heelkunde van hoge kwaliteit

- Registers zouden routinematig goede gegevens moeten registreren van zowel indicaties als resultaten van majeure vasculaire heelkunde, of ze nu open dan wel endovasculair zijn. Audits van deze resultaten zouden de regel moeten zijn, niet de uitzondering.
- Om voldoende volumes van zowel open heelkunde als EVAR te garanderen, en om kosten-effectief gebruik van dure technologie te waarborgen, zou EVAR enkel ter beschikking mogen worden gesteld van een beperkt aantal vasculaire heelkunde centra met tertiaire verwijsfunctie. Deze tertiaire centra worden gevormd op basis van beschikbare technologie, bewezen kwaliteit (o.a. aangetoond door goede samenwerking met EUROSTAR), goede samenwerkingsverbanden om voldoende volume te genereren en een goede geografische spreiding.
- Majeure vasculaire heelkunde kan niet worden uitgevoerd op een veilige, kosten-effectieve en kwalitaitief hoogstaande wijze in te veel centra met te lage volumes. Wij adviseren concentratie van majeure vasculaire heelkunde in een beperkt aantal “high tech” tertiaire zorgcentra.

Verbeteren van de informatie

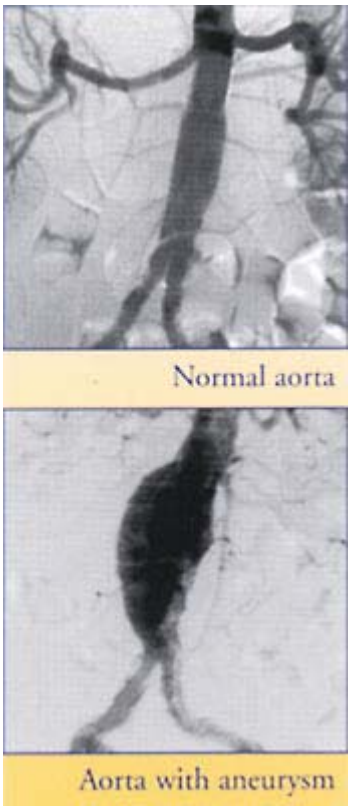
- Andere dokters dan vasculaire chirurgen en interventionele radiologen zouden gemoderniseerde medische kennis moeten verwerven over AAA, specifiek over de gepaste indicaties van interventies.
- Terwijl “informed consent” en consumentenautonomie een na te streven doel is, eist dit in de behandeling van AAA moeilijke afwegingen tussen concurrerende risico’s, te maken met oudere patiënten met chronische vasculaire ziekte. We adviseren meer studie over welke informatie moet worden gegeven, en hoe deze moet aangereikt worden.

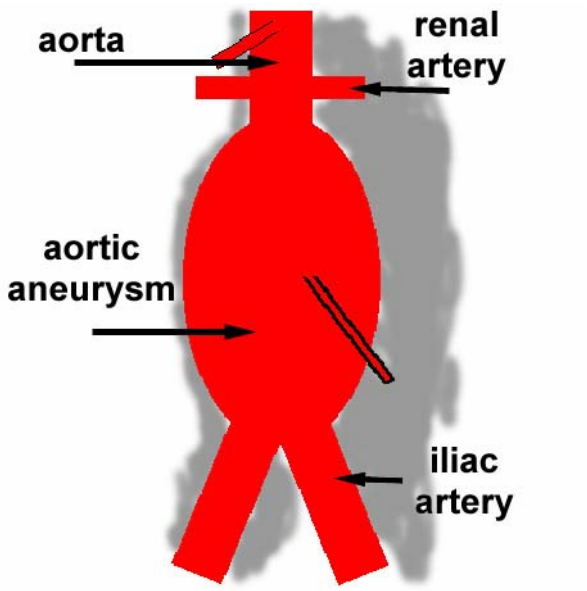
Inhoudstafel

1. EPIDEMIOLOGY

An aortic aneurysm is the dilatation (widening or bulge) of a portion of the aorta, usually at a weak spot in the aortic wall (see Figure 1.1).

Figure 1.1



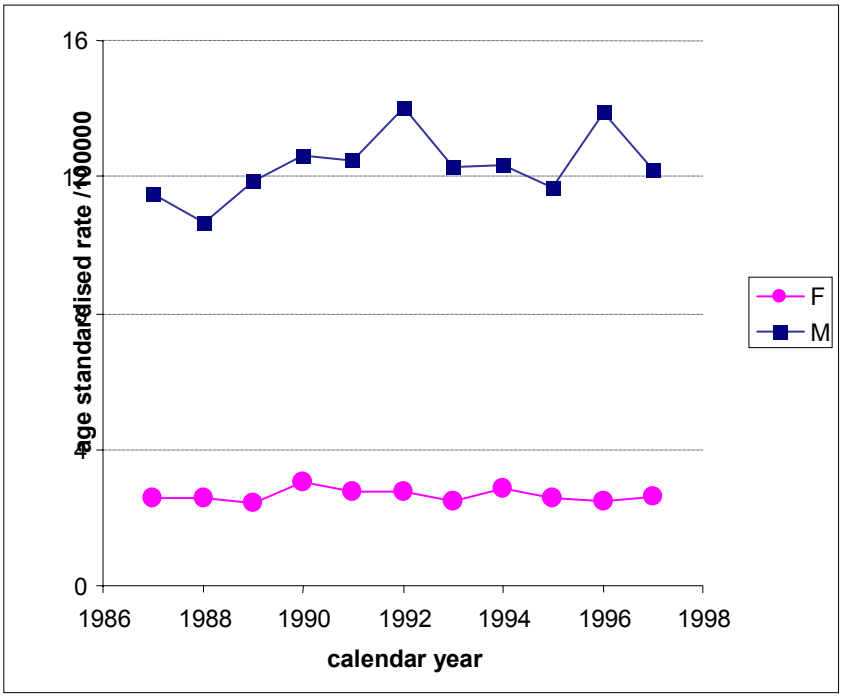


The aorta is the largest artery, carrying the blood that is pumped out of the heart and distributes it, via its many branches, to all the organs of the body. The aorta projects upwards from the heart in the chest and then arches downwards, travelling through the chest (the thoracic aorta) and into the abdomen (the abdominal aorta). Most aortic aneurysms occur in the abdominal aorta. Abdominal aortic aneurysm (AAA) is defined as a dilatation of the aorta greater than 3 cm or 150% of the aortic diameter at the diaphragm (Infra to suprarenal ratio, I/S). The normal diameter of the Infrarenal Aorta is 21 – 22 mm (male) and 19 mm (female).[1, 2]

The most important determinants of AAA are gender and age. AAA is predominantly a male disease, although a unique absolute diameter may be biased by the different sizes of men and women. However, the gender difference in age standardised mortality is high: among Belgian men, age standardised AA mortality (aortic aneurysm, ICD 441; all) was 4.6 times higher than among women (see figure 1.2). The risk of death by AA is negligible before age 50 , and then doubles with every increase of age of 7 years; it is 100 times larger in men 35 year older (see figure 1.3). The absolute risk of dying of an AA

before age 75 is low: 4.3 per 1000 for men and 0.6 per 1000 for women. As women grow older than men, the difference in absolute numbers is less pronounced. In 1997, 192 women died of AA, and 515 men. It may be noted in the Einstein year that Albert Einstein fell victim to a ruptured AA.

Figure 1.2: Age standardised mortality of aortic aneurysms (all).[3] Note the gender difference and the limited change over time.



The most important other determinant of AAA is familial predisposition. Abdominal aortic aneurysms are a familial disorder, possibly polygenetic in origin.[4] The most common other characteristics are smoking, peripheral vascular disease and other cardiovascular disease.[5] While high blood pressure is not a risk factor for aortic aneurysm, it is for rupture of an aortic aneurysm.[6, 7] Female sex protects against having an aortic aneurysm, but increases the risk of rupture when having such an aneurysm.[6] One of the potential explanation is that women have a smaller aorta, and that the risk of rupture increases with relative size, not absolute size.

Figure 1.3: AAA mortality rate by age and gender (logarithmic scale). Note the sharp age dependency, with the risk of rupture. Women reach in average the same mortality level 15 year later. The risk doubles with every increase of 7 years of age. The reliability of AA as cause of death is moderate – part of the deaths are registered as acute deaths.

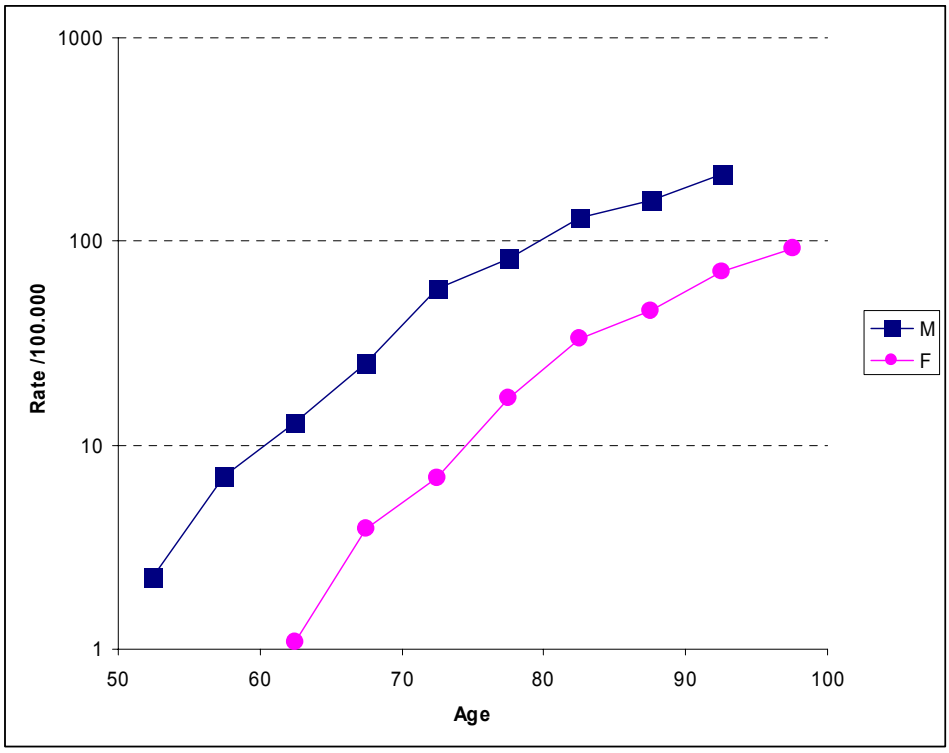
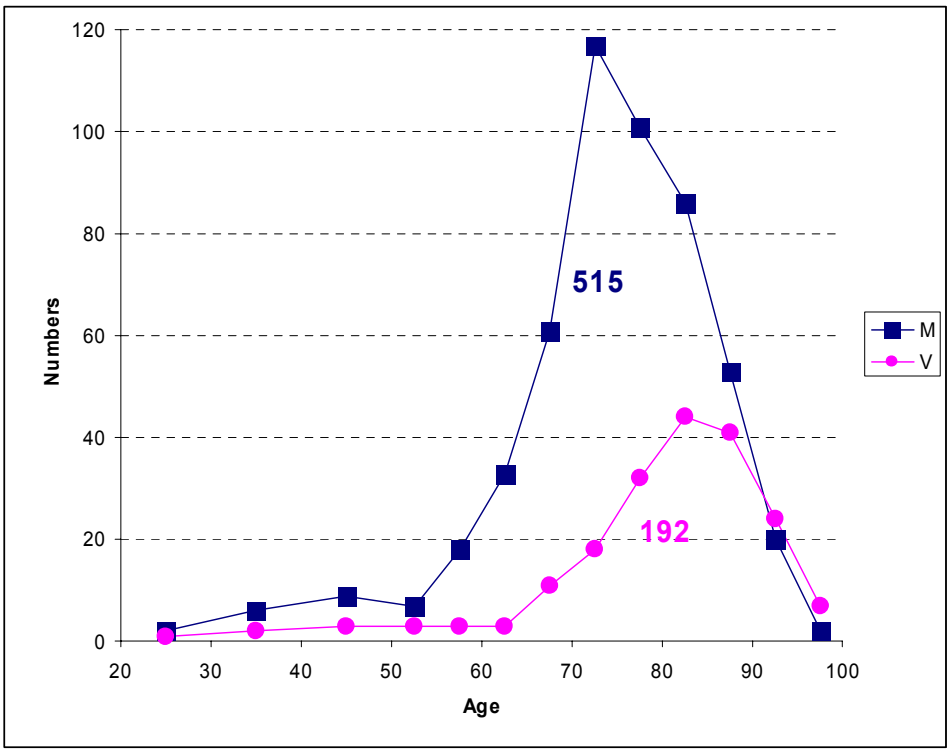


Figure 1.4: Absolute numbers of death by aortic rupture (AA; all) in 1997.

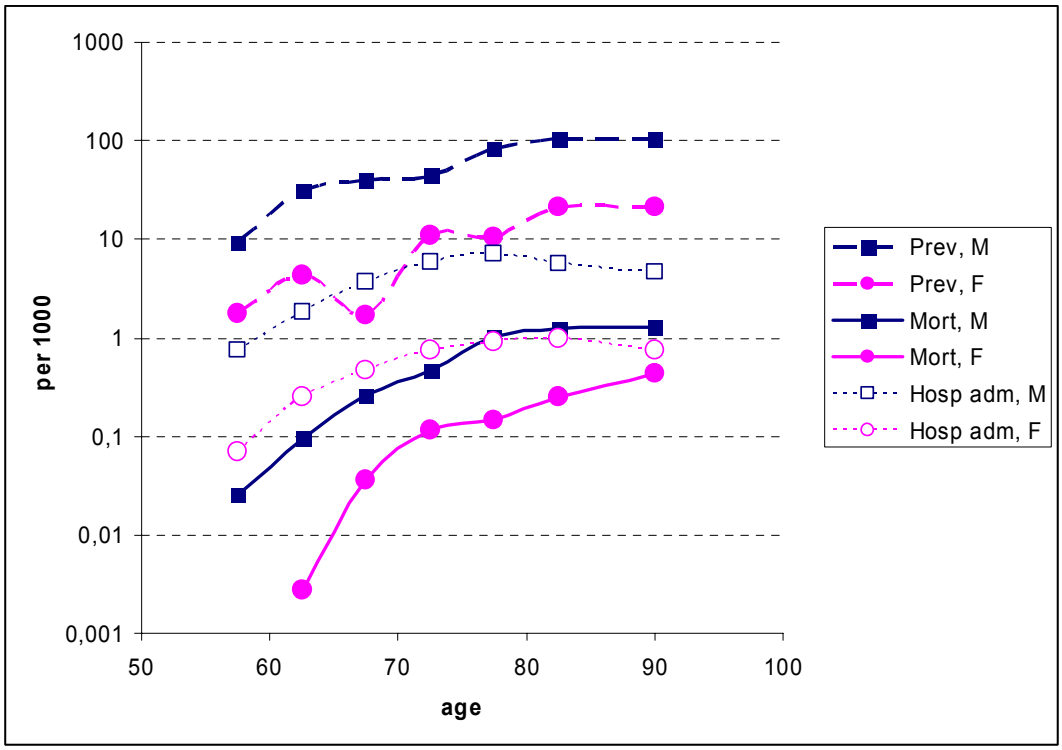


Since 1987, there was little change over time in AA mortality. This is comparable to the Netherlands. That stabilisation is thought to be caused by improved risk distribution (predominantly less smoking in cohorts born after 1920) balancing increased survival of cardiovascular disease patients.[8] However, it has to be noted that the time trends (pronounced increase in AAA mortality in many populations since the Second World War, followed by constant rates since the end of the 80s) remain ill understood.

The prevalence of AAA in ultrasonographic screening studies shows that about 5 percent of men older than 65 years of age have an occult small aneurysm (3 to 6 cm in diameter).[5] Prevalence increases 2 to 5 times in the presence of a family history of aneurysm, clinical vascular disease or both.[9] In Rotterdam (population 55 and older), the prevalence (> 3.5 cm or I/S > 150%) was 4.1% (3.3 – 5.0) among men and 0.7 % (0.4 – 1.0) among women (see figure 1.5).[10] In Liège, the prevalence of AAA > 30 mm in the 41% responders of a population based survey was 3.8% (28/727); the prevalence of aneurysms > 4.0 cm was 2/727 (0.28 %) and of > 5.5 cm 1/727 (0.14 %).[11] Extrapolated to the Belgian population, we expect some 50.000 men and 10.000 women with a small sonographically detectable aneurysm. The annual mortality rate of all AA (cfr supra) of 500 men and 200 women is consistent with the Netherlands, and an annual probability of death from AAA, given an occult aneurysm, around 1 and 2%.

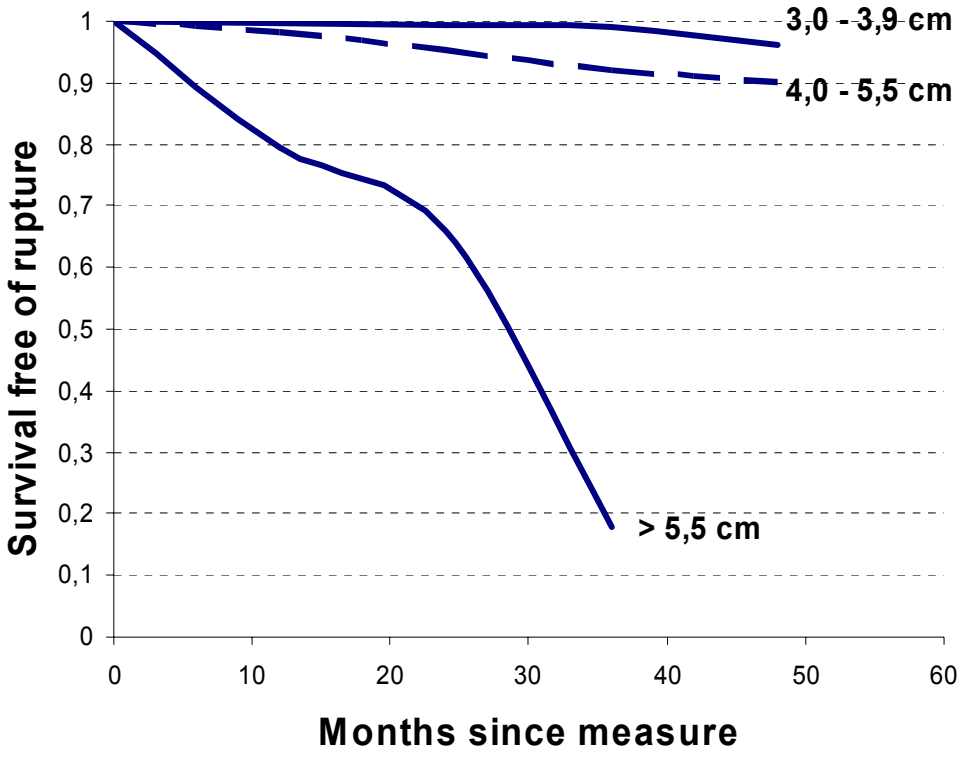
Most commonly, AAAs arise below the renal arteries, and remain asymptomatic for many years. Symptoms may occur from pressure effects on adjacent structures, (e.g. causing back pain or abdominal throbbing), from embolisation of intramural thrombus, or in association with other vascular complaints such as intermittent claudication. Most aneurysms are incidentally discovered during routine physical examination, during a diagnostic imaging study, or during surgery for other abdominal pathology. In the absence of symptoms related to an aneurysm, the threat that the aneurysm will rupture is the major consideration. Only 10 to 30 percent of patients survive the rupture of an AAA; a minority will reach the hospital alive, and of these, only about half survive the emergency surgical repair.[12] However, patients with AAA are most often elderly males at high cardiovascular risk. Few patients with small aneurysms die from a ruptured aneurysm; approximately two third will die from another cardiovascular cause. When the diameter of the aneurysm exceeds 5.5 cm, the risk of rupture increases markedly (see figure),[7] and most vascular surgeons recommend repair of aneurysms larger than 5.5 cm, provided that the patient is fit for surgery. The annual risk of rupture of small aneurysms varied from 1% for aneurysm of < 4 cm to more than 2% for one of < 5.5 cm. However, as there are many more small aneurysms than big ones, a sizeable proportion of the ruptures occur in the smaller aneurysms. The risk of rupture is significantly associated with female sex, larger initial aneurysm diameter, current smoking and higher mean blood pressure. Medical treatment is therefore based on adequate risk management (particularly smoking cessation and blood pressure control).

Figure 1.5: Prevalence (1990-92), mortality (2000) and hospital admission rates (2000) of AAA in the Netherlands.[8] The prevalence increases with age among men from 1% to 10%, among women from 0.2% to 2%. The annual mortality is in average 90 times less than the prevalence. The annual mortality of detectable aneurysms is around 1%, the annual probability of hospital admission of detectable aneurysms is around 10%.



The natural history of an untreated aneurysm is one of continued expansion. The mean growth rate in the UK Small Aneurysm Trial (SAT) was 2.6 mm/yr (95% CL -1.0; 6.1 mm year), accelerating with time and expansion of the aneurysm.[13] Typical growth rates are 2.7 mm/yr for aneurysms of 40-45 mm and 4.0 mm/yr for aneurysms of 50-55 mm.[13] This is lower than generally cited, as most series reported growth rates from patient series truncated by surgery. Many patients can be seen to have linear or accelerating expansion, although 6.4% experienced a steady reduction in AAA diameter. A noticeable feature of some patients is "growth spurts" followed by periods of stasis. Continuing smoking is the only notable predictor of growth rate (except for time and size of the aneurysm), although the effect is too small to warrant different screening intervals for smokers and non-smokers.

Figure 1.6: Rupture probability since start of follow up.[6] Among aneurysms < 4 cm, the probability was 1% over 3 years, then increasing. Among aneurysms 4 – 5.5 cm, the annual probability of rupture was 2% over 4 years.



Key messages

- There are 50,000 men and 10,000 women living in Belgium with an abdominal aorta aneurysm (AAA) exceeding 35mm or 150% of the infrarenal aorta diameter (estimates based on the Rotterdam Study). The large majority are small AAA without signs or symptoms.
- The most important determinants of an AAA are age, sex, familial history, a history of cardiovascular disease and smoking. The typical AAA patient is an elderly male suffering from vascular disease who smokes.
- Untreated AAA expand. Growth rates are highly variable, but time and size dependent. Typical growth rates are 2.7 mm/y for an aneurysm of 40-45 mm and 4.0 mm/y for an aneurysm of 50-55 mm. Medical treatment is not known to be effective, except for smoking cessation.
- The annual mortality by rupture of an AAA is between 1 to 1.5%; in Belgium, 700 patients were notified as dead from an aortic aneurysm, but this is likely an underestimate (death is sudden and remains unexplained by elderly patients). The rupture probability is sharply dependent of the AAA diameter, increasing till 2.2% for aneurysms of 50-55 mm. The rupture probability increases rapidly to high values in aneurysms of 55 mm and more. The rupture risk is higher in women.
- Competing risks of death are high in these patients, and few patients with an AAA die of it. Two third will die of another cardiovascular cause (heart disease, stroke).

2. OBJECTIVES: CHOICE OF INTERVENTIONS FOR ABDOMINAL AORTIC ANEURYMS

Abdominal aortic aneurysm is a progressive disorder, characterised by continuing expansion of the aneurysm and ultimately rupture. Still, good clinical practice recommends watchful waiting for smaller aneurysms (see below for criteria). The average patient is old, with concurrent vascular disease and high competing risks of mortality. This introduces a clinical dilemma and difficult risk communication.

As the aneurysm reaches 5.5 cm, growth rates and rupture probabilities become sufficiently high to warrant an intervention. Open abdominal surgery repairing the aneurysm is a major intervention, at high risk of mortality and morbidity, to be performed in increasingly frail elderly. A more conservative approach has been introduced, that evades the high risks and perils of open surgery: endovascular graft repair (EVAR) of AAA. A stentgraft is introduced by endovascular route through the iliac artery. However, this technology is still new. It trades the high short term morbidity of mortality of open surgery for higher long term complication rates and need for surveillance.

Specific questions are:

- What is the state of the art of effectiveness and cost-effectiveness of endovascular graft repair of AAA, compared to watchful waiting and open repair?
- For which patient groups EVAR is a better choice than watchful waiting and open repair?
- What are the best conditions for safe use of EVAR?

3. TECHNOLOGY DESCRIPTION

Close to all aneurysms will expand and may ultimately rupture, but as persons with such aneurysms are often elderly males with vascular disease, death of another cause is (much) more frequent. The choice is between watchful waiting, a safe procedure when the aneurysm is small and an intervention, a safer procedure when the aneurysm is large. The intervention may be open surgery, a major surgical intervention with (very) high short term term risks but good long term results or endovascular stent grafting, an endovascular procedure with lower short term risks, but with unknown and certainly not so good long term results.

A recent seminar in the prestigious Lancet, from the Belgian Université de Liège, summarised the state of the art in patients fit for surgery: watchful waiting for AAA with a diameter under 5 cm, intervention in few selected patients at high risk at a diameter between 5 and 5.5 cm and in all patients at a diameter over 5.5 cm.[14]

Proposed schedule [14]:

∅ < 5.0 cm	*wait*
∅ > 5.5 cm	*repair*
∅ 5.0 -5.5 cm	
risk factors† present	*repair*
risk factors† absent	*wait*

† Risk factors are: female sex, familial cases, proved rapid growth

3.1. WATCHFUL WAITING

Two large randomized trials have addressed the issue of whether watchful waiting for small abdominal aortic aneurysms is an acceptable alternative for intervention. Patients with asymptomatic aneurysms (diameter 4.0 to 5.5 cm) were randomly assigned to either early elective (open) surgery or a period of surveillance for rapid expansion and the development of symptoms, with a protocol recommending surgery when the diameter exceeded 5.5 cm. The United Kingdom Small Aneurysm Trial, in which ultrasonographic surveillance was used, showed that the cumulative 6-year survival rate was 64 percent in both treatment groups, the risk of aneurysm rupture was 1 percent per year, and the 30-day operative mortality among patients who underwent elective repair was 5.6 percent.[15, 16] The Aneurysm Detection and Management (ADAM) Veterans Affairs Cooperative Study, in which surveillance was primarily conducted by computed tomography (CT), showed a six-year cumulative survival rate of 74 percent in each treatment group, rates of rupture of 0.6 percent per year, and operative mortality of 2.7 percent.[17] The absolute differences between the two trials probably relate to the different populations studied: patients in the ADAM study cohort were more fit.[17, 18] Both studies demonstrated that elective surgery for small aneurysms does not improve six-year survival. Longer-term follow-up, to 9 years, in patients in the United Kingdom trial showed no significant difference in the mean survival between the surgery group and the surveillance group (6.7 years and 6.5 years, respectively).[18] The marginal late benefit in overall survival in the surgery group

was largely attributable to changes in lifestyle, including smoking cessation prompted by surgery.[19] The higher costs of treatment associated with a policy of early intervention make ultrasonographic surveillance for men with small AAA diameters the more cost-effective option.

Screening intervals of 36, 24, 12, and 3 months for male patients with AAA diameter 35, 40, 45, and 50 mm, respectively, yield less than a 1% chance of exceeding 55 mm.[13] Other screening intervals are comparable.[4] On this basis, approximately 5 percent of patients are considered for intervention at each surveillance visit.

The risk of rupture is four times as high among women than among men.[18] The fact that aneurysms rupture at smaller diameters in women may simply reflect that women are smaller than men, with a fixed diameter representing a greater dilatation as a proportion of the original diameter.[1] For women, the threshold diameter of 5.5 cm for aneurysm repair is probably too high, but trial data do not permit the specification of a lower threshold. If women were considered for surgery when their aneurysms reached a diameter of 5 cm, screening intervals of 12 months could be recommended for aneurysms with diameters of 3.0 to 4.4 cm, and intervals of 6 months for aneurysms with diameters of 4.5 to 5.0 cm. However, UKSAT also showed that the higher operative mortality in females might balance the advantage of earlier repair, and operative repair of aneurysms $\leq$ 5.5 mm in women remains debatable.[18]

There is little evidence that any medical treatment slows down aneurysm expansion. Smoking is the only risk cardiovascular risk factor that truly counts– smoking cessation has a probable effect.[13] Aneurysms expanded more rapidly (but by a modest mean of 0.4 mm per year) in current smokers than in former smokers (mean, 0.25 cm per year). As most patients with aneurysms have vascular disease, appropriate cardiovascular risk management will prolong life in ways other than by slowing the expansion of aneurysms.

While there is no evidence that treatment of smaller aneurysms improve outcomes, patients' preferences for the choice between early and deferred intervention should be considered. 94% of the aneurysms grow, and the awareness that one may have to undergo major surgery in the future may impair one's quality of life. In the United Kingdom Small Aneurysm Trial, there were small differences in the quality of life (as evaluated by a short questionnaire) at one year between those assigned to early surgery and those assigned to ultrasonographic surveillance.[19] Survivors of early elective surgery perceived their health to be better than did patients in the surveillance group. This may be – among others - a psychological consequence of the large investment they made in their health.

Key messages

- In aneurysms of < 5.5 cm, watchful waiting is the preferred treatment. Screening intervals of 36, 24, 12, and 3 months for male patients with AAA diameter 35, 40, 45, and 50 mm, respectively, yield less than a 1% chance of rupture. With this schedule, in average 5% will be eligible for aneurysm repair at each round.
- For women, the threshold diameter of 5.5 cm for aneurysm repair is probably too high, but trial data do not permit the specification of a lower threshold (partly because aortic aneurysms are rare among women). Higher operative mortality in females might balance advantage of earlier repair at 5.0 cm.
- Mortality by heart disease or stroke is a much greater cause of death in patients with small aortic aneurysms than aortic rupture. Appropriate cardiovascular risk management will prolong life much more than (small) aneurysm repair.

3.2. OPEN SURGERY

The current standard operation for abdominal aortic aneurysms was developed in the mid 1950s and is a major intervention with potentially many and dangerous complications and a high risk of death. It consists of replacement of the weakened, dilated portion of the aorta with an artificial graft manufactured from a polyester material (Polyester). The abdomen is opened to expose the aorta which is then temporarily clamped above and below the aneurysm. It is usually possible to place the upper clamp just below the origins of the branches to the kidneys so that the kidneys continue to receive blood flow throughout the operation. Blood flow to the legs is interrupted while the aorta is clamped but this is not usually a problem. The aneurysm itself is then opened. The graft is inserted by sewing it to the normal calibre aorta above and below the opened aneurysm so that it lies within what was the inside of the aneurysm. Many aneurysms can be repaired with a simple, straight tubular graft although if the aneurysm extends further downwards, bifurcated grafts ("trousers" ("broek/carrefour") can be used to replace the main arteries to the legs (arteria iliaca) as well.

When the clamps have been removed and blood flow is re-established through the graft, the wall of the aneurysm is closed over the graft. Most patients will be monitored in an Intensive Care Unit for the first 24 to 48 hours after operation and will be fit for discharge home after 7 to 10 days. Full convalescence from any major operation of this type may be expected to take up to 4 weeks. As mentioned before, it is a major abdominal operation which carries a high risk of severe complications and death. Up to 15% of patients who underwent an open repair needed to undergo a second operation, typically to treat a bowel obstruction, false aneurysm, hernia, continued aneurysmal dilation of the more proximal aorta, dilation of the iliac arteries, or erosion between the graft and surrounding structures.

Bleeding is an obvious risk in an operation which opens and closes the aorta and great care is taken to seal the suture lines at the ends of the graft blood-tight. Blood loss during a routine operation typically averages 500 to 1000 ml but may be much greater if the intervention doesn't work out as planned. Most patients will require blood transfusion during or after the operation.

Respiratory complications can occur after any painful abdominal operation which discourages deep breathing and coughing, particularly when the patients are likely to be elderly, have smoked in the past or have pre-existing lung disease.

The single greatest source of post-operative complications in aneurysm surgery is the heart. Most patients undergoing aneurysm repair have other cardiovascular diseases. They are male, smokers, old, have some degree of coronary artery disease and many will have a history of a previous heart attack or hypertension. The heart is stressed by blood loss and the major changes in blood flow which occur with clamping and unclamping the aorta.

Rates of lung and heart disease complicating surgery are dependent of the pre-existing prevalence of lung and heart disease. Published figures of mortality and morbidity rates complicating open repair vary considerably. Blankensteijn et al. documented a striking disagreement in reported mortality and morbidity rates rates between hospital-based and population-based studies of elective AAA-surgery.[20] The mean 30-day mortality rates of the population-based studies were similar: 8.2% (6.4%-10.6%) for the prospective and 7.4% (7.0%-7.7%) for the retrospective series. These figures were significantly higher than the remarkably similar hospital-based mortality rates: 3.8% (3.0%-4.8%) for the prospective and 3.8% (3.5%-4.2%) for the retrospective series. Retrospective hospital series showed nearly always the lowest complication rates. Population based series include all hospitals, and all series, while more selected studies will omit hospital or patient series with poor results. (see table)

However, unselected results of US patients of 1998 and 1998 showed great variance in operation results obtained among low volume and high volume hospitals and surgeons.[21] Low volume surgeons (< 8 interventions/year) in low volume hospitals (< 27.5 interventions/year) had an operative mortality of 6.4%, while high volume surgeons (>17.5 interventions/year) in high volume hospitals (> 60.5 interventions/year) had an operative mortality of 3.6%. Low volume hospitals had, adjusted for surgeon volume, an operative mortality of 0.6% higher compared to high volume hospitals. In the US, lack of (maintained) experience of the surgeon may cause death in one patient in 44 and lack of sufficient volume of the hospital may cause death in one patient in 167. An inexperienced surgeon in an inexperienced hospital may cause death in one patient in 36. It is important to realise that the outcome is always co-dependent of the state of the patient before the intervention: the better the health status, the better the outcome. The best outcomes are obtained in healthy persons with good cardiovascular disease status and small aneurysms, which need no intervention.

In the Dutch hospital register of 1990, the hospital operative mortality rate for non-ruptured AAA surgery was 6.8 per cent in 1289 patients, doubling per age group of 10 years.[22] In Belgium, no data on outcome of open repair or of effect of volume of hospital or surgeon are available.

Table 3.1: Complication rates of open surgery in percentages (95 % confidence limits between parentheses).[20] Population based studies are studies were the patients are identified by national or regional registries. Reporting of other complications than mortality were variably complete (see the full article for more details), the weighted averages take this into account.

	Population based studies			Hospital based studies	
	Prospective	Retrospective	Weighted	Prospective	Retrospective
Studies	2	13		9	32
Patients	692	21409		1677	12019
mortality (%)	8.2 (6.4-10.6)	7.4 (7.0-7.7)	7.40	3.8 (3.0-4.8)	3.8 (3.5-4.2)
cardiac complications	10.6 (8.5-13.2)	11.1 (9.1-13.6)	10.80	12.0 (10.5-13.9)	8.9 (8.4-9.5)
cerebral complications	1.4 (0.7-2.6)	1.3 (0.7-2.5)	1.30	0.6 (0.3-1.5)	0.7 (0.4-1.3)
pulmonary complications	5.3 (3.8-7.3)	10.5 (8.0-13.5)	7.50	9.8 (8.3-11.6)	3.5 (3.1-4)
Renal complications	7.0 (5.3-9.2)	9.0 (6.7-12.1)	7.80	4.8 (3.8-6.2)	3.6 (2.9-4.4)
Gastrointestinal	0.2 (0.0-0.9)	2.1 (1.0-4.0)	0.90	13.0 (11.3-14.9)	1.7 (1.4-2.2)
Limb ischemia	0.5 (0.2-1.3)	1.9 (0.7-5.5)	0.80	5.8 (4.2-7.9)	3.7 (2.7-5.0)
Haemorrhage	0.2 (0.0-0.9)	1.6 (0.8-3.3)	0.80	6.2 (4.7-8.1)	0.7 (0.5-1.0)
wound infection	NA	2.1 (1.0-4.3)	2.10	1.5 (0.9-2.5)	4.1 (3.5-5.4)

The long-term prognosis is related to the associated co-morbidity and cardiovascular disease. Long-term survival is shortened by heart failure and chronic lung disease. Overall, AAA repair is very durable with few long-term complications (<5% false aneurysm). In general, the survival rate of people with successful aortic aneurysm repair is comparable to that of people in the age-matched population at large who have never had an aneurysm. Common long-term complications are impotence (if the blood vessels in the pelvis which supply the penis are involved in the aneurysm process) or failure of ejaculation, which is produced by the almost unavoidable damage to nerve fibres which surround the lower end of the aorta.

Key messages

- **Open aortic repair is complicated by high mortality and severe morbidity immediately after the intervention. In unselected population based registers, mortality was 7 %, cardiac, pulmonary and renal complications are observed in respectively 11%, 8% and 8% of the populations. In the US MEDICARE hospital register, mortality varied from 3.6% to 6.4%, depending on experience of surgeon and hospital.**
- **In the US, volume of surgeon and volume of hospital are important predictors of mortality. In Belgium, no data are available.**
- **Except for impotence and failure of ejaculation, the long term prognosis of successful open surgery is excellent. Complications or aneurysm related mortality after successful open surgery are rare. Heart disease, lung disease among (ex-)smokers and stroke will cause most deaths in patients with a repaired aneurysm.**

3.3. ENDOVASCULAR REPAIR (EVAR)

3.3.1. Introduction

Endovascular aneurysm repair (EVAR) is a minimally-invasive (without a large abdominal incision) procedure performed to repair an abdominal aortic aneurysm. EVAR may be performed in an operating room, radiology department, or a catheterization laboratory. The treating doctor may be a vascular surgeon or an interventional radiologist. He may use general anaesthesia or regional anaesthesia (epidural or spinal anaesthesia). The doctor will make a small incision in each groin to visualize the femoral arteries in each leg. With the use of special endovascular instruments, along with x-ray images for guidance, a stentgraft will be inserted through the femoral artery and advanced up into the aorta to the site of the aneurysm. A stentgraft is a long cylinder-like tube made of a thin metal framework (stent), while the graft portion is made of various materials such as Polyester and may cover the stent. The stent helps to hold the graft in place. The stentgraft is inserted into the aorta in a collapsed position and placed at the aneurysm site. Once in place, the stentgraft will be expanded (in a spring-like fashion), attaching to the wall of the aorta to support the wall of the aorta. The aneurysm will eventually shrink down onto the stent-graft.

The main idea supporting the rationale behind EVAR is to reduce the severe postoperative mortality and morbidity of open repair, and to speed recovery and reduce costs through decreased length of stay in hospital and intensive care. Postoperative mortality and morbidity is indeed reduced by EVAR, but this has been supplanted by many other problems, casting doubt on the overall effectiveness and durability of EVAR.

3.3.2. Specific EVAR problems

Some complications noted with open repair are shared with EVAR but most are either specific to or much more common with EVAR.

- Endoleak

The word endoleak appears for the first time in a letter in 1996; endoleaks are highly specific to endovascular aneurysm repair.[23, 24] Blood can continue to enter the aneurysm sac. Persistent endoleaks may be capable of pressurizing the aneurysm sac, and ultimately lead to rupture. Endoleaks are categorized into five types, of which three are frequent:

Type 1: leakage around the points of proximal or distal fixation.

Type 2: blood entering the aneurysm sac in a retrograde manner through a patent inferiormesenteric artery or lumbar artery.

Type 3: extravasations of blood through a defect of the material or a not well closed joint.

Type 1 or 3 endoleak after endovascular repair are associated with an increased risk of rupture or device failure and must be treated. Type 2 leaks may not cause long-term problems and may not require therapy in most cases, as long as it is not associated with aneurysm expansion. However, type 2 endoleaks are associated with a higher probability of secondary interventions, conversion to open surgery, and increased costs.[25] Although the initial hospital length of stay was shorter with EVAR than with open repair, this advantage was lost during a 26-month follow-up interval, because of frequent readmissions for treatment of procedure-related complications, chiefly endoleaks.[26] It should be added that endoleaks type 2 have been over treated, and that in the future re-intervention rates might decline by a better understanding of which endoleaks need treatment.

- Migration

Surgical grafts are fixed by proximal and distal sutures, but stentgrafts are held in place through a combination of radial force (from the stent), hooks or barbs, and longitudinal support (stiffness). Migration or dislocation at the graft ends or modular junctions may result not only from inadequate grip or seal, but also from inability of a relatively inflexible device to resist or adjust to the strong distorting forces applied by shrinking AAA dimensions after successful exclusion. An ideal means of fixation has not yet been discovered, and stentgraphs may slip from their position. Movement of the device from its initial location potentially can lead to late type I endoleak, AAA sac revascularization, enlargement, and rupture.

Late migration rates were high with early prototypes.[27] In the experience with five more recent different devices, the migration rate was 0% with three of the devices (Ancure, Talent, Excluder), but close to 8% with the other two devices (AneuRx, Zenith; 8.5%).[28] There was a series of other reports documenting high migration rates of the AneuRx device.[29, 30] These devices are no longer used in Belgium.

- Rupture

AAA rupture has been a most alarming complication of EVAR, as its motivation is to prevent rupture. It may result from failure to achieve AAA exclusion or occur even with apparently successful exclusion. The annual rate of AAA rupture after EVAR is close to 1%. In the EUROSTAR registry data the risk for rupture shows a rising slope, with 1-year risk of 0.4%, 2-year risk of 2.6%, reaching 3.3% at 4 years and 6.1% at five years.[31, 32] Part of this duration dependent rise has been caused by second generation stentgrafts and may be better with newer generation stentgrafts. Five year survival freedom of aneurysm was 97% (diameter 40-54 mm), 95% (diameter 55-64 mm) and 90.5% (diameter 65 mm), and was predicted by size of aneurysm, type I and 3 endoleak (but not 2, causing more secondary interventions), endograft migration or kinking.[32]

- Mechanical failure

The stentgraft is a marriage of both a metal stent and a Polyester graft, which is subjected to the strong forces of the aortic blood flow and the squeezing vessel wall. With hindsight, the technology has been more demanding than expected and the durability of the stentgraft remains questioned.

Late structural failure has been observed with most of the endograft devices. In a ten-year experience, 14% of the implanted stentgrafts showed structural failures in 5 of the 7 devices used.[33] Death was caused by device failure in three of these patients.[33] Devices that were redesigned after structural failures are EVT/Ancure, Lifepath, Talent, Zenith.[27, 34] Devices that were withdrawn because of structural failure were Stentor (MinTec), Vanguard II,[27, 34] and Ancure. Problems have been signalled in AneuRx but the article of FDA-authors has been withdrawn from the Journal of Vascular Surgery after legal threats from MEDTRONIC. [35]

Structural failures have been late observations, often appearing as late as 2 years. With routine surveillance these problems often have been missed or discovered late, and when fully investigated most structural problems have increased over time. These late failures have prompted the FDA to extend the observation period for endografts.

Devices can be redesigned but some causes of device failure are caused by the hemodynamic changes induced. These occur after more years. To fit, the implanted device is oversized, but this may later cause progressive neck dilatation, especially with larger AAAs. Successful AAA sac exclusion may squeeze and kink a successful device by the distorting forces of the shrinking aneurysm.

The technology of EVAR is yet far from established, and too many clinical problems seem to have been caused by untimely diffusion of an emerging technology. Financial interests have hindered full and open documenting of these structural failures. This lack of information and the structural nature of the failures themselves, caused by insufficient understanding and controlling of the changing haemodynamic forces in the stented aorta, raised strong questions about the durability of EVAR. Lack of confidence in the even intact and clinically successfully placed stentgraft mandates indefinite surveillance, which is further increasing costs beyond what can be saved.

Key messages

- Compared to open surgery (larger aneurysms ≥ 5.5 cm), EVAR has a smaller postoperative morbidity and mortality over the short term, but more complications over medium and long term, mandating intensive surveillance and requiring more often secondary interventions.
- Complications specific to EVAR are endoleaks, stent migration and mechanical failure. Stent migration and endoleaks type 1 and 3 require intervention, endoleak type 2 requires monitoring.
- Device failures have been observed in all older devices. Newer generation devices show better results, but long term results are lacking.

4. REVIEW OF CLINICAL EFFECTIVENESS

4.1. QUESTIONS TO STUDY

Before an emerging technology enters the phase of diffusion, clinical benefit should be beyond reasonable doubt and the costs should be proportional to the benefits. The standard best treatment is: watchful waiting for all aneurysms under 5.5 cm and for all aneurysms in patients unfit for surgery, open repair for all larger aneurysms over 5.5 cm in patients fit for surgery. This chapter considers the clinical evidence that EVAR offers benefits to the known standard treatment.

This leads to three questions addressed in a literature study:

- Is there sufficient evidence to support that EVAR is clinically more effective than open surgery in patients with suitable aneurysm morphology?
- Is there sufficient evidence to support that EVAR is clinically more effective than watchful waiting in patients with suitable aneurysm morphology, and unfit for surgery?
- If EVAR is better than open repair, what are the possibilities of active repair in patients with smaller aneurysms (< 5.5 cm)?

4.2. INTRODUCTION

Evaluation of trials of emerging interventional technology such as EVAR is far from straightforward. When interpreting the evidence, a few principles have to be taken into account.

4.2.1. Interpreting effectiveness of emerging technology

Technology is introduced earlier in the stage of development than drugs, and evolves more rapidly than drugs. Older technology knows more device related complications and failures and such technology is soon replaced by subsequent innovations. The actually used endoprotheses in Belgium are from the newer generation. With prolonged follow-up, endoprotheses that are longer in use show more complications, suggesting increased complication rates over time. As these are older generation endoprotheses, this complication rate may not apply to the newer generation. Of recently designed endoprotheses, long term follow-up is missing, and improved design may only be hypothetically better.

The outcomes of EVAR and open surgery depend, besides the health an aneurysm status of the patients, on the experience of the operator, the quality of the team and the equipment of the hospital. The experience is less with EVAR than with Open surgery, as EVAR is new and open surgery is a tried and true procedure. Over future time, the results of EVAR should therefore be more prone to improve than those of Open surgery.

4.2.2. Assessing interventions in cardiovascular frail patient groups

Interventions with very different characteristics, to be used in elderly and cardiovascular frail patient populations are compared. This makes controlled comparison difficult, as the comparability is by definition poor. EVAR will be typically used for patients with a good aneurysm morphology but at poor general health. Open repair will be typically used for patients with all types of aneurysm but at better general health. The time dimension varies crucially. Open repair will be characterised by severe short term complications, caused by major surgery. EVAR will be characterised by many long term complications, caused by specific device problems.

Non-randomised studies suffer from "confounding by indication": patients may be selected for EVAR because of poor health or for open surgery because of a poor aneurysm. Inferior long term results for EVAR may therefore be caused by a worse patient mix at onset. Randomised studies avoid confounding by indication, but use only patient populations eligible for both interventions. External validity may be difficult to assess, as either EVAR was deployed in patients with rather poor aneurysm anatomy or open surgery may be used in patients with poor health status.

4.2.3. Assessing health outcomes in groups with differential follow-up

The hardest endpoint is "all cause" mortality. However, competing risks of mortality are high in these frail patients, higher than the probability of death by rupture or severe complication after the peri-procedural period. A reduction of aneurysm related mortality can not easily be demonstrated, against the "deafening noise" of competing cardiovascular mortality.

All cause mortality can be divided in "aneurysm related causes" and "other causes", but this is less straightforward than suggested by endograft stenting interested parties. Aneurysm repair is executed in frail patients, and competing mortality may cause mortality selection. Major surgery kills the patients already on death row. Patients may survive EVAR better, to die little time later of the same cause of death. As peri-procedural event of open surgery, the death will be marked aneurysm related, after EVAR it will be labelled cardiovascular or pulmonary. Labelling peri-procedural mortality as "aneurysm related" will bias outcomes against open surgery.

The difficulties of correctly assigning procedure related mortality to the one or other cause of death are recently labelled "sticky bias". In the case of aneurysm surgery, the patient carried the "sticker" "recently operated aneurysm". The cause of death will more easily be allocated to the intervention and aneurysm. If a myocardial infarction happens post procedure: has it been caused by the stress of the procedure, or was it bound to happen with or without the procedure? The true underlying cause of death (cardiovascular disease) is missed.

Generic health related quality of life is another important endpoint. The major aim of aneurysm repair is extending life with life years lived in good health. However, the used methods are not very sensitive to discrete changes in quality of life of limited duration (such as interventions), or to limited changes in quality of life (such as worrying about the risk of rupture).

Morbidity after successful open repair is rather low (after the period of revalidation), most morbidity concentrates in the peri-procedural period. Morbidity after successful EVAR seems much higher. But treatment is unblinded, and therefore outcome after treatment is always evaluated by prior knowledge of the treatment. The higher needs of follow-up for EVAR compared to open surgery may increase spuriously detection rates, if patients with EVAR are easily subjected to overdiagnosis and overtreatment of suspected device failure with unknown prognosis.

4.2.4. Undisclosed data

The euphoric content and the enthusiastic advices of academics of the Stanford group, trialling AneuRx devices of Medtronic inc., were not supported by the lack of appropriate surgical controls.[36-39] We went specifically looking for data of the pivotal trial offered to the FDA, containing longer term follow-up. The original paper documenting the trial results shows only limited follow-up.[40] We could find no article presenting a fair comparison with the original open surgery group. We found background information in an article of the Wall Street Journal of July 2004.[35]

The Wall Street Journal writes that in May 2004, an article called "Aneurysm-related mortality rates in the US AneuRx clinical trial" appeared in the Journal of Vascular Surgery's online preview section, written by Dr. Tavris, two FDA colleagues, as well as Dr. Greenfield, the University of Michigan vascular-surgery professor. Tavris c.s. suggested that the mortality rate for patients getting the AneuRx exceeded that for surgical patients by three years or more after the treatment, because the AneuRx had little advantage in preventing immediate post-surgical deaths and caused or allowed more problems down the road. It concluded that open surgery was safer than endovascular treatment with AneuRx.

The device's maker, Medtronic Inc. objected to the FDA that the authors used confidential data without permission. Its lawyer threatened the editors of the Journal of Vascular Surgery with "criminal and civil sanctions" if they did not pull the article from the Web site. In the end, the FDA asked the journal to remove the paper from the site, and in late June the agency officially withdrew it from publication. No later fair comparisons have been published, only uncontrolled series.

While the paper may have been disputable, absent information can not be disputed. The Wall Street Journal adds that AneuRx has annual sales of nearly $200 million and notes that Zarins, professor in vascular surgery at Stanford, acts as a consultant for Medtronic.

4.3. METHODS AND RESULTS

To answer the first question, we searched the literature for prospective randomised controlled trials. To increase the evidence base, we included prospective non-randomised controlled trials. Indeed, the published randomised clinical trials are all European (DREAM and EVAR), while the non-randomised controlled trials are mostly from the US. Interpretation of the non-randomised evidence has to be prudent, however, as there were always serious imbalances in prognostic indicators such as age, disease history, and aneurysm size.

Endovascular treatment, using industrially available endografts, was compared with traditional open surgery in the elective treatment of unruptured aorta-aneurysms in the usual patient population. Patient populations at high risk or with specific characteristics were excluded. Studies with fifty or less patients in one of both study arms or with less than one year follow-up were excluded. Retrospective case series comparing open surgery and EVAR were excluded as selection by outcome is hard to avoid and impossible to verify. Patients in both arms (open surgery and EVAR) had to answer to the same in- and exclusion criteria for the study. Historical controls were acceptable, consecutive contemporary controls not, as confounding by indication will lead to differential prognosis. Minor imbalances between health status (predicting more use of EVAR) and aneurysm anatomy (predicting more use of open surgery) were acceptable. Studies documenting only consecutive contemporary case series were excluded, as confounding by indication (EVAR for those unfit for surgery and open surgery for those unfit for EVAR) will bias the comparison.

We searched the following literature databases: Medline, National Guideline Clearinghouse, Cochrane Collaboration and Centre of Reviews and Dissemination (includes DARE, NHS EED, HTA). For efficiency, the literature search algorithm (in appendix) was taken over from the CCOHTA systematic review and updated (databases last accessed 16 Augustus 2005). Scanning references of the selected papers (particularly the systematic reviews detected) did not yield additional studies.

4.4. SELECTED STUDIES

The search methods yielded 529 papers. 499 papers were rejected as either not relevant (not comparing the two treatments, EVAR or open surgery), or not inclusive. Studies comparing open surgery and EVAR were excluded if the abstract mentioned that the data were collected retrospectively, one of the treatment arms had 50 patients or less or the study reported only short term follow-up (30 days). 32 papers were included for further scrutiny.

4.4.1. Systematic reviews

Five studies described systematic reviews and are considered as such.[41-45] All only considered short term follow-up. We checked their search results to compare with our selection, but this yielded no additional references. Study selection of observational studies was in general arbitrary. Most studies rejected by us were rejected because of small samples and no follow-up. Single centre studies were nearly always heavily confounded by indication, and comparisons were not appropriate (see further).

4.4.2. Randomised controlled trials

Seven papers described two randomised controlled trials of a sufficient sample size and good quality, DREAM and EVAR-1 (EVAR-2 describes patients at high risk for surgery only, and is included in part two, comparisons of watchful waiting with open surgery).[46-52] These were included in the evidence base.

4.4.3. Comparative controlled trials without randomisation

Twenty papers described non-randomised prospective controlled studies with documented medium term follow-up. The quality was often poor, including the "pivotal trials" for device accreditation introduced at the FDA. Main problems were obvious imbalance between cases and controls and obvious imbalance in follow-up of cases and controls. The population that generated the cases and controls is never described in the pivotal device trials, which makes external validity hard to assess. The low mortality in the control population suggests a population at low risk.

Selection and follow-up procedures are poorly described, and results may be generated by differential loss of follow-up. Case definition and case ascertainment in follow-up is poorly defined. As patients with EVAR are closely monitored, this may make complication and intervention rates higher in the intervention group. The pivotal trials don't mention if the patients are treated by the same or different teams. As they come from many different centres, different experience may bias outcomes.

The large unrandomised multicentre trials show strong prior preferences of the treating surgeons: EVAR for small aneurysms in patients less fit for surgery and open repair for large aneurysms in patients fit for surgery. This violates the principle of clinical uncertainty that guides clinical research. With the hindsight confirming the true clinical uncertainty, the surgical overconfidence in the benefits of EVAR was a serious mistake.

Five papers describe various features of the pivotal AneuRx trial or the Stanford Medical School experimenting with these new technology.[36-38, 40, 53] Even more papers have been published about smaller patient series. The long term experience of the EVAR-arm is well documented, but it was unclear how control patients were selected, if these papers described the same or other patients and if was guarded against confounding by indication or outcome. Follow-up of the control patients has not been published. The authors have known interests in Medtronic (the producer of the AneuRx stentgraft) and act for Medtronic.[35] This is not exceptional in this field of highly commercial academic research, but Zarins and Arko heavily promote the widespread use of EVAR. For comparison with other long term outcome, we included the experience of the AneuRx stentgraft, but only the comparison published in the multi-centre trial. As published follow-up was short and number of control cases small, this does contribute little to the end results.

One study was rejected because it used contemporary consecutive controls.[54] Bias by indication was handled by propensity scores. These included unfavourable health status of EVAR patients, but did not include unfavourable anatomy in the open surgery group, favouring therefore EVAR over open surgery. The presented data showed a survival benefit for the open surgery group (with a better health status). Inclusion of the raw data would have disfavoured EVAR. No adjusted data were shown, so we could not include statistically adjusted outcomes.

Two papers describe the experience of a single centre, where the EVAR series are both confounded by indication and by the learning curve. They show poor results for EVAR, that may be attributable to poor patient selection and lack of experience.[55, 56] We excluded both papers. Inclusion of the data would have disfavoured EVAR.

One paper was excluded for a highly imbalanced follow-up and unlikely outcome.[57] While EVAR patients were older and with significant high morbidity

in the EVAR group, only one died after intervention, during follow-up of 24 months. In a life table population of 145 persons or 72 years old from the general population, 10 deaths are expected. An observed mortality of one is ten times lower and statistically highly significant. In the open repair population, loss to follow-up was 25%, in the EVAR group it was 45%.

12 papers described 9 studies that were included. Description of the included studies is in table. 7 studies were pivotal multicentre trials, intended for FDA accreditation of a specific device and 2 were single centre studies. Other single centre studies were excluded, as they either had too few cases, too little follow-up or incomparable series of cases and controls. No multi-centre non-randomised studies were identified that had not as aim to compare EVAR and open surgery.

One of the included single centre studies used two control populations, a relatively recent historical control population, and a contemporary control population. This study showed that, at least in the Netherlands, the contemporary control population did worse, suggesting that EVAR was reserved for patients at relatively good prognosis: at one year follow-up, absolute survival was 10% less.[58] Strangely, the authors concluded "EVAR offered considerable benefits compared with conventional open repair at early and mid-term follow-up", while EVAR did not better than the historical controls after more than 9 month follow-up.

We included all cause mortality and reintervention rates in our assessment of medium term outcomes of unrandomised studies, as these are most comparable. For other endpoints (major adverse events and quality of life) we only considered the evidence of randomised trials. Standardising major adverse events over different studies is difficult. The overview of unrandomised comparative studies only confirms the results of the randomised trials and the Eurostar register.

We used only published data, which may be presented in different formats. Most studies showed Kaplan Maier survival curves, as particularly in the second year loss to follow-up was large. This poses the problem of the denominator, as the censoring hazard varies between studies. To pool endpoints with different follow-up, we used the observed absolute numbers of death as numerator, multiplied with 1/(1-cumulative survival at 12 or 24 months) as denominator. The denominator then takes into account differential loss to follow-up and is to be considered as "all patients attributing to mortality over the entire period considered". If no absolute numbers of events were given, the patient population at risk was considered the population at risk at the end of the interval + half of the patients withdrawn during the interval. If no absolute numbers of events or populations at risk were given, the survival data were not used.

Reintervention rates were calculated as annual probabilities in the follow-up period considered. For pooling, they are weighted by the number of included cases and the mean duration of follow-up. Reintervention rates consider all reinterventions, and are surgeon dependent. Monitoring is more intense after EVAR, which may identify more problems which remains undetected after open surgery. However, for clinical practice and patients' quality of life, the observed experience is most meaningful.

Post hoc, we added three papers describing administrative databases, comparing short term mortality of open surgery and EVAR.[59-61] While confounding by indication obviously exists, it compares day-to-day practice to the practice of experienced centres engaged in trials.

Key messages

- Two randomised trials described two to four years follow-up of patients randomised between EVAR and Open repair. The RCT were judged to be of moderate and good quality.
- Seven so called "pivotal" multi centre trials described one to six years follow-up of the use of a specific device, for accreditation by the FDA. Comparability of (not randomised) patient groups was poor. The pivotal trials were judged to be of poor quality.
- Single centre trials compare EVAR and open surgery patients in observational design. Most studies could not be interpreted, as the inclusion criteria caused imbalance between the comparisons.

Table 4.1: Overview of studies selected in the review of clinical evidence

Randomised controlled trials

DREAM[46, 49]

Prospective randomised clinical trial conducted in 26 Dutch centres contributing 342 patients for randomisation and 4 Belgian centres contributing 9 patients during 11.2000 – 12.2003. All had an AAA of > 5.0 cm and were candidates for both interventions. 8 devices were used; Zenith, Talent and Excluder in 83% of the cases. The denominator (all patients registered for eligibility) and the selection process are not documented.

Patient populations are slightly imbalanced (due to randomisation of a still limited number of patients); EVAR patients are 1 year older, and 9% more smoked and had lung disease. The mean aneurysm diameter was 60.0 and 60.6 mm. Outcomes are well defined and the follow-up is equal in both arms. Aneurysm related mortality is biased by definition (any death 30 days after invention and/or during admission): cardiovascular frailty and the longer period at risk in open surgery will classify more mortality as aneurysm mortality than in EVAR. Two-year outcomes are available.

The intention to treat analysis implies a period between randomisation and actual intervention.

The study was financially supported by a grant from the Netherlands National Health Insurance council.

EVAR-1[51, 52]

Prospective randomised clinical trial conducted in 34 UK centres registered 4799 patients between 9-1999 and 12-2003. 30% were considered suitable for inclusion in EVAR-1, and 10% in EVAR-2 37% were considered unsuitable. Of the 1423 eligible patients for EVAR-1, 76% accepted randomisation; 7% declined randomisation as they preferred EVAR, 14% preferred open surgery. In 84% of patients Zenith or Talent was used, in 15% of patients devices of nine other types were used (in less than 1% no commercial device).

Patient populations are close to identical. Mean aneurysm diameter is 6.5 cm (eligibility was limited to patients > 5.5 cm).

Outcomes are well defined and the follow-up is equal in both arms. Aneurysm related mortality is biased by definition (any death 30 days after invention), but this classification may be overruled by post-mortem findings. The proportion of patients with a post-mortem is not shown.

The intention to treat analysis implies a period between randomisation and actual intervention. For comparability with the other trials, if available, the on-treatment results were compared.

The study was financially supported by a grant from the UK National Health Service.

Multicentre "pivotal" trials

These are prospective clinical trials approved by the FDA for accreditation of a stentgraft for commercial use in clinical practice.

1- Ancure trial[62-64]

Prospective clinical "pivotal trial" testing Excluder device

684 patients enrolled in 21 centres. Data describe 268 patients, enrolled in 18 institutions, treated with the EGS delivery system (11.1995-02.1998) followed by 305 patients enrolled in 21 institutes, treated with the Ancure delivery system (last date mentioned 08.2002) and 111 current open surgery controls, enrolled in 18 institutes (11.1995-02.1998). If not mentioned specifically, the pooled data of both delivery systems are presented. From the intervention group of 573 patients, 319 patients are studied for longer term follow-up after successful implantation.

Control patients are well described, and were patients eligible for EVAR, but with difficult anatomical access. They did not contain anatomically complex aneurysms.

Follow-up and outcome criteria are not described, the main comparison is for all cause mortality.

It is not mentioned if treatment options were executed by the same surgeons/centres. Mortality follow-up is till five years.

The Ancure trial is financed "in part" by Guidant. The authors declare no conflict of interests.

2- AneuRx[40]

Prospective clinical "pivotal" trial testing AneuRx device.

250 patients enrolled in 12 institutions during 1996-97 to be treated with the AneuRx device. The first 60 patients (5 per institution) were obligatory treated with open surgery. Patients are at average risk, but later inclusions with EVAR were 4 years older. The aneurysm size was identical, and all patients were eligible for EVAR. The EVAR group includes the 50 first patients in the learning curve.

Follow-up data are well described, but only for the EVAR group. A later paper by independent investigators is retracted after threats with legal prosecution for use of confidential data.

For comparative purposes, the EVAR group has a worse prognosis and interpretation of the observed benefit of open surgery is not possible. We included the trial for being a "pivotal" trial, although the quality was poor. It does not add much weight, as the numbers of open surgery were small.

The authors declare no conflict of interests.

3- Excluder [65]

Prospective clinical "pivotal trial" testing Excluder device

19 centres enrolled 334 patients during 01.2000 – 07.2001 in the comparative trial.

Same inclusion criteria hold for cases and controls, all eligible for surgery. Selection of case and control is based on anatomy of aneurysm and patient preference.

Not mentioned if treatment options were executed by the same surgeons/centres

1 year follow-up only, more and longer follow-up in EVAR group.

Source of financing is not mentioned. The authors are paid consultants and/or receive research funding of Gore, Medtronic, Guidant and Boston Scientific.

4- Powerlink [66, 67]

Prospective clinical "pivotal trial" testing Powerlink device

15 centres enrolled 258 patients during 07.2000 – 03.2003

Average surgical risk, theoretical aneurysm > 45 mm (but not clear, Carpenter seems not to know it), many smaller aneurysms.

Selection for open surgery not mentioned, large difference in aneurysm size.

Not mentioned if treatment options were executed by the same surgeons/centres

Follow-up methods for control population not mentioned, but follow-up seems good.

Ascertainment method for outcomes (> 30 days) not mentioned.

Source of financing is not mentioned. Dr Carpenter declares to own shares in Endologix.

5- Talent [68]

Prospective clinical "pivotal trial" testing Talent device

17 centres enrolled 366 patients during 03.1999 – 09.2000

Low surgical risk, aneurysm > 40 mm

Selection of control patients based on same inclusion criteria but ineligible anatomy or refusal of EVAR

Not mentioned if treatment options were executed by the same surgeons/centres

Follow-up methods for control population not mentioned, follow up limited (mean follow-up less than one year), poor reporting of endpoints.

Ascertainment of outcomes (> 30 days) not mentioned.

Suspect long period without update over longer period.

The source of financing is not mentioned. Criado receives funding of Medtronic.

6- Vanguard [69]

Prospective clinical "pivotal trial" testing Vanguard device

Seventeen centres enrolled 366 patients during 08.1997 – 09.1998

Average surgical risk, theoretical aneurysm > 50 mm, practical many more exceptions at smaller aneurysms.

Selection method for control population not mentioned,

Follow-up methods for control population not mentioned.

Not mentioned if treatment options executed by the same surgeons/centres

Ascertainment method for outcomes (> 30 days) not mentioned.

Withdrawn during study (death or censoring): 20% months 1-12, 84% months 1-24

All costs are paid by Boston Scientific. Each of the study centres received financial support. Authors are paid consultants to Boston Scientific.

7- Zenith [70]

Prospective clinical "pivotal trial" testing Zenith device

15 centres enrolled 280 patients during 01.2000 – 07.2001 in the comparative trial. Another 100 and 52 patients were enrolled in a 'high risk' group and a 'roll in' group (group that included surgeons and hospitals not yet familiar with the technique), but these are not taken into account here.

Average surgical risk, age < 80 year, life expectancy > 2 years.

All eligible for surgery, selection of case and control based on anatomy of aneurysm.

Not mentioned if treatment options were executed by the same surgeons/centres

Short follow-up (1 year), follow-up more intense in EVAR group, but endpoints well ascertained.

Supported by Cook. Authors declare to have received research funding from Cook, Boston Scientific, Guidant, Medtronics, Suzer-Vascutek, Gore.

Large single centre studies with appropriate comparisons

Two studies entered comparisons that were more balanced; one (Twente) using historical controls.

1- Perugia [71]

Single large vascular centre from Perugia (Italy) testing 8 different devices

1119 patients recruited during 01.1997 – 12.2003

Average surgical risk, no other exclusions mentioned

Selection of open repair based on same inclusion criteria except for aneurysm anatomy and longer life expectancy (14% of open surgery patients),

Patients treated by the same surgical teams.

Follow-up more intense in EVAR group

Funding source not mentioned.

2- Twente [58]

Single large vascular centre from Twente (Netherlands) testing 3 different devices

93 EVAR patients recruited during 04.1998 – 01.2003, 82 contemporary controls, 93 historical controls from 1993-1998. Historical open surgery had better outcomes than contemporary open surgery.

Average surgical risk, no other exclusions mentioned

Patients treated by the same surgical teams.

Follow-up according to EUROSTAR protocol, more intense in EVAR group.

Unequal follow-up: After one year, in the historical control population 9% is censored without dying, in the EVAR group 31% is censored. After two years, in the historical control population 16% is censored without dying, in the EVAR group 53% is censored.

Funding source not mentioned.

4.5. CLINICAL RESULTS OF EVAR VERSUS OPEN REPAIR IN PATIENTS AT AVERAGE RISK

4.5.1. Assessment of the evidence base

EVAR-1 was a trial of good quality, with all key elements well documented and with sufficient power to detect meaningful clinical benefit of intervention over control. DREAM was a trial of moderate quality. Patient selection and the process between assessment of eligibility, randomisation and actual intervention were not documented in the central publications. The sample was too small to detect meaningful clinical benefit, and might have caused clinically important lack of balance in age, smoking and lung disease.

The pivotal trials were of poor quality. The source population was never documented, the selection process for EVAR or open surgery was not documented either. Patient populations were imbalanced and the patients did not receive the best available treatment, which is watchful waiting for patients with AAA under 5.5 cm. AAA treated were in average 5.6 mm smaller than in DREAM (which included patients > 5.0 cm) and 10 mm smaller than in EVAR (which included patients > 5.5 cm). Good results may be caused by an excellent prognosis. The recent Powerlink protocol included aneurysms of 40 mm and over, AND rapidly growing aneurysms, the mean "maximal" aneurysm diameter was 51 mm.[66]

4.5.2. Patient populations

In the EVAR populations, there is little difference in age between the three designs (RCT, non-randomised multicentre trials, single centre trials). EVAR-1 is an older population, which might be correlated to the larger aneurysm, a consequence of delayed intervention. The EVAR population op the pivotal multicentre trials shows small aneurysms: the stentgraft technology pushed surgeons towards earlier intervention at smaller diameters. While they had smaller aneurysms, prevalence of heart disease was higher in the EVAR populations.

In the open surgery populations, the population of the pivotal trials is younger, with more women and more smokers. The higher fraction of women and smokers is likely caused by the more demanding anatomy of the aneurysms.

In direct comparisons, the DREAM trial is less well balanced, a consequence of smaller numbers. Lung disease and smoking is more prevalent in the EVAR arm. In the pivotal trials, patients of open surgery are younger, more often female and smoker and with larger aneurysms. This is a consequence of selection by indication: patients elected for open surgery show less co-morbidity, but more demanding aneurysm morphology.

It is to note that the operative mortality of open surgery is considerably less than in unselected population studies. This may endanger external validity. The low mortality might be caused by surgeon experience in high volume centres, but also by exclusion of poor patients. The selected populations are likely populations at less than average risk.

Further, the EVAR trial shows that 37% of recruited patients were eligible for an intervention but not eligible for EVAR: the need for open surgery will remain.

4.5.3. Short term outcomes

As might be expected, the less invasive intervention shows better outcomes. The mortality of open surgery in the industry trials is low, likely a consequence of selection of patients at good prognosis. However, even in that design EVAR is better on the short term. In unselected patients, EVAR shows 3% less mortality. The intervention takes 40 minutes less, the patients stay 2.2 days less in intensive care, the hospital stay is 6 days shorter and EVAR patients consume 1000 ml blood less. In the DREAM trial, EVAR patients suffered two times less from moderate and severe systemic complications than open surgery patients, but suffered twice as much from local or implant related complications.[49]

4.5.4. Intermediate term outcomes

The mortality advantage of EVAR is not sustained for long (see Forrest plots). This is likely a consequence of competing death risks in frail patients. Open surgery stresses the frail patient, and causes mortality selection: the survivors are more fit. In EVAR, the frail patients survive, but only for a short while, to die of a cardiovascular cause that would have killed the patient during open surgery. All designs show consistently the same pattern over the first one to two year: increased mortality in the EVAR group catching up the open surgery group.

While EVAR is superior in the short term, it is inferior over medium term in the survivors. Annual re-intervention probabilities are around 7% (EVAR-1), 8% (device trials) and 9% (single centre trials). Re-intervention rates of open surgery are even often not mentioned, which might be a consequence of unequal follow-up and case ascertainment, too. However, cited re-intervention rates in open surgery are rarely over 2 %.

EVAR-1 gives complication and re-intervention rates over four years of follow-up. By 4 years, the proportion of patients with at least one complication after AAA repair was 41% in the EVAR group, compared with 9% in the open surgery group.[51] Overall rates of complications were 17.6 per 100 person years in the EVAR group and 3.3 per 100 person years in the open repair group (hazard ratio 4.9, 95% CI 3.5–6.8).[51] Similarly, the proportion of patients with at least one reintervention by 4 years was 20% in the EVAR group and 6% in the open repair group. (hazard ratio 2.7, 1.8–4.1).

4.5.5. Quality of life

Both EVAR and DREAM trial also studied health related quality of life (HRQL). At baseline, the EQ-5D[72] scores were similar in both groups in EVAR-1 and DREAM, but significantly worse than a reference population.[48, 51] Although asymptomatic, the knowledge of having a potentially life-threatening disease does have an impact on HRQL.

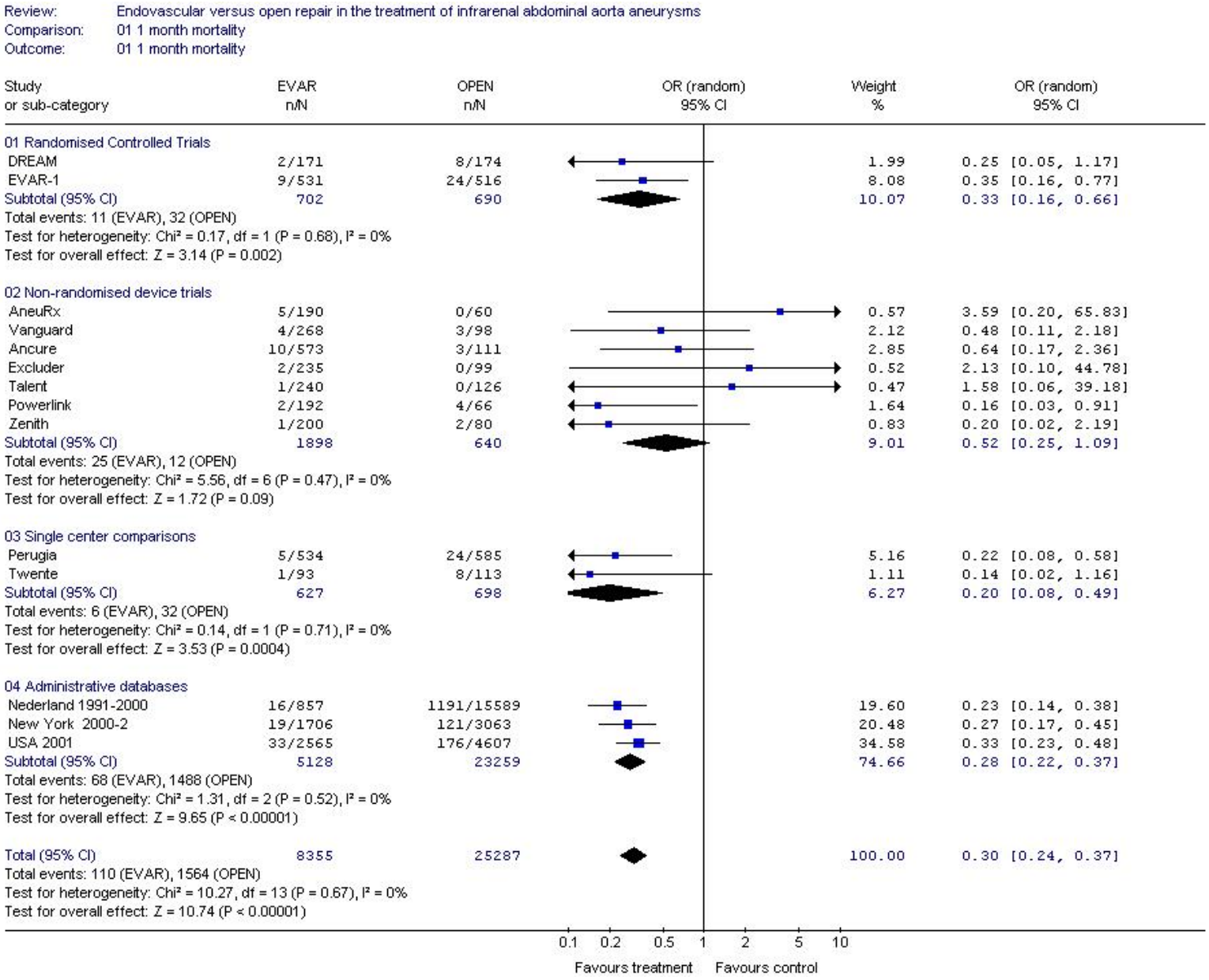
The open repair group had a significantly diminished HRQL at 0–3 months in both trials. This can easily be explained by the more demanding and stressful intervention, leading to a more prolonged stay in both ICU and the hospital.

After this short post-operative period, the findings diverge in both trials. HRQL had recovered by 3–12 months and at 12–24 months after randomisation there was no difference between the groups in EVAR-1. EVAR-1 did therefore not show that the need for continued surveillance in the EVAR group affected quality of life scores. DREAM showed that at 6 months and beyond, patients reported a better HRQL after Open surgery than after EVAR. This may not be specific to the intervention, as it is also observed in other major life events, such as cancer surgery. People experience a relatively better HRQL after a period of severe illness or major surgery.

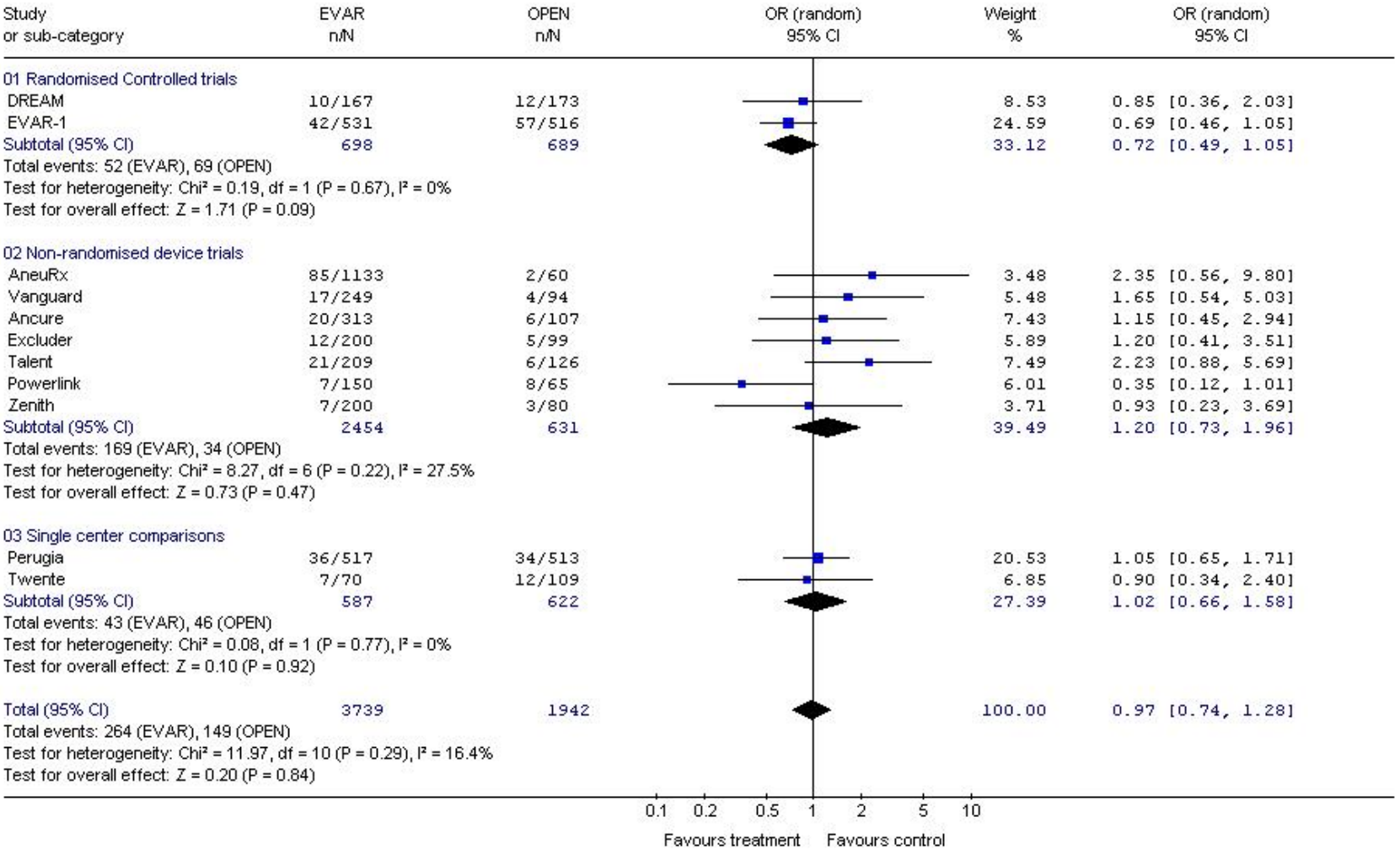
Key points

- **The need for open surgery will not disappear after the introduction of endovascular repair. The fraction of patients eligible for an intervention that could not be treated with EVAR was larger as the fraction that could be.**
- **Before the intervention, quality of life of both EVAR and open surgery patients is worse than in the reference population. The knowledge of a potentially life-threatening illness reduces health related quality of life.**
- **EVAR is a less invasive intervention. In the shorter term, EVAR has important advantages over open surgery.**
- **Over one to two years, the mortality advantage of EVAR over open surgery fades rapidly. Open surgery advances the time of death in vascular frail patients, but moderately. At two years of follow-up, all survival advantage has disappeared.**
- **In the longer term follow-up, DREAM and EVAR-1 disagree over quality of life.**
- **Summarising, EVAR has better short term results but worse long term results. The survival advantage disappears after one to two year follow-up after intervention.**

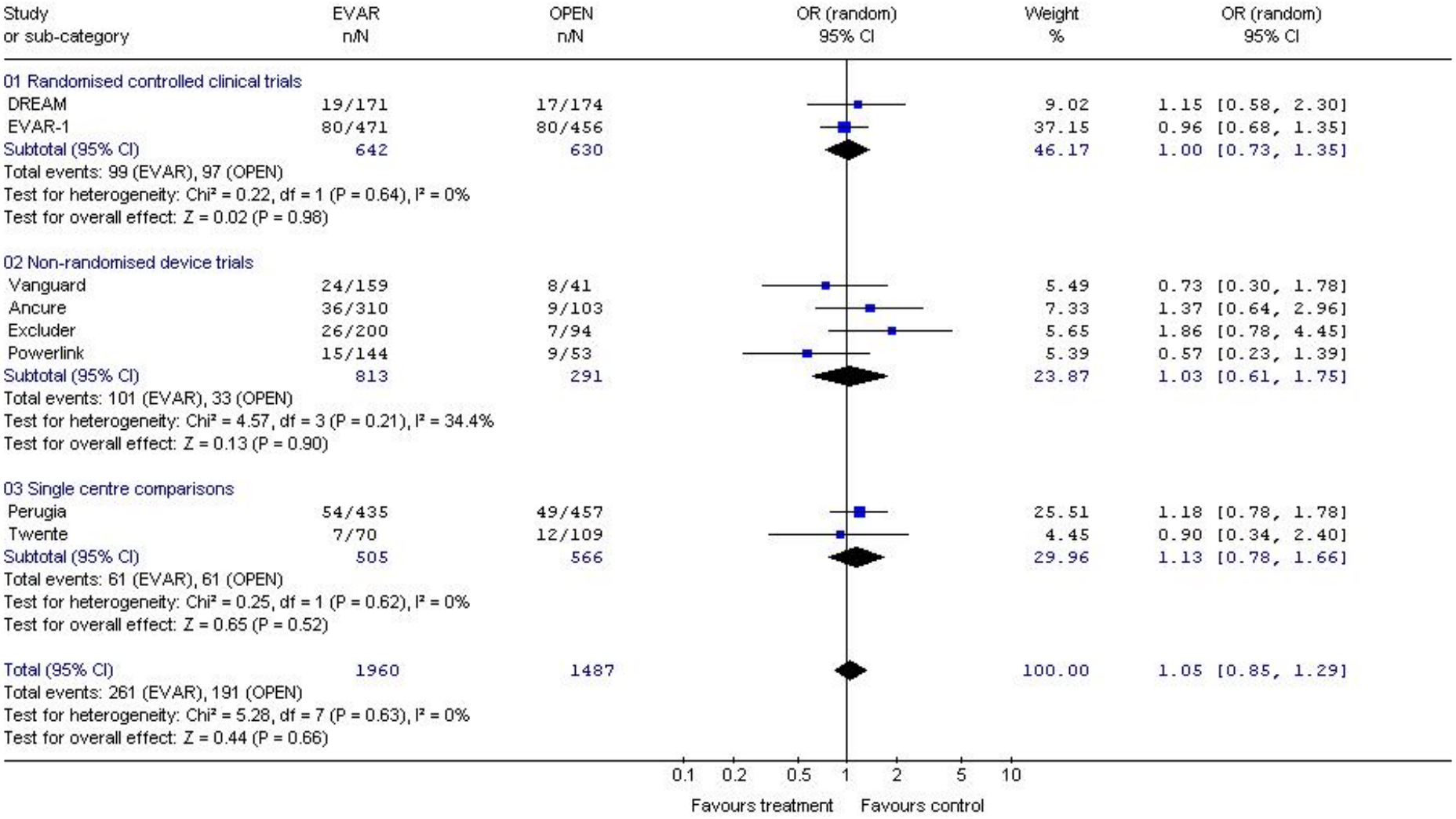
Figure 4.1; Meta Analyses of studies comparing endovascular treatment versus open repair treatment (mortality data at 1 month, 1 year and 2 years after operation).



Review: Endovascular versus open repair in the treatment of infrarenal abdominal aorta aneurysms
Comparison: 02 1 year mortality
Outcome: 01 Mortality one year after intervention



Review: Endovascular versus open repair in the treatment of infrarenal abdominal aorta aneurysms
Comparison: 03 2 year mortality
Outcome: 01 2 year mortality, calculated from survival tables



4.6. CLINICAL RESULTS OF EVAR VERSUS WATCHFUL WAITING IN PATIENTS UNFIT FOR SURGERY

EVAR was originally developed for treating patients unfit for surgery. The risk of rupture can be as high as 25% per year for aneurysms with diameters greater than 6 cm, the survival less than two years (unpublished figures cited in article)[73]. When we watch the first Forrest plot of first month results, the relative risk reduction is strikingly homogeneous across studies. This implies that patients at highest risk have most benefit, so in theory EVAR would be an excellent solution for these patients.

As the technology developed, EVAR has been used increasingly in patients judged fit for open repair, substituting open repair. The technique was originally created to be of benefit for unfit patients, and soon sold to public, media and politicians as their one and only salvation,[74] but the original rationale of the technique for unfit patients has never been rigorously examined, except for the EVAR-2 trial published in June 2005. The hypothesis underlying EVAR trial 2 was that, for unfit patients with an AAA of at least 5.5 cm in diameter, EVAR compared with no intervention would reduce the risk of aneurysm-related death from rupture and improve long-term survival and health-related quality of life (HRQL).

EVAR-2 is a trial of moderate quality. It was obviously hard to motivate both surgeons and patients to adhere to protocol, and cross over rates to treatment were high. Mortality in these frail patients was very high: only 36% survived for four years. However, pending further evidence EVAR-2 presents the only interpretable and comparable data.

4.6.1. Patient population

The included patients were those eligible for inclusion in the EVAR-1 trial, but considered unfit for surgery. Of those that were available and accepting inclusion in EVAR 1 or 2, 49% were deemed unsuitable for EVAR device and 12% were deemed unfit for surgery and included in EVAR-2. Of those that were eligible for EVAR-2, 26% refused randomisation. Those that refused had comparable risk profiles as those that accepted. Taking into account loss to follow-up and censoring, mortality was 64% after four year. This was not surprising. The mean age of 76.4 y, 85% were male, 94.5% were smokers or former smokers, 69% had a history of cardiac disease and the median AAA diameter was 6.4 cm.

4.6.2. Mortality, morbidity, re-intervention and quality of life

As the time line between EVAR and no intervention is very different, it makes no sense to compare short term and long term outcomes. All cause mortality was higher in the EVAR-group, but not significantly (hazard ratio 1.21, which means an increased mortality of 21%). If the period after randomisation was divided in the first six months and the period after those six months, the mortality hazard of EVAR compared to no intervention (NoI) was 1.31 (95% CI 0.70-2.45) and 1.18 (0.80 – 1.73). Aneurysm related mortality was higher in EVAR in the first six month – HR 1.67 – but lower in the second – HR 0.53. Due to small numbers, these differences were far from statistically significant. In a context of competing death risks, this may be explained by mortality selection. In the later period, fewer survivors are selected by mortality and therefore more fit. Extending the follow-up will not likely offer a lot, as close to 2 patients in 3 were dead four years after randomisation.

In the EVAR group, 20 patients died of an AAA rupture or an intervention, in the NoI groups this was 22. The rupture rate in the NoI group was 9% per year. The procedural mortality of elective endovascular interventions was 7%, comparable to the Belgian EUROSTAR patients: the EUROSTAR database of Belgian patients shows rather high mortality in patients less fit for surgery (chapter 8 table 3). Short term mortality in patients aged 80 and over was 16/250 (6.4%), in patients unfit for surgery it was 26/417 (6.2%), in patients with ASA class 3 and 4 it was 29/419 (6.9%). Aorta ruptures were traded off for procedural mortality. In total, 144 patients died: 44 (29.6%) of an AAA or an intervention. 32 (22.5%) died of coronary heart disease, 27 (19%) died of lung disease or lung cancer, 29% of other causes of death.

47 of 172 patients in the no intervention group required an intervention during surveillance after a median time of 163 days. However, of these 47, 28 were crossing over because of patient or surgeon preference. 16 were treated because of symptoms (11) or fast growth (5). 2 survived an aorta rupture. Of the EVAR group, 150 of 166 had their allotted intervention after a median time of 57 days (14 died before). By 4 years, 43% of patients in the EVAR group had had at least one postoperative complication compared with 18% in the NoI group (hazard ratio 5.3, 2.8–10). 26% of patients in the EVAR group had needed at least one reintervention compared with 4% in the no intervention group (hazard ratio 5.8; 2.4–14.0). There were no consistent differences in HRQL between both groups.

Key messages

- **While EVAR was developed for patients unfit for surgery, and sold as such to the public, this has never been tested in a proper research protocol. The first results of a randomised trial were published in 2005.**
- **There was no significant difference between the EVAR group and the no intervention group for all-cause mortality (hazard ratio 1.21, 95% CI 0.87–1.69).**
- **Morbidity and re-intervention rates were five to six times higher in EVAR than in the no intervention group. This result was statistically highly significant.**
- **There were no apparent differences in quality of life between EVAR and no intervention.**
- **Pending further evidence, EVAR increases the risk of morbidity and interventions, without decreasing mortality in patients unfit for surgery.**

5. REVIEW OF COST EFFECTIVENESS

Whenever there is clinical equipoise about the effectiveness of interventions, questions about cost-effectiveness are raised. Without firm evidence of the superiority of a new intervention, as is the case for EVAR, the methods available for cost-effectiveness analysis are limited and the results fraught with uncertainty. This does not mean that economic evaluations are useless. They can provide useful insights into the variables that are determinant for the cost-effectiveness of the intervention.

The value for money of endovascular abdominal aneurysm repair (EVAR) has been investigated in a number of studies. Most of the earlier studies relied on modelling techniques to estimate the cost-effectiveness of EVAR relative to open AAA repair. The input variables are usually based on published small non-randomised clinical studies, as there was no evidence from RCTs or large registries available at the time of modelling. As a consequence, the models rely on less accurate evidence that inevitably introduces uncertainty in the model. The influence of uncertainty about the value of input variables is tested in sensitivity analyses. These show the range within which the results of the model vary when the value of one or multiple uncertain input variables is changed.

Very recently, two RCTs have published interim results: the EVAR 1 trial and DREAM. Both studies attached an economic component to their design. The EVAR 1 trial has published preliminary results of the economic analysis in June 2005[51], DREAM published its economic evaluation in September 2005[75]. These economic evaluations have the advantage that they rely on real data for the estimation of costs and outcomes. On the other hand, the follow-up in RCTs is limited, which also limits the cost-effectiveness estimate to the follow-up period of the trial. This is a disadvantage, especially if the long term outcomes are important and may change the balance for cost-effectiveness.

Given the large number of uncertain input variables in the cost-effectiveness models, the possibilities for deviations from the base-case estimate of the cost-effectiveness ratio are legion. We will limit our discussion of the economic models to the major factors that determine the cost-effectiveness of the intervention. In addition, we will briefly describe the major cost-drivers for EVAR.

5.1. METHODOLOGY OF THE LITERATURE REVIEW

During the clinical literature search, some economic and cost studies were encountered. To check whether the search results included all major economic evaluations, we performed an additional search in Medline, using the following search strategy: *Aortic Aneurysm, Abdominal/ AND exp "costs and cost analysis"/ NOT *Mass screening/. Subsequently, the cascade method was used to retrieve additional articles on the economics of EVAR.

Data were extracted in tabulated form for all full economic evaluations that compared costs and outcomes of open AAA repair and EVAR (see Appendix). Partial evaluations, such as cost descriptions, cost-outcome descriptions or cost analyses (definitions according to Drummond et al. 1997, see table in Appendix), were only used for the general discussion about the main cost drivers of the open versus endovascular procedure. Our main focus was on the relative cost-effectiveness, cost-benefit and cost-utility of EVAR as compared to open AAA repair.

Quality assessment was done using the checklist for economic evaluations of Drummond et al.[76]. This checklist does not result in one quality score and hence final appreciation of the quality of economic studies remains opinion-based.

5.2. RESULTS

5.2.1. Costs of EVAR and potential evolutions

There is consensus in literature that EVAR reduces the ICU stay, total hospital length of stay, blood transfusions and operative time.[77-81] Despite the shorter hospital stay in patients undergoing an endovascular AAA repair, EVAR is more costly than open surgery. The major cost driver is the endovascular graft.[78, 81-83] The cost of the endovascular graft makes up about 57% of the total inpatient cost of EVAR. [79, 80, 82, 83]

Experience in the US showed that device costs are generally low in the pre-reimbursement phase and increase thereafter, sometimes to more than the double of the initial price.[82] Therefore, older cost studies, performed in the era before the commercialisation of the endovascular graft (September 1999), are no longer relevant. In the pre-commercialisation phase, the price of the endovascular grafts was about US$5,000 - US$6,000 (€3,850 – €4,620). This price increased to US$8,000 - US$10,000 (€6,160 - €7,701) in the post-commercialisation phase. [77, 78, 80, 82] Over and above the cost of the graft itself comes the cost of all disposable ancillary supplies needed to place the graft. The difference between the cost of the endovascular graft and the standard graft for open AAA repair thus becomes larger.

In Belgium, the reimbursement of the endovascular graft, including the ancillary supplies, is about €6,000. The standard graft for open AAA repair is reimbursed between € 126 per 10 cm length for the straight graft and € 793 for the bifurcated graft.[2]

It is uncertain how the price of the endovascular grafts will evolve in the future. American studies do not expect a decrease in prices. [78, 82] On the one hand, companies continue to invest in research and development for the endovascular graft, which pressures the prices upward, but on the other hand more competitors are entering the market. The effect of increased competition will be determined by the number of patients eligible for AAA repair, which is limited. The final effect of the industry dynamics, given these two trends working in opposite directions, is difficult to predict.

The price increase of the endovascular grafts threatens the relative cost-effectiveness of the endovascular procedure. But there is more. The endovascular procedure requires more imaging pre-operatively and regular CT imaging during follow-up, which is not standard practice after open surgery.[79] These follow-up procedures were found to be the second most important determinant for the difference between open AAA repair and EVAR, more important than the costs of re-interventions and procedure-related complications. The latter have a huge impact on patients' outcome, however. Likewise, patients who have had an open AAA repair need more home care after discharge than patients who have had an EVAR.[84] This has cost implications but also implications for patients' quality of life. These aspects are taken into account in the economic models discussed in the next paragraph. The follow-up protocol for EVAR patients may change if more long-term clinical

[2] The presented figures are weighted averages of the reimbursement rates of the different types of grafts. The weights are defined by the number of grafts reimbursed in 2004.

evidence becomes available. [79] More frequent testing may be needed if the long-term complication rate is high, or, if complications are limited or technological improvements are realised with positive effects on long-term outcome, less rigorous follow-up may be needed.

Increasing experience with the endovascular technique may cut on the initial costs of EVAR: e.g. operating room time, length of stay and intensive care unit stay may diminish further. However, at the current price of endovascular grafts, it is unlikely that the EVAR procedure will ever become less costly than the open surgical procedure.[80] The savings would have to compensate for the 50% difference in costs between EVAR and open AAA repair due to the higher device cost. Given the already short length of stay of EVAR patients, this will be very unlikely.

Key messages:

- **EVAR is more costly than open AAA repair.**
- **The major cost driver of initial intervention is the endovascular graft, making up about 57% of the total inpatient procedure cost. Post-intervention follow-up costs are higher due to the higher frequency of imaging.**
- **At the current price of the endovascular grafts, EVAR is unlikely to reach cost parity with open surgical AAA repair, even if other cost factors would decrease as a consequence of increased experience with the procedure.**
- **Price evolutions of the endovascular grafts and changes in follow-up protocols are uncertain because highly dependent on industrial dynamics and technological developments.**

5.2.2. Cost-effectiveness

The literature search revealed five full economic evaluations, all four of them being cost-effectiveness analyses.[75, 85-88] One other study was called a cost-benefit analysis by the authors but was actually a cost-outcome description according to our definitions.[89] Finally, the EVAR trial 1 included information on costs and outcomes in terms of quality of life and is therefore also discussed in this paragraph, although it is a cost-outcome description rather than a full economic evaluation.[51] The seven studies are summarised in the data extraction tables in Appendix.

Economic evaluations alongside clinical trials

One economic evaluation was performed alongside the DREAM trial. The results are published in September 2005 as part of a PhD thesis. [75] The evaluation is limited to the cost-effectiveness of EVAR compared to open AAA repair in the first year after surgery. The main outcome measure is one-year quality adjusted survival time (called QALYs). In addition, the investigators looked at complication free survival time and one-year survival as a secondary outcome measures.

The study found an incremental cost of € 4,300 per patient for EVAR relative to open surgery, taking all direct costs into account, including patient time, productivity losses and travel expenses. The benefits were in favour of EVAR if expressed in terms of complication-free survival or in terms of life years gained. But, in terms of quality adjusted lifetime, open surgery was better (open AAA repair offered 0,01 QALYs more than EVAR). The difference in QALYs was, however, not significant. The incremental cost-effectiveness ratio was 76,100 € per complication-free life year gained and 171,500 € per life year gained. Open surgery was less costly and more effective in terms of QALYs gained and hence dominated EVAR. Taking into account variability in costs and outcomes in a bootstrap analysis, there is still a 65% chance that open surgery dominates EVAR. With an assumed cost-effectiveness threshold of 25,000 €/QALY gained, above which society is no longer willing to pay for an intervention, EVAR is not cost-effective compared to open AAA repair.

The relevance and usefulness of the second economic evaluation alongside a clinical trial [86] is questionable. The study uses an observational design in a very small sample of patients (7 treated with EVAR, 31 with open surgery) with variable follow-up (2-14 months) and uses "number of hospitalisation days avoided" as the effectiveness measure. [86] The results are perhaps useful for hospital managers in Canada, who whish to know whether the additional costs of the endovascular procedure are compensated by the savings from reduced length of stay, but generalizability is very limited. The study finds that the costs of the endovascular graft are responsible for 80.8% of the difference in costs between the open and the endovascular procedure and that about 5.1 hospitalisation days can be avoided by EVAR.

Economic models

Three studies modelled the long-term cost-effectiveness of EVAR relative to open AAA repair based on effectiveness data in terms of incremental cost per QALY. Modelling input data were retrieved from observational clinical studies[85, 87] or randomized controlled trials[88] (clinical effectiveness, complications) and health insurance and/or hospital accounting systems (costs). [85, 87, 88] Despite differences in assumptions, e.g. with respect to mortality rates, utilities, intervention costs and cost-effectiveness threshold values, the models built before the publication of the RCTs [85, 87] reach similar conclusions, while the post-RCT model concludes the opposite.[88] The major determinants for the long-term cost-effectiveness of EVAR as compared to open AAA repair are late mortality and morbidity (systemic-remote complications, long-term failures, rupture) after surgery and endovascular treatment. Long term morbidity and mortality after EVAR must be lower to make EVAR a cost-effective alternative to open surgery. [87]

According to the third economic model [88], that directly introduced the short term results of the two RCTs (EVAR 1 and DREAM) in its model, EVAR is not

cost-effective relative to open AAA repair in patients fit for surgery under base-case assumptions. The threshold value for cost-effectiveness was set at 30,000£/QALY. Only if the endovascular procedure would cost as much as open AAA surgery, there is a small chance (13.2%) that EVAR becomes cost-effective (according to a probabilistic sensitivity analysis). Similarly, for re-intervention rates half of those assumed in the base-case scenario, there is a 0.3% chance that EVAR becomes cost-effective relative to open surgery. The study moreover shows that open repair dominates EVAR if the mortality rate of open AAA repair becomes smaller than 3%. At a mortality rate after open repair between 3% and 11%, open AAA repair remains more cost-effective than EVAR. Only for a mortality rate between 11% and 40%, the incremental cost per QALY of EVAR is lower than 30 000 £/QALY.

In addition to patients fit for surgery, the study also modelled the cost-effectiveness of EVAR for patients unfit for surgery with large aneurysms (6.5 cm diameter) compared to conservative therapy. The model and input parameters were much less well explained than the previous model. Some input values were based on models and not on actually observed data from EVAR-2. Therefore, the results should be interpreted with caution. The model suggests that for this patient population EVAR is highly cost-effective. EVAR produced an incremental benefit of 1.64 QALYs at an incremental cost of £14,077. The incremental cost-effectiveness ratio amounts to £8,573 per QALY, which is well below the applied threshold of 30,000 £/QALY. However, this is inconsistent with the results of the EVAR-2 trial, in which EVAR was not better than watchful waiting.[88] An intervention with inferior or equal outcomes compared with its best alternative can only be cost-effective if it is less costly, which is not the case for EVAR.

Interestingly, only one of the models found that the relative immediate cost of the procedures is critical for the relative cost-effectiveness ratio of EVAR.[85]

Cost-outcome descriptions

The cost-outcome description based on the results of the EVAR trial 1 also mentions a 5-day shorter hospital length of stay with EVAR than with open surgery.[51] The cost of the main procedure was almost 2.7 times higher for EVAR than for the open procedure (UK£7,569 versus UK£2,811). This cost difference was not compensated by the savings generated by a shorter hospital stay: the total cost of the primary hospital admission was still higher for EVAR than for open AAA repair (UK£10,819 versus UK£9,240). Including the costs of 4 years of follow-up, adverse events and secondary AAA procedures inflates the difference to UK£3,313 (EVAR: UK£13,258; Open AAA repair: UK£9,945). This is due to the much higher costs of surveillance and secondary AAA interventions in the EVAR group as compared to the open AAA repair group.

The outcomes in terms of health-related quality of life were not different between the two procedures 3 to 24 months after randomisation. Immediately after the procedure, up to 3 months post-intervention, EVAR had higher quality of life scores than open AAA repair. The clinical outcomes have been discussed earlier. They lead to the conclusion that in the mid-term, up to 4 years after the intervention, the initial benefits of EVAR are fading away; the endovascular intervention leads to more late complications, increased need for surveillance and more re-interventions. While aneurysm-related mortality is still 3% lower for EVAR patients after 4 years, overall mortality is not different.

Likewise, a cost-outcome description, based on 20 open AAA repairs and 9 endovascular AAA repairs performed in Belgium, showed that hospital length of

stay was significantly longer in patients undergoing open surgery than in patients undergoing EVAR (11 versus 5 days).[89] Also intensive care unit stay was shorter for EVAR than for open AAA repair. The savings obtained from the shorter hospital length of stay did not, however, compensate the high cost of the endovascular graft. The total costs were not significantly different between the two interventions. This is in concordance with other studies on the cost of EVAR.[82]

5.3. CONCLUSION COST-EFFECTIVENESS OF EVAR

Up till now, there is insufficient evidence to justify EVAR for broad indications on economic grounds. According to the existing clinical evidence the long-term outcomes are disappointing and cannot justify the high amount of additional resources needed for EVAR as compared to open AAA repair.

The items that most strongly drive the incremental cost of EVAR as compared to open AAA repair upwards are the endovascular graft cost and the imaging cost during follow-up. Regular radiographic surveillance (with CT) is routine in patients that have undergone an endovascular procedure, mostly at 3, 6 and 12 months after the procedure and annually thereafter. For patient who have undergone an open AAA repair this is not standard practice. It is yet uncertain whether improvements in the endovascular procedure will be able to reduce to number of follow-up imaging tests and at the same time improve clinical outcomes. Such savings, as well as potential savings from lowered graft prices, are still highly speculative.

Key messages:

- **The existing cost-effectiveness evaluations of EVAR compared to open AAA repair do not provide justification for widespread use of EVAR.**
- **Uncertainty around the estimates of cost-effectiveness of EVAR is still large.**
- **Major determinants for the cost-effectiveness of EVAR relative to open AAA repair are the numbers of life years saved, the numbers of life year saved free from major complications, and the cost difference of EVAR relative to open AAA repair.**

6. EXPERIENCE WITH THE INTRODUCTION OF ENDOVASCULAR TREATMENT IN SELECTED COUNTRIES

6.1. UNITED STATES: FDA APPROVAL OF ENDOPROTHESES FOR AAA REPAIR

The first endovascular grafts for abdominal aortic aneurysm repair were approved by the FDA in September 1999. It concerned the Ancure Tube and Bifurcated Endovascular Grafting System (Guidant) and the AneuRx (Bifurcated) Stent Graft System (Medtronic). The approval was based on clinical studies on safety and short term effectiveness produced by the manufacturing companies and recommendations from external experts. The approval was conditional upon long term effectiveness evaluations of the devices as well as the continuation of a training and proctoring programme for their use.

Two years after the initial approval, in 2001, the FDA published a public health notification that warned for the risks associated with the AneuRx Stent Graft System. Long-term follow-up data showed serious adverse events (ruptures and deaths) in patients treated with this endovascular graft. The FDA recommended selecting patients for endovascular AAA repair based on the expected long-term AAA-related mortality, experience of the interventionist or institution, surgical risk factors, life expectancy and the patients' willingness to comply with the follow-up schedule.(FDA Public Health Notification December 17, 2003)

In addition, problems also appeared with respect to the Ancure endograft System. The company deliberately underreported the incidents that caused or could cause harms and complications to the patients that received an Ancure graft. This led to a criminal investigation and withdrawal of the FDA approval in March 2001. In September 2001 the device was reintroduced with FDA-approved modifications in the device's warning to customers and instructions to doctors but in June 2003, Guidant decided to remove the Ancure endograft system from the market.(FDA Consumer Magazine, 37; 6, Nov-Dec 2003)

In the meantime, other endovascular devices for AAA repair have gained FDA pre-marketing approval.

6.2. EXPERIENCE IN OTHER COUNTRIES

Since 1989, when the first experiments with EVAR began, the enthusiasm for endovascular AAA repair has increased in many countries throughout the world. Although it was clearly recognized by most practitioners that this technology was still in its experimental phase, the attractiveness of a minimally invasive treatment of AAA was strong.

The introduction of the technology in routine clinical practice was tempered in most countries, because HTA reports systematically concluded that the evidence was not yet sufficiently strong to draw any meaningful conclusions about the effectiveness and cost-effectiveness of the endovascular AAA repair technique. HTA reports were produced in France in 1995 (ANDEM), in Spain in 1997 (AETS) and in Canada (CCOHTA), the USA (MDRC), British Columbia (BCOHTA) and Australia (Centre for Clinical Effectiveness at Monash University and MSAC) in 1998. The main policy recommendation resulting from these reports was to limit the use of EVAR to clinical trials or prospective registries.

The recommendations were, however, not always translated in enforceable regulation: registries were voluntary and reimbursement was not conditional upon participation in a clinical trial or registration. Hence, the diffusion of the technology in different countries actually highly depended on the interest of vascular surgeons and interventional radiologists.

We performed a survey in all members of the International Network of Agencies for Health Technology Assessment (INAHTA) about their experience with the introduction of EVAR in their country. We asked about the existing of a data registration system and regulatory measures to control the diffusion of this emerging technology. Nine agencies responded to our survey.

6.2.1. Denmark

In Denmark, the National Board of Health recommends the limitation of endovascular AAA repair to a few major hospitals for reasons of quality assurance. However, no reimbursement restrictions will be imposed. Up till now, only two hospitals in Denmark are doing EVAR; one hospital performed 50 interventions up until May 2003, the other performed 34 interventions.

Outcomes of the procedures are registered in the Danish vascular registry. Annual reports are made and audit is performed if quality problems are notified.

6.2.2. Finland

The use of endovascular grafts is not restricted in Finland. There is no nationwide outcome data collection system, although some hospitals collect data for their own use.

6.2.3. Sweden

In Sweden, the use of endovascular grafts is not regulated by government or authorities. Reimbursement of the insertion of endovascular grafts does not differ from other procedures, i.e. the procedure is classified within the DRG-system and carries a similar weight to the corresponding open surgical procedure. Outcome data is collected and audited as other vascular procedures in the national Swedish Vascular Registry - Swedvasc, to which all Swedish vascular centres participate.

6.2.4. France

In France, the use of the endovascular grafts is regulated by public French authorities. A follow-up procedure, including data collection on all patients receiving an endovascular graft, was introduced in 2001, following a recommendation of the "Agence Française de Sécurité Sanitaire des Produits de Santé" (AFSSAPS). The physicians supply the data to the industry, who then summarizes the data twice a year and sends them to AFSAPS. Data are collected on the indication for implantation and complications during follow-up. Primary analysis showed that the criteria for implantation of an endoprothesis were not always met. Precise figures could not be presented because of incomplete or imprecise data supply.

Conditions for implantation are clearly defined in French regulations (http://agmed.sante.gouv.fr/htm/10/endropo/procsuiv.pdf). They relate to the follow-up of patients, the supply of data on patients with an endoprothesis, and training of the physicians who implant endoprotheses. Reimbursement is conditional upon compliance with these rules.

6.2.5. United Kingdom

In the UK, an interim guidance was published by NICE in 2003 on the safe and efficacious use of the EVAR procedure. The guidance set out the conditions under which the procedure could be used. Reimbursement of the procedure is a matter for local negotiation between trusts and their funders, the primary care trusts. Funding is not mandatory, but if the primary care trusts purchase the procedure locally then they should ensure that clinicians/trusts act in accordance with the recommendations in the guidance.

The Registry of Endovascular Treatment of Aneurysms (RETA) was established to facilitate efficient and timely analysis of outcomes. The register is run by the Vascular Society in the UK.

6.2.6. Canada

The Canadian Coordinating Office for Health Technology Assessment (CCOHTA) performed a survey in 2001 to determine the use of EVAR in Canada. There were no federal legal arrangements with respect to the use of EVAR, except that the grafts used require federal government licensing approval. Payment for the devices is done through the individual hospital's budget. The actual practice of AAA repair is regulated provincially, through each province's college of physicians and surgeons.

The survey revealed that 52% of the responding vascular surgeons used EVAR as an investigational procedure, 17% used EVAR based on the evidence in the medical literature, 10% based on expert opinion and 5% on patient demand. It is unclear what proportion of vascular surgeons participates in randomized clinical trials to assess the outcomes of the procedure.

6.2.7. Australia

Following the review on EVAR versus open AAA repair of 1998 and the recommendations of MSAC, an 'interim funding' arrangement was introduced into the Medical Benefits Schedule of Australia for endovascular aneurysm repair procedures performed in the private system. It stipulated that surgeons performing the procedure must submit their audit data to the "Australian Safety and Efficacy Register of New Interventional Procedures – Surgical" (ASERNIP-S). Originally, the government hoped to link payment to surgeons performing privately to data submission, but the Royal Australasian College of Surgeons overruled this. Subsequently, the interim funding has been extended to allow the government to assess mid to long term follow-up of patients who received an endovascular graft between November 1999 and May 2001 and whose results have been audited. Audit reports, with aggregate data, are publicly available through the website of ASERNIP-S (http://www.surgeons.org/asernip-s/auditAAA.htm). The audit reports are submitted to government at six monthly intervals.

In the public system, hospitals are responsible for allocating how they deliver their services. Public hospitals receive their funding allocation from the State Governments and are less under control of the Federal Government.

6.2.8. United States (Veterans Affairs)

Veterans Affairs (VA) is sponsoring the OVER (Open Versus Endovascular Repair) trial. The purpose of this multi-centre (35 sites) RCT is to compare EVAR with standard open AAA surgery. Long and short-term results as well as the cost and quality of life associated with these two strategies for AAA repair will be compared.

6.2.9. Israel

Placement of endovascular aortic aneurysm grafts is not regulated in Israel. The procedure is performed in public hospitals throughout the country. Outcome data are not systematically collected or used by the Ministry of Health for assessment purposes.

7. EXPERIENCE WITH THE INTRODUCTION OF ENDOVASCULAR TREATMENT IN BELGIUM

7.1. THE INTRODUCTION OF EVAR IN BELGIUM

The first commercial endovascular grafts for EVAR were introduced in 1995 in a very limited number of (university) hospitals. From 1997 onwards, the technique was diffused quite rapidly to several other university and non-university hospitals. The grafts were made available by the manufacturers at no or low costs (personal communication of several experts). And although no specific reimbursement code was present, most surgeons and radiologists performing this procedure were able to keep the cost for the patients limited by substituting with other codes. However, in 2000 a so-called 'rule of interpretation' (note CGV 2000/198 Insurance Committee) allowing the use of these other non-specific codes for EVAR was vetoed by the Minister of Social Affairs based upon concerns about effectiveness and added value of the new technique. As a response, part of the firms stopped providing hospitals with free or cheap endovascular grafts. In the press, headlines such as 'Health insurance deadly inefficient. How technological innovation is being reserved for the rich' occurred simultaneously.[74] A so-called 'convention' for the reimbursement of the endovascular graft in well specified conditions and as part of a experimental but potentially innovative technology was instituted in 2001 (using Article 35 category 5 of the health insurance law) and this for an evaluation period of 5 years. The conditions in the convention were proposed by the Technical Council for Implants and a committee of experts 'Commission Peer Review Endoprostheses'.

In the 2001 RIZIV/INAMI convention, the patient inclusion and exclusion criteria for reimbursement had been clearly defined (table 7.1). Added to the patient criteria, other minimal criteria for previous experience, around the clock availability of a multidisciplinary team, intensive care and emergency medicine (table 7.2). Informed consent of the patient was mandatory. Every individual file had to be sent to the 'College of medical directors' of the RIZIV/INAMI. Files were then transferred to the peer review committee. The college had the mandate to refuse reimbursement. A detailed registration of patient characteristics (in agreement with Eurostar) and follow-up after at least 1, 3, 6 and 18 months was mandatory.

Annually, 380 patients could be eligible for reimbursement. This means, that by taken into consideration the high requirements in the convention, the criterion of an experience of at least 20 implants under supervision and the fact that a small number of centres were already implanting a much higher number of endovascular grafts annually, is was estimated that 20 to 25 hospitals would participate. In reality, by the end of 2004 about 70 centres had entered the convention. The large gap between the numbers expected to cover more than 20 interventions in 70 centres (which is over 5000, at expected distributions: some centres show high volumes) and the numbers observed remain to be explained. In the subsequent forty months EUROSTAR registry (2001-2004), only 20 centres of the 70 reached twenty interventions. Experts suggested that the definition of "under supervision" was creatively interpreted, aided by the industry which organised "training courses". The convention was further interpreted in other lucrative ways, combining the high reimbursement code for open repair with the paid costs of the endostent. This gave a further financial incentive of 3000 Euro per endovascular intervention.

In the next section, the Belgian data from the Eurostar registry are analysed in detail. Cost estimations for EVAR and open surgery are made based on the data from all sickness funds via IMA (Intermutualistisch Agentschap).

Inclusion criteria

fusiform aneurysm with a diameter of > 5 cm of the aorta, or

fusiform aneurysm with a diameter of 4-5 cm and:

- diameter is the double of the native aorta, or
- evidence of growth of > 0.5 cm over 6 months, or
- symptomatic patient with backache or abdominal pain and palpable and painful aneurysm
- insured patient < 65 yrs.
- Family history of aneurysm (1st degree relatives), or
- Fusiform aneurysm of the arteria iliaca of > 2 cm, or
- Saccular aneurysm (real or false aneurysm, posttraumatic or caused by dissection, penetrating ulcer), regardless of the diameter

Anatomical criteria:

- Proximal neck with minimal length of 1 cm and diameter 10-20% smaller than available device, and
- Distal dock with minimal length of 1 cm and diameter 10-20% smaller than available device, and
- Iliofemoral and/or brachial access sufficient for available device

Exclusion criteria

General criteria

- Life expectancy less than 2 years
- Infectious aneurysm of infectious arteritis
- Active infectious syndrome
- Haemophilia or known bleeding disorder
- Marfan's syndrome and other genetic connective tissue disorders

Anatomical criteria

- proximal neck with an angulation of more than 70% and/or serious circular calcifications
- thrombus of more than 3 mm in the proximal neck or in the zone spreading over more than one third of the circumferential
- iliac malformations and – calcifications making it impossible to place the introducer
- Type of aneurysm where the occlusion of a major artery will be inevitable:
    - arteria renalis accessoria supplying more than halve of a functional kidney
    - permeable arteria mesenterica inferior feeding the arc of Rolan with a clear stenosis or occlusion of the arteria mesenterica superior
    - the artery of Adamkiewiecz of subrenal origin (evidence from arteriography)

Table 7.1: Patient inclusion and exclusion criteria of the 2001 convention art. 35, 5

Minimal requirements for the endovascular team and the hospital:.

- Daily experience with endovascular procedures and surgical treatment of aortic aneurysms
- At least 2 full time specialists in vascular surgery and interventional radiology, with 50% of their activity related to vascular interventions
- 24 hours access to medical imaging (C-arm, subtraction techniques, spiral CAT)
- Vascular surgeon on call to deal with complications
- The hospital has an intensive care unit and a specialised emergency room
- The interventional specialist had a specific training in EVAR and performed more than 20 EVAR procedures before 2001.
- A prior positive advice from the peer review committee and from the College of medical directors was needed before the hospital could enter the convention.

Table 7.2: Criteria for the endovascular specialists and the hospital

7.2. BELGIAN EXPERIENCE: THE EUROSTAR REGISTRY

7.2.1. Introduction

In Belgium, the inclusion of all patients with endovascular graft treatment of abdominal aortic aneurysms in the international EUROSTAR registry became mandatory with the start of convention in 2001, at least for those patients where a reimbursement of the prosthesis by the health insurance was asked. Before 2001, some centres were already participating in the Eurostar registry voluntarily.

The operative data and results from follow up examinations, as well as several outcomes (death, rupture, conversion to open repair) are sent by the physicians to the RIZIV/INAMI, which then transfers the case report forms to the EUROSTAR data management centre. As of July 2005, a total of 7202 patients have been recruited internationally in the EUROSTAR registry. Results are regularly updated and published on the EUROSTAR web site (last report published in July 2005[90]).

At the end of 2004, the individual patient's data from all Belgian centres were made available to the KCE. The data of 1437 patients recruited in Belgian hospitals and with operative data from April 2001 to October 2004 were thus analyzed, and are presented below.

7.2.2. Summary of results from all Belgian centres

This section presents a summary of results of the analysis of the 1,437 patients from Belgian centres included in the EUROSTAR database, at the time of end 2004. The complete report is appendix.

Summary of Results:

Recruitment of Patients and Hospitals Volume

While the Eurostar protocol inclusion criteria mentions a minimum of 10 cases treated per year, many hospitals did not fulfil this criterion. On the 70 hospitals that were included in the registry, 28 hospitals (40%) recruited 10 patients or less during the whole follow up period, and 50 hospitals (71%) recruited 20 patients or less. 7 hospitals (10%) recruited more than 50 patients in total.

Patient's Risk Profile

The average age of patients at operation was 72.7 years (range 46.9- 96.6). Older patients were recruited as long as the study progressed (% of patients above 80 years was 10% in 2001, 25% in 2004). The majority of patients were male (94%). Approximately 30% of the patients were considered unfit for open AAA procedure, and 8% were unfit for general anaesthesia. The mean aneurysm diameter (D3) was 56.6 mm (median 55 mm, range 25 to 130 mm), with 25% of the patients having an aneurysm size smaller or equal to 50 mm (Q1).

Operative Data

On the 1437 patients with operative data, 26% experienced an unexpected complication during the operation (17.5% had an endoleak, 3.3% had an inadvertently blocking of sides branches, 2.7% had any device related complication, for 0.9% there was a failure to complete procedure and 3.3% had an arterial complication).

Post Operative Data

On the 1437 patients with operation data, 15% had a post operative complication before discharge (10% had a systemic complication, 1.9% had a procedure and device related complication, 5.0% had an access site and lower limb complication and 1.1% had an abnormality detected on abdominal X-ray).

The average hospital stay was 6.3 days (median 4 days, range 0 to 165 days).

Accounting at Follow Up Visits

Approximately 13% of the patients were lost to follow up after operation before any scheduled visit was performed. The percentage of patients lost to follow up varies greatly between the centres, with some centres having repeatedly over the years a poor follow-up (see appendix).

At the time the database was closed for analysis (November 2004), only half of the patients had a follow up of 1 year, 20% a follow up of 2 years and less than 5% a follow up of 3 years. The percent of patients lost to follow up after 6 months is 22-23% for patients operated in 2001-2002 and 58% for patients operated in 2003, indicating that the follow up is quite poor and/or that the registration of follow up data is slow.

Table 7.3: Baseline Demographics and Pre-Operative Characteristics

Category	Subgroup	N= 1437	
		n	%
Year of operation	2001	286	19.9
	2002	458	31.9
	2003	487	33.9
	2004	206	14.3
Gender	Male	1352	94.1
	Female	85	5.9
Age at operation	Mean (SD)	72.7	7.6
	Range	47	97
	≤ 60 years	81	5.6
	60- 80 years	1105	76.9
	> 80 years	250	17.4
ASA Profile	1	201	14.0
	2	816	56.8
	3	375	26.1
	4	44	3.1
SVS-ISCVS risk factor score	Diabetes (51)	161	11.6
	Tobacco Use (46)	758	54.5
	Hypertension (39)	931	66.6
	Hyperlipidemia (54)	777	56.2
	Cardiac disease (48)	836	60.2
	Carotid-artery disease (62)	333	24.2
	Renal disease (59)	219	15.9
	Pulmonary disease (57)	650	47.1
Sum of SVS/ISCVSC risk factors scores	Mean (SD)	4.3	2.7
Factors Relevant to Indication	Previous Lapa (18)	371	26.1
	Obesity (19)	436	30.7
	Unfit for open AAA repair (20)	417	29.4
	Unfit for general anaesthesia (25)	119	8.4
Maximal Size of Aneurysm (37)	Mean (SD)	56.6	11.0
	Range	25	130
	Median (Q1-Q3)	55	(50-61)
A () indicates the number of missing values.			

Early Events (Mortality, Conversion, Rupture)

A total of 38 patients died within 30 days of operation or at hospital during prolonged hospitalization: the early mortality rate is 2.6%. Early conversion rate is 0.6%, and no patient had a rupture within 30 days after operation.

Results from multivariate logistic regression show that increasing age, increasing ASA score and unfit for surgery status increase the risk of death at 30 days. Relationship of AAA size and early mortality is less straightforward, as a high mortality is observed for patients with small aneurysms (<5 cm). After more detailed analyses (see appendix), mortality of small aneurysms (4.0 cm – 5.5 cm) seems consistent with the EUROSTAR international results [91].

Table 7.4: Early Mortality† by Selected Baseline Factors and Results from Logistic Regression

	N	n	%	Odds Ratio*	95%CI	
All Patients	1437	38	2.6	--	-	-
Gender						
Male	1352	36	2.7	Ref	-	-
Female	85	2	2.4	0.98	(0.22,	4.38)
Age Category						
< 60 years	82	1	1.2	Ref	-	-
60-<70 years	401	6	1.5	0.92	(0.10,	8.26)
70-<80 years	704	15	2.1	1.25	(0.16,	10.08)
≥ 80 years	250	16	6.4	2.72	(0.33,	22.40)
ASA-Class						
1	201	0	0.0	Ref		
2	816	9	1.1	Ref		
3	375	23	6.1	5.24	(2.18,	12.60)
4	44	6	13.6	9.37	(2.65,	33.11)
Fit for Surgery						
Yes	1000	12	1.2	Ref	-	-
No	417	26	6.2	2.48	(1.12,	5.52)
Size of Aneurysm						
<50 mm	216	7	3.2	Ref	-	-
50-<55 mm	457	6	1.3	0.38	(0.12,	1.19)
55-<60 mm	278	8	2.9	0.68	(0.23,	2.01)
≥ 60 mm	449	15	3.3	0.56	(0.21,	1.48)

* all results from logistic regression are adjusted for gender, age category, ASA-class, fit for surgery and size of aneurysm. 58 observations were deleted due to missing value of explanatory variables. Max R-square 0.18.

† Defined as death within 30 days after operation or during prolonged hospitalisation

Important Complications during First 30 Days

The initial clinical success is another outcome measure measuring the success of the endovascular operation [92]. The percentage of patients with initial clinical success is 82%. Main reasons of failure (18%) include Type I or Type 2 endoleak (5.9%), graft infection/thrombosis (5.6%) and no successful deployment of device at intended location (3.3%).

Table 7.5 : Counts (%) of Patients with Initial Clinical Success at 30 Days, and Reasons for Failure (Important Complications)

	N = 1437	
	n	%
Initial Clinical Success (at 30 days)	1176	81.8
Initial Clinical Failure	261	18.2
No successful deployment at intended location	47	3.3
Death	32	2.2
Type I or Type 2 endoleak	85	5.9
Graft infection/thrombosis	80	5.6
Aneurysm expansion	37	2.6
Rupture or conversion	8	0.6
Graft migration or failure of device integrity	42	2.9
Note : a patient may have several reasons of clinical failure.		

Volume Outcome Relationship

Assessing and measuring the association between the volume of procedures performed by a site and the outcome of this procedure is not an easy task, as shown by the amount of literature already published on the subject [93].

In 2002, Laheij et al [94]analyzed the influence of the team experience performing endovascular repair on several outcomes (short and long term mortality, need for secondary intervention) for 2863 patients included in the EUROSTAR registry. Their results showed a clear relationship between the experience of the team and the outcomes: patients who underwent EVAR by the most experienced teams (highest quartile, 92 patients or more) had a 40% lower mortality rate and a 68% lower secondary intervention rate than patients who underwent EVAR by the least experienced teams (lowest quartile, first 11 patients).

Analysis of Belgian data shows that, when the volume of hospitals is dichotomized with a cut off of 20 patients recruited, there is a numerical difference in early mortality in small centres (3.7%) compared to big centres (2.1%). Adjusted for the age, gender, ASA category, AAA size and fit for surgery status, the Odds ratio and 95% CI are 1.49 (0.71, 3.13), p=0.292. If the largest centre (N=144) is withdrawn, results show a smaller association (OR and 95% CI: 1.28 (0.64, 2.57), all results in appendix).

Table 7.6: Effect of Volume of Hospital on Short Term Mortality

			Early Death		
Volume of Hospitals	**N Hospitals**	**N Patients**	**n**	**%**	**Odds Ratio 95%CI**
≤20 patients	50	482	**18**	**3.7**	1.49 (0.71, 3.13)
> 20 patients	20	955	**20**	**2.1**	
Comparison adjusted for age, gender, size of aneurysm, fit for surgery status and ASA classification, and for intra-clustering of data (GEE approach)					

There is no association between the volume of hospital (dichotomized) and the initial clinical success rate.

Table 7.7: Effect of Volume of Hospital on Initial Clinical Failure

			ICF		Odds Ratio
Volume of Hospitals	**N Hospitals**	**N Patients**	**n**	**%**	**95% CI**
≤20 patients	50	482	**87**	**18.0**	0.94 (0.59, 1.48)
> 20 patients	20	955	**174**	**18.2**	
Comparison adjusted for age, gender, size of aneurysm, fit for surgery status and ASA classification, and for intra-clustering of data (GEE approach) ICF = Initial Clinical Failure					

Outcomes Assessed on Long Term (2 years)

Several outcomes have been studied (see list below). Rates and survival functions at 1Y and 2Y are presented below. After 2 years, the proportion of patients surviving the operation was 86.4%. The proportion of patients without any post operative complication after 2 years was 78.3%.

Table 7.8: Several Outcomes at 1 and 2 years after Operation

				Survival Function (%)		Cumulative Death (%)	
Endpoint	N events	N years follow up	Rate /100 py	1Y	2Y	1Y	2Y
Death	116	1375	8.4	91.7	86.4	8.3	13.4
Rupture, Conversion, Death	129	1373	9.4	91.1	84.7	8.9	15.4
Any Post Op complication *	197	1301	15.1	85.7	78.3	14.3	21.7
Any Endoleak	404	1041	38.8	69.8	66.1	30.2	33.9
Any post op abnormality or complication**	567	984	57.6	57.2	49.0	42.8	51.0
Any secondary intervention ***	76	1312	5.8	97.1	92.1	5.9	7.8

*Any post operative complication is defined as any procedure or device related complication after operation (graft migration, graft thrombosis, secondary intervention, rupture) or any important event (rupture, conversion, death)

** including any clinical or imaging abnormality

**Secondary intervention performed during operation (conversion to open repair) or during follow up period (secondary intervention transfemoral, transabdominal or extra anatomic).

7.2.3. Comparison of results between EUROSTAR Belgium data with four randomized controlled trials

A comparison of outcome results between the Belgian centres participating to the EUROSTAR registry and outcome results of 4 international RCTs follows. The purpose of these comparisons is to assess whether the results of the Belgian registry are consistent with the results published in the literature. Some caution is always needed in the interpretation of such comparisons, as outcomes are not adjusted for individual baseline characteristics: the matching of the inclusion criteria is only a tentative to compare similar patients between the RCTs and the registry data. Also, the quality and consistency of the follow-up is much better in the RCTs than in registry data.

The four international RCTs are:

- **UKSAT** (UK Small Aneurysms Trial): a comparison of elective **open repair** to **surveillance** for patients with small aneurysms (4.0 to 5.5 cm).
- **DREAM** (Dutch Randomized Endovascular Aneurysm Management) Trial: a comparison of **open repair** and **endovascular repair** for patients with aneurysm of at least 5 cm.
- **EVAR-1**: a comparison of **open repair** and **endovascular repair** for patients with aneurysms of at least 5.5 cm.
- **EVAR-2**: a comparison of **endovascular repair** and **no intervention** for patients unfit for open surgery and with aneurysm of at least 5.5 cm.

For each comparison, a selection of the patients from Belgian centres in EUROSTAR registry has been performed, to select only patients fulfilling main inclusion criteria of each trial (age, size of aneurysm, fit for surgery status). Baseline characteristics are summarized and main outcomes are compared.

Small Aneurysms (EUROSTAR VS UKSAT)

When the main inclusion criteria of the UKSAT trial (age between 60-76 years, aneurysm size between 4 and 5.5 cm and patients fit for open surgery) are applied on the EUROSTAR registry data from Belgian centres, patients in the EUROSTAR registry have on average the same age, have slightly larger aneurysms and male patients are more represented than in the UKSAT trial. The 30 day mortality is low (0.8%), and survival curves at 1 year and 2 years, as well as death rates within 6 months, seem comparable to the surveillance arm of UKSAT.

Table 7.9: Comparison of UKSAT and EUROSTAR (Belgium)

	Open Repair	Surveillance	EUROSTAR* Belgium
Inclusion Criteria			
Age	60-76 years		
Aneurysm Size	4.0-5.5 cm		
Fit for Surgery	Yes		Same
N patients	563	527	361
Baseline Characteristics			
Mean Age (SD)	69.3 (4,4)	69.2 (4.4)	69.2 (4.1)
Sex (% Male)	83%	82%	97%
Aneurysm Size Mean (SD)	4.63 (0.40)	4.61 (0.37)	5.04 (0.39)
Outcome Results			
30-d mortality	5.8%	--	0.8%
survival at 1 year (KM)	92% †	96% †	97%
survival at 2 years (KM)	87% †	91% †	93%
N patients years follow up	2262	2022	403
death rates 0-6 months (/100 pat years)	11.4	4.6	4.9

* patients from EUROSTAR Belgian centres are selected based on UKSAT inclusion criteria.

† data from UKSAT were provided by Dr Janet Powell.

Large Aneurysms (EUROSTAR vs. EVAR I and DREAM)

EVAR I

When the main inclusion criteria of the EVAR I trial (age at least 60 years, aneurysm size at least 5.5 cm and patients fit for open surgery) are applied on the EUROSTAR registry data from Belgian centres, patients in the EUROSTAR registry have on average the same age, the same size of aneurysm and male patients are more represented than in the EVAR I trial. The 30 day mortality is 1.6%, comparable to the 1.7% mortality observed in the endovascular arm of EVAR-1. Survival curves at 1 year and 2 years are also comparable.

Table 7.10: Comparison of EVAR I and EUROSTAR (Belgium)

	Open Surgery	EVAR	EUROSTAR* Belgium
Inclusion Criteria			
Age	at least 60 years		
Aneurysm Size	at least 5.5 cm		
Fit for Surgery	Yes		Same
N patients	539	543	444
Baseline Characteristics			
Mean Age (SD)	74.0 (6.1)	74.2 (6.0)	73.8 (6.5)
Sex (% Male)	91%	91%	95%
Aneurysm Size Mean (SD)	6.5 (1.0)	6.5 (0.9)	6.4 (0.9)
Outcome Results			
30-d mortality	4.7%	1.7%	1.6%
survival at 1 year (KM)	90% †	93% †	95%
survival at 2 years (KM)	85% †	85% †	86%

† indicates that data are estimated visually from published survival curve.

* patients from EUROSTAR Belgian centres are selected based on EVAR I inclusion criteria.

DREAM

When the main inclusion criteria of the DREAM trial (no restriction on age, aneurysm size at least 5 cm and patients fit for open surgery) are applied on the EUROSTAR registry data from Belgian centres, patients in the EUROSTAR registry are on average slightly older, male patients are less represented, and aneurysm size is slightly smaller than in the DREAM trial. The 30 day mortality is 1.1%, comparable to the 1.2% mortality observed in the endovascular arm of DREAM. Survival curves at 1 year and 2 years are also comparable.

Table 7.11: Comparison of DREAM and EUROSTAR (Belgium)

	Open Surgery	EVAR	EUROSTAR * Belgium
Inclusion Criteria			
Age	No restriction		same
Aneurysm Size	at least 5 cm		
Fit for Surgery	Yes		
N patients	178	173	814
Baseline Characteristics			
Mean Age (SD)	69.6 (6.8)	70.7 (6.6)	72.2 (7.5)
Sex (% Male)	90%	93%	95%
Aneurysm Size Mean (SD)	6.0 (0.85)	6.06 (0.90)	5.83 (0.89)
Outcome Results			
30-d mortality **	4.6%	1.2%	1.1%
survival at 1 year (KM)	93% †	96% †	96%
survival at 2 years (KM)	90%	90%	90%

* patients from EUROSTAR Belgian centres are selected based on DREAM inclusion criteria

† indicates that data are estimated visually from published survival curve.

** 30 day mortality and hospital mortality yin case of prolonged hospitalization.

Patients unfit for open procedure (EUROSTAR VS EVAR-2)

When the main inclusion criteria of the EVAR-2 trial (at least 60 years old, aneurysm size at least 5.5 cm and patients unfit for open surgery) are applied on the EUROSTAR registry data from Belgian centres, patients in the EUROSTAR registry are on average the same age, have the same aneurysm size and male patients are more represented than in the EVAR 2 trial. The 30 day mortality is 5.4%, lower than the 9% mortality (7% if elective case only) reported in the EVAR arm. Survival curves at 1 year and 2 years seem also better for patients in the registry than patients in the EVAR arm.

Table 7.12: Comparison of EVAR 2 and EUROSTAR (Belgium)

	No intervention	EVAR	EUROSTAR* Belgium
Inclusion Criteria			
Age	at least 60 years		
Aneurysm Size	at least 5.5 cm		
Fit for Surgery	No		same
N patients	172	166	240
Baseline Characteristics			
Mean Age (SD)	76.0 (6.7)	76.8 (6.2)	76.0 (6.6)
Sex (% M)	85%	85%	94%
Aneurysm Size Mean (SD)	6.3 (?)	6.4 (?)	6.5 (1.1)
Outcome Results			
30-d mortality	--	9% **	5.4%
survival at 1 year (KM)	81% †	79% †	83%
survival at 2 years (KM)	70%†	61% †	78%

* patients from EUROSTAR Belgian centres are selected based on EVAR II inclusion criteria

† indicates that data are estimated visually from published survival curve.

** 7% if only elective surgery is considered

7.2.4. Validation of the Belgian EUROSTAR registry data with Belgian claims data

Comparison of Claims data and Registry Data

Table 7.13 presents a comparison of the data from the IMA report (claims data) and the Eurostar report on Belgian centres (European registry). The main difference between the 2 reports lies in the number of data available at the time of analysis: while the EUROSTAR registry is based on data until October 2004 and contains 1437 patients, the IMA report has data available until mid 2003 and contains half of the EUROSTAR population (720 patients). The baseline characteristics of the patients (gender, age) are comparable. Duration of hospitalization is slightly higher in IMA report. Mortality rates at 1, 3 and 12 months are comparable.

Table 7.13 : Comparison of IMA and EUROSTAR reports on Belgian Centres

	IMA	EUROSTAR
Data Included in Analysis		
First operation	May 2001	April 2001
Last operation	Mid 2003	October 2004
Number of hospitals	64	70
Number of patients included	720	1437
N Operations in 2001	217	286
N Operations in 2002	322	458
N Operations in 2003	181	487
N Operations in 2004	-	206
Baseline Demographics		
Male (% men)	663 (92%)	1352 (94%)
Age mean/median	71.7/72	72.7/73.2
Length of Stay (days)		
LOS mean/median	9.6/6	6.3/4.0
Mortality		
Mortality at 1 month	2.2%	2.4%
Mortality at 3 months	4.3%	4.0%
Mortality at 1 year	8%	8.3%

The claims data were used for 2 purposes: on the one hand to estimate the cost of endovascular intervention in Belgium (full report in appendix), and on the other hand to validate the mortality data of the EUROSTAR registry, as claims data do not have the problems of patients being lost to follow up or under reporting of outcomes (death).

Results from Coupling Claims Data and Registry Data

The coupling of EUROSTAR registry data was performed at the KCE. As no identifying patient number was available to make the link between the registry data and the claims data, matching was used with main demographic variables (hospital, gender, birth year, operation date, admission and discharge dates, methodology described in appendix).

The total number of patients in the claims database was 720. On the same period, the registry contained 1116. A total of 604 records from the claims database could be matched to the registry database (84%). The 116 patients (16%) that could not be matched are probably due to encoding errors in one of the variables used for matching.

The coupling procedure also revealed some inconsistencies in the coding of the hospitals in the registry database. For some patients, the registry contained the hospital of admission, and not the hospital of the operation, as would be expected.

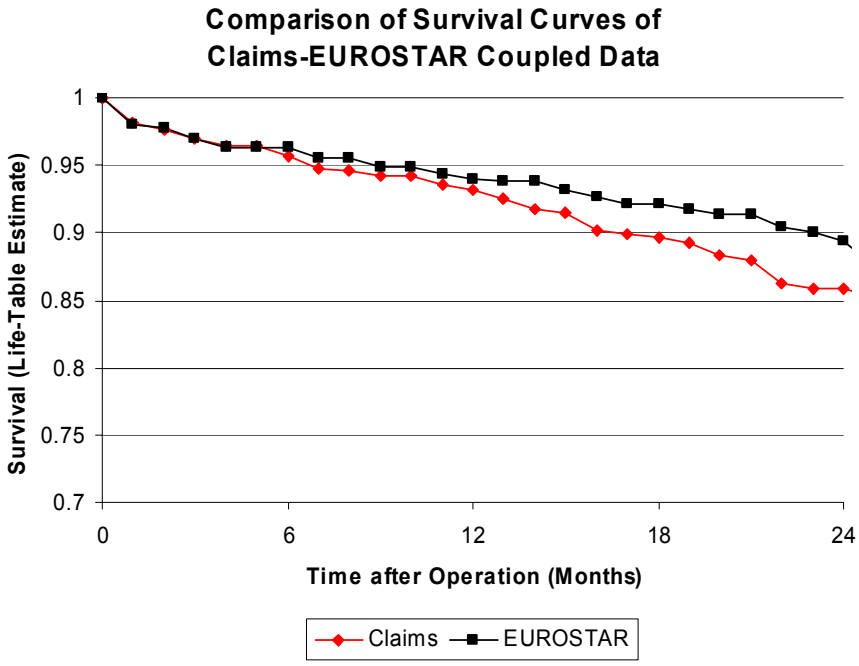
Validation of Mortality Data in Registry

Claims data contained mortality data until December 2003. A total of 66 deaths were observed during that period. 41 of these deaths were also observed in the EUROSTAR registry, implying that 25 deaths were not described in the registry. As the majority of these "missing" deceases occurred in 2003, a possible explanation is that hospitals are very slow at sending their data back to the EUROSTAR data management centre. Survival curves (Life-Table Estimates) based on the 2 datasets show that within the first year of follow up, registry data mortality are practically equivalent at claims mortality data. After 1 year of follow up the registry mortality data are slightly underestimated.

Table 7.14: Comparison of Death reported Belgium Eurostar Registry and Claims Data

	Coupled Database		
	Claims	Eurostar	
Source Database	720	1116	
Coupled Database	604	604	
Mortality Data			"Missing Death" in Eurostar
Death in 2001	3	2	1
Death In 2002	22	17	5
Death in 2003	41	22	19
Death in 2004	-*	9	-*
Total	66	50	25
* claims contain mortality data until December 2003.			

Figure 7.1


Comparison of Survival Curves of
Claims-EUROSTAR Coupled Data
Survival (Life-Table Estimate)
1
0.95
0.9
0.85
0.8
0.75
0.7
0
6
12
18
24
Time after Operation (Months)
Claims
EUROSTAR

Key messages

- In Belgium, a convention for the reimbursement of the endovascular treatment of AAA was instituted in 2001 for an evaluation period of 5 years. Inclusion of patients in the international EUROSTAR registry was part of that convention. We used the EUROSTAR data from April 2001 and October 2004 for this analysis.
- Many more centres than anticipated recruited patients (70 centres, N=1437), with a small volume per centre: between April 2001 and October 2004, 50 centres treated up to 20 patients only.
- The mean age of patients was 72.7 years, with 17% of patients above 80 years. 29% of the patients were considered unfit for open repair. The mean size of aneurysm was 56.6 mm, with 25% of the patients with an aneurysm size $\leq$ 50 mm, and half of the patients $\leq$ 55 mm.
- Short term mortality (30 days and in hospital death) was 2.6%. At 2 years, cumulative mortality was 13.4%. Secondary intervention rate was 7.8% at 2 years.
- In hospitals with up to 20 patients, mortality was 3.6%, and 2.1% for hospitals with more than 20 patients. The higher mortality of 49% (confidence limits -29%, + 213%) is not statistically significant, but comparable to findings in the European EUROSTAR study and consistent with a learning curve.
- Results of EVAR after 2 years were compared to 4 RCTS trials (DREAM, EVAR-1, EVAR-2 and UKSAT). For small aneurysms, results of EVAR are similar to the surveillance arm, for large aneurysms results are similar to the EVAR arm from EVAR-1 and DREAM (patients fit for surgery). For patients unfit for surgery (EVAR-2), results are better.
- Endovascular interventions were also retrieved from the claims data (IMA). The coupling of the EUROSTAR data and the claims data revealed that:
- A lot of interventions registered in the EUROSTAR data could not be retrieved in the claims database, suggesting that no reimbursement was asked.
- After 2 years, there is an underestimation of the observed mortality in the EUROSTAR registry. This could be partly explained by slow transfer of data to the registry data centre.

7.3. COSTS OF ENDOVASCULAR TREATMENT IN BELGIUM

7.3.1. Cost analysis of endovascular treatment

This section presents a summary of a short term cost analysis on patients treated with endostent in Belgium, from May 2001 to October 2003. Cost data were available from health insurers (claims data). The complete report is presented in appendix. The results are illustrative only. They must not be interpreted as a direct comparison of the costs of the two techniques, as patient selection is different, indications for open surgery may vary and long term costs are omitted.

Selection Criteria for Endovascular Repair

We used the following codes to retrieve patients with endostent treatment: 687061, 687083, 687105, 687120, 687142, 687164 en 687186 (see description in appendix) from the introduction of new codes for endostents, in May 2001, until October 2003.

Population with Endovascular Repair

We analysed cost data of 720 patients. 92% of these patients were male, and their mean age was 71.7 years. The mean LOS was 9.6 days (median 6 days). 64 hospitals were included in the study, with a maximal volume of 84 stents. 8 hospitals treated 1 patient only.

Costs of Endovascular Treatment

The subsequent table presents a summary of the costs for patients treated with endovascular treatment. The mean (median) cost of hospitalisation was 11486 (10360) €. The mean (median) preoperative costs (90 days before hospitalisation) were 3794 (2523) € per patient, for which imaging costs contribute for a mean (median) of 562 (525) € per patient. Mean (median) post operative costs (120 days after end of hospitalisation) were 1830 (420) € per patient, imaging costs being a large part: mean (median) of 383 (339) € per patient. A skewed distribution with high costs in a minority of patients will cause the mean to be (much) larger than the median.

Table 7.15: Medical Insurance Costs (in €) for patients with Endovascular Treatment (N=720)

	All Costs		Imaging Only	
	Mean	Median	Mean	Median
Hospitalisation	11486	10360		
All Pre-op. costs *	3794	2523	562	525
All Post op. costs (45 days) **	805	175	215	184
All post op costs (120 days) **	1830	420	383	339
* pre-operative costs include costs 90 days before placement of stent ** post operative costs after end of hospitalisation				

7.3.2. Cost analysis of open repair treatment

Selection Criteria for Open Repair

We used the following procedure codes to retrieve patients with open surgery: 237031-237042, 237053-237064, 237075-237086, 237090-237101 (description in appendix), from April 2001 to end 2003. At earlier dates, no specific EVAR codes were available and nomenclature codes might have confounded open surgery and the endovascular intervention.

Costs of Open Repair

We choose to retrieve all patients with open repair procedure from the health insurers' data. Coupling of the procedure with the diagnosis of AAA would have yielded more precise estimates, but this is a demanding procedure. We assumed that the costs of AAA as indication for open surgery would be comparable to the costs of other indications (thrombosis, claudicatio, etc). The cost data of 2 large academic hospitals confirmed this assumption (UZ Leuven and UZ Gent).

The subsequent table presents a summary of the costs for patients treated with open surgery. The mean (median) cost of hospitalisation was 7924 (6126) €. The mean (median) preoperative costs (90 days before hospitalisation) were 2931 (1870) € per patient, for which imaging costs contribute for a mean (median) of 437 (399) € per patient. Mean (median) post operative costs (120 days after end of hospitalisation) were 2015 (586) € per patient, imaging costs being a smaller part: mean (median) of 112 (12) € per patient.

Table 7.16: Medical Insurance Costs (in €) for patients with Open chirurgical treatment for All Indications (N=5,121) from 1/5/2001 to end 2003.

	All Costs		Imaging Only	
	Mean	Median	Mean	Median
Hospitalisation	7924	6166		
All Pre-op. costs *	2931	1870	437	399
All Post op. costs (45 days) **	977	248	55	0
All post op costs (120 days) **	2015	586	112	12
* pre-operative costs include costs 90 days before chirurgical intervention ** post operative costs after end of hospitalisation				

Conclusion

The results of this limited exercise must be interpreted with caution. However, these recent Belgian cost data are consistent with the findings of EVAR and DREAM,[51, 75] suggesting that EVAR procedures cost (in the shorter term) 3500 Euro more than open surgery.

Key messages

- **Costs of AAA endovascular repair in Belgium were estimated at 11500 € (median 10400 €). Costs of open AAAA repair in Belgium were estimated at on average 7900 € (median 6200€).**
- **The relative and absolute difference between the costs of endovascular repair and open surgery is comparable to those observed in the randomised controlled trials.**

8. ETHICAL ISSUES

In this part, we discuss shortly the different perspectives and preferences for the most important stakeholders.

8.1. PATIENT PERSPECTIVE

Endovascular AAA repair has tangible advantages over open surgery over the shorter term. Open surgery knows high rates of mortality and major complications, and quality of life is lower after open surgery in the first three months following the procedure.[50, 51] This is not in the least surprising, given the comparison of an endovascular intervention and open surgery and made undoubtedly the main attraction of EVAR. However, these benefits are not durable: the mortality advantage soon disappears. After three months, the patient that survived open surgery free of complications has an excellent prognosis and needs little follow up. The patient that has had an endovascular repair faces a lifelong follow-up for life, and for the time being re-intervention rates of 6% per year. In the EVAR-1 trial, quality of life of EVAR patients was not lower, but in the DREAM trial it was. [50] Therefore, patients' preferences for one treatment or another will be strongly determined by their time preference. Patients with a strong time preference will prefer the intervention with the lowest short term risk (EVAR). Patients who wish to avoid all risks will prefer an intervention with the lower risks, while the "gambler", who is not afraid of taking risks, may prefer the short pain of the open surgery intervention over the long follow-up of surgery. All treatment choice should always involve a careful weighting of risks and benefits, given the patients' own choice. In general, open repair is more suited for AAA patients that are healthy and expect a long life free of disease, banking on the better long term results of open surgery.[95] EVAR is more suited for AAA patients that have more life limiting illness: the three to five weeks free of major complications saved by EVAR weighs more heavily in a short life expectancy free of major disease.

If choice for EVAR is dependent of the patient payment, the high costs of the endograft causes inequity, as the endograft is a heavier burden for the less wealthy. However, if access of the endograft is restricted based on financial criteria for all, the autonomy of the wealthier patient is restricted. It may be paradoxical that we allow buying expensive cars instead of cheap ones, while not allowing buying expensive health care technology, because it can not be made available to all. So it is with expensive cars. The dilemma between equity for all and freedom of choice for the better off in the use of effective but not cost-effective health care technology ought not to be solved by dogmatic principles, but by a political decision, well informed by ethical debate on the conflicting perspectives of equity and freedom.

However, the concept of autonomy and free choice requires balanced information of both parties, patient and doctor. The patient is dependent on the doctor's information, knowledge and judgement. If emerging technology such as EVAR or carotid artery stenting is executed in not accredited centres by not accredited doctors, poor quality and high costs to the patient may be the consequence. The society has the duty to protect patient safety and to assure good quality of care, regardless of the source of payment. In emerging technology, benefits are often overstated and harms underrated (EVAR is a good example, actually). The autonomy of patient and doctor is subordinate to (and dependent on) safety and quality.

8.2. CARE PROVIDER PERSPECTIVE

The care provider refers here to the system delivering care: hospital, surgeon, radiologist, etc.

Doctors want the best for the patient, and it is to the vascular surgeon's credit that they searched for better solutions than the heavy aorta surgery. Compared to open surgery, EVAR knows excellent short term results. The lower level of complication rates and service use (length of stay in operating room and intensive care unit, blood use, etc) is financially attractive to the care provider, particularly if the stentgraft is paid for. The long term need for follow-up and re-interventions of EVAR, rarely complicated by major events, creates a stable patient population and assures future financing: the care provider is better served by a constant flow of diagnostic and therapeutic interventions (if these are rather harmless) and income than by a single 'big bang'.

Added to the more attractive long term perspective in volume of interventions of EVAR, the financial incentive for the use of EVAR is in the order of magnitude of 3000 € per intervention: the stentgraft costs 6000 €, but saves 3000 € in health care resources (length of stay, length of stay in ICU, length of stay in operator room). From a rational care provider perspective, the care provider ought to maximise the endovascular interventions in order to optimize income, to increase patient satisfaction and to save on resource costs.

As mentioned before, the autonomy of patient and doctor is subordinate to (and dependent on) safety and quality of the interventions. The State should guarantee safety and quality of health care. Therefore, accreditation of doctor and centre and effective registering and auditing of the quality of outcome of expensive interventions not reimbursed by health insurance remains an ethical requirement, whatever the source of payment and the type of regulation.

8.3. HEALTH CARE PAYER PERSPECTIVE

The health care payer refers here to all societal health care payers, except for the individual patient. The health care payer redistributes scarce health care resources, to allow equitable access to health care for all. As such, it is his ethical duty to use resources wisely, and to buy the most health. Investing in cost-ineffective interventions either wastes money to the health care sector (leaving more efficient interventions unpaid for), or to the tax payer. EVAR is not cost-effective, and should not be financed. However, EVAR is a promising technology that might be a more cost-effective future approach. This implies that EVAR needs to be implemented in an experimental setting, to optimise efficiency.

For the time being, the financing system offers strong incentives to perform EVAR, which is more costly in the short term and in the long term. This is an inefficient and irrational waste of scarce resources. A rational health care payer should give financial incentives to perform open surgery and to experiment prudently with EVAR to discover the optimal indication and the more cost-effective use. In the future, the health care payer should learn from these mistakes, and avoid creating incentives for the more expensive and less cost-effective technology.

8.4. INDUSTRIAL MANUFACTURER PERSPECTIVE

The medical industry is an important stakeholder who drives emerging technology. It is to the credit of the medical industry to develop more effective health care technology, able to substitute for severe and demanding open surgery. The highly bumpy road of endovascular stentgrafts development shows that the stentgraft development was not an easy ride. Massive investments in research are required, and it is expected that the industry wants to recoup the costs of development. However, to function optimally, the medical industry needs appropriate "checks and balances" of the health care payer. Endovascular treatment was introduced when long term safety and durability was unknown and effectiveness was unknown and even not properly researched in randomised controlled trials. A policy of "dumping" of free endografts was followed by severe pressure on policy makers to accredit the technology and then by high costs of endografts after accreditation. The introduction of EVAR technology should be opened up to impartial ethical investigation of the promotion methods: both industry and society will fare better in an ethical atmosphere allowing mutual trust in fair trading practices. Indeed, in an ambiance of mutual hostility, the health care payer should block all experiments in expensive technology till proven cost-effective by the industry. This would slow down return on investments, slow down innovative technology and slow down the industry as a whole. The safe introduction of emerging technology is a common task of industry, provider and payer. It is the classic prisoner's dilemma of game theory: [96] if the one takes a free ride at the expense of the others, all lose out in the long term.

Key messages

Ethical and political dilemmas rise through the financial regulation of effective but expensive and not cost-effective technology:

If EVAR is not financed and not made available,

- EVAR is not available to those who wish the intervention with lower short term risks.
- Autonomy of patient and doctor is harmed.
- Without returns on investment, the medical industry might abstain from further development of innovative technology, depriving future patient populations of superior medical technology.

If EVAR is not financed by the society, but made available to individual patients,

- EVAR is available to those who have the important financial resources to pay for it.
- Equity between patients is harmed.
- Asymmetry of information creates an incentive for treatment decisions not in the best interest of the patient.

If EVAR is financed by the society,

- Financial resources are spent that are not available for better (more cost-effective) use elsewhere.
- Either social injustice arises with other patient groups, deprived of similar expensive technology. Or injustice arises with other societal aims, as rising costs of health care reduce other budgets (education, economy, pension, …).

9. IMPLEMENTATION AND FINANCING OF EVAR

9.1. RATIONAL PROVISION OF VASCULAR SERVICES

The specific implementation of EVAR is not in the scope of this project: specific implementation of such a technology requires other technical skills and another approach. As long as EVAR is not cost-effective, implementation in routine health care is no issue, and its' use remains experimental, pending better health effects, lower costs and certain durability. However, if EVAR is cost-effective in the future, introduction of EVAR will challenge the existing health system. EVAR being an endovascular intervention, it requires high imaging skills, expensive technology and much experience. But it can not substitute open surgery: the specific competence of the vascular surgeon in open repair remains needed. The large body of literature about volume-outcome relationships shows that the best quality is not maintained at lower volumes, both of hospital of surgeon. By expanding the number of interventions, the personal experience per intervention is diluted: better interventions may paradoxically result in lower quality, if experience in performing each intervention drops below a certain threshold. The same principles apply to endovascular and open interventions for carotid artery stenosis or to interventions for peripheral limb ischemia. Multiplying the numbers of rules and regulations for each technology generates a bureaucracy that is rarely if ever able to enforce these rules. It creates lack of transparency for the patient (and his GP), as some hospitals may be accredited for the one technology but not for the other.

Principles of good organisation are based on principles of parsimony. That means: keep it simple. Two contradictory principles are to be combined: decentralisation of services and centralisation of technology and competence. In a modern health care delivering optimal care, we must address questions of optimal planning. Patients need sufficient access to services, particularly in case of emergency outside working hours (a frequent occurrence in vascular surgery). Doctors and hospitals need sufficient patients to maintain experience, improve quality and receive a cost-effective return on the necessary and expensive investments. The present haphazard and unplanned provision of vascular services may endanger public health: we observed a high use of potentially dangerous vascular interventions, both in carotid artery stenosis and in endovascular aorta repair. 25% of the AAA entered in EUROSTAR had a too small diameter according to any guideline or according to the "convention". This is not acceptable. However, blaming (only) the doctor is dishonest, if the entire system forces to maximal, not optimal use.

Health care needs for major vascular interventions have been calculated in a "frugal" planned health care system.[97] Frugal can here be described as highly efficient, highly planned but inadequately financed and less satisfying for the patient. The number of major vascular interventions needed in the frugal health care system of the UK is estimated at 80 per 100,000 inhabitants.[97] A full time equivalent (fte) vascular surgeon should perform in average 3 interventions per week, during 40 weeks per year: there is 1.0 fte vascular surgeon needed per 150,000 inhabitants. A vascular surgeon should at least 0.5 of his fte be occupied by vascular surgery. A desirable workload for 4.0 fte surgeons (including holidays, continuing education, and a family life) is therefore generated by a unit of 600,000 population. Units should not drop under 3.0 fte vascular surgeons for 400,000 inhabitants. Vascular surgeons need to be occupied by vascular surgery at least half of the time. In a frugal health care system, Belgium would need 75 fte vascular surgeons in 20 centres.

Belgium does not need a frugal system: such a 'frugal' organisation would lower both patient and doctor satisfaction. However, there is no sensible way the health care system can guarantee sufficient quality at acceptable costs in more than 70 vascular centres. If patient safety and quality of care is an ethical requirement, we can argue about the desirable density of tertiary care services, but not about the principle of centralisation of these services. Vascular surgery has to be concentrated in a limited number of "high tech" vascular units to give the best quality at acceptable costs. Maintaining the current situation necessarily leads to a waste of resources, suboptimal quality of care and burgeoning but ineffective bureaucracy.

EVAR can be implemented in vascular units of tertiary care services that have been accredited for use. Such tertiary care services have a multi-disciplinary vascular team, all the necessary equipment and the personnel to do all vascular interventions. Volume-outcome relationship in vascular surgery, both for open surgery and for EVAR [21] [94] should be translated in clear criteria, including the whole major vascular surgery and EVAR activity. Taken into account the relatively low number of eligible patients, the number of centres is expected to be less then or at most equal to the current number of centres for cardiac surgery.

9.2. FINANCING OF EVAR

The present financing system showed a strong financial incentive for EVAR: Open surgery costs (roughly) 8000 Euro, EVAR costs 5000 Euro plus 6000 Euro for the endograft. The care provider, i.e. vascular interventionist and hospital, receives the same amounts for open surgery or EVAR, plus the endograft, pocketing 3000 Euro per endograft. In addition, the hospital stay is expected to be shorter for EVAR patients, again stimulating the use of EVAR. This is an irrational policy with several financial incentives promoting the least cost-effective intervention.

From a general point of view, the same problem¸ elective AAA repair, should be financed with the same investments of resources. In a prospective system of financing, the care problem is financed, not the specific technology. We therefore suggest the same reimbursement for open surgery and endovascular repair. It cannot be justified that the vascular surgeon receives the same fee for a less invasive and shorter procedure. The data from IMA showed that in over three quarters of the EVARs indeed the classical code is billed by the vascular surgeon to health insurance. More balanced reimbursement of the physicians' fee, will situate the financial incentive at the most cost-effective intervention, open surgery, while allowing the care provider to experiment prudently with EVAR. If the added costs of the endostent are rolled off to the patient, the situation is essentially unchanged, the care provider pocketing 3000 Euro but now at the cost of the patient.

10. DISCUSSION AND CONCLUSIONS

10.1. A FAILED EXPERIMENT

EVAR has been called a "failed experiment".[98] The introduction of EVAR certainly was a failure in evidence based medicine and in the wise use of scarce resources. It was not in marketing. Ancure, AneuRx and Zenith have been used in 70.000 patients before any proper trial demonstrated effectiveness or cost-effectiveness over open surgery.[75] Endografts were originally developed to treat patients unfit for surgery, but this use has never been properly examined till EVAR-2 appeared, in June 2005. In EVAR-2, the results of EVAR were not better than watchful waiting. However, it was the use in patients unfit for surgery that was used as a battering ram to claim reimbursement.[74] There was no solid proof of effectiveness, the costs of endoprotheses were high and the durability and long term safety of the then available devices was questionable. Rutherford and Krupski signalled in 2004 16 devices of which 4 had made it to the US market. Ancure (18,000 patients) has been retracted in 2003, Medtronic (AneuRx) forced FDA-authors to retract a paper from the Journal of Vascular Surgery by threatening with lawsuits for using confidential outcome data. Since then, controlled long term follow-up data have not been made available.

While EVAR was proclaimed as a life saving device in patients unfit for surgery, it was increasingly used in patients that do not benefit of surgery, or of any other intervention except for watchful waiting. EVAR has the best results in small aneurysms, but rupture probabilities of small aneurysms are small, and it is highly unlikely that an intervention with an equally small but real mortality risk will improve their survival. A recent not randomised "pivotal" trial included already patients with aneurysms of 4 cm OR fast growing aneurysms.[66] Given a prevalence of aorta aneurysms among the population of about 5%, the burden to the health care budget of such a practice would be intolerably high.

In Belgium, the safe introduction of this emergent technology may be called a failure, too. After the convention regulated the technology, vascular surgery departments feared missing the train: EVAR was touted as the final solution of AAA, soon replacing open surgery. The technology diffused rapidly over Belgium, with in 2004 69 hospitals executing EVAR. 25% of the interventions were on aneurysms of 5 cm and smaller, another 25% were on aneurysms between 5.0 and 5.5 cm. While many patients received interventions without evidence of benefit, they did not receive interventions with evidence of benefit. In these elderly patients with declared vascular disease we may expect that at least 80% should benefit from statins. In the EVAR trial 36% were taking statins, in the Belgian EUROSTAR population this was 18% (Johan Vanoverloop, Nationaal Verbond van Socialistische Mutualiteiten). Taking into account the high cardiovascular disease mortality in these vascular frail patients, this was a missed opportunity to extend life of patients with an intervention that is known to be highly effective. However, being an AAA patient was then insufficient indication for statin treatment: bureaucratic rules, not based on current best evidence, might have hindered optimal use. We note that cardiovascular disease management in general practice is one of the future subjects of the KCE.

We conclude that commercial interests and a highly attractive new technology and drove a technology, originally developed for limited indications in patients unfit for surgery to wide use. As an innovative experiment intended to extend life of patients unfit for surgery, the introduction of EVAR was a failure.

10.2. A FAILED EXPERIMENT IS NOT A FAILED TECHNOLOGY

It is often noted that from an experimental drug in the laboratory to approval for clinical use in patients it takes 12 year. Add the development time from testable idea till an experimental drug, and the period is 16 to 20 year. EVAR has been first used in 1990, and the hypothesis may be forwarded that most problems have been generated by the hasty introduction of an immature technology. Tens of thousands patients became the experimental material. However, while the introduction of this innovative technology should be called a failure, the technology is not. EVAR has clear and tangible benefits. These benefits are now small compared to the costs. But they are important for the individual patient put before the choice between heavy open surgery with high short term mortality and complication rates and a less invasive endovascular intervention. The great success of EVAR was partly caused by the good intentions of well meaning surgeons that wished to save their patients the dreadful experience of open repair. Policy choices ignoring patient and surgeon preferences might be not durable.

We conclude that EVAR is an effective intervention, which decreases the short term risks of mortality and severe complications. However, the mortality decrease is not sustained over a longer period, and the severe complications of open surgery are replaced by high re-intervention rates. In the DREAM and EVAR trials, some 0 to 3 weeks of life were saved by the endovascular intervention.

Add the high costs of the endograft, and we conclude that endovascular interventions for AAA are not cost-effective. In terms of opportunity costs: by paying for endovascular interventions, we miss the opportunity to pay for better interventions that save more life at fewer costs.

10.3. THE FUTURE OF EVAR

EVAR is a promising new technology. It is not cost-effective, but it may be. To be a better deal, three problems have to be solved. These problems all have attainable solutions.

The first problem is the price of the endograft. At the current price, there is a wide gap between costs and effects, and the intervention is never cost-effective. If the society wishes to pay for expensive endografts, it seems reasonable to negotiate with the industry to get a better price. If prices are maintained, the choice for open surgery is a wiser use of resources.

The second problem is the lack of sustainability of the decreased mortality. The frail patients that die after open surgery, will die soon after EVAR too, obliterating the difference with open surgery. If risk models can identify these patients, the decreased mortality can be maintained over longer periods, increasing the health effects.

The third problem is the high re-intervention rate after EVAR. Some of the re-interventions are not necessary, some of the re-interventions can be prevented by further improvement of the design of EVAR. Lower re-intervention rates will decrease health care costs.

We conclude that EVAR is not cost-effective compared to open repair, but that this is pending on the future evolution of these four variables: the cost of the endograft, the identifiability of patients with poor outcomes after EVAR, improved endograft design to lower re-intervention needs and identification of unnecessary treatment in follow-up. It is expected that progress will be made in all of these. Therefore, we conclude that a careful, prudent and restrained use

of EVAR can be motivated to sustain technological innovation. Maintenance of registries is mandatory, and the quality of participation in such registries is an important indicator of scientific quality.

10.4. IMPROVING CLINICAL PRACTICE

The actual guidelines suggest treating electively aneurysms over 5.5 cm or aneurysms over 5.0 cm with risk factors (female sex, familial history, documented fast growth of > 0.5 cm/6 months). Treating smaller aneurysms is not in the best interest of the patient, and wastes money to the health care sector. For women, familial cases and aneurysms with documented fast growth (increase of > 0.5 cm in 6 months), the threshold is 5.0 cm. Other indications have to be discussed with the monitoring committee, and mustn't be reimbursed without approval of the committee. The radiology results should be available for auditing, if necessary. Emergency treatment is no part of this advice.

It is an essential competence of the team of radiologist and vascular surgeon to be capable to decide about the technical feasibility of EVAR and to order a stentgraft of the exact dimensions. Advice of the manufacturing industry is welcome, as their personnel have a large experience, but this advice should never replace the local decision process of radiologist and surgeon.

Medical cardiovascular risk management was poor. If only 17.7% were treated with statins, major opportunities for delaying cardiovascular death have been missed. AAA patients are elderly patients with important co-morbidity, and are likely best served by a multi-disciplinary approach. Geriatrician and general practitioner should be made part of the decision process. Obviously, the decision to intervene remains the final responsibility of the interventionist, be it interventional radiologist of vascular surgeon.

To help in the decision process, the knowledge of the referring doctor about the indications of treatment should be improved. He should particularly be more aware of the fact that the decision to intervene is a complex one that surpasses his competence. Actually, the best predictor of prognosis in EVAR is "the subjective assessment of the surgeon" (personal communication, Jaap Buth). It is good to remember that evidence based medicine remains an art, not a science. Statements about aorta aneurysms as "ticking time bombs" are poor clinical practice. A male smoker of over 70 with an aorta aneurysm is a walking arsenal of time bombs in heart and brain. Such statements endanger the risk communication of the surgeon with the patient, and might force him to inappropriate treatment, as the fear of the patient is a health problem in its' own.

Key messages

- EVAR was introduced too soon in its' development as an immature technology. This was leading to uninformed experimentation in tens of thousands of patients in uncertain indications, which proved to be inappropriate in the RCT.
- Good randomised controlled trials with sufficient follow-up were published in 2005, showing small but tangible benefits at prohibitive costs in patients fit for surgery. Patients unfit for surgery are also unfit for EVAR.
- If it needs further demonstration: experimental trials without proper control groups yield no interpretable results.
- EVAR is a promising technology. To be a cost-effective choice, the costs of the design have to lower, indication setting for EVAR has to improve and the long term re-intervention rates have to decrease. In the meantime, EVAR should not be made available in standard health care, as it wastes scarce resources to the health care budget.
- EVAR should only be used in patients fit for surgery and in an aneurysm that is sufficiently large (> 5.5 cm, or > 5.0 cm with associated and documented risk factors).
- The choice between EVAR and open repair is best made by a multidisciplinary vascular team. The final decision of the intervention is the unique responsibility of the interventionist (vascular surgeon or interventional radiologist). Appropriate follow-up of a frail patient with multiple co-morbidities is as important as the intervention.
- Referring doctors need updated information about AAA. The decision to intervene is a complex one, balancing expected harms and benefits in vascular frail patients. An AAA in a vascular frail patient is but one time bomb among many.

11. POLICY RECOMMENDATIONS

11.1. AVOIDING INAPPROPRIATE USE OF DANGEROUS AND EXPENSIVE EMERGEING TECHNOLOGY

The introduction of EVAR in Belgium (and the rest of the World, for that) was a failure. Emerging technology of high complexity and unproven effectiveness should not be introduced in routine health care.

The "convention" included a limiting series of administrative medical rules defining good clinical practice. The convention showed that it is impossible to define such an all inclusive set of rules. Guidelines guide, but rules direct: the wish to make the rules all inclusive makes the inclusion criteria far too large. As the rules can not be enforced, they are inefficient, adding only extra costs and a high bureaucratic load. We advise against the further use of such elaborate systems of rules.

The evidence based indication for any AAA repair is an AAA $\geq$ 5.5 cm. AAA < 5.0 cm must never be treated by EVAR or open repair. AAA between 5.0 and 5.5 cm may be treated in certain conditions. Exceptions to this simple rule are rare and should be treated in few selected highly specialised centres. AAA repair in aneurysms < 5.5 cm (males > 60 year) or < 5.0 cm (females, males < 60 year) needs auditing of the specified motivation, to protect patient safety. This considers nearly 50% of the patients entered in EUROSTAR.

11.2. REGULATING EVAR

EVAR is not cost-effective. The main reason is the high costs of the endostent. We advise against introduction of EVAR in routine health care.

The present financing system gave a strong financial incentive to use of EVAR instead of the best standard health care (open repair or watchful waiting). We advise against further reimbursement of endografts separate from the intervention. We advise to reimburse "AAA repair" at comparable prices, at whatever technology is used. This puts the incentive back at the more cost-effective standard health care.

Emerging technology must never be financed by routine health care budgets or by the individual patients. Rolling off the responsibility of safe introduction of emerging technology to the individual medical doctor, or even his patient, is an irresponsible health policy practice that inevitably leads to repeating the same mistakes over and over again. We advise to earmark sufficient budgets for experimenting with emerging technology in a controlled scientific environment. We note that the responsible introduction of emerging technology is a subject of a future KCE-report that will address these issues in more scientific detail.

Transferring costs of emerging technology to the patient can not be considered an ethical practice, as the costs of intervention are certain but the benefits not (as it is an emerging technology). Therefore, experiments with emerging technology at the expense of the patient can not be considered in his best interests. We advise policy measures to reduce this unethical practice: experiments should be financed by the society, not by the individual.

Emerging technology has to be separated from effective, but not cost-effective technology. The society should not reimburse technology that is not cost-effective, but the autonomous patient has the right to decide over his own budget. A tension exists between the autonomy of the patient and social justice.

We recommend studying specific regulatory policies and their ethical consequences for effective, but not cost-effective health technology.

To make EVAR cost-effective, the following is needed:

- Lower costs of the endostent.
- Longer term follow-up to assess durability of the endostent
- Improved adverse risk selection: exclusion of patients at high risk of death by co-morbid conditions
- Avoidance of inappropriate re-interventions in follow-up

We advise to revise this report within five years (2010).

11.3. PROVISION OF VASCULAR SURGERY OF HIGH QUALITY

EVAR must not be introduced outside a vascular surgery environment of high technical skills and materials and sufficient volumes to maintain experience and good quality.

The need for sufficient volume to maintain quality, experience and efficient use of expensive technology can not be argued. In the interest of patient safety, we advise centralisation of vascular surgery in selected and planned tertiary care centres.

Capacity planning was outside the scope of this project. However, extrapolating from the UK, Belgium would need minimally 20 vascular care centres with 75 full time vascular surgeons. There is insufficient workload for more than 30 vascular centres and 120 full time vascular surgeons. Increasing the supply increases the demand, which in the case of vascular surgery may induce harmful treatment.

To be able to assess the quality of services, and to guarantee patient safety, indications and outcomes of major vascular surgery should be monitored in routine and audited if necessary. We strongly recommend registries of major elective vascular surgery (carotid artery endarterectomy, carotid artery stenting, open AAA repair, EVAR). These registers should collect the necessary data according to international standards, and should be analysed in routine by specialised statistical services.

The Eurostar registry showed good to excellent compliance of most of the Belgian centres. However, a few centres used EVAR, but "lost" all or nearly all patients to follow-up. We recommend verification and legal action for contract violation for all centres which lost more than 75% of EVAR-patients (except for the very small with < 5 patients). No system can function without respecting the agreed rules.

11.4. IMPROVING INFORMATION AND EDUCATION OF PRIMARY CARE PROVIDERS AND PATIENTS

Experts signalled lack of knowledge of AAA among general practitioners. Talking about ticking time bombs to elderly male smokers with multiple vascular morbidity is ridiculous, but puts the careful vascular surgeon in a difficult position. We recommend the provision of correct and transparent information, and we recommend further study to improve the access to that information.

Informed consent of the patient is an ethical requirement, but the choice between EVAR and open surgery involves complex trade-offs between different risks, different time horizons and likely different bills to pay. We recommend

further study to define what information the patient needs, about which issues, and how this information is given to patients. We add the reminder that most vascular patients are old, and often with beginning cognitive impairment.

Key messages

Careful experimenting with EVAR

- In AAA of smaller than 5.5 cm, treatment by either EVAR or open surgery should be the motivated exception, watchful waiting the rule. In AAA of larger than 5.5 cm, treatment by either open surgery or EVAR should be the rule , watchful waiting the motivated exception.
- EVAR is not cost-effective. Financial incentives must be given to open surgery, and not to EVAR. The added costs of EVAR should be carried by research budgets supported by proper research protocols, not by the health care budget. These clinical research budgets should be joint investments in emerging technology by both industry (R&D) and society (medical research).

Provision of vascular surgery of high quality

- Registers should collect routinely high quality data of indications and outcomes of major elective vascular interventions, albeit open or endovascular.
- To guarantee sufficient volume of both open repair and EVAR, and to guarantee cost-effective use of expensive technology, EVAR should only be made available to those vascular centres with a tertiary care function. We advice that EVAR is made available in a limited number of centres based on population density and geographical distribution, rather than on the number of EVAR performed.
- Major vascular surgery cannot be performed safely, cost-effectively and with good quality in too many centres with too low volumes. We advise concentration of major vascular surgery in a limited number of high tech tertiary care centres.

Improving information

- Other doctors than vascular surgeons and interventional radiologists should be updated about the basics of AAA, particularly the appropriate indications for intervention.
- While informed consent and patient autonomy is a desirable goal, in treatment of AAA it asks for complex trade offs between competing risks, to be made by elderly with chronic vascular disease. We advise more study about which information should be given, and how.

12. APPENDICES

APPENDIX 1: SEARCH ALGORITHM CLINICAL EFFECTIVENESS

1 (aortic aneurysm, abdominal and (blood vessel prosthesis implantation or stents)).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (1918)

2 (aaa or aortic or aorta).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (157259)

3 aneurysm.mp. [mp=title, original title, abstract, name of substance word, subject heading word] (63494)

4 (endoluminal or intravascular or endovascular or transfemoral).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (38570)

5 (endograft or stent or prosthesis or graft).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (238751)

6 exp ABDOMEN/ (54924)

7 abdominal.mp. [mp=title, original title, abstract, name of substance word, subject heading word] (140933)

8 (repair or reparation).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (110580)

9 2 and 3 (26948)

10 1 or (4 and 5 and 6) (1948)

11 6 or 7 (177953)

12 3 and 11 and 8 (3349)

13 10 or 12 (4138)

14 limit 13 to clinical trial (238)

15 limit 13 to meta analysis (6)

16 limit 13 to randomized controlled trial (84)

17 14 or 15 or 16 (243)

18 (clinical trials or comparative study or double-blind method or random allocation).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (1419121)

19 (random or controlled trial or controlled clinical trial or double blind or meta analysis or meta analyses or metaanalysis or research integration or research overview or quantitative overview or methodologic reviews or methodologic review or methodologic overview or methodologic overviews or systematic overviews or systematic reviews or systematic review or integrative research or quantitative synthesis or comparative study or comparative studies or rct or rcts).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (1408529)

20 (10 or 12) and 19 (681)

21 17 or 20 (813)

22 limit 21 to yr="2000 - 2005" (529)

APPENDIX 2: ECONOMIC DATA EXTRACTION

1. Economic evaluations alongside clinical trials

Author	Prinssen et al. 2005		
Country	NL		
Design	Cost-effectiveness analysis, alongside an RCT		
Perspective	Societal		
Time window	One year		
Interventions	EVAR versus Open AAA repair		
Population	Patients included in the DREAM trial		
Assumptions			
Data source for costs	Observation (case report forms, patient diaries, …), Dutch costing manual and existing data (e.g. for cost of hospital stay on an intensive care unit) Price year 2003		
Cost items included	Pre-operative work-up, operative costs, hospital stay, outpatient visits, GP visits, home care, medication, major investigations (angiography, CT angio, Duplex scanning), productivity losses, time, travel and other private costs incurred by patients and their family		
Data source for outcomes	Observation (clinical outcomes and EQ-5D)		
Discounting	No		
Costs	Total direct costs EVAR: € 18 542 Total direct costs Open AAA repair: € 13 592 Incremental cost EVAR: € 4 300 (95% C.I.: 2 770-5 830)		
Outcomes		EVAR	Open AAA repair
	QALYs	0.72	0.73
	Complication-free survival		
	Incremental QALYs EVAR: 0.10 QALYs Incremental QALYs EVAR: 1.64 QALYs		
Cost-effectiveness	Assumed threshold: €25 000/QALY Cost per complication-free life year gained: 76 100 € Cost per LYG: 171 500 € Cost per QALY: open AAA repair dominant to EVAR (less costly and more effective, albeit marginally and not significant more effective)		
Sensitivity analysis	Bootstrapping (used to estimate the confidence interval around the ICER): 95% of the bootstrap replicates show better effectiveness in terms of event-free survival at higher costs 85% of the bootstrap replicates show better effectiveness in terms of LYG at higher costs 65% of the bootstrap replicates show **worse** effectiveness in terms of QALYs gained (at one year) at a higher cost. At a threshold value for cost-effectiveness of 25 000 €/QALY, open surgery is more cost-effective than EVAR for all bootstrap replicates.		
Conclusions	EVAR is not cost-effective relative to open surgery and should not be applied routinely. The limited (early) survival benefit does not justify the incremental cost.		
Remarks			

2. Economic models

Author	Forbes et al. 2002
Country	Canada
Design	Cost-effectiveness analysis
	Observational design
Perspective	Hospital
Time window	Initial hospitalisation and follow-up (2-14 months)
Interventions	EVAR versus Open AAA repair
Population	7 patients electively treated with EVAR; 31 patients electively treated with open AAA repair
Time period	1998
Assumptions	Costs
	Ward bed/day: CA$375.6
	ICU bed/day: CA$966.96
	Open graft: CA$374
	Endovascular bifurcated graft: CA$7,000
	Endovascular vanguard extension: CA$2,500
	Embolisation: CA$ 900
	CT: CA$450
	Additional radiology equipment for EVAR: CA$1,475
Data source for costs	Hospital cost centre
Cost items included	Hospitalisation: hospital stay, preoperative and postoperative embolisation, grafts, endovascular equipment
	Follow-up with computed tomography
	Incremental costing approach (costs common to both interventions not included)
Data source for outcomes	Observation
Discounting	No
Costs	EVAR: CA$14,967
	Open: CA$4,823
	Significantly different
Outcomes	Expressed as "reduction in hospital length of stay"
	Open: 10.7 days
	EVAR: 5.6 days
	Significantly different
Cost-effectiveness	Additional cost per day reduction in hospital length of stay:
	CA$1 604
Conclusions	EVAR is more expensive than open AAA repair
	The cost of the endovascular graft accounted for 57.3% of the total cost of EVAR and 80.8% of the difference in costs between the 2 procedures.
	In addition, the cost of follow-up is higher in EVAR than in open AAA repair.
Remarks	Uncommon expression for the incremental cost-effectiveness of the intervention.

	Follow-up varied between 2 and 14 months. Only patients who survived postoperatively were included in the analysis.		
	No microcosting		
	No sensitivity analysis		
Author	Patel et al. 1999		
Country	US		
Design	Cost-effectiveness analysis, using Markov modelling		
Perspective	Health care system		
Time window	Lifetime costs and outcomes		
Interventions	EVAR versus Open AAA repair		
Population	Hypothetical cohort of 70-year old male patients with 5 cm AAA		
Assumptions		**Open AAA repair**	**EVAR**
	Mortality	4.8%	1.2%
	Morbidity		
	Stroke % (utility)	0.5% (0.4)	0%
	Dialysis-dependent renal failure % (utility)	0.6% (0.68)	0%
	Major amputation % (utility)	0.3% (0.8)	0%
	AMI % (utility)	2.9% (0.87)	1% (0.87)
	Conversion rates to Open		
	Immediate conversion		2% (16.3% mortality)
	Late conversion to Open		4% (7.4% mortality)
	Reinterventions		
	Reoperation for haemorrhage	1.4% (US$1,740)	
	Graft thrombosis	0.9% (US$5,710)	4.4% (US$6,205)
	Endoleak		11.2% (85% stent placements (US$3,210), 15% coil embolisations (US$4,005)
	Cost initial hospitalisation	US$16,016	US$20,083
	Cost graft	US$650	US$8,000
	LOS	10 days	3 days
Data source for costs	Literature and one hospital's cost accounting system Price year 1997		
Cost items included	Initial hospitalisation costs, costs of complications, subsequent interventions and follow-up		
Data source for outcomes	Literature, large multicentre studies (Open AAA) and clinical trials (EVAR) Life expectancy: life tables for US population; taking into account excess mortality of 7.7% in patients surviving stroke, excess mortality of 1.5% in patients who survive AMI and excess mortality in patients on dialysis (according to US Renal Data System).		
Discounting	3%, both outcomes and costs		
Costs		**Open AAA repair**	**EVAR**
	Procedural cost	US$16,016	US$20,083
	Total cost	US$19,314	US$28,901

	Incremental cost EVAR: US$9,587		
Outcomes	**QALYs**	7.53 QALYs	7.95 QALYs
	Incremental QALYs EVAR: 0.42 QALYs		
Cost-effectiveness	**Incremental cost-effectiveness ratio (ICER):** ICER=US$22,826/QALY		
Sensitivity analysis	**Increase of cost of endograft to US$12,000 =>** ICER= US$32,881/QALY **ICER >US$60,000 (threshold) if** ○ combined mortality and long-term morbidity rate of open AAA repair <4.7% (base-case 9.1%) ○ combined mortality and long-term morbidity rate of EVAR is >5.7% (base-case 2.2%) ○ mortality rate of EVAR is >4.4% (base-case 1.2%) ○ initial hospital cost of EVAR >US$35,000 ○ initial hospital cost of Open AAA repair <US$1,300 ○ conversion rate to open repair >30% (base case 4%)		
Conclusions	• If late complications (e.g. endoleak, aneurysm expansion and rupture) do not occur, EVAR is a cost-effective alternative to open AAA repair. • Crucial variables for result are mortality rate associated with open and endovascular AAA repair and the combined mortality-morbidity rate. Mere attainment of the mortality rate of open repair may not be sufficient for EVAR to justify widespread use of aortic endografts. (too much variation still) • Morbidity rates, hospital costs, rates of reinterventions, costs of reinterventions, costs of morbidity, quality adjustment factors, excess mortality rates, procedural disutilities, discount rate and cohort age have relatively little effect on the cost-effectiveness ratio.		
Remarks	Initial hospital costs of EVAR are about 25% higher than those of Open AAA repair. The most influential variables are the cost of the endograft, the length of hospital stay and the length of stay in the intensive care unit. But, in this analysis, the additional costs of the endograft were not offset by the savings from shorter length of stay in intensive care or total length of stay.		

Author	Bosch et al. 2002		
Country	US		
Design	Cost-effectiveness analysis, using Markov modelling		
Perspective	Societal		
Time window	Lifetime costs and outcomes		
Interventions	EVAR versus Open AAA repair		
Population	Cohort of 70-year old men with AAA between 5 and 6 cm		
Time period	2000		
Assumptions	There are no more than two percutaneous procedures in follow-up After surgery, only a secondary surgical procedure would be performed if additional therapy was needed. Markov cycles are one month		
		Open AAA repair	**EVAR**
	Mortality		
	Procedure	4.0%	3%
	Emergent repair ruptured aneurysm		64% (US$25,803)
	After rupture, before patient reached operating room		15%
	Percutaneous treatment		0.01% (US$11 941)
	Excess mortality risk ratio	1.81	1.81
	Morbidity (cardiac, cerebral, renal and pulmonary)	32%	13%
	Morbidity after emergent surgical repair		53%
	Immediate conversion to Open		3% (16.3% mortality after immediate conversion)
	Complications		
	Annual rupture rate after endovascular repair		1%
	Annual long-term failure rate, excluding ruptures, requiring treatment	1%	8%
	Costs procedure	US$23,484	US$19,642
	Cost graft	Not given	US$10,000
	Costs follow-up imaging (per visit)	/	US$483
	Quality of life adjustments	-30% for two months	-10% for one month
	LOS	9 days	4 days
	Annual costs and utilities (U) of long term morbidity: • Cardiac (1st year/thereafter): US$18,380/US$3,039; U: 0.9 • Cerebral (1st year/thereafter): US$28,551/10,634; U: 0.63 • Renal, dialysis dependent (1st year/thereafter): US$14,341/8,445; U: 0.68 • Pulmonary: US$ 5,242; U: 0.91		
Data source for	Medicare reimbursement rates, hospital database, literature		

costs	Price year 2000
Cost items included **Data source for outcomes**	Procedure costs (hospitalisation, physician, patient), costs of morbidity and mortality, follow-up costs Short term results: meta-analysis of 9 published studies
Discounting	3%
Costs	EVAR: US$ 39,785 Open: US$37,606
Outcomes	EVAR: 6.74 QALYs Open: 6.52 QALYs
Cost-effectiveness	**ICER**: US$9,905/QALY Cost-effectiveness threshold: US$75 000/QALY
Sensitivity analysis	Results sensitive to systemic-remote complication rate, long-term failures and ruptures after endovascular and open repair Results insensitive to immediate conversion rate and procedure mortality rate. **ICER >US$75 000/QALY (threshold) if** ○ Systemic-remote complication rate EVAR >19% ○ Systemic-remote complication rate Open <27% ○ Endovascular annual long-term failure rate, excluding ruptures >13% ○ Endovascular annual rupture rate >1.5% ○ Cost ratio of endovascular repair versus open surgery >1.4 ○ Excess mortality risk ratio in patients with systemic-remote complications <1.4 ○ Open surgery annual long-term failure rate <0.5% **One-way sensitivity analysis long-term failure and rupture rates:** If the annual rate for procedures in follow-up exceeded 12%, the ICER was > US$100 000/QALY. If the annual rupture rate was increased from 1% to 1.6%, with the annual rate for procedures in follow-up kept constant at 8%, EVAR is dominated by Open AAA repair.
Conclusions	• EVAR is a cost-effective alternative to open AAA repair. • Results are highly dependent on uncertain outcomes, particularly long-term failure and rupture rates. • These sensitivities are notable, as studies have published results of EVAR and Open repair that exceed the boundaries for cost-effectiveness of EVAR relative to Open aneurysm repair
Remarks	Only limited long-term follow-up data are available. Therefore, a lot of uncertainty remains about the value of the model input parameters. No data from RCTs were available.

Author	Michaels et al. 2005		
Country	UK		
Design	Cost-effectiveness analysis, using Markov modelling		
Perspective	NHS		
Time window	Base-case: 10 years; alternative scenarios with longer and shorter time window tested		
Interventions	RC1: EVAR versus Open AAA repair RC2: EVAR versus conservative management		
Population	RC1. Hypothetical cohort of 70-year old patients with 5.5 cm AAA, fit for surgery RC2: Hypothetical cohort of 80-year old patient with 6.5 cm AAA, unfit for surgery		
Assumptions		**Open AAA repair**	**EVAR**
	Mortality	5.8%	1.85%
	Probabilities		
	Endoleak at 30 days		17.6%
	New endoleak (per month)		4.9%
	Reintervention in pat with endoleak		0.84%
	Reintervention in pat without endoleak		3.1%
	Failed reintervention, continued endoleak		19.7%
	Spontaneous closure of endoleak		6%
	• **Conversion rates to Open**		
	Immediate conversion		1.9% (16.3% mortality)
	Late conversion to Open		12.3% (7.4% mortality)
	Cost graft repair	£4,269	£8 769
	Follow-up costs (per month)		£41.5
	Cost of reintervention	£4,790	£4,790
	Utility loss after intervention	For 4 weeks	For 2 weeks
Data source for costs	NHS reference costs for 2003-2004 + primary data collection fro incremental cost of endovascular repair Price year 2004		
Cost items included			
Data source for outcomes	Literature, clinical trials (EVAR 1 and DREAM), Eurostar registry, models Life expectancy: life tables		
Discounting	3.5%, both outcomes and costs		
Costs	**RC1: Incremental cost EVAR:** £11,449 **RC2: Incremental cost EVAR:** £14,077		
Outcomes	**RC1: Incremental QALYs EVAR:** 0.10 QALYs **RC2: Incremental QALYs EVAR**: 1.64 QALYs		
Cost-effectiveness	**RC1: ICER:** 110,000 £/QALY **RC2: ICER**: 8,579 £/QALY		
Sensitivity analysis	Probabilistic sensitivity analysis (Monte Carlo simulation):		

	RC1 All simulations showed a cost/QALY > £30,000 There was 5.3% chance that EVAR was dominated by open surgical repair If the cost of EVAR would equal the cost of open AAA repair, there is a 13.2% chance that the ICER is below £30 000/QALY. If the rate of re-interventions is halved, there is a 0.3% chance that the ICER is below this threshold. RC2: All simulations showed a cost/QALY < £30,000 Over a range of different assumptions the ICER of EVAR consistently exceeded £30,000/QALY compared with observation.
Conclusions	• EVAR is not cost-effective relative to open surgery in patients who are fit for surgery. • EVAR is highly cost-effective in patients unsuitable for open AAA surgery.
Remarks	

3. Cost-outcome descriptions

Author	EVAR trial participants		
Country	Multiple countries		
Design	Cost-outcome description Observational design		
Perspective	Hospital		
Time window	4 years of follow-up after intervention		
Interventions	EVAR versus open AAA repair		
Population	Patients included in the RCT "EVAR 1" (aneurysms >5.5cm)		
Assumptions			
Data source for costs	Trial case record forms + questionnaires sent to 41 centres (21 completed forms received)		
Cost items included	Centre-specific resource use: staffing, equipment, consumables, routine outpatient follow-up outside trial. Local unit costs used where possible, otherwise national unit costs from routine UK NHS sources		
Data source for outcomes	EQ-5D and SF-36 questionnaires		
Discounting	3.5%		
Costs		**EVAR (n=543)**	**Open AAA repair (n=518)**
	Primary hospital admission	UK£ 10,819	UK£ 9,204
	Procedure	UK£ 7,569	UK£ 2,811
	Hospital stay	UK£ 3,015	UK£ 6,304
	Other	UK£ 235	UK£ 89
	Secondary procedures, adverse events, scans	UK£ 2,439	UK£ 741
	Secondary AAA procedures	UK£ 1,056	UK£ 200
	Other adverse events	UK£ 294	UK£ 359
	Outpatients/CT/US scan	UK£ 1,089	UK£ 182
	Total cost up till 4 year FU	UK£ 13,258	UK£ 9,945
Outcomes		**EVAR**	**Open AAA repair**
	EQ-5D		
	Baseline	0.75	0.74
	0-3 months	0.73	0.67
	3-12 months	0.71	0.73
	12-24 months	0.74	0.75
	Other outcome measures: clinical outcomes and SF-36 physical component and mental component summary not presented here but fully presented in the article.		
Cost-effectiveness	In the long term (up till 4 years) EVAR is more expensive and leads to worse outcomes in terms of health-related quality of life than open AAA repair.		
Sensitivity analysis	NA		
Conclusions	• Late complications are much greater after EVAR than open repair. This has important implications for the surveillance and costs of the procedure. • Requirements for surveillance are higher for EVAR than for open AAA repair		

	• Early after the intervention, health-related quality of life is lower for the open AAA repair group but between 3 and 24 months after the procedure, health related quality of life was similar for both groups.
	• Midterm results show a 3% aneurysm related survival advantage for EVAR, with increased need for reinterventions and surveillance. There is no overall mortality advantage.
Remarks	Long-term cost-effectiveness analysis is being performed based on these data.

Author	Ceelen et al. 1999		
Country	Belgium		
Design	Cost-outcome comparison, observational design		
Perspective	1. hospital; 2. patient; 3. health insurance (RIZIV/INAMI)		
Time window	Initial hospitalisation		
Interventions	EVAR versus Open AAA repair		
Population	20 patients treated electively with Open Surgery; 9 patients treated with EVAR		
Time period	Not specified		
Data source for costs	Hospital bills		
Cost items included	all hospitalisation-related items **Cost implants (perspective RIZIV/INAMI)** Open implant: BEF 38,296 (€957) Endoprothesis: BEF 153,293 (€3 832)		
Data source for outcomes	Observation		
Discounting	no		
Costs	Operating time, ICU stay and hospital length of stay significantly longer in open treatment than in EVAR		
		Open AAA repair	**EVAR**
	Hospital perspective	BEF 382,995 (€9 494)	BEF 361,938 (€8 972)
	Health insurance perspective	BEF 357,565 (€8 939)	BEF 317,733 (€7 943)
	Patient perspective	BEF 24,969 (€624)	BEF 66,309 (€1 657)
Outcomes	EVAR: 1 endoleak that sealed spontaneously Open AAA repair: pulmonary dysfunction (4), prolonged ileus (1), limb oedema (1) No mortality.		
Conclusions	EVAR is associated with shorter ICU and hospital length of stay than open AAA repair. Costs are not significantly different between the two procedures from the perspective of the hospital or RIZIV. However, from the patients' perspective the endovascular treatment is much more costly (due to high implant cost).		
Remarks	This is a cost-outcome description rather than cost-benefit analysis. No cost-benefit ratio has been calculated. No sensitivity analysis was performed. The price year and year of patient inclusion was not mentioned, which makes assessment of relevance, given the state-of-the art technology, difficult.		

APPENDIX 3: CLASSIFICATION OF ECONOMIC STUDIES

		Are both costs (inputs) and consequences (outputs) of the alternatives examined?		
		No		**Yes**
		Examines only consequences	Examines only costs	
Is there a comparison of two or more alternatives?	**No**	**Partial evaluation**		**Partial evaluation**
		Outcome description	Cost description	Cost-outcome description
	Yes	**Partial evaluation**		**Full economic evaluation**
		Efficacy or effectiveness evaluation	Cost analysis	Cost-minimisation analysis (CMA) Cost-effectiveness analysis (CEA) Cost-utility analysis (CUA) Cost-benefit analysis (CBA)

Source: Drummond MF, O'Brien B, Stoddart GL, Torrance GW. Methods for the Economic Evaluation of Health Care Programmes. 2nd edition. Oxford University Press. Oxford. 1997: p.10.

APPENDIX 4: QUALITY ASSESSMENT TOOL FOR ECONOMIC EVALUATIONS

Study design

The research question is stated

The economic importance of the research question is stated

The viewpoints of the analysis are clearly stated and justified

The rationale for choosing the alternative programmes or interventions compared is stated

The alternatives being compared are clearly described

The form of economic evaluation used is stated

The choice of form of economic evaluation is justified in relation to the questions addressed

Data collection

The sources of effectiveness estimates used are stated

Details of the design and results of effectiveness study are given (if based on a single study)

Details of the method of synthesis or meta-analysis of estimated are given (if based on an overview of a number of effectiveness studies)

The primary outcome measure(s) for the economic evaluation are clearly stated

Methods to value health states and other benefits are stated

Details of the subjects from whom valuations were obtained are given

Productivity changes (if included) are reported separately

The relevance of productivity changes to the study question is discussed

Quantities of resources are reported separately from their unit costs

Methods for the estimation of quantities and unit costs are described

Currency and price data are recorded

Details of currency of price adjustments for inflation or currency conversion are given

Details of any model used are given

The choice of model used and the key parameters on which it is based are justified

Analysis and interpretation of results

Time horizon of costs and benefits is stated

The discount rate(s) is stated

The choice of rate(s) is justified

An explanation is given if costs or benefits are not discounted

Details of statistical tests and confidence intervals are given for stochastic data

The approach to sensitivity analysis is given

The choice of variables for sensitivity analysis is justified

The ranges over which the variables are varied are stated

Relevant alternatives are compared

Incremental analysis is reported

Major outcomes are presented in a disaggregated as well as aggregated form

The answer to the study question is given

Conclusions follow from the data reported

Conclusions are accompanied by the appropriate caveats

Source: Drummond MF et al. [76]

APPENDIX 5: DATA EXTRACTION TABLE: CLINICAL RESULTS OF EVAR VERSUS OPEN REPAIR IN PATIENTS AT AVERAGE RISK

Table Comparative trials: baseline comparisons between EVAR and OPEN

	EVAR							
	N (1)	Age (2)	Diameter (3)	% male (4)	% heart disease (5)	% prior MI (6)	COPD (7)	former smoking (8)
Randomised controlled trials								
DREAM	171	69.5	60.6	93%	41%	13%	27%	65%
EVAR-1	543	74.0	65.0	91%	44%			89%
Subtotal	714	72.9	63.9	91%	43%	13%	27%	83%
Multicentre comparative trials								
Ancure	573	72.8		96%	57%	35%	26%	82%
AneuRx	190	73.0	56.0	90%	84%		23%	85%
Excluder	235	73.0	55.6	87%				
Powerlink	192	73.0	51.0	89%	46%	24%	32%	83%
Talent	240		56.7	90%	38%	38%	21%	74%
Vanguard	268		54.0			33%	31%	86%
Zenith	200	71.0	56.2	94%		37%	20%	87%
Subtotal	1898	72.6	55.0	92%	56%	34%	26%	82%
Single centre comparisons								
Perugia	534	73.0		94%	46%		56%	
Twente	93		60.2					
Subtotal	627	73.0	60.2	94%	46%		56%	
grand total	3239	72.8	58.2	92%	50%	32%	32%	83%
	Open							
	N	Age	Diameter	% male	% heart disease	% prior MI	COPD	former smoking
Randomised controlled trials								
DREAM	174	70.7	60.0	90%	47%	16%	18%	54%
EVAR-1	539	74.2	65.1	91%	44%			87%
Subtotal	713	73.3	63.9	91%	45%	16%	18%	79%
Multicentre comparative trials								

Ancure	111	71.6		97%	61%	39%	30%	90%
AneuRx	60	69.0	56.0	85%	87%	25%	27%	93%
Excluder	99	70.1	58.6	74%				
Powerlink	66	69.0	58.0	86%	59%	29%	24%	86%
Talent	126			80%	25%	30%	18%	82%
Vanguard	98		57.0			39%	34%	97%
Zenith	80	69.0	63.8	89%		29%	18%	95%
Subtotal	640	70.0	58.8	85%	53%	32%	25%	90%
Single centre comparisons								
Perugia	585	72.0		90%	37%		38%	
Twente	113		60.6					
Subtotal	698	72.0	60.6	90%	37%		38%	
grand total	2051	72.1	61.9	89%	44%	28%	30%	84%

Difference between EVAR and open

	N	Age	Diameter	% male	% heart disease	% prior MI	COPD	former smoking
Randomised controlled trials								
DREAM		-1.2	0.6	2.8%	-5.6%	-2.1%	9.7%	10.9%
EVAR-1		-0.2	-0.1	0.3%	-0.3%			1.9%
Subtotal		-0.4	0.1	0.9%	-1.6%	-2.1%	9.7%	4.2%
Multicentre comparative trials								
Ancure		1.2		-1.5%	-4.5%	-3.8%	-3.9%	-8.1%
AneuRx		4.0		5.0 %	-3.0%	9.0%	-4.0%	8.0%
Excluder		2.9	-3.0	13.1%				0.0%
Powerlink		4.0	-7.0	2.2%	-13.3%	-4.3%	7.5%	-3.6%
Talent		0.0		10.0%	13.0%	8.0%	3.0%	-8.0%
Vanguard		0.0	-3.0			-5.9%	-3.1%	-11.1%
Zenith		2.0	-7.6	4.8%		8.3%	2.0%	-8.5%
Subtotal		2.7	-3.8	6.8%	3.0%	1.5%	0.6%	-7.6%
Single centre comparisons								
Perugia		1.0		3.9%	9.5%		17.5%	
Twente		0.0	-0.4					
Subtotal		1.0	-0.4	3.9%	9.5%		17.5%	
grand total		0.7	-3.7	3.4%	6.2%	3.7%	2.5%	-1.0%

(1) Numbers of patients entered in trial arm; in trials: with intention to treat.
(2) Mean age of patients in years
(3) Mean maximal diameter of aorta aneurysm in mm
(4) Proportion of male patients
(5) Proportion of patients with heart disease. Definition may vary across trials. If available, coronary heart disease was used.
(6) Proportion of patients with a history of a myocardial infarction.
(7) Proportion of patients with lung disease. Definition may vary across trials. If available, chronic obstructive lung disease was used.
(8) Proportion of current and former smokers. Definition of former smoker may vary across trials.

Table Outcomes of EVAR and Open surgery

EVAR

	Procedural characteristics				Mortality			Re-intv.
	LO intv (1)	LOS ICU (2)	LOS (3)	Blood use (4)	1 month (5)	1 year (6)	2 year (7)	annual prob (8)
Randomised controlled trials								
DREAM	135	0.67	6.0	394	1.2%	5.8%	11.1%	
EVAR-1	182	0.70	10.3	164	1.7%	7.9%	17.0%	6.9%
Subtotal	171	0.69	9.3	219	1.6%	7.4%	15.6%	6.9%
Multi-centre comparative trials								
Ancure	156	0.34	4.3	567	1.7%	6.4%	11.6%	
AneuRx	186	0.90	3.4	641	2.6%	4.2%	16.9%	5.9%
Excluder	144	0.25	2.0	310	0.9%	6.0%		7.0%
Powerlink	136	0.80	3.3	341	1.0%	4.7%	10.4%	6.3%
Talent	172	0.60	4.6	346	0.4%	10.0%		
Vanguard		0.86	3.6	457	1.5%	6.8%	15.1%	8.8%
Zenith	153	0.40	2.6	299	0.5%	3.5%		11.0%
Subtotal	157	0.54	3.6	448	1.3%	6.2%	13.0%	7.9%
Single centre comparisons								
Perugia	120		2.0	200	0.9%	6.9%		9.3%
Twente	148	0.31	9.2	355	1.1%	10.0%	15.9%	8.0%
Subtotal	124	0.31	3.1	223	1.0%	7.4%	15.9%	9.1%
grand total	154	0.57	4.7	354	1.3%	6.7%	14.1%	8.0%

OPEN

	Procedural characteristics				Mortality			Re-intv.
	LO intv	LOS ICU	LOS	Blood use	1 month	1 year	2 year	annual prob
Randomised controlled trials								
DREAM	151	3.00	13.0	1654	4.6%	7.2%	9.8%	
EVAR-1	205	2.40	15.7	896	4.7%	11.0%	17.5%	2.4%
Subtotal	192	2.55	15.0	1081	4.6%	10.1%	15.6%	2.4%
Multicentre comparative trials								
Ancure	174	1.08	7.5	1051	2.7%	5.6%	8.7%	
AneuRx	216	2.50	9.4	1596	0.0%	3.3%		
Excluder	196	2.79	9.8	1590	0.9%	5.1%		

Powerlink	222	4.10	9.5	1538	6.1%	12.2%	17.1%	
Talent	221	2.30	8.7	1542	0.0%	4.8%		
Vanguard		3.25	9.0	1367	3.1%	4.3%	19.7%	
Zenith	239	3.40	8.8	1676	2.5%	3.8%		2.5%
Subtotal	209	2.65	8.9	1459	2.8%	5.6%	14.6%	2.5%
Single centre comparisons								
Perugia	180		6.0	1400	4.1%	6.7%		1.0%
Twente	199	4.80	17.1	2715	7.1%	11.0%	11.0%	
Subtotal	183	4.80	7.8	1613	4.6%	7.4%	11.0%	1.0%
grand total	193	2.77	10.6	1380	4.2%	7.7%	14.9%	1.7%

	Difference EVAR compared to OPEN							
	Procedural characteristics				Mortality			Re-intervention
	LO intv	LOS ICU	LOS	Blood use	1 month	1 year	2 year	annual prob
Randomised controlled trials								
DREAM	-16	-2.33	-7.0	-1260	-3.4%	-1.4%	1.3%	
EVAR-1	-23	-1.70	-5.4	-732	-3.0%	-3.1%	-0.6%	4.5%
subtotal	-21	-1.85	-5.8	-862	-3.1%	-2.7%	-0.1%	
Multicentre comparative trials								
Ancure	-18	-0.74	-3.2	-484	-1.0%	0.8%	2.9%	
AneuRx	-30	-2	-6	-955	2.6%	0.9%		
Excluder	-52	-2.54	-7.8	-1280	0.0%	0.9%		
Powerlink	-86	-3.30	-6.2	-1197	-5.0%	-7.6%	-6.7%	
Talent	-49	-1.70	-4.1	-1196	0.4%	5.3%		
Vanguard		-2.40	-5.4	-910	-1.6%	2.6%	-4.6%	
Zenith	-86	-3.00	-6.2	-1377	-2.0%	-0.3%		8.5%
subtotal	-52	-2.11	-5.3	-1011	-1.5%	0.8%	-1.6%	
Single centre comparisons								
Perugia	-60		-4.0	-1200	-3.2%	0.2%		8.2%
Twente	-51	-4.49	-7.9	-2360	-6.0%	-1.0%	4.9%	
subtotal	-59	-4.49	-4.7	-1390	-3.6%	0.0%	4.9%	
grand total	-40	-2.19	-5.9	-1026	-2.9%	-1.0%	-0.9%	6.2%

(1) Length of the intervention in minutes
(2) Length of stay in intensive care unit in days
(3) Length of stay in hospital in days
(4) Blood use in ml
(5) 30 day mortality
(6) One year mortality; if available 1.0 minus survival calculated by Kaplan Maier method
(7) One year mortality; if available 1.0 minus survival calculated by Kaplan Maier method
(8) Annual re-intervention probability

APPENDIX 6: ANALYSIS OF EUROSTAR BELGIAN CENTRES DATA

1. INTRODUCTION

In Belgium, all patients with endovascular graft treatment of abdominal aortic aneurysms have to be included in the international EUROSTAR registry. The operative data and results from follow up examinations, as well as several outcomes (death, rupture, conversion to open repair) are sent by the physicians to the RIZIV/INAMI, which then transfers the case reports forms to the EUROSTAR data management centre. As of July 2005, a total of 7202 patients have been recruited internationally in the EUROSTAR registry. Results are regularly updated and published on the EUROSTAR web site (last report published in July 2005[90]).

At the end of 2004, the individual patient's data from all Belgian centres were made available to the KCE. The data of 1437 patients recruited in Belgian hospitals and with operative data from April 2001 to October 2004 were thus analyzed, and are presented below.

2. METHODOLOGY

Early Mortality

Early mortality is usually defined as mortality within 30 days of operation or mortality during hospital stay, in case of prolonged hospitalization. This definition is based on the exact date of death, and exact date of hospital discharge (definition 1). The definition used by the EUROSTAR data centre (definition 2) is slightly different, in the sense that it defines early death as all death occurring before the first follow up visit (scheduled at Month 1). As the follow up examinations were not always performed exactly as scheduled, a small difference exists between the 2 approaches. A third approach consists of removing from the definition patients who died in the hospital during prolonged hospitalization, but after the 30 days limit, and thus examining 30 days mortality strictly (definition 3).

Results for open conversion rates at 30 days and rupture rates at 30 days are calculated using the same definitions.

The influence of the following specific baseline factors on the early mortality rate is assessed using a multivariate logistic regression: Age at operation (<60, 60-80, >80 years), gender, ASA classification (I, II, III, IV), Initial size of maximal aneurysm diameter D3 (<55 mm, 55-64 mm, > 64 mm) and fitness for open repair status (yes/no)

Initial Clinical Success

Another measure of an operation success is the initial clinical success outcome, which accounts not only for early mortality but also for any important complication occurring within 30 days after operation.

"Clinical success consists in the following: successful deployment of the device at the intended location; absence of mortality, type I and type 2 endoleak, graft infection, or thrombosis; absence of aneurysm expansion (diameter > 5 mm or volume > 5%), aneurysm rupture, or conversion to open repair; absence of graft migration or failure of device integrity; absence of type 2 endoleak with aneurysm expansion; and maintenance of the above criteria for 30 days" [92].

A table indicating which of the EUROSTAR variables were used to apply this definition is provided in the appendices of this report.

Follow Up Data

Follow up measurements were scheduled at 1 month, 3, 6, 12, 18 months, 2 and 3 years after operation date.

As follow up measurements were not always performed on the exact time that was scheduled by the protocol, months of follow up were redefined based on the date of examination (to avoid Month 1 measurements actually performed 3 months after operation, for instance), using the following windows of days

Month/ year	Time Window (in days from operation)
1 month	1 – 52
3 months	53 – 131
6 months	132-259
12 months	260 – 439
18 months	440 – 624
2 years	625-836
3 years	> 837

If two examinations were categorized in the same time window, a worst case scenario was applied (i.e., keeping the examination where abnormalities are present, if any).

Volume-Outcome Relationship

To explore the relationship between hospital volume (total number of patients recruited) and outcome (early mortality and initial clinical failure at 30 days), summary descriptive statistics are presented by categories of hospital volume (<=10 patients, 10 to 20, 20 to 30, … >100 patients).

To test the hypothesis that early mortality is higher in smaller centres, multivariate logistic regression methods were used, considering volume as a dichotomous variable (<= 20 patients / > 20 patients) or as a continuous variable (increase of 10 patients). This comparison was adjusted for age, gender, size of aneurysm, ASA score and fit for surgery status. To account for the correlations between the patients within each hospital, the GEE method was used (considering all the patients in a hospital as independent from each other would tend to underestimate the standard errors of the parameters, and hence inflate the Type I error rate).

Outcomes assessed on Long Term

To assess the survival over 2 years, the non-parametric Kaplan-Meier (KM) estimator of the survival function was calculated on the entire follow up period. In survival analyses, patients who are lost to follow up are censored on the last day they are known to be alive. In this case, patients with no follow up data available were censored on their date of discharge, and patients with follow up data were censored on the last date of follow up examination available. Patients with no follow up dates and no discharge date are censored at the date of operation. Exact date of death was used in calculations for patients who died during the study.

Other events of interest were also analyzed, using the same methodology:

- Time to rupture, conversion or death

- Time to post operation complication = rupture, conversion or death, or any non intentional procedure or device complication after operation (graft migration, graft thrombosis, secondary intervention, rupture)

- Time to First Endoleak (excluding endoleaks occurring during operation). A sensitivity analysis was performed including endoleaks occurring during operation.

- Time to any complication or abnormality after the operation, including rupture, conversion and death.

- Time to any secondary intervention

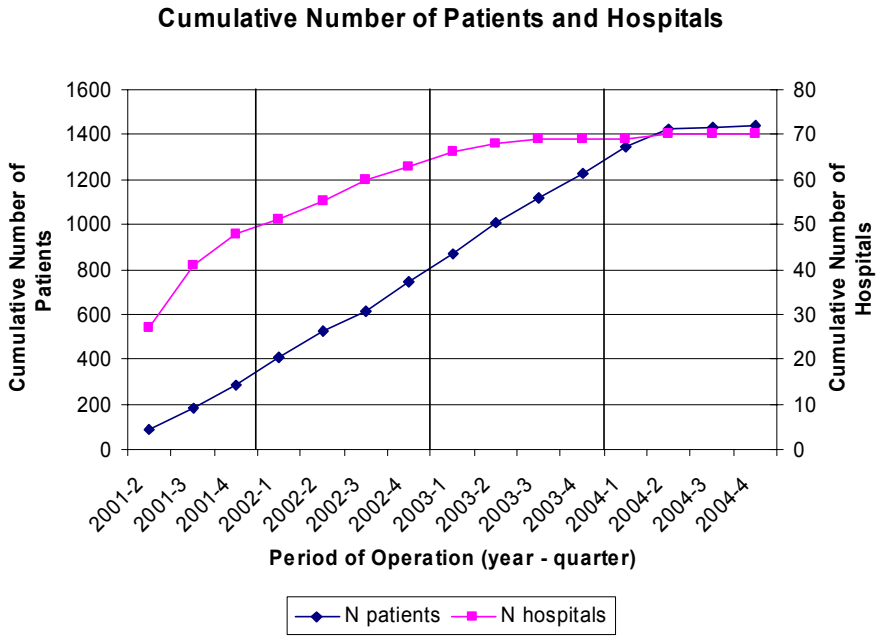
A multivariate Cox PH regression model was used to assess the influence of baseline factors.

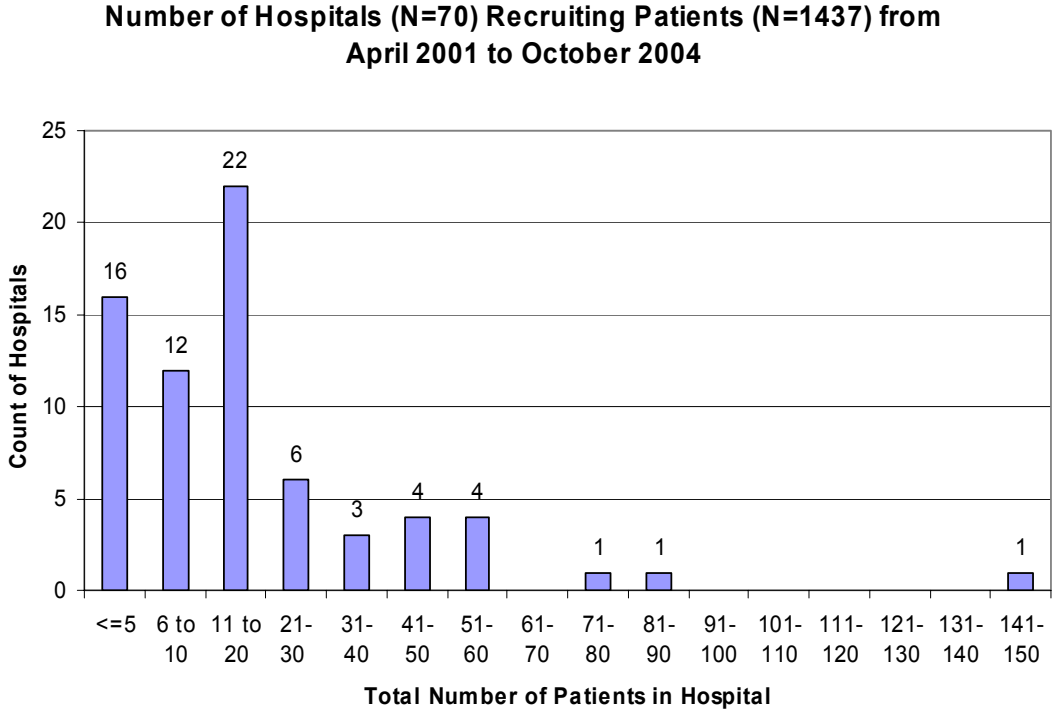
3. RESULTS

Recruitment of Patients and Hospitals Volume

A total of 1437 patients were recruited in 70 Belgian hospitals from April 2001 to October 2004. Approximately 500 operations/year were performed in 2002 and 2003. For 2004, at the time of locking the database for analysis, the registry included data on approximately 200 operations.

While the Eurostar protocol inclusion criteria requires a minimum of 10 cases treated per year, many hospitals did not fulfil this criteria. On the 70 hospitals that were included in the registry, 28 hospitals (40%) recruited 10 patients or less during the whole follow up period, 50 hospitals (71%) recruited 20 patients or less and 7 hospitals (10%) recruited more than 50 patients.





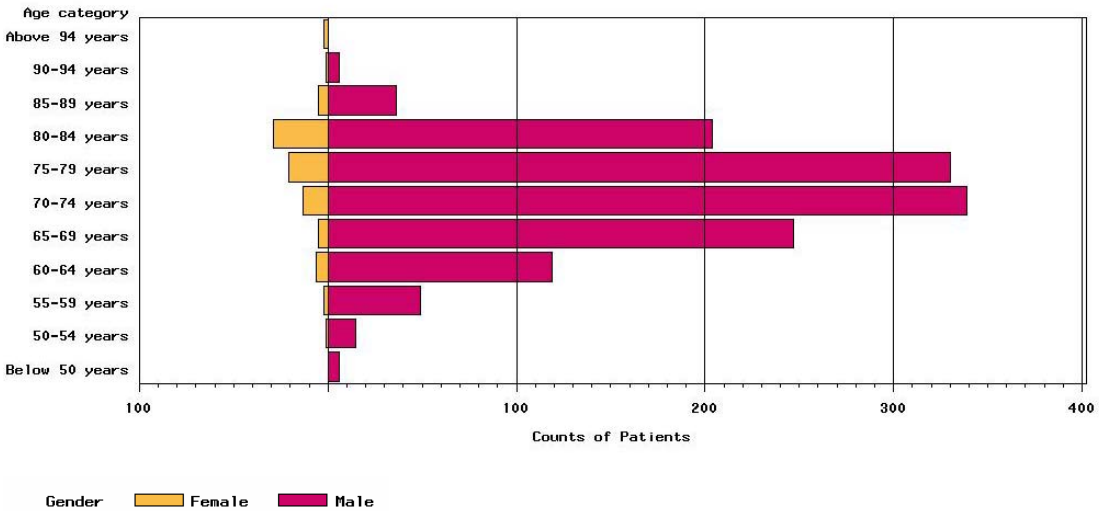
Patient's Risk Profile

The average age of patients at operation is 72.7 years (range 46.9- 96.6). Older patients are recruited as long as the study progresses (% of patients above 80 years is 10% in 2001, 25% in 2004). This relationship is not observed for the size of the aneurysm. The majority of patients are male (94%), who are on average younger than female (mean age for male is 72.5 years; mean age for female is 76.9 years). Demographic information is summarized graphically in the demographic pyramid.

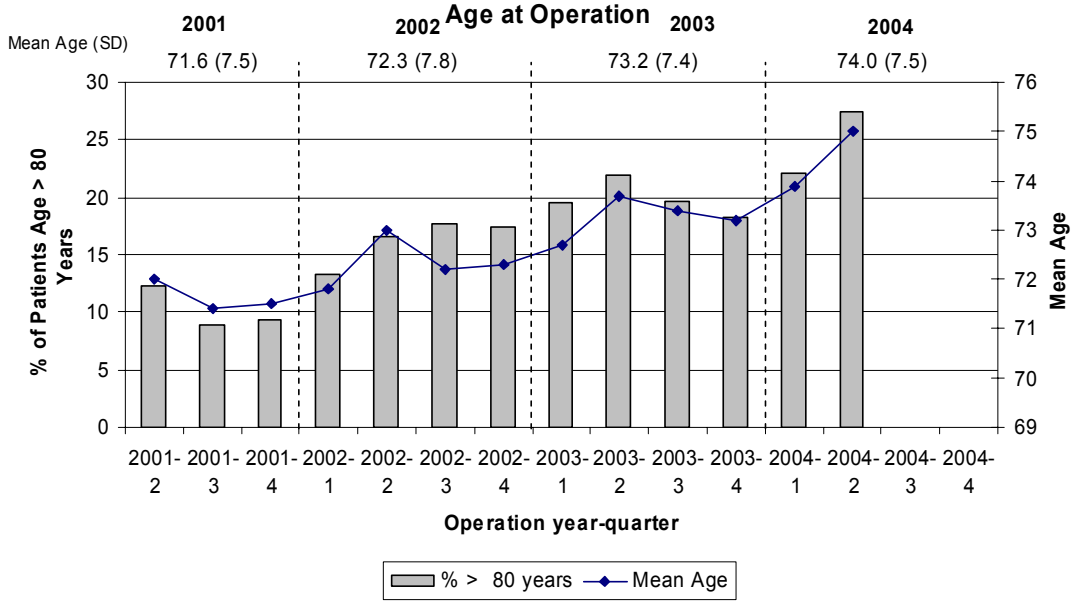
The majority of the patients recruited had an ASA classification of 2 (57%). 3% of the patients were classified as ASA 4. Of the SVS risk scores factors, hypertension, hyperlipidemia and cardiac risk were the most common among patients.

Approximately 30% of the patients were considered unfit for open AAA procedure, and 8% were unfit for general anaesthesia. The mean aneurysm diameter (D3) was 56.6 mm (median 55mm, range 25 to 130 mm), with 25% of the patients having an aneurysm size smaller or equal to 50 mm (Q1).

Demographic Pyramid



Mean Age Male 72.5 (7.5), Mean Age Female 76.9 (8.2)



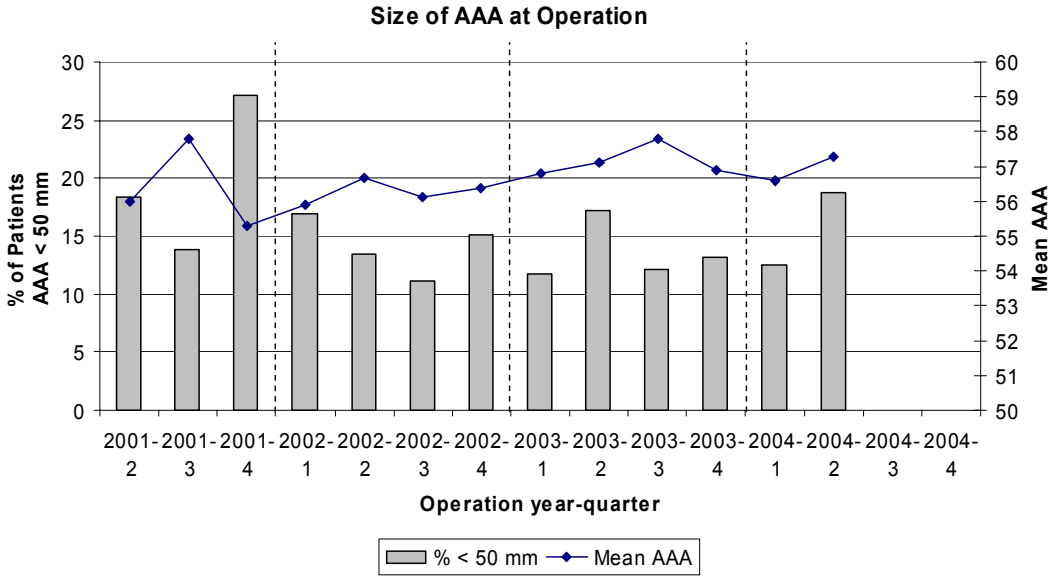
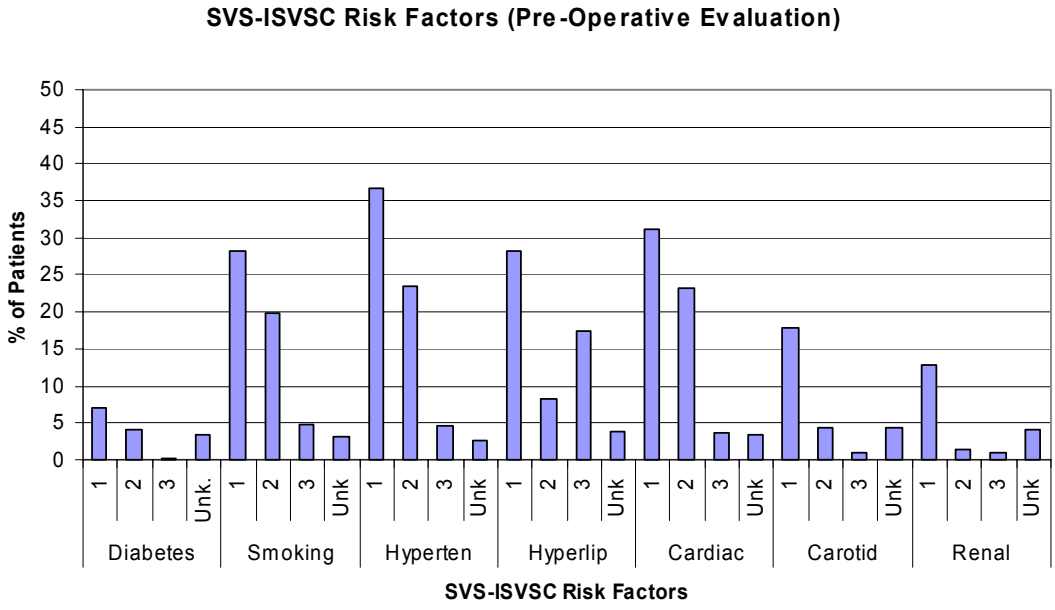
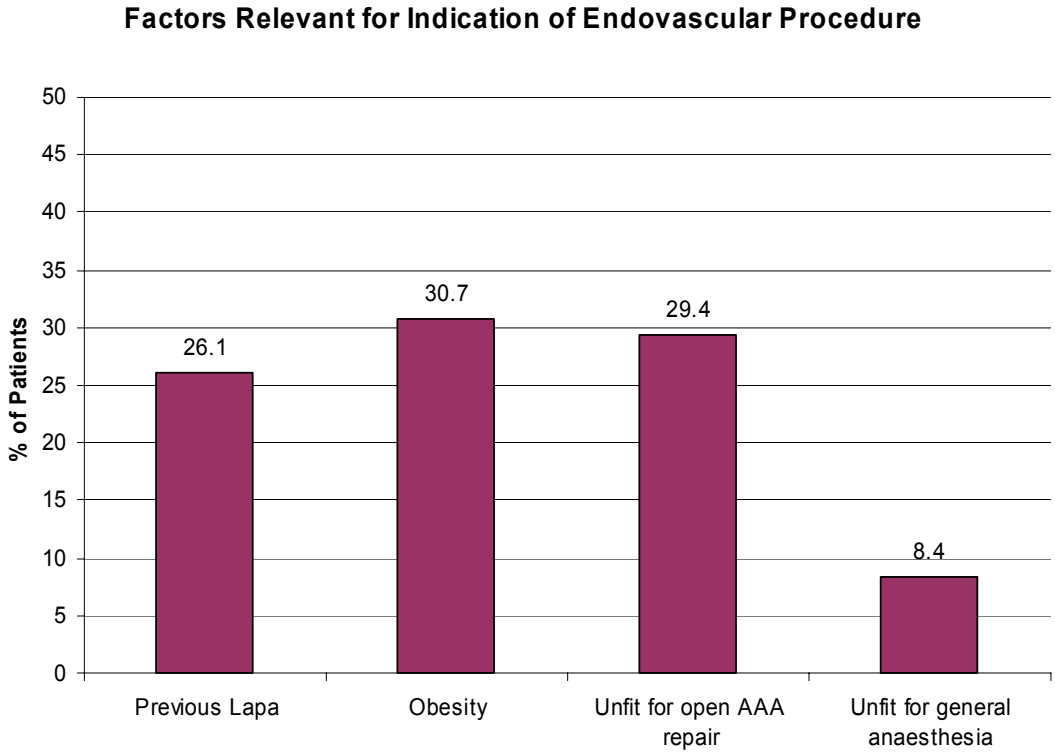


Table 12.1: Baseline Demographics and Pre-Operative Characteristics

Total		N= 1437	
Category		n	%
Year of operation	2001	286	19.9
	2002	458	31.9
	2003	487	33.9
	2004	206	14.3
Gender	Male	1352	94.1
	Female	85	5.9
Age at operation	Mean (SD)	72.7	7.6
	Range	47	97
	≤ 60 years	81	5.6
	60- 80 years	1105	76.9
	> 80 years	250	17.4
ASA Profile	1	201	14.0
	2	816	56.8
	3	375	26.1
	4	44	3.1
SVS-ISCVS risk factor score	Diabetes (51)	161	11.6
	Tobacco Use (46)	758	54.5
	Hypertension (39)	931	66.6
	Hyperlipidemia (54)	777	56.2
	Cardiac disease (48)	836	60.2
	Carotid-artery disease (62)	333	24.2
	Renal disease (59)	219	15.9

	Pulmonary disease (57)	650	47.1
Sum of SVS/ISCVSC risk factors scores	Mean (SD)	4.3	2.7
Factors Relevant to Indication	Previous Lapa (18)	371	26.1
	Obesity (19)	436	30.7
	Unfit for AA (20)	417	29.4
	Unfit for general anaesthesia (25)	119	8.4
Maximal Size of Aneurysm (37) (mm)	Mean (SD)	56.6	11.0
	Range	25	130
	Median (Q1-Q3)	55	(50-61)
A () indicates the number of missing values for that category.			





Operative and Post Operative Data

Operative Data

On the 1437 patients with operative data, 26% experienced an unexpected complication during the operation (17.5% had an endoleak, 3.3% had an inadvertently blocking of sides branches, 2.7% had any device related complication, for 0.9% there was a failure to complete procedure and 3.3% had an arterial complication).

Table 12.2: Counts (%) of Patients with Any Problem* during Operation (Operative Data)

	N= 1437	
Description	**n**	**%**
Any Problem* during Operation	**371**	**25.8**
Any Endoleak at Final Angiography	**251**	**17.5**
Proximal anastigmatic endoleak	25	1.7
Midgraft endoleak from prosth. fabric	10	0.7
Midgraft endoleak of limb. prosth. connection	9	0.6
Distal anastomotic endoleak	15	1.0
Perfusion from Lumbar or IMA	173	12.0
Perfusion from int. iliac artery	13	0.9
Other	15	1.0
Type of Endoleak		
Endoleak Type I	40	2.8
Endoleak Type 2	185	12.9
Endoleak Type 2I	19	1.3
Blocking of Sides Branches	**291**	**20.3**
Blocking Intentional	217	15.1
Renal artery	5	0.3
Accessory renal artery	34	2.4
One internal iliac artery	149	10.4
Two internal iliac arteries	29	2.0
Blocking Inadvertently	47	3.3
Renal artery	5	0.3
Accessory renal artery	3	0.2
One internal iliac artery	36	2.5
Two internal iliac arteries	3	0.2
Intra-Operative Complications		
Any Device Related Complication	**39**	**2.7**
Inability to advance delivery sheath	8	0.6
Inability to deploy device	1	0.1
Device occlusion (unresolved)	1	0.1
Device Migration	13	0.9
Other	18	1.3
Any Failure to Complete Procedure	**13**	**0.9**
Conversion to open procedure	3	0.2
Extra-Anatomic bypass	4	0.3
Other	8	0.6

	N= 1437	
Description	**n**	**%**
Any Arterial Complications	**48**	**3.3**
Thrombus (unsatisfactory resolved)	5	0.3
Emboli (unsatisfactory resolved)	4	0.3
Occlusion of renal artery	9	0.6
Other	31	2.2
* Note: including endoleak, blocking of sides branches (not intentional), devices related complication, failure to complete procedure and arterial complications		

Post Operative Data

On the 1437 patients with operation data, 15% had a post operative complication before discharge (10% had a systemic complication, 1.9% had a procedure and device related complication, 5.0% had an access site and lower limb complication and 1.1% had an abnormality detected on abdominal X-ray).

The average hospital stay was 6.3 days (median 4 days, range 0 to 165 days, Table 12.4).

Table 12.3: Counts (%) of Patients with Post Operative Complication to Discharge

	N=1437	
Description	**n**	**%**
Any Post Operative Complication Until Discharge*	**220**	**15.3**
Any Systemic Complication	**144**	**10.0**
Cardiac	45	3.1
Cerebral	6	0.4
Pulmonary	35	2.4
Renal	32	2.2
Hepatobiliary	5	0.3
Bowel	14	1.0
Sepsis	15	1.0
Other	44	3.1
Laparotomy for systemic comp.	3	0.2
Any Procedure and Device Related Complication	**27**	**1.9**
Graft Migration	3	0.2
Complete Graft Thrombosis	1	0.1
One Limb Graft Thrombosis	11	0.8
Secondary Intervention transfemoral	12	0.8
Secondary Intervention transabdominal	6	0.4
Secondary Intervention extra-anatomic	7	0.5
Any Access Site and Lower Limb Complication	**72**	**5.0**
Bleeding, haematoma, false aneurysm	39	2.7

	N=1437	
Description	**n**	**%**
Arterial thrombosis	7	0.5
Peripheral emboli	8	0.6
Other	23	1.6
Any Abnormality Detected on Plain Abdominal X-Ray	**16**	**1.1**
Graft Migration	1	0.1
Severe Angulation	10	0.7
Other	5	0.3
* Note: including systemic complications, procedure and device related complications, access site and lower limb complications and abnormalities seen on abdominal X-ray		

Table 12.4: Duration of Hospital Admission (Days)

Days till discharge from hospitalization					
N	**Mean**	**Median**	**Std Dev**	**Min**	**Max**
1430	6.3	4.0	9.9	0.0*	165.0
Note: 7 patients stayed less than 1 day in the hospital (2 of them because they died)					

Accounting at Follow Up Visits

Accounting at follow up examinations is described below. Approximately 13% of the patients were lost to follow up after operation before any scheduled visit was performed. At the time the database was closed for analysis (November 2004), only half of the patients had a follow up of 1 year, 20% a follow up of 2 years and less than 5% a follow up of 3 years. All follow up results are therefore presented up to 2 years of follow up. For patients operated in 2004, some hospitals seem to send their follow up results by batches, and not on a continuous basis, implying that these data have not been sent yet to the EUROSTAR centre.

An estimation of the number of patients lost to follow up after 6 months (i.e., patients whose last visit is within 6 months of operation and for whom no report of death has been notified) is presented in Table 12.5. This estimation is based on the fact that 6 month follow up data from patients operated in 2001, 2002 and 2003 should have been available at the EUROSTAR centre in October 2004. With this assumption, percent of patients lost to follow up after 6 months is 22-23% for patients operated in 2001-2002 and 58% for patients operated in 2003, indicating that the follow up is quite poor and that the registration of follow up data is slow.

Flow Chart of Patients Accounting in Follow Up Visits

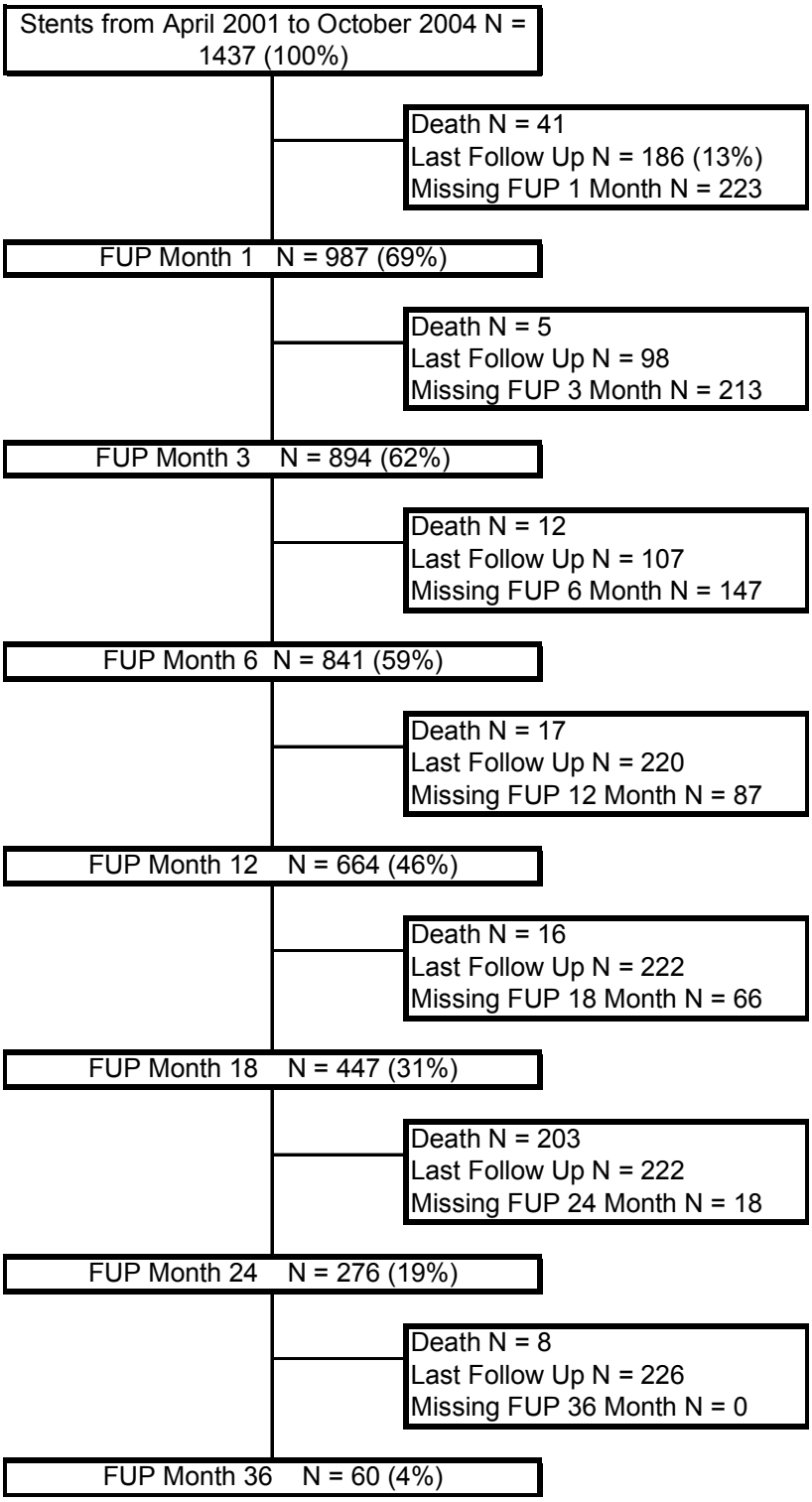


Table 12.5: Number of Patients Lost To Follow Up

Year	N	N death	N alive	Lost to Follow Up After Operation*		Lost to Follow Up Within 6 Months After Operation**	
				n	%	n	%
2001	286	24	262	22	8.4	58	22.1
2002	458	46	412	37	9.0	94	22.8
2003	487	43	444	54	12.2	257	57.8
2004	206	3	203	73	36.0	-	-
total	1437	116	1321	186	14.1		

N = N patients operated
* patients for whom no follow up is available
** patients for whom last follow up was within 6 months of operation

Early Events (Mortality, Conversion, Rupture)

A total of 116 deaths (8.1% of patients), 16 conversions to open repair (1.1%) and 1 rupture were observed during the follow up period.

A total of 38 patients died within 30 days of operation or at hospital during prolonged hospitalization: the early mortality rate is 2.6% (definition 1). Using the definition of Eurostar data centre (definition 2, which is based on the follow up month, and not on the exact date), the early mortality is 3.1%. If only deaths occurring within 30 days of operation are included (definition 3), the early death percentage is 2.2% (see appendices of this report). These definitions are described in the methodology section.

Table 12.6: Counts (%) of Patients with Death, Conversion or Rupture (Definition 1: based on date of event and date of discharge)

		Early *		Late		Total	
Event	N	n	%	n	%	n	%
Death	1437	**38**	**2.6**	78	5.4	116	8.1
Conversion	1437	8	0.6	8	0.6	16	1.1
Rupture	1437	0	0.0	1	0.1	1	0.1

* Early events defined as occurring within 30 days of date of operation, or before discharge of prolonged hospital stay.

Mortality rates ranged from 2.5% in 2001 to 0.5% in 2004, which may be partially explained by the fact that some hospitals have not returned yet their follow up examinations for 2004.

Results from multivariate logistic regression show that increasing age, increasing ASA classification and unfit for surgery status increase the risk of death at 30 days. Relationship of AAA size and early mortality is less straightforward, as a high mortality is observed for patients with small aneurysms (<5 cm).

Table 12.7: Early Mortality by Selected Baseline Factors and Results from Logistic Regression

	N	n	%	Odds Ratio*	95%CI	95% CI
All Patients	1437	38	2.6	--	-	-
Gender						
Male	1352	36	2.7	ref	-	-
Female	85	2	2.4	0.98	0.22	4.38
Age Category						
< 60 years	82	1	1.2	ref	-	-
60-<70 years	401	6	1.5	0.92	0.10	8.26
70-<80 years	704	15	2.1	1.25	0.16	10.08
≥ 80 years	250	16	6.4	2.72	0.33	22.40
ASA-Class						
1	201	0	0.0	Ref		
2	816	9	1.1	Ref		
3	375	23	6.1	5.24	2.18	12.60
4	44	6	13.6	9.37	2.65	33.11
Fit for Surgery						
Yes	1000	12	1.2	ref	-	-
No	417	26	6.2	2.48	1.12	5.52
Size of Aneurysm						
<50 mm	216	7	3.2	Ref	-	-
50-<55 mm	457	6	1.3	0.38	0.12	1.19
55-<60 mm	278	8	2.9	0.68	0.23	2.01
≥ 60 mm	449	15	3.3	0.56	0.21	1.48

* all results from logistic regression are adjusted for gender, age category, ASA-class, fit for surgery and size of aneurysm. 58 observations were deleted due to missing value of explanatory variables. Max R-square 0.18.

In order to further investigate whether the somewhat higher than expected mortality observed in the group of patients with small aneurysms (<50 mm, 7 deaths on 216 patients, 3.2%) was consistent with the international literature, additional analyses have been performed, to compare these results to the overall EUROSTAR registry data. In a study published in 2004, investigating the effect of the diameter of AAA on the outcome[91]. The study was based on all EUROSTAR registry data available at that time, i.e. 4392 patients. Table 12.8 presents the results of the comparison. For the 3 categories of aneurysms (40 to 54 mm, 55 to 64 mm and above 65 mm) the short term mortality rates are consistent with the global EUROSTAR registry. The small part of patients with an aneurysm below 40 mm was not studied in [91], but seems to represent a slightly different population of patients.

Table 12.8 : Baseline Demographics and Outcome Results by Initial Size of Aneurysms

	EUROSTAR BELGIUM (N=1400)									EUROSTAR ALL (N=4392)		
								Early Death				Early Death
AAA size	N	%	Mean Age	% age > 80	% male	% unfit	% asa 3 or 4	n	%	N	%	%
< 40 mm	38	3	72	24	95	21	32	3	7.9	not studied		
40 to <55 mm	635	45	72	12	93	23	24	10	1.6	1962	45	1.6
55 to <65 mm	474	34	73	19	95	33	30	12	2.5	1528	35	2.6
>= 65 mm	253	18	75	26	94	38	41	11	4.4	902	21	4.1

Important Complications during First 30 Days

The percentage of patients with initial clinical success[92] is 82%. Main reasons of failure (18%) include Type I or Type 2 endoleak (5.9%), graft infection/thrombosis (5.6%) and no successful deployment of device at intended location (3.3%).

Table 12.9: Counts (%) of Patients with Initial Clinical Success at 30 Days, and Reasons for Failure (Important Complications)

	N = 1437	
	n	%
Initial Clinical Success (at 30 days)	1176	81.8
Initial Clinical Failure	261	18.2
No successful deployment at intended location	47	3.3
Death	32	2.2
Type I or Type 2 endoleak	85	5.9
Graft infection/thrombosis	80	5.6
Aneurysm expansion	37	2.6
Rupture or conversion	8	0.6
Graft migration or failure of device integrity	42	2.9
Note : a patient may have several reasons of clinical failure.		

Volume Outcome Relationship

Association between Volume and Early Mortality

Early mortality (within 30 days, or during hospitalization) is presented by hospital, categorized on their total volume, in Table 12.10. In hospitals with very low volume (≤ 10 patients recruited, the case for 28 hospitals), the early mortality rate is 3.5%, whereas the largest centre (144 patients) has a 0% early mortality. Figure 12.1 presents these aggregated data, and Figure 12.2 presents the individual data by hospital, for all hospitals (these data are also in the appendices of this report).

Table 12.10: Early Death by Category of Hospital Volume

			Early Death	
Hospital Category (Total Volume)	N Hospitals	N Patients	n	%
Categorized per 10 patients				
≤10	28	144	5	3.47
11-20	22	338	13	3.85
21-30	6	146	3	2.05
31-40	3	104	2	1.92
41-50	4	182	3	1.65
51-60	4	222	6	2.70
61-70	0	0		
71-80	1	76	4	5.26
81-90	1	81	2	2.47
91-100	0	0		
>100	1	144	0	0.00
Categorized with Cut Off 20 patients				
≤20	50	482	**18**	**3.7**
> 20	20	955	**20**	**2.1**
TOTAL	**70**	**1437**	**38**	

When the volume of hospitals is dichotomized with a cut off of 20 patients recruited, there is a numerical difference in early mortality in small centres (3.7%) compared to big centres (2.1%). The odds ratio and 95% CI is 1.81 (0.88, 3.7), indicating that the odds of early mortality in small centres are almost twice large than in large centres. This difference is not statistically significant (p=0.106, Table 12.11, with adjustment for correlations within hospitals – GEE approach). Adjusted for the age, gender, ASA category, AAA size and fit for surgery status, the OR decreases to 1.49 (0.71, 3.13), p=0.292. If the largest centre (N=144) is withdrawn, results show a smaller association.

Table 12.11: Results of Logistic Regression for Volume-Outcome Relationship

	Odds Ratio	95%CI	p-value
Volume Dichotomized (cut off 20 patients <= 20 vs. > 20 patients)			
Unadjusted	1.81	(0.95, 3.46)	0.071
Unadjusted (GEE)*	1.81	(0.88, 3.7)	0.106
Adjusted **	1.49	(0.71, 3.13)	0.292
Without Largest centre (N=144)***	1.28	(0.64, 2.57)	0.481
Volume Continuous (increase of 10 patients)			
Unadjusted	0.89	(0.80, 1.00)	0.045
Unadjusted (GEE)*	0.89	(0.78, 1.02)	0.089
Adjusted **	0.91	(0.80, 1.04)	0.160
Without Largest centre (N=144)***	0.99	(0.86, 1.14)	0.875
* with GEE approach to take into account the intra hospital clustering of patients **Comparison adjusted for age, gender, size of aneurysm, fit for surgery status and ASA classification, and for intra-clustering of data (GEE approach) *** adjusted comparison without data from largest centre (N= 144 patients recruited)			

Some precautions are needed in the interpretation of these results, as the distribution of patients per centre is very unequal (and there is a large gap between the medium size hospitals and the largest hospital). More observations are needed to have stronger conclusions. Also, a decreasing relationship between volume-outcome does not necessarily imply that the large volume of the hospital is the cause of the low mortality (learning by doing effect), as 'selective referral effects' may also play a role (high quality hospitals which have better outcome are likely to get more cases).

Figure 12.1: Early Death by Category of Hospital Volume

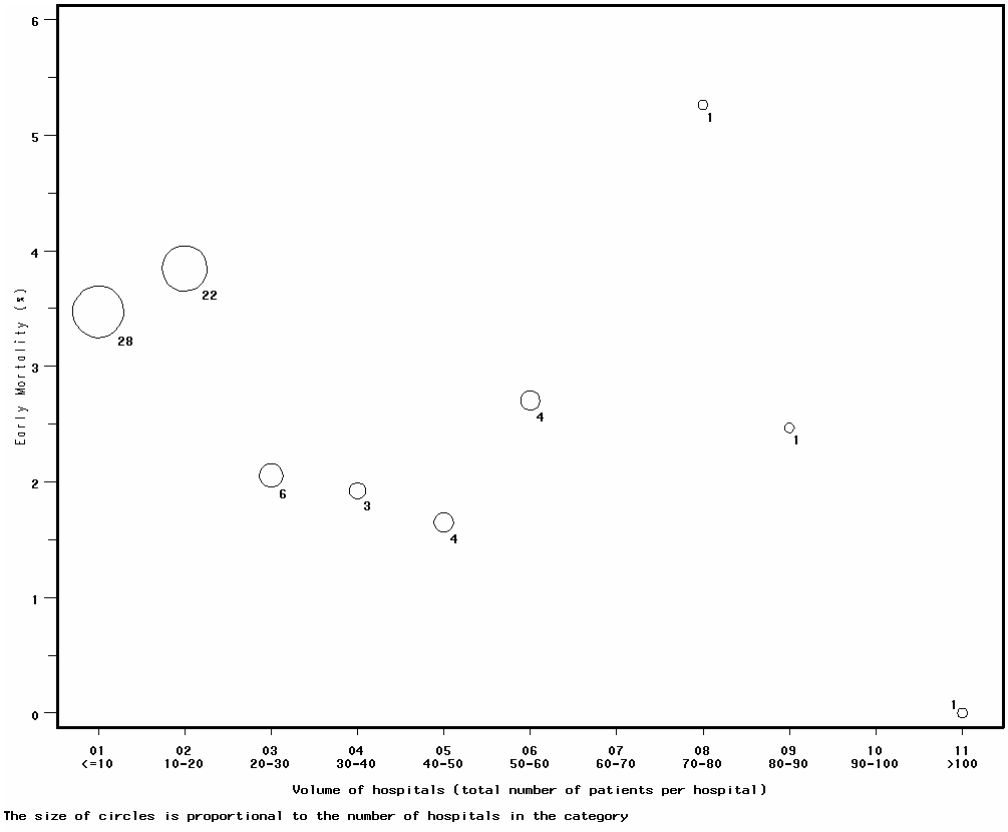
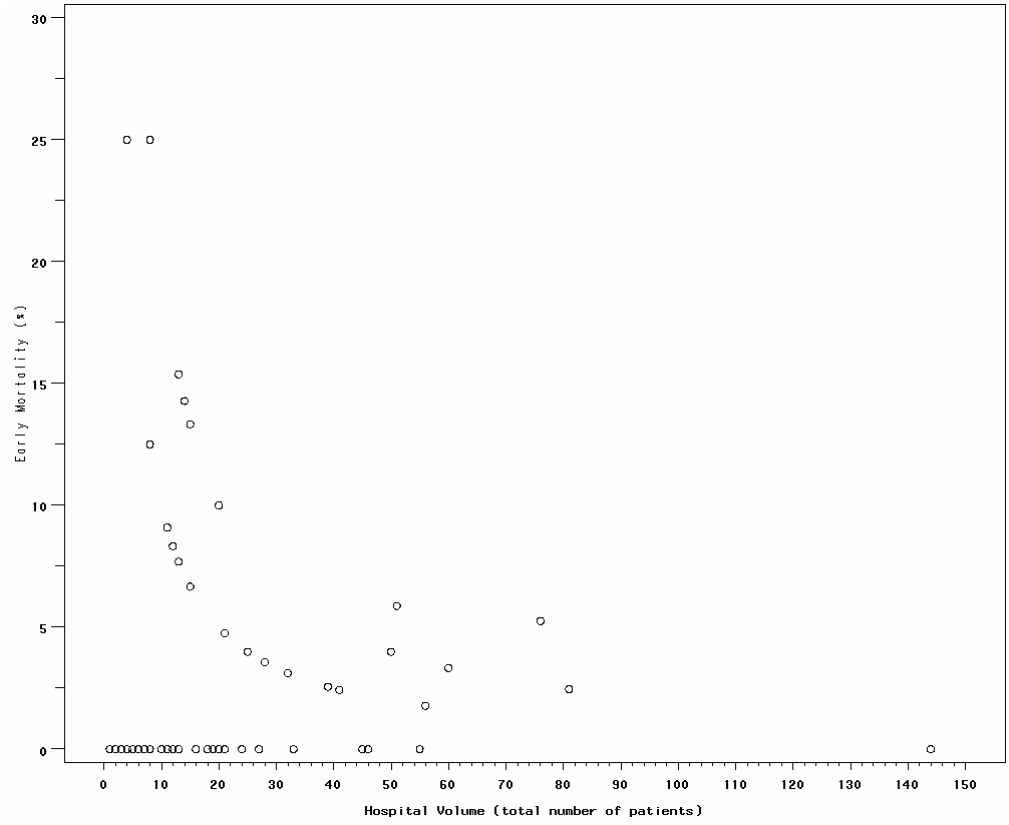


Figure 12.2: Early Death by Category of Hospital Volume (Not Aggregated)



Association between Volume and Initial Clinical Failure

Initial Clinical Failure (within 30 days after operation) is presented by hospital, categorized on their total volume, Table 12.12. In hospitals with low volume (≤ 20 patients recruited), the initial clinical failure rate is 18.0%, whereas hospitals with a larger volume (>20 patients) recruited have a 18.2% initial clinical failure rate. There is thus no association between hospital volume (dichotomized) and initial clinical failure rates (results in Table 12.13).

Table 12.12: Initial Clinical Failure by Category of Hospital Volume

			Initial Clinical Failure	
Hospital Category (Total Volume)	N Hospitals	N Patients	n	%
Categorized per 10 patients				
<=10	28	144	31	21.5
11-20	22	338	56	16.6
21-30	6	146	21	14.4
31-40	3	104	22	21.2
41-50	4	182	43	23.6
51-60	4	222	47	21.2
61-70	0	0		
71-80	1	76	15	19.7
81-90	1	81	12	14.8
91-100	0	0		
>100	1	144	14	9.7
Categorized with Cut Off 20 patients				
<=20	50	482	87	**18.0**
> 20	20	955	174	**18.2**
TOTAL	**70**	**1437**	**261**	**18.2**

Table 12.13: Results of Logistic Regression for Volume-Outcome (Initial Clinical failure) Relationship

	Odds Ratio	95%CI	p-value
Volume Dichotomized (cut off 20 patients <= 20 vs. > 20 patients)			
Unadjusted	0.99	(0.74, 1.31)	0.937
Unadjusted (GEE)*	0.99	(0.63, 1.56)	0.961
Adjusted **	0.94	(0.59, 1.48)	0.779
Without Largest centre (N=144)***	0.84	(0.54, 1.31)	0.448

* with GEE approach to take into account the intra hospital clustering of patients
**Comparison adjusted for age, gender, size of aneurysm, fit for surgery status and ASA classification, and for intra-clustering of data (GEE approach)
*** adjusted comparison without data from largest centre (N= 144 patients recruited)

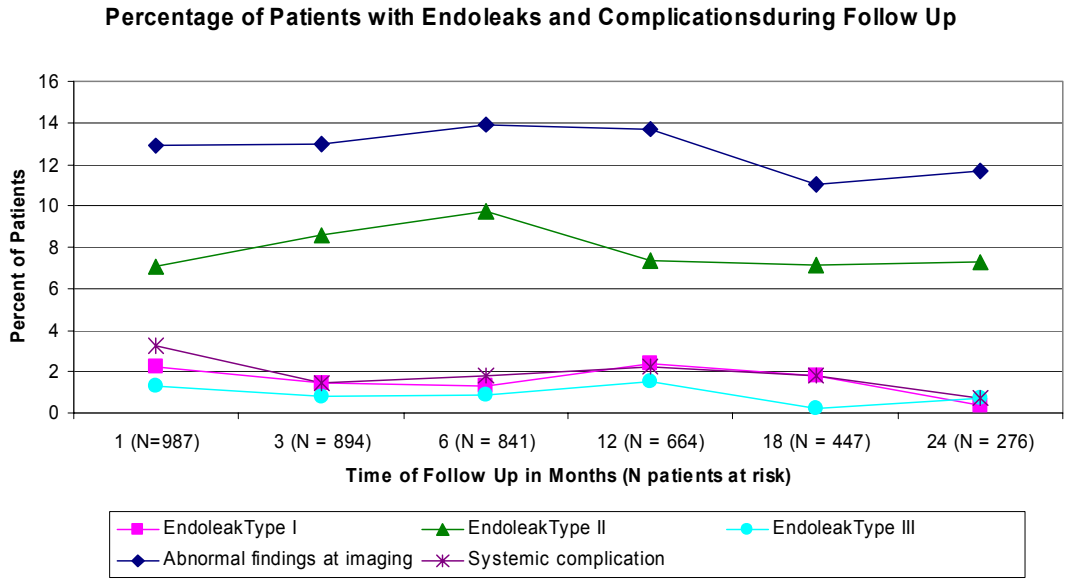
Outcomes Assessed on Long Term (2 years)

Several outcomes have been studied (see list below). Rates and survival functions at 1Y and 2Y are presented below. After 2 years, the proportion of patients surviving the operation was 86.4%. The proportion of patients without any post operative complication after 2 years was 78.3%.

Table 12.14: Outcomes after 1 and 2 years.

				Survival Function (%)		Cumulative Death (%)	
Endpoint	**N events**	**N years follow up**	**Rate /100 py**	**1Y**	**2Y**	**1Y**	**2Y**
Death	116	1375	8.4	91.7	86.4	8.3	13.4
Rupture, Conversion, Death	129	1373	9.4	91.1	84.7	8.9	15.4
Any Post Op complication *	197	1301	15.1	85.7	78.3	14.3	21.7
Any Endoleak	404	1041	38.8	69.8	66.1	30.2	33.9
Any post op abnormality or complication**	567	984	57.6	57.2	49.0	42.8	51.0
Any secondary intervention ***	76	1312	5.8	97.1	92.1	5.9	7.8

*Any post operative complication is defined as any procedure or device related complication after operation (graft migration, graft thrombosis, secondary intervention, rupture) or any important event (rupture, conversion, death)
** including any clinical or imaging abnormality
**Secondary intervention performed during operation (conversion to open repair) or during follow up period (secondary intervention transfemoral, transabdominal or extra anatomic).



Stratified Survival Analyses

The survival curves stratified separately for several pre-operative factors (ASA, size of maximal aneurysm diameter D3, status for open AAA repair) are displayed in the appendices of this report, and show consistent results with early mortality results. Over the 3 years follow up period, survival curves are consistently lower for patients with higher ASA pre-operative classification, for patients with pre-operative aneurysm diameter >64 mm (there is no observed difference on survival curves between patients with aneurysm diameter <55 mm and patients with aneurysm diameter from 55 to 64 mm), and for patients who were unfit for open AAA repair.

3. APPENDICES FOR EUROSTAR DATA

Definition of initial clinical success

Clinical success is defined as the following[92]: successful deployment of the device at the intended location; absence of mortality, type I and type 2 endoleak, graft infection, or thrombosis; absence of aneurysm expansion (diameter > 5 mm or volume > 5%), aneurysm rupture, or conversion to open repair; absence of graft migration or failure of device integrity; absence of Type 2 endoleak with aneurysm expansion; and maintenance of the above criteria for 30 days.

Definition of Clinical Success based on Forbes[92] and Eurostar data

n	FORBES et al	EUROSTAR	
		Variable	Description
1	no successful deployment of the device at the intended location	POSTV001	Device related complications intraoperatively -inability to advance delivery sheath -inability to deploy device -device occlusion (unresolved) -one device limb occluded (unresolved) -device stenosis (unresolved) -one device limb stenotic (unresolved) -device migration -other
		POSTV011	Failure to complete procedure: -Conversion to open procedure -Extra anatomic bypass -other
2	Mortality		Date of death
3	Type I or type 2 endoleak	OPERV043, 044, 045, 046 FOLV007, 008, 009	Type I or Type 2 endoleak
4	Graft infection or thrombosis	POSTV018	Arterial complications - Thrombus(unsatisfactory resolved) - Emboli (unsatisfactory resolved) - Occlusion of renal artery - Other
		POSTV060, 62, 64	Access site and Lower Limb Complications: - Arterial thrombosis - Peripheral emboli - Amputation
		POSTV 46, 48	Procedure and device related complication: - Complete graft thrombosis - One limb graft thrombosis
		FOLV012	Stenosis/thrombosis (during follow up)
		FOLV025, 026	Graft stenosis Graft thrombosis
5	aneurysm expansion (diameter > 5 mm or volume > 5%)	PREV031, FOLV019	Baseline and follow up data D3 max
6	aneurysm rupture, or conversion to open repair	POSTV012, POSTV053, FOLV033	Conversion to open repair and rupture date
7	graft migration or failure of device integrity	POSTV044, 52	Procedure and device related complication: - Graft migration - Secondary intervention transabdominal
		POSTV068	Abnormalities seen on Abdominal X-Ray Graft migration, severe angulation, suture breakage, stent breakage, other
		FOLV11, 13	Kinking of stent graft Graft migration
		FOLV024	Graft migration
		FOLV037	Abnormalities seen on Abdominal X-Ray (FUP) Graft migration, severe angulation, suture breakage, stent breakage, other

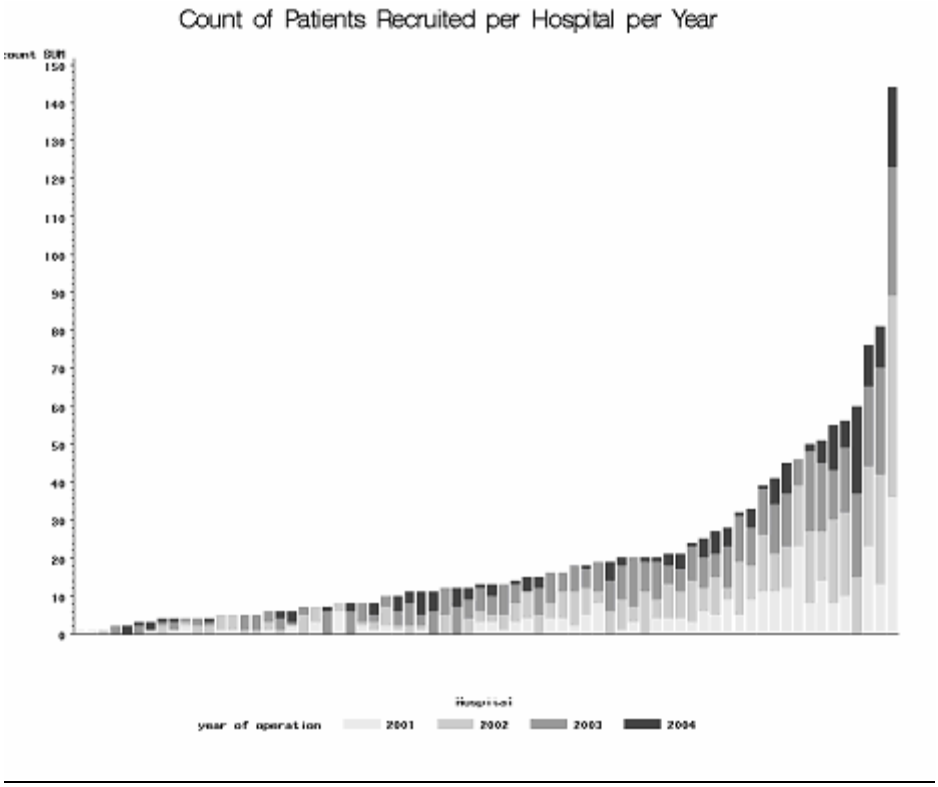
Individual hospital data (table)

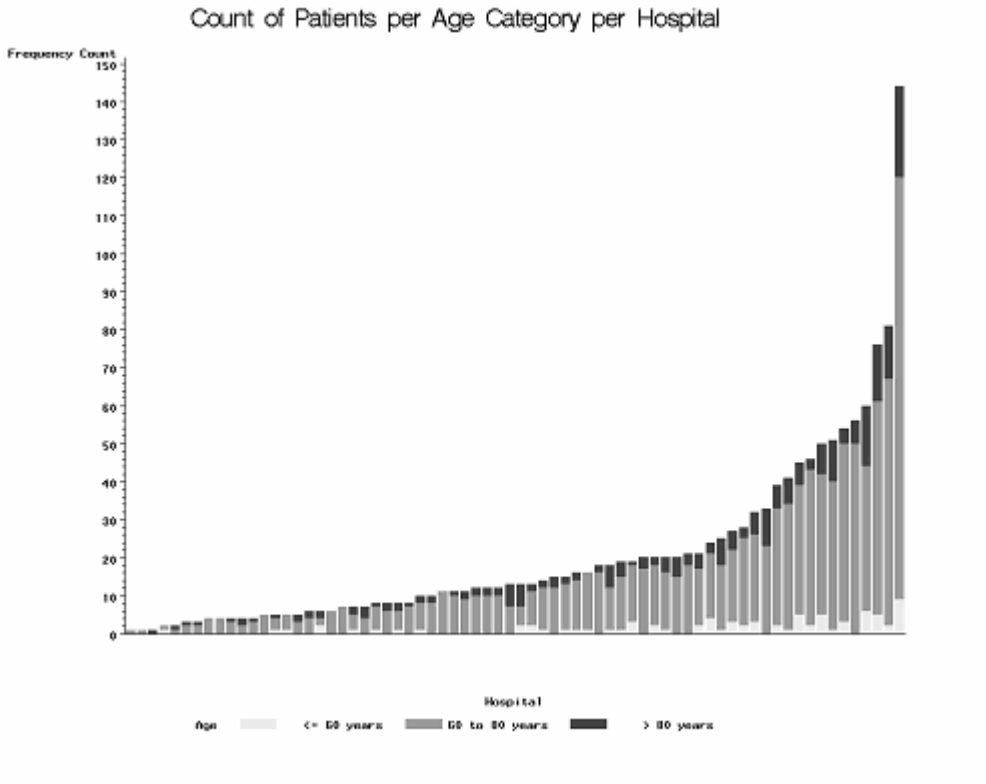
Baseline Patient's Characteristics and Outcome Data by Hospital

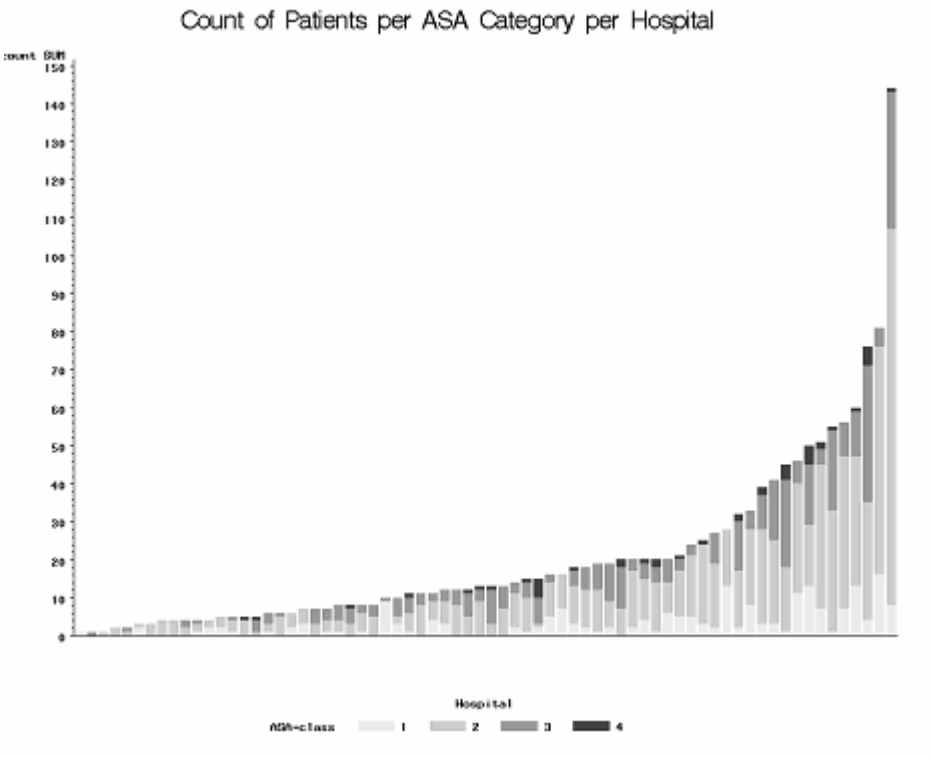
Obs	N	Age	% male	ASA	AAA	N Death Early	% Early death	% Death	% Problems at operation	% Initial Clinical Failure
1	144	72.3	94.4	2.2	56.3	0	0.0	10.4	31.3	9.7
2	76	73.2	93.4	2.6	59.5	4	5.3	11.8	19.7	19.7
3	41	74.6	90.2	2.3	55.7	1	2.4	2.4	24.4	17.1
4	3	73.9	100	1.3	54.7	0	0.0	0.0	33.3	0.0
5	11	72.5	100	2.5	57.5	1	9.1	9.1	27.3	27.3
6	51	73.9	92.2	2.0	59.7	3	5.9	17.6	47.1	43.1
7	55	71.9	100	2.4	54.5	0	0.0	9.1	10.9	1.8
8	46	72.7	91.3	1.9	53.9	0	0.0	0.0	26.1	30.4
9	56	72.5	98.2	2.0	58.0	1	1.8	3.6	35.7	16.1
10	7	70.2	100	1.6	52.4	0	0.0	0.0	57.1	42.9
11	28	71.0	89.3	1.5	56.4	1	3.6	3.6	7.1	14.3
12	39	72.5	94.9	2.3	58.2	1	2.6	2.6	38.5	20.5
13	20	73.9	100	2.8	58.4	0	0.0	15.0	15.0	10.0
14	81	73.5	91.4	1.9	57.0	2	2.5	8.6	28.4	14.8
15	16	72.9	87.5	1.8	58.1	0	0.0	0.0	25.0	25.0
16	20	71.8	85.0	2.1	56.3	0	0.0	0.0	20.0	5.0
17	13	77.6	76.9	2.4	49.6	1	7.7	15.4	46.2	23.1
18	21	75.1	85.7	2.1	53.0	1	4.8	28.6	28.6	33.3
19	16	68.9	100	1.6	51.3	0	0.0	0.0	18.8	18.8
20	10	72.6	90.0	1.2	54.0	0	0.0	0.0	50.0	40.0
21	18	73.4	100	2.2	55.1	0	0.0	0.0	16.7	0.0
22	60	72.6	91.7	2.0	53.9	2	3.3	5.0	45.0	25.0
23	4	67.5	75.0	2.0	51.0	0	0.0	25.0	75.0	75.0
24	5	72.6	100	1.6	64.8	0	0.0	0.0	0.0	40.0
25	12	70.5	100	2.0	56.3	1	8.3	8.3	33.3	25.0
26	20	72.3	95.0	2.4	54.7	0	0.0	0.0	30.0	20.0
27	25	74.6	100	2.0	60.2	1	4.0	12.0	20.0	8.0
28	32	72.9	96.9	2.5	60.7	1	3.1	6.3	21.9	28.1
29	13	73.7	100	2.8	58.1	0	0.0	7.7	38.5	46.2
30	45	71.3	95.6	2.7	59.3	0	0.0	15.6	6.7	2.2
31	33	75.2	84.8	1.9	55.1	0	0.0	3.0	12.1	15.2
32	19	73.6	94.7	2.3	58.3	0	0.0	0.0	10.5	0.0
33	50	70.4	94.0	2.3	57.9	2	4.0	10.0	40.0	42.0
34	27	71.9	88.9	2.2	55.7	0	0.0	7.4	22.2	7.4
35	4	69.1	100	2.0	56.5	0	0.0	0.0	25.0	25.0
36	6	75.8	83.3	2.3	56.2	0	0.0	0.0	16.7	33.3

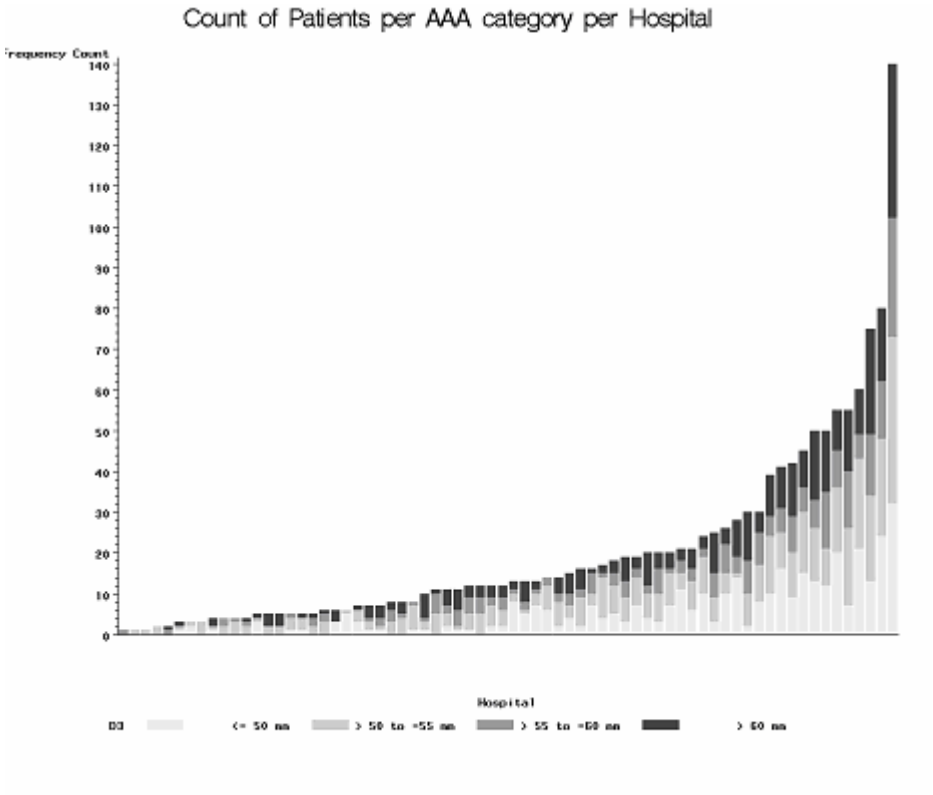
Obs	N	Age	% male	ASA	AAA	N Death Early	% Early death	% Death	% Problems at operation	% Initial Clinical Failure
37	8	69.1	100	2.4	62.2	2	25.0	25.0	12.5	12.5
38	19	68.9	100	2.4	55.1	0	0.0	0.0	5.3	5.3
39	4	76.4	100	2.5	55.8	1	25.0	25.0	25.0	50.0
40	12	74.0	100	2.3	57.6	0	0.0	8.3	25.0	8.3
41	18	74.3	94.4	2.2	53.2	0	0.0	0.0	33.3	11.1
42	14	70.2	92.9	2.1	50.9	2	14.3	21.4	28.6	35.7
43	15	73.9	100	2.3	57.4	2	13.3	20.0	26.7	26.7
44	13	73.2	100	2.5	49.8	2	15.4	15.4	15.4	23.1
45	8	75.0	100	2.8	60.9	0	0.0	12.5	0.0	12.5
46	11	73.1	90.9	2.3	58.5	1	9.1	9.1	0.0	0.0
47	4	75.8	100	2.0	53.8	0	0.0	0.0	0.0	0.0
48	1	65.2	100	1.0	60.0	0	0.0	0.0	0.0	0.0
49	24	69.7	100	1.9	53.4	0	0.0	0.0	12.5	8.3
50	1	75.5	100	3.0	52.0	1	100	100	0.0	100
51	21	71.5	90.5	2.0	54.8	0	0.0	9.5	47.6	19.0
52	5	75.5	100	2.0	58.0	0	0.0	0.0	20.0	20.0
53	15	71.9	100	3.0	62.1	1	6.7	26.7	13.3	13.3
54	10	72.7	80.0	2.2	66.5	0	0.0	0.0	30.0	0.0
55	20	73.8	95.0	2.0	53.6	2	10.0	10.0	10.0	20.0
56	1	88.0	100	2.0	55.0	0	0.0	0.0	0.0	0.0
57	11	73.5	90.9	1.8	62.9	0	0.0	0.0	45.5	27.3
58	7	73.6	100	2.6	60.4	0	0.0	0.0	14.3	14.3
59	8	75.4	100	2.1	58.9	1	12.5	25.0	50.0	37.5
60	12	73.7	100	2.7	56.4	0	0.0	16.7	0.0	16.7
61	6	69.1	100	2.2	53.6	0	0.0	0.0	33.3	16.7
62	3	74.7	100	2.0	53.3	0	0.0	0.0	66.7	33.3
63	4	76.0	75.0	1.5	57.6	0	0.0	0.0	25.0	0.0
64	6	73.3	83.3	1.7	47.8	0	0.0	0.0	16.7	0.0
65	2	68.1	100	2.0	52.0	0	0.0	0.0	0.0	0.0
66	7	76.0	85.7	2.3	60.6	0	0.0	0.0	28.6	0.0
67	8	74.3	100	2.4	52.9	0	0.0	12.5	12.5	12.5
68	5	71.4	100	2.4	56.4	0	0.0	0.0	0.0	0.0
69	2	74.6	100	2.5	61.5	0	0.0	0.0	0.0	50.0
70	5	72.6	100	3.0	60.2	0	0.0	0.0	20.0	40.0

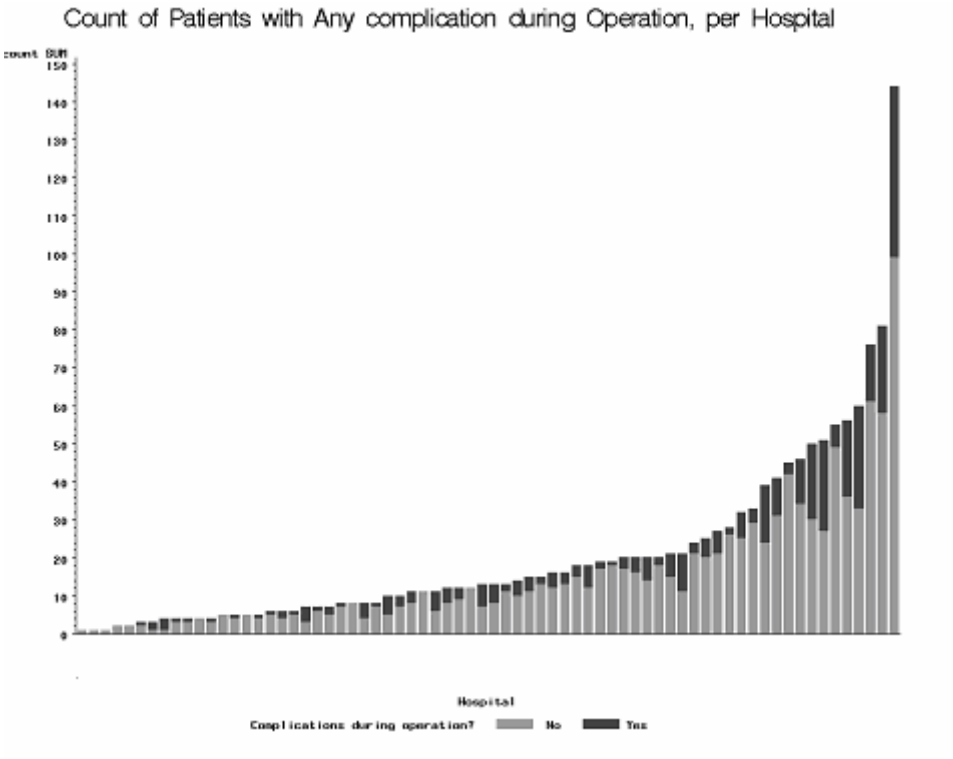
Individual Hospital Data (graphics)

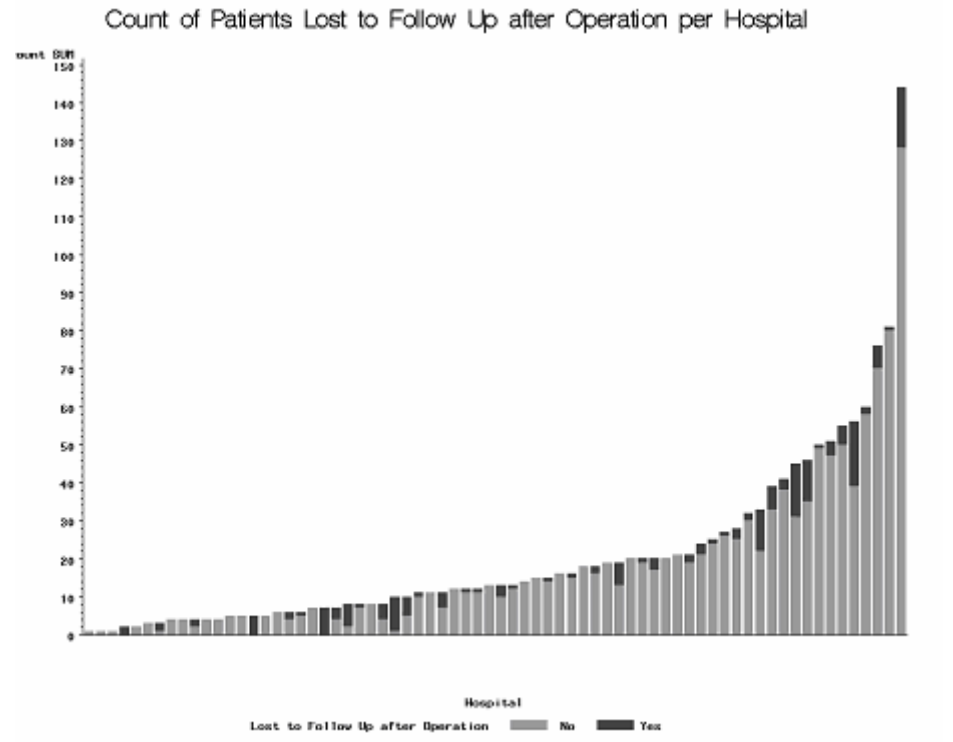





Count of Patients per ASA Category per Hospital
Hospital
ASA-class
1
2
3
4


Count of Patients per AAA category per Hospital
Frequency Count
Hospital
<= 50 mm
> 50 to <=55 mm
> 55 to <=60 mm
> 60 mm


Count of Patients with Any complication during Operation, per Hospital
count SUM
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
Hospital
Complications during operation?
No
Yes


Count of Patients Lost to Follow Up after Operation per Hospital
count SUM
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
Hospital
Lost to Follow Up after Operation
No
Yes

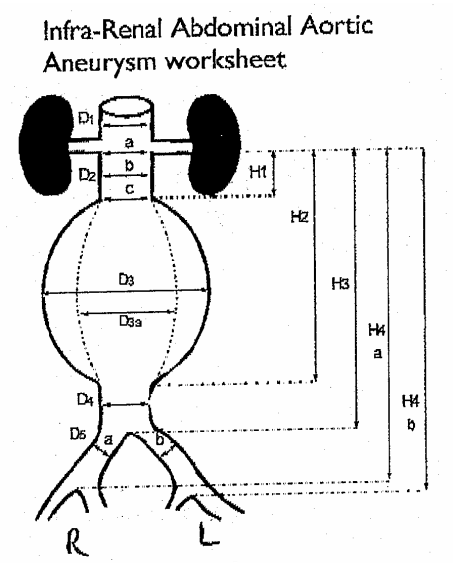
ADDITIONAL TABLES

Aortic Measurements (Pre-Operative)

Measurements (mm) of Infra-Renal Abdominal Aortic Aneurysms

Label	N	Mean	Lower Quartile	Median	Upper Quartile	Std Dev	Min	Max
D1	307	24.4	22.0	24.0	27.0	3.6	14.0	43.0
D2a	301	24.3	22.0	24.0	26.0	3.7	14.0	40.0
D2b	**1366**	**24.1**	**22.0**	**24.0**	**26.0**	**3.3**	**14.0**	**40.0**
D2c	238	25.8	23.0	25.0	28.0	5.5	11.0	53.0
D3	**1400**	**56.6**	**50.0**	**55.0**	**61.0**	**11.0**	**25.0**	**130.0**
D3a	179	35.0	29.0	35.0	39.0	9.6	15.0	90.0
D4	205	30.5	23.0	28.0	34.1	11.3	11.0	80.0
D5a	488	18.0	12.0	14.0	20.0	10.7	5.0	93.0
D5b	461	16.8	12.0	14.0	18.0	9.0	7.0	90.0
H1	**1367**	**28.9**	**20.0**	**25.0**	**35.0**	**12.9**	**2.0**	**90.0**
H2	189	109.7	98.0	110.0	123.0	23.0	35.0	190.0
H3	**1339**	**118.4**	**107.0**	**120.0**	**130.0**	**20.9**	**50.0**	**239.0**
H4a	228	156.2	140.0	157.0	172.0	27.1	81.0	230.0
H4b	215	164.3	149.0	165.0	180.0	24.5	80.0	245.0

Note: mandatory measurements are indicated in bold.



Short Term Mortality Results

Table 12.15 Counts (%) of Patients with Death, Conversion or Rupture (Definition 2: based on EUROSTAR definition)

		Early		Late		Total	
Event	N	n	%	n	%	n	%
Death	1437	**44**	**3.1**	72	5.0	116	8.1
Conversion	1437	7	0.5	9	0.6	16	1.1
Rupture	1437	0	0.0	1	0.1	1	0.1

* Definition based on the last follow up available. Early death is defined as patients not having a follow up after 1 month.

Table 12.16 Counts (%) of Patients with Death, Conversion or Rupture (Definition 3: based on exact date of event)

		Early*		Late		Total	
Event	N	n	%	n	%	n	%
Death	1437	**32**	**2.2**	84	5.8	116	8.1
Conversion	1437	8	0.6	8	0.6	16	1.1
Rupture	1437	0	0.0	1	0.1	1	0.1

* Early events defined as occurring within 30 days of date of operation (not taking into account the prolonged hospitalisation).

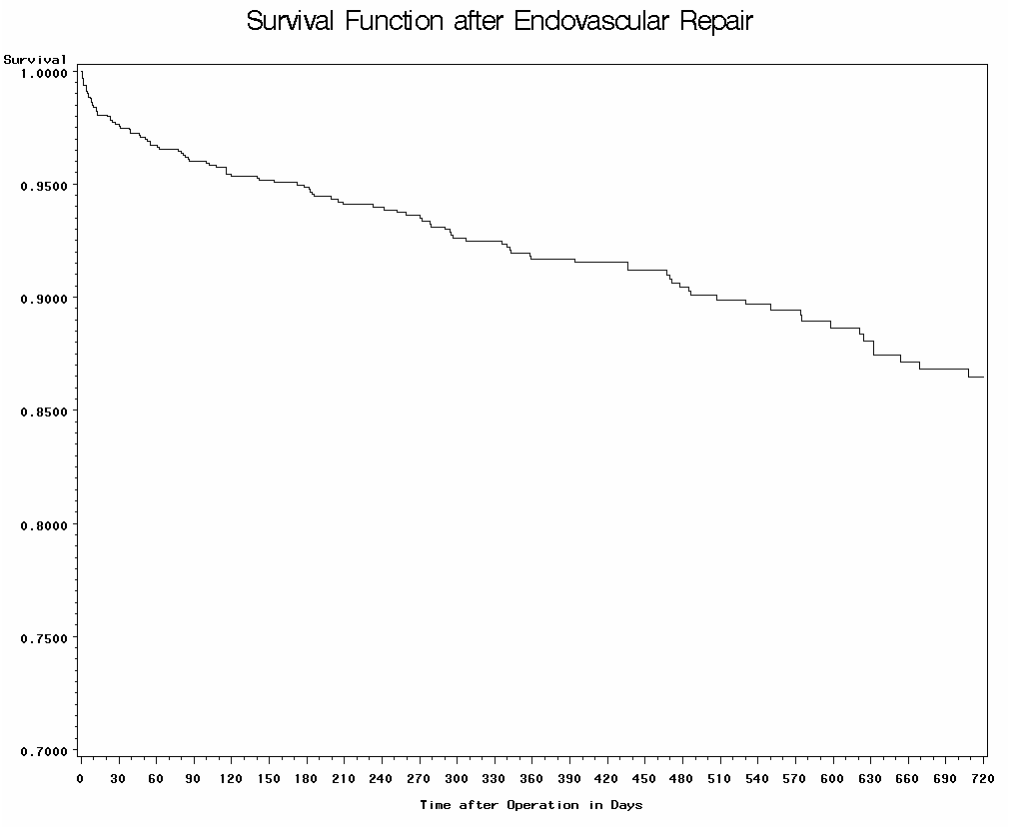
Long Term (2Y) Mortality Results

Survival Function (Freedom from Death)

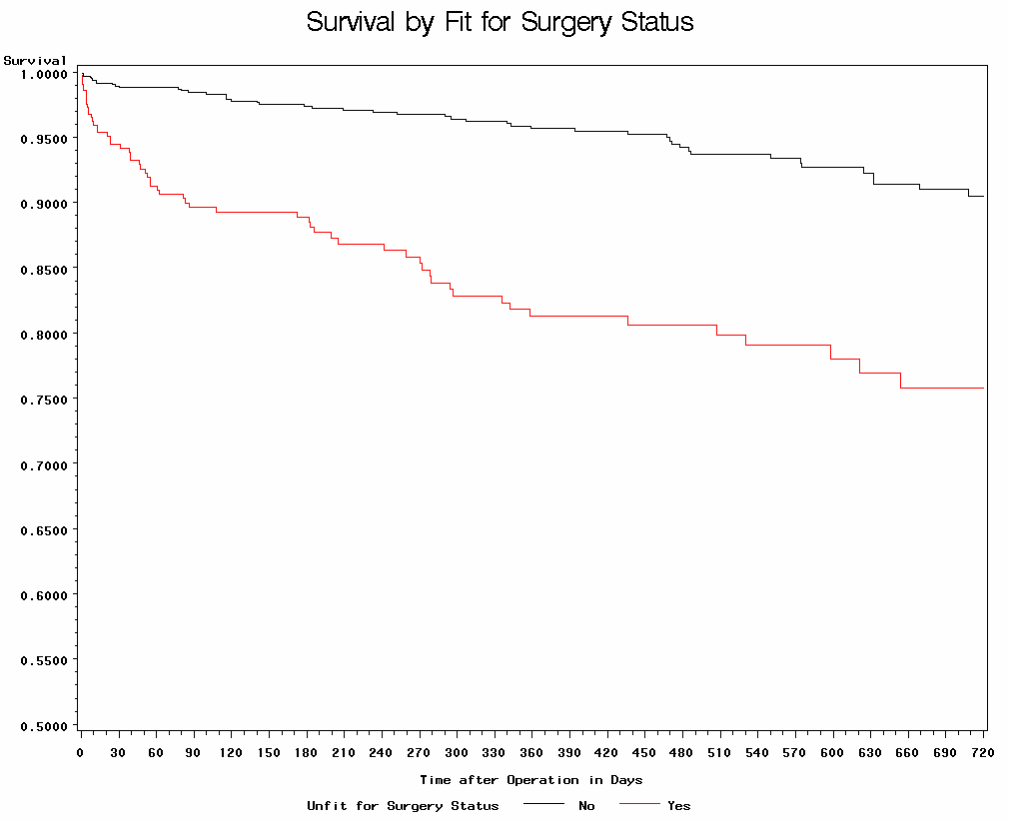
The cumulative percentage of death (taking into account the censoring) is 2.4% at 30 days, 8.3% at 1 year and 13.9% at 2 years.

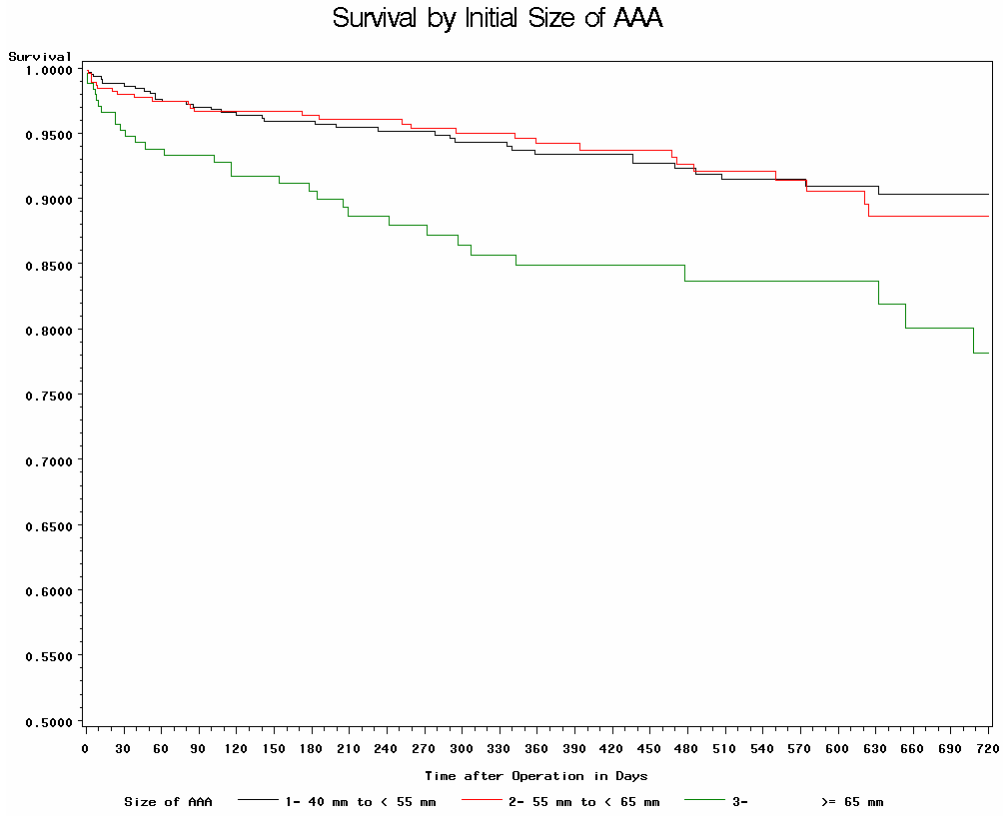
Table 12.17 Survival Function (KM) at Specific Time Points (Event = Death)

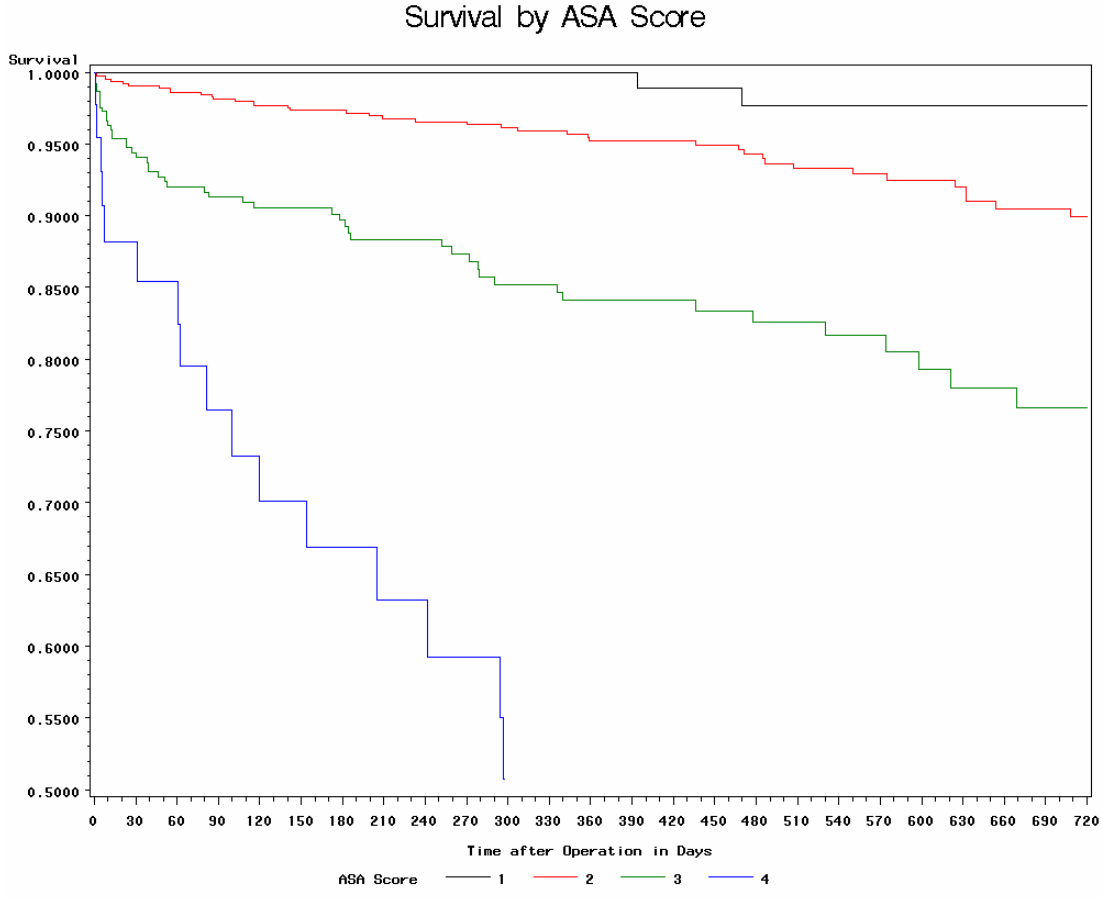
Product-Limit Survival Estimates						
Time list	TIME IN STUDY	Survival	Failure	Survival SE	Number Failed	Number Left
0.00	**0.00**	1.0000	0	0	0	1437
30.00	**30.00**	**0.9757**	**0.0243**	**0.00426**	**32**	**1178**
91.00	**86.00**	0.9601	0.0399	0.00555	50	1076
182.00	**182.00**	0.9476	0.0524	0.00647	63	921
365.00	**359.00**	0.9170	0.0830	0.00871	88	651
730.00	**728.00**	0.8604	0.1396	0.0145	111	179
1095.00	**872.00**	0.8060	0.1940	0.0287	116	28



Stratified Survival Functions




Survival by Initial Size of AAA
Survival
1.0000
0.9500
0.9000
0.8500
0.8000
0.7500
0.7000
0.6500
0.6000
0.5500
0.5000
0 30 60 90 120 150 180 210 240 270 300 330 360 390 420 450 480 510 540 570 600 630 660 690 720
Time after Operation in Days
Size of AAA
1- 40 mm to < 55 mm
2- 55 mm to < 65 mm
3- >= 65 mm


Survival by ASA Score
Survival
1.0000
0.9500
0.9000
0.8500
0.8000
0.7500
0.7000
0.6500
0.6000
0.5500
0.5000
0 30 60 90 120 150 180 210 240 270 300 330 360 390 420 450 480 510 540 570 600 630 660 690 720
Time after Operation in Days
ASA Score
1
2
3
4

APPENDIX 7: ANALYSIS OF BELGIAN CLAIMS DATA[3*]

Introduction

The population studied is the total Belgian population. The first endostents taken into account for this study were placed in May 2001. The data are complete until mid-2003.

This study will examine the placement of abdominal endostents in 720 patients. Six patients were hospitalised more than once. Only the first hospitalisation of every patient is taken into account in this report.

In most of these patients only one stent has been placed during hospitalisation. However in 29 cases two stents, and in 4 cases up to 3 stents have been placed.

The distribution of the hospitalisations over time is represented in table 1.

After June 2003, the data are clearly not complete anymore. To examine the post-operation costs, we will only consider the hospitalisations till end February 2003. By doing this, a complete follow-up of 4 months is possible.

Table 1: Number of hospitalisations recorded over time (endovascular treatment)

Month:	N:	Month:	N:	Month:	N:
01/01	0	01/02	30	01/03	22
02/01	0	02/02	17	02/03	27
03/01	0	03/02	38	03/03	36
04/01	3	04/02	24	04/03	26
05/01	46	05/02	25	05/03	21
06/01	22	06/02	41	06/03	25
07/01	19	07/02	13	07/03	15
08/01	25	08/02	15	08/03	6
09/01	22	09/02	25	09/03	3
10/01	23	10/02	32	10/03	0
11/01	32	11/02	25	11/03	0
12/01	25	12/02	37	12/03	0

3 Author and contributors are Johan Vanoverloop (IMA), Ilana Widera (IMA), Bernard Debbaut (IMA), Murielle Lona (former IMA), Patrick Galloo (IMA).

1. Population

a. Sex

663 of the 719 patients are men (92,2%). For 1 patient, information of the gender is missing.

b. Age

Because of privacy reasons, we only dispose of the year of birth of the patients. The age has thus been calculated by taking the difference between the first day of the hospitalisation and the 15th of June of the year of birth.

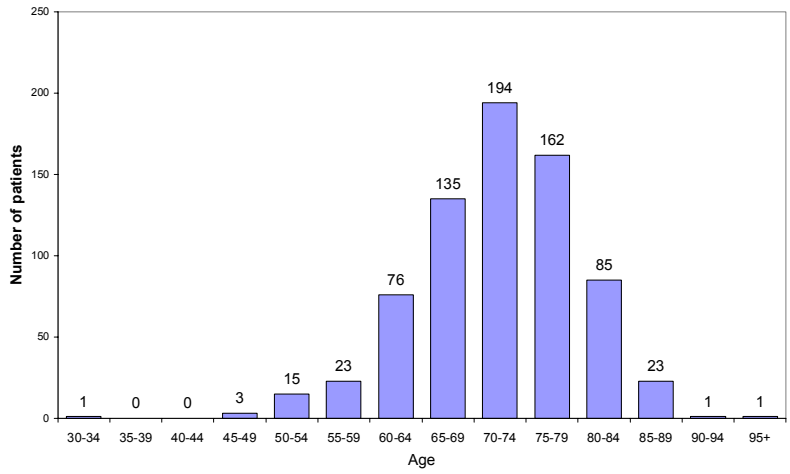
The mean age is 71,7 years (the median: 72 years). The youngest patient is 30 years old, the oldest patient is 96. Figure 1 represents the distribution of age.

c. Preferential tariff

In the Belgian system, some people have lower medical patient costs because of their personal situation (the disabled persons, poor people, ..).

25,4 % of the patients in our study are in this situation and have a so-called preferential tariff.

Figure 1: distribution of age of the patients with endostent placement



2. Length of stay

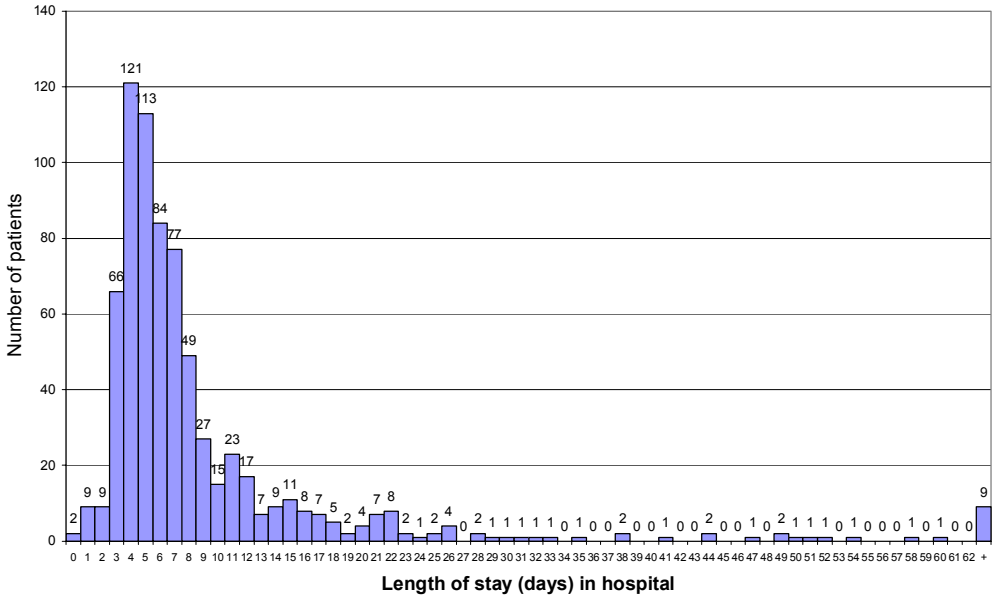
The length of stay is defined as the number of days between the beginning and the end of the hospitalisation. The mean length of stay is 9,6 days, varying between 0 and 325 days. The distribution is much skewed (figure 2). The most occurring values are 4 and 5 days. The median is 6 days.

Endostents are placed in 64 hospitals. The maximum number of placements is 84. Eight hospitals placed only 1 stent during the period under study.

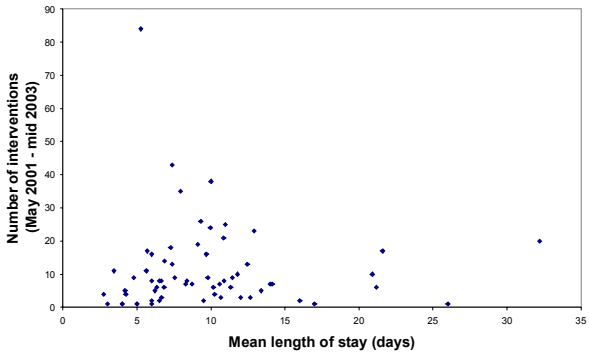
In a next step we look at the relation between the volume of a hospital during the period of study and the length of stay. Indeed, we expect a negative relationship: the more experience the hospital has in placing stents, the shorter we expect the length of stay will be.

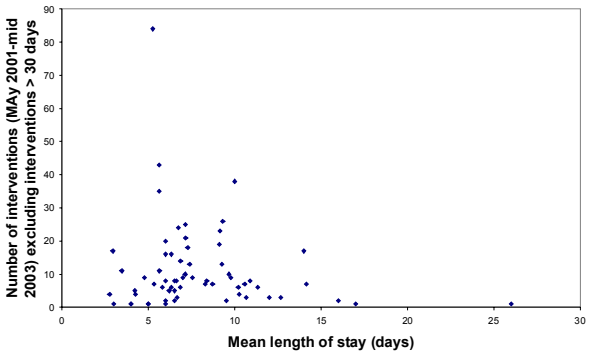
Besides the total number of hospitalisations, we also look at the hospitalisations that did not exceed a length of stay of 30 days (96% of the cases). There seems to be no linear relation between length of stay and volume (figures 3 and 4).

Figure 2: Distribution of the Length of Stay in hospital



Figures 3 and 4: average length of stay in function of the number of interventions in a hospital





3. Medical insurance cost (MI cost) of the hospitalisation

a. individual variation

There is a large variation in the MI costs (figure 5). The lowest cost is 2.864 € and the highest cost is 63.723 €. The mean MI cost amounts to 11.486 € and the median MI cost amounts to 10.360 €.

The correlation between the MI cost and the length of stay is 0,76. Figures 6 and 7 show there is a linear relationship between length of stay and MI cost. Each dot represents a hospitalisation.

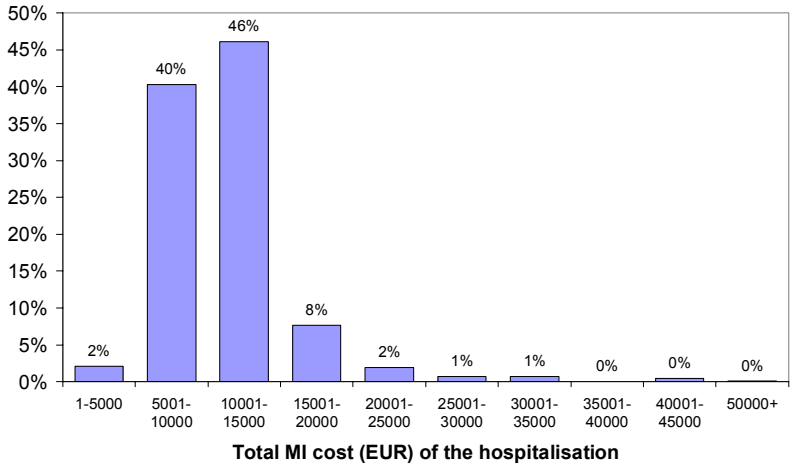
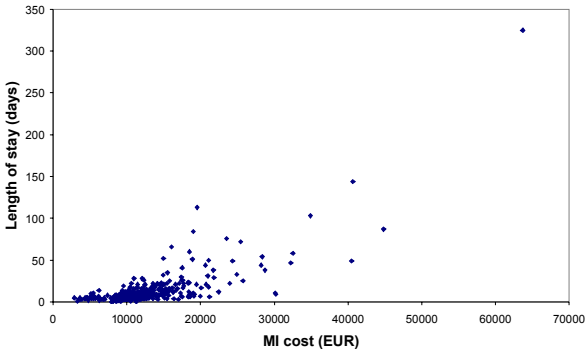
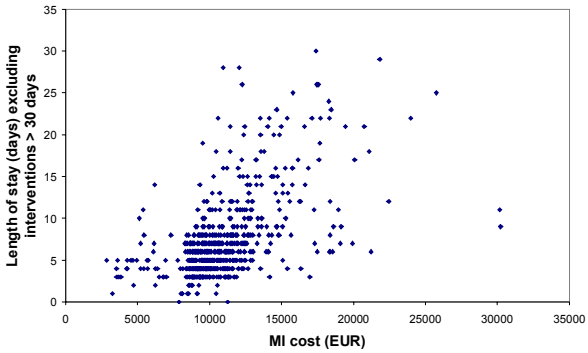


Figure 5: distribution of the total MI cost of the hospitalisation





Figures 6 and 7: Total MI cost in function of length of stay

b. interhospital variation

The lowest mean MI cost of a hospital is 6.638 €, the highest mean MI cost is 20.081 €.

The mean MI cost amounts to 11.389 €. The boxplot underneath shows the distribution of the MI cost for all hospitals, not taking into account the hospitalisations that exceeded 30 days.

Figures 9 and 10 show the relationship between the mean MI cost and the cumulative number of placements during the period of investigation. The figure on the right hand is without the hospitalisations longer than 30 days. In both figures, each dot represents a hospital.

As is the case with length of stay, there does not seem to be a negative relationship: experience in a hospital does not reduce the total MI cost.

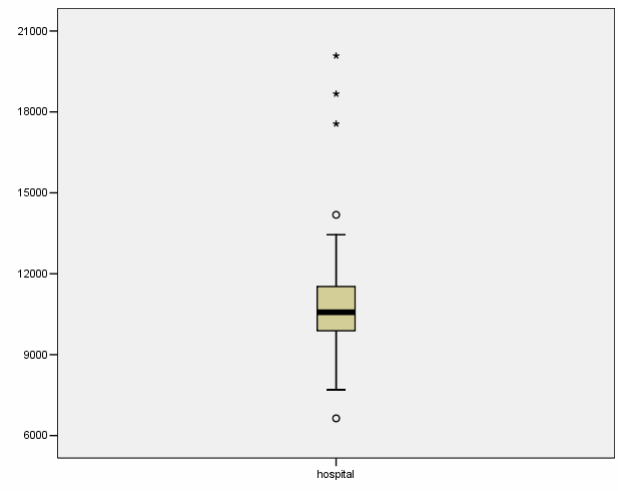
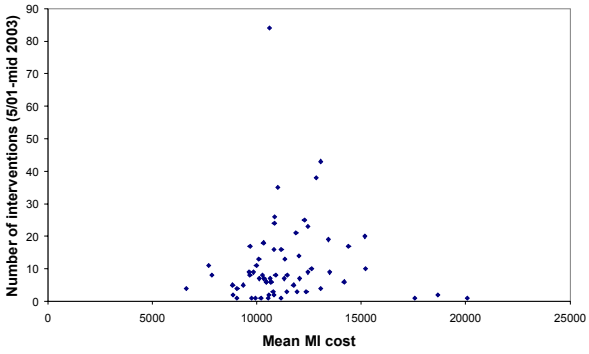
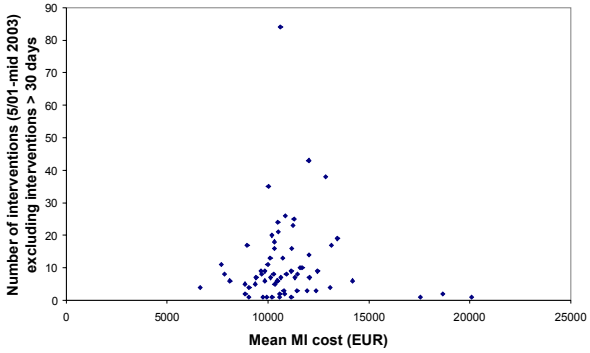


Figure 8: Boxplot of the mean MI cost per hospital, Excluding hospitalisations > 30 days





Figures 9 and 10: mean MI cost per hospital in function of the number of interventions

4. Patient cost

a. individual variation

The patient cost of an individual hospitalisation varies from 0 € to 2.414 €. The mean patient cost is 147 €, the median patient cost is 117 €.

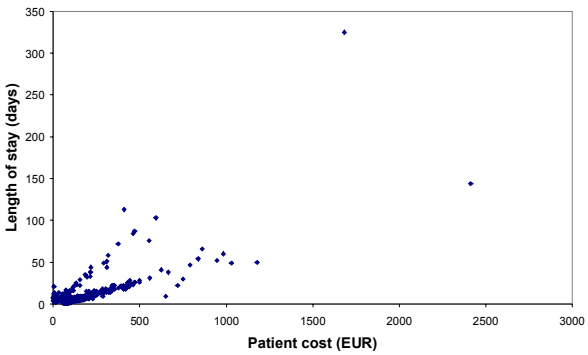
There exists a linear relationship between the patient cost and the length of stay. One can clearly distinguish 2 groups of patients: those with and those without the preferential tariff (the first group has lower patient costs). Remark also the existence of a small group with no patient costs (figures 11 and 12).

The correlation between length of stay and patient cost is 0,89 in the first group and 0,91 in the second group (excluding the hospitalisations which last longer than 30 days).

b. interhospital variation

The mean patient cost of an individual hospital varies between 18 € and 432 €. (figure 13).

Figures 11 and 12: patient cost in function of the length of stay in a hospital



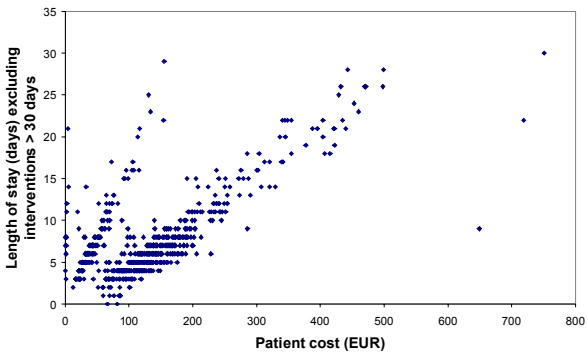


Figure 13: boxplot of the mean patient cost per hospital, Excluding hospitalisations > 30 days

5. Pre-operative costs

5.1. All MI costs 90 days before the day of the placement of the endostent.

- individual variation

The total MI cost 90 days before the day of the placement of the first endostent varies between 3 € and 51.769 €. The mean MI cost totals to 3.794 € and the median MI totals to 2.523 € (figure 14).

- interhospital variation

The mean MI cost of a hospital varies from 1.704 € to 26.034 € (figure 15).

Figure 14: distribution of the MI cost, 90 days before the placement of the endostent

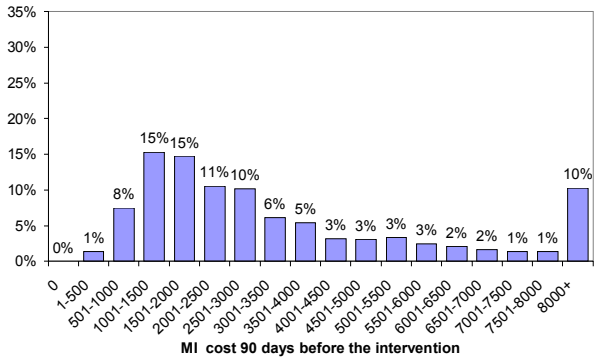
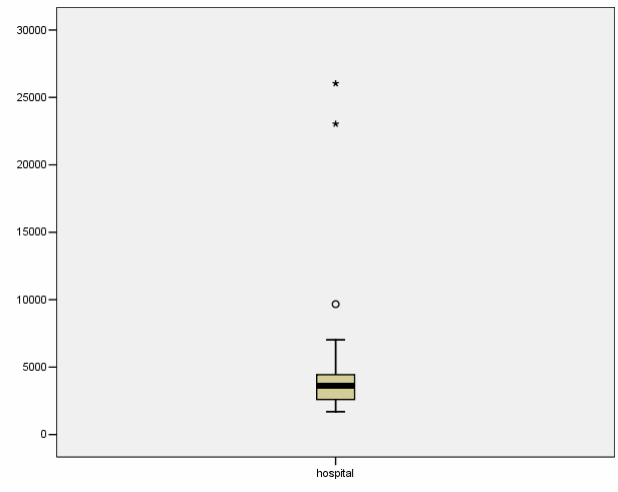


Figure 15: boxplot of the mean MI costs per hospital, 90 days before the placement of the stent.



5.2. All patient costs 90 days before the day of the placement of the endostent.

- individual variation

The patient costs, 90 days before the day of the first placement varies from 0 € to 2.805 €. The mean patient cost is 250 € and the median is 203 € (figure 16).

- interhospital variation

The variation of the mean-patient cost between the different hospitals is represented in the boxplot underneath.

Figure 16: distribution of the patient cost, 90 days before the placement of the hospitalisation

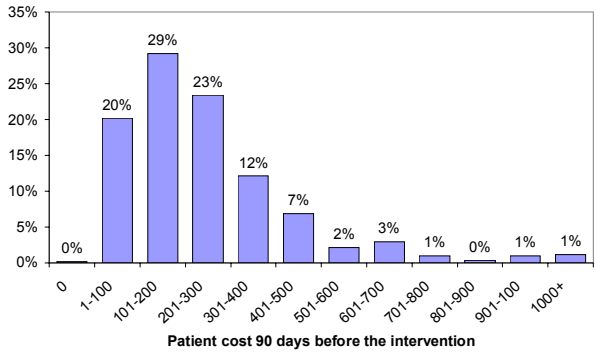
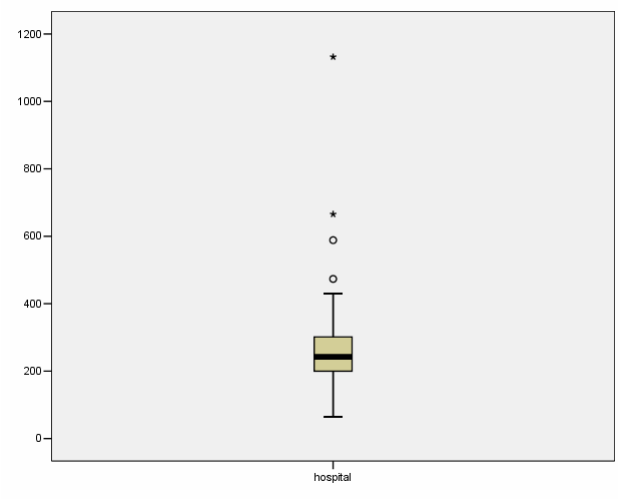


Figure 17: boxplot of the mean patient cost per hospital, 90 days before the placement of the endostent



5.3. All imaging costs, 90 days before the day of the placement of the first endostent

- individual variation

MI costs for imaging vary between 0 € and 2.868 €, with a mean value of 562 € and a median of 525 €. Three percent of the hospitalisations are characterised by high MI costs for imaging (> 1200 €).

- interhospital variation

The variation of the pre-operative MI costs for imaging between the different hospitals is shown in figure 19.

Figure 18: distribution of the MI cost for imaging, 90 days before the placement of the stent

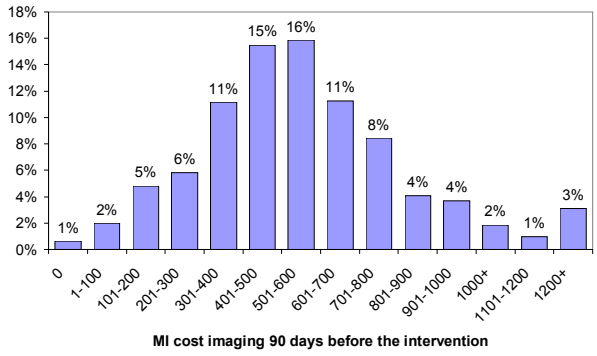
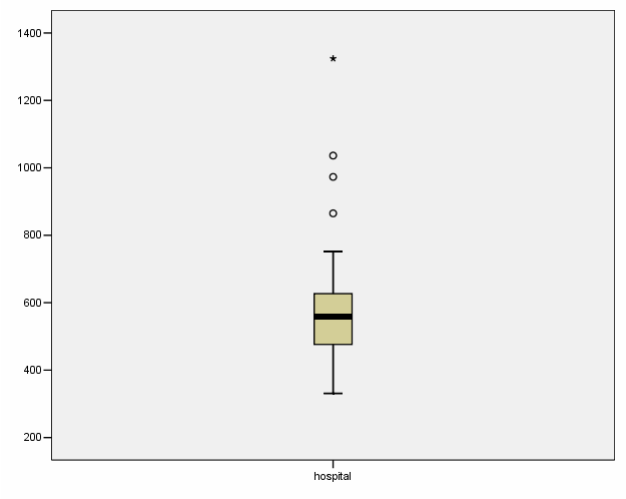


Figure 19: boxplot of the mean MI cost for imaging per hospital, 90 days before the placement of the endostent.



6. Post-operative costs

A first check-up of the patient is normally to be expected around 1 month after the intervention and a second check-up 3 months after the intervention. In order to be sure to cover these costs, we will investigate all medical costs 45 days and 120 days after the end of the hospitalisation.

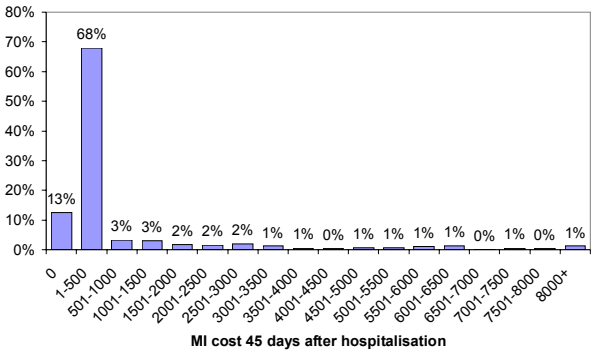
As mentioned before, only the hospitalisations which can be followed-up in time during 4 months are taken into account (583 patients).

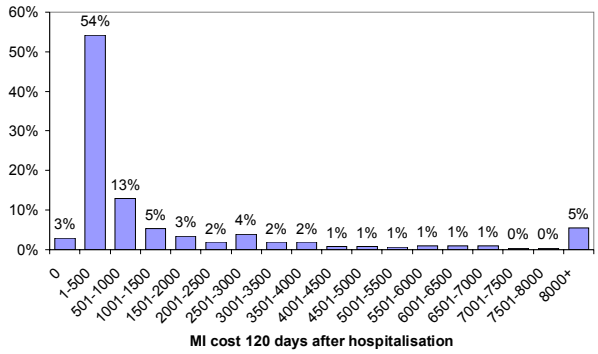
6.1 All MI costs, without the costs for medication and for visits to the GP or to specialists.

The MI costs, 120 days following the final day of the hospitalisation, vary between 0 € and 28.196 €. The MI costs after 45 days vary from 0 € to 14.981 €.

The mean MI cost aggregates to 805 € after 45 days and 1.830 € after 120 days. De medians are respectively 175 € and 420 €.

Figures 20 and 21: distribution of the MI cost, 45 and 120 days after the hospitalisation

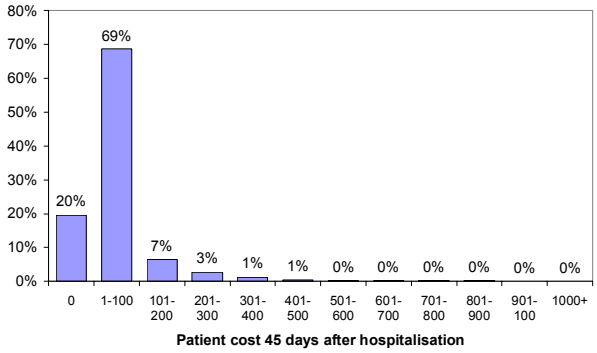


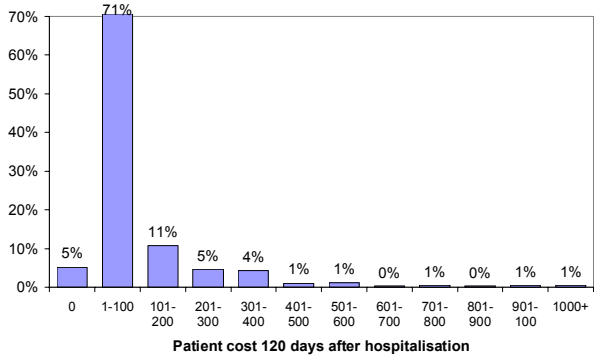


6.2. Post-operative patient cost, without the costs for medication and for visits to the GP or to specialists.

The mean patient cost, 45 days after the hospitalisation, is 41 €. After 120 days, the mean patient cost is 94 €. The medians are respectively 10 € and 29 €.

Figures 22 and 23: distribution of the patient cost, 45 and 120 days after the hospitalisation



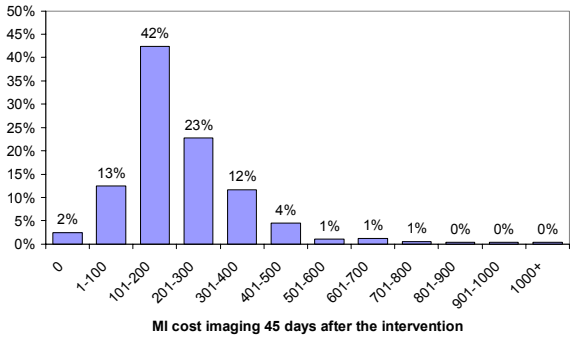


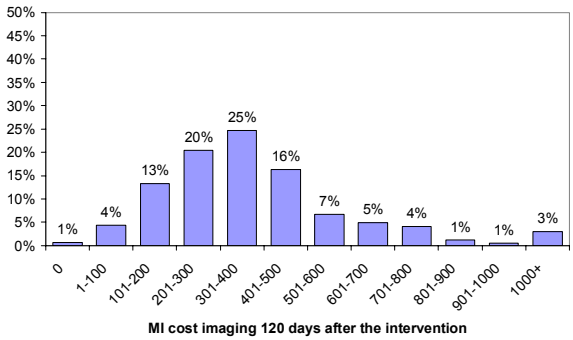
6.3. Medical cost for post-operative imaging

The distribution of the medical costs for imaging after 45 and 120 days after the placement of the endostent is represented in the figures under.

The mean medical cost for imaging is 215 € after 45 days and 383 € after 120 days (the medians are 184 € and 339 € respectively).

Figures 24 and 25: distribution of the MI cost for imaging, 45 and 120 days after hospitalisation





7. Mortality

For deceased patients, we only dispose of the year and month of death (for privacy reasons). This implies that we are not able to calculate exact mortality rates on day 0, 1, 2 etc.

Therefore we calculated the difference between the month of decease and the month of placement in order to make a life table.

Mortality data are available till 31/12/2003. The life table is represented on the next page (table 2).

There is a remarkable increase in mortality over time (table 3).

- 5/217 (2,3%, exact CI: 0,8% - 5,3%) within 3 months of the interventions started in 2001
- 13/322 (4,0%, exact CI: 2,2% - 6,8%) within 3 months of the interventions started in 2002
- 13/181 (7,2%, exact CI: 3,9% - 12,0%) within 3 months of the interventions started in 2003.

The mortality within 1 month has also increased from 1,4% in 2001 to 3,9% in 2003.

This increase is function of an increased age of the patient over time.

In 2001, the mean age was 71 years, in 2002 it was 71,5 years and in 2003 it was 73 years (the medians are 71, 72 and 74 years). The percentage of patients of 80 years and more increased from 12,0% in 2001 to 13,7% in 2002 to 22,1% in 2003.

Figure 26 shows that the first quartile, the median and the third quartile of age slowly start increasing in 2002.

No differences are found in mortality between men and women or between patients with and without preferential tariff (table 4).

Patients who deceased within 3 months are on average 3 years older, have higher total MI costs 90 days before the intervention, just like higher MI costs for medication 90 days before the intervention (table 5). The MI costs for imaging are not different for the deceased and the non deceased. High MI costs pre-operative can be considered as a proxy of higher severity of the pathology of the patient.

Mortality within 3 months is not significantly different for the several types of abdominal endostents that were used (table 6).

The proportion of the different types of endostents stays the same over time, hence the increase in mortality in 2003 cannot be caused hereby. Also, the number of hospitalisations with more than 1 type of endostents did not change over time (table 7).

Moreover the hospitals were split into 2 groups: hospitals with a high and with a low number of abdominal endostents placed (The cut-off was put on 20 endostents). There is a significantly lower mortality rate in the group of hospitals with high volume (table 8).

Table 2: Life table for Mortality after Abdominal Endostent Placement

Month:	Deceased	Censored	Effective Sample Size	Survival	Survival SE	Cumulative Failure
0	16	0	720	1.000	0	0
1	7	0	704	0.978	0.005	2.2%
2	8	0	697	0.968	0.006	3.2%
3	3	3	687.5	0.957	0.007	4.3%
4	1	6	680	0.953	0.008	4.7%
5	6	6	673	0.951	0.008	4.9%
6	5	25	651.5	0.943	0.009	5.7%
7	2	23	622.5	0.936	0.009	6.4%
8	3	27	595.5	0.933	0.009	6.7%
9	1	32	563	0.928	0.010	7.2%
10	2	28	532	0.926	0.010	7.4%
11	1	22	505	0.923	0.010	7.7%
12	2	36	475	0.921	0.010	7.9%

Table 3: Mortality within one month and within 3 months in function of the year of hospitalisation.

	Year of placement:											
	2001				2002				2003			
Deceased:	N	%	LCL	UCL	N	%	LCL	UCL	N	%	LCL	UCL
Month 0	3	1,4	0,3	2,9	6	1,9	0,7	4,0	7	3,9	1,6	7,8
M. 0,1 or 2	5	2,3	0,8	5,3	13	4,0	2,2	6,8	13	7,2	3,9	12,0
Denominator	217				322				181			

LCL = lower confidence limit, UCL = upper confidence limit

Figure 26: Median and quartile trace lines for age over time.

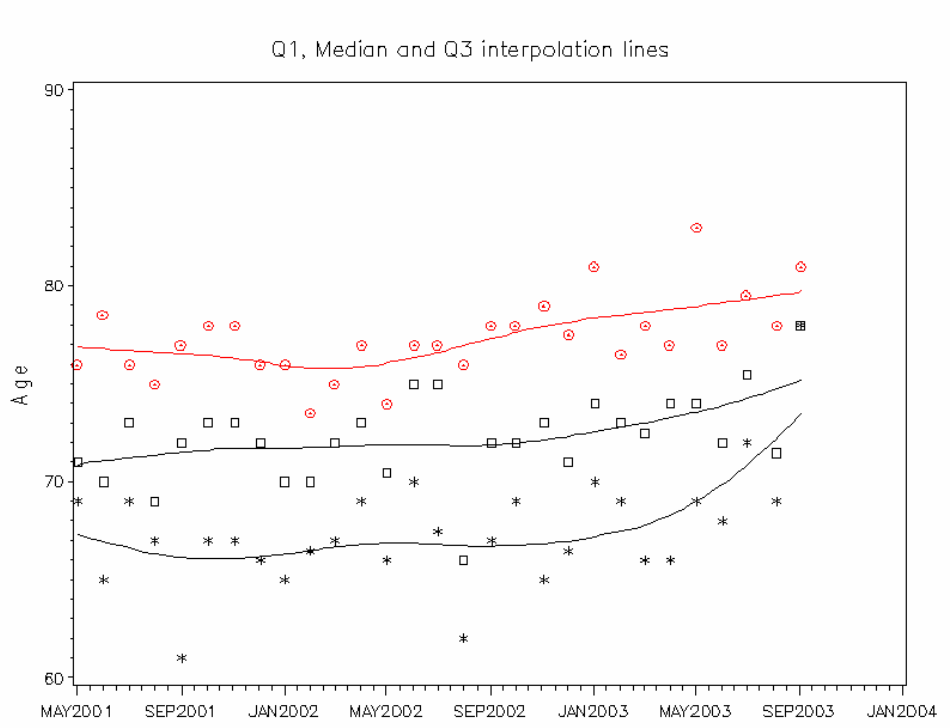


Table 4: Relationship between mortality and sex, preferential tariff and hospitalisation before the intervention.

	Number of patients	Deceased < 3 months	Odds-ratio (CI)
Men	663	4,4%	1
Women	56	3,6%	0,8 (not sign.)
Without preferential tariff	597	4,5%	1
With preferential tariff	195	5,6%	1,7 (not sign.)
With hospitalisation 90 days before	572	3,3%	1
Without hospitalisation 90 days before	148	8,1%	2,6 (1,2-5,4)

CI = confidence interval

Table 5: Deceased versus non-deceased: mean age, mean total MI cost and mean MI cost for medication and imaging 90 days before the intervention

	Deceased < 3 months	Not deceased < 3 months
Mean age	76 years	71,5 years
Mean total MI cost, 90 days before the intervention	4.592 €	3.758 €
Mean MI cost for medication, 90 days before the intervention	323 €	195 €
Mean MI cost for imaging, 90 days before the intervention	469 €	566 €

Table 6: Mortality in function of endostent type used.

Endostent type (nomenclature)	Number	% deceased < 3 months	95% exact LCL	95% exact UCL
687061	461	2,8%	1,5%	4,8%
687083	193	6,7%	3,6%	11,2%
687105	26	11,5%	2,5%	30,2%
687120	19	10,5%	1,3%	33,1%
687142	27	11,1%	2,4%	29,2%
687164	8	12,5%	0,3%	52,7%
687186	7	0%		

Table 7: Endostent type used in function of the year of hospitalisation

Endostent type (nomenclature)	Number	In 2001	In 2002	In 2003
687061	461	56,6%	57,5%	56,7%
687083	193	19,5%	25,7%	26,3%
687105	26	3,5%	2,2%	4,6%
687120	19	3,1%	0,8%	4,1%
687142	27	3,9%	3,1%	3,1%
687164	8	2,0%	0,8%	0%
687186	7	0%	1,7%	0,5%
% hospitalisations with > 1 endostent		3,7%	2,2%	2,2%

Table 8: Mortality in function of the number of abdominal endostents placed in a hospital

Hospital: number of abdominal endostents	number	Deceased < 3 months	Odds-ratio (CI)
< 20	381	5,8%	1
20 and more	339	2,7%	0,45 (0,20-0,98)

In logistic regression, next variables turn out to be significant in explaining mortality within 3 months.

- Age (LFT)
- Medical cost for medication 90 before the intervention (DMEDPRE, units in 100 EUR)
- Presence of a hospitalisation, 3 months before the intervention (NZKH, 0=absence 1=presence)
- An intervention with endostent type 687061 (687061, 0=no 1=yes)
- The volume of the hospital (NEP, continuous variable).

Table 9: estimates and odds-ratios of the logistic regression

	Estimate	Standard error	Significance level	Odds-Ratio	Lower CL	Upper CL
LFT	0,077	0,028	0,005	1,08	1,02	1,14
DMEDPRE	0,153	0,051	0,003	1,17	1,05	1,29
NZKH	-0,785	0,402	0,051	0,46	0,21	1,00
687061	-0,902	0,393	0,022	0,41	0,19	0,88
NEP	-0,035	0,015	0,022	0,97	0,94	0,99

The R^2 of this model is only 0,05 (max-rescaled: 0,16).

The volume of the hospital is also significant when it is put in the regression as a binary variable (p-value = 0.046).

However, leaving out the hospital with the maximum number of endostents, the volume of the hospital is not significant anymore (Still a p-value of 0,10 remains).

8. Rehospitalisations

Hospitalisations were followed up during 3 months.

Only one patient was rehospitalised within 3 months (hospitalisation in open surgery).

9. Complications

Hospitalizations are followed during 90 days, starting at the day of the stent placement. All patients had medical costs after the placement. The denominator is thus the number of all the hospitalisations till end march 2003 (N=622).

Possible complications are: complications of the lung, digestive complications and complications of the kidneys. For the placement of classic stents and vascular complications, the follow-up started the day after the endostent placement, since it is difficult to consider their presence the day of the intervention as a complication.

- Vascular complications: 35 patients (5,6%, exact CI: 4,0% - 7,7%)

Two of the 35 patients with vascular complications deceased within 3 months (5,7%, exact CI: 0,7% - 19,2%).

- Complications of the lung: 29 patients (4,7%, exact CI: 3,1% - 6,6%)

Three of the 29 patients with complications of the lung deceased within 3 months (10,3%, exact CI: 2,2% - 27,4%).

- Digestive complications: 18 patients (2,9%, exact CI: 1,7% - 4,5%)

Two of the 18 patients with digestive complications deceased within 3 months (11,1%, exact CI: 1,4% - 34,7%).

- Complications of the kidneys : 8 patients (1,3%, exact CI: 0,6% - 2,5%)

Five patients had already hemodialysis before the intervention. In this situation, it cannot be considered as a complication of the intervention. Of these 5 patients, one deceased within 3 months.

Eight other patients with hemodialysis however did not receive hemodialysis before the intervention. Three of these 8 patients deceased within 3 months (37,5%, exact CI: 8,5% - 75,5%).

- Classic stents: 0 patients

There were no patients with this kind of complications within 3 months (they were only found in the group with thoracal endostents).

Tables 10 to 14 describe the definitions of the different types of complications used above in terms of nomenclature.

Table 10: Definition of vascular complications

Dilatation – percutaneous	589050	589061
Endovascular catheters – recanalisation – vascular	589175	589186
Endovascular percutaneous dilatation – artery	589094	589105
Revascularisation – with graft	235093	235104
Revascularisation – bypass	235115	235126
Embolectomy – thrombectomy	235130	235141

Table 11: Definition of lung complications

Scintigraphy of the lung	442396	442400
	442411	442422
	442455	442466
	442492	442503

Table 12: Definition of digestive complications

Left colonoscopy	473130	473141
Total colonoscopy	473174	473185
Jejunoscopy	473093	473104
Exploratory laparotomy	243633	243644
Total colectomy	243036	243040
Segmentary colectomy	243051	243062
Idem with colostomy	243073	243084
Segmentary resection of the small bowel	243235	243246

Table 13: Definition of complications of the kidneys

Hemodialysis	470466	
	470470	470481
	470492	470503

Table 14: Definition of classic stents

Classic stents	613550-613686
	614316-614342
	613771-613826

10. Surgical acts being charged in case of endostent placement

The following table describes the percentages of the surgical acts were used during the endostent placements (more than 1 act is possible during an intervention).

The combinations of the different acts are represented in the table on the next page.

(e.g. in 67,2% of the hospitalisations, one act with number 237075-237086 and one act with number 589094-589105 has been charged).

Table 15: Presence of Surgical Acts during Endostent Placement

Nomenclature	Percent
237031-237042	5,0 %
237053-237064	1,1 %
237075-237086	77,0 %
237090-237101	1,1 %
589094-589105	71,9 %
236014-236025	4,6 %
236051-236062	0,7 %
236073-236084	0 %
236095-236106	0,1 %
589050-589061	21,7 %
589072-589083	17,1 %

Table 16: Presence of combined surgical acts during endostent placement

%	237031	237053	237075	237090	589094	236014	236051	589050	589072
67.2	0	0	1	0	1	0	0	0	0
9.2	0	0	1	0	0	0	0	1	1
4.4	0	0	0	0	0	0	0	1	1
3.6	1	0	0	0	1	0	0	0	0
3.5	0	0	1	0	0	0	0	0	0
2.2	0	0	1	0	0	0	0	1	0
1.5	0	0	0	0	0	0	0	1	0
1.3	0	0	0	0	0	0	0	0	0
1.0	0	0	1	0	0	0	0	0	1
1.0	0	0	0	0	1	0	0	0	0
0.8	0	0	1	0	1	0	0	1	1
0.6	1	0	0	0	0	0	0	1	1
0.4	0	0	1	0	1	0	0	1	0
0.4	0	1	0	0	1	0	0	0	0
0.4	0	1	0	0	0	0	0	1	0
0.4	1	0	0	0	0	0	0	1	0
0.3	0	0	1	1	1	0	0	0	0
0.3	0	0	0	0	1	1	0	0	0
0.3	0	0	0	1	1	0	0	0	0
0.3	1	0	1	0	1	0	0	0	0
0.1	0	0	1	0	1	0	0	0	1
0.1	0	0	1	1	0	0	0	0	0
0.1	0	0	0	0	1	0	0	1	0
0.1	0	0	0	0	1	0	1	0	0
0.1	0	0	0	1	0	0	0	0	0
0.1	0	1	0	0	0	0	0	1	1
0.1	1	0	0	0	0	0	0	0	0

11. Type of endostents being used

The table underneath shows the proportion of the different types of endostents that have been used (more than 1 type for a single intervention is possible).

The columns on the right-hand side show the mean and median MI cost of an intervention for each. The combinations are shown in table 18.

Table 17: Presence of different types of endostents and MI cost of the hospitalisation

Nomenclature	Percent	Mean MI cost	Median MI cost
687061	64,0 %	10.917 €	9.797 €
687083	26,8 %	13.383 €	11.803 €
687105	3,6 %	13.027 €	10.720 €
687120	2,6 %	14.094 €	13.640 €
687142	3,8 %	8.715 €	6.149 €
687164	1,1 %	10.090 €	10.438 €
687186	1.0 %	7.684 €	7.322 €

Table 18: Presence of combined endostent types

%	687061	687083	687105	687120	687142	687164	687186
61.9	1	0	0	0	0	0	0
25.6	0	1	0	0	0	0	0
3.3	0	0	1	0	0	0	0
2.6	0	0	0	1	0	0	0
2.2	0	0	0	0	1	0	0
1.0	0	0	0	0	0	0	1
1.0	1	0	0	0	1	0	0
1.0	1	1	0	0	0	0	0
0.7	0	0	0	0	0	1	0
0.3	0	1	0	0	1	0	0
0.1	0	0	1	0	0	1	0
0.1	0	0	1	0	1	1	0
0.1	1	0	0	0	1	1	0

12. Description of Codes

Codes for Endovascular Repair

Code	Dutch	French
687061	Endoprothesen : bifurcatie-endoprothese met contralaterale poot	Endoprothèses : endoprothèse de la bifurcation avec segment contralatéral
687083	Endoprothesen : bifurcatie-endoprothese met contralaterale poot en iliacale en/of aorta-extensies	Endoprothèses : endoprothèse de la bifurcation avec segment contralatéral et extensions iliaques et/ ou aortiques
687105	Endoprothesen : aorta-uni iliacale endoprothese met occlusieplug	Endoprothèses : endoprothèse aorto-iliaque ipsilatérale avec bouchon d'occlusion
687120	Endoprothesen : aorta-uni iliacale endoprothese met occlusieplug en iliacale en/of aorta-extenties	Endoprothèses : endoprothèse aorto-iliaque ipsilatérale avec bouchon d'occlusion et extensions iliaques
687142	Endoprothesen : endoprothese , bedoeld als extensie ter hoogte van de arteria iliaca ter behandeling van een persisterend 'endoleak' op een aorta-endoprothese	Endoprothèses : endoprothèse servant d'extension au niveau de l'artère iliaque pour le traitement d'un 'endoleak' persistant à une endoprothèse aortique
687164	Endoprothesen : Endoprothese, bedoeld als extensie ter hoogte van de abdominale aorta ter behandeling van een persisterend 'endoleak' op een orta-endoprothese	Endoprothèses : Endoprothèse servant d'extension au niveau de l'aorte abdominale pour le traitement d'un 'endoleak' persistant à une endoprothèse aortique
687186	Endoprothesen : rechte abdominale aortaprothese	Endoprothèses : prothèse aortique abdominale droite

Codes for Open Repair

Code	Dutch	French
237031-237042	Heelkunde - Verstrekkingen die tot het specialisme heelkunde (D) behoren - Verstrekkingen inzake heelkunde op de bloedvaten - Slagaders van het abdomen : Heelkunde op de aortabifurcatie onder de nierslagaders : resectie van de aortabifurcatie, tweezijdige intra-abdominale pontages, tweezijdige iliacale endarteriëctomieën	Chirurgie - Prestations relevant de la spécialité en chirurgie (D) - Prestations de chirurgie des vaisseaux - Artères de l'abdomen : Chirurgie du carrefour aortique en dessous des artères rénales : résection du carrefour aortique, pontages intra-abdominaux bilatéraux, endartérectomies illiaques bilatérales
237053-237064	Heelkunde - Verstrekkingen die tot het specialisme heelkunde (D) behoren - Verstrekkingen inzake heelkunde op de bloedvaten - Slagaders van het abdomen : Heelkunde op de aortabifurcatie onder de nierslagaders : resectie van de aortabifurcatie, tweezijdige intra-abdominale pontages, tweezijdige iliacale endarteriëctomieën, geassocieerd met een andere vasculaire reconstructie, met uitzondering van de iliacale (bij voorbeeld : mesenteriale, renale of femorale revascularisatie)	Chirurgie - Prestations relevant de la spécialité en chirurgie (D) - Prestations de chirurgie des vaisseaux - Artères de l'abdomen : Chirurgie du carrefour aortique en dessous des artères rénales : résection du carrefour aortique, pontages intra-abdominaux bilatéraux, endartérectomies illiaques bilatérales, associées à une autre reconstruction vasculaire, à l'exception des illiaques (par exemple : revascularisation mésentérique, rénale ou fémorale)
237075-237086	Heelkunde - Verstrekkingen die tot het specialisme heelkunde (D) behoren - Verstrekkingen inzake heelkunde op de bloedvaten - Slagaders van het abdomen : Heelkunde op de aortabifurcatie onder de nierslagaders : resectie van de aortabifurcatie, tweezijdige intra-abdominale pontages, tweezijdige iliacale endarteriëctomieën, geassocieerd met verscheidene vasculaire reconstructies, met uitzondering van de iliacale	Chirurgie - Prestations relevant de la spécialité en chirurgie (D) - Prestations de chirurgie des vaisseaux - Artères de l'abdomen : Chirurgie du carrefour aortique en dessous des artères rénales : résection du carrefour aortique, pontages intra-abdominaux bilatéraux, endartérectomies illiaques bilatérales, associées à une reconstruction vasculaire multiple, illiaque exceptée
237090-237101	Heelkunde - Verstrekkingen die tot het specialisme heelkunde (D) behoren - Verstrekkingen inzake heelkunde op de bloedvaten - Slagaders van het abdomen : Revascularisatie van één enkele abdominale slagader door endarteriëctomie, endoaneurysmorrhafie, pontage of resectie met enten of anastomose	Chirurgie - Prestations relevant de la spécialité en chirurgie (D) - Prestations de chirurgie des vaisseaux - Artères de l'abdomen : Revascularisation d'une seule artère abdominale par endartérectomie, endoanévrismorraphie, pontage ou résection avec greffe ou anastomose

APPENDIX 8: METHODOLOGY FOR COUPLING EUROSTAR DATA TO CLAIMS DATA

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Bewerking op de gegevens

In de IMA-dataset werden de thoracale endoprothesen (nomenclatuur 687201) verwijderd. Het totale aantal patiënten bedraagt 720. De Eurostar dataset werd beperkt tot dezelfde periode als de IMA-dataset (april 2001 tot en met september 2003). Daardoor blijven 1116 patiënten in deze set.

Omdat in de IMA-dataset de geboortedatum op 15 juni van elk jaar werd geplaatst (anonomisatiestap), werd uit deze dataset enkel het geboortejaar weerhouden. De eventuele datum van overlijden werd op de 15e van de maand van overlijden geplaatst.

Beschrijvende resultaten

Unieke observaties

Er wordt gekeken of de combinaties van mogelijke koppelingsvariabelen (Tabel 1), per dataset, uniek zijn.

Tabel 1 Koppelingsvariabelen

Nr	Naam
1	Ziekenhuis
2	Geslacht
3	Geboortejaar
4	Datum van de ingreep
5	Datum opname (eerste facturatie)
6	Datum ontslag (laatste facturatie)

Als koppelingsvariabele zou ook de maand en het jaar van overlijden, die, wanneer in beide sets aanwezig, gebruikt kunnen worden, maar dit is niet nodig gebleken. Na december 2003 zijn geen overlijdens meer geregistreerd in de IMA-dataset.

De volgende resultaten worden bekomen :

Tabel 2 Uniciteit van een reeks van koppelingsvariabelen

Variabelen	Dubbels in de dataset	
	IMA	*Eurostar*
1,2,3	143	290
1,2,3,4	4	6
1,2,3,4,5	2	6
1,2,3,4,5,6	0	3
2,3,4,5,6	1	7

Correctheid ziekenhuis in de registratie

De ziekenhuizen in de EUROstar registratie en die waar de ingreep werd uitgevoerd (IMA) zijn niet altijd dezelfde. Voor 72 patiënten in 6 ziekenhuizen uit de IMA-dataset wordt het ziekenhuis van de ingreep niet teruggevonden als een ziekenhuis in de EUROstar registratie. Het ziet er dus naar uit dat in de EUROstar registratie veeleer het verblijfsziekenhuis van de patiënt werd opgegeven i.p.v. het prestatieziekenhuis. Zo valt op te merken dat de Eurostar registratie zelfs psychiatrische ziekenhuizen bevat (62 patiënten), waar deze ingreep onmogelijk kan hebben plaats gehad. Vandaar dat ook de uniciteit van de observaties is onderzocht zonder het ziekenhuis (variabele 1, zie tabel 2).

Koppelingsprocedure

De koppeling gebeurt gefaseerd. Het eerste deel wordt uitgevoerd op twee datasets die enkel de koppelgegevens bevatten en de patiëntcodes van de IMA en EUROstar-datasets. Deze datasets zijn uitgebreid met de provincie-code van het ziekenhuis. Eerst worden observaties geselecteerd waarvan de koppelingsvariabelen het sterkst overeenkomen (Tabel 3).

Tabel 3 Koppelingsprocedure en voorwaarden per variabele

		Fase						
Nr	Naam	1	2	3	4	5	6	7
1	Ziekenhuis	=	=	=	=	=	p	p
2	Geslacht	=	=	=	=	=	=	=
3	Geboortejaar	=	=	=	=	=	=	=
4	Datum ingreep	=	=	±1*	±1*	±1*	=	±1*
5	Datum opname	=	=	±1*	±1*	±30*	±1*	±30*
6	Datum ontslag	=	=	±1*	±30*	±30*	±1*	±30*
x	Leeftijd	=						
Aantal koppelingen		136	139	148	60	57	54	12
Niet-unieke		0	0	0	1	0	0	0

=: gelijke waarden, p: postcode, *: tolerantie op de koppelingswaarde

Tijdens de eerste fase wordt ook de leeftijd meegenomen om unieke combinaties te vinden. Vanaf de derde fase wordt een verschil toegelaten tussen de datums van ontslag, opname en interventie. Dit verschil neemt toe van maximaal 1 dag tot maximaal 1 maand (30 dagen). De laatste twee fasen maken niet meer gebruik van de ziekenhuiscode, maar van de provincie-code die aangeeft in welke provincie het ziekenhuis zich bevindt. Het weglaten van het ziekenhuis kan namelijk tot gevolg hebben dat patiënten met dezelfde karakteristieken, maar behandeld in duidelijk geografisch gescheiden ziekenhuizen toch met elkaar gekoppeld zouden worden. Door de koppeling te beperken tot ziekenhuizen uit dezelfde provincie, wordt dit vermeden. Uiteindelijk worden zo toch nog 66 patiënten teruggevonden, waaronder een groot aantal uit de psychiatrische instellingen.

Met de hier geschetste procedure is er maar 1 niet-unieke koppeling in fase 4. Hier worden twee Eurostar-observaties gekoppeld aan 1 IMA-observatie. Vermits ook door inspectie van de koppelgegevens niet kan uitgemaakt worden welke van de twee de beste koppeling oplevert (ze verschillen enkel in ontslagdatum), wordt deze observatie geweerd. Het totaal aantal gekoppelde observaties wordt dan 604 op een totaal van 720 observaties in de IMA-dataset. Het koppelingspercentage bedraagt 83,9%.

Het tweede deel van de koppeling bestaat erin om de volledige oorspronkelijke datasets te koppelen. Dit gebeurt door de lijst van gekoppelde observaties die in het eerste deel werd opgesteld door middel van hun respectievelijke patiëntencodes samen te brengen in 1 dataset. De IMA-gegevens worden als determinerend genomen voor de koppelingsvariabele "ziekenhuis". Tegelijkertijd worden de ziekenhuisidentificaties en patiëntcodes geanonimiseerd.

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Wettelijk depot : D/2005/10.273/32

KCE reports

1. Effectiviteit en kosten-effectiviteit van behandelingen voor rookstop. D/2004/10.273/1.
2. Studie naar de mogelijke kosten van een eventuele wijziging van de rechtsregels inzake medische aansprakelijkheid (fase 1). D/2004/10.273/2.
3. Antibioticagebruik in ziekenhuizen bij acute pyelonefritis. D/2004/10.273/5.
4. Leukoreductie. Een mogelijke maatregel in het kader van een nationaal beleid voor bloedtransfusieveiligheid. D/2004/10.273/7.
5. Het preoperatief onderzoek. D/2004/10.273/9.
6. Validatie van het rapport van de Onderzoekscommissie over de onderfinanciering van de ziekenhuizen. D/2004/10.273/11.
7. Nationale richtlijn prenatale zorg. Een basis voor een klinisch pad voor de opvolging van zwangerschappen. D/2004/10.273/13.
8. Financieringssystemen van ziekenhuisgeneesmiddelen: een beschrijvende studie van een aantal Europese landen en Canada. D/2004/10.273/15.
9. Feedback: onderzoek naar de impact en barrières bij implementatie – Onderzoeksrapport: deel 1. D/2005/10.273/01.
10. De kost van tandprothesen. D/2005/10.273/03.
11. Borstkankerscreening. D/2005/10.273/05.
12. Studie naar een alternatieve financiering van bloed en labiele bloedderivaten in de ziekenhuizen. D/2005/10.273/07.
13. Endovasculaire behandeling van Carotisstenose. D/2005/10.273/09.
14. Variaties in de ziekenhuispraktijk bij acuut myocardinfarct in België. D/2005/10.273/11.
15. Evolutie van de uitgaven voor gezondheidszorg. D/2005/10.273/13.
16. Studie naar de mogelijke kosten van een eventuele wijziging van de rechtsregels inzake medische aansprakelijkheid. Fase II: ontwikkeling van een actuarieel model en eerste schattingen. D/2005/10.273/15.
17. Evaluatie van de referentiebedragen. D/2005/10.273/17.
18. Prospectief bepalen van de honoraria van ziekenhuisartsen op basis van klinische paden en guidelines: makkelijker gezegd dan gedaan.. D/2005/10.273/19.
19. Evaluatie van forfaitaire persoonlijk bijdrage op het gebruik van spoedgevallendienst. D/2005/10.273/21.
20. HTA Moleculaire Diagnostiek in België. D/2005/10.273/23, D/2005/10.273/25.
21. HTA Stomamateriaal in België. D/2005/10.273/27.
22. HTA Positronen Emissie Tomografie in België. D/2005/10.273/29.
23. HTA De electieve endovasculaire behandeling van het abdominale aorta aneurysma (AAA). D/2005/10.273/32

Inlichtingen

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