Transcatheter aortakunstklep implantatie (TAVI): een Health Technology Assessment actualisatie

KCE reports 163A

Federaal Kenniscentrum voor de Gezondheidszorg
Centre fédéral d'expertise des soins de santé
2011

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Contact

Federaal Kenniscentrum voor de Gezondheidszorg (KCE)
Administratief Centrum Kruidtuin, Doorbuilding (10e verdieping)
Kruidtuinlaan 55
B-1000 Brussel
Belgium

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

Email: info@kce.fgov.be
Web: http://www.kce.fgov.be

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MATTIAS NEYT, HANS VAN BRABANDT, STEFAAN VAN DE SANDE, STEPHAN DEVRIESE

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Titel:	Transcatheter aortakunstklep implantatie (TAVI): een Health Technology Assessment actualisatie.
Auteurs:	Mattias Neyt (KCE), Hans Van Brabandt (KCE), Stefaan Van de Sande (KCE), Stephan Devriese (KCE)
Externe experten:	Edouard Benit (Jessa Hasselt); Johan Bosmans (UZA); Christophe Dubois (UZLeuven); Patrick Galloo (Socialistische Mutualiteit); Jacques Goldstein (Belgian TAVI Group Coordinator); Paul Herijgers (UZLeuven); Bruno Krug (UCLouvain); Mark Lamotte (IMS Health Consulting); Victor Legrand (CHU-ULG); Michael Rosseel (Sted. ZH Aalst); Lydie Vancauwenberghe (Medtronic); Robert Van Den Oever (Christelijke Mutualiteit); Jean-Louis Vanoverschelde (UCLouvain); Michel Verhasselt (Edwards).
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Externe validatoren:	Wim Daenen (Prof.em. cardiale heelkunde, KUL); Ken Redekop (Erasmus Universiteit Rotterdam, Institute for Medical Technology Assessment, the Netherlands); Ingrid Zechmeister (Ludwig Boltzmann Institut für Health Technology Assessment, Austria)
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VOORWOORD

Voor de bejaarde patiënt met een ernstig vernauwde aortaklep die te ziek is om nog geopereerd te worden is er die innovatieve technologie die het onmogelijke lijkt mogelijk te maken: een kunstklep die via een bloedvat in de lies in het hart wordt ingebracht. Wel met een prijskaartje om van te duizelen, en dus met grote commerciële belangen in het geding. Maar met daarnaast beperkte klinisch-epidemiologische data, die al bij al eerder verontrustend zijn.

Dit was de situatie in 2008, toen het KCE een eerste rapport over het onderwerp publiceerde, met de aanbeveling om de technologie alsnog niet terug te betalen, en te wachten op meer gegevens. Maar intussen bleef de polemiek woeden, tot en met het etaleren van dramatisch-heroïsche verhalen in de pers, werden posities ingenomen, met argumenten over en weer.

Gelukkig bleef daarnaast de bereidheid bestaan om ook objectief naar de data te kijken. Met de medewerking van de Belgische TAVI werkgroep kon het KCE de link leggen tussen de pas gepubliceerde resultaten van een grote trial en de kostengegevens van de Belgische ziekenhuisrealiteit. Het resultaat vindt u in de volgende bladzijden. Wij hopen dat het zal kunnen bijdragen tot het maken van de juiste keuzen voor de patiënt en voor de ziekteverzekering.

Jean Pierre CLOSON
Adjunct Algemeen Directeur

Raf MERTENS
Algemeen Directeur

Samenvatting

INLEIDING

Transcatheter aortaklep implantatie (Transcatheter Aortic Valve Insertion – TAVI) is een techniek waarbij een kunstklep in een vernauwde aortaklep ingeplant wordt zonder dat hiervoor het hart moet worden stilgelegd. Er bestaan twee mogelijkheden. In een eerste variante wordt de kunstklep via een slagader ingebracht, meestal de arteria femoralis, en in dat geval spreekt men van "trans-femorale TAVI". Indien door uitgesproken atheromatose geen van de beide arteriae femorales toegankelijk is, kan een TAVI ook rechtstreeks gebeuren doorheen de thoraxwand en de punt van het hart (apex), en in dat geval spreekt men van "trans-apicale TAVI".

In Europa zijn sinds 2007 twee verschillende TAVI kleppen gecommercialiseerd: de Sapien® klep van Edwards Lifesciences en de CoreValve® van Medtronic. Van beide types werden er reeds duizenden geïmplanteerd.

Het KCE heeft in 2008 een eerste rapport over deze techniek gepubliceerd. Er werd besloten dat een terugbetaling van TAVI op dat ogenblik niet kon verdedigd worden om redenen van veiligheid voor de patiënt en omdat de doelpopulatie niet voldoende gedefinieerd was. Er werd voorgesteld om dit advies te herbekijken bij de bekendmaking van de resultaten van de PARTNER (Placement of AoRtic TraNscathetER valve) trial, een gerandomiseerde klinische studie met de Sapien® klep die op dat ogenblik reeds lopende was. Deze resultaten werden gepubliceerd in September 2010 en Juni 2011. Bijkomende analyses ervan kwamen beschikbaar via de verslagen van een meeting van de Amerikaanse Food and Drug Administration (FDA) op 20 Juli 2011. We namen ook contact op met de studie sponsor van wie we nog extra gegevens ontvingen.

Onderhavig rapport heeft de volgende doelstellingen:

1. Kritische analyse van de PARTNER studie
2. Gezondheidseconomische studie over TAVI op basis van de PARTNER resultaten en kostengegevens uit België

DE PARTNER STUDIE

DESIGN

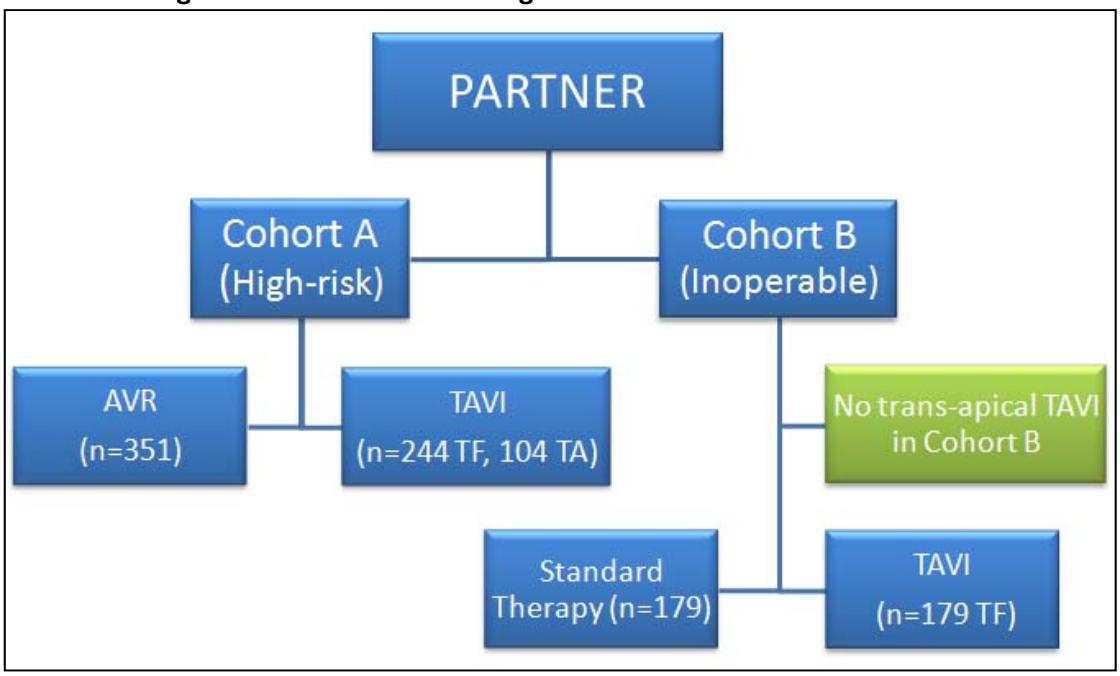
De PARTNER studie is een onderzoek dat onder auspiciën van de FDA uitgevoerd werd om de veiligheid en de werkzaamheid van de Sapien® klep na te gaan. Deze studie was voor de fabrikant noodzakelijk om een aanvraag te kunnen doen om de klep op de Amerikaanse markt toe te laten.

De PARTNER trial is een open-label gerandomiseerde studie, gesponsord door Edwards Lifesciences. Ze werd uitgevoerd in 25 centra, waarvan 21 in de VS, 3 in Canada en 1 in Duitsland. Hoog-risico patiënten met een ernstige symptomatische aortastenose bij wie een heelkundige aortaklepvervanging in overweging genomen werd, waren potentiële kandidaten om aan de studie deel te nemen. Na screening werden ze gestratifieerd in twee groepen (Figuur 1):

1. Cohorte A omvatte de hoog-risico patiënten. Zij hadden een geschat operatief mortaliteitsrisico van minstens 10% volgens de STS-score[a], of van minstens 15% omwille van andere ernstige problemen die niet in deze score vervat waren.
2. Cohorte B omvatte patiënten die als inoperabel beschouwd werden door minstens twee hartchirurgen, hetzij omwille van anatomische factoren (thoraxwand misvorming, herhaalde voorgaande thoracale ingrepen, sterk verklakte – zgn. porselein – aorta, sekwellen van radiotherapie), hetzij omwille van geassocieerde ernstige medische problemen.

[a] Society of Thoracic Surgeons' risk model

Figuur 1. PARTNER trial design



De TAVI groep bevat in cohorte A een trans-femorale (TF) en een trans-apicale (TA) subgroep. In cohorte B wordt enkel de trans-femorale benadering aangewend. AVR: heelkundige "aortic valve replacement".

Hierna volgde een tweede stratificatie in functie van het feit of het bij de betrokken patiënt al dan niet technisch mogelijk was om langsheen een arteria femoralis met de benodigde katheters toegang te krijgen tot het hart.

- *Cohorte A patiënten* werden gerandomiseerd naar trans-femorale of trans-apicale TAVI naargelang er al dan niet een trans-femorale toegangsmogelijkheid bestond, versus de klassieke heelkundige behandeling (aortic valve replacement – AVR). In de analyse van het primaire eindpunt van de studie (totale mortaliteit) werden beide TAVI variantes gecombineerd vergeleken met heelkunde.
- *Cohorte B patiënten* met een trans-femorale toegangsmogelijkheid, werden gerandomiseerd naar trans-femorale TAVI versus een "standard therapy". Deze laatste omvatte naast medicatie, in de meeste gevallen ook een ballon valvuloplastie van de aorta, een techniek waarbij de vernauwde aortaklep met een ballon opengerokken wordt. De studie sponsor opteerde ervoor om cohorte B patiënten zonder trans-femorale toegang niet in de studie op te nemen, ofschoon hierop aanvankelijk wel door de FDA aangedrongen werd.

PARTNER COHORTE A RESULTATEN

In cohorte A werden 348 patiënten toegewezen aan TAVI en 351 aan AVR. Hun gemiddelde leeftijd was 84 jaar en 57% waren mannen. De klinische karakteristieken van de twee groepen bij inclusie waren vergelijkbaar.

Tabel 1. Totale mortaliteit in de beide PARTNER cohortes

	COHORT A			COHORT B		
	TAVI	AVR	p	TAVI	STANDARD	p
	N=348	N=351		N=179	N=179	
30-day mort. n (%)	12 (3,4)	22 (6,5)	0,07	9 (5,0)	5 (2,8)	0,41
1-year mort. n (%)	84 (24,2)	89 (26,8)	0,44	55 (30,7)	89 (49,7)	<0,001

De geobserveerde 1-jaars mortaliteit bedroeg in de Standard Therapy groep 49.7%. In de Kaplan-Meier analyse bekwam men een geschatte 1-jaars mortaliteit van 50.7%.

De waargenomen mortaliteitsresultaten zijn weergegeven in Tabel 1. In cohorte A was het verschil in overlijdensrisico na 30 dagen tussen de twee behandelingsgroepen niet statistisch significant. Na 1 jaar was er geen verschil. Er waren significant meer vasculaire complicaties na TAVI (17.0 vs. 3.8% na 30 dagen, p<0.001) maar meer bloedingen na AVR (19.5% vs. 9.3%, p<0.001). Er waren significant meer beroertes na TAVI, zowel na 30 dagen (5.5% vs. 2.4%) als na verloop van 1 jaar (8.3% vs. 4.3%).

Het aantal her-hospitalisaties was vergelijkbaar in beide behandelingsgroepen. De functionele klasse was na 30 dagen beter voor de patiënten van de TAVI groep maar was na 6 maanden of na 1 jaar niet meer verschillend.

PARTNER COHORTE B RESULTATEN

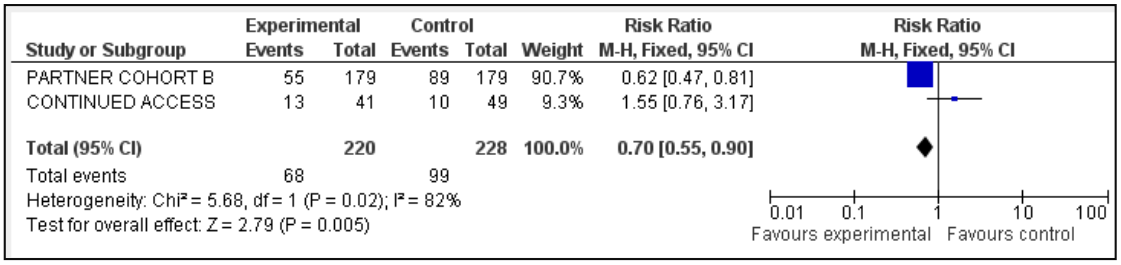
In cohorte B werden 179 patiënten toegewezen aan trans-femorale TAVI en 179 aan de zogenaamde "standard therapy". De gemiddelde leeftijd was 83 jaar en 46% waren mannen. De patiëntenkarakteristieken bij inclusie in de studie vertoonden vrij grote verschillen tussen de twee groepen in tegenstelling tot wat men van een gerandomiseerde toewijzing van behandeling zou verwachten. Hierdoor leken patiënten in de TAVI groep algemeen minder ziek dan de controles in de "standard therapy" groep.

Volgens het studieprotocol was een patiënt inoperabel wanneer 2 hartchirurgen besloten dat hij niet kon geopereerd worden. Twee subgroepen van patiënten werden hierbij onderscheiden: zij die inoperabel waren om anatomische reden, en zij die inoperabel waren om medische reden. De TAVI groep in cohorte B bevatte relatief meer patiënten die anatomisch inoperabel waren.

In de oorspronkelijke studie zoals ze in de New England Journal of Medicine gepubliceerd werd, gaf een behandeling met TAVI een absolute 1-jaars mortaliteitsreductie van 20% (30.7% vs. 50.7%, p<0.001) ten opzichte van "standard therapy".

Toen de inclusie van patiënten in de cohorte B in maart 2009 beëindigd was, gaf de FDA toestemming aan de deelnemende hartcentra om verder nieuwe patiënten volgens hetzelfde gerandomiseerd cohorte B protocol te behandelen. Zodoende werden tussen maart 2009 en augustus 2009 nog eens 90 patiënten gerandomiseerd. Dit verlengstuk van de oorspronkelijke ("pivotal") PARTNER studie werd de "Continued Access study" genoemd. Merkwaardig genoeg vond men op weliswaar kleinere aantallen, een absolute 12.7% *hogere* 1-jaars mortaliteit in de TAVI groep ten opzichte van de controle. De gepoolde resultaten van de pivotal trial en de Continued Access studie worden weergegeven in een meta-analyse in Tabel 2.

Tabel 2. Gepoolde 1-jaars mortaliteit van cohorte B patiënten uit de Pivotal trial en de Continued Access studie.



Meta-analyse software RevMan 5.1 (Cochrane Collaboration)

Via de studie sponsor bekwamen we de resultaten van een subgroep analyse die de overleving van de anatomisch inoperabele met de medisch inoperabele vergeleek. Deze worden weergegeven in Tabel 3.

Tabel 3. Subgroep analyse van de totale mortaliteit van de medisch en anatomisch inoperabele patiënten.

	ANATOMICALLY INOPERABLE		MEDICALLY INOPERABLE	
	TAVI	STANDARD	TAVI	STANDARD
	N=53	N=37	N=126	N=142
1-yr. mort.	24,5%	52,4%	33,3%	50,3%

Bron: studie sponsor (I. Merioua en J. Goldstein, 10 augustus 2011).

De resultaten van TAVI waren in de anatomisch inoperabele patiënten (mortaliteitsreductie van 27.9%) gunstiger dan in de medisch inoperabele (mortaliteitsreductie van 17.0%).

In de oorspronkelijk gepubliceerde resultaten waren er veel meer vasculaire complicaties in de groep die met TAVI behandeld werden dan in de "standard therapy" groep (30.7% vs. 5.0% na 30 dagen). Zoals in cohorte A waren er ook significant meer beroertes in de TAVI groep, zowel na 30 dagen (6.7% vs. 1.7%) als na verloop van 1 jaar (10.6% vs. 4.5%). Hospitalisaties die verband hielden met de aortastenose waren significant minder vaak noodzakelijk voor de TAVI patiënten (22.3% na 1 jaar) dan voor de "standard therapy" groep (44.1%). Na 1 jaar hadden 74.8% van de overlevende patiënten na TAVI weinig of geen cardiale symptomen tegenover 42.0% van deze uit de "standard therapy" groep. We beschikken niet over cijfers van deze secundaire eindpunten in de Continued Access studie of in de hogervermelde subgroepen.

KRITISCHE ANALYSE

Interne validiteit

Een kritische analyse van de gebruikte methodologie in de PARTNER studie wijst op een vrij groot risico op bias, vooral in cohorte B.

De ongelijke verdeling van de basiskarakteristieken tussen de studiegroepen ten voordele van TAVI doet de vraag rijzen of de randomisatie van de patiënten wel correct verlopen is. De randomisatie procedure is overigens niet nauwkeurig beschreven in het studieprotocol en ons verzoek tot meer uitleg bij de studie sponsor bracht geen duidelijkheid. Het feit dat de hoofdauteur van de studie grote financiële belangen had bij het aantonen van de werkzaamheid van TAVI doet de wenkbrauwen fronsen.

Ook de onverwachte resultaten van de Continued Access studie die tegengesteld waren aan die van de pivotal trial doen vragen rijzen.

De zogenaamde "standard therapy" omvatte bij 84% van de patiënten in cohorte B een ballon-valvuloplastie van de aorta. Dit is een behandelingsvorm die volgens internationale praktijkrichtlijnen soms verantwoord kan zijn, maar allesbehalve de standaard is in de aanpak van aortastenose bij hoogbejaarde mensen. Het is trouwens ook een zeer ingrijpende techniek met eigen ernstige risico's, waarvan nooit de meerwaarde ten opzichte van een strikt medische behandeling aangetoond werd.

Bij bejaarden met ernstige aortaklepstenose en ernstige co-morbiditeit is om het even welke ingreep op de aortaklep als een palliatieve therapie te beschouwen. De beslissing ertoe wordt bepaald door de vraag of kan verwacht worden of de levenskwaliteit van de patiënt in kwestie, met zijn bijkomende ernstige niet-cardiale problemen, zal verbeteren. Dit werd in de PARTNER studie onvoldoende aangetoond.

Externe validiteit

De 30-daagse mortaliteit na trans-femorale TAVI in de PARTNER is de laagste die ooit in een TAVI studie gerapporteerd werd (3.7% in cohorte A, 6.4% in cohorte B en 4.8% gemiddeld over de 2 cohortes). Dit is verrassend als men weet dat 19 van de 21 deelnemende Amerikaanse centra geen voorafgaande ervaring hadden met TAVI, en dat zij gebruik maakten van oudere modellen van de Sapien® klep. In de FRANCE-2 Registry (2010/2011) rapporteerden ervaren teams een 30-daagse mortaliteit na trans-femorale TAVI van 7.8%. Aangezien dit register zowel hoog-risico als inoperabele patiënten bevat moet dit cijfer dus vergeleken worden met het gemiddelde van de beide PARTNER cohortes, m.n. 4.8%, dat dus heel wat lager ligt. Het Belgisch register publiceerde betere cijfers (6.0%) dan de Franse, maar blijkens objectieve parameters gaat het hier om mensen die minder ziek zijn dan de PARTNER cohorte A of cohorte B patiënten.

Patiënten die anatomisch inoperabel zijn hebben een betere levensverwachting dan de medisch inoperabele omdat zij niet noodzakelijk nog andere medische aandoeningen hebben die hun overleving hypothekeert. Uit de subgroepanalyse blijkt dat de impact van TAVI in vergelijking met Standard Therapy bij hen nog gunstiger is dan in het geval van de medisch inoperabele patiënten.

WAT BRENGT DE PARTNER STUDIE BIJ?

Bij hoog-risico patiënten (cohorte A)

De PARTNER studie toont, spijts een reëel risico op bias, geen betere resultaten voor TAVI dan voor klassieke chirurgie bij patiënten met een hoog operatief risico. Daarnaast gaat TAVI gepaard met een dubbel zo groot risico op beroerte dan na heelkunde, maar met minder bloedingen. Mede wegens de hoge kostprijs betekent dit dat deze techniek in haar huidige vorm bij deze mensen niet kan aanbevolen worden. Deze stelling is in overeenstemming met het Amerikaanse standpunt waar de FDA momenteel enkel toelating tot markttoegang overweegt voor TAVI bij patiënten van het PARTNER Cohorte B type.

Bij inoperable patiënten (cohorte B)

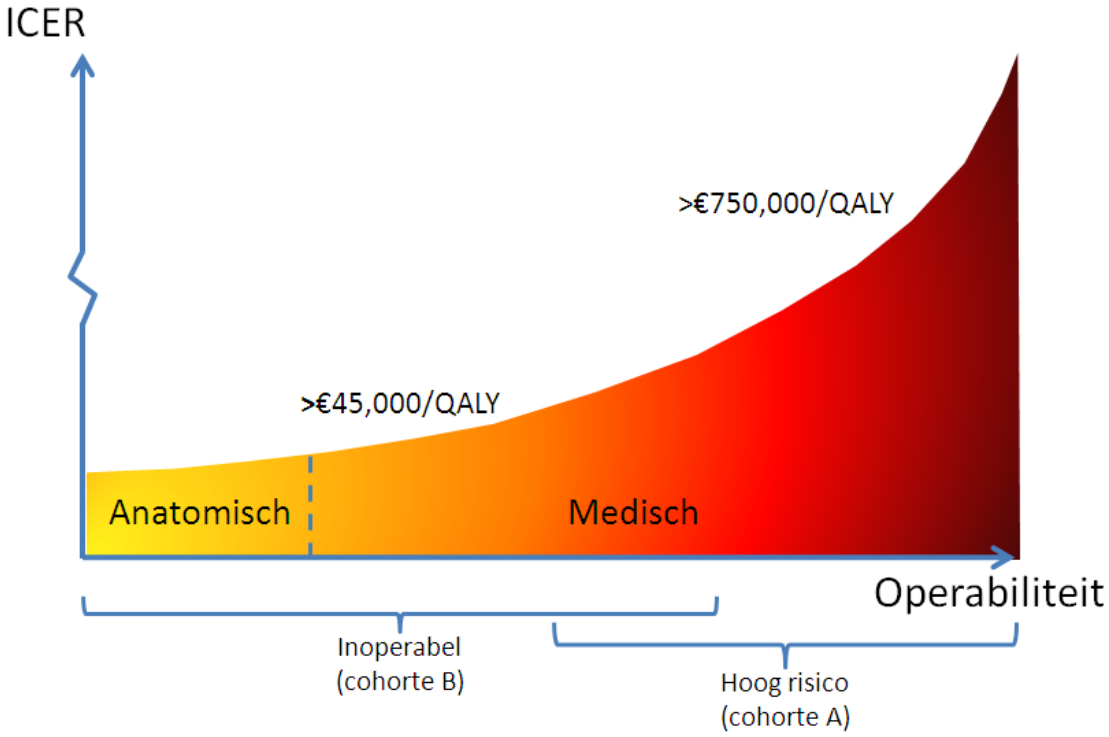
Bij inoperabele patiënten geeft een behandeling met TAVI een absolute 1-jaars mortaliteitsreductie van 20% ten opzichte van Standard Therapy. Ofschoon dit resultaat spectaculair oogt moet het wel genuanceerd worden in het licht van het feit dat de levensverwachting van deze patiënten beperkt is, wat men ook doet voor de behandeling van hun aortastenose, dit als gevolg van hun hoge leeftijd en hun co-morbiditeit. Daarenboven worden de zeer gunstige bevindingen van de pivotal trial niet bevestigd in de weliswaar kleinere Continued Access studie.

KOSTEN-EFFECTIVITEIT

Bij hoog-risico patiënten (cohorte A)

Op basis van de wetenschappelijke evidentie is het niet opportuun om een terugbetaling van TAVI te overwegen *voor het type patiënten van cohorte A*. Een terugbetaling vragen voor een interventie die niet beter maar wel duurder is (€43,600 voor de TAVI interventie, inclusief een kost van €18,000 voor de Sapien® klep, versus €23,700 voor AVR), zou vanzelfsprekend resulteren in een niet-efficiënt gebruik van de beperkte beschikbare middelen. Zelfs indien er rekening wordt gehouden met de (niet-significante) verschillen in mortaliteit op 30 dagen en na 1 jaar blijft de incrementele kosten-effectiviteitsratio (ICER) gemiddeld boven de €750,000 per gewonnen levensjaar aangepast voor de levenskwaliteit (QALY) [incrementele kost (IC): €20,400; incrementeel effect (IE): 0.03 QALYs] (Figuur 2). Enkel indien de prijs van TAVI die van AVR benadert en/of indien TAVI in de toekomst beter zou presteren dan AVR kan deze conclusie wijzigen.

Figuur 2. De kosteneffectiviteit van TAVI



ICER: incrementele kosteneffectiviteitsratio; QALY: voor kwaliteit van leven aangepast levensjaar.

Bij inoperabele patiënten (cohorte B)

Voor cohorte B zijn de resultaten voor de *pivotal trial* in detail gepubliceerd. Op basis van deze gegevens, en een levenslange extrapolatie van het mortaliteitsvoordeel, bekomen we een ICER van €37,400 per QALY (IC: €34,600; IE: 0.92 QALYs). Op basis van bijkomende gegevens uit de FDA analyse lijkt een levenslange extrapolatie niet gewettigd. Indien we de extrapolatietermijn beperken tot drie jaar, dan stijgt de gemiddelde ICER tot meer dan €70,000 per QALY (IC: €33,500; IE: 0.47 QALYs).

De resultaten van de *Continued Access trial* van cohorte B waren slechter voor TAVI dan voor de controlegroep. Gegevens over het aantal neveneffecten en impact op levenskwaliteit waren voor deze populatie niet beschikbaar. Enkel de impact op mortaliteit kon zodoende aangepast worden voor de gecombineerde populatie (t.t.z. pivotal + Continued Access). Met een levenslange extrapolatie van het mortaliteitsvoordeel resulteert dit in een ICER van €44,900 per QALY (IC: €33,200; IE: 0.74 QALYs) (Figuur 2). Aangezien er geen goede redenen zijn om de Continued

Access populatie uit te sluiten kan men dit resultaat uiteindelijk als basisscenario weerhouden.

In België is er geen expliciete drempelwaarde voor de kosteneffectiviteit. Enkel NICE (National Institute of Health and Clinical Excellence, UK) heeft expliciet een drempelwaarde opgenomen in zijn farmaco-economische richtlijnen met een bereik van £20 000 tot £30 000 per gewonnen QALY, t.t.z. ~€22,800 en ~€34,200. Indien we deze cijfers toepassen op de resultaten van onze economische evaluatie resulteert dit in een kans dat TAVI bij inoperabele patiënten als kosten-effectief kan worden aanschouwd van 9.2% tot 36.7%.

Er is echter een *subgroep* die een sterkere reductie van de mortaliteit laat optekenen, m.n. de *anatomisch inoperabele patiënten*. Voor deze subgroep hebben we enkel de impact op mortaliteit in de pivotal trial vanwege de studie sponsor kunnen bekomen. De ICER voor de anatomisch inoperabele patiënten ligt ongeveer €11,000 lager, terwijl hij in de medisch inoperabele ongeveer €5,000 hoger ligt dan in de groep in zijn geheel (Figuur 2). Verdere informatie voor deze subgroup betreffende de impact op het aantal events en de levenskwaliteit, voor zowel de pivotal als Continued Access populatie, is vereist voor een verdere verfijning van de economische evaluatie.

Indien men bereid zou zijn om de hoge prijs voor TAVI terug te betalen, dan is het aangeraden om zich in de eerste plaats te richten tot deze groep van anatomisch inoperabele patiënten. Op basis van de PARTNER studie en de karakteristieken van de Belgische TAVI populatie blijkt het te gaan om ongeveer 10% van de mensen die momenteel een TAVI ondergaan, d.w.z. 25 à 30 patiënten per jaar.

CONCLUSIES

Voorzichtigheid is geboden bij de interpretatie van de bevindingen van de PARTNER studie. Kritische analyse toont aan dat als gevolg van methodologische tekortkomingen, de gepubliceerde resultaten de klinische effectiviteit van TAVI misschien overschatten.

TAVI kan slechts overwogen worden bij patiënten die inoperabel zijn. Indien de in-operabiliteit het gevolg is van *anatomische* beperkingen, dan kan terugbetaling van TAVI verantwoord zijn. Dergelijke patiënten zijn klinisch eenvoudig identificeerbaar, hun levensverwachting is niet gecompromiteerd door bijkomende ernstige medische aandoeningen en ze vertegenwoordigen de populatie bij wie TAVI het meest kosten-effectief is.

Bij patiënten die omwille van ernstige *medische* co-morbiditeiten als inoperabel worden beschouwd, is een veel hogere bereidwilligheid tot betalen voor een gewonnen QALY nodig om de interventie acceptabel te maken. Bovendien is het oordeel of een patiënt operabel is met hoog risico, of dat hij als inoperabel beschouwd wordt, zeer subjectief. Buitenlandse ervaring en analyse van de karakteristieken van patiënten die in België reeds met TAVI werden behandeld tonen aan dat men in de praktijk geneigd is om de grenzen van operabiliteit te verleggen en het toepassingsgebied van TAVI te verbreden, mogelijks mede op vraag van de patiënten zelf. Toch kan op basis van de huidige wetenschappelijke kennis een uitbreiding van het gebruik van TAVI naar hoog-risico patiënten of naar operabele laag-risico patiënten niet aanbevolen worden.

De geschatte jaarlijkse behoefte aan TAVI wegens anatomische beperkingen in België bedraagt 25 à 30. Praktisch kan dit best gerealiseerd worden in 1 of 2 hartcentra met een grote ervaring op het gebied van klepchirurgie en de interventionele cardiologie. Deze kunnen bijvoorbeeld geselecteerd worden aan de hand van hun actuele ervaring met TAVI in combinatie met het aantal geïsoleerde aortaklepvervangingen dat zij jaarlijks uitvoeren. Hierbij zou een aantal van 100 gevallen per jaar als ondergrens kunnen gebruikt worden. In 2008 voerden 2 Belgische centra minstens 100 geïsoleerde aortaklepvervangingen uit.

De PARTNER trial geeft geen antwoord op de vraag over de werkzaamheid van trans-apicale TAVI bij inoperabele patiënten of over de klinische effectiviteit van de CoreValve® prothese. Er werden ook geen andere bronnen gevonden die het standpunt dienaangaande zouden veranderen in vergelijking met het KCE rapport van 2008.

AANBEVELINGEN[b]

- **Een patiënt met een symptomatische ernstige aortastenose en ernstige medische co-morbiditeiten, bij wie een correctie van de aortastenose opportuun geacht wordt, wordt bij voorkeur heelkundig behandeld en komt niet in aanmerking voor een terugbetaling van TAVI, zelfs indien het geschat mortaliteitsrisico van de operatie hoog of zeer hoog is.**
- **Een patiënt met een symptomatische ernstige aortastenose, bij wie een correctie van de aortastenose opportuun geacht wordt, maar die omwille van anatomische factoren inoperabel wordt beschouwd door een hartchirurg die onafhankelijk is van het hartteam dat de patiënt behandelt, komt in aanmerking voor behandeling met, en terugbetaling van TAVI met de Sapien® klep, indien men bereid is om een relatief hoge prijs voor TAVI te betalen.**
- **Een patiënt met een symptomatische ernstige aortaklepstenose en met ernstige co-morbiditeiten, maar die omwille van medische factoren inoperabel wordt beschouwd, komt niet in aanmerking voor terugbetaling van TAVI.**
- **Om een voldoende workflow te garanderen zou de TAVI behandeling moeten gelimiteerd worden tot 1 of 2 Belgische centra.**
- **Bijkomende reglementaire maatregelen en een goede registratie zijn vereist om te garanderen dat de patiëntenselectie correct gebeurt.**
- **Er kan geen advies gegeven worden over de terugbetaling van trans-apicale TAVI of van de CoreValve® prothese.**

b Alleen het KCE is verantwoordelijk voor de aanbevelingen aan de overheid.

Scientific summary

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LIST OF ABBREVIATIONS

6MWT	6-minute walk test
AS	aortic stenosis
AT	as-treated
AVR	aortic valve replacement
BACTS	the Belgian Association for Cardio-Thoracic Surgery
BAV	Balloon aortic valvuloplasty
BCIS	British Cardiovascular Intervention Society
CABG	coronary artery bypass graft surgery
CE	Conformité Européenne
CEA-curves	cost-effectiveness acceptability curves
COPD	Chronic Obstructive Pulmonary Disease
DGTHG	The German Society of Cardiovascular and Thoracic Surgeons
EACTS	European Association for Cardio-Thoracic Surgery
EAPCI	European Association of Percutaneous Interventions
ESC	European Society of Cardiology
FDA	Food and Drug Administration
IC	incremental cost
ICER	incremental cost-effectiveness ratio
IDE	Investigational Device Exemption
IE	incremental effect
IMA-AIM	Intermutualistisch Agentschap – Agence Intermutualiste
INAMI	l'Institut National d'Assurance Maladie Invalidité
ITT	Intention To Treat
LYG	life-year gained
MACCE	Major Adverse Cardiac and Cerebrovascular Events
MKG-RCM / AZV-SHA	Minimale Klinische gegevens – Résumé Clinique Minimal / Anonieme Ziekenhuisverblijven – Séjours Anonymes Hospitaliers
NSA	non-surgical approach
NYHA	New York Heart Association
PARTNER	Placement of AoRTic TraNscathetER Valve trial
PMA	pre-market approval
QALY	quality-adjusted life-year
QoL	Quality of Life
RIZIV	Rijksinstituut voor Ziekte- en Invaliditeitsverzekering
SCTS	Society of Cardiothoracic Surgeons
SOI	severity of illness
STS	Society of Thoracic Surgeons
TA	transapical
TAVI	transcatheter aortic valve insertion
TCT	Transcatheter Cardiovascular Therapeutics

TCT	Technische Cel – Cellule Technique
TF	transfemoral
TIA	transient ischemic attack

1 INTRODUCTION

In 2008, the KCE published a report on transcatheter aortic valve insertion (TAVI) in patients with a degenerative aortic valve stenosis who were at very high risk for a standard surgical aortic valve replacement (AVR).[1] It concluded that the safety of the technique as compared to AVR was unsure, and recommended to postpone a decision on reimbursement until the results of a then ongoing randomised trial (the PARTNER-US study) would become available. These were expected to provide mortality rates in relation to the management of aortic stenosis by medical treatment, standard AVR or TAVI. The present document is a sequel to our 2008 report and therefore, the reader is referred to this for background information on aortic stenosis, surgical AVR and the performance of TAVI obtained from non-randomised registries.

The scope of the present report is essentially limited to:

1. A critical appraisal of the PARTNER trial
2. The application of the PARTNER trial results in a health economic model

The first human TAVI has been performed in 2002.[2] Continued technical improvements of the system and in the protocol for device delivery were implemented. In recent years several TAVI devices have been developed and at least 20 types are currently being tested at various stages in humans, in animal models or in laboratories. Currently, two different aortic valves for transcatheter use have received European CE (Conformité Européenne) marking: the Sapien® valve (Edwards Lifesciences) and the CoreValve® (Medtronic). In Europe, thousands of both devices have been implanted, mostly in patients with symptomatic aortic stenosis (AS) at very high risk or contra-indications for AVR. Until now these devices have not yet been approved in the US for clinical use. In November 2010, based on the results of the PARTNER Cohort B, Edwards Lifesciences submitted an application for a pre-market approval (PMA) of the Sapien valve system for trans-femoral delivery in inoperable patients. On July 20 2011, a US Food and Drug Administration (FDA) advisory panel recommended approval of the device.[3] The decision of the FDA consequential to this advice is not yet known.

Until recently, the assessment of the clinical effectiveness of TAVI as compared to AVR or medical therapy had to rely on patient series that were most often steered by the valve manufacturers. In 2008, we performed a comprehensive survey of these registry data.[1, 4] TAVI was shown to be feasible in most of the patients if attempted by experienced teams. Since there were no control groups in the registries it remained unclear whether TAVI performed better in improving a patient's life expectancy or quality of life as compared to other treatment strategies.

Safety, defined as the 30-day post-procedural all-cause mortality,[5] was also called into question. From recently published series of high risk patients that actually underwent AVR, we estimated operative mortality to be 5.8%.[6] Based on registries, 30-day mortality rate for trans-femoral TAVI was estimated to be 8.1%. We concluded that safety issues and short-term survival represented a major drawback for the implementation of TAVI in high risk patients and that results from the PARTNER trial had to be awaited before further using this technique in routine clinical practice and before considering its reimbursement.[1]

A first part of the results of the PARTNER trial (patient Cohort B) were simultaneously presented at the TCT (Transcatheter Cardiovascular Therapeutics) congress on September 23, 2010 and published online in The New England Journal of Medicine.[7] The other part of the trial (Cohort A) was presented on April 3, 2011 at the American College of Cardiology 2011 Scientific Sessions and published in June 2011.[8] Additional data on the PARTNER trial were obtained from the FDA's website, from web-posted press releases and conference proceedings and through contacts with the manufacturer.

These data will be further discussed in the present report and will be used to feed an economic model.

2 THE PARTNER TRIAL

In 2007, the US Food and Drug Administration (FDA) has granted the Edwards Sapien transcatheter valve an Investigational Device Exemption (IDE) to be used in a randomised controlled trial: the PARTNER (Placement of AoRTic TraNscathetER Valve) trial (ClinicalTrials.gov identifier NCT00530894). The FDA provides such an IDE to allow an investigational device to be used in a clinical study in order to collect safety and effectiveness data required to support a "pre-market approval" (PMA) application which is mandatory for class III devices, the highest risk class.

The PARTNER trial is a randomised, open label trial sponsored by Edwards Lifesciences. It should be noted that ambiguity may arise resulting from the misleadingly homonymic labelling of the European observational PARTNER EU study, which is only a registry of patients treated with the Edwards Sapien transcatheter valve within Europe.[9]

The purpose of the PARTNER trial was to determine the safety and effectiveness of the Edwards Sapien® Transcatheter Heart Valve together with its delivery systems (trans-femoral and trans-apical) in patients with severe symptomatic aortic stenosis for whom conventional AVR was associated with (very) high risk.[7] In the participating centres, all patients evaluated for severe aortic stenosis and estimated at high risk for AVR had to be screened in order to determine study eligibility (Figure 1). Of 3105 patients that were screened, 1057 (34%) underwent randomisation in the PARTNER trial. Exclusion criteria were a bicuspid or non-calcified aortic valve, acute myocardial infarction, coronary artery disease requiring revascularisation, a left ventricular ejection fraction of less than 20%, a diameter of the aortic annulus of less than 18 mm or more than 25 mm, severe mitral or aortic regurgitation, a transient ischemic attack or stroke within the previous 6 months, and severe renal insufficiency (creatinine >3.0 mg/dL). Patients with a life expectancy less than 12 months due to non-cardiac co-morbid conditions were excluded from entry to the study.

Eligible patients were stratified into cohorts for operability. "High risk" or "inoperable" status were defined as follows (Figure 1):

- "High risk patients": those who were potential candidates for surgery but were at high surgical risk, as defined by a Society of Thoracic Surgeons (STS) risk score of 10% or higher, or by the presence of coexisting conditions that would be associated with a predicted risk of death by 30 days after surgery of 15% or higher. These patients were allocated to Cohort A.
- "Inoperable patients": those who were not considered to be candidates for surgery because they had coexisting conditions that would be associated with a predicted probability of 50% or more of either death by 30 days after surgery or a serious irreversible condition. At least two surgeon investigators have to agree that the patient was not a suitable candidate for surgery. Both medical and anatomic factors may lead to the surgeons' conclusion of inoperability. These patients were allocated to Cohort B.

Next, a second stratification of patients was based on trans-femoral accessibility. Patients considered at high surgical risk and eligible for trans-femoral access were randomised to TAVI or surgical AVR. Randomisation was accomplished according to a non-specified "computer-generated randomisation scheme". Patients at high surgical risk who were not eligible for trans-femoral access were randomised to trans-apical TAVI or surgical AVR. Those patients who were considered inoperable were randomised to TAVI or standard management if they were eligible for trans-femoral access. Those who were inoperable and but not eligible for trans-femoral delivery were excluded from randomisation into the trial ("Not in Study" in Figure 1). Numerical data of the number of patients screened, enrolled and treated per protocol in the different study arms are available from Figure 1.

Most of the participating sites were located within the US. TAVI was a relatively new procedure in the US at the time the trial was conducted and 19 of the 26 sites involved had no previous experience with TAVI.[10]

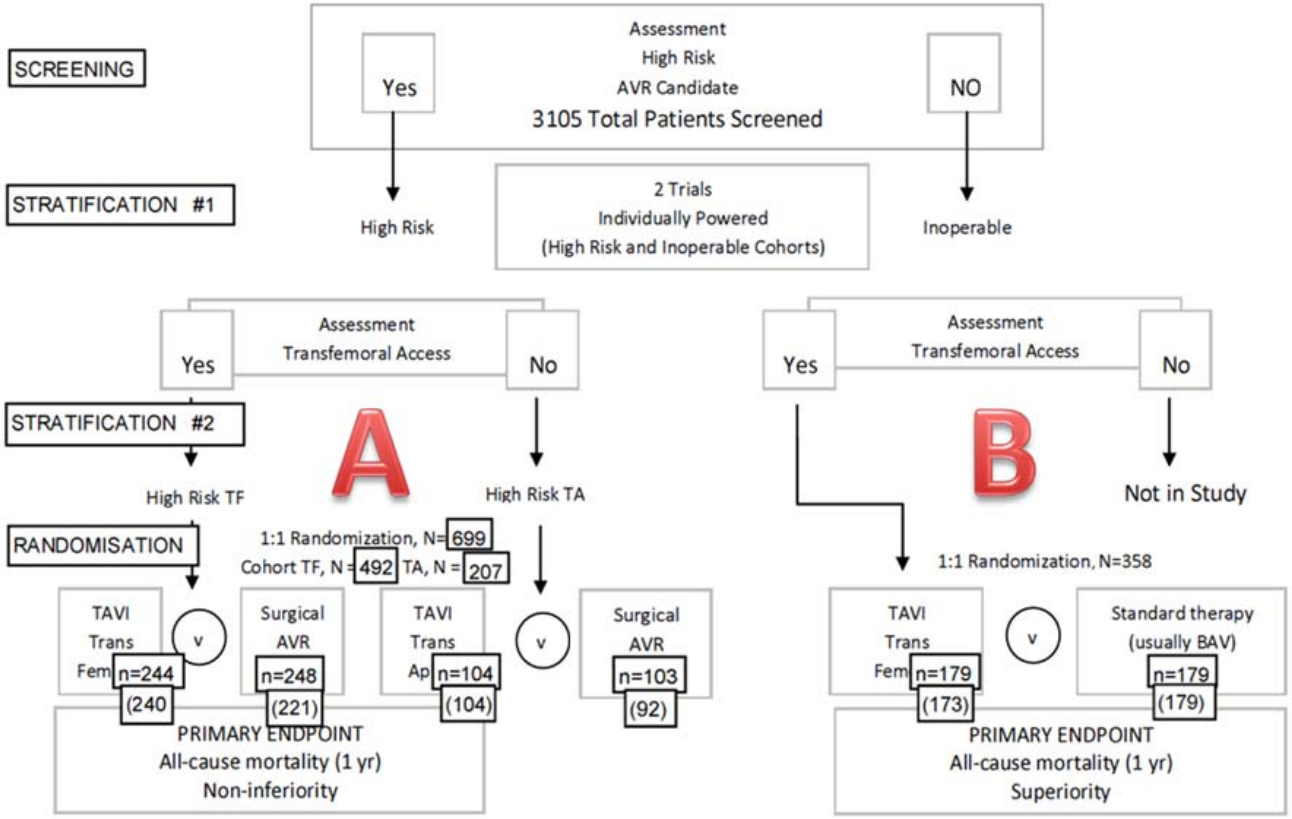
The primary study endpoint in Cohort A was freedom from death at one year (non-inferiority) in the combined trans-femoral and trans-apical patients. In Cohort B primary endpoints were (1) freedom from death over the duration of the trial (superiority) and (2) composite of death and recurrent hospitalisation. Of note, the latter co-primary endpoint has only been added to the study protocol in January 2009.[11]

Secondary endpoints were (1) separate analyses of the primary endpoint in the trans-apical and trans-femoral groups (Cohort A), (2) functional improvement from baseline, (3) freedom from MACCE[a] at 30 days, 6 and 12 months, (4) evidence of prosthetic valve dysfunction at 30 days, 6 and 12 months (Cohort A), (5) length of index hospital stay, (6) total hospital days from the index procedure to one year post procedure, (7) improved Quality of Life (QoL) from baseline at 30 days, 6 and 12 months, (8) valve function at 30 days, 6 and 12 months. QoL was assessed by means of the "Kansas City Cardiomyopathy" instrument, EuroQoL and SF-12.

In addition to the above primary and secondary endpoints, an expanded safety composite event is defined, including death, MI, stroke, aortic valve re-intervention, recurrent hospitalisation and procedure access complications (unplanned surgical vascular conduit, unplanned vascular grafting intervention, repair of thoracic or abdominal aorta, or access wound infection).

a Major Adverse Cardiac and Cerebrovascular Events

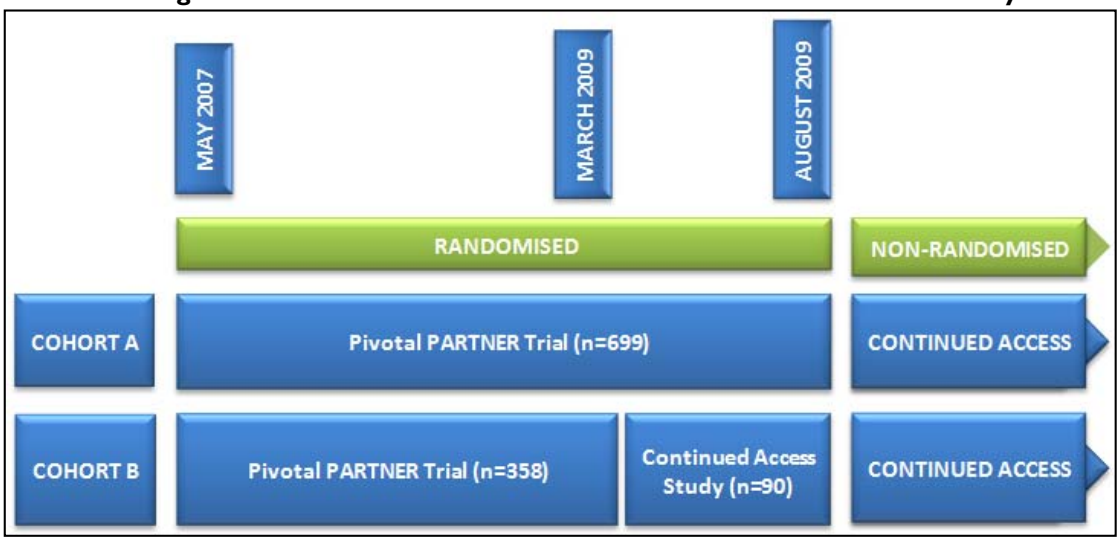
Figure 1. Patient allocation in the PARTNER trial.



Adapted from Leon et al.[7] The numbers related to the Cohort A part of the trial as they were initially published[7] differ slightly from those published later on. Here, the numbers correspond with the final data provided by Smith et al.[8] The number of patients treated in accordance with their randomisation is indicated between brackets.

In March 2009 coincident with completion of enrolment into the Cohort B study, the FDA authorised the PARTNER trial investigators to begin a Continued Access study. At the onset, the Cohort B Continued Access study protocol was the same as the randomised PARTNER study until August 2009, when Cohort A enrolment was completed. In August 2009, the Continued Access study was expanded to allow enrolment of Cohort A subjects in a non-randomised protocol. Randomisation for the Cohort B group was also discontinued at that time (Figure 2). Enrolment in the non-randomised Continued Access cohort is ongoing. As of November 1, 2010, 160 non-randomised patients have been enrolled.

Figure 2. Timeline of PARTNER trial and the Continued Access study



Data source: FDA.[11]

2.1 PARTNER TRIAL RESULTS – COHORT A

The Cohort A results were published in print in June 2011.[8] The allocation of patients after randomisation is depicted in Figure 1. The absolute number of patients allocated to different subgroups of Cohort A as reported in the "supplementary appendix" to the NEJM paper on the Cohort B[7] were slightly different from those in the final publication. In Figure 1, these numbers have been adapted to correspond with the data provided in the final Cohort A article.

A total of 699 patients were stratified to the high-risk Cohort A and represent the intention-to-treat (ITT) population. Based on trans-femoral accessibility, 492 were stratified in the trans-femoral group and 207 in the trans-apical group. Enrolment was concluded in August 2009.[11] Randomisation allocated 244 patients to TAVI and 248 to AVR in the trans-femoral group and 104 patients to TAVI and 103 to AVR in the trans-apical group. Analyses are presented for the combined trans-apical/trans-femoral approaches and for the approaches separately.

Time from randomisation to treatment was 10.6 days in the TAVI and 15.6 days in the AVR Group. 42 of 699 patients were not treated as assigned by randomisation: 4 (1.1%) in the TAVI group and 38 (10.8%) in the AVR group. Non-treatment in the AVR Group were mainly due to refusal (17=4.8%) or withdrawal (11=3.1%).

Baseline characteristics of patients are shown in Table 1.

Table 1. Baseline medical characteristics of PARTNER trial enrolees by treatment allocation

	COHORT A		COHORT B	
	TAVI	AVR	TAVI	STANDARD
N	348	351	179	179
Age (yr)	83,6	84,5	83,1	83,2
Male sex (%)	57,8	56,7	45,8	46,9
STS score	11,8±3,3	11,7±3,5	11,2±5,8	12,1±6,1
Logistic EuroSCORE	29,3±16,5	29,2±15,6	26,4±17,2	30,4±19,1
NYHA class II - %	5,7	6	7,8	6,1
NYHA class III or IV - %	94,3	94	92,2	93,9
Coronary artery disease - %	74,9	76,9	67,6	74,3
Previous myocardial infarction - %	26,8	30	18,6	26,4
Previous CABG - %	42,6	44,2	37,4	45,6
Previous PCI - %	34,0	32,5	30,5	24,8
Previous Balloon aortic valvuloplasty	13,4	10,2	16,2	24,4
Cerebral vascular disease - %	29,3	27,4	27,4	27,5
Peripheral vascular disease - %	43,0	41,6	30,3	25,1
COPD - %: Any	43,4	43,0	41,3	52,5
COPD - %: Oxygen-dependent	9,2	7,1	21,2	25,7
Creatinine >2 mg/dL - %	11,1	7,0	5,6	9,6
Atrial fibrillation - %	40,8	42,7	32,9	48,8
Previous pacemaker - %	20	21,9	22,9	19,5
Pulmonary hypertension - %	42,4	36,4	42,4	43,8
Liver disease - %	2,0	2,6	3,4	3,4
Moderate or severe mitral regurg. - %	19,8	21,3	22,2	23,0
Frailty - %	15,6	17,6	18,1	28,0

The mean age of patients in the TAVI group was almost 1 year lower than in the AVR group: 83.6±6.8 vs. 84.5±6.4. About 57% of the enrolees were men. The STS score and the Logistic EuroSCORE were 11.8±3.3 and 29.3±16.5 in the TAVI group and 11.7±3.5 and 29.2±15.6 in the AVR group, indicating a similar estimated operative risk. Apart from age, the presence of concurrent cardiovascular disease and other co-morbid conditions was well balanced between the two groups.

2.1.1 Mortality

The primary endpoint, death from any cause at 1 year, was 24.2% in the TAVI group and 26.8% in the AVR group (Table 2). This difference was within the non-inferiority margin. Similarly, there were no statistical differences in the rates of death at 1 year between the trans-femoral group and the surgical group or between the trans-apical and the surgical group.

Table 2. Early and late mortality of PARTNER Cohort A patients.

COHORT A mortality (%)	All patients				Trans-femoral group				Trans-apical group			
	All TAVI		Surgery		Trans-femoral		Surgery		Trans-apical		Surgery	
	30 d	1 yr	30 d	1 yr	30 d	1 yr	30 d	1 yr	30 d	1 yr	30 d	1 yr
ITT	3,4	24,2	6,5	26,8	3,3	22,2	6,2	26,4	3,8	29,0	7,0	27,9
As treated	5,2	23,7	8,0	25,2	3,7	21,3	8,2	25,2	8,7	29,1	7,6	25,3

ITT: Intention to treat analysis (n=699).

In the ITT analysis, the rates of death from any cause at 30 days were 3.4% in the TAVI group and 6.5% in the surgical group (p=0.07).

The 30-day "as treated" mortality figures is especially relevant for assessing the safety of the different procedures. In the TAVI group, 30-day "as treated" mortality was 5.2% (3.7% in the trans-femoral, and 8.7% in the trans-apical group). In the surgical group, it was 8.0% overall.

2.1.2 Re-hospitalisations, cardiac symptoms

Recurrent hospitalisation rates were similar, both at 30 days and at 1 year for the two patient groups. At 1 year, rehospitalisation occurred in 58 patients (18.2%) in the TAVI group and in 45 (15.5%) in the AVR group.

NYHA (New York Heart Association) functional class at 30 days was better for the TAVI group, but no longer differed at 6 months and at 1 year.

A 6MWT was carried out at baseline after randomisation. At 30 days, among patients who could perform 6-minute walk tests (6MWT), patients in the TAVI group walked farther than those in the surgical group. At 1 year, 152 out of 264 (58%) surviving TAVI patients and 175 out of 262 (66%) surviving surgical patients were able to perform a 6MWT. There was no significant between-group difference.

2.1.3 Stroke

Stroke was a pre-specified secondary end point. In a retrospective analysis neurologic events were further divided in subgroups where major stroke was defined by a score of at least 2 on the modified Rankin scale (which ranges from 0 to 6, with higher scores indicating greater disability).

Strokes were observed more frequently in the TAVI group than in the AVR group, both at 30 days (5.5% vs. 2.4%, p=0.04) and at 1 year (8.3% vs. 4.3%, p=0.04). Major strokes occurred more frequently in the TAVI group than in the AVR group at 30 days (3.8% vs. 2.1%, p=0.20) and at 1 year (5.1% vs. 2.4%, p=0.07).

2.1.4 Vascular complications

Vascular complications and bleeding were pre-specified secondary safety endpoints of the study, including haematoma at access site, false aneurysm, arterio-venous fistula, retroperitoneal bleeding and peripheral ischemia. Major vascular complications were defined as: (1) any thoracic aortic dissection, (2) access site or access-related vascular injury leading to either death, need for significant blood transfusions (>3 units), unplanned percutaneous or surgical intervention, or irreversible end-organ damage, (3) distal embolisation (non-cerebral) from a vascular source requiring surgery or resulting in amputation or irreversible end-organ damage, or (4) left ventricular perforation. At 30 days, the TAVI group had a significantly higher rate of vascular complications than did the surgical group (17.0% vs. 3.8%, p<0.001). The TAVI group had also a significantly higher rate of *major* vascular complications than did the surgical group (11.0% vs. 3.2%, p<0.001).

The TAVI group had lower rates of major bleeding events (9.3% vs. 19.5%, p<0.001).

2.1.5 Paravalvular leaks

Moderate or severe paravalvular regurgitation was more frequent in the TAVI group than in the surgical group at 30 days (12.2% vs. 0.9%) and at 1 year (6.8% vs. 1.9%) (P<0.001 for both comparisons).

2.1.6 Pacemaker insertion and atrial fibrillation

A substantial number of patients already had a permanent pacemaker at baseline: 20.0% in the TAVI group and 21.9% in the surgical therapy group. At 1 year, a new pacemaker was implanted in 5.7% of TAVI patients and in 5.0% of surgical therapy patients.

The TAVI group had lower rates of new-onset atrial fibrillation (8.6% vs. 16.0%), p=0.006).

2.2 PARTNER TRIAL RESULTS – COHORT B

Between May 2007 and March 2009, a total of 358 patients with AS who were no candidates for standard surgery were enrolled in Cohort B at 21 sites (mostly in the US) and were randomly assigned to TAVI (179 patients) or standard therapy (179 patients).[7] Patients were followed for at least 1 year (median follow-up period, 1.6 years; maximum, 2.8 years). "Standard therapy" in the control patients encompassed balloon aortic valvuloplasty in most (84%) of the patients.

Baseline characteristics of patients are shown in Table 1. Their mean age was 83.1±8.6 year in the TAVI group and 83.2±8.3 in the controls. Somewhat less than half of the enrolees were men. The STS score and the Logistic EuroSCORE were 11.2±5.8 and 26.4±17.2 in the TAVI group and 12.1±6.1 and 30.4±19.1 in the control group, indicating a slightly poorer prognosis in the latter. The EuroSCORE was statistically significantly higher in the control group (p=0.04). In the control group there were more patients with COPD (Chronic Obstructive Pulmonary Disease) (52.5 vs. 41.3%, p=0.04) and more with atrial fibrillation (48.8 vs. 32.9%, p=0.04).

The PARTNER study protocol stipulates that both medical and anatomic conditions may lead to the surgeons' conclusion of inoperability if that condition would be associated with a predicted probability mortality of 50% or more by 30 days after surgery. Prohibitive medical conditions include highly compromised respiratory disease, severe immunosuppressive diseases or advanced multi-system dysfunction whereas prohibitive anatomic conditions include porcelain aorta, chest wall radiation or deformity, and multiple previous interventions. Most of these characteristics are not included in the operative risk scores. Patients with co-existing "anatomic conditions" that contributed to the surgeons' decision that a patient was not a suitable candidate for surgery were better represented in the TAVI group than in de standard therapy group (29.6 vs. 20.7%, p=0.05) (Table 3).

Table 3. Anatomic abnormalities at baseline in PARTNER trial enrolees, by cohort and treatment group (%)

	COHORT A			COHORT B		
	TAVI	AVR	p	TAVI	STANDARD	p
Extensively calcified aorta - %	0,6	1,1	0,69	19,0	11,2	0,05
Effects of chest-wall irradiation - %	0,9	0,9	1,00	8,9	8,4	1,00
Chest-wall deformity - %	0,0	0,3	1,00	8,4	5,0	0,29
All anatomically inoperable*	estimated 1 - 2 %		N.S.	29,6	20,7	0,05

Source: NEJM papers,[7, 8] and study sponsor (Table 5)(I. Merioua and J. Goldstein – August 10, 2011). *: Some patients have more than one of the anatomic characteristics.

General frailty was more often present in the control group (28.0 vs. 18.1%, p=0.09). Frailty was assessed by quantifying the ability of patients to perform activities of daily living, and by performing a hand grip and a walk test.

The average total time of the procedure was 262 minutes (min: 139 - max: 616) with an average skin to skin time of 150 minutes (34-553). Total fluoroscopy time was 29 minutes (10-68) and on average 132 mL (10-450) of contrast medium was administered.[3]

2.2.1 Mortality

The rate of death from any cause over the duration of the trial was the primary endpoint in Cohort B of the PARTNER trial.

Of the 179 patients assigned to TAVI, 6 did not receive the device of whom 2 died before the scheduled TAVI. 11 of the 173 patients that received the device died in the first 30 days after the procedure, indicating an "as treated" mortality rate of TAVI of 6.4%. Intention to treat analysis showed a 30-day mortality rate of TAVI of 5.0%. At 1-year follow-up, the rate of death from any cause (the primary end point), was 55/176 or 30.7% in the TAVI group, as compared with 89/179 or 49.7% in the standard therapy group (hazard ratio, 0.55; 95% CI 0.40-0.74; p<0.001) (Table 4).

Data related to the randomised Continued Access Cohort B subgroup are available from the "Briefing Document for the Circulatory Systems Device Panel Advisory Committee" presented by the sponsor at the July 20, 2011 FDA meeting (Figure 2).[11] The mean follow-up time for these patients was 7 months. Results are depicted in Table 4. Remarkably, in the Continued Access study as compared to the pivotal trial, TAVI performed worse than "standard therapy" because of an unexpectedly lower mortality of control patients. Whereas TAVI outperformed standard therapy by an absolute 20% lower 1-year mortality in the pivotal trial, survival of TAVI patients in the Continued Access study was an absolute 12.7% lower.

Table 4. Early and late mortality in the pivotal PARTNER trial and the Continued Access study

STS score	PIVOTAL COHORT B			CONTINUED ACCESS		COMBINED	
	TAVI	STANDARD	p	TAVI	STANDARD	TAVI	STANDARD
	N=179	N=179		N=41	N=49	N=220	N=228
30-day mort. n (%)	9 (5,0)	5 (2,8)	0,41	4 (9,8)	1 (2,1)	13 (5,9)	6 (2,7)
1-year mort. n (%)	55 (30,7)	89 (49,7)	<0,001	13 (34,3)	10 (21,6)	68 (31,4)	99 (43,7)

"Standard" indicates medical treatment, along with balloon aortic valvuloplasty in most (84%) of the patients.

Upon our request, the study sponsor provided a subgroup analysis comparing the outcomes in anatomically and medically inoperable patients, shown in Table 5.

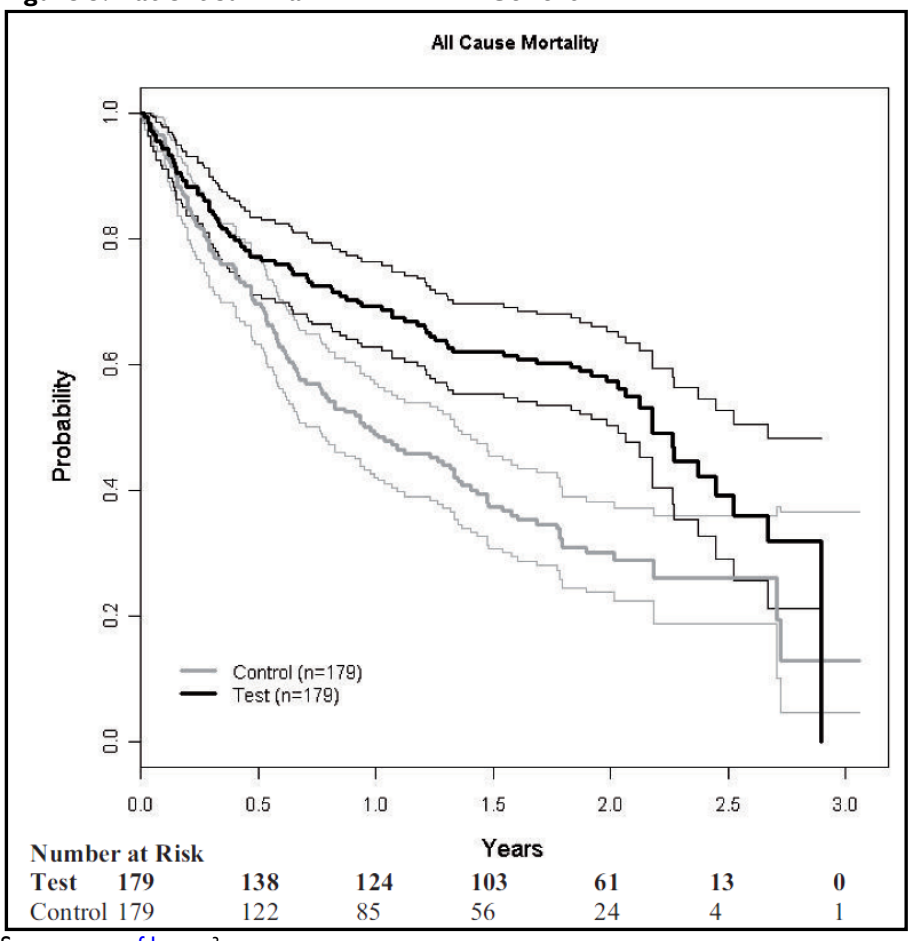
Table 5. Outcomes in anatomically and medically inoperable Cohort B patients in the PARTNER trial

	Medically inoperable		Anatomically inoperable	
Statistics	TAVI - TF	Control	TAVI - TF	Control
No. of patients	126	142	53	37
No. of person-years	173.0	146.8	85.2	39.7
Early death (days <= 30)	8 (6.3%)	4 (2.8%)	1 (1.9%)	1 (2.7%)
Death at 1 year	42 (33.3%)	70 (49.3%)	13 (24.5%)	19 (51.4%)
Late death (days > 30)	53 (42.1%)	90 (63.4%)	17 (32.1%)	24 (64.9%)
All Death	61 (48.4%)	94 (66.2%)	18 (34.0%)	25 (67.6%)
KM survival rate at 30 days	93.7	97.2	98.1	97.3
KM survival rate at 1 year	66.7	49.7	75.5	47.6

TF: transfemoral;
Source: Study sponsor (I. Merioua and J. Goldstein – August 10, 2011).

Long term survival of Cohort B patients has been presented at the July 20, 2011 FDA meeting. Kaplan-Meier survival estimates (along with their 95% confidence intervals) are shown in Figure 3.

Figure 3. Patient survival in PARTNER Cohort B



Source: www.fda.gov [3]

2.2.2 Re-hospitalisations, cardiac symptoms and QoL

The co-primary endpoint was the rate of a hierarchical composite of the time to death from any cause, or the time to the first occurrence of repeat hospitalisation due to valve-related or procedure related clinical deterioration. The superiority of TAVI related to this endpoint was confirmed (observed in 42.5% of patients in the TAVI group and in 70.4% of controls). Reduced hospitalisation for aortic stenosis or its treatment was 22.3% (TAVI) vs. 44.1% (control) at one year.

At 30 days, 6 months, and 1 year, symptoms were significantly reduced in the TAVI group. At 1 year, 74.8% of the surviving patients who had undergone TAVI, as compared with 42.0% of the surviving patients who had received standard therapy, were asymptomatic or had mild symptoms (NYHA class I or II) (P<0.001).

The 6-minute walk test (6MWT) was a pre-specified secondary endpoint in the study. It could reportedly be performed in only a subgroup of patients, owing to the presence of coexisting conditions in many of the patients. At 1 year, a paired analysis of the distance covered during a 6-minute walk test showed that there was significant improvement after TAVI (P = 0.002) and no change after standard therapy (P = 0.67). The article does not provide numerical data on this item.

2.2.3 Stroke

Strokes were observed more frequently in the TAVI group than in the standard therapy group at 30 days (6.7% vs. 1.7%, p=0.03) and at 1 year (10.6% vs. 4.5%, p=0.04). The number of strokes observed in the TAVI group and reported at the July 20, 2011 FDA panel were higher than those published: 7.3% at 30 days, and 11.2% at 1 year. The number of all neurological events (ischemic, hemorrhagic, unspecified) over the whole study period was more than 3 times higher in the TAVI group (n=25, 14%) as compared to the control group (n=8, 4.5%). Of note, of 8 neurological events observed in the control group over the entire study period, only 2 occurred in truly medically treated patients (one at the day of randomisation and one at the third day after randomisation.[3] Six other events occurred in control patients who underwent AVR (n=1) or balloon valvuloplasty (n=5).

2.2.4 Vascular complications

At 30 days, TAVI, as compared with standard therapy, was associated with a higher incidence of major vascular complications (16.2% vs. 1.1%, p<0.001).

The FDA in its assessment of the PARTNER results introduced a combined endpoint that probably better grasps the number of hemorrhagic vascular complications than those reported by the investigators who treated "vascular complications " and "major bleeding" separately. The FDA defined hemorrhagic vascular complications as (1) haematoma at access site >5 cm, (2) false aneurysm, (3) arterio-venous fistula, (4) retroperitoneal bleeding, (5) peripheral ischemia/nerve injury, (6) transfusion for catheterisation complication and (7) vascular surgical repair. This endpoint occurred in 55.9% of TAVI patients within the first 30 days.[3]

2.2.5 Paravalvular leaks

A paravalvular leak refers to the condition where aortic valve regurgitation occurs because of valve-annulus mismatching in a way that during diastole, part of the blood that is ejected into the aorta can flow back between the prosthesis and the aortic wall. Moderate or severe paravalvular aortic regurgitation was present in 11.8% of the patients in the TAVI group at 30 days and in 10.5% at 1 year.

At 1 year, 15.6% of TAVI patients had moderate or severe aortic regurgitation.[3]

2.2.6 Pacemaker insertion

A substantial number of patients already had a permanent pacemaker at baseline: 22.9% in the TAVI group and 19.5% in the standard therapy group. At 1 year, a new pacemaker was implanted in 4.5% of TAVI patients and in 7.8% of standard therapy patients.

2.3 PARTNER TRIAL – DISCUSSION

The PARTNER-US trial currently represents the one and only randomised controlled trial on TAVI. Before, our knowledge of the safety and the performance of TAVI was based on uncontrolled patient registries.[1] This trial enrolled the highest-risk patients ever seen in any cardiovascular trial by virtue of their age and severity of co-morbid conditions.[12]

2.3.1 Methodological quality

We assessed the methodological quality of the PARTNER trial with the instrument developed by the Dutch Cochrane Centre,[b] in which 9 questions related to study design have to be answered. The resulting assessment is summarised hereafter ("☺" indicates low risk of bias, "☹" indicates high risk of bias and "?" indicates the item is not clearly reported by the authors).

3. Patients randomised to intervention/control? …….. ☺
4. Concealment of allocation? …… ?
5. Patients blinded to treatment allocation? ……. ☹
6. Investigators blinded to treatment allocation? ……. ☹
7. Assessors blinded to treatment allocation? ……. ☹
8. Baseline comparable in study groups? ..... in Cohort A ☺, in Cohort B ☹
9. Many drop-outs? ……..…..…….. ☺
10. Intention to treat analysis? ……. ☺
11. Apart from the intervention, similar treatment in both groups?..... ?

In contrast to the authors' claim that "baseline characteristics of patients in the two groups were generally well balanced", we find them to be unevenly distributed in Cohort B. This may be due to the play of chance, or it may be caused by a flawed randomisation. The trial protocol is very cryptic in its description of the randomisation process by stating that "randomisation was accomplished according to a computer-generated randomisation scheme". Under these circumstances, the treatment sequence is adequately randomised, but it does not exclude the investigators being aware of the treatment allocation of patients they were considering for the study. Our inquiry of the sponsor did not lead to additional information on the procedure they followed to guarantee concealment of allocation.

Blinding of investigators and patients obviously is impossible and/or ethically unjustified in this type of study. The protocol stipulated that all members of the clinical events committee were blinded to the primary results of the study. Later inquiry by the FDA revealed that the investigators went against this rule.[3]

In Cohort A, among the 699 patients, 42 did not undergo the assigned procedure: 4 (1.1%) in the transcatheter group and 38 (10.8%) in the surgical group. In Cohort B, of the 179 patients assigned to TAVI, 6 (3.4%) did not receive a transcatheter heart valve. Patients were followed for at least 1 year.

The analyses were performed with data from the intention-to-treat population, which included all patients who underwent randomisation, regardless of the treatment actually received. As-treated analyses started at the time of induction of anaesthesia in the procedure room.

The overall assessment of the methodological quality of this trial based on both the Dutch Cochrane instrument and the Jadad score (2/5),[13] indicates a substantial risk of bias.

b http://dcc.cochrane.org/beoordelingsformulieren-en-andere-downloads

The primary effectiveness and safety endpoint for Cohort A was freedom from all cause mortality at 1 year in the ITT population. The test was performed as a one-sided non-inferiority test. The rationale for choosing non-inferiority testing instead of superiority testing in the Cohort B analysis is not straightforward. What is the use of showing that a new device, that is 6 times more expensive than an alternative, performs not worse in terms of survival?

2.3.2 Conflicts of interest

The PARTNER trial was sponsored by Edwards Lifesciences. Of 22 authors of the PARTNER trial, 1 is employed by Edwards Lifesciences and 1 is member of the board. 8 authors received consultancy payments that were not related to the PARTNER trial from Edwards, and 4 disclosed a financial interest in TAVI through stock or stock options.

Dr. Martin Leon, the co-principal investigator of the PARTNER trial, who initiated the development of the Sapien heart valve, is reported to have received $6.9 million from Edwards Lifesciences when it purchased Percutaneous Valve Technologies, the heart valve company he founded.[14] The deal reportedly also included to Mr. Leon the chance to earn an additional $1.5 million if the product achieved certain milestones, one of which related to the number of patients successfully treated.[15]

Mr. Leon reveals owing stock options in Sadra Medical, a company involved in "the development of minimally invasive alternatives to traditional surgical aortic valve replacement" (http://www.sadramedical.com).

2.3.3 Control treatment

Of 351 patients randomised to the control arm in the high risk surgery Cohort A, 38 (10.8%) did not undergo surgery.

Patients randomised to the control arm in the non-surgical Cohort B received "standard therapy". Balloon aortic valvuloplasty (BAV) was performed in 114 of them (63.7%) during the 30 days after randomisation and in an additional 36 patients (20.1%) more than 30 days after randomisation. The clinical effectiveness and safety of BAV is disputed by some experts.[16] The European Society of Cardiology's clinical guidelines stipulate that "BAV could be considered as a *palliative* measure in individual cases when surgery is contraindicated because of severe co-morbidities".[17] In the American heart Association's 2008 update on valvular heart disease, it is concluded that "BAV might be reasonable for *palliation* in adult patients with AS in whom AVR cannot be performed because of serious comorbid conditions".[18]

Despite the fact that all the patients in Cohort B were determined not to be suitable candidates for surgery, 12 (6.7%) of the patients who were assigned to standard therapy underwent aortic-valve replacement, 5 (2.8%) underwent placement of a conduit from the left ventricular apex to the descending aorta plus aortic valve replacement, and 4 (2.2%) underwent TAVI at a non-participating site. The 1-year rates of death of those patients were 33%, 80%, and 0%, respectively.

2.3.4 Baseline risk of PARTNER enrolees

As discussed earlier, the estimation of a patient's risk for AVR was of primary importance for his/her enrolment and subsequent stratification into one of the PARTNER trial's cohorts (Figure 1). The operative risk of those patients can be estimated through 4 different (groups of) parameters:

- Quantitative risk scores (STS score and EuroSCORE) that combine several risk factors (cf. appendix)
- Individual medical risk factors, some of which are not accounted for in the abovementioned risk scores
- Anatomic characteristics of patients rendering the technical act of cardiac surgery difficult or even impossible to be performed
- Clinical feeling of the physicians involved

In this paragraph we first compare the differences in baseline characteristics between Cohort A and B patients. These differences are the result of the initial stratification of patients ("stratification #1" in Figure 1). Next, we analyse baseline differences between patient groups within the two study cohorts, i.e. after the second stratification procedure (related to trans-femoral accessibility) and the randomisation.

2.3.4.1 *Comparison of patient characteristics in Cohort A vs. Cohort B*

In this paragraph we discuss differences in baseline characteristics of Cohort A vs. Cohort B patients.

Quantitative operative risk scores

A patient's eligibility for Cohort B was not dependent on any particular risk factor but resulted from a general clinical assessment of the surgeons and cardiologists involved. Stratification of patients into Cohort A on the other hand was based on the patients' STS risk score and had to be 10% or more. However, if this score was lower than 10%, a patient could still be enrolled if the investigators agreed that the predicted mortality was presumed to be 15% or higher, because of unfavourable patient characteristics not captured by the STS score. Correspondingly, any STS score could have been appropriate to allocate a patient to any cohort of the PARTNER trial. As shown in Table 1, there are no major differences in the average quantitative risk scores between the trial cohorts.

Table 6. Operative risk scores and observed mortality risk in PARTNER Cohort A patients

	COHORT A	
	TAVI	AVR
STS score	11,8±3,3	11,7±3,5
Logistic EuroSCORE	29,3±16,5	29,2±15,6
30-day mortality	ITT: 3,4	ITT: 6,5
	AT: 5,2	AT: 8,0

Figures refer to % mortality; ITT: intention to treat analysis; AT: "as treated" analysis.

Table 6 shows that currently available risk scores perform poorly in predicting the operative risk of patients considered for TAVI: an STS score of 11.7% and a EuroSCORE of 29.2% correspond with an observed operative risk of 8.0%. It has been amply demonstrated that the EuroSCORE performs badly in those cases. In a US study from the Mayo Clinic, data from 1177 patients that underwent an isolated AVR between 2000 and 2006 were analysed.[6] In the highest risk tertile of patients, based on the logistic EuroSCORE, 30-day mortality was estimated at 23.6%, which sharply contrasted with an observed mortality of 5.8%. In this respect, some scientists have argued that using the EuroSCORE in TAVI studies "could be interpreted as deliberate and unfair, not to say unethical, in bedevilling the surgical procedure for these patients".[19] Although the STS-score in the PARTNER trial outperformed the EuroSCORE, it has been stressed that both models have suboptimal discriminatory power.[20, 21]

Individual risk factors

Before enrolment into the PARTNER trial, patients were stratified as "high risk for operation" or "inoperable" (Figure 1). Although one would therefore expect more severe co-morbid conditions in Cohort B, most of the registered co-morbidities were equally represented in the two cohorts (Table 7). Some however were more prevalent in either one of the cohorts.

Table 7. Medical baseline characteristics of PARTNER trial enrolees, by cohort

	COHORT A	COHORT B
N	699	358
Age (yr)	84,1	83,2
Male sex (%)	57,3	46,4
NYHA class II - %	5,9	7,0
NYHA class III or IV - %	94,2	93,1
Coronary artery disease - %	75,9	71,0
Previous myocardial infarction - %	28,4	22,5
Previous CABG - %	43,4	41,5
Previous PCI - %	33,3	27,7
Previous Balloon aortic valvuloplasty	11,8	20,3
Cerebral vascular disease - %	28,4	27,5
Peripheral vascular disease - %	42,3	27,7
COPD - %: Any	43,2	46,9
COPD - %: Oxygen-dependent	8,2	23,5
Creatinine >2 mg/dL - %	9,1	7,6
Atrial fibrillation - %	41,8	40,9
Previous pacemaker - %	21,0	21,2
Pulmonary hypertension - %	39,4	43,1
Liver disease - %	2,3	3,4
Moderate or severe mitral regurg. - %	20,6	22,6
Frailty - %	16,6	23,1

Percentages depicted are calculated averages of the published subgroup numbers (TAVI, standard treatment, surgery) shown in Table 1. COPD: chronic obstructive pulmonary disease.

More patients in Cohort B had oxygen-dependent chronic obstructive pulmonary disease (COPD), more of them previously underwent balloon valvuloplasty or more were frail. Coronary artery disease, previous myocardial infarction and peripheral vascular disease were more prevalent in Cohort A.

Anatomic characteristics

Prohibitive anatomic conditions are relatively easy to recognise clinically, and include porcelain aorta, chest wall radiation or deformity, and multiple previous interventions. Most of these characteristics are not included in the quantitative risk score instruments. As expected, almost all patients presenting with one of these anatomic abnormalities are found in cohort B patients (Table 8).

Table 8. Anatomic abnormalities at baseline in PARTNER trial enrolees, by cohort

	COHORT A	COHORT B
Extensively calcified aorta - %	0,9	15,1
Effects of chest-wall irradiation - %	0,9	8,7
Chest-wall deformity - %	0,2	6,7

Percentages depicted are calculated averages of published subgroup (TAVI, standard treatment, surgery) figures as depicted in Table 3.

The correspondence of the average quantitative operative risk scores in the PARTNER cohorts as shown in Table 6 may result from the fact that Cohort B mixes patients with high and low operative risk scores. Patients deemed inoperable because of prohibitive anatomic conditions have a low STS score in the absence of medical co-morbid conditions.

Clinical feeling

Apart from differences in the prevalence of prohibitive anatomic abnormalities, quantitative operative risk scores and the prevalence of co-morbid conditions are similar in both study cohorts. Correspondingly, it appears that the clinical feeling of the physicians is key in the assessment of the medical status and the subsequent stratification of patients into either one of the study cohorts.

The intra- and inter-observer variability in the estimation of the operative risk in an elderly patient with severe aortic stenosis and significant co-morbidities is not clear. In cohort A, the observed (as treated) operative mortality (8.0% - Table 6) is lower than what would have been expected from the mortality enrolment criterion (STS score of ≥10%, or coexisting condition that would be associated with a predicted operative risk of death of ≥15%).

In a TAVI feasibility study, Svensson et al. reported on the fate of patients that were referred to their respective institutions for potential TAVI, but who ultimately were not treated as such.[22] Of the 71 patients referred to Medical City Hospital, Dallas, 14.1% (n=10) received a conventional surgically inserted valve with no peri-operative deaths. For the 92 patients referred to the Cleveland Clinic, 20% (n=19) had conventional open surgery with no operative deaths.

2.3.4.2 Patient characteristics within the PARTNER cohorts subgroups

In this paragraph, we discuss the observed differences in baseline characteristics of patients within both PARTNER trial cohorts, resulting from the randomisation process. Ideally, randomisation should lead to an even distribution of risk factors across patient groups within each cohort.

Quantitative operative risk scores and individual risk factors

Table 1 shows baseline characteristics of PARTNER enrolees in both cohorts, by treatment group. In Cohort A, co-morbidities are well balanced over the two study groups. In Cohort B on the other hand, and in contrast to the investigators' claim, baseline characteristics are unevenly distributed among the two study groups and most discrepancies favour survival in the TAVI patients.

EuroSCORE, COPD and atrial fibrillation are statistically significantly ($p<0.05$) more prevalent in the control group. There are also more patients with a previous myocardial infarction (26.4 vs 18.6%, p=0.10) and less patients with an extensively calcified aorta (11.2 vs. 19.0%, p=0.05) whereas control patients have a lower left ventricular ejection fraction than TAVI patients (51.1% vs. 53.9%, p=0.06). Patients with "frailty" are overrepresented in the Standard Therapy arm of Cohort B. All these imbalances might be due to chance but they may as well result from a flawed randomisation. All the same, they may have a substantial impact on the final results of the study leading to better outcomes in the TAVI treated group.

Anatomic characteristics

Within Cohort B, patients with prohibitive anatomic conditions are unevenly distributed between the study groups. The total number of patients with anatomic prohibitive conditions was 53 (29.6%) in the TAVI group and 37 (20.7%) in the control group (Table 3). They have a better prognosis because they do not necessarily have severe co-morbid conditions. In a post hoc subgroup analysis, the 1-yr survival following TAVI is an absolute 8.8% better in the anatomically inoperable subgroup of patients than in the medically inoperable (Table 5).

88 out of 358 (25%) of PARTNER Cohort B patients presented with 1 or more of these anatomical characteristics. In Cohort A, anatomical prohibitive abnormalities were present in 1 to 2% of patients (i.e. 7 to 14 out of 699). Hence, these abnormalities are found in about 10% of the overall PARTNER population (Table 3).

Patient frailty might also be considered as an anatomic prohibitive condition. It is more often present in standard care group of Cohort B (bottom line of Table 1). Frail patients are typically those in whom an invasive procedure has a higher risk for complications.[23]

Consequently, an under-representation of those patients in the TAVI subgroup leads to an under-estimation of complications.

Clinical feeling

Obviously, clinical feeling should not play a role in the randomisation process. However, if concealment of allocation was not adequate – which cannot be excluded from the paper and could not be clarified by our inquiry of the sponsor – the clinical feeling of participating investigators may have played a role.

2.3.5 Continued Access study

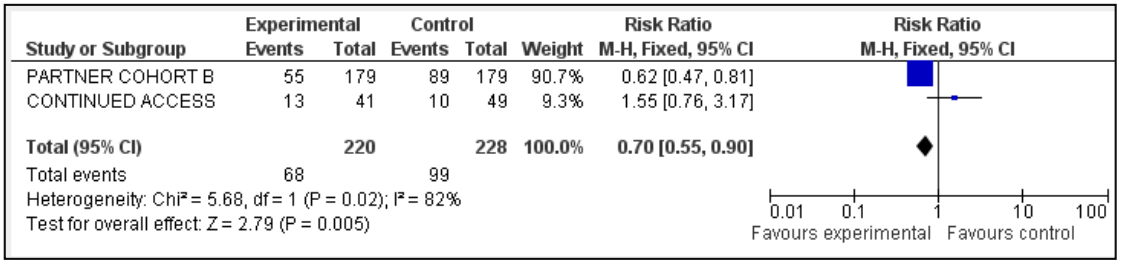
Data related to the randomised Continued Access Cohort B subgroup were presented by the sponsor at the July 20, 2011 FDA meeting and results are depicted in Figure 4.[11] These data show that 1-year mortality in the Continued Access control group is more than twice as high than in the control group of the pivotal Cohort B (50.7% vs. 21.6%) (Table 9).

Table 9. Pivotal and Continued Access study results

	PIVOTAL COHORT B		CONTINUED ACCESS	
	TAVI	STANDARD	TAVI	STANDARD
STS score	11.2±5.8	12.1±6.1	12,1±6,7	13,3±6,9
N	179	179	41	49
Logistic EuroSCORE	26.4±17.2	30.4±19.1	27,5±17,7	32,8±21,2
30-day mort.	5,0%	2,8%	4 (9,8)	1 (2,1)
1-yr. mort.	30,7%	50,7%	34,3%	21,6%

Since the Continued Access study protocol (until August 2009, n=90 - Figure 2) was the same as the pivotal PARTNER study, it is appropriate to pool the mortality data from both patient populations in a meta-analysis as presented in Figure 4.

Figure 4. Risk ratio for all-cause 1-year mortality of TAVI in inoperable patients. Meta-analysis of PARTNER Cohort B and Continued Access patients.



Source: KCE. Meta-analysis software from the Cochrane Collaboration, RevMan 5.1

Obviously, the pooled mortality risk ratio becomes higher than the treatment effect initially published by Leon et al.[7] The impact of this consideration will be further discussed in the chapter on cost-effectiveness of TAVI.

2.3.6 Risk of stroke in the PARTNER trial

In both PARTNER cohorts, the incidence of stroke in patients treated with TAVI was about 10% at 1 year, which was twice as high than in the control patients. The aetiology of stroke lies within the uncontrollable embolisation of debris from the native aortic valve at the time of dilatation and insertion of the prosthesis. Furthermore, the space contained between the aortic wall and the prosthesis might remain a source of embolic material after the implantation procedure. It has been shown by magnetic resonance imaging that in up to 84% of TAVI patients new clinically silent cerebral lesions develop. Recent studies have evaluated the feasibility of embolic protection devices during TAVI, but their role remains currently undefined.[24, 25]

2.3.7 The trans-apical TAVI approach

Patients assessed for inclusion in the PARTNER trial and deemed inoperable at screening were contemplated for inclusion in Cohort B. Those with no adequate trans-femoral access route could reasonably have been considered for trans-apical TAVI, as initially proposed by the FDA.[3] This proposition was however declined by the sponsor and these patients were excluded from the study with no further data collection (Figure 1).

In Cohort A, trans-apical TAVI is performed in patients in whom there was no acceptable trans-femoral access route. The number of patients in Cohort A that were allocated to trans-apical TAVI did not allow to provide sufficient statistical power to reach robust conclusions on this subgroup. Furthermore, no comparison can be made between outcomes in trans-femoral and trans-apical TAVI from Cohort A because of baseline differences between those patient groups, their stratification being based upon the availability of a trans-femoral access.

Thus, the PARTNER trial does not add to our knowledge of the performance of trans-apical TAVI, since patients that were potentially eligible for the trans-apical approach were deliberately excluded from entry in Cohort B. Cohort A was insufficiently powered to compare trans-apical TAVI with surgery, and trans-apical TAVI could not be compared to trans-femoral TAVI because of baseline differences of patients.

2.3.8 Comparison of PARTNER trial data with results from case series

In our previous report on TAVI, observational data made us conclude that the early procedural mortality after TAVI, defined as all-cause 30-day mortality, might be higher than following conventional surgery. Based on then recently published series of high risk patients that actually underwent AVR, we estimated operative mortality to be 5.8%.[6] Based on data from recent registries, 30-day mortality rate for trans-femoral Sapien® TAVI was estimated to be 7.9%.[1, 4, 26]

The 30-day "as treated" mortality of AVR observed in PARTNER Cohort A (8.0%) was higher than our 2008 estimate (Table 10). The trans-femoral TAVI procedural mortality in Cohort A (3.7%) was unexpectedly low and this figure represents the lowest mortality rate ever reported in any TAVI series. Combining the mortality rates of trans-femoral TAVI from both PARTNER cohorts leads to an average 30-day mortality rate of 4.8%. This is substantially lower than our estimate from earlier case series. It is also substantially lower than mortality rates from registries published in 2010 and 2011.[10, 27, 28] This observation dissolves our initial safety concerns with TAVI,[1] at least in the Cohort A type of patients.

Table 10. 30-day mortality (as treated, %) following TAVI and AVR in very high risk patients, estimated in the 2008 KCE TAVI report[1] and observed in the PARTNER trial and in recent patient series

	region	time window	n**	surgical AVR	trans-femoral Sapien®	trans-apical Sapien®
2008 KCE TAVI report estimates*	Europe	< 2008	518	5,8	7,9	13,7
Thomas	Europe	2007-2009	463		6,3	10,3
Rodés-Cabau	Canada	2005-2009	168		9,5	11,3
FRANCE-2 Registry	France	2010-2011	810		7,8	11,5
PARTNER Cohort A	US	2007-2009	344	8,0	3,7	8,7
PARTNER Cohort B	US	2007-2009	179		6,4	
PARTNER Cohort A+B	US	2007-2009	523		4,8	

Series published in 2010 and 2011 with at least 100 patients and selected from Coeytaux[28] and Buellesfeld[27]. AVR: (surgical) aortic valve replacement. *: numbers refer to Figure 7.1 in 2008 KCE TAVI report.[1] Thomas: SOURCE Registry[29]. Rodés-Cabau: [30]. FRANCE-2 data presented at EuroPCR, May 2011. **: refers to the number of trans-femoral TAVI in the corresponding study.

Key points

GENERAL REMARKS

- **TAVI is a highly invasive and challenging procedure addressing elderly people in poor general condition. The procedure takes on average over 4 hours (skin-to-skin time 2 to 3 hours). It involves prolonged general anaesthesia, the administration of contrast media, and trans-oesophageal echocardiography. It is complicated with hemorrhagic vascular adverse events in more than 50% of patients.**
- **Differentiating "patients who cannot undergo surgery" (PARTNER Cohort B) from "surgical high-risk patients" (Cohort A) essentially relies on the clinical feeling of the physicians involved.**
- **The treatment effect of TAVI may be overestimated in PARTNER because of methodological concerns and a potential impact of conflicts of interest. Long term outcomes related to a residual aortic regurgitation after TAVI, and the long term durability of the prosthesis remain unknown.**

PARTNER Cohort A

- **In patients with aortic stenosis who are at very high surgical risk, TAVI and surgery are associated with a similar mortality rate at 30 days and 1 year and produce similar improvements in cardiac symptoms.**
- **The abovementioned observation dissolves our initial safety concerns of TAVI, but the approximate doubling in the rate of stroke 1 year after TAVI (8.3%) compared to surgery (4.3%) remains a concern.**
- **The 30-day mortality rate of TAVI observed in Cohort A of the PARTNER trial is the lowest ever reported in a TAVI study although most of the participating centres had no previous experience with TAVI.**

PARTNER Cohort B

- **The PARTNER trial does not allow to assess the performance of trans-apical TAVI in inoperable patients.**
- **In patients with severe aortic stenosis who are no candidates for surgery, TAVI significantly reduces the rate of death from any cause (ARR 20% at 1 year) as compared with standard therapy.**
- **In the Continued Access population (n=90), TAVI had an absolute 12.7% higher mortality at 1 year as compared with standard therapy.**
- **Standard therapy included a balloon aortic valvuloplasty in most patients, a procedure considered as a palliative measure that has never been shown to be more effective than medical treatment.**
- **Stroke rate at 1 year was twice as high in TAVI patients compared to standard therapy (10.6% vs. 4.5%).**
- **In Cohort B, patients with prohibitive anatomical conditions were unevenly represented in both study groups. Subgroup analysis of those patients showed a more favourable effect of TAVI at 30 days (4.4% absolute survival difference) and after 1 year (8.8% absolute difference) compared to patients with medical prohibitive conditions.**

3 COMPARATIVE EFFECTIVENESS OF THE SAPIEN® AND COREVALVE® DEVICES

Currently, two different percutaneous aortic valves have received a CE label and are widely used throughout Europe: Edwards' Sapien® valve and Medtronic's CoreValve®. The Sapien® valve is a bio-prosthetic valve made of bovine pericardial tissue mounted into a balloon expandable stainless steel open-cell stent. The valve is available in two sizes (23 and 26 mm) and can be implanted using the trans-femoral (22/24 Fr introducers) or trans-apical (26 Fr introducer) approach. The CoreValve® consists of a tri-leaflet bio-prosthetic porcine pericardial tissue valve, mounted into a self-expandable nitinol frame available in two sizes, 26 and 29 mm (18 Fr introducer). The CoreValve today has the advantage of a smaller introducer size for trans-femoral access in comparison with the Sapien® valve. This size allows for a larger use of trans-femoral implantation in smaller arteries (6.0 mm) and for access through the subclavian artery.[31]

Until recently, the safety and performance of these valves was derived from uncontrolled patient series. By the end of 2010, the results of the first ever RCT on TAVI, the PARTNER trial, studying the Sapien® valve was published as discussed previously.

In December 2010, Medtronic launched an FDA approved clinical trial to study TAVI using the CoreValve® 18 Fr device in high risk patients with symptomatic aortic stenosis (ClinicalTrials.gov identifier NCT01240902). Patients will be randomised one-to-one to either TAVI with CoreValve® or to surgical AVR. Patients deemed at extreme risk will not be randomised to optimal medical management, but they will be evaluated against "a performance goal derived from contemporary studies" (sic). The first implants in this "Medtronic CoreValve® U.S. Pivotal Clinical Trial" occurred in December 2010. Overall, the trial will enrol more than 1,300 patients at 40 U.S. clinical sites.

So far, there have been no randomised head-to-head comparisons between the two valve types. According to experts and based on uncontrolled observational studies from different investigators in diverse patient groups, it is assumed that mortality outcomes and clinical effectiveness with both valve types are comparable.[32] A consistently reported observation from registries however is the higher need for permanent pacemaker implantation following CoreValve® TAVI.[32, 33] In a systematic review of the literature, data from case series indicated that the incidence of pacemaker implantation following TAVI is higher with the CoreValve® prosthesis (5 studies, mean 20.8%, range 9.3–30.0%) than with the Sapien® prosthesis (6 studies, mean 5.4%, range 0–10.1%). The mean incidence of pacemaker implantation following conventional AVR was 7.0% (range 3–11.8%, median 7.2%).[33] The Belgian registry reports that new pacemaker implantation at 1 month occurred more often in CoreValve® recipients: in 22% of patients vs. in 5% of Sapien® recipients.[19]

4 BELGIAN TAVI DATA

4.1 BELGIAN TAVI REGISTRY

During the preparation of this report, we had several contacts with Belgian experts in TAVI. They keep close contacts with each other in a distinct Working Group, currently representing 22 Belgian TAVI centres. Each centre has chosen to use only 1 of the 2 currently CE-labelled percutaneous valves as shown in Table 11.

Table 11. Belgian TAVI centres in alphabetical order along with the percutaneous aortic valve brand they support

CHR Citadelle	Sapien	St Jan Brugge	CoreValve
CHU Charleroi	Sapien	St Jan Brussel	CoreValve
CHU Liège Sart Tilman	CoreValve	St Luc Bouge	Sapien
Gilly	Sapien	Stedelijk ZH Aalst	CoreValve
H Hart Roeselare	CoreValve	UCL Mont Godinne	Sapien
Imelda Bonheiden	CoreValve	UCL Saint Luc	Sapien
Jessa Hasselt	CoreValve	ULB Erasmus	Sapien
Jolimont	Sapien	UZ Antwerpen	CoreValve
KULeuven	Sapien	VUB Jette	CoreValve
Namur	CoreValve	ZNA Midddelheim	CoreValve
OLV Aalst	Sapien	ZOL Genk	Sapien

Source: Prof. J. Bosmans, UZ Antwerpen

Data from the Belgian TAVI registry have recently been published.[19] The authors report data from 328 patients, treated in 15 centres in Belgium up to April 2010. Follow-up time is not reported. Eight centres implanted 141 CoreValve® (18F trans-femoral or sub-clavian) and 7 centres implanted 187 Sapien® valves (99 trans-femoral and 88 trans-apical).

Baseline characteristics of Belgian patients along with those from the PARTNER trial are shown in Table 12. A number of baseline characteristics are ambiguously reported in the publication and are therefore not mentioned.

Table 12. Baseline characteristics of patients included in the PARTNER-US study cohorts and in the Belgian TAVI registry

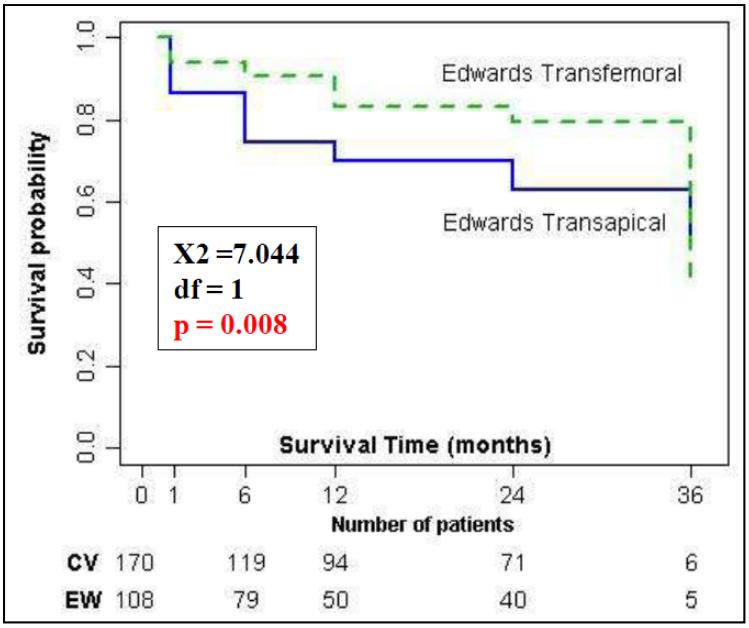
	COHORT B		COHORT A		BELGIUM
	TAVI	STANDARD	TAVI	AVR	EDWARDS
N	179	179	348	351	187
Age (yr)	83,1	83,20	83,6	84,5	83±6
Male sex (%)	45,80	46,90	57,8	56,7	47,0
Logistic EuroSCORE	26,4±17,2	30,4±19,1	29,3±16,5	29,2±15,6	30±16
NYHA class II - %	7,8	6,1	5,7	6	20
NYHA class III or IV - %	92,2	93,9	94,3	94	80
Coronary artery disease - %	67,6	74,3	74,9	76,9	59
Previous CABG - %	37,4	45,6	42,6	44,2	25
Cerebral vascular disease - %	27,4	27,5	29,3	27,4	27
Peripheral vascular disease - %	30,3	25,1	43	41,6	38
Extensively calcified aorta - %	19,0	11,2	0,6	1,1	7

Data sources: PARTNER A: Smith et al.[8], PARTNER B: Leon et al.[7], Belgian Registry: Bosmans et al.[19] TAVI: Transcatheter Aortic Valve Insertion. AVR: (surgical) Aortic Valve Replacement.

The age and the EuroSCORE of Belgian patients is similar to those of the PARTNER trial patients. Belgian patients may be less sick, as far as suggested by the (limited) available baseline characteristics. Less than 10% of PARTNER patients are in NYHA functional class II, in contrast to 20% of the Belgian patients. Coronary artery disease is more prevalent in the PARTNER patients (70%) than in Belgian patients (59%) and more patients had a history of CABG in the PARTNER population (40% vs. 25%). The proportion of patients with porcelain aorta in the Belgian series (7.0%) matches the average proportion over the mixed PARTNER cohorts (7.9%).

The 30-day mortality of Belgian patients treated with the trans-femoral Sapien® device is reported to be 6% in 99 patients from a total of 328 TAVIs.[19] In May, 2011, updated and longer-term outcomes following CoreValve® and Sapien® TAVI in Belgium were presented at the EuroPCR2011 meeting (Figure 5).[34] Trans-femoral Sapien® patients in this series constitute 173 out of a total of 600 TAVIs. Visual assessment of the Kaplan-Meier graphs indicates an unchanged (6%) 30-day mortality rate in the updated population (Figure 5). Based on the timeframes presented in these communications[19, 34] it can be estimated that about 270 TAVI procedures have been performed in Belgium between April 2010 and May 2011.

Figure 5. Patient survival in Belgian TAVI Registry



Adapted from EuroPCR2011[34]

4.2 BELGIAN SICKNESS FUNDS DATA

4.2.1 Data source

IMA-AIM[c] disposes of most data related to the compulsory health insurance available from the Belgian sickness funds.

Particularly relevant to this study, the data contains per patient the following information (among others):

- The amount reimbursed by the compulsory health insurance (RIZIV[d]-INAMI) per health care related item (nomenclature code) or pharmaceutical product (CNK code).
- The amount of the co-payment to be paid by the patient.
- The date of the reimbursement.
- Socio-demographic information on the patient: age, gender, year and month of decease if the patient is deceased.

As TAVI is currently not reimbursed by the compulsory health insurance, there is no direct way to identify TAVI patients or conservative treatment patients in the reimbursement data of the compulsory health insurance as registered by the Belgian Sickness Funds. However, with the cooperation of the Belgian TAVI working group centre (see Table 11) we obtained aggregated data through IMA-AIM of the TAVI patients and of the conservative treatment patients. The TAVI Working Group identified 325 patients with a TAVI between 1st June 2006 and 30th June 2010 and 72 patients with conservative treatment.

The TAVI Working Group provided information on valve type, approach and date of implant (TAVI). Furthermore, data from a series of 72 consecutive inoperable patients with severe aortic stenosis, treated conservatively before the introduction of TAVI in Belgium, were provided via Prof. J. Bosmans (University Hospital Antwerp). In these patients, the date of the decision for accepting a conservative treatment was used as the "date of intervention".

IMA-AIM provided the following aggregated information:

- Distribution of age at TAVI date and gender
- Survival analysis
- Descriptive statistics[e] on a number of cost groups (health care related items and pharmaceutical products, see the appendix in the supplement to this report for details).
- Descriptive statistics on total costs reimbursed 30 days before and 30 days after TAVI
- Descriptive statistics on total costs reimbursed in the TAVI hospital stay (entire stay and split into pre- and post-TAVI [includes day of implant]).

The descriptive statistics on costs are based on 310 TAVI patients and 71 conservative treatment patients because of incomplete reimbursement data for some patients. The cost results are used in the economic model and are therefore presented in chapter 6 on cost-effectiveness.

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c Intermutualistisch Agentschap – Agence Intermutualiste (http://www.cin-aim.be)

d Rijksinstituut voor Ziekte- en Invaliditeitsverzekering (RIZIV); l'Institut National d'Assurance Maladie Invalidité (INAMI)

e Mean, SD, median, Q1, Q3, 95% confidence interval of the mean.

4.2.2 Patient characteristics

4.2.2.1 Valve type and approach

About 70% of the patients received TAVI femoral (see Table 13). For Edwards Sapien, this constituted about half of the patients, while for CoreValve, it was the approach for the vast majority of the patients.

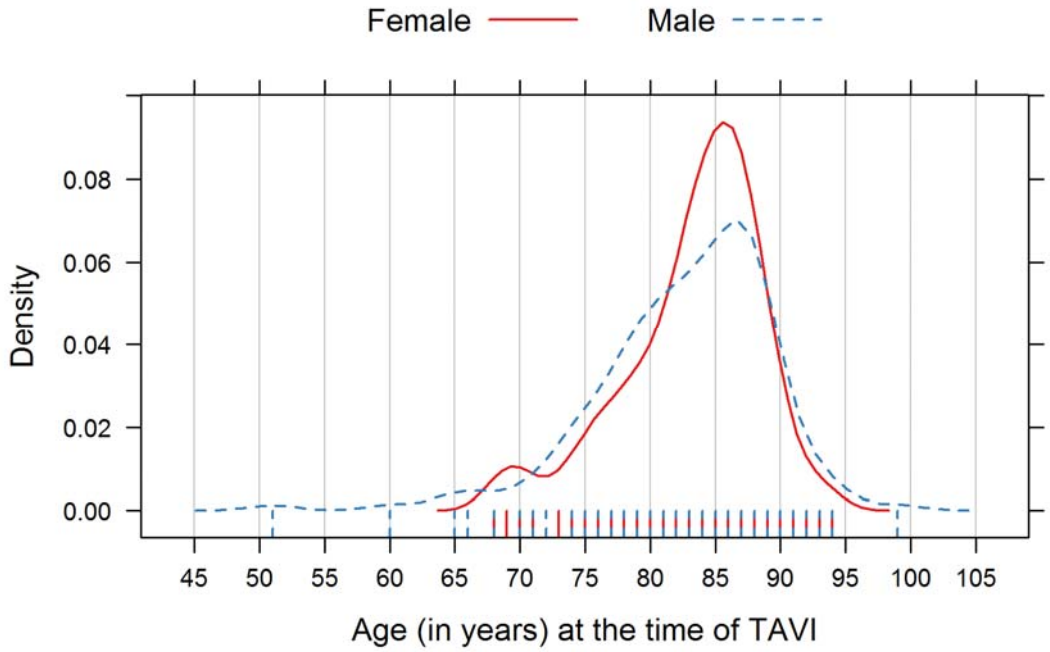
Table 13 Number of patients by valve type and approach

	Apical		Femoral		Subclavicular		Total	
	N	%	N	%	N	%	N	%
CoreValve			126	94.7%	7	5.3%	133	40.9%
Edwards	88	45.8%	104	54.2%			192	59.1%
Total	88	27.1%	230	70.8%	7	2.2%	325	100.0%

4.2.2.2 Age and gender

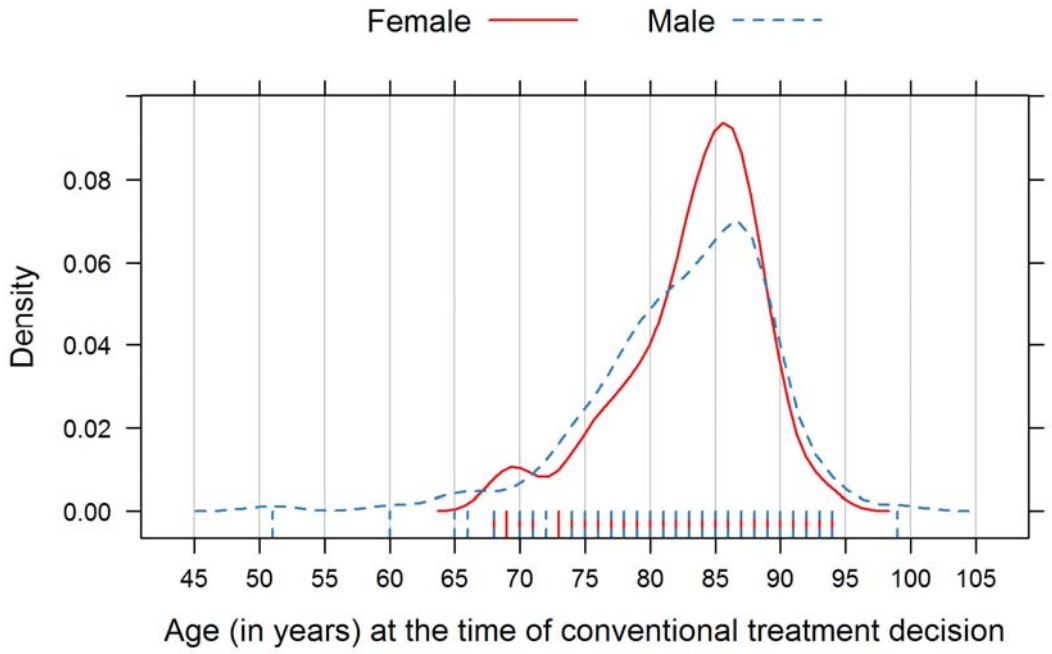
There are about as many female TAVI patients than male TAVI patients (respectively 52.6% and 47.4%). On average, the female TAVI patients are about 9 months older than the male TAVI patients (respectively female M=83.32, SD=5.24; male M=82.58, SD=6.74; see also Figure 6).

Figure 6 Age and gender distribution of TAVI patients



The conservative treatment patients are on average slightly younger than the TAVI patients (female N=51, M=81.94, SD=4.87; male N=20, M=79.20, SD=5.87; see also Figure 7).

Figure 7 Age and gender distribution of conservative treatment patients



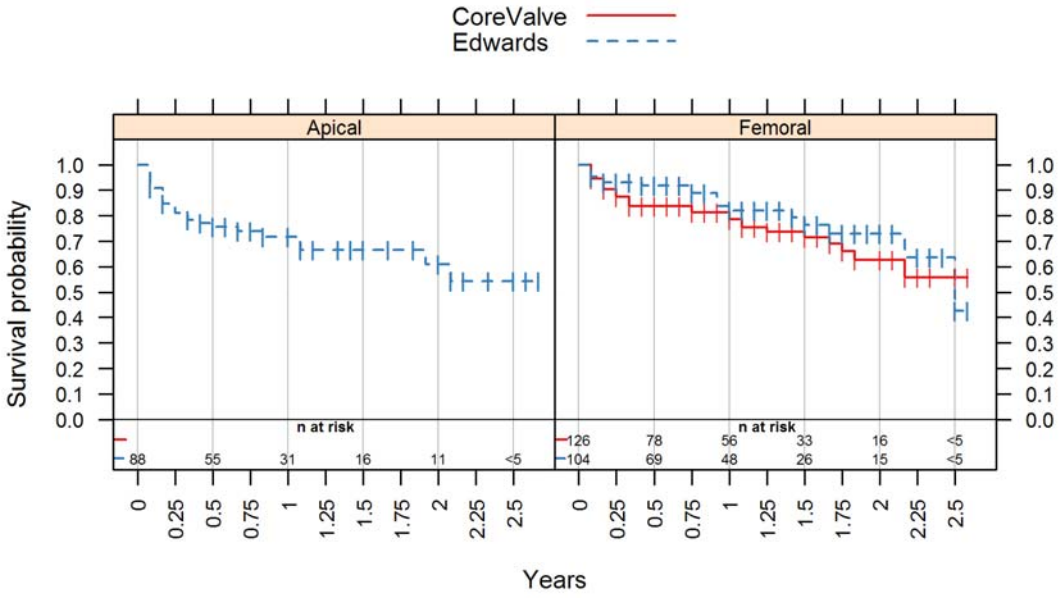
4.2.2.3 Survival analysis

Based on the availability of year and month of decease, product limit (Kaplan-Meier) survival probability estimates were calculated for the TAVI patients and conservative treatment patients. Confidence intervals for these estimates reported in the text are based on a logarithmic transformation of the survival probability estimates.

Due to the observational nature of the data, the difference in survival between the valve type and approach groups does not imply a causal link. Other unaccounted for factors can possibly explain the differences found. Therefore, no formal statistical models where developed to assess possible differences. Also, the cost-effectiveness analyses considers only the survival as reported in RCT studies.

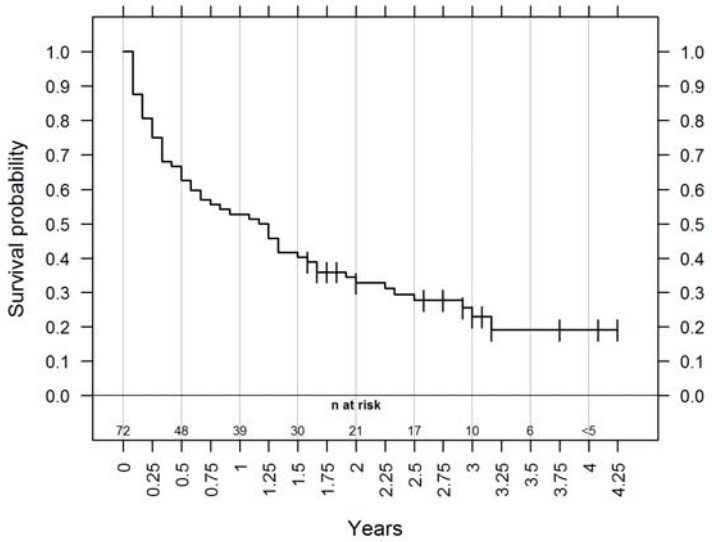
The probability to survive beyond one year in the apical approach is estimated at 0.72 (CI: 0.62, 0.83) for patients with Edwards Sapien valves (see Figure 8). For the femoral approach, the probability to survive beyond one year for the patients with Edwards Sapien valves is estimated at 0.82 (CI: 0.73, 0.91). For CoreValve, the probability to survive beyond one year is estimated at 0.78 (CI: 0.71, 0.87). The results beyond 2 years shown in Figure 8 should be considered with caution given the somewhat limited period of data available (as evidenced by the number of patients at risk).

Figure 8 Kaplan-Meier survival probability estimates for TAVI patients by valve type and approach (subclavicular approach is not shown because of the small number of patients).



Patients with conservative treatment are estimated to survive beyond one year with a probability of 0.53 (CI: 0.42, 0.66) (see Figure 9). Similar to the TAVI patients, the results beyond 2.5 years shown in Figure 9 should be considered with caution given the somewhat limited period of data available (as evidenced by the number of patients at risk).

Figure 9 Kaplan-Meier survival probability estimates for conservative treatment patients



4.3 BELGIAN DATA AVR PATIENTS

4.3.1 Data source

The TCT[f] disposes of a pathology and expenditure database of all Belgian hospital stays: MKG-RCM / AZV-SHA[g].

Particularly relevant to this study, the data contains per hospital stay the following information (among others):

- The amount reimbursed by the compulsory health insurance (RIZIV-INAMI) per health care related item (nomenclature code some of which are grouped) or pharmaceutical product (CNK code).
- The date of the reimbursement.
- Socio-demographic information on the patient: age and gender.
- Pathology related information: ICD-9-CM diagnostic and procedure codes and severity of illness[h].

Hospital stays were selected based on the presence of ICD-9-CM procedure codes in Table 11 between 2004 and 2007. Additionally, only hospital stays with reimbursement of the valve implant (nomenclature code 684740) were selected. In case patients had more than one hospital stay with these characteristics (0.65%), only the first was taken into account. A total of 9 213 hospitals stays were retained.

Table 14 ICD-9-CM case selection codes

ICD-9-CM	Description
3520	Replacement of unspecified heart valve
3521	Replacement of aortic valve with tissue graft

Descriptive statistics for total costs of reimbursements were calculated for the hospital stay, both for the entire stay and for the pre- and post intervention part of the hospital stay. Also these statistics were calculated for the following subgroups:

- Severity of illness 1 or 2 versus 3 or 4.
- Age < 70 years versus age >= 70 years.

These costs calculations are used in the economic model and are presented in chapter 6 on cost-effectiveness.

4.3.2 Patient characteristics

There were somewhat more male than female AVR patients (respectively 58.2% and 41.8%). The patients with severity of illness 1 or 2 where slightly younger than those with severity 3 or 4 (respectively severity of illness (SOI) 1 or 2: p=20%, M=68.1, SD=12.4; SOI 3 or 4: p=80%, M=71.1, SD=11; see also Figure 10).

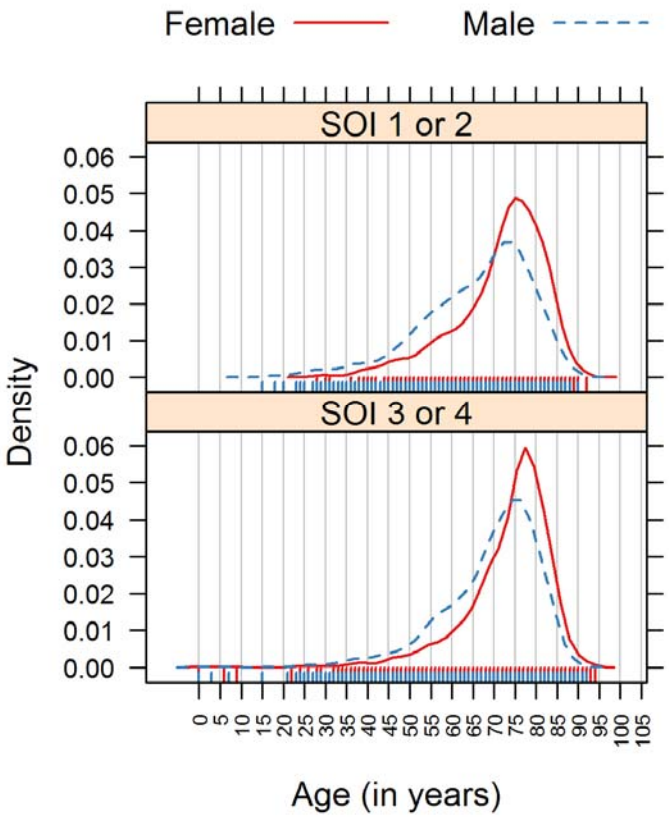
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f Technische Cel – Cellule Technique (http://tct.fgov.be).

g Minimale Klinische gegevens – Résumé Clinique Minimal / Anonieme Ziekenhuisverblijven – Séjours Anonymes Hospitaliers.

h Each hospital stay is attributed a severity of illness score of 1 (minor), 2 (moderate), 3 (major) or 4 (extreme) based on pathology and patient information (https://tct.fgov.be/webetct/etct-web/html/nl/fbho_faq.jsp#hfd4).

Figure 10 Age and gender of AVR patients by severity of illness category



5 ORGANISATIONAL ISSUES

5.1.1 TAVI reimbursement abroad

A question on whether or not TAVI is reimbursed and under which conditions was sent to INAHTA members (International Network of Agencies for Health Technology Assessment). International reimbursement of TAVI is very different (Table 15). In some countries there is no reimbursement (Scotland and Australia). In others it is conditional (Austria, Canada and Spain). In Germany, Lithuania and Switzerland it is reimbursed without specific conditions. In several other countries, the discussion on reimbursement is currently going on.

The situation in Germany is particularly interesting. With a nearly twice as high reimbursement for TAVI (€36,000) as compared to open surgery (mean ca. €17,500), it becomes financially interesting for hospitals to perform TAVI. In 2010, nearly 25% of all aortic valve replacements in Germany were done in a minimally-invasive way. Nearly 100 hospitals perform TAVI. The German Society of Cardiovascular and Thoracic Surgeons (DGTHG) has established a national registry to monitor the introduction of TAVI at http://www.aortenklappenregister.de (website in German). The data in this registry are neither population-based nor complete. Therefore, interpretation of outcomes is difficult. Nevertheless, in 2010, 3629 TAVI procedures were registered and mortality ranged around 7.7%. The registry has shown that many patients received TAVI, although their valves could also have been replaced by open surgery. As open valve replacement has a mortality of only 3%, this broadening of indication may put patients' lives at unnecessary risks. DGTHG has issued a position statement in order to remind their members of the professional duties: http://www.aortenklappenregister.de/images/pdf/2009-06_aortenklappen.pdf (in German, English Abstract available) and http://www.dgthg.de/node/284 (personal communication).

This situation in Germany shows that (because of financial incentives or other reasons) overuse of the technique is possible, which might results in no better or even worse outcomes (for high-risk and low-risk operable patients) and an enormous waste of resources.

Table 15. International TAVI reimbursement*

Australia	**Percutaneous aortic valve replacement does not have Therapeutic Goods Administration approval** for use in Australia but is obtainable via a special access scheme or via clinical trial notification as part of a clinical trial or registry. The technology is unlikely to be reimbursed in Australia at this time. In the public sector, the procedure would be provided at the expense of the public hospital providing the service and in the private sector it may be possible that Private Health Funds would consider reimbursement on a case-by-case basis.
Austria	TAVI will be reimbursed from 2012 on. It will be a **conditional reimbursement**. The specialized centres have to be permitted by the regional funds responsible for reimbursement of hospitals. The reimbursement rate will be from January on about 27,000 points**.

Canada	- The Medtronic **CoreValve** Revalving System is **not currently authorized for marketing** in Canada. It has been made available for PAVI/TAVI procedures, but only under Health Canada's Special Access Program for medical devices, which allows doctors to gain access to medical devices that have not yet been approved for sale in Canada on a compassionate basis. There are very specific requirements that must be met to gain access to unapproved medical devices; such devices may be made available by the Canadian regulator for emergency use cases or when conventional therapies have failed, are unavailable, or are unsuitable to treat a patient. - The Edwards **SAPIEN** Transcatheter Heart Valve was just **recently (22 June 2011) authorized** by Health Canada for sale in Canada; prior to this approval, this valve was also available for PAVI/TAVI but only under Health Canada's Special Access Program for medical devices, as above. - The TAVI/PAVI procedure is performed in Canada. Because health care funding in Canada is decentralized and a responsibility of each Canadian province or territory, each of these regions in Canada independently establish a physician reimbursement code and amount reimbursed for the PAVI/TAVI procedure. - As far as criteria for patients who will have access to publicly funded TAVI/PAVI, there is a group of Canadian cardiac surgeons currently developing specific written criteria. Individual provinces/territories may develop their own patient reimbursement criteria as well. - Based on a document of one hospital, the SAPIEN device costs CAD20,000 (~€14,400, exchange rate 8 September, 2011)
Canada (province of Quebec)	*Province of Quebec*: There are no specified conditions for reimbursement, however the Ministry of Health has recommended a **maximum number of TAVI of 300 for the province of Quebec** (about 8 million inhabitants).
Canada (province of Alberta)	*Province of Alberta*: PAVI physician fees are covered through our public health care system. Specific technologies are **not specified** for the procedure. It would be covered by Alberta Health Services through public funds. Alberta Health Services would decide which device(s) they would be providing to the patient.
Germany	Since 2010, German hospital can obtain **reimbursement** for endovascular valve implantation, which is nearly twice as high (€36,000) as compared to open surgery (mean ca. €17,500). Reimbursement of individual TAVI cases is not checked by German Statutory Health Insurances in such detail, that would allow to detect whether the patient was a true candidate for TAVI.
Lithuania	In 2009, the first TAVI procedure was carried out in Lithuania. In the first half of 2011, three such operations were carried out. Currently, there are **no special conditions for reimbursement** of TAVI and the first interventions were fully reimbursed by the National Health Insurance Fund under the Ministry of Health.

Scotland	TAVI is **not routinely reimbursed** in NHS Scotland. There is no TAVI service. However, a small number of patients have been referred to NHS England to receive this procedure.
Spain (Galicia)	In the Galician Health Government the SAPIEN and Corevalve valves were approved under a **conditional coverage scheme** in june 2008 for the treatment of severe aortic-valve stenosis in patients > 75 years that present comorbidities that make them inadequate candidates for conventional surgery (high operative risk patients). The results of the mandatory registry are being analyzed at present and **reimbursement indications will be reviewed** during this year.
Switzerland	TAVI is **reimbursed** without specific restrictions.
The Netherlands	Based on the results of the PARTNER trial, the competent authorities are **discussing the conditions for TAVI reimbursement**.
United States	On 20 July, 2011, an **FDA advisory panel recommended approval** of Edward's Sapien® device in PARTNER Cohort B type patients, but a formal market approval has not yet been granted.

* Remark: the content displayed in this table is based on personal communication. This list is not complete since answers were not received from all INAHTA members. The answers were not checked for correctness.
** 1 Point = 1 euro (year 2005). 1 Point = Cost-Equivalence Rate Based on the year 2005.

5.1.2 Professional associations' statements

A limited search for position statements from professional organisations revealed a 2011 consensus document originating from the US and an updated 2010 statement from Belgian professionals, both issued after the results of the PARTNER trial had become available.

Two older documents were identified and are of interest in relation to the proposed minimally required professional skills and institutional infrastructure: the 2008 European position statement and a British consensus document.

5.1.2.1 US TAVI expert consensus document

This paper represents a professional society overview from the American College of Cardiology Foundation and the Society of Thoracic Surgeons.[12] It stresses that the availability and reimbursement of TAVI should be limited to centres of excellence and should be implemented by multidisciplinary heart teams using standardised protocols. It also emphasises the need for the establishment of a registry to perform post-market surveillance, outcome measurement and comparative effectiveness research.

This document does not yet specify quantitative operator and/or institutional requirements, nor does it take cost-effectiveness of TAVI into consideration. It stresses that the adoption of TAVI is currently to be limited to the population studied in the PARTNER trial. The authors notice that the 30-day mortality rates in PARTNER are better than those reported from European registries and they wonder whether these remarkable results will be reproducible in real world practice after commercialisation.

Of note, this document was published on-line on June 27, 2011, at a time when TAVI was even not yet approved for market introduction in the US. Only US centres that participated in the PARTNER trial (Continued Access) and those that took part in Medtronic's CoreValve® trial are allowed to treat patients with TAVI in the US. As mentioned earlier, on July 20 2011, an FDA advisory panel recommended approval of Edward's Sapien® device in PARTNER Cohort B type patients, but a formal market approval has not yet been granted.[3]

5.1.2.2 Belgian cardiac surgeons

A position statement has been issued by the BACTS, the Belgian Association for Cardio-Thoracic Surgery on December 9, 2010 (appendix 8.6). Next to similar US infrastructural and organisational recommendations, it formulates two propositions that are specifically related to the Belgian health care context. It is proposed that heart centres that want to practice TAVI should have at least a yearly volume of 100 patients undergoing aortic valve surgery. A second proposition formulated by the BACTS is the requirement for each patient of an a priori approval for TAVI by a cardiologist and a cardiac surgeon appointed by the RIZIV/INAMI. They have to be independent from the requesting heart team.

According this document, eligible patients might be those with a contraindication for surgery and/or at least a logistic EuroSCORE >20% and STS-score >10%. On the other hand, the authors confess that the EuroSCORE and STS-score are not accurate predictors of mortality for this high risk population.

This statement does not consider the cost-effectiveness of TAVI, although "the very high cost of the prosthesis" is admitted.

5.1.2.3 European professional societies' position statement

Similarly to the previous statements, recommendations related to professional and infrastructural requirements are listed. It is argued that TAVI should "currently be restricted to patients at high-risk or with contra-indications for surgery" but the results of the PARTNER trial were not yet known at the moment this statement was issued (published ahead of print on May 13, 2008).

The authors contend that TAVI should be restricted to a limited number of high-volume centres.

5.1.2.4 British position statement

A position statement from the British Cardiovascular Intervention Society (BCIS) and the Society of Cardiothoracic Surgeons (SCTS) is available on-line and copied in appendix 8.7. It is argued that occasional practice and small volume TAVI units should be actively discouraged. A minimum annual number of 24 cases per TAVI unit is considered to be reasonable, "but given the learning curve and infrastructure needed we believe somewhere in the order of > 50 cases per year to be optimal".

6 COST-EFFECTIVENESS OF TAVI

The 2008 KCE report on percutaneous aortic valves recommended to reconsider the decision whether to reimburse PAV technology when the results of the ongoing US based RCT (PARTNER IDE) become available. If this RCT provides evidence on safety and effectiveness of the PAV, its acceptability (cost-effectiveness) and affordability (budget impact) need to be assessed.[1]

In this chapter the cost-effectiveness of TAVI versus relevant comparators is calculated. We remark that the cost-effectiveness is calculated for a PARTNER-like population since the treatment effect is only available for this RCT. It is not clear in how far the Belgian population that actually received TAVI reflects the PARTNER population.

6.1 METHODS

In the methods section several aspects of the model are described: analytic technique, perspective, population, intervention and comparator, time window and discounting, model structure, and the values (and uncertainty) for input parameters. Belgian pharmacoeconomic evaluation guidelines[35] are followed and more details are provided in the relevant sections. Details on both sensitivity and scenario analyses are also provided. In a subsequent section, results are presented.

6.1.1 Analytic technique

A Markov simulation model is developed in Excel in order to assess the efficiency of TAVI. Both cost-effectiveness (with outcomes expressed in life-years gained) and cost-utility analyses (with life-years gained adjusted for quality of life) are performed.

The @Risk adds-on tool is used for probabilistic modeling and probabilistic sensitivity analyses. Half-cycle corrections are performed.

6.1.2 Perspective

In accordance with the Belgian pharmacoeconomic guidelines, the analysis includes direct health care costs from the perspective of the health care payer. Payments out of the government's health care budget as well as patients' co-payments are included. Since baseline employment rates are expected to be low in this population, indirect productivity costs are ignored.

6.1.3 Population

The model simulates a hypothetical cohort of 1,000 TAVI-eligible patients. The type of participants considered reflects the PARTNER-US patients: patients with severe aortic stenosis and cardiac symptoms for whom conventional surgery to replace the aortic valve was associated with high risk.[7]

The PARTNER study (NCT00530894) incorporated two parallel prospective, multicenter, randomized, active-treatment-controlled clinical trials.[7] Patients were divided into two cohorts: those who were considered to be candidates for surgery despite the fact that they were at high surgical risk (cohort A) and those who were not considered to be suitable candidates for surgery (cohort B). In the first cohort, TAVI could be performed transfemoral or transapical (in case of no transfemoral access).

The average age was 84 and 83 years, in cohort A and B, respectively. The proportion of males was 57% and 46%, respectively. This is reflected in the model and taken into account when extrapolating the short-term results into lifetime outcomes.

6.1.4 Intervention and comparators

Two relatively mature technologies are in clinical use: the SAPIEN Transcatheter Heart Valve (Edwards Lifesciences) and the CoreValve Revalving System (Medtronic).[36] The Edwards SAPIEN heart-valve system (Edwards Lifesciences) is used in the PARTNER-US study. This economic evaluation is restricted to this system of aortic valve implantation.

The comparator is different for the two cohorts. In the high surgical risk patients (cohort A) this is surgical valve replacement (AVR). In the non-operable patients (cohort B) this is a 'non-surgical approach' (NSA).

6.1.5 Time horizon and discount rate

A lifetime horizon is applied if the intervention has an impact on mortality after one year. This is the case for TAVI in inoperable patients (cohort B) in comparison with CT. In this case, survival data are extrapolated (6.1.8) to extend the time window beyond the trial follow-up period until all patients in the model died. In an alternative scenario, the time horizon is restricted to 3 years. We come back to this in our discussion (see part 6.3).

In contrast, the trial results for high-risk patients (cohort A) did not show significant survival differences after one year. Therefore, in this case, the model's time horizon is restricted to the one-year trial follow-up period. For the base-case, conform to the Belgian guidelines, future costs and benefits are discounted at a rate of 3% and 1.5%, respectively (or 0.247% and 0.124% on a monthly basis). For cohort B, these rates are changed in scenario analyses (0). With a 1-year time horizon, this is not useful for cohort A and therefore not implemented.

6.1.6 Modeling approach and structure

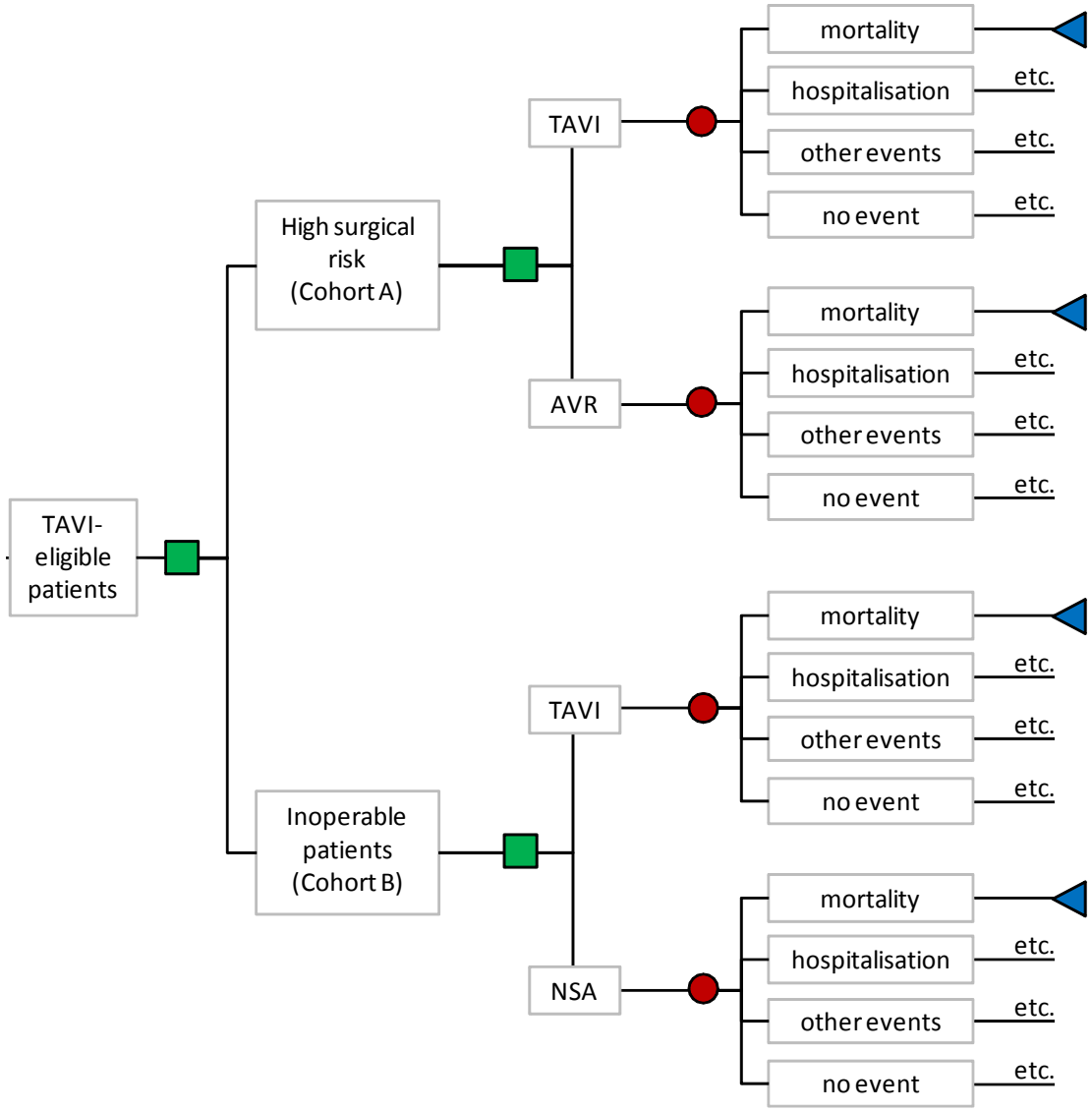
We want to calculate the cost-effectiveness of a PARTNER-like population, but for the Belgian context. In our approach, we use the data of the PARTNER trial to model the treatment effect on mortality (see 6.1.7 and 6.1.8), quality of life (6.1.9) and other events (6.1.10). For context-specific costs for certain events, we rely on Belgian cost data (6.1.11).

The Markov model with monthly cycles is shown in Figure 11. TAVI's cost-effectiveness is calculated in a similar way for cohort A and B but with another comparator (AVR and NSA, respectively).

The incremental effects are based on the published mortality data at 30 days and at one year, quality of life data (EQ-5D), and extrapolation scenarios (lifetime horizon for cohort B).

For incremental costs, the initial cost differences between TAVI and the surgical intervention during hospitalization and between TAVI and NSA are taken into account. The impact of including events occurring after the initial hospitalization will also be included. The number of events is based on the published RCT, and costs for initial interventions and events are based on Belgian data. Details on probabilities are mentioned in part 6.1.7 and 6.1.10. Details on costs are provided separately in part 6.1.11.

Figure 11. TAVI model.



AVR: aortic valve replacement; NSA: non-surgical approach; TAVI: transcatheter aortic valve insertion.
The green square is a choice node, the red dots are chance nodes and the blue triangles are end nodes.

6.1.7 Mortality (treatment effect and extrapolation)

Both intention-to-treat (ITT) and as-treated (AT) analyses results are presented. Intention-to-treat analysis started at the time of randomization, and the as-treated analysis started at the time of induction of anesthesia in the procedure room.[8] The primary data analysis was performed in the ITT population. In this cost-effectiveness analysis, ITT results are implemented in the model. As such, mortality is included similarly over all treatment groups. In cohort A, the mean (±SE) interval between randomization and treatment was significantly longer in the surgical group than in the transcatheter group (15.6±1.1 days vs. 10.6±0.7 days, P<0.001).[8] In cohort B, there is only a delay between randomization and treatment in the TAVI group. In this group, after randomization, the median time to TAVI was 6 days (interquartile range, 3 to 11).[7]

Differences in time between randomization and actual treatment can distort results. For example, a person dying one day after randomization is counted in all groups in the ITT analysis. In contrast, with the as-treated analysis, this person would only be taken into account in the NSA group and not for AVR or TAVI if the procedure was planned a couple of days later. On the other hand, especially with a procedure being planned up to on average 15 days after randomization, 30-day mortality since randomization can differ substantially from 30-day mortality since treatment.

In the base case scenario, ITT results will be used in cohort A and B. In a scenario analysis, the as-treated mortality rates will be applied that were published for cohort A. The rates of death at 30 days were higher among patients who had undergone transapical placement than among those who had undergone transfemoral placement.[8] Therefore, next to an analysis for the cohort as a whole, subgroup analysis will also be performed for the transapical and transfemoral approach.

A validity check was applied to check whether the modeled one-year mortality was consistent with the published rates.

Cohort A

The primary hypothesis in cohort A of the PARTNER-US trial was that transcatheter replacement is not inferior to surgical replacement.[8]

At 30 days, in the *intention-to-treat analysis*, the rates of death from any cause were 3.4% in the transcatheter group and 6.5% in the surgical group (P = 0.07). In the transfemoral cohort, the rates of death from any cause at 30 days were 3.3% in the transcatheter group and 6.2% in the surgical group (P = 0.13). Among patients in the transapical-placement cohort, the rates of death at 30 days were 3.8% in the transcatheter group and 7.0% in the surgical group (P = 0.32).[8] In the *as-treated analysis*, the rates of death were 5.2% in the transcatheter group and 8.0% in the surgical group (P = 0.15).[8]

At one year, The rates of death from any cause were 24.2% in the transcatheter group and 26.8% in the surgical group (P = 0.44).[8]

These probabilities are included in the model as beta distributions.[37] The parameters are shown in Table 16. Full details for alternative scenarios (including one-year mortality and parameters of the beta distributions) are provided in appendix 8.3.

The monthly mortality rate between the second month and one year is deducted from the one-month and 1-year mortality and is assumed to be constant over this period.

Table 16. Model input variables: mortality

	Average		Beta distribution	
	publication	model	alpha	beta
Cohort A (ITT, All)*				
TAVI				
30 days	3.4%	3.4%	12	336
1 year	24.2%	24.2%	84	263
month 2-12		2.2%		
AVR				
30 days	6.5%	6.5%	22	317
1 year	26.8%	26.8%	89	243
month 2-12		2.2%		
Cohort B				
TAVI				
30 days	5.0%	5.0%	9	170
1 year	30.7%	30.7%	55	124
month 2-12		2.6%		
NSA				
30 days	2.8%	2.8%	5	174
1 year	49.7/50.7%	50.0%	89	89
month 2-12		5.9%		

AVR: aortic-valve replacement; ITT: intention-to-treat; NSA: non-surgical approach; TAVI: transcatheter aortic valve insertion.
The source for data on cohort A is based on Smith et al.[8]. For cohort B, this is Leon et al.[7]
The alpha parameter equals the number of events. The beta parameter equals the number at risk minus the number of events.
* The beta parameter was adjusted so that the average value equals the published mortality probability.

Cohort B

Of the 179 patients assigned to TAVI, 6 (3.4%) did not receive a transcatheter heart valve of which 2 patients died before the scheduled implantation. In the first 30 days after the procedure, 11 of the 173 patients who underwent TAVI (6.4%) died.[7] Based on the ITT analysis, 9 of the 179 patients (5.0%) died after 30 days.[i] In the NSA group, 5 of the 179 patients died (2.8%). These proportions are included in the model as beta distributions. In a scenario analysis, the higher 30-day mortality after procedure is modeled.

At 1-year, 55 of the 179 patients (30.7%) died in the TAVI group, as compared with 89 of the 179 patients (49.7%) in the NSA group.[7] Again, these probabilities are modeled as beta distributions (Table 16).

6.1.8 Extrapolation

In the base case scenario, both for cohort A and B, mortality is modeled in accordance with published 30 day and one-year results.

In cohort A, the time window is limited to one year since survival rates at 1 year are similar.

In cohort B, there are significant differences in mortality at one year. After one year, the calculated mortality rate between month 2 and 12 is used for extrapolating results to a lifetime horizon. In this extrapolation scenario, the constant monthly mortality rate increases yearly according to the age- and sex specific mortality rates of the total Belgian population.

[i] "At 30 days after randomization, the rate of death from any cause was 5.0% in the TAVI group as compared with 2.8% in the standard-therapy group (P = 0.41)".[7] This is different from the number of deaths 30 days after the procedure due to the difference in timeframe.

In our discussion, we will compare the results of this extrapolation with the results from other analyses.

6.1.9 Utilities

Cohort A

At 30 days, more patients in the transcatheter group than in the surgical group had a reduction in symptoms to NYHA class II or lower (P<0.001). Among patients who could perform 6-minute walk tests, patients in the transcatheter group walked farther than those in the surgical group (P = 0.002).[8] The NYHA functional class was no longer different at 6 months. At 1 year, patients in the two study groups had an improvement in cardiac symptoms and the 6-minute walk distance, with no evidence of significant between-group differences.[8] 152 out of 264 (58%) surviving TAVI patients and 175 out of 262 (66%) surviving surgical patients were able to perform a 6MWT.

According to the study protocol, quality of life was also measured with the EQ-5D questionnaire that allows mapping of health status to population-level utility weights. This is an important metric for cost-effectiveness analysis. No further information is provided on the mapping of the health states to utility weights. The EQ-5D results are not published (yet). These data were requested directly from the study sponsor and the FDA. Unfortunately, we did not receive these data in due time. We made the assumption that QoL in the TAVI group was similar to QoL measured in the TAVI group in cohort B (see Table 17). For the AVR group, we assumed QoL of survivors was the same as for the TAVI group, with exception of the first month reflecting the difference between the percutaneous intervention and the open-heart surgery. For this first month, QoL in the AVR group was assumed to be arbitrarily 0.1 point lower than in the TAVI group. A scenario analysis is performed assuming QoL is arbitrarily 0.1 lower in the AVR group versus the TAVI group during every month of the first year.

Cohort B

TAVI was associated with a significant reduction in symptoms, as assessed with the use of the NYHA classification system and the results of a 6-minute walk test.[7] At 1 year, 74.8% of the surviving patients who had undergone TAVI, as compared with 42.0% of the surviving patients who had received standard therapy, were asymptomatic or had mild symptoms (NYHA class I or II) (P<0.001). The 6-minute walk test could be performed in only a subgroup of patients, owing to the presence of coexisting conditions in many of the patients. At 1 year, a paired analysis of the distance covered during a 6-minute walk test showed that there was significant improvement after TAVI (P = 0.002) and no change after standard therapy (P = 0.67).[7]

The EQ-5D quality of life measure was used. This generic utility measure was applied both at baseline and after 1, 6 and 12 months. The results were provided by the study sponsor and are described in Table 17. These values are included in the model. Uncertainty was incorporated by modeling utilities with a beta distribution with the same average and standard deviation. An adjustment of 0.02 was added in the control group, i.e. the difference in baseline values between the TAVI and control group. A linear extrapolation between values is assumed between baseline, 1, 6 and 12 months. After 12 months, quality of life remains at the QoL-level of month 12.

Table 17. EQ-5D values (cohort B)

EQ-5D Utilities	TAVI	NSA
Baseline	0.59 ± 0.23	0.57 ± 0.23
1 month	0.71 ± 0.23	0.64 ± 0.22
6 months	0.72 ± 0.26	0.66 ± 0.24
12 months	0.72 ± 0.24	0.62 ± 0.23

Average ± standard deviation

NSA: non-surgical approach; TAVI: transcatheter aortic valve insertion.

6.1.10 Repeat hospitalization, stroke and other events

Several clinical outcomes at 30 days and 1 year are mentioned in the publications of the TAVI RCTs. The probability that certain events occur is described in this part. For the costs per event, we refer to part 6.1.11.5.

Repeat hospitalizations is included in the model, both for cohort A and B. For the other events, we focus on those that differ significantly between both treatment groups in cohort A or B, being stroke or TIA, vascular complications, major bleeding, and cardiac reintervention.

Cohort A

Table 18 shows the clinical outcomes in cohort A. Most important differences are noticed in major strokes, vascular complications, major bleeding and new-onset atrial fibrillation.

Table 18. Clinical outcomes at 30 days and 1 year (cohort A, ITT, All patients)

Increase 30days vs 1 year:
+n: absolute number
+n: percentage point (ppt)

Table 2. Clinical Outcomes at 30 Days and 1 Year in the Intention-to-Treat Population.*

Outcome	30 Days				1 Year			
	Transcatheter Replacement (N=348)	Surgical Replacement (N=351)	P Value		Transcatheter Replacement (N=348)	Surgical Replacement (N=351)	P Value	
	no. of patients (%)				*no. of patients (%)*			
Death								
From any cause	12 (3.4)	22 (6.5)	0.07		84 (24.2)	89 (26.8)	0.44	
From cardiac causes	11 (3.2)	10 (3.0)	0.90	*+13.8*	47 (14.3)	40 (13.0)	0.63	*+11.8*
Repeat hospitalization	15 (4.4)	12 (3.7)	0.64	+43	58 (18.2)	45 (15.5)	0.38	+33
Death or repeat hospitalization	25 (7.2)	33 (9.7)	0.24		120 (34.6)	119 (35.9)	0.73	
Stroke or transient ischemic attack								
Either	19 (5.5)	8 (2.4)	0.04		27 (8.3)	13 (4.3)	0.04	
Transient ischemic attack	3 (0.9)	1 (0.3)	0.33		7 (2.3)	4 (1.5)	0.47	
Stroke								
Minor	3 (0.9)	1 (0.3)	0.34	*+1.3*	3 (0.9)	2 (0.7)	0.84	*+0.3*
Major	13 (3.8)	7 (2.1)	0.20	+4	17 (5.1)	8 (2.4)	0.07	+1
Death from any cause or major stroke	24 (6.9)	28 (8.2)	0.52		92 (26.5)	93 (28.0)	0.68	
Myocardial infarction	0	2 (0.6)	0.16		1 (0.4)	2 (0.6)	0.69	
Vascular complication								
Any	59 (17.0)	13 (3.8)	<0.001	*+0.3*	62 (18.0)	16 (4.8)	<0.001	*+0.3*
Major	38 (11.0)	11 (3.2)	<0.001	+1	39 (11.3)	12 (3.5)	<0.001	+1
Acute kidney injury								
Creatinine >3 mg/dl (265 μmol/liter)	4 (1.2)	4 (1.2)	0.95		12 (3.9)	8 (2.7)	0.41	
Renal-replacement therapy	10 (2.9)	10 (3.0)	0.95	*+5.4*	18 (5.4)	20 (6.5)	0.56	*+6.2*
Major bleeding	32 (9.3)	67 (19.5)	<0.001	+17	49 (14.7)	85 (25.7)	<0.001	+18
Endocarditis	0	1 (0.3)	0.32	*+3.5*	2 (0.6)	3 (1.0)	0.63	*+1.1*
New-onset atrial fibrillation†	30 (8.6)	56 (16.0)	0.006	+12	42 (12.1)	60 (17.1)	0.07	+4
New pacemaker	13 (3.8)	12 (3.6)	0.89		19 (5.7)	16 (5.0)	0.68	

* All percentages are Kaplan–Meier estimates at the specific time point and thus do not equal the number of patients divided by the total number in the study group.
† The presence of new-onset atrial fibrillation was determined in an electrocardiography core laboratory.

ITT: intention-to-treat
Source: Smith et al., 2011[8]

Not all of these events where included in the model. This mainly depends on the possible impact of including the event in the model (i.e. putting a focus on incremental effects and trying to avoid double counting). As mentioned above, due to similar mortality rates at one year, the time horizon of our model is restricted to one year in cohort A.

Included variables in the base case:

- Repeat hospitalization: There are non-significantly more repeat hospitalizations in the TAVI group, both at 30 days and during the first year. There is no double counting with the initial intervention since it is explicitly called 'repeat' hospitalization.
- Major Stroke: In combination with minor stroke and TIA, significantly more events occur in the TAVI group. Major stroke alone differs non-significantly between the TAVI and the AVR group, both at 30 days and afterwards with an extra 4 events and 1 event up to one year in the TAVI and AVR group, respectively (see Table 18). Double counting of costs with repeat hospitalizations is possible. Therefore, results both with (i.e. base case) and without (i.e. scenario) including major stroke as a separate event are calculated.

Not included variables (but included in scenario analysis because the composite event 'Stroke or TIA' differs significantly between TAVI and AVR):

- TIA: The event occurs infrequently. After the first month the events is observed another 4 and 3 times in the TAVI and AVR group, respectively. This event is included in a scenario analysis.
- Minor stroke: Similar as for TIA, the event occurs infrequently and only occurs one time after the first month in the AVR group. Together with TIA, this event is included in a scenario analysis.

Not included variables (to avoid double counting and because of probably limited incremental impact after 30 days)

- Vascular complications: The event occurs frequently. However, no Belgian cost data for vascular complications are at our disposal. Excluding this event after 30 days does not seem to be a problem since 1) it occurs infrequently after 30 days, and 2) it does not cause an incremental cost since the increment of vascular complications is the same in both groups (Table 18). This event mainly occurs during the first 30 days. It is possible that most of the costs for vascular complications are captured by the cost during the initial hospitalization or a repeat hospitalization during the first 30 days (which is included in the base case scenario).
- Major bleeding: The reasoning is similar to that for vascular complications. The event occurs frequently. However, no Belgian cost data for major bleedings are at our disposal. Excluding this event after 30 days does not seem to be a problem since it does not cause an incremental cost (17 and 18 extra bleedings after 1 month in the TAVI and AVR group, respectively (Table 18)). This event mainly occurs during the first 30 days. It is possible that most of the costs for major bleedings are captured by the cost during the initial hospitalization or a repeat hospitalization during the first 30 days (which is included in the base case scenario).
- New-onset atrial fibrillation: No Belgian cost data are at our disposal. It is observed more often in the AVR group (42 vs. 60 events in the TAVI and AVR group, respectively). However, it occurs most of the times during the first 30 days and is probably already included in the costs of the initial hospitalization or repeat hospitalizations. In contrast, after 30 days, it is observed more often in the TAVI group, i.e. another 12 vs 4 events in the TAVI and AVR group, respectively (Table 18).

We discuss the possible impact of in- or exclusion of events on results in the section with scenario analyses.

The number of included events is modeled as a beta distribution. The values used in the model are shown in Table 19 for the 'ITT (All patients)' group. The values for the other groups (ITT (transfemoral (TF)); ITT (transapical (TA)); AT (All patients)) that are modeled in scenario analyses are presented in appendix 8.4. The alpha parameter equals the number of events in the RCT. The beta parameter is adjusted to equal the published percentage of events. This is necessary since, as mentioned by the authors, all percentages are Kaplan-Meier estimates at the specific time point and thus do not equal the number of patients divided by the total number in the study group.[8] Table 19 shows this adjustment succeeded for all events (i.e. the published percentage of events equals the modeled percentage of events). The number of events for the first 30 days is included in the model after adjusting for the size of the cohort (i.e. 1000 patients in the model vs. 348 and 351 in the TAVI and AVR group of the RCT). The number of events after 30 days up to one year are included in a similar way in the model. One extra step is taken: i.e. expressing the number of events as a percentage of events versus the number of survivors (instead of just adding an equal number of events to every month). This percentage is also used to model the number of events during the extrapolation period. As an internal validity check, the modeled number of events after one year was compared with the published data. The outcomes were equal in all cases.

Table 19. Modeled clinical outcomes at 30 days and 1 year (cohort A, ITT, All patients)

	Average		Beta distribution			Average		Beta distribution	
	publication	model	alpha	beta		publication	model	alpha	beta
Repeat hospitalization					**TIA**				
TAVI					**TAVI**				
30 days	4.4%	4.4%	15	326	30 days	0.9%	0.9%	3	345
1 year	18.2%	18.2%	58	261	1 year	2.3%	2.3%	7	298
Number of events between month 2-12:					Number of events between month 2-12:				
n in trial*		43			n in trial		4		
n in model**		123.6			n in model		11.5		
AVR					**AVR**				
30 days	3.7%	3.7%	12	312	30 days	0.3%	0.3%	1	334
1 year	15.5%	15.5%	45	245	1 year	1.5%	1.5%	4	262
Number of events between month 2-12:					Number of events between month 2-12:				
n in trial		33			n in trial		3		
n in model		94.0			n in model		8,5		
Major stroke					**Minor stroke**				
TAVI					**TAVI**				
30 days	3.8%	3.8%	13	329	30 days	0.9%	0.9%	3	345
1 year	5.1%	5.1%	17	317	1 year	0.9%	0.9%	3	345
Number of events between month 2-12:					Number of events between month 2-12:				
n in trial		4			n in trial		0		
n in model		11.5			n in model		0		
AVR					**AVR**				
30 days	2.1%	2.1%	7	327	30 days	0.3%	0.3%	1	334
1 year	2.4%	2.4%	8	326	1 year	0.7%	0.7%	2	283
Number of events between month 2-12:					Number of events between month 2-12:				
n in trial		1			n in trial		1		
n in model		2.8			n in model		2.8		

ITT: intention-to-treat

*: the difference between the modeled number of events after 30 days and 1 year.

**: the number of events in the trial is extrapolated to the number of events if this would be a cohort of 1000 patients. In the trial, the TAVI and AVR group included 348 and 351 patients, respectively.

Cohort B

Table 20 shows the clinical outcomes in cohort B. Again, repeat hospitalizations are included in the model, together with the most important differences in events, being: stroke or TIA, vascular complications, major bleeding and cardiac reintervention.

Table 20. Clinical outcomes at 30 days and 1 year (cohort B)

Increase 30days vs 1 year:
+n: absolute number
+n: percentage point (ppt)

Table 2. Clinical Outcomes at 30 Days and 1 Year.*

Outcome	30 Days			1 Year		
	TAVI (N=179)	Standard Therapy (N=179)	PValue†	TAVI (N=179)	Standard Therapy (N=179)	PValue†
	no. of patients (%)			no. of patients (%)		
Death						
From any cause	9 (5.0)	5 (2.8)	0.41	55 (30.7)	89 (49.7)	<0.001
From cardiovascular cause†	8 (4.5)	3 (1.7)	0.22 +16.7	35 (19.6) +34	75 (41.9)	<0.001
Repeat hospitalization§	10 (5.6)	18 (10.1)	0.17 +30	40 (22.3) +61	79 (44.1)	<0.001
Death from any cause or repeat hospitalization§	19 (10.6)	22 (12.3)	0.74	76 (42.5)	126 (70.4)	<0.001
Stroke or TIA						
All	12 (6.7)	3 (1.7)	0.03	19 (10.6)	8 (4.5)	0.04
TIA	0	0	—	1 (0.6)	0	1.00
Stroke						
Minor	3 (1.7)	1 (0.6)	0.62 +2.8	4 (2.2) +2.8	1 (0.6)	0.37
Major	9 (5.0)	2 (1.1)	0.06 +5	14 (7.8) +5	7 (3.9)	0.18
Death from any cause or major stroke	15 (8.4)	7 (3.9)	0.12	59 (33.0)	90 (50.3)	0.001
Myocardial infarction						
All	0	0	—	1 (0.6)	1 (0.6)	1.00
Periprocedural	0	0	—	0	0	—
Vascular complications						
All	55 (30.7)	9 (5.0)	<0.001 +0.6	58 (32.4) +1.1	13 (7.3)	<0.001
Major	29 (16.2)	2 (1.1)	<0.001 +1	30 (16.8) +2	4 (2.2)	<0.001
Acute kidney injury						
Creatinine >3 mg/dl (265 μmol/liter)¶	0	1 (0.6)	1.00	2 (1.1)	5 (2.8)	0.45
Renal-replacement therapy‖	2 (1.1)	3 (1.7)	1.00 +5.5	3 (1.7) +7.3	6 (3.4)	0.50
Major bleeding	30 (16.8)	7 (3.9)	<0.001 +10	40 (22.3) +13	20 (11.2)	0.007
Cardiac reintervention						
Balloon aortic valvuloplasty	1 (0.6)**	2 (1.1)	1.00	1 (0.6)	66 (36.9)††	<0.001
Repeat TAVI††	3 (1.7)	NA	—	3 (1.7)	NA	—
Aortic-valve replacement	0	3 (1.7)	0.25	2 (1.1)**	17 (9.5)	<0.001
Endocarditis	0	0	—	2 (1.1)	1 (0.6)	0.31
New atrial fibrillation	1 (0.6)	2 (1.1)	1.00	1 (0.6)	3 (1.7)	0.62
New pacemaker	6 (3.4)	9 (5.0)	0.60	8 (4.5)	14 (7.8)	0.27

Source: Leon et al., 2011[7]

Similar to our approach for cohort A, events are included mainly depending on the predicted impact of including the event in the model and the possibility of double counting. In contrast to cohort A, a lifetime horizon is applied in cohort B.

Included variables in the base case:

- Repeat hospitalization: There are significantly more repeat hospitalizations in the NSA group during the first year. There is no double counting with the initial intervention since it is explicitly called 'repeat' hospitalization.
- Major Stroke: In combination with minor stroke and TIA, significantly more events occur in the TAVI group. Major stroke alone differs non-significantly between the TAVI and the NSA group. The difference occurs especially during the first 30 days with 9 and 2 events in the TAVI and NSA group, respectively (see Table 20). Double counting of costs with repeat hospitalizations is possible. Therefore, results both with (i.e. base case) and without (i.e. scenario) including major stroke are calculated.
- Cardiac reintervention: This differs significantly between the two treatment groups with more balloon aortic valvuloplasty (see Table 22) and AVR in the NSA group and some repeat TAVIs in the TAVI group (see Table 23). In the base case, these events are also included. In an alternative scenario, they are excluded since it is possible that there is double counting with costs of repeat hospitalizations that were already included.

Not included variables (but included in scenario analysis because the composite event 'Stroke or TIA' differs significantly between TAVI and NSA):

- TIA: The event occurs only once in the TAVI group within 1 year. The event is only included in the model together with minor strokes in a scenario analysis.
- Minor stroke: The event occurs infrequently and only occurs one time after the first month in the TAVI group. Together with TIA, this event is only included in a scenario analysis.

Not included variables (to avoid double counting and because of probably limited incremental impact after 30 days)

- Vascular complications: The event occurs frequently. However, no Belgian cost data for vascular complications are at our disposal. Excluding this event after 30 days does not seem to be a problem since 1) it occurs infrequently after 30 days, and 2) the number of events after 30 days is infrequent and similar (Table 20). This event mainly occurs during the first 30 days. It is possible that most of the costs for vascular complications are captured by the cost during the initial hospitalization or a repeat hospitalization during the first 30 days (which is included in the base case scenario).
- Major bleeding: Again, the reasoning is similar to that for vascular complications. The event occurs frequently. However, no Belgian cost data for major bleedings are at our disposal. Excluding this event after 30 days does not seem to be a major problem since it would only result in a minimal incremental cost (10 and 13 extra bleedings between month 2 and 12 in the TAVI and NSA group, respectively (Table 20)). This event mainly occurs during the first 30 days. It is possible that most of the costs for major bleedings are captured by the cost during the initial hospitalization or a repeat hospitalization during the first 30 days (which is included in the base case scenario).

Similar as for cohort A, these events are modeled as beta distributions (Table 21).

Table 21. Modeled clinical outcomes at 30 days and 1 year (cohort B)

	Average		Beta distribution			Average		Beta distribution	
	publication	model	alpha	beta		publication	model	alpha	beta
Repeat hospitalization					**TIA**				
TAVI					**TAVI**				
30 days	5.6%	5.6%	10	169	30 days	0%	0%	0	179
1 year	22.3%	22.3%	40	139	1 year	0.6%	0.6%	1	178
Number of events between month 2-12:					Number of events between month 2-12:				
n in trial*		30			n in trial		1		
n in model**		167.6			n in model		5.6		
NSA					**NSA**				
30 days	10.1%	10.1%	18	161	30 days	0%	0%	0	179
1 year	44.1%	44.1%	79	100	1 year	0%	0%	0	179
Number of events between month 2-12:					Number of events between month 2-12:				
n in trial		61			n in trial		0		
n in model		340.8			n in model		0		
Major stroke					**Minor stroke**				
TAVI					**TAVI**				
30 days	5.0%	5.0%	9	170	30 days	1.7%	1.7%	3	176
1 year	7.8%	7.8%	14	165	1 year	2.2%	2.2%	4	175
Number of events between month 2-12:					Number of events between month 2-12:				
n in trial		5			n in trial		1		
n in model		27.9			n in model		5.6		
NSA					**NSA**				
30 days	1.1%	1.1%	2	177	30 days	0.6%	0.6%	1	178
1 year	3.9%	3.9%	7	172	1 year	0.6%	0.6%	1	178
Number of events between month 2-12:					Number of events between month 2-12:				
n in trial		5			n in trial		0		
n in model		28			n in model		0		

NSA: non-surgical approach; TAVI transcatheter aortic valve insertion.
*: the difference between the modeled number of events after 30 days and 1 year.
**: the number of events in the trial is extrapolated to the number of events if this would be a cohort of 1000 patients. In the trial, the TAVI and NSA group included both 179 patients.

In cohort B, of the 179 patients assigned to standard therapy, balloon aortic valvuloplasty was performed in 114 patients (63.7%) during the 30 days after randomization and in an additional 36 patients (20.1%) more than 30 days after randomization.[7] These probabilities are taken into account as beta distributions (Table 22).

Table 22. Cardiac reintervention: valvuloplasty in the NSA group

	Average		Beta distribution	
	publication	model	alpha	beta
Valvuloplasty				
NSA				
30 days	63.7%	63.7%	114	65
1 year	83.8%	83.8%	150	29
Number of events between month 2-12:				
n in trial*		36		
n in model**		201.1		

NSA: non-surgical approach.
*: the difference between the modeled number of events after 30 days and 1 year.
**: the number of events in the trial is extrapolated to the number of events if this would be a cohort of 1000 patients. In the trial, the NSA group included 179 patients.

Three patients in the TAVI group (1.7%) had to undergo an additional procedure (repeat TAVI) to treat clinically significant aortic regurgitation (paravalvular in two patients and transvalvular in one).[7] In the NSA group, almost 10% of patients had an AVR within the first year. The parameters in the model for the number of repeat TAVIs and aortic-valve replacements is presented in Table 23.

Table 23. Cardiac reintervention: repeat TAVI and aortic-valve replacement

	Average		Beta distribution	
	publication	model	alpha	beta
Repeat TAVI				
TAVI				
30 days	1.7%	1.7%	3	176
1 year	1.7%	1.7%	3	176
Number of events between month 2-12:				
n in trial*		0		
n in model**		0		
NSA: not applicable				
Aortic-valve replacement				
TAVI				
30 days	0%	0%	0	179
1 year	1.1%	1.1%	2	177
Number of events between month 2-12:				
n in trial		2		
n in model		11.2		
NSA				
30 days	1.7%	1.7%	3	176
1 year	9.5%	9.5%	17	162
Number of events between month 2-12:				
n in trial		14		
n in model		78.2		

NSA: non-surgical approach.
*: the difference between the modeled number of events after 30 days and 1 year.
**: the number of events in the trial is extrapolated to the number of events if this would be a cohort of 1000 patients. In the trial, the NSA group included 179 patients.

We check the possible impact of in- or exclusion of events in scenario analyses.

6.1.11 Costs

We have cost data at our disposal for several Belgian populations:

- 310 TAVI patients: IMA data (i.e. information on all costs, both during hospitalization as well as ambulatory costs), type of valve (Edwards or CoreValve), approach (femoral, apical or subclavicular). (see 4.2)
- 9213 AVR patients: TCT data (i.e. information on costs during hospitalization, no ambulatory costs), age category, severity of illness. (see 4.3)
- 71 NSA patients: IMA data. (see 4.2)

6.1.11.1 Non-comparability of Belgian TAVI, AVR and NSA groups

The costs for the three Belgian populations cannot be compared as such. The groups are not classified based on a randomization procedure and the characteristics of these patients can be quite different. This is already clear when the pre-intervention costs are compared for the Belgian TAVI and NSA samples (for which we have all reimbursement data at our disposal). Table 24 shows that transapical TAVI patients had more healthcare expenditures the year before the intervention in comparison with the transfemoral TAVI patients. During the first year before the intervention, this difference was about €4000. A similar difference of more than €4000 is noticed when comparing the CoreValve and Edwards transfemoral patients. This indicates it is difficult and inappropriate to interpret cost differences after the procedure between the different populations.

Table 24. Total healthcare expenditures before TAVI and CT

	CoreValve	Edwards		NSA
	TF	TF	TA	
pre 30	5,235 €	5,784 €	6,413 €	8,958 €
pre 60	8,600 €	9,763 €	11,496 €	11,796 €
pre 90	10,781 €	12,833 €	16,083 €	13,556 €
pre 120	12,404 €	15,589 €	18,412 €	16,286 €
pre 150	13,787 €	17,362 €	19,796 €	18,171 €
pre 180	15,710 €	18,902 €	21,145 €	19,731 €
pre 360	22,530 €	26,851 €	30,917 €	28,499 €

NSA: non-surgical approach; TA: transapical; TF: transfemoral.

Also the TAVI patients in our Belgian sample do not have similar characteristics as those in the PARTNER trial. This is clear when the patient characteristics between the PARTNER trial population and those of the Belgian sample are compared. Table 12 in part 4.1 shows differences in NYHA class, coronary artery disease and previous CABG.

Adjustments for differences in characteristics are not possible as this information is missing at individual patient level. Furthermore, even if this kind of information would be available, it cannot be ruled out that a treatment effect model does not correct for all observed or unobserved characteristics and that the estimated treatment effect is biased.[38] A simple comparison of observational cost data may provide misleading results.

Fortunately, data from the PARTNER RCT are available which, due to randomisation, better exclude the influence of confounding factors on the treatment effect, both on mortality, quality of life and adverse events. Belgian costs are then allocated to the relevant interventions and events. Using this methodology the following assumptions on costs are made:

- The costs for the TAVI and AVR interventions for a Belgian PARTNER-like population are similar to the intervention costs for the Belgian sample of TAVI and AVR patients.
- The costs for specific events are the same across populations (e.g. the cost of a stroke is the same for a patient in the TAVI, AVR or NSA group).
- These assumptions are made since this is the best data we currently have at our disposal. We come back to these assumptions in our discussion.

The following table provides an overview of the cost data used in the model. Further details for all these costs are provided in the following parts.

Table 25. Average costs

Input variable	Average cost	Details in part
TAVI (cohort A)		6.1.11.2
TF	€40,917	
TA	€49,799	
All	€43,571	
TAVI (cohort B)	€40,057	6.1.11.6
NSA (cohort B)	€3170	6.1.11.6
AVR (cohort A)	€23,749	0
Balloon aortic valvuloplasty	€489	6.1.11.4
Repeat hospitalization	€5983	6.1.11.5
Stroke		6.1.11.5
minor	€4679	
major	€12,493	
TIA	€3946	6.1.11.5
Follow-up fees	€43.2/month	6.1.11.7
Follow-up drugs	€20.5/month	6.1.11.7

6.1.11.2 TAVI

Financial data are at our disposal of 310 TAVI patients. The costs for the different type of valves and subpopulations are different (Table 26). However, it cannot be excluded that this difference is caused by the choice of device and/or access or if this is due to e.g. a different patient selection. Since the RCTs are performed for the Edwards SAPIEN valve, we perform our analysis with the costs of this valve.

Table 26. TAVI intervention costs (CoreValve vs Edwards)

	N	Mean	St.dev.
Edwards			
TF	99	23,002 €	11,979 €
TA	84	32,732 €	18,277 €
CoreValve			
TF	120	19,341 €	10,690 €
Subclavicular	7	15,160 €	7,335 €

TA: transapical; TAVI: transcatheter aortic valve insertion; TF: transfemoral.
These costs do not include the cost of the device.

The data includes services that may not be part of the standard procedure. Being a percutaneous technique, the use of extracorporeal circulation can be questioned. In some cases, this may be justified, but not systematically.[i] Therefore, an adjustment is made (Table 27) to exclude the costs of the following nomenclature codes:

- 229596/229600: Surgery of the heart or the intra-thoracic great vessels, including valvuloplasty or valve replacement, with the use of extracorporeal circulation.

[i] We notice there is a clear difference in registration of these codes when comparing Edwards and CoreValve cases. The nomenclature codes 229596/229600 are only registered in 1 CoreValve case (1/127 or 0.8%) and 687536/687540 in 5 CoreValve cases (5/127 or 3.9%). This contrasts with the percentages of registered codes in the Edwards cases (see Table 27).

- 687536/687540: Disposable cardiotomy set, including membrane oxygenator for extracorporeal circulation, irrespective of the number of elements, for patients 7 years of age or older.

On the other hand, the TAVI cost and a procedure fee should be taken into account. In our analysis, a TAVI device cost of €18,000 (source: personal communication) is taken into account. This is arbitrarily set at €10,000 in a scenario analysis. For the procedure fee, an arbitrary fee of €1500 is included. The fee for valvuloplasty (238313/ 238324) and AVR (229596/229600) are €488.75 and €2565.94, respectively. In scenario analyses, the fee is changed between these values (€500, €1000, €2000 and €2500).

Table 27. TAVI costs (after adjustments)

	TF	TA	All§
TAVI (uncorrected)			
N	99	84	
Mean	**23,002 €**	**32,732 €**	**25,910 €**
St.dev	11,979 €	18,277 €	
St.dev mean	1,204 €	1,994 €	
Correction (minus)			
229596/229600*	52.5%	76.2%	
Cost (€2565.94)	**-1,348 €**	**-1,955 €**	**-1,529 €**
687536/687540**	24.2%	48.8%	
Cost (€978.58)	**-237 €**	**-478 €**	**-309 €**
	21,417 €	**30,299 €**	**24,071 €**
Correction (plus)			
Device cost	18,000 €	18,000 €	18,000 €
Fee***	1,500 €	1,500 €	1,500 €
TAVI cost (after correction)	**40,917 €**	**49,799 €**	**43,571 €**

TA: transapical; TAVI: transcatheter aortic valve insertion; TF: transfemoral.
§: this cost is based on a weighted average of the TF and TA group. The weight is determined by the number of TF and TA patients in the PARTNER trial, being 244 and 104, respectively.
* RIZIV/INAMI nomenclature code: "Surgery of the heart or the intra-thoracic great vessels, including valvuloplasty or valve replacement, with the use of extracorporeal circulation".
** RIZIV/INAMI nomenclature code: "Disposable cardiotomy set, including membrane oxygenator for extracorporeal circulation, irrespective of the number of elements, for patients 7 years of age or older".
*** The amount of this fee is changed in a scenario analysis (see 0).

The intervention costs after correction (Table 27) are use in the model. This cost is the highest in the transapical approach. To incorporate uncertainty, based on the central limit theorem,[k] the uncorrected average TAVI cost is modeled as a normal distribution with its observed mean and standard deviation of the mean. The corrections are added/subtracted as deterministic values. No difference can be made between patients from cohort A or B. Therefore, it is assumed that these costs are equal in both groups. For cohort B, the cost of the transfemoral approach is included. For cohort A, an analysis is performed separately for all, TF and TA TAVI patients.

k The central limit theorem states that the sampling distribution of the mean will be normally distributed irrespective of the underlying distribution of the data with sufficient sample size.37

6.1.11.3 AVR

The cost of AVR is based on a sample of 9213 patients. This sample contains both older/younger patients with a different severity of illness. The PARTNER study mainly includes older patients with multiple co-morbidities. We take this into account by selecting the older AVR patients (age ≥ 70) with a higher SOI index (3 or 4). This provides an average AVR cost of €23,749 (Table 28), modeled as a normal distribution based on the central limit theorem. We note that the mere selection of people over 80 with SOI 3 or 4 would not result in higher costs (on average €23,772).

Table 28. AVR costs (depending on age and SOI)

Patient group	N	Mean	St.dev	St.dev mean
All	9213	21,880 €	12,354 €	129 €
Age				
<70	3373	20,927 €	12,145 €	209 €
<80	7414	21,698 €	12,783 €	148 €
≥70	5840	22,430 €	12,440 €	163 €
≥80	1799	22,628 €	10,371 €	245 €
SOI				
1 or 2	1845	16,043 €	2,894 €	67 €
3 or 4	7368	23,341 €	13,344 €	155 €
Age & SOI				
≥70 and SOI 3 or 4	4811	23,749 €	13,273 €	191 €
≥80 and SOI 3 or 4	1506	23,772 €	10,903 €	281 €

AVR: aortic valve replacement; SOI: severity of illness.

6.1.11.4 Balloon aortic valvuloplasty

For the cost of balloon aortic valvuloplasty, the RIZIV/INAMI nomenclature code 238313/238324 is taken into account ("Reconstruction of the deep venous system by means of open valvuloplasty of one or more valves or transposition of another vein"). The fee for this code is €488.75. Only this cost is included explicitly. If this procedure would include a hospitalization, then these costs are already included in the model as 'repeat hospitalization' (see 6.1.10).

In the TAVI group, a standard balloon aortic valvuloplasty was also performed, followed by transfemoral insertion of either a 22- or 24-French sheath, depending on the selected size of the valve (23 mm or 26 mm).[7] However, to avoid double counting, this cost is not included separately since it is part of the TAVI procedure, for which the cost is already included in the analysis (see 6.1.11.2).

6.1.11.5 Repeat hospitalization, stroke and TIA

Costs for the events repeat hospitalization, stroke and TIA are based on the APR-DRG costs for these categories as published by the technical cell (www.tct.fgov.be, Table 29). For repeat hospitalization, we included the cost of the APR-DRG 'heart failure'. For stroke, the four categories (minor, moderate, major and extreme) were reclassified as minor stroke and major stroke. The uncertainty around these numbers is incorporated as a gamma distribution. The parameters of this distribution are determined to reflect both the mean and the P5 and P95 values. The number of events is based on published trial results (see 6.1.10). It is assumed that the cost of one specific event is the same across all treatment groups.

Table 29. Costs of repeat hospitalization, stroke and TIA

Cost item	Mean	Probability distribution	Mean	P5	P95	Source
Repeat hosp.	5,983 €	gamma	5,983 €	1,339 €	15,596 €	TCT, APR-DRG 194 (Heart failure)
Stroke						TCT, APR-DRG 045 (CVA with stroke)
minor	4,679 €	gamma	3,292 €	932 €	6,842 €	minor
		gamma	6,066 €	1,574 €	17,285 €	moderate
major	12,493 €	gamma	9,593 €	1,630 €	27,526 €	major
		gamma	15,392 €	2,631 €	40,079 €	extreme
TIA	3,946 €	gamma	3,946 €	974 €	9,942 €	TCT, APR-DRG 047 (TIA)

CVA: cerebrovascular accident; hosp.: hospitalization; P5/95: 5th and 95th percentile; TCT: technical cel; TIA: transient ischemic attack.

6.1.11.6 Intended treatment vs actual treatment

For cohort A, both an 'intention-to-treat' and an 'as-treated' analysis are performed since these data are available.

For cohort B, only ITT results are presented. However, not all patients actually received TAVI in the TAVI group and the non-surgical approach is not well defined and heterogeneous. The cost of the initial procedure is adjusted for this.

Of the 179 patients assigned to TAVI, 6 (3.4%) did not receive a transcatheter heart valve: 2 patients died before the scheduled implantation, transfemoral access was unsuccessful in 2 patients, and the intraprocedural annulus measurement was too large in 2 patients.[7] Similarly, in our cohort of 1000 patients, the complete TAVI procedure cost was assigned to 96.6% (173/179) of patients, 1.1% were assigned no costs because they died before the procedure and 2.2% was assigned the procedure cost without the TAVI device cost of €18,000. This results in an average cost of €40,057 instead of €40,917 (Table 27).

In the NSA group, a similar adjustment is made. Despite the fact that all the patients in this cohort of the PARTNER study were determined not to be suitable candidates for surgery, 12 of the patients who were assigned to standard therapy (6.7%) underwent aortic-valve replacement, 5 (2.8%) underwent placement of a conduit from the left ventricular apex to the descending aorta plus aortic valve replacement, and 4 (2.2%) underwent TAVI at a nonparticipating site outside the United States.[7] Therefore, the cost of AVR is assigned to 9.5% (6.7% + 2.8%) of the patients, and the TAVI cost to 2.2%. This results in an additional cost of €3170 for the NSA group.

6.1.11.7 Follow-up

A theoretical follow-up cost was included in the model. The composition of this cost can be found in Table 30 and amounts €518 per year or €43.2 monthly. This monthly expense is attributable to the number of surviving patients. It is assumed that this cost is similar in all treatment groups (TAVI, AVR and NSA). The large uncertainty around this number is modeled as a uniform distribution (+/- 50%).

Table 30. Theoretical follow-up cost

Description	# / year	Nomenclature code	Fee
Consultation cardiologist	4	102093/102594	€34.50
Electrocardiogram	4	475075/475086	€17.18
Echo 1*	1	469814/469825	€67.16
Echo 2**	3	469630/469641	€67.16
Echo 3***		469652/469663	€38.75
TEE 1§	1	469836/469840	€113.01
TEE 2§§		469674/469685	€58.12
Average yearly cost			**€518.31**

/ year: number per year.
*: "Full transthoracal ultrasound bilan of the heart... "
**: "Repetition within the calendar year of nomenclature code 469814/469825... "
***: "Limited transthoracal ultrasound bilan of the heart... "
§: "Full transesophageal ultrasound bilan of the heart... "
§§: "Limited transesophageal ultrasound bilan of the heart... "
Remark: According to a last-minute remark of experts, TEE 1 and TEE 2 is not part of the follow-up procedure. Excluding these items from the theoretical follow-up would lower this monthly cost with €7.1. We did not rerun the simulation since this is a negligible amount and because the actual costs of these items are already higher. The probabilistic sensitivity analysis also showed that the uncertainty around this cost item had little influence on the incremental cost-effectiveness ratios (ICERs).

To check these costs, we looked at the actual expenditures for these nomenclature codes (see Table 31). After one year, these costs are somewhat higher in the TAVI groups (both TF and TA) and lower in the NSA group. However, these differences are difficult to interpret and possibly indicate differences in the populations since they already existed before the index date. Double counting of costs that were already included in the modeled repeat hospitalizations is also possible. Therefore, in a conservative approach, we preferred to apply the lower theoretical monthly cost.

Table 31. Actual expenditures for Nomenclature codes mentioned in Table 30

	CoreValve	Edwards		NSA
	TF	TF	TA	
pre 30	119 €	142 €	150 €	131 €
pre 60	215 €	249 €	266 €	168 €
pre 90	223 €	315 €	368 €	195 €
pre 120	322 €	374 €	417 €	224 €
pre 150	359 €	408 €	462 €	243 €
pre 180	390 €	441 €	484 €	253 €
pre 360	517 €	575 €	608 €	335 €
post 30	231 €	281 €	332 €	131 €
post 60	329 €	384 €	427 €	169 €
post 90	362 €	415 €	470 €	204 €
post 120	379 €	436 €	495 €	229 €
post 150	398 €	442 €	524 €	272 €
post 180	417 €	463 €	551 €	290 €
post 360	596 €	614 €	745 €	433 €

NSA: non-surgical approach; TA: transapical; TF: transfemoral.
Remark: the numbers are calculated for patients surviving the follow-up period.

Similarly, a cost for drugs was included in the model. The selected drugs were the following: acenocoumarol, aspirin, clopidogrel, dalteparin, danaparoid, enoxaparin, fenprocoumon, heparin, nadroparine, ticlopidine, tirofiban, and warfarin. Table 32 shows the aggregated costs. Again, as mentioned in part 6.1.11.1, the cost differences are difficult to interpret. This is clearly shown comparing the CoreValve and Edwards TAVI. The expenditures in the post period are higher in the CoreValve group. In contrast, this was the opposite when looking at the pre period group. In our model we included the yearly cost observed in the Belgian Edwards group of €246 per year, or €20.5 per month. We assumed this monthly cost to be the same for all our treatment groups (AVR, TAVI and NSA). The large uncertainty around this number is modeled as a uniform distribution (+/- 50%).

Table 32. Actual expenditures for a selection of drugs

	CoreValve	Edwards		NSA
	TF	TF	TA	
pre 30	32 €	39 €	51 €	33 €
pre 60	54 €	66 €	92 €	48 €
pre 90	70 €	91 €	114 €	58 €
pre 120	83 €	111 €	132 €	75 €
pre 150	98 €	127 €	156 €	91 €
pre 180	115 €	149 €	178 €	101 €
pre 360	187 €	238 €	311 €	215 €
post 30	55 €	31 €	55 €	32 €
post 60	127 €	63 €	80 €	77 €
post 90	169 €	80 €	103 €	107 €
post 120	205 €	97 €	120 €	126 €
post 150	230 €	102 €	128 €	151 €
post 180	261 €	113 €	139 €	161 €
post 360	491 €	246 €	242 €	308 €

NSA: non-surgical approach; TA: transapical; TF: transfemoral.
Remark: the numbers are calculated for patients surviving the follow-up period.

There is the possibility that there are differences in cardiac revalidation between the TAVI, AVR and NSA groups. However, it is not clear how big this difference is and how long this difference remains. Table 33 shows the expenses in the TAVI and NSA groups before and after the index date. Again, differences are difficult to interpret. For AVR, we do not have this information (TCT data only contains expenses during hospitalization and no ambulatory data). We did not include this cost in our model.

Table 33. Actual expenditures for cardiac revalidation

	CoreValve	Edwards		NSA
	TF	TF	TA	
pre 30	27 €	40 €	78 €	19 €
pre 60	32 €	53 €	92 €	26 €
pre 90	46 €	66 €	97 €	40 €
pre 120	49 €	79 €	104 €	44 €
pre 150	53 €	89 €	106 €	44 €
pre 180	63 €	95 €	110 €	46 €
pre 360	72 €	118 €	125 €	59 €
post 30	221 €	207 €	445 €	118 €
post 60	240 €	226 €	468 €	143 €
post 90	258 €	242 €	469 €	157 €
post 120	257 €	248 €	477 €	138 €
post 150	259 €	250 €	486 €	173 €
post 180	261 €	265 €	491 €	169 €
post 360	295 €	305 €	543 €	210 €

NSA: non-surgical approach; TA: transapical; TF: transfemoral.
Remark: the numbers are calculated for patients surviving the follow-up period.

6.1.12 Uncertainty

6.1.12.1 Probabilistic (sensitivity) analysis

The impact of uncertainty around all the model's input parameters on the results was modeled probabilistically. The applied distribution depends on the type of variable:[37] transition probabilities (mortality, chance for modeled events) and utilities are modeled as beta distributions. This distribution is limited to the 0-1 scale and reflects the possible outcomes for these variables. Strict correlation was imposed between the modeled probabilities at 30 days and 1 year. As such, illogical scenarios are excluded (e.g. a higher mortality or number of events after one year versus after 30 days would be possible if this correlation was not included in the model). Due to the central limit theorem, TAVI and AVR costs were modeled as normal distribution around the mean.

1,000 Latin Hypercube simulations were performed. Outcomes with their surrounding uncertainty are presented for incremental costs, incremental effects, and the incremental cost-effectiveness ratio (ICER). Results are shown on the cost-effectiveness plane and cost-effectiveness acceptability curves (CEA-curves). In our probabilistic sensitivity analysis, rank correlation coefficients are calculated between the output values (the ICERs) and the sampled input values to indicate the relative importance of variables and their uncertainty on the uncertainty surrounding the outcomes.

6.1.12.2 Scenario analyses

Several scenario analyses are already mentioned in the previous parts. Table 34 presents an overview of these scenarios.

Table 34. Overview of scenario analyses

Base case	Scenario
Cohort A	
- Results of the published ITT analysis, including all patients, are used (ITT, All).	- ITT results for the transfemoral (ITT, TF) and transapical (ITT, TA) subgroups are modelled. - As-treated results for all patients are also modeled separately (AT, All).
- TAVI device cost: €18,000	- TAVI device cost: €10,000
- QoL: a utility value that is 0.1 better in the TAVI group versus the AVR group during the first month.	- A utility value that is 0.1 better in the TAVI group versus the AVR group during the whole first year.
	- A combination of the previous two scenarios.
Cohort B	
- The events repeat hospitalization, major stroke and cardiac reinterventions are taken into account.	- Only repeat hospitalization is taken into account. - Only repeat hospitalization and major stroke are taken into account. - Repeat hospitalization, minor and major stroke, and TIA are taken into account.
- A lifetime time horizon.	- A 3-year time horizon.
- Discount rate: 1.5% for effects and 3% for costs	- 0%, 3%, and 5% for both costs and effects and 3% and 5% for costs in combination with no discounting for effects.
- 30-day mortality: 5% (9/179)	- 30 day mortality of 6.15% (11/179)
- Adjusted TAVI and NSA cost for performed initial interventions: €40,057 for TAVI and €3170 for NSA.	- No adjusted cost: €40,917 for TAVI.
- TAVI device cost: €18,000	- TAVI device cost: €10,000
- Procedure fee: €1500	- Procedure fee: €500, €1000, €2000, and €2500

AT: as-treated; ITT: intention-to-treat; NSA: non-surgical approach; QoL: quality of life; TA: transapical; TF: transfemoral; TAVI: transcatheter aortic valve insertion.
Remark: Due to the one-year time horizon, no discount rate scenario is modelled for cohort A.

Results of these analyses will be presented on a tornado graph.

Just before finalizing this report, extra information was retrieved from the FDA analyses and received from industry, which is also modeled in scenario analyses.

First, an FDA analysis was performed for the data gathered during the 'continued access' period in cohort B (see 2.3.5). Mortality in the TAVI group was worse than in the non-surgical approach group. In this 'continued access' subgroup, TAVI is being dominated by NSA: it is more expensive and outcomes are worse. The outcomes of the pivotal trial and the continued access were combined. The weighted 30-day and 1-year mortality (Table 35) is used to model TAVI's cost-effectiveness.

The weights are based on the number of participants in both groups, being 179 in both the TAVI and NSA group in the pivotal trial and 41 and 49 in the TAVI and NSA group, respectively, in the continued access.

Table 35. Scenario analysis pivotal trial versus continued access (cohort B)

	TAVI	NSA
	Cohort B (pivotal trial)	
30-day mortality	5.0%	2.8%
1-year mortality	30.7%	49.7%
	Cohort B (continued access)	
30-day mortality	9.8%	2.1%
1-year mortality	34.3%	21.6%
	cohort B (combined)	
30-day mortality	5.9%[a]	2.7%[b]
1-year mortality	31.4%[c]	43.7%[d]

NSA: non-surgical approach; TAVI: transcatheter aortic valve insertion.
The weight of the pivotal trial to combine the results of the pivotal trial and continued access is 81.36% in the TAVI group and 78.51% in the NSA group.
Uncertainty was modeled with beta distributions. The parameters for the pivotal trial are mentioned in Table 16. For the combined data it is as follows (alpha, beta): a (13, 207); b (6, 220); c (68, 149); d (99, 128).

Secondly, results were provided for the subgroup analysis of inoperable patients because of anatomical reasons versus inoperable patients for other reasons (co-morbidities). We further refer to these two groups as 'technical' and 'non-technical' inoperable patients. The results were only provided for the pivotal trial (and not for the continued access) and for the primary endpoint (and not for other events or QoL). Table 36 shows that although the reduction in mortality is observed in both subgroups, it is larger in the technical inoperable group (absolute 27.9%) than in the non-technical inoperable group (absolute 17%). The implications on the intervention's cost-effectiveness will be calculated in a scenario analysis.

Table 36. Scenario analysis technical versus non-technical inoperable patients (cohort B)

	TF	NSA
	cohort B (non-technical inoperable)	
30-day mortality	6.3%[a]	2.8%[b]
1-year mortality	33.3%[c]	50.3%[d]
	cohort B (technical inoperable)	
30-day mortality	1.9%[e]	2.7%[f]
1-year mortality	24.5%[g]	52.4%[h]

NSA: non-surgical approach; TF: transfemoral; TAVI: transcatheter aortic valve insertion.
Uncertainty was modeled with beta distributions. The parameters are as follows (alpha, beta): a (8, 118); b (4, 138); c (42, 84); d (70, 69); e (1, 52); f (1, 36); g (13, 40); h (19, 17).

6.2 RESULTS

The results are presented separately for cohort A, i.e. high-risk operable patients (6.2.1), and cohort B, i.e. inoperable patients (6.2.2).

6.2.1 Cohort A, high-risk patients

6.2.1.1 Base-case results

Table 37 presents the disaggregated results for TAVI in cohort A, i.e. high-risk operable patients. Based on the results of the PARTNER trial, the incremental effects of TAVI in comparison with AVR are minimal. In combination with substantial incremental cost, this results in relatively very high ICERs. This is not only the case for the groups as a whole, but also for the transfemoral and transapical groups separately. Similar results are found for the as-treated group.

This contrast between minimal gains and substantial expenses is also shown on the cost-effectiveness plane (Figure 12). The cost-effectiveness acceptability curve (Figure 13) indicates that a willingness-to-pay for a life-year gained of more than €750,000 is needed to have about 50% chance the intervention is considered cost-effective in this cohort of patients.

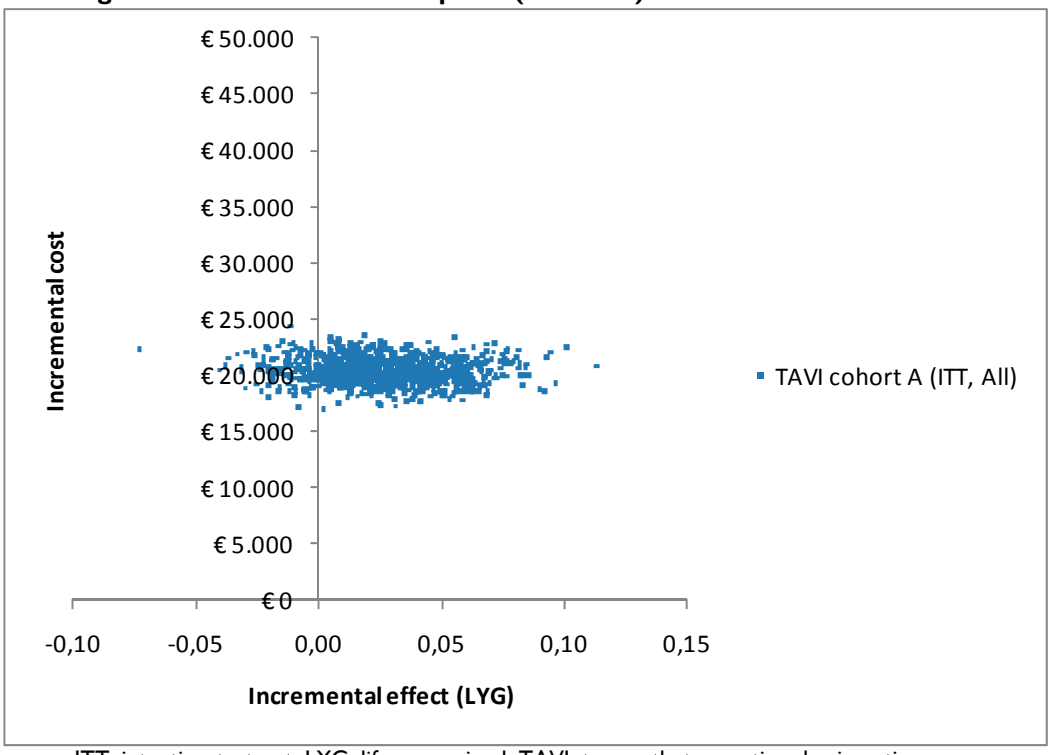
Table 37. IC, IE & ICERs for cohort A (base case results)

Cohort A	ITT, All	ITT, TF	ITT, TA	AT, All
IC	€ 20,397	€ 17,708	€ 26,685	€ 20,289
	€ 18,278 € 22,617	€ 15,173 € 20,366	€ 22,622 € 30,672	€ 18,154 € 22,400
IE (LYG)	0.03	0.03	0.01	0.02
	-0.02 0.08	-0.02 0.09	-0.08 0.10	-0.03 0.07
IE (QALY)	0.03	0.03	0.01	0.02
	-0.01 0.07	-0.01 0.08	-0.05 0.08	-0.01 0.06
ICER (€/LYG)**	*€ 759,072*	*€ 521,967*	*€ 2,849,957*	*€ 1,012,300*
ICER (€/QALY)**	*€ 749,416*	*€ 546,384*	*€ 1,810,667*	*€ 912,206*

AT: as-treated; IC: incremental cost; ICER: incremental cost-effectiveness ratio; IE: incremental effect; ITT: intention-to-treat; LYG: life-year gained; QALY: quality-adjusted life-year; TA: transapical; TF: transfemoral.

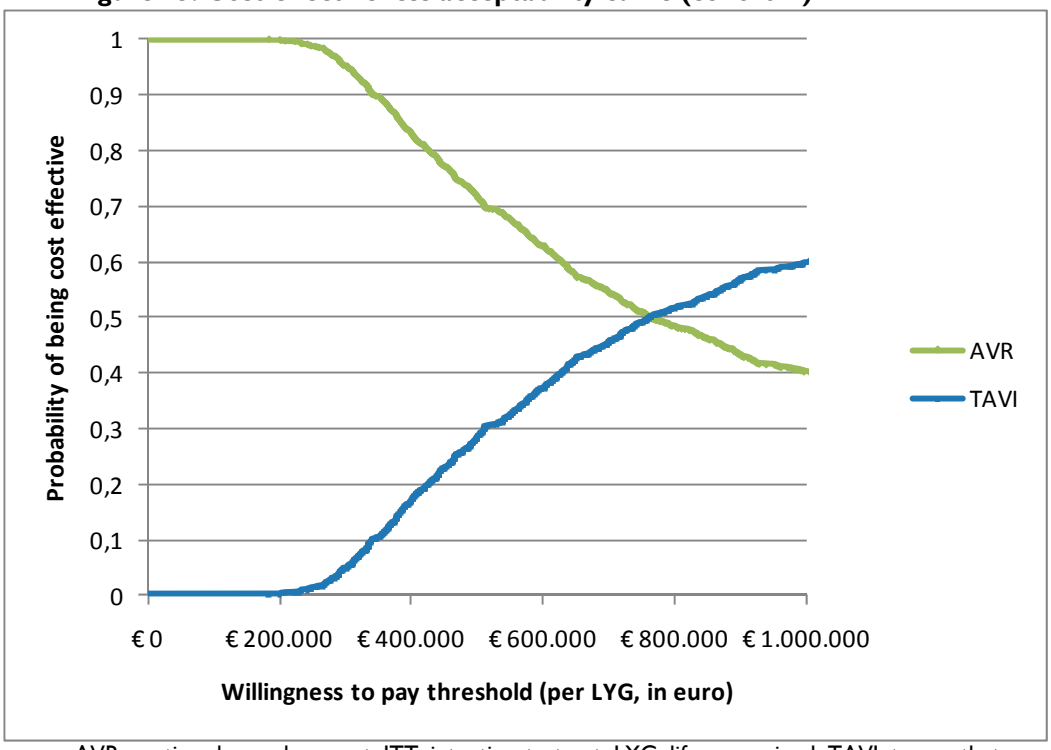
**: The probabilistic average and 95%CI are mentioned where appropriate. This approach is not reliable in case the simulated ICERs are spread over several quadrants of the cost-effectiveness plane. As an alternative (in italics), in these cases, the presented ICERs are calculated by dividing the mean incremental cost by the mean incremental benefit.

Figure 12. Cost-effectiveness plane (cohort A)



ITT: intention-to-treat; LYG: life-year gained; TAVI: transcatheter aortic valve insertion.
Remark: results for cohort A are only presented on the CE-plane and CEA-curve per LYG. This is due to space considerations and because QoL in cohort A is based on assumptions (related to QoL measurements in cohort B). This choice is arbitrarily. Results per QALY are available in Table 37.

Figure 13. Cost-effectiveness acceptability curve (cohort A)



AVR: aortic-valve replacement; ITT: intention-to-treat; LYG: life-year gained; TAVI: transcatheter aortic valve insertion.

6.2.1.2 Scenario analyses

Table 38 shows the results of three scenario analyses. With a decrease of the TAVI cost from €18,000 to €10,000, the average ICER remains above €450,000 per LYG or per QALY gained. If a QoL improvement of 0.1 is assumed for the entire first year, this becomes about €200,000/QALY. Even a combination of the two previous assumptions leads to an ICER of more than 120,000/QALY.

Table 38. IC, IE & ICERs for cohort A (scenario analyses)

Cohort A (ITT, All)	TAVI, €10.000		QoL difference 0,1		Comb. previous two ass.	
IC	€ 12,397		€ 20,397		€ 12,397	
	€ 10,278	€ 14,617	€ 18,278	€ 22,617	€ 10,278	€ 14,617
IE (LYG)	0.03		0.03		0.03	
	-0.02	0.08	-0.02	0.08	-0.02	0.08
IE (QALY)	0.03		0.10		0.10	
	-0.01	0.07	0.07	0.14	0.07	0.14
ICER (€/LYG)**	*€ 461,360*		*€ 759,072*		*€ 461,360*	
ICER (€/QALY)**	*€ 455,461*		€ 204,913		€ 124,632	
			€ 145,707	€ 296,398	€ 84,913	€ 184,886

AT: as-treated; IC: incremental cost; ICER: incremental cost-effectiveness ratio; IE: incremental effect; ITT: intention-to-treat; LYG: life-year gained; QALY: quality-adjusted life-year; TA: transapical; TF: transfemoral.
** see explanation in Table 37.

6.2.2 Cohort B, inoperable patients

6.2.2.1 Base case

Cohort B shows better results than those for cohort A. The incremental costs are higher when comparing TAVI with NSA, being on average about €34,600 (95% CI 29,900 – 38,600). However, based on the results of the PARTNER trial, the incremental effects are higher: 1.16 LYG (95% CI 0.65 – 1.75) or 0.92 QALYs (95% CI -0.29 – 1.90). The ICER becomes about €31,900 per LYG (95% CI 20,300 – 51,600) or on average €37,400 per QALY gained (Table 39). Results are also presented on the cost-effectiveness plane (Figure 14).

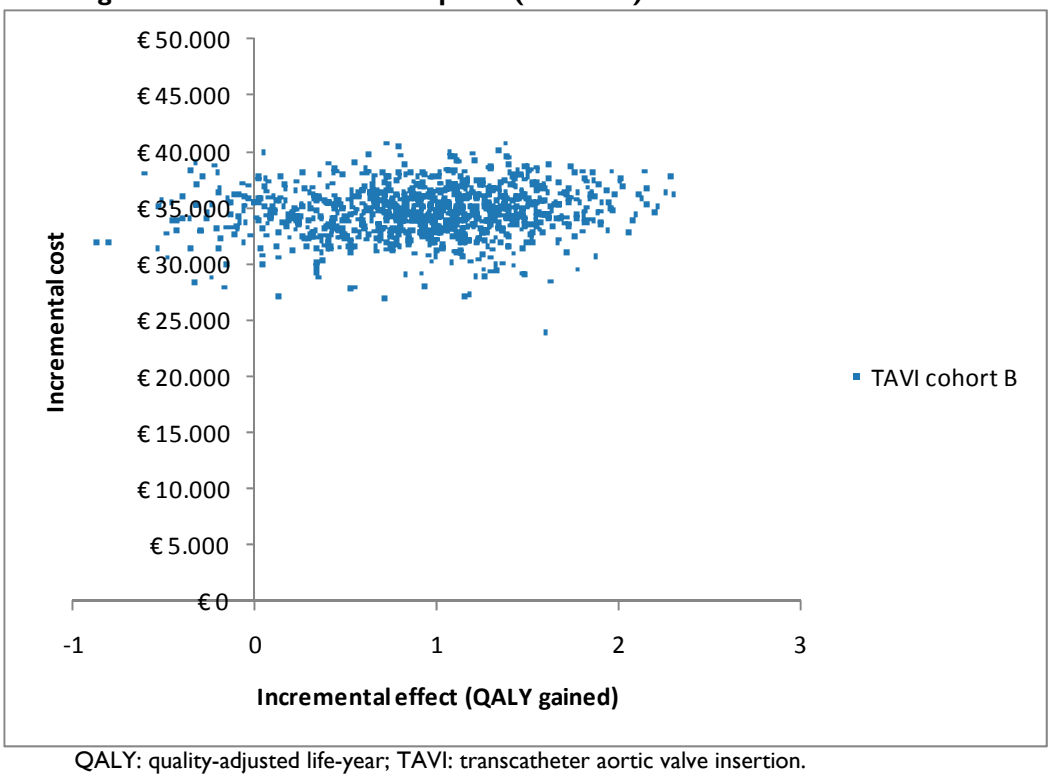
The cost-effectiveness acceptability curve (Figure 15) indicates that a willingness-to-pay for a quality-adjusted life-year of €35,000 is needed to have about 50% chance the intervention is considered cost-effective in this cohort of patients.

Table 39. IC, IE & ICERs for cohort B (base case and alternative results)

Cohort B	Base case[a]	Alternative 1[b]	Alternative 2[c]	Alternative 3[d]
IC	€ 34,590	€ 36,174	€ 37,087	€ 37,291
	€ 29,881 € 38,631	€ 32,287 € 39,065	€ 33,013 € 40,499	€ 33,168 € 40,769
IE (LYG)	1.16	1.16	1.16	1.16
	0.65 1.75	0.65 1.75	0.65 1.75	0.65 1.75
IE (QALY)	0.92	0.92	0.92	0.92
	-0.29 1.90	-0.29 1.90	-0.29 1.90	-0.29 1.90
ICER (€/LYG)	€ 31,856	€ 33,405	€ 34,217	€ 34,405
	€ 20,259 € 51,554	€ 21,215 € 54,680	€ 21,986 € 55,574	€ 22,116 € 55,863
ICER (€/QALY)**	*€ 37,432*	*€ 39,146*	*€ 40,134*	*€ 40,355*

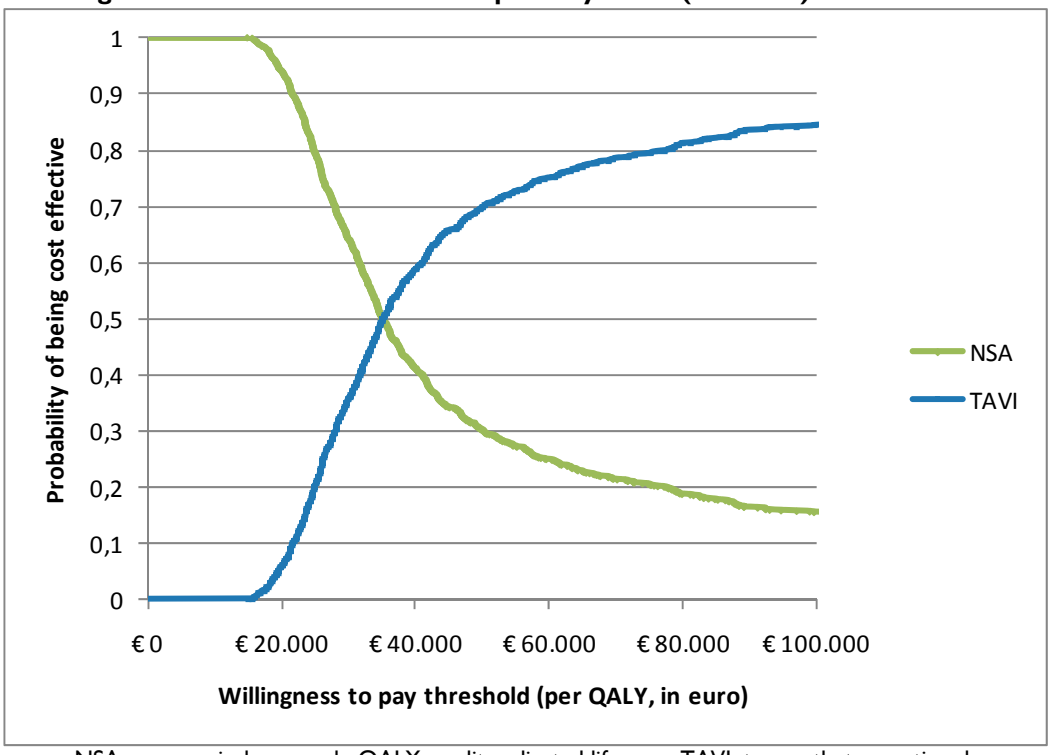
IC: incremental cost; ICER: incremental cost-effectiveness ratio; IE: incremental effect; LYG: life-year gained; QALY: quality-adjusted life-year; TIA: transient ischemic attack.
a: the events repeat hospitalization, major stroke and cardiac reinterventions are taken into account.
Scenario analyses (see 6.2.2.2):
b: only repeat hospitalization is taken into account.
c: only repeat hospitalization and major stroke are taken into account.
d: repeat hospitalization, minor and major stroke, and TIA are taken into account.
**: see explanation in Table 37.

Figure 14. Cost-effectiveness plane (cohort B)



QALY: quality-adjusted life-year; TAVI: transcatheter aortic valve insertion.
Remark: for cohort B, results are presented on the CE-plane and CEA-curve per QALY gained. This is due to space considerations and because QoL in cohort B is measured directly. Results per LYG are available in Table 39.

Figure 15. Cost-effectiveness acceptability curve (cohort B)



NSA: non-surgical approach; QALY: quality-adjusted life-year; TAVI: transcatheter aortic valve insertion.

6.2.2.2 *Scenario analyses*

Modeled events

A first part of sensitivity analyses is already presented in Table 39. Depending on which events are included in the model, with the possibility of double counting, TAVI's ICER increases slightly from €37,400 per QALY up to €40,400 per QALY. This shows that the results are rather robust for the question about the cost of which events should be included explicitly. We remark that these assumptions only have an impact on incremental costs and that costs for major bleeding and vascular complications are not separately included. The incremental effects are the same across these scenario's which all take into account the published mortality rates. While it is difficult to have a preference between one of these scenario's, we chose to perform the other scenario analyses with the most optimistic scenario.

Time horizon

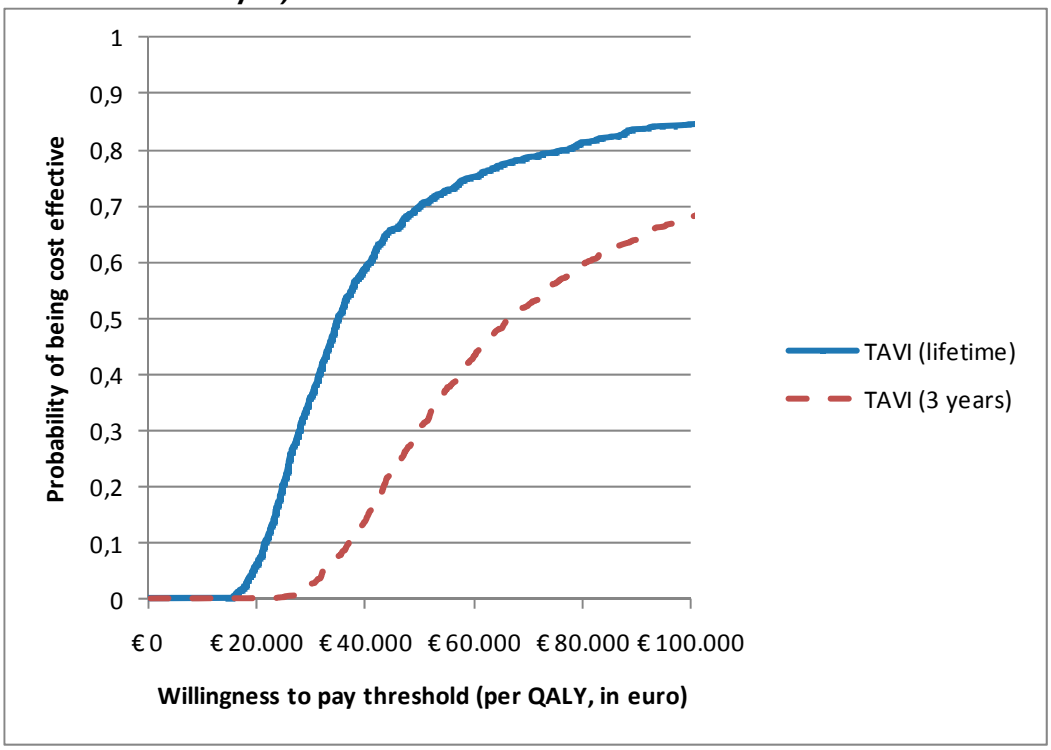
Results are much more sensitive to the extrapolation of trial results. If mortality rates are extrapolated only for the first three years, then results are much less favorable with an average ICER of more than €70,000 per QALY gained (Table 40). This makes sense since the incremental cost of the intervention is caused in the short-term and possible benefits in the longer term. The cost-effectiveness acceptability curve shows that a much higher willingness-to-pay for a QALY is needed of €66,600 to have a 50% chance the intervention is considered cost-effective (Figure 16). We come back to this in our discussion (part 6.3).

Table 40. IC, IE & ICERs for cohort B (time horizon scenario analysis)

Cohort B	Lifetime		3 years	
IC	€ 34,590		€ 33,512	
	€ 29,881	€ 38,631	€ 28,641	€ 37,264
IE (LYG)	1.16		0.55	
	0.65	1.75	0.28	0.80
IE (QALY)	0.92		0.47	
	-0.29	1.90	-0.29	1.09
ICER (€/LYG)	€ 31,856		€ 68,208	
	€ 20,259	€ 51,554	€ 41,372	€ 117,859
ICER (€/QALY)**	*€ 37,432*		*€ 71,573*	

IC: incremental cost; ICER: incremental cost-effectiveness ratio; IE: incremental effect; LYG: life-year gained; QALY: quality-adjusted life-year.
** see explanation in Table 37.

Figure 16. Cost-effectiveness acceptability curve (cohort B, time horizon scenario analysis)



QALY: quality-adjusted life-year; TAVI: transcatheter aortic valve insertion.

Discount rate

Following the pharmaco-economic guidelines, results are presented for different discount rate scenarios (Table 41). With an often used 3% discount rate for both costs and effects, the ICER is on average almost €40,000 per QALY gained.

Table 41. IC, IE & ICERs for cohort B (discount rate scenario analyses)

Cohort B	C: 3%; E: 1.5%	C: 0%; E: 0%	C: 3%; E: 0%
IC	€ 34,590	€ 34,719	€ 34,590
	€ 29,881 € 38,631	€ 29,797 € 38,890	€ 29,881 € 38,631
IE (LYG)	1.16	1.23	1.23
	0.65 1.75	0.68 1.85	0.68 1.85
IE (QALY)	0.92	0.97	0.97
	-0.29 1.90	-0.28 2.00	-0.28 2.00
ICER (€/LYG)	€ 31,856	€ 30,194	€ 30,106
	€ 20,259 € 51,554	€ 19,327 € 48,567	€ 19,136 € 48,681
ICER (€/QALY)**	*€ 37,432*	*€ 35,619*	*€ 35,486*

Cohort B	C: 5%; E: 0%	C: 3%; E: 3%	C: 5%; E: 5%
IC	€ 34,525	€ 34,590	€ 34,525
	€ 29,868 € 38,515	€ 29,881 € 38,631	€ 29,868 € 38,515
IE (LYG)	1.23	1.10	1.03
	0.68 1.85	0.61 1.65	0.57 1.54
IE (QALY)	0.97	0.88	0.82
	-0.28 2.00	-0.29 1.81	-0.28 1.70
ICER (€/LYG)	€ 30,063	€ 33,640	€ 36,019
	€ 19,068 € 48,760	€ 21,456 € 54,490	€ 22,963 € 58,583
ICER (€/QALY)**	*€ 35,420*	*€ 39,403*	*€ 41,991*

IC: incremental cost; ICER: incremental cost-effectiveness ratio; IE: incremental effect; LYG: life-year gained; QALY: quality-adjusted life-year.
** see explanation in Table 37.

30-day mortality and unadjusted TAVI intervention cost

The impact of a higher 30-day mortality, with an equal 1-year mortality, results in somewhat better outcomes. This is due to the use of mortality between the 2nd and 12th month for extrapolating results after the first year. Including an unadjusted TAVI and NSA cost, assuming all patients actually received an Edwards SAPIEN valve and none in the NSA group has surgery, results in an average ICER of €41,800 per QALY gained.

Table 42. IC, IE & ICERs for cohort B (30-day mortality and unadjusted TAVI intervention cost scenario analyses)

Cohort B	Base case	30-day mortality	Unadj. Cost TAVI
IC	€ 34,590	€ 34,812	€ 38,619
	€ 29,881 € 38,631	€ 29,962 € 39,008	€ 33,823 € 42,744
IE (LYG)	1.16	1.24	1.16
	0.65 1.75	0.58 2.07	0.65 1.75
IE (QALY)	0.92	0.98	0.92
	-0.29 1.90	-0.27 2.12	-0.29 1.90
ICER (€/LYG)**	€ 31,856	€ 31,637	€ 35,591
	€ 20,259 € 51,554	€ 17,338 € 55,413	€ 22,740 € 57,775
ICER (€/QALY)**	*€ 37,432*	*€ 35,618*	*€ 41,792*

IC: incremental cost; ICER: incremental cost-effectiveness ratio; IE: incremental effect; LYG: life-year gained; QALY: quality-adjusted life-year.
** see explanation in Table 37.

TAVI device cost and fee

Next to the time horizon, the price of the device also has a substantial impact on TAVI's cost-effectiveness. Lowering the price from €18,000 to €10,000 per device results in an ICER of about €30,000 per QALY gained (Table 43). In contrast, the amount of the fee has a relatively small impact on the ICER.

Table 43. IC, IE & ICERs for cohort B (TAVI cost and fee scenario analyses)

Cohort B	TAVI €10,000	fee €500	fee €1,000
IC	€ 26,906	€ 33,607	€ 34,098
	€ 22,228 € 30,989	€ 28,909 € 37,660	€ 29,395 € 38,145
IE (LYG)	1.16	1.16	1.16
	0.65 1.75	0.65 1.75	0.65 1.75
IE (QALY)	0.92	0.92	0.92
	-0.29 1.90	-0.29 1.90	-0.29 1.90
ICER (€/LYG)	€ 24,735	€ 30,945	€ 31,400
	€ 15,715 € 39,832	€ 19,687 € 50,054	€ 19,958 € 50,804
ICER (€/QALY)**	*€ 29,117*	*€ 36,368*	*€ 36,900*

Cohort B	fee €1,500 (Base case)	fee €2,000	fee €2,500
IC	€ 34,590	€ 35,081	€ 35,573
	€ 29,881 € 38,631	€ 30,368 € 39,116	€ 30,854 € 39,602
IE (LYG)	1.16	1.16	1.16
	0.65 1.75	0.65 1.75	0.65 1.75
IE (QALY)	0.92	0.92	0.92
	-0.29 1.90	-0.29 1.90	-0.29 1.90
ICER (€/LYG)	€ 31,856	€ 32,311	€ 32,767
	€ 20,259 € 51,554	€ 20,564 € 52,303	€ 20,866 € 53,053
ICER (€/QALY)**	*€ 37,432*	*€ 37,963*	*€ 38,495*

IC: incremental cost; ICER: incremental cost-effectiveness ratio; IE: incremental effect; LYG: life-year gained; QALY: quality-adjusted life-year.
** see explanation in Table 37.

Pivotal and continued access results

In this 'continued access' subgroup, TAVI is being dominated by NSA: it is more expensive and outcomes are worse. If the results of this continued access group are combined with those of the pivotal trial, the ICER increases on average to 42,600 per LYG and €44,900 per QALY (Table 44).

Table 44. IC, IE & ICERs for cohort B (with pivotal and combined trial results)

Cohort B	Pivotal		Combined	
IC	€ 34,590		€ 33,243	
	€ 29,881	€ 38,631	€ 27,452	€ 37,773
IE (LYG)	1.16		0.88	
	0.65	1.75	0.39	1.41
IE (QALY)	0.92		0.74	
	-0.29	1.90	-0.44	1.69
ICER (€/LYG)	€ 31,856		€ 42,647	
	€ 20,259	€ 51,554	€ 23,655	€ 86,311
ICER (€/QALY)**	*€ 37,432*		*€ 44,932*	

IC: incremental cost; ICER: incremental cost-effectiveness ratio; IE: incremental effect; LYG: life-year gained; QALY: quality-adjusted life-year.
** see explanation in Table 37.

Technical vs non-technical inoperable patients

Although a reduction in mortality is observed in both subgroups, it is larger in the technical inoperable group, which results in an ICER of about €26,500 per QALY. In the non-technical group, it is about €42,300 per QALY.

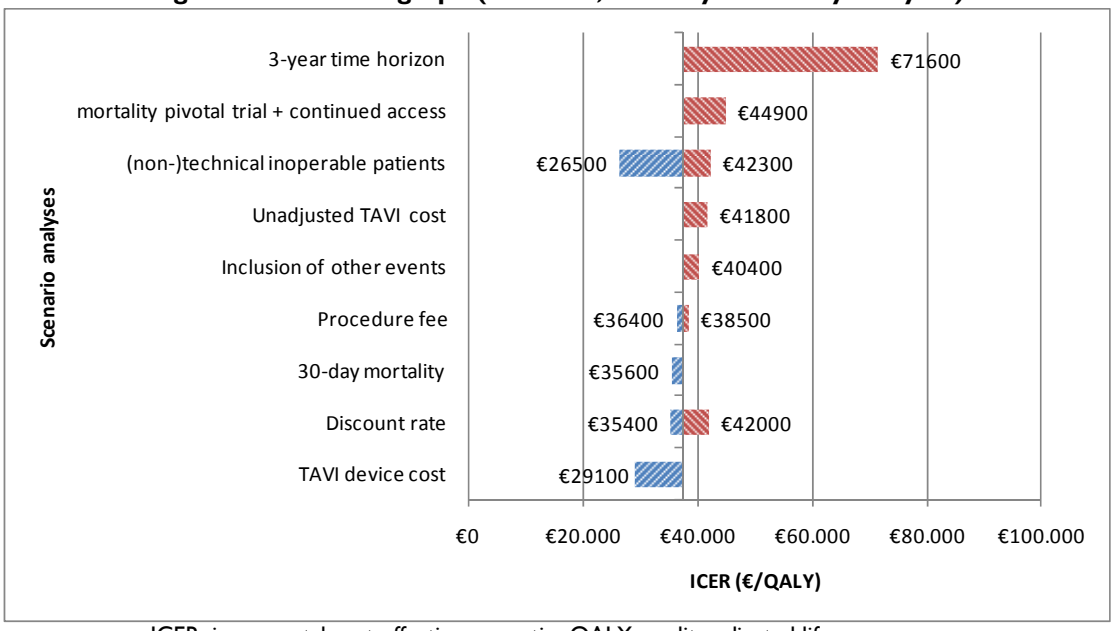
Table 45. IC, IE & ICERs for cohort B (technical versus non-technical inoperable patients)

Cohort B	Non-technical inoperable		Technical inoperable	
IC	€ 34,285		€ 36,123	
	€ 29,229	€ 38,647	€ 30,350	€ 41,850
IE (LYG)	1.00		1.78	
	0.45	1.64	0.60	3.27
IE (QALY)	0.81		1.36	
	-0.30	1.77	-0.15	2.88
ICER (€/LYG)**	*€ 34,301*		€ 24,270	
			€ 11,942	€ 53,898
ICER (€/QALY)**	*€ 42,285*		*€ 26,482*	

IC: incremental cost; ICER: incremental cost-effectiveness ratio; IE: incremental effect; LYG: life-year gained; QALY: quality-adjusted life-year.
** see explanation in Table 37.

Figure 17 provides an overview of all these scenario analyses. It shows the importance of the extrapolation assumption, the increase of the ICER if the results of the continued access group are included, the better results for technical inoperable patients, and the impact of a device price reduction.

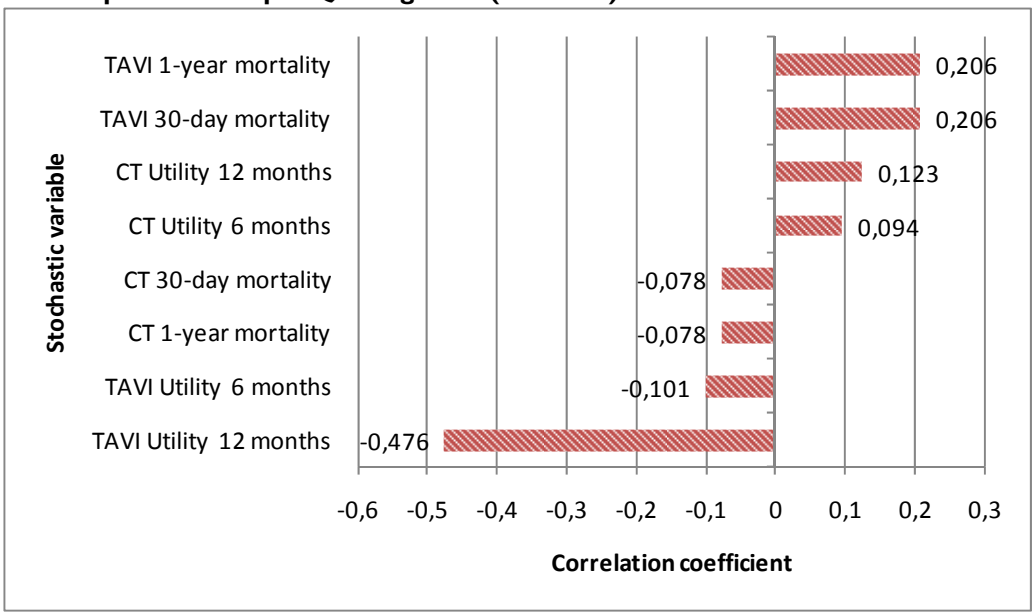
Figure 17. Tornado graph (cohort B, one-way sensitivity analyses)



ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year.

Figure 18 presents the correlation coefficients between the stochastic input variables and the uncertainty around the calculated ICERs. It shows that the most important stochastic variables in the model are the one-year mortality and utility in the TAVI group.

Figure 18. Correlation coefficients between input variables and ICERs expressed as € per QALY gained (cohort B)



CT: conservative therapy; TAVI: transcatheter aortic valve insertion.
The correlation coefficients between the 30-day and one-year mortality rates are the same since a perfect correlation between these two variables was implied to avoid illogical results (see part 6.1.12.1).

6.3 DISCUSSION

6.3.1 Cohort A

One can wonder why a cost-effectiveness analysis was done for cohort A since the clinical trial results already showed that the two groups (TAVI and AVR) are very similar in terms of mortality outcomes and that the risk of stroke is higher in the TAVI group. Furthermore, TAVI is more expensive than AVR: €43,600 for the TAVI intervention, including a cost of €18,000 for the Sapien valve®, vs. €23,700 for AVR. If a technology is not superior to an alternative in terms of clinical benefits and more expensive, why bother with cost-effectiveness since this analysis is time- and resource-consuming. The reason is that we explicitly want to show the result if we take into account the non-significant differences in mortality. This should avoid (useless and time-consuming) future discussions about the cost-effectiveness of TAVI in cohort A.

From an economic perspective, based on the results of the PARTNER trial, it makes sense that TAVI reimbursement is difficult to justify in patients similar to those in cohort A.

6.3.2 Cohort B

Based on the mortality differences in the combined trial (pivotal + Continued Access), the cost-effectiveness of TAVI in comparison to NSA was on average €44,900 per QALY gained. In Belgium, there is no explicit (range of) threshold value(s) to state whether or not an intervention is cost effective. NICE, the National Institute for Health and Clinical Excellence in the UK, is the only HTA institute with an explicit ICER threshold range mentioned in its guidelines.[39] The guiding principles are as follows:

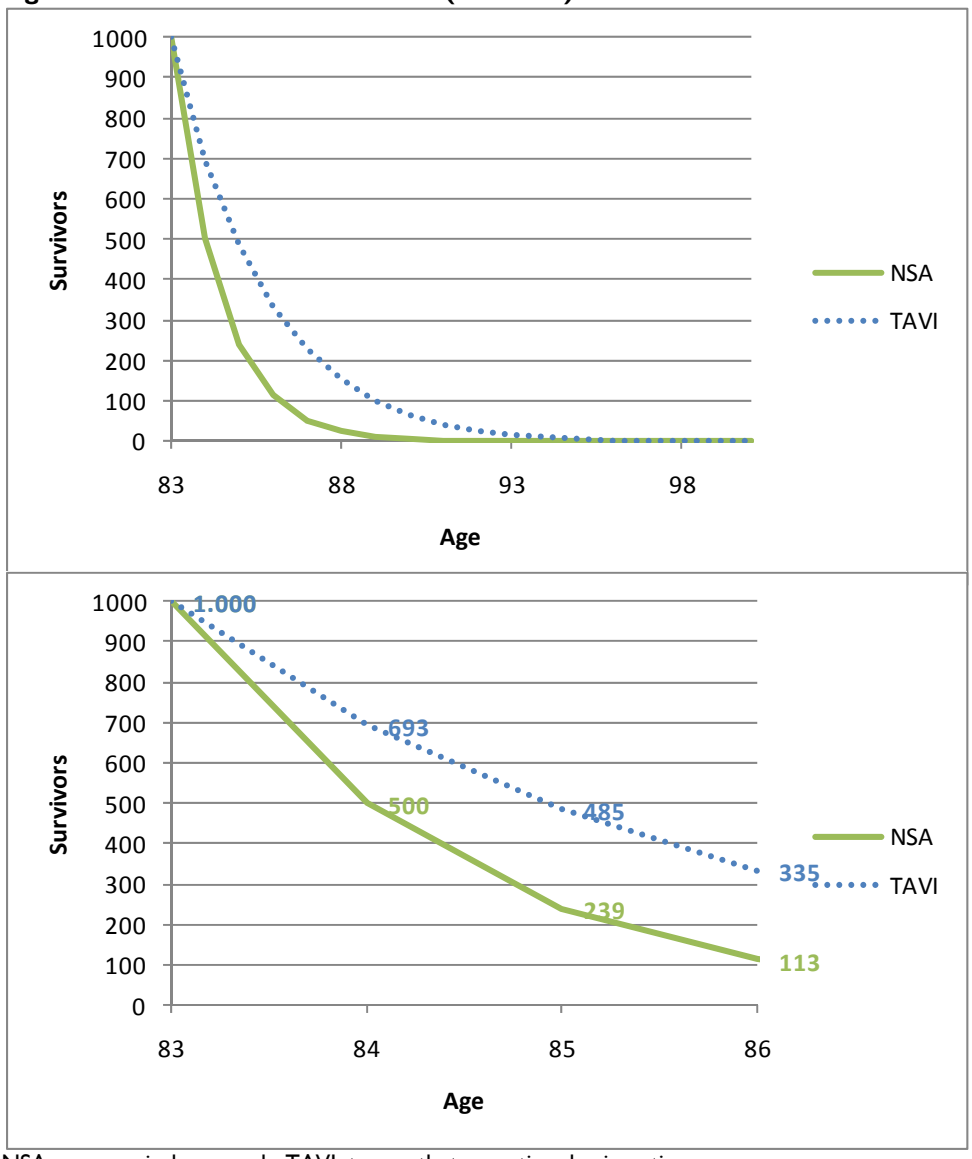
- For interventions with an ICER < £20,000/QALY gained, decisions will primarily be guided by cost-effectiveness considerations. In principle, the recommendation will be to provide this intervention, unless there are major doubts about the plausibility of and/or certainty around the estimated ICER. Thus, account is taken of the results of the sensitivity analysis and potential limitations to the generalizability of the findings regarding effectiveness.
- For interventions with an ICER between £20,000/QALY gained and £30,000/QALY gained, NICE takes account of the following factors:
  - The degree of (un)certainty about the ICER.
  - Whether there are strong reasons to indicate that the assessment of the HRQoL has inadequately captured, and may therefore misrepresent, the health utility gained.
  - The innovative nature of the technology, specifically where the innovation adds benefits of a substantial nature compared with available alternatives which may not have been captured in the QALY measure.
- For interventions with an ICER > £30,000/QALY gained the same factors will be taken into account. A stronger case is needed on these factors to approve such interventions.

Applying these thresholds of about € 22,800 and € 34,200 (exchange rate August, 2011: £1 = ~€1.14) to the uncertainty around the calculated ICERs results in a chance of 9.2% and 36.7% of TAVI being considered cost-effective.

For several reasons, the ICER might even be higher because of 1) the influence of a higher stroke rate on the long-term follow-up costs, 2) the optimistic assumption that quality of life remains constant after one year (instead of decreasing with increasing age), 3) a possible overtreatment of the NSA population increasing the costs in this group (e.g. >80% valvuloplasty and several AVR in this 'inoperable' group); and 4) the extrapolation assumption with a constant monthly mortality rate increasing yearly according to the age- and sex specific mortality rates of the total Belgian population. The latter means that the survival benefit remains in the long-term, which is discussed in the next paragraph.

A most important influential factor in the modeling result is the way the short-term trial results are extrapolated. In the base case, we used the published mortality rates at 30 days and 1 year, and we based our extrapolation on the mortality rates between the 2nd and 12th month. However, only longer-term follow-up can exclude whether or not this is appropriate. Figure 19 shows the survival curves based on our model with a closer look at the first three years.

Figure 19. Modelled survival curves (cohort B)

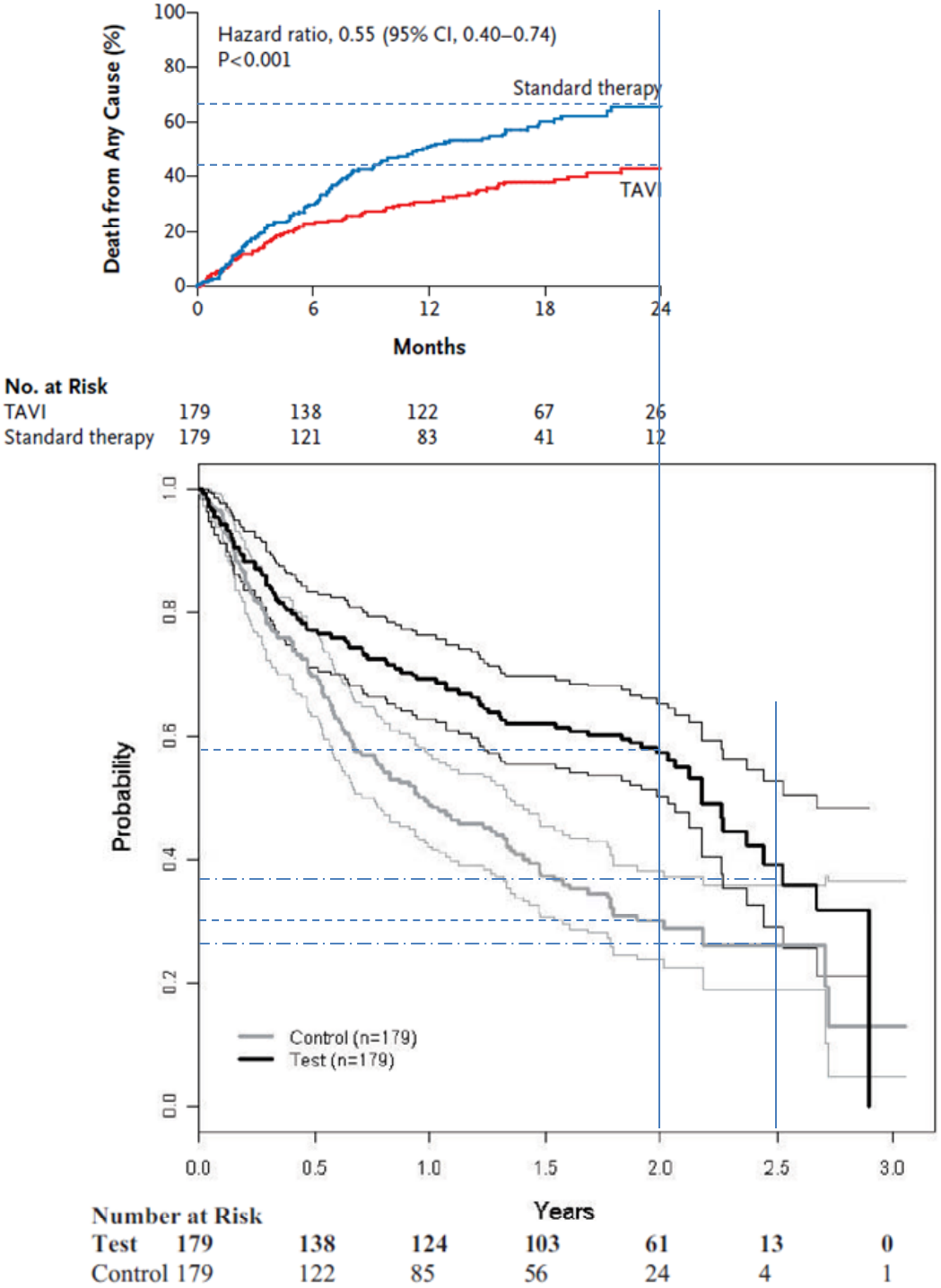


NSA: non-surgical approach; TAVI: transcatheter aortic valve insertion.

Longer term follow-up is available from both the publication of Leon et al.[7] and from the FDA analysis. As noted by FDA, there are limited data beyond 2 years from the PARTNER trial and the long-term mortality benefit of the SAPIEN remains unclear. Comparing our analysis and the published inverse survival curve (Figure 20, top) indicates our model might overestimate the long-term mortality rate. Nevertheless, this is the case for both NSA and TAVI, keeping a similar distance between both curves. As a result, the area between the curve, which determines the incremental effect, remains about the same for the first years. On the other hand, the FDA analysis, although based on relatively small numbers, indicates this advantage might not sustain over time (Figure 20, bottom). Between 2 and 2.5 years after the initial TAVI procedure, the shape of the survival curve seems to be less optimistic. In this case, an analysis with a shorter time horizon would be more appropriate.

This would have a negative influence on TAVI's cost-effectiveness. Using the data of the pivotal trial, the cost-effectiveness of TAVI in comparison to NSA would increase from on average €37.400 per QALY with a lifetime extrapolation to about €70,000 per QALY with a 3-year time horizon.

Figure 20. Published survival curves (cohort B, top: Leon et al.[7]; bottom: FDA analysis[11])



TAVI: transcatheter aortic valve implantation.

A limitation of our analysis is that the costs of an event are similar between all groups. It is possible that the intensity of a repeat hospitalisation is different between the TAVI and NSA group. Our analysis probably does not disfavour TAVI since, based on an FDA analysis, the median number of hospital days through one year is higher in the TAVI group. In contrast, based on the published data, we incorporated a higher number of repeat hospitalizations in the NSA group. Moreover, we did not include cost consequences of vascular complications and major bleedings to avoid possible double counting with the cost of the initial procedure and repeat hospitalizations. The FDA analysis, with another definition for these events than in the published trial data, has indicated 90 and 100 vascular complications in the TAVI group after 30 days and one year, respectively. In contrast, this was only 25 in the NSA group with no further events afterwards. For bleedings, according to the FDA analysis, this was 29 and 31 events in the TAVI group after 30 days and one year, respectively, and only 4 after 30 days with no further events afterwards in the NSA group. Therefore, if these events would be included in the economic evaluation, the ICERs would further increase since this is mainly a problem in the TAVI cohort.

As mentioned in the medical overview, combining the results of TAVI in those better-off patients with those presenting with severe medical co-morbidities may lead to an underestimation of the effectiveness of TAVI in the anatomic subgroup (and vice versa). Whereas in the former group treatment of the aortic stenosis is aimed at care and palliation, in the latter it may lead to cure. It would be interesting to perform a subgroup analysis of the comparative effect of TAVI and standard treatment in this subgroup. The study sponsor noticed that the study was designed and powered to detect a difference in mortality between the TAVI group and the standard therapy group in a population of inoperable patients with severe aortic stenosis based on the entire cohort and not for specific subgroups. Nevertheless, especially because of the uneven distribution of such patients over the two treatment arms and their greater potential for improvement with TAVI, this subgroup analysis is of the utmost importance. The survival gain of TAVI versus NSA after one year was larger in the anatomic inoperable patients (27.9%) in comparison to the medical inoperable patients (17%). A scenario analysis on the pivotal trial including the mortality differences showed that the ICER is about €11,000 lower in the anatomic inoperable subgroup in comparison to the estimate for the group as a whole. For the medical inoperable subgroup, this is about €5,000 higher. Unfortunately, no data were received on the number of events or QoL gain in both subgroups, nor were these data available for the combined pivotal and Continued Access trial. If the number of events and QoL gain are more advantageous in the anatomic inoperable patients, than the cost-effectiveness of TAVI might further improve in this subgroup and vice versa in the medical inoperable subgroup. This kind of information is necessary to further refine the calculations of this economic evaluation. Providing such data in a transparent way to HTA institutions for further analysis would be a step forward.

Key points

The cost-effectiveness is calculated for a PARTNER-like population in a Belgian context. In our approach, data from the PARTNER trial are used to model the treatment effect on mortality, quality of life and other events. For context-specific costs, we rely on Belgian cost data.

PARTNER Cohort A

- **A substantial incremental cost for TAVI versus AVR in combination with minimal incremental effects results in relatively very high ICERs. This is the case for all performed subgroup analyses.**
- **The average ICER is about €750,000 per LYG or per QALY gained.**
- **With a decrease of the TAVI device cost from €18,000 to €10,000, the average ICER remains above €450,000 per LYG or per QALY gained.**
- **Results on the EQ-5D utility values for cohort A are not available yet.**

PARTNER Cohort B

- **Based on the results of the pivotal PARTNER trial, and assuming a lifetime treatment effect, the average ICER is about €37,400 per QALY.**
- **Lowering the price from €18,000 to €10,000 per device results in an ICER of about €30,000 per QALY gained.**
- **Results are very sensitive to the extrapolation of trial results. If mortality rates are extrapolated only for the first three years, then results are much less favorable with an average ICER of more than €70,000 per QALY gained.**
- **A larger mortality reduction is noticed in the technical inoperable patients. This lowers the average ICER of this subgroup with about €11,000 per QALY whereas it increases with about €5,000 per QALY in the non-technical subgroup.**
- **In the 'continued access' group, TAVI is being dominated by NSA: it is more expensive and outcomes are worse.**
- **Including the result of the continued access group, the ICER increases to €44,900 per quality-adjusted life-year. Since there is no good reason to restrict the analysis to the pivotal trial, this result should rather be considered as the base case.**
- **Relying on the results of the subgroup analysis in the pivotal trial, it is very probable that the ICER of €44,900 per QALY will increase for the non-technical inoperable patients and decrease for the technical inoperable patients.**
- **No results on mortality, events and QoL are available for the combined trial (i.e. pivotal + continued access) in combination with the technical versus non-technical subgroup analysis. If this information becomes available, the economic evaluation could be refined.**

7 DISCUSSION

In the present report, we critically appraise the results of the PARTNER trial, the first ever randomised controlled trial studying the safety and effectiveness of TAVI. This trial assessed the performance of the Edwards Sapien® device in high-risk patients with severe symptomatic aortic stenosis. Patients were stratified into two cohorts:

- In Cohort A, including patients at high risk for standard surgery, patients were randomised to TAVI or surgical aortic valve replacement
- In Cohort B, inoperable patients were randomised to TAVI or to a non-surgical approach, i.e. medical treatment in combination with a balloon aortic valvuloplasty in most patients

The PARTNER trial does not allow to assess the performance of trans-apical TAVI, since inoperable patients with no trans-femoral access route were excluded from entry in Cohort B, whereas in Cohort A trans-apical TAVI could not be compared to trans-femoral TAVI because of baseline differences of patients.

Our report does not allow to make firm conclusions on other types of percutaneous valves such as Medtronic's CoreValve®. An FDA approved randomised controlled trial studying the CoreValve® has been launched in the US in December 2010 and is still ongoing (ClinicalTrials.gov identifier NCT01240902). Patients are randomised one-to-one to either TAVI with CoreValve® or to surgical AVR. Patients deemed at extreme risk will not be randomised.

There have been no randomised head-to-head comparisons between different percutaneous valve types.

7.1 PARTNER COHORT A

In Cohort A patients, TAVI and surgery were associated with similar mortality rates at 1 year and produced similar improvements in cardiac symptoms (Table 46). This observation dissolves our initial safety concerns with TAVI,[1] at least in the Cohort A type of patients, although the significant doubling in the rate of stroke (including TIA) after TAVI as compared to surgery (8.3% vs. 4.3% at 1 year) remains problematic. From a medical point of view TAVI might be considered as an alternative to surgery for high-risk patients who are willing to accept a higher risk of stroke.[36]

In these patients, TAVI comes at a much higher cost. Including a device cost of €18.000, TAVI's cost-effectiveness is on average €750.000 per QALY compared to surgery (Table 46) (incremental cost (IC): €20,400; incremental effect (IE): 0.03 QALYs). The modest benefits related to the less invasive nature of the procedure do not weigh against these extra costs. From an economic point of view, it is hard to defend TAVI reimbursement as an efficient use of available (limited) resources. This can be altered if TAVI costs become similar to those of AVR.

Table 46. Clinical effectiveness of TAVI in the PARTNER trial and cost-effectiveness of TAVI based on the results from PARTNER and Belgian cost data

	COHORT A	COHORT B
	Patients at high risk for surgery	Patients who cannot be operated
CLINICAL EFFECTIVENESS	TAVI and surgical AVR are associated with similar rates of survival and similar improvement in cardiac symptoms. TAVI carries a twice as high risk of stroke compared to surgery.	TAVI leads to an absolute 1-year mortality risk reduction of 20% and to improved cardiac symptoms compared to standard treatment. Stroke rate at 1 year is twice as high in TAVI patients. 1. Patients with prohibitive anatomy: TAVI may be therapy of choice (Δ survival at 1 year= 27.9%) 2. Patients with severe medical co-morbidities: TAVI acceptable as a palliative intervention if a higher risk of stroke is accepted. (Δ survival at 1 year= 17.0%)
ICER	On average €750,000 per QALY gained.	On average €44,900 per QALY gained. Result sensitive to time horizon/extrapolation (lifelong versus 3-year extrapolation), price of the device and 1-year mortality rates. Better results for anatomic inoperable patients.

7.2 PARTNER COHORT B

In Cohort B patients, i.e. those who cannot undergo valve surgery according to two cardiac surgeons, TAVI significantly reduces the rate of death from any cause as compared with a non-surgical approach (absolute risk reduction 20.0%). The latter, somewhat equivocally referred to by the investigators as "standard therapy", encompassed balloon valvuloplasty, an intervention that is acceptable as a palliative measure only.[17, 18] TAVI also significantly improves cardiac symptoms and reduces the need for repeat hospitalisations. Stroke (including TIA) rate at 1 year however was twice as high in TAVI patients compared to the non-surgical approach (10.6% vs. 4.5%).

Data from 90 patients enrolled in the randomised Continued Access Cohort B and followed for a mean of 7 months, are available from the July 20, 2011 FDA documents. Remarkably, in these patients TAVI performed worse than "standard therapy" because of a much lower mortality of control patients in the Continued Access patients, as compared to control patients in the pivotal trial. Whereas TAVI outperformed standard therapy by an absolute 20% lower 1-year mortality in the pivotal trial, survival of TAVI patients in the Continued Access study was an absolute 12.7% lower. Still, after combining the results of the pivotal trial and the Continued Access study, TAVI significantly reduces 1-year mortality as compared with standard therapy.

The overall benefit of TAVI in those patients seems to outweigh the risks and therefore it may be appropriate to consider and discuss TAVI with patients who can otherwise not be operated.

Only looking at the pivotal trial results, and including a lifelong extrapolation of the mortality benefit, the ICER is €37,400 per QALY gained (IC: €34,600; IE: 0.92 QALYs). This ICER might increase if the costs of stroke, which occurs more often in the TAVI group, would be included separately and/or if valvuloplasty and AVR would not be performed in such large numbers as in the trial's NSA group. This ICER is also very sensitive to the extrapolation assumption. Based on the FDA longer-term follow-up analysis, lifelong extrapolation of the mortality advantage may be overoptimistic.

Restricting the time horizon to three years results in an increased ICER of €71,600 per QALY (IC: €33,500; IE: 0.47 QALYs).

For the continued access population only results on mortality were available and not for other events or QoL. Combining the mortality data from both the pivotal and continued access trial, and including a lifelong extrapolation, results in an ICER of €44,900 per QALY (IC: €33,200; IE: 0.74 QALYs). Since there is no good reason to exclude the continued access population, this result should rather be seen as the base case. In Belgium, no explicit threshold value exists. Applying NICE's explicit threshold values of £20,000 and £30,000 per QALY, results in an 9.2% and 36.7% chance, respectively, that TAVI is considered as being a cost-effective intervention.

There is however a subgroup of patients that might have a greater advantage of receiving TAVI. These are the anatomical inoperable patients. In the pivotal trial, the absolute mortality gain was an absolute 17 percentages in the non-anatomical inoperable group versus an absolute 27.9 percentages in the anatomical inoperable group. This results in an improved ICER for the latter group (about €11,000 per QALY lower) and vice versa for the other group (about €5,000 per QALY higher).

Results of this subgroup analysis were only available for the pivotal trial and for the mortality endpoint. Further refinement of the cost-effectiveness calculation is only possible if further details for the whole population (pivotal and continued access) and for all relevant outcomes (mortality, events and QoL) are available. Without these data, the performed analyses show that, if one is willing to pay the considerable amount for the QALYs gained, reimbursement of TAVI could in the first place focus on the well-defined subgroup of anatomical inoperable patients.

7.3 INTERNAL VALIDITY OF THE PARTNER TRIAL

The internal validity of the PARTNER trial is threatened by a number of methodological study characteristics that may have lead to an overestimation of the treatment effect of TAVI. This concern is further strengthened by the fact that in the randomised *Continued Access population of Cohort B*, 1-year survival of patients treated with TAVI was worse than those receiving standard therapy. Although this may be due to a play of chance, it remains a remarkable observation.

Some of the PARTNER trial investigators had a clear *financial interest* in the demonstration of a beneficial effect of TAVI.

The *randomisation procedure* was not clearly described in the study protocol. Concerns were raised by the observation of an uneven distribution of baseline characteristics of patients in Cohort B, all of them favouring TAVI. This may possibly be consequential to an absence of the investigators' concealment of allocation.

Control therapy in Cohort A was described as surgical aortic valve replacement, but it is not known to what extent modern minimal invasive surgical techniques were used. Furthermore, more than 10% of the patients randomised to surgery were not treated as assigned. The so-called "standard therapy" in the control group of Cohort B included a balloon valvuloplasty, representing an invasive treatment in its own right that has not been clearly shown to be superior to a strictly non-invasive medical treatment. Despite the fact that all the patients in Cohort B were determined not to be suitable candidates for surgery, almost 10% of them did undergo surgery.

7.4 EXTERNAL VALIDITY OF THE PARTNER TRIAL

7.4.1 The heart team's skills

The 30-day mortality rate of trans-femoral TAVI observed in Cohort A of the PARTNER trial (3.7%) is the lowest ever reported in a TAVI study. Combining the trans-femoral TAVI mortality rates from both cohorts results in an average of 4.8% (Table 10). Of note, the US investigators involved in PARTNER were relatively inexperienced at the time of the trial. Their performance is remarkable in comparison with that reported in recent series by experienced interventionalists. For example in the FRANCE-2 registry, between January 2010 and March 2011, 810 patients were treated with an up-to-date trans-femoral Edwards Sapien device, with an observed 30-day mortality rate of 7.8%.

7.4.2 Patient selection: cohort A versus cohort B

The clinical differentiation of PARTNER Cohort A from Cohort B patients is not straightforward and essentially based on the clinical feeling of the physicians involved. Cohort A patients are those suitable for surgery but with a high operative risk of death. Cohort B patients in the FDA's definition are those who have been determined by a cardiac surgeon to be inoperable for open aortic valve replacement and in whom existing co-morbidities would not preclude the expected benefit from correction of the aortic stenosis.[11]

So far, this distinction has never been made in TAVI registries. They mostly enrol patients based on quantitative operative risk scores or on physician preferences. In the FRANCE-registry, no particular inclusion or exclusion criteria are required by the French government.[1] In the Belgian register, TAVI is considered in patients who are "not good candidates" for surgical aortic valve replacement.[19] Baseline characteristics of Belgian patients suggest that they are on average in a better condition than those in either of the PARTNER cohorts (Table 12).

In the US, the ongoing premarket approval procedure by the FDA is limited to TAVI in inoperable patients, and does not consider PARTNER Cohort A type of patients.[11] This means that TAVI is currently not considered for US market approval in patients who are operable, even in those at high risk for surgery. With the PARTNER Cohort A results in mind, the question raises whether those patients will continue to be eligible for TAVI in Europe.

7.4.3 Patient selection: anatomical versus medical inoperable patients

Cohort B represents a mix of two patient populations that were clearly defined by the investigators from the start of the trial. 75% of them were inoperable because of severe co-morbid medical conditions. These patients who by definition have a limited life expectancy may benefit from a correction of the aortic stenosis for palliative symptomatic reasons. 25% of Cohort B patients were inoperable because of prohibitive anatomical conditions, including porcelain aorta, chest wall deformity, and multiple previous interventions. These patients not necessarily have serious non-cardiac co-morbidities and they may benefit from TAVI for both symptomatic and prognostic reasons. In the PARTNER trial, their 1-year mortality following TAVI was lower than in the medically inoperable patients but still their prognosis was poor, because of their advanced aged and presumably the presence of serious medical co-morbid conditions as well. Further studies are needed to define the role of TAVI in patients with an anatomically inoperable aortic stenosis who are otherwise healthy. They may represent a population for which TAVI becomes the treatment of choice.

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[1] http://www.has-sante.fr/portail/jcms/c_1052048/protheses-valvulaires-aortiques

In the Belgian registry the proportion of patients with porcelain aorta was 7.0%, closely corresponding to 7.9% in the mixed PARTNER cohorts. Exact Belgian figures for other prohibitive anatomical characteristics are not provided, but one can expect that they are similar to those in PARTNER as well. It can be estimated that in the mixed PARTNER population 10% of patients are treated with TAVI because of anatomical abnormalities.

7.4.4 Physicians' preferences

A physician's performance in estimating the operative risk of a patient with aortic stenosis and significant co-morbidities has not been clearly established and may be subject to bias. In this respect, ethical questions come into play. Depending on the physicians' preferences, less sick patients may be treated by TAVI although they could reasonably have open AVR. On the other hand, some patients may be offered TAVI although their co-morbidities preclude any significant improvement in their quality of life with a correction of the aortic stenosis. In a recent comment, the FDA deplores that whereas the PARTNER trial protocol defined patients who should not have surgery due to extensive co-morbidities, it did not actively consider patients who should not have TAVI.

7.4.5 Patients' values

Patient preferences have to be taken into consideration before proceeding to TAVI. A patient with severe co-morbidities may primarily be interested in an improvement of quality of life and not so much in a prolongation of life. In these instances symptoms due to the aortic stenosis and those resulting from unrelated co-morbid conditions have to be carefully balanced. In a recently published survey, Belgians rated heroic end-of-life measures second only to redundant paperwork as the most important source of waste in the health care system.[40]

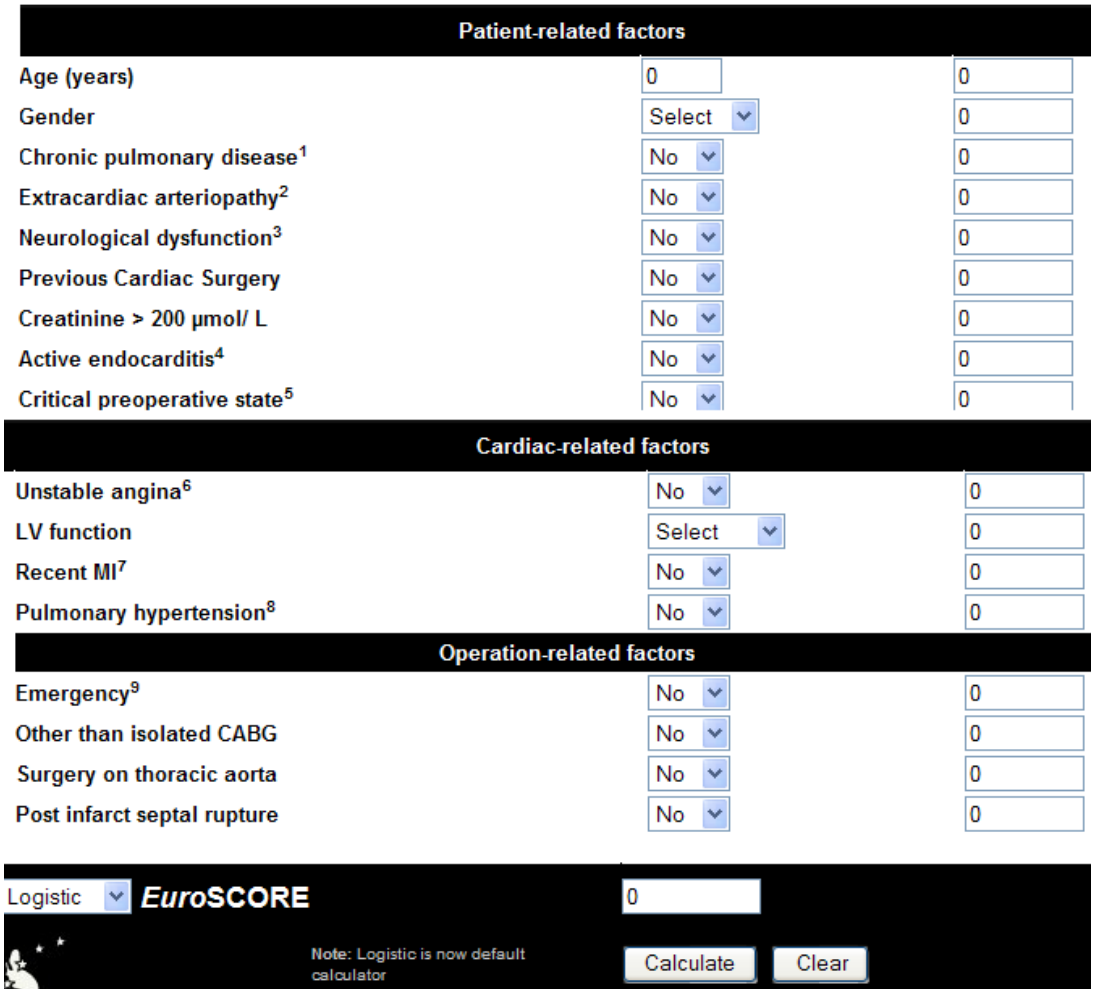
Moreover, the potential risk of inducing stroke by TAVI may lead a patient to opt for a conservative treatment, or to prefer a higher operative mortality risk from surgery.

8 APPENDIX

8.1 EUROSCORE

The EuroSCORE provides a method of predicting the operative mortality for patients undergoing cardiac surgery. Two risk calculators are available on the website of EuroSCORE (http://www.euroscore.org): the simple additive EuroSCORE and the full logistic EuroSCORE. The full logistic version reportedly produces a more accurate risk prediction than the simpler additive model. Predicted mortality is calculated as described in Roques et al.[41] The clinical parameters that are taken into account in order to calculate the EuroSCORE are depicted in Figure 21.

Figure 21. Calculation of the logistic EuroSCORE (http://www.euroscore.org/calc.html)



8.2 THE SOCIETY OF THORACIC SURGEONS' RISK SCORE

The earliest Society of Thoracic Surgeons' (STS) risk models were developed 20 years ago for isolated coronary artery bypass graft surgery (CABG). Subsequently, similar models have been developed for isolated valve replacement and combined CABG plus valve replacement. Because surgical practice and outcomes are changing rapidly, these models are updated periodically to reflect contemporary experience. A complete revision of all STS risk models for adult cardiac surgery has been undertaken, and implemented in January 2008.[42]

An online STS risk calculator is available from http://209.220.160.181/STSWebRiskCalc261/de.aspx.

8.3 MORTALITY RATES FOR ALTERNATIVE SCENARIOS

In the base case scenario, ITT results are used for calculating TAVI's cost-effectiveness in cohort A. Scenario analyses are performed for the 'as-treated' group, the transapical, and the transfemoral approach. Table 47 presents the mortality rates and applied distribution for these scenarios.

Table 47. Model input variables: mortality

	Average		Beta distribution	
	publication	model	alpha	beta
Cohort A (ITT, TF)				
TAVI				
30 days	3.3%	3.3%	8	236
1 year	22.2%	22.2%	54	189
month 2-12		2.0%		
OPT				
30 days	6.2%	6.2%	15	227
1 year	26.4%	26.4%	62	173
month 2-12		2.2%		
Cohort A (ITT, TA)				
TAVI				
30 days	3.8%	3.8%	4	100
1 year	29.0%	28.8%	30	74
month 2-12		2.7%		
CT				
30 days	7.0%	7.0%	7	93
1 year	27.9%	27.8%	27	70
month 2-12		2.3%		
Cohort A (AT, All)				
TAVI				
30 days	5.2%	5.2%	18	326
1 year	23.7%	23.7%	81	261
month 2-12		1.9%		
CT				
30 days	8.0%	8.0%	25	288
1 year	25.2%	25.2%	78	232
month 2-12		1.9%		

AT: as treated; ITT: intention-to-treat; TA: transapical; TF: transfemoral. The source for data on cohort A is based on the appendix of Smith et al.[8].

The alpha parameter equals the number of events. The beta parameter equals the number at risk minus the number of events. The beta parameter was adjusted so that the average value equals the published mortality probability.

8.4 EVENT RATES FOR ALTERNATIVE SCENARIOS

Table 48. Modeled clinical outcomes at 30 days and 1 year (cohort A, ITT, TF approach)

	Average		Beta distribution			Average		Beta distribution	
	publication	model	alpha	beta		publication	model	alpha	beta
Repeat hospitalization					**TIA**				
TAVI					**TAVI**				
30 days	4.6%	4.6%	11	228	30 days	1.3%	1.3%	3	227
1 year	18.5%	18.5%	42	185	1 year	1.8%	1.8%	4	218
Number of events between month 2-12:					Number of events between month 2-12:				
n in trial*		31			n in trial		1		
n in model**		127.0			n in model		4.1		
AVR					**AVR**				
30 days	3.1%	3.1%	7	219	30 days	0%	0%	0	248
1 year	15.9%	15.9%	32	169	1 year	0.6%	0.6%	1	167
Number of events between month 2-12:					Number of events between month 2-12:				
n in trial		25			n in trial		1		
n in model		100.8			n in model		4.0		
Major stroke					**Minor stroke**				
TAVI					**TAVI**				
30 days	2.9%	2.9%	7	237	30 days	0.8%	0.8%	2	242
1 year	3.8%	3.8%	9	228	1 year	0.8%	0.8%	2	242
Number of events between month 2-12:					Number of events between month 2-12:				
n in trial		2			n in trial		0		
n in model		8.2			n in model		0		
AVR					**AVR**				
30 days	1.7%	1.7%	4	231	30 days	0%	0%	0	248
1 year	1.7%	1.7%	4	231	1 year	0.6%	0.6%	1	167
Number of events between month 2-12:					Number of events between month 2-12:				
n in trial		0			n in trial		1		
n in model		0			n in model		4.0		

ITT: intention-to-treat; TF: transfemoral.

*: the difference between the modeled number of events after 30 days and 1 year.

**: the number of events in the trial is extrapolated to the number of events if this would be a cohort of 1000 patients. In the trial, the TAVI and AVR group included 244 and 248 patients, respectively.

Table 49. Modeled clinical outcomes at 30 days and 1 year (cohort A, ITT, TA approach)

	Average		Beta distribution			Average		Beta distribution	
	publication	model	alpha	beta		publication	model	alpha	beta
Repeat hospitalization					**TIA**				
TAVI					**TAVI**				
30 days	3.9%	3.8%	4	100	30 days	0%	0%	0	104
1 year	17.5%	17.6%	16	75	1 year	3.7%	3.7%	3	78
Number of events between month 2-12:					Number of events between month 2-12:				
n in trial*		12			n in trial		3		
n in model**		115.4			n in model		28.8		
AVR					**AVR**				
30 days	5.1%	5.1%	5	93	30 days	1.1%	1.1%	1	90
1 year	14.7%	14.8%	13	75	1 year	3.7%	3.7%	3	78
Number of events between month 2-12:					Number of events between month 2-12:				
n in trial		8			n in trial		2		
n in model		77.7			n in model		19.4		
Major stroke					**Minor stroke**				
TAVI					**TAVI**				
30 days	5.8%	5.8%	6	98	30 days	1.0%	1.0%	1	103
1 year	8.3%	8.3%	8	88	1 year	1.0%	1.0%	1	103
Number of events between month 2-12:					Number of events between month 2-12:				
n in trial		2			n in trial		0		
n in model		19.2			n in model		0		
AVR					**AVR**				
30 days	3.2%	3.2%	3	91	30 days	1.1%	1.1%	1	90
1 year	4.3%	4.3%	4	89	1 year	1.1%	1.1%	1	90
Number of events between month 2-12:					Number of events between month 2-12:				
n in trial		1			n in trial		0		
n in model		9.7			n in model		0		

ITT: intention-to-treat; TA: transapical

*: the difference between the modeled number of events after 30 days and 1 year.

**: the number of events in the trial is extrapolated to the number of events if this would be a cohort of 1000 patients. In the trial, the TAVI and AVR group included 104 and 103 patients, respectively.

Table 50. Modeled clinical outcomes at 30 days and 1 year (cohort A, AT, All patients)

	Average		Beta distribution			Average		Beta distribution	
	publication	model	alpha	beta		publication	model	alpha	beta
Repeat hospitalization					**TIA**				
TAVI					**TAVI**				
30 days	5.1%	5.1%	17	317	30 days	0.9%	0.9%	3	341
1 year	17.0%	17.0%	53	259	1 year	2.3%	2.3%	7	298
Number of events between month 2-12:					Number of events between month 2-12:				
n in trial*		36			n in trial		4		
n in model**		104.7			n in model		11.6		
AVR					**AVR**				
30 days	5.4%	5.4%	16	281	30 days	0.3%	0.3%	1	312
1 year	14.7%	14.7%	40	232	1 year	1.5%	1.5%	4	262
Number of events between month 2-12:					Number of events between month 2-12:				
n in trial		24			n in trial		3		
n in model		76.7			n in model		9.6		
Major stroke					**Minor stroke**				
TAVI					**TAVI**				
30 days	3.8%	3.8%	13	331	30 days	0.9%	0.9%	3	341
1 year	5.2%	5.2%	17	310	1 year	0.9%	0.9%	3	341
Number of events between month 2-12:					Number of events between month 2-12:				
n in trial		4			n in trial		0		
n in model		11.6			n in model		0		
AVR					**AVR**				
30 days	2.3%	2.3%	7	298	30 days	0.3%	0.3%	1	312
1 year	2.7%	2.7%	8	288	1 year	0.3%	0.3%	1	312
Number of events between month 2-12:					Number of events between month 2-12:				
n in trial		1			n in trial		0		
n in model		3.2			n in model		0		

AT: as-treated.
*: the difference between the modeled number of events after 30 days and 1 year.
**: the number of events in the trial is extrapolated to the number of events if this would be a cohort of 1000 patients. In the trial, the TAVI and AVR group included 344 and 313 patients, respectively.

8.5 DEFINITIONS IN THE PARTNER STUDY PROTOCOL

Repeat hospitalization

Recurrent Hospitalization: Rehospitalization for symptoms of heart failure, angina or syncope due to aortic valve disease requiring aortic valve intervention or intensified medical management, hospitalization for complications from the procedure, such as infection, renal failure, etc.[43]

Repeat hospitalization because of valve- or procedure-related clinical deterioration.[8]

Stroke (& TIA)

A transient ischemic attack (TIA) is a fully reversible neurologic event that lasts less than 24 hours and if an imaging study is performed, shows no evidence of infarction.[43]

Stroke: A neurological deficit lasting > 24 hours, or lasting < 24 hours with a brain imaging study showing infarction.[43]

Major stroke was defined by a score of at least 2 on the modified Rankin scale (which ranges from 0 to 6, with higher scores indicating greater disability).[8]

Vascular complications

Vascular complications include the following:[43]

1. Hematoma at access site >5 cm
2. False aneurysm
3. Arterio-venous fistula
4. Retroperitoneal bleeding
5. Peripheral ischemia/nerve injury
6. Any transfusion required will be reported as a vascular complication unless for a clinical indication clearly other than catheterization complication.
7. Vascular surgical repair

Major bleedings

Bleeding Event:[43]

- Any episode of major internal or external bleeding that causes death, hospitalization or permanent injury (e.g., vision loss) or necessitates transfusion of greater than 3 units PRBCs or pericardiocentesis procedure.
- The complication bleeding event applies to all patients whether or not they are taking anticoagulants or antiplatelet drugs, since bleeding events can occur in patients who are not receiving anticoagulants. Embolic stroke complicated by bleeding is classified as a neurologic event under embolism and is not included as a separate bleeding event.
- Hemorrhage that requires 2 or more units of transfusion within the index procedure shall be reported as serious adverse events.

Hemorrhage: See "Bleeding event"[43]

- Events which are excluded are: those due to liver disease, myocardial infarction, or systemic infection. Reported as major or minor as defined below:
  - Major: Requires intervention.
  - Minor: Does not require intervention.

8.6 BACTS POSITION STATEMENT ON TAVI

Approved by the board of the BACTS at December 7th, 2010.

1. The board of the BACTS endorses the position statement concerning transcatheter valve implantation for patients with aortic stenosis, published by the European Association for Cardio-Thoracic Surgery (EACTS) and the European Society of Cardiology (ESC), in collaboration with the European Association of Percutaneous Interventions (EAPCI), and published in the European Heart Journal 2008; 29: 1463-1470 and the European Journal of Cardio-Thoracic Surgery 2008; 34: 1-8.
2. The field is in full development, the techniques have not yet come to full maturity, therefore, frequent reassessment of the position statement is necessary. Therefore, this position statement is only valid until the end of 2011.
3. Conventional surgical implantation of an aortic heart valve prosthesis is still the golden standard. Surgical aortic valve replacement has been shown to be an effective treatment, and is widely available in Belgian centers. Only when this cannot be done with a predicted mortality of less than 10%, transcatheter valve implantation might be appropriate in a subset of these patients.

4. The Euroscore and STS score are not accurate predictors of mortality, since these scores are not validated for this high risk population. Recent peer-reviewed publications have demonstrated that logistic Euroscore is a severe overestimation of operative risk in the targeted patient population. Nevertheless since no more accurate scoring systems are available, and in the light of the position statement of the EACTS and ESC, a joint decision should be taken by a team of cardiac surgeons and cardiologists with a vast experience in heart valve surgery and percutaneous interventions for structural heart disease. Patients with a contraindication for surgery and/or at least a logistic Euroscore > 20% and STS score>10% might be eligible for the procedure. For inoperable patients was shown in the cohort B of the Partner Trial (N. Engl. J. Med. 2010;363:1597-607) that TAVI significantly improved survival in comparison with conservative treatment including balloon valvuloplasty.
5. To maintain the probability of success as high as possible, only patients with calcific aortic valve stenosis should be accepted. Patients with significant lesions of other valves, or patients with significant coronary artery disease that cannot be treated by percutaneous interventions should be operated.
6. Preference of the patient is not sufficient to choose for a transcatheter heart valve procedure over conventional surgery.
7. The anticipated survival of the patient should be at least 18 months once the aortic valve stenosis has been treated.
8. Since a vast experience in heart valve surgery is necessary, and the technique is not yet a validated, effective treatment, the centers that perform these procedures should have at least a yearly volume of 100 patients undergoing aortic valve surgery. The centers should be obliged to participate in a database to demonstrate safety and efficacy of transcatheter heart valve procedures. Reimbursement should be made dependent on such a participation in a database.
9. Because of the very high cost of the prosthesis, an a priori approval by a cardiologist and a cardiac surgeon appointed by the RIZIV/INAMI, and independent from the requesting team of interventional cardiologist and cardiac surgeon should be granted for reimbursement. The request should be made by an interventional cardiologist and cardiac surgeon together that will perform the procedure together. The criteria that the patient meets to make the request for transcatheter heart valve procedure reasonable should be detailed and entered in a national database. It should be possible to check these criteria in the patient files by site visits of a team of cardiologist and cardiac surgeons appointed by the RIZIV/INAMI at any time. At least all criteria that are included in the calculation of the Euroscore and STS score should be detailed.
10. The center should be sufficiently equipped to perform transcatheter procedures safely, according to the guidelines published by the European Association for Cardio-Thoracic Surgery (EACTS) and the European Society of Cardiology (ESC), in collaboration with the European Association of Percutaneous Interventions (EAPCI), and published in the European Heart Journal 2008; 29: 1463-1470 and the European Journal of Cardio-Thoracic Surgery 2008; 34: 1-8.
11. Since an important learning curve is present, reimbursement should only be granted to those centers that demonstrate that already 10 transcatheter aortic valves have been placed in collaboration between cardiologists and cardiac surgeons in patients that fulfil the criteria mentioned above.

8.7 BRITISH POSITION STATEMENT

A position statement of the British Cardiovascular Intervention Society (BCIS) and the Society of Cardiothoracic Surgeons (SCTS) – no date mentioned – available from http://www.bcis.org.uk/resources/documents/BCIS%20SCTS%20position%20statement.pdf

TAVI is a novel therapy which may be used as an alternative to standard surgical aortic valve replacement. The procedure is performed on the beating heart without the need for a sternotomy or cardiopulmonary bypass. Currently, 2 devices are CE marked and the procedure may be performed via the transfemoral, subclavian or transapical approaches. A group of members of BCIS and SCTS with experience in the technique and knowledge of the TAVI literature have agreed the following consensus statements.

(1) TAVI should currently be reserved for patients who have been considered by a multidisciplinary team (including 2 surgeons and 2 interventional cardiologists) who consider the risk/benefit ratio of open heart surgery and TAVI to favour TAVI. The usual "high risk" patient will have a logistic Euroscore of >20 or an STS score of >10.

(2) In general TAVI should be performed for symptomatic severe degenerative aortic stenosis. Under exceptional circumstances and after full discussion within a multidisciplinary team, other forms of aortic valve disease such as a failing aortic bio-prosthesis may be treated.

(3) TAVI should be performed by a multidisciplinary team (MDT) drawn from a minimum of 2 interventional cardiologists, 2 cardiothoracic surgeons, cardiac anaesthetists and cardiac imaging specialists.

(4) Patients should be screened into a TAVI programme by this MDT team and not by any individual speciality.

(5) There should be formal training of the implanting team which should include:

- - Didactic theoretical training.
- - Simulator training if available.
- - A visit to an experienced centre to observe TAVI cases.
- - Support for the initial cases at any site by a proctor.

(6) Any hospital wishing to set up a TAVI programme should have the following minimum infra-structure available:

- The ability to set up an MDT (as above).
- Immediate availability of trans-thoracic and transoesophageal echocardiography.
- Availability of a dedicated cardiac catheter lab or hybrid theatre.
- A theatre with "C" arm screening facilities is generally not appropriate for TAVI procedures .
- CT scanning facilities
- Immediate availability of perfusion services in case of the need for emergency femoro-femoral bypass.
- On-site availability of a surgical recovery area and intensive care with staff experienced in looking after patients following surgical aortic valve replacement.
- Robust arrangements for immediate renal support if necessary.
- Immediate access to vascular surgeons and interventional radiologists to deal with major peripheral vascular complications.
- The above requirements will mean that this procedure should only be performed in a unit currently carrying out surgical aortic valve replacement.

(7) Any unit performing the procedure has to provide procedural, outcome and follow-up data, (in the form of the agreed BCIS/SCTS dataset), to a centrally held DOH database for event tracking.

(8) It is the view of BCIS and SCTS that the TAVI procedure should be performed by centres which can provide the above infrastructure and that the procedure should only be done by highly experienced interventional cardiologists and cardiothoracic surgeons. We believe occasional practice and small volume TAVI units should be actively discouraged. It is difficult to stipulate a minimum number of cases per year for a TAVI programme. Competence is obviously more important than numbers. However a minimum annual number of 24 cases per TAVI unit may be reasonable, but given the learning curve and infrastructure needed we believe somewhere in the order of > 50 cases per year to be optimal.

(9) Finally we have carefully considered the question of the timing of further studies, in particular a randomised clinical trial. We believe that UK centres need to get beyond their learning curve before entering into a randomised trial. During this run-in phase centres must enter data using the agreed dataset so as to create a prospective cohort study (as described above). We believe that, at the correct time in the development of this technology, UK centres should be strongly encouraged to participate in a RCT. Equally we believe an RCT comparing TAVI with conventional AVR should be conducted before widespread dissemination of TAVI into a population who would be considered low/moderate risk for conventional AVR.

(10) In general we support the position paper produced and published by the European Societies (ESC & EACTS)

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