Tiotropium in de behandeling van Chronisch Obstructief Longlijden (COPD): Health Technology Assessment

KCE reports 108A

Federaal Kenniscentrum voor de Gezondheidszorg
Centre fédéral d'expertise des soins de santé
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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, ANN VAN DEN BRUEL, JEANNINE GAILLY,
NANCY THIRY, STEPHAN DEVRIESE

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Auteurs :	Neyt Mattias, Van den Bruel Ann, Gailly Jeannine, Thiry Nancy, Devriese Stephan
Externe experten :	Chevalier Pierre (RIZIV/INAMI, Brussels), Decramer Marc (Gasthuisberg, Leuven), Delaunois Luc (UCL, Brussels), Louis Renaud (Université de Liège, Liège)
Externe validatoren :	Prof. Dr. Wilfried De Backer (UZA, Antwerp), Prof. Dr. Jan Degryse (KUL, Leuven), Prof. Dr. Oscar Franco (University of Warwick, UK)
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Disclaimer:	De externe experten hebben aan het wetenschappelijke rapport meegewerkt dat daarna aan de validatoren werd voorgelegd. De validatie van het rapport volgt uit een consensus of een meerderheidsstem tussen de validatoren. Alleen het KCE is verantwoordelijk voor de eventuele resterende vergissingen of onvolledigheden alsook voor de aanbevelingen aan de overheid.
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VOORWOORD

Tiotropium (Spiriva®) is een langwerkend medicijn dat helpt om de luchtwegen open te zetten. Langwerkende luchtweg-verwijdende middelen worden aanbevolen bij de behandeling van ernstige vormen van chronisch obstructief longlijden.

In België wordt Spiriva door het RIZIV terugbetaald sinds 1 maart 2004. In de oorspronkelijke aanvraag van het bedrijf werd voorop gesteld dat de kosten voor terugbetaling gecompenseerd zouden worden omdat de patiënten door het gebruik van dit medicijn minder opflakkeringen van hun ziekte zouden krijgen en daarom minder andere medische kosten zouden veroorzaken. De beslissing voor terugbetaling werd wel gekoppeld aan een herziening van die beslissing na maximaal 36 maanden. Bij die herziening in 2007 werd echter vastgesteld dat er geen aantoonbaar voordeel verbonden was aan het gebruik van tiotropium ten opzichte van vergelijkbare medicijnen en dat bovendien ook geen vermindering werd waargenomen van andere medische kosten. Toch werd de terugbetaling van dit veel duurdere medicijn voortgezet. Ondertussen kregen in 2007 al meer dan 86 000 patienten minstens één Spiriva voorschrift en kostte de terugbetaling bijna €22 miljoen aan het RIZIV en bijna €5 miljoen uit de portemonnee van de patiënt.

Het RIZIV vroeg aan het KCE om een 'health technology assessment' van tiotropium te maken bij de behandeling van chronisch obstructief longlijden. Welke evidence is er voor de waarde van deze behandeling ten opzichte van alternatieve behandelingen? Wordt al dit geld goed besteed? We hebben geprobeerd deze vragen op een objectieve en transparante manier te beantwoorden. Aan de lezer om uit te maken of de huidige situatie optimaal is en aan de beleidsmakers om te beslissen of er iets moet veranderen.

Gert Peeters
Adjunct algemeen directeur a.i.

Jean-Pierre Closon
Algemeen directeur a.i.

Samenvatting en toelichtingen

INLEIDING

Chronisch Obstructief Longlijden (COPD) is een progressieve ziekte, gekenmerkt door een niet volledig omkeerbare luchtwegvernauwing, met belangrijke extrapulmonale effecten. De impact van COPD op de individuele patiënt hangt af van de ernst van de symptomen (vooral kortademigheid en een verminderd inspanningsvermogen), systemische effecten, en eventuele comorbiditeiten – niet alleen van de mate van luchtwegvernauwing. Echter, omwille van standaardisering wordt de ernst van de ziekte ingedeeld volgens de mate van luchtwegvernauwing, zoals aanbevolen door de Global Initiative for Chronic Obstructive Lung Disease (GOLD).

COPD kan samen voorkomen met astma, de andere grote chronisch obstructieve luchtwegaandoening, hoewel de onderliggende luchtwegontsteking totaal verschillend is.

Verschillen in methoden, diagnostische criteria en analysetechnieken tussen studies leiden tot variabele schattingen van de prevalentie. Volgens de Gezondheidsenquête van 2004 bedroeg de zelfgerapporteerde prevalentie van COPD 5,3% van de totale Belgische bevolking, met een scherpe stijging na de leeftijd van 65 jaar. Naast leeftijd is roken de belangrijkste determinant voor de ontwikkeling en progressie van COPD. In België rookt 28 % van de mensen van 15 jaar en ouder, en meer bij mannen dan bij vrouwen in alle leeftijden, vooral in de geboortecohorten van voor 1950.

Het 2001 Global Burden of Disease rapport schatte dat 3,8% van de mortaliteit in landen met hoge inkomens gerelateerd was aan COPD. In België is de leeftijdsspecifieke mortaliteit (1997) minder dan 1% voor de leeftijd van 60 jaar, maar deze stijgt snel met stijgende leeftijd tot 8,6% bij de 80 à 84-jarigen.

Tiotropium (Spiriva®) is een langwerkende antiocholinergische bronchodilator, gebruikt bij de onderhoudsbehandeling van COPD. Andere langwerkende bronchodilatoren die momenteel in België op de markt zijn, zijn salmeterol en formoterol, beide ß2-agonisten. Internationale richtlijnen bevelen het gebruik van langwerkende bronchodilatoren aan voor patiënten die symptomen blijven vertonen ondanks adequate behandeling met kortwerkende bronchodilatoren.

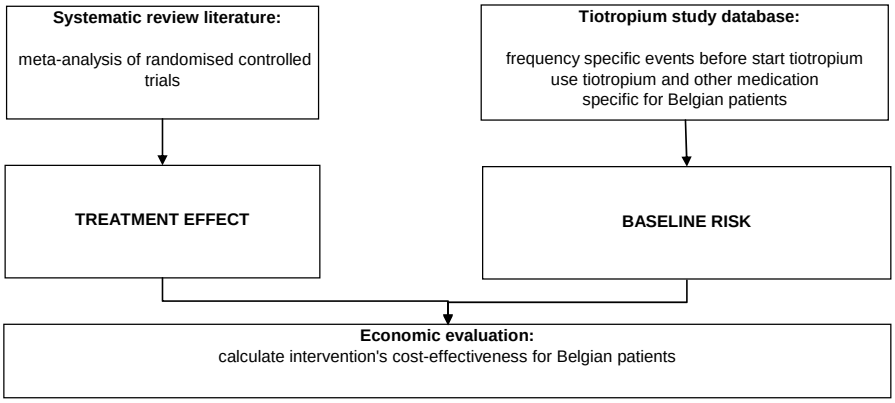
De terugbetaling werd goedgekeurd vanaf 1 maart 2004, deels gebaseerd op de stelling dat de budgetimpact gecompenseerd zou worden door kostenbesparingen door minder ziekenhuisopnamen en een verminderd gebruik van antibiotica en orale corticosteroïden. Aangezien het om een Klasse I geneesmiddel ging, d.w.z. een geneesmiddel met een toegevoegde therapeutische waarde in vergelijking met bestaande alternatieven, werd de terugbetalingsbeslissing binnen 36 maanden herzien. Hierbij werd geconcludeerd dat het gebruik van tiotropium geen voordelen opleverde in vergelijking met langwerkende $ß_2$-agonisten, dat de prijs van tiotropium hoger was dan die van deze alternatieven, en dat de introductie van tiotropium de kosten voor andere geneesmiddelen niet verminderde. De terugbetalingsmodaliteiten werden na deze herziening echter niet gewijzigd. Sindsdien zijn er nieuwe studies gepubliceerd die in deze HTA in rekening worden gebracht.

Uitgaven voor tiotropium stegen van bijna € 12 miljoen naar meer dan € 26 miljoen tussen 2004-2007. In dezelfde periode steeg het aantal patiënten dat minstens een voorschrift voor tiotropium kreeg van 57 000 tot 86 000. Een maand behandeling met tiotropium kost € 51,75 terwijl salmetrol € 31,24 en formoterol ongeveer € 35 kosten.

ONDERZOEKSVRAGEN

- Wat is de werkzaamheid van tiotropium bij COPD patiënten op uitkomsten relevant voor de patiënt?
- Wat is de kosteneffectiviteit van tiotropium in werkelijke omstandigheden, waarbij het basisrisico van Belgische patiënten gecombineerd wordt met het behandelingseffect van de gerandomiseerde studies (RCT's)?

Figuur 1: Gebruik van specifieke bronnen voor verschillende doeleinden



KLINISCHE GEGEVENS

De beschikbare studies werden samengevat voor patiënt-relevante uitkomsten, namelijk opstoten, ziekenhuisopnamen, mortaliteit, kwaliteit van leven en kortademigheid. Gebruikte databanken: INAHTA, CRD (HTA en DARE), NICE, de Cochrane Database of Systematic Reviews, Medline en Embase. Aanvullend aan gepubliceerde studies werd ook naar ongepubliceerde studies gezocht op de websites van FDA en EMEA, in de registers van klinische trials, en door experts van het domein te contacteren. De meta-analyse bevat uiteindelijk 16 RCT's.

WERKZAAMHEID

We vonden studies die tiotropium vergeleken met placebo, ipratropium (kortwerkend anticholinergicum), salmeterol (langwerkende $ß_2$-agonist) en salmeterol/fluticasone (combinatie van een langwerkende $ß_2$-agonist met een inhalatiecorticosteroid).

De resultaten van de meta-analyse worden vermeld in Tabel 1. Vergeleken met placebo, vermindert tiotropium het aantal patiënten met minstens één opstoot, de opstootfrequentie, het aantal patiënten met minstens één ziekenhuisopname, opnamefrequentie, en verbetert significant de kwaliteit van leven en de kortademigheid. Een studie, de UPLIFT studie, draagt bijna de helft van de patiënten bij aan de meta-analyse en had de langste follow-up (4 jaar).

Vergeleken met ipratropium, verbetert tiotropium dezelfde uitkomsten significant, behalve het aantal patiënten met minstens één ziekenhuisopname.

Vergeleken met salmeterol en salmeterol/fluticasone zijn geen van de uitkomsten significant, behalve mortaliteit in het voordeel van salmeterol/fluticasone, en de opstootfrequentie. Voor de opstootfrequentie vermeldt één studie geen exacte niet-significante resultaten, terwijl de tweede studie resultaten vermeldt met een marginaal significant betrouwbaarheidsinterval in het voordeel van tiotropium. Twee studies rapporteren niet-significante p-waarden voor de opnamefrequentie.

PUBLICATIEBIAS

Funnel plots werden gemaakt wanneer vijf of meer studies beschikbaar waren voor één specifieke vergelijking en uitkomst, wat mogelijk was voor de placebogecontroleerde vergelijking voor opstoten en ziekenhuisopnamen. Beide funnel plots vertoonden asymmetrie. Een statistische test voor asymmetrie (Egger's test) op de plot voor opstoten toonde een statistisch significante publicatiebias ($p = 0{,}008$), wijzend op een tekort aan studies met minder positieve resultaten.

Tabel 1: resultaten van de meta-analyse van klinische werkzaamheid (tiotropium vs comparator)

Comparator	Placebo	Ipratropium	Salmeterol	Salmeterol/fluticasone
Uitkomst				
Opstoten				
Proportie patiënten met ≥1 opstoot OR (95% BI)	0,77 (0,67 - 0,88)	0,64 (0,44 - 0,92)	0,86 (0,67 - 1,11)	0,88 (0,71 - 1,10)
Opstoot frequentie Gemiddeld verschil/patient-jaar (95% BI)	-0,31 (-0,46 – (-0,17))	-0,23 (-0,31 – (-0,15))	-0,16 (-0,29 –(-0,03)) + niet-significant resultaat in 1 studie	NB
COPD gerelateerde ziekenhuisopnamen				
Proportie patiënten met ≥1 opname OR (95% BI)	0,88 (0,79-0,97)	0,59 (0,32-1,09)	0,54 (0,29-1,01)	0,78 (0,57-1,06)
Opname frequentie Gemiddeld verschil/patient-jaar (95% BI)	-0,04 (-0,08 – (-0,01))	-0,06 (-0,09 – (-0,03))	Niet-significante resultaten in 2 studies	NB
Mortaliteit, OR (95% BI)	0,89 (0,78-1,02)	1,52 (0,41-5,69)	0,54 (0,03-8,80)	1,84 (1,07-3,17)
Levenskwaliteit, OR voor klinisch relevante verbetering (95% BI)	1,65 (1,40-1,94)	1,99 (1,38-2,89)	1,26 (0,96-1,67)	0,79 (0,62-1,00)
Kortademigheid, OR (95% BI)	1,76 (1,44-2,14)	2,05 (1,32-3,20)	1,08 (0,81-1,42)	NB

OR: odds ratio; BI: betrouwbaarheidsinterval; NB: niet beschikbaar

VEILIGHEID

Neveneffecten werden geanalyseerd op basis van de RCT's uit de meta-analyse, specifiek literatuuronderzoek voor observationele studies, het FDA goedkeuringsdossier en post-marketing surveillance gegevens van internationale en nationale instanties. Twee neveneffecten komen significant meer voor met tiotropium versus placebo, ipratropium of salmeterol, nl. droge mond en urineweginfecties. De gegevens suggereren ook een mogelijk verhoogd risico op hartritmestoornissen.

GEZONDHEID-ECONOMISCHE EVALUATIE

De gezondheidseconomische evaluatie bestaat uit een systematisch literatuuroverzicht en een kosten-nuts analyse waarbij observationele gegevens werden gecombineerd met de resultaten van de meta-analyse.

LITERATUUR

Voor het opzoeken van de economische literatuur over het gebruik van tiotropium bij COPD patiënten werden verschillende databanken geconsulteerd: de CRD (HTA en NHS EED), CDSR Technology Assessment databases, de websites van HTA instituten vermeld op de INAHTA website, Medline, Embase, Econlit, en CDSR Economic Evaluation databases.

Op basis van de gevonden economische evaluaties verbetert tiotropium significant de gezondheidswinst in vergelijking met ipratropium (gewonnen QALY's en vermeden opstoten), en lijkt kosteneffectief te zijn. In vergelijking met salmeterol, zijn de resultaten (in QALY's of in vermeden opstoten) geassocieerd met niet-significante en brede betrouwbaarheidsintervallen. Hierdoor kon geen duidelijke conclusie over de kosteneffectiviteit van tiotropium getrokken worden. Studies die kostenbesparingen rapporteerden voor tiotropium waren deterministisch, zonder betrouwbaarheidsinterval rond de totale incrementele kosten.

Resultaten met uitkomsten uitgedrukt in natuurlijke eenheden (vermeden opstoot) waren ook meer in het voordeel van tiotropium, maar nog steeds niet significant. Maar, de interpretatie van resultaten uitgedrukt in ziektespecifieke uitkomsten is moeilijk.

KOSTEN-NUTS ANALYSE

Basis risico

Er werd een grote observationele databank samengesteld op basis van twee gegevensbronnen: de IMA (het Intermutualistisch Agentschap) databank van gezondheidszorguitgaven en patiëntkenmerken, en de MKG-MFG (Minimale Klinische Gegevens; MKG – Minimale Financiële Gegevens; MFG). Op die manier waren er gegevens beschikbaar over gebruik van gezondheidszorg, patiëntkenmerken en ziekenhuisopname voor ongeveer 102 800 patiënten met minstens een voorschrift voor tiotropium tussen 1 maart 2004 en 31 december 2005. Deze administratieve gegevens bevatten geen enkele klinische informatie, en zijn dus niet geschikt om effectiviteitsanalyses te doen. Wel werden de gegevens gebruikt om medicatiegebruik, opstoten, ziekenhuisopnamen en andere gezondheidszorg uitgaven te analyseren.

Ongeveer 56 000 'regelmatige' tiotropium gebruikers werden geselecteerd voor verdere analyses. Een groot percentage van deze populatie gebruikt andere langwerkende bronchodilatatoren en geïnhaleerde corticosteroïden naast tiotropium.

Opstoten werden gedefinieerd als de afgifte van systemische corticosteroïden en antibiotica binnen de 7 dagen; in het jaar voorafgaand aan de eerste tiotropium aflevering was de gemiddelde opstootfrequentie 0,18 opstoten/patiënt jaar. Een Studie heeft aangetoond dat ongeveer 23% van alle COPD opstoten met antibiotica+systemische corticosteroiden worden behandeld; de 'echte' opstootfrequentie is dus ongeveer 0,80 opstoten/patiënt jaar, identiek aan de frequentie in de UPLIFT studie. Aanvullend hadden de patiënten 0,14 opstoot-gerelateerde ziekenhuisopnamen/patiënt jaar in het jaar voorafgaand aan de eerste tiotropium aflevering, met een gemiddelde kostprijs van €5600 per ziekenhuisopname.

Economisch model

Een kosten-nuts analyse werd uitgevoerd, gezien het vermijden van opstoten en aan opstoot-gerelateerde ziekenhuisopnamen een invloed kan hebben op de levenskwaliteit (QoL). De analyse werd uitgevoerd vanuit het standpunt van de gezondheidszorgbetaler, met inbegrip van de kosten betaald door de ziekteverzekering en het remgeld van de patiënt. Er is geen bewijs dat het ziekteverloop op lange termijn gewijzigd wordt door het gebruik van tiotropium in vergelijking met zijn relevante comparatoren, zoals salmeterol. Daarom werd een korte termijn horizon van een jaar toegepast. Deze periode omvat belangrijke klinische eindpunten, zoals opstoten en aan opstoten gerelateerde ziekenhuisopnamen, en seizoensvariaties. De populatie was een meer geselecteerde subgroep van 'regelmatige' tiotropium gebruikers. De comparator bestaat uit een combinatie van andere geneesmiddelen, zoals andere korte en langwerkende bronchodilatoren en inhalatiesteroiden, zoals ook het geval is in de UPLIFT studie en de obervationele gegevens. Informatie over basisrisico's voor bepaalde voorvallen (bijv. opstoten en opstoot-gerelateerde ziekenhuisopnamen) zonder tiotropium en kosten voor andere medicatie zijn gebaseerd op het jaar vóór het eerste tiotropium attest. Details over de kosten voor tiotropium zijn gebaseerd op het eerste jaar na het eerste attest. Informatie over prijzen/kosten voor ziekenhuisopnamen was gebaseerd op de volledige databank, informatie over 'utilities' was gebaseerd op de literatuur. Voor het behandelingseffect werden de resultaten van de UPLIFT studie gebruikt voor de basisanalyse, zowel omdat het de grootste studie is met de langste follow-up periode, en omdat het tiotropium evalueerde bij patiënten die hun eerdere behandeling verder namen, wat ook in onze gegevens werd vastgesteld. In deze studie was het relatief risico voor COPD opstoten 0,86 (95% BI: 0,81 – 0,91; p-waarde <0,001) en voor opstoot-gerelateerde ziekenhuisopnamen 0,94 (95% BI: 0,82 – 1,07; p-waarde = 0,34). Probabilistische modellering, die rekening hield met de onzekerheid rond de input variabelen, en scenario analyses werden uitgevoerd.

In dit model is de geschatte gemiddelde incrementele kost per patiënt €373 (95% BI 279 – 475). Deze incrementele kost bestaat uit de volgende drie elementen: incrementele kost medicatie (€428), lagere kost aan ziekenhuisopnamen (-€48), en de lagere kost aan opstoten (-€6). Het incrementele voordeel uitgedrukt als gewonnen QALY's bedraagt gemiddeld 0,00048. Dit is zeer laag omwille van de combinatie van de volgende factoren: a) een laag aantal ziekenhuisopnamen zonder behandeling met tiotropium, b) een niet-significant behandelingseffect (gemiddeld 0,94) met betrekking tot het vermijden van opstoot-gerelateerde ziekenhuisopnamen, en c) de relatief korte duur waarin dit voorval QoL beïnvloedt. In combinatie met de niet-verwaarloosbare incrementele kosten resulteerde dit in een ongunstige ICER van €1 244 023 per gewonnen QALY. De voornaamste reden voor de ongunstige kosteneffectiviteit van tiotropim is het feit dat het duurder is dan de comparatoren en de goede resultaten die reeds worden bekomen met deze alternatieven. Indien de prijs van tiotropium zou dalen tot €31,24 voor 30 eenheden, d.i. de prijs van salmeterol, dan zou de budgettaire impact voor zowel het RIZIV als het remgeld van de patiënt, op basis van de gegevens uit 2007, dalen tot ongeveer €16 miljoen, ofwel een kostenbesparing van ongeveer €10,5 miljoen per jaar.

CONCLUSIES

Langwerkende bronchodilatoren worden aanbevolen voor patiënten die symptomen blijven vertonen ondanks een adequate behandeling met kortwerkende bronchodilatoren. De richtlijnen verkiezen niet een bepaalde langwerkende bronchodilatator boven een andere. Op basis van een systematisch literatuuroverzicht is tiotropium niet superieur aan salmeterol voor klinisch relevante uitkomsten. Daarbij is tiotropium duurder, waardoor de kosteneffectiviteit ongunstig uitvalt. Samenvattend kan gesteld worden dat tiotropium zijn verdiensten heeft, maar te duur is, zowel vanuit medisch standpunt als dat van de betaler.

BELEIDSAANBEVELINGEN

PRIJS EN TERUGBETALING:

- Een hogere prijs voor tiotropium dan die van de alternatieven kan niet verdedigd worden op basis van de huidige studies.
- Als het bedrijf dat tiotropium op de markt brengt niet akkoord gaat met een prijsdaling, moet de terugbetaling van het product gestopt worden, gezien er een valabel en goedkoper alternatief bestaat.

DE HERZIENINGSPROCEDURE:

- Indien gegevens over de effectiviteit in de realiteit worden gevraagd voor de herzieningsprocedure, kunnen administratieve gegevens de verzameling van prospectieve gegevens niet vervangen, omwille van een gebrek aan klinische informatie. Als de herziening steunt op effectiviteitsgegevens uit de reële praktijk, moet de opzet van de gegevensverzameling en analysemethoden vooraf worden gespecificeerd.
- Het moet vanaf het begin duidelijk zijn wat de gevolgen zijn indien bepaalde 'beloftes' niet worden waargemaakt. Dit kan inhouden dat de beslissing tot terugbetaling wordt geannuleerd, de prijs moet dalen, de firma een bepaald bedrag moet terugbetalen, enz.
- Een bedrijf dat er niet in slaagt de gevraagde informatie te leveren voor een revisieprocedure, moet hiervoor niet beloond worden.

VERDER ONDERZOEK:

- De identificatie van subgroepen die mogelijk meer voordeel halen uit een behandeling met tiotropium dan de algemene COPD populatie.
- Voordelen en risico's van het combineren van verschillende langwerkende bronchodilatoren.
- De invloed van tiotropium op de levenskwaliteit (gemeten met generische instrumenten) per opstoot of ziekenhuisopname.

Scientific summary

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ABBREVIATIONS

AAPCC	American Association of Poison Control Center
AHRQ	Agency for Health Research and Quality
ATS	American Thoracic Society
BCFI / CBIP	Belgian Center for Pharmacotherapeutical Information (Belgisch Centrum voor Farmatherapeutische Informatie / Centre Belge d'Information Pharmacothérapeutique)
BOLD	Burden of Obstructive Lung Disease
CDSR	Cochrane Database of Systematic Reviews
CEA	Cost-Effectiveness Analysis
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
CTG/CRM	Drug Reimbursement Commission (Commissie Tegemoetkoming Geneesmiddelen / Commission de remboursement des medicaments)
CUA	Cost-Utility Analysis
DALY	Disability Adjusted Life Years
DARE	Database of Abstracts of Reviews of Effects
DDD	Defined Daily Dose
DRC	Drug Reimbursement Commission (= CTG/CRM)
ECG	Electrocardiogram
ERS	European Respiratory Society
FEV_1	Forced Expiratory Volume in one second
FVC	Forced Vital Capacity
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HTA	Health Technology Assessment
ICD-9-CM	International Classification of Diseases, Ninth Revision, Clinical Modification
ICER	Incremental Cost-Effectiveness Ratio
ICPC	International classification of primary care
ICS	Inhaled corticosteroids
ICSI	Institute for Clinical Systems Improvement
IMA	Common Sickness Funds Agency (Intermutualistic agency)
INAHTA	International Network of Agencies for Health Technology Assessment
LAAC	Long-acting anticholinergics
LABA	Long-acting betaagonists
LOS	Length of stay
LYG	Life-Years Gained
MFD	Minimal Financial Data (see MFG/RFM)
MCD	Minimal Clinical Data (see MKG/RCM)
MeSH	Medical Subject Headings (NLM)
MFG/RFM	Minimal Financial Data (Minimale Financiële Gegevens - Résumé Financier Minimum)
MKG/RCM	Minimal Clinical Data (Minimale Klinische Gegevens - Résumé Clinique Minimal)
NHANES	National Health and Nutrition Examination Survey
NHIS	National Health Interview Survey
NHS	National Health System (UK)
NHS EED	NHS Economic Evaluation Database

NICE	National Institute for Health and Clinical Excellence
NIHDI	National Institute for Health and Disability Insurance (= RIZIV/INAMI)
NIS / NSI	National Institute for Statistics (Nationaal Instituut Statistiek / Institut National de Statistiques)
NLM	National Library of Medicine (US)
NNT	Number needed to treat
OR	Odds Ratio
PaO2	arterial pressure of oxygen
PaCO2	arterial partial pressure of CO2
QALY	Quality-Adjusted Life Year
QoL	Quality of Life
QT	The QT interval is a measure of the time between the start of the Q wave and the end of the T wave on the electrocardiogram. The QT interval is dependent on the heart rate and has to be adjusted to aid interpretation by using a simple formula that leads to the heartrate-corrected QT interval or QTc
RCT	Randomised Controlled Trial
RIZIV/INAMI	National Institute of Health and Disability Insurance (Rijksinstituut voor Ziekte en Invaliditeits Verzekering / Institut National d'Assurance Maladie - Invalidité) (= NIHDI)
RR	Relative Risk
SAAC	Short-acting anticholinergics
SABA	Short-acting betaagonists
SD	Standard Deviation
SE	Standard Error
SGRQ	St George's Respiratory Questionnaire
SIGN	Scottish Intercollegiate Guidelines Network
TCT	Technical Cel (Technische Cel / Cellule Technique)
TDI	Transitional Dyspnoea Index
TGR / CTM	Technische Geneeskundige Raad / Conseil Technique Medical
US	United States
WHO	World Health Organization
YLD	Years of Life with Disability
YLL	Years of Life Lost

1 INTRODUCTION

1.1 DISEASE AND POPULATION

Chronic Obstructive Pulmonary Disease (COPD) is characterized by airflow limitation that is not fully reversible, with some significant extrapulmonary effects that may contribute to the severity in individual patients. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles or gases. The chronic airflow limitation characteristic of COPD is caused by a mixture of small airway disease (obstructive bronchiolitis) and parenchymal destruction (emphysema), the relative contributions of which vary from person to person.[1]

Key indicators for COPD are dyspnoea, that is progressive and persistent, chronic cough, chronic sputum production, and a history of exposure to risk factors. These indicators are not diagnostic themselves, but increase the probability of COPD. The actual diagnosis is made with spirometry.[1] Worldwide, cigarette smoking is the most important risk factor of COPD, although in some countries, air pollution from the burning of wood or other biomass fuels has also been identified as a risk factor.[1]

COPD has a variable natural history and not all individuals follow the same course. However, COPD is generally a progressive disease, especially if a patient's exposure to noxious agents continues. The impact of COPD on an individual patient depends on the severity of symptoms (especially breathlessness and decreased exercise capacity), systemic effects, and any comorbidities the patient may have—not just on the degree of airflow limitation.[1]

For reasons of standardisation, staging of severity is recommended by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) according to the degree of airflow limitation (Table 1).[1]

Table 1: GOLD stages of severity

Stage I	Mild	FEV1/FVC <0.70 FEV1≥80% predicted
Stage II	Moderate	FEV1/FVC <0.70 50% ≤ FEV1 < 80% predicted
Stage III	Severe	FEV1/FVC <0.70 30% ≤ FEV1 < 50% predicted
Stage IV	Very severe	FEV1/FVC <0.70 FEV1 < 30% predicted or FEV1 < 50% predicted plus chronic respiratory failure

FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; respiratory failure: arterial pressure of oxygen (PaO_2) less than 60 mm Hg with or without arterial partial pressure of CO_2 ($PaCO_2$) greater than 50 mm Hg while breathing air at sea level.

However, because the process of aging does affect lung volumes, the use of this fixed ratio may result in overdiagnosis in the elderly. Using the 5% lower limit of normal may minimise misclassification.[1]

COPD can coexist with asthma, the other major chronic obstructive airway disease characterized by an underlying airway inflammation. However, the underlying chronic airway inflammation is very different in these two diseases. The chronic inflammation of asthma, in which many cells and cellular elements play a role, is associated with airway hyperresponsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning.

These episodes are usually associated with widespread, but variable, airflow obstruction within the lung that is often reversible either spontaneously or with treatment.[2] Individuals with asthma who are exposed to noxious agents, particularly cigarette smoke, may also develop fixed airflow limitation and a mixture of "asthma-like" and "COPD-like" inflammation. Furthermore, there is epidemiologic evidence that longstanding asthma on its own can lead to fixed airflow limitation. Other patients with COPD may have features of asthma such as a mixed inflammatory pattern with increased eosinophils.

Thus, while asthma can usually be distinguished from COPD in untreated patients on first presentation, in some individuals with chronic respiratory symptoms and fixed airflow limitation it remains difficult to differentiate the two diseases.[3] The following table presents some clinical features of both COPD and asthma.

Table 2: Clinical features differentiating COPD and asthma

	COPD	**Asthma**
Smoker or ex-smoker	Nearly all	Possibly
Symptoms under age 35	Rare	Common
Chronic productive cough	Common	Uncommon
Breathlessness	Persistent and progressive	Variable
Night time waking with breathlessness and/or wheeze	Uncommon	Common
Significant diurnal or day to day variability of symptoms	Uncommon	Common

In addition, patients may have several comorbidities, such as lung cancer, musculoskeletal dysfunction, osteoporosis, diabetes mellitus, dyslipidaemia, anaemia, pneumonia, or pulmonary embolism. The prevalence of these comorbidities varies between studies. Tobacco smoking is a risk factor for many of these comorbidities as well as for COPD. Other factors such as polypharmacy, medication interactions, lack of treatment of comorbidities, diagnosis coding accuracy, and lack of specific case definitions for comorbidities add to the complexity of studying comorbidities. However, recent large epidemiologic studies have confirmed the independent detrimental effects of these comorbidities on patients with COPD. On the other hand, many of these comorbidities are now considered to be part of the nonpulmonary sequelae of COPD.[4]

The aim of this chapter is to provide background information on the prevalence and mortality of COPD worldwide and in Belgium. When available, regional data for Belgium are presented.

1.2 PREVALENCE OF COPD

1.2.1 Methods used to determine prevalence

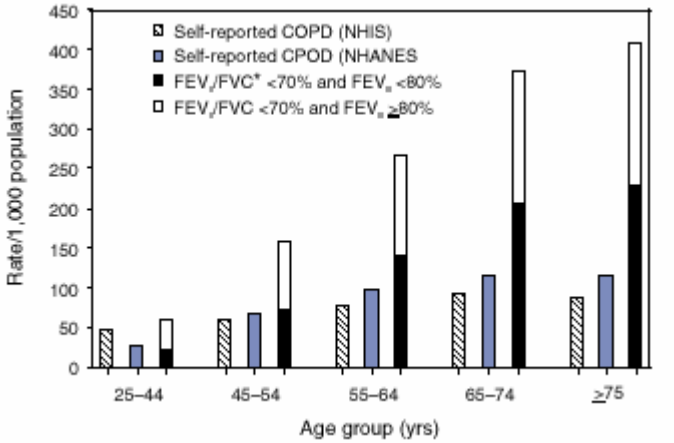
Across studies, differences in survey methods, diagnostic criteria, and analytic approaches lead to variable estimates of prevalence. COPD can be defined based on:

- Patient self-report
- Symptoms
- Clinical examination
- Spirometry with or without a bronchodilator

The lowest estimates of prevalence are usually those based on self-reporting of a doctor diagnosis of COPD or equivalent condition followed by spirometry-based and symptom-based estimates. This likely reflects the widespread underdiagnosis of COPD as well as the fact that those with mild COPD may have no symptoms, or else symptoms, such as chronic cough and sputum, that are not perceived as abnormal.

These self-reported estimates may have value, however, since they may most accurately reflect the burden of clinically significant disease that is of sufficient severity to require health services.[1] The difference between self-reported prevalence and spirometry-based prevalence is shown in Figure 1, based on the National Health Interview Survey (NHIS) and the Third National Health and Nutrition Examination Survey (NHANES III).[5]

Figure 1: Estimated prevalence of self-reported COPD, by age group, United States (US)



Source: Mannino et al.[5]
Questionnaire data from the NHIS (1988-1994), and questionnaire and pulmonary function data from the NHANES III (1988-1994)
FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; NHANES: National Health and Nutrition Examination Survey; NHIS: National Health Interview Survey.

In the Copenhagen City Heart Study, a symptom-based estimate was substantially higher than a spirometry-based estimate of prevalence in a stratified random sample of Copenhagen residents aged 20–90 years. Symptoms, defined as daily phlegm ≥ 3 months for ≥ 1 year, were reported by 10.1% of the population, whereas only 3.7% were found to have a FEV_1/FVC <70%, FEV_1 <60% predicted. The latter diagnostic criterion corresponds to more severe COPD compared to most spirometric definitions which use FEV_1/FVC <70%, FEV_1 <80% predicted.[6]

In addition to differences in the definition of COPD, differences in diagnostic criteria can also influence prevalence estimates. In the past, various criteria were used to define spirometry-based airflow obstruction. The American Thoracic Society (ATS) and the European Respiratory Society (ERS) used different definitions; other definitions can be found in the literature. This has led to marked differences in reported prevalence of COPD, as demonstrated by Viegi et al.[7] (Table 3). The large difference between ERS and ATS criteria was explained by the large number of cases with mild airflow obstruction as defined by the ATS. This prompted the GOLD initiative to propose a universal definition and staging of COPD in 2002, which was subsequently adopted by the professional organisations.[1]

Table 3: prevalence of COPD using various definitions in the Po Delta Study (in %)

	ERS	**European clinical practice criteria**	**ATS (1986 Criteria)**
Diagnostic criteria	FEV_1/VC < 88% pred (men) FEV_1/VC < 89% pred (women)	FEV_1/FVC < 70%	FEV_1/FVC < 75%
Prevalence			
Age 25–73 yr	11	18	40
Age ≥ 45 yr	12	29	57

FEV_1: forced expiratory volume in one second; FVC: forced vital capacity. Pred.: predicted; VC: vital capacity. Source: (Viegi et al.[7])

1.2.2 Worldwide prevalence

In a comprehensive review, Halbert et al.[8] summarized a large number of studies on prevalence of COPD, published between 1990 and 2004. Based on 37 studies, the overall pooled estimate was 7.6% (95% CI 6.0–9.5). Limiting the analyses to the good quality studies, prevalence was 6.8% (95% CI 5.2–8.9). Studies that used spirometry (n=26) reported a higher prevalence of 9.2% (95% CI 7.7–11.0) than studies (n=7) using self-reported diagnosis: 4.9% (95% CI 2.8–8.3). Thirteen studies that used a spirometry-based definition used the GOLD criteria, whereas older ERS criteria and ATS criteria were used in two studies each. Significant differences in prevalence were found for age, smoking status, gender and study setting (see Table 4).

Table 4: COPD prevalence according to age, smoking status, gender, and study setting (in %).

	Estimates	Total population	Pooled prevalence %	p-value
Overall	37	4 123 646	7.6 (6.0–9.5)	
Age				
<40 yrs	9	25 362	3.1 (1.8–5.0)	0.0001
≥40 yrs	34	46 095	9.9 (8.2–11.8)	
40–64 yrs	23	30 942	8.2 (6.5–10.3)	
≥65 yrs	11	15 153	14.2 (11.0–18.0)	
Smoking status				
Smoker	17	24 122	15.4 (11.2–20.7)	0.0001
Ex-smoker	16	14 521	10.7 (8.1–14.0)	
Never-smoker	16	32 542	4.3 (3.2–5.7)	
Gender				
Male	27	327 293	9.8 (8.0–12.1)	0.0002
Female	27	356 398	5.6 (4.4–7.0)	
Study setting				
Urban	12	44 153	10.2 (7.4–13.9)	0.0438
Mixed	21	4 075 965	6.1 (4.9–7.7)	
Rural	4	3 482	8.0 (3.9–15.8)	

Source: Halbert et al. [8]

The Burden of Obstructive Lung Disease (BOLD) Initiative is a worldwide multi-centre study on the prevalence of COPD, with a spirometry-based definition of COPD, using the GOLD criteria.[9] Population-based sampling of adults aged 40 years or older was performed in 12 sites across the world, including over 9 000 participants. Pre- and post-bronchodilator spirometry testing was done on all participants, and all spirometry data were reviewed for quality. Questionnaires were used to obtain information about respiratory symptoms, health status, exposure to risk factors, and economic data about the burden of COPD. The prevalence of COPD stage II or higher was 10.1% (SE 4.8) overall, 11.8% (SE 7.9) for men, and 8.5% (SE 5.8) for women. The prevalence of COPD that was GOLD stage I or higher (postbronchodilator FEV_1/FVC <0.7) varied significantly across sites (p<0.0001).

1.2.3 Belgian data

In Belgium, based on the Health Interview Survey of 2004, the self-reported prevalence of COPD was 5.3% of the total population.[10] Overall, prevalence was similar in men (5.4%) and in women (5.2%), and increased sharply after the age of 65 (Table 5). There was a significantly higher prevalence in the Walloon region (7.2%) compared to the Flemish (4.1%) and Brussels region (5.8%) ($p<0.05$). In addition, prevalence increased with decreasing level of education and was significantly higher in urban areas compared to rural areas. Compared to the previous Health Interview Survey in 2001, prevalence was stable and no significant trends were identified.

Table 5: Health Interview Survey 2004

	Prevalence (%)	
	Men	**Women**
All ages	5.4	5.2
Flemish region	4.1	4.1
Brussels region	5.8	5.7
Walloon region	7.7	6.8
15-64 years	4.0	4.8
Flemish region	2.7	3.5
Brussels region	3.7	4.6
Walloon region	5.9	6.9
≥65 years	14.3	9.6
Flemish region	12.3	8.6
Brussels region	13.5	10.6
Walloon region	18.7	10.9

In a study in general practices in the Brussels region, patients aged 35-70 years had spirometry performed.[11] Patients already using bronchodilators were excluded, i.e. patients with a known diagnosis of COPD or asthma, representing 7.3% of that age group. In the remaining patients, 23% responded positive to at least one answer of a questionnaire asking about symptoms of cough, wheezing or breathing difficulties. Airflow obstruction was defined spirometrically as FEV_1/FVC ratio <88.5% of the predicted value for men, and <89.3% of the predicted value for women, which the authors state to be the criteria of the European Respiratory Society. However, the ERS criteria used the ratio of the FEV_1/VC and not FEV_1/FVC (see Table 3). Airflow obstruction was thus diagnosed in 18% of those with at least one positive symptom on the questionnaire, and in 4% of those without symptoms. Overall prevalence of airflow obstruction was 7.4% of patients not already diagnosed with COPD or asthma.

1.3 INCIDENCE OF COPD

1.3.1 Worldwide incidence

In a Dutch prospective cohort study of smokers aged 40-65 years, the estimated cumulative incidence of COPD GOLD stage II was 8.3% (95% CI 5.8-11.4) after a mean follow-up of 5.2 years, with a mean annual incidence of 1.6%. No participant developed severe airflow obstruction. The risk of developing moderate COPD in smokers with baseline mild COPD (GOLD I) was five times higher than in those with normal baseline spirometry.[12]

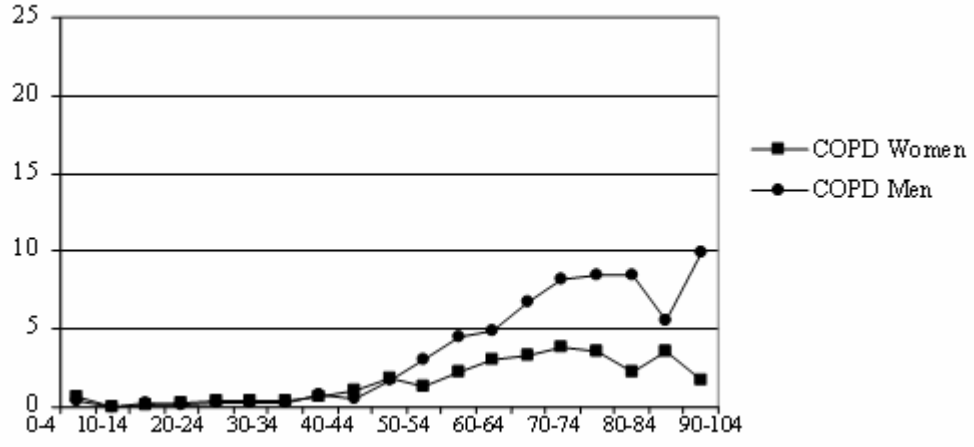
In a Norwegian population-based study, the cumulative incidence of COPD among adult persons at risk was 6.1% (95% CI 4.0-8.1) during a nine-year follow-up.[13]

Another study in Sweden found that during the observation period of seven years, the cumulative incidence was 4.9% (95% CI 3.6-6.5) for GOLD II and higher, and 11.0% (95% CI 9.0-13.4) for GOLD I or higher. Cumulative incidence was more than six times higher among smokers (10.8%) compared to non-smokers (1.6%).[14]

1.3.2 Belgian data

Intego is a morbidity registration in more than 50 general practices in Flanders. Illnesses are classified according to the ICPC-2 codes.[15] Estimations are based on a physician diagnosis. Based on these data, the incidence of COPD is 1.8 (95% CI 1.6-2.0) per 1000 patient years in the total Flemish population in general practice. Figure 2 shows the incidence of COPD in the different age categories, illustrating the increase of COPD from 50 years of age onwards. Only 6% of all diagnoses are made before the age of 45. The incidence reported here is lower than in the studies cited above: this can be explained by the fact that this incidence is estimated on the entire population, and not only in adults at risk, i.e. smokers.

Figure 2: Incidence of COPD per 1000 patient years in the practice population by age



Source: Intego database[15]

1.4 SMOKING PREVALENCE

1.4.1 Worldwide

Cigarette smoking is one of the most important determinants of the development and progression of COPD. Based on the data of the NHANES III study, Stang et al.[16] derived a model to estimate a spirometry-based COPD prevalence using age-specific smoking prevalence. Prevalence in never smokers (men) increased from 2% at the age of 40, to 10% in men more than 75 years of age. Current smokers had a prevalence of 17% at the age of 40, to 43% in men more than 75 years of age. However, COPD was defined based on the old ATS criteria, leading to high prevalence estimates.

In addition to measuring COPD prevalence, the BOLD study assessed the impact of smoking on COPD prevalence, and found an odds ratio (OR) of 1.20 (95% CI 1.14-1.25) per 10 pack years increment in ever smokers for the prevalence of GOLD stage II or higher.[9] Substantial heterogeneity was found between sexes (p=0.047); the pooled OR was 1.28 (95% CI 1.15–1.42) for women and 1.16 (1.12–1.21) for men. For age, the overall pooled OR estimate per 10-year increment was 1.94 (95% CI 1.80–2.10), after adjusting for years of education, smoking status, and pack-years. However, although age and smoking are strong contributors to COPD, they do not fully explain variations in disease prevalence; other factors, such as gender, also seem to be important.

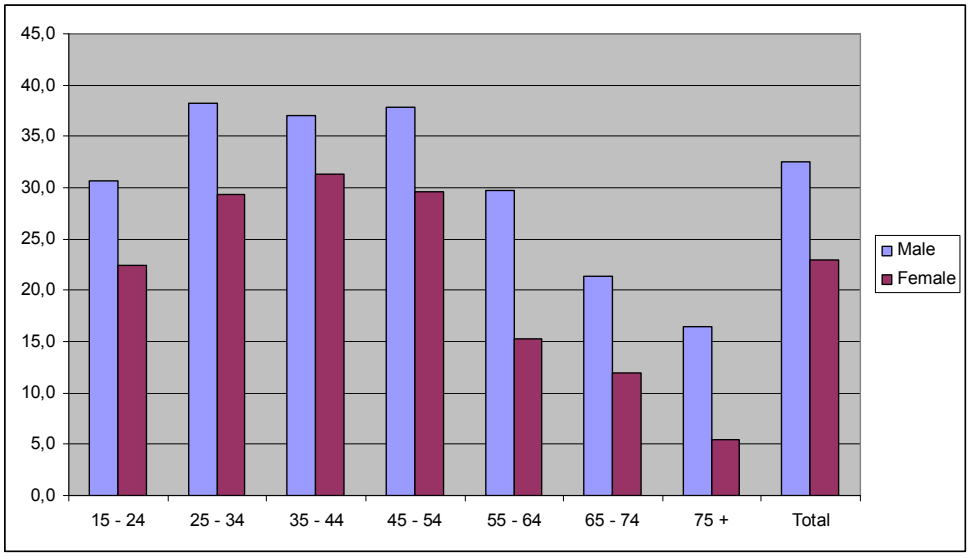
In a meta-analysis, Gan et al.[17] demonstrate that women who smoke experience a faster decline of lung function with increasing age than men who smoke.

1.4.2 Belgian data

Based on the Heath Interview Survey of 2004, 28% of the Belgian population ≥15 years of age smoke.[10] Compared to the Health Interview Survey of 1997 and 2001, absolute prevalence is slightly lower, although this is not significant after adjusting for age and gender, suggesting these changes are caused by demographic differences rather than real differences in smoking behaviour. At all ages, smoking prevalence is higher in men than in women (Figure 3), especially in the birth cohorts before 1950: almost 70% of men aged 45-54 and 55-64 respectively have ever been a regular smoker during their lifetime, compared to 52% and 29% of women of the same age groups.

There is no significant difference in smoking prevalence between the three regions of Belgium.

Figure 3: Smokers (%) according to sex and age in the Belgian population



Source: Health Interview Survey 2004, Scientific Institute for Public Health

Since 1984, smoking prevalence appears to decline in men, and remains relatively stable in women (Table 6).

Table 6: Evolution in the percentage of smokers in Belgium according to sex

Year	Men	Women	Total
1984	47%	26%	36%
1985	45%	27%	35%
1986	46%	26%	35%
1987	42%	26%	32%
1988	42%	24%	32%
1989	39%	26%	32%
1990	38%	26%	32%
1991	33%	24%	29%
1992	31%	21%	26%
1993	31%	19%	25%
1994	33%	19%	26%
1995	33%	24%	28%
1996	34%	27%	30%
1997	31%	22%	26%
1998	30%	23%	27%
1999	31%	26%	29%
2000	36%	26%	31%
2001	34%	22%	28%
2002	33%	25%	29%
2003			28%
2004 *			28%
2005 **	35%	24%	29%

Source: Vlaams Instituut voor Gezondheidspromotie
No further information was provided in the original report on the missing data or the meaning of the symbols.

1.5 MORTALITY

1.5.1 Worldwide

Mortality data for COPD have been inaccurate in the past, due to inconsistent use of terminology for COPD, and the lack of widely accepted diagnostic standards for the diseases that are included in the coding within the COPD spectrum.[1]

According to the World Health Organization (WHO), COPD was the cause of death in 4.1% of males and 2.4% of females in Europe in 1997.[18] The mortality rates due to COPD in European countries are two to three times higher for males than for females, with no country below or above these ratios. In contrast, more women than men died of COPD in the USA and Canada since the year 2000. Although the mortality rates were still higher in men than in women, it reflects the different age structure of the population for both sexes, with women living longer and, therefore, being more at risk of developing COPD. In addition, women have smoked in increasing numbers since about 1940.[19] COPD is the fourth leading cause of death in the USA.

The Global Burden of Disease project of the World Bank/World Health Organisation of 2001 estimated that 3.8% of mortality in high income countries was due to COPD. In addition, COPD was responsible for 2.86 million years lived with disability (YLD, or the equivalent years of healthy life lost through time spent in states of less than full health), representing 4.0% of the total YLD and 5.28 million disability adjusted life years (DALYs), representing 3.5% of the total DALYs.[20] DALYs for a disease are the sum of the years of life lost due to premature mortality (YLL) in the population and the years lost due to disability (YLD) for incident cases of the health condition.

Death rates from COPD have been rising steadily over the past few decades, opposite to the trend for cardiovascular diseases. In the period of 1965–1998, death rates from coronary heart disease in males in the USA dropped by 59%, and deaths from strokes and other cardiovascular diseases decreased by 64% and 35%, respectively. Over the same period, deaths from COPD increased by 163%.[1] This is explained by the worldwide epidemic of smoking and the changing global demographics, with more people in developing countries living longer and, therefore, being at risk of COPD for longer.[19]

1.5.2 Belgian data

Age adjusted mortality rates for Belgium were calculated based on the data of the Scientific Institute for Public Health.[21] These data originate from the vital statistics of the Flemish and Walloon community, and are available for the years 1987-1997. Cause-specific mortality rates were calculated for the ICD codes 491 (chronic bronchitis), 492 (emphysema) and 496 (COPD, not otherwise specified), for the entire population and for men and women separately. In contrast to the worldwide increase of COPD-specific mortality rates, mortality rates in Belgium have declined slightly both in men and women in the period 1987-1997 from 1050/100 000 to 918/100 000. Age-specific mortality rates (per 100 000) for the adult population are listed in the following table. In general, these mortality rates are in agreement with the reported mortality rates worldwide, and are significantly higher in men than in women. Before the age of 60, mortality rates are less than 1% and increase with increasing age.

Table 7: COPD mortality rates (per 100 000) according to age and gender, in 1997

Age (years)	total	men	women
20 - 24	79.8	109.6	51.7
25 - 29	94.8	143.2	46.3
30 - 34	114.6	165.3	61.3
35 - 39	166.3	225.7	106.5
40 - 44	201.0	258.9	141.8
45 - 49	308.7	382.0	233.6
50 - 54	485.0	615.0	353.7
55 - 59	714.4	955.5	480.4
60 - 64	1051.6	1439.5	690.9
65 - 69	1745.5	2454.3	1137.8
70 - 74	2876.0	4128.7	1920.4
75 - 79	4648.4	6396.3	3514.0
80 - 84	8624.8	11511.6	7171.5
85 - 89	13988.3	18027.0	12481.7
90 - 94	22630.7	27975.9	21160.3
95+	34687.7	42267.4	33154.4

Source: Scientific Institute for Public Health[21]

key points

- **There are no good prevalence estimates on COPD. These estimates highly depend on the definition and criteria used.**
- **In Belgium, self-reported prevalence is 5.3%, with higher prevalence in the Walloon region.**
- **Spirometry-based estimates are not available for Belgium; in general, these estimates are higher.**
- **The incidence of COPD increases at the age of 50. Only 6% of all diagnoses are made before the age of 45.**
- **Smoking is the most determinant factors of COPD in Western countries.**
- **In Belgium, smoking prevalence has declined in men, but not in women over the past decades.**
- **Mortality rates are 1.1% in people 60-64 years of age and 8.6% in 80-84 years of age.**

1.6 TECHNOLOGY OVERVIEW

Tiotropium (Spiriva®, Boehringer Ingelheim) is a long-acting anticholinergic agent, used in patients with COPD. The aim of treatment with tiotropium is to improve the lung function of these patients. This drug has a quaternary ammonium structure related to that of ipratropium bromide. Similar to ipratropium, tiotropium binds M1, M2 and M3 muscarinic receptors. The GOLD guideline recommends long-acting bronchodilating agents to patients with stage II COPD or higher. According to GOLD, there is insufficient evidence to recommend one long-acting bronchodilator over another.[1] The ATS/ERS (American Thoracic Society/European Respiratory Society) recommends long-acting bronchodilators in patients with persistent symptoms.[22] Next to tiotropium, the long-acting bronchodilators available in Belgium, and thus possible alternatives, are salmeterol, formoterol, and oxitropium (not available anymore since 2006).

Tiotropium is a once-daily inhaled maintenance prescription treatment for COPD. It is distributed in boxes of 30 capsules, packed in three blister packs. The HandiHaler device is needed to inhale the powder from the tiotropium capsules (Figure 4).

Figure 4: The Spiriva® HandiHaler®



Source: www.spiriva.com

1.6.1 Reimbursement in Belgium

Boehringer Ingelheim received its first licence for tiotropium in Belgium on May 6, 2002 (source: www.fagg.be). A first application for reimbursement was submitted on May 13, 2002. Nonetheless the Drug Reimbursement Commission (DRC (CTG/CRM)) formulated a positive advice to the Minister of Health, the Minister of Budgets did not approve the reimbursement (date of publication and date of commencement: November 21, 2002). A new application was submitted on July 9, 2003, stating that the budget impact for the Health Insurer would be compensated by cost savings on other direct costs, estimated to be -€3, -€4.9, and -€6.4 million for the first, second, and third year, respectively.

In the first place, cost savings were expected due to less hospitalisations (-€7.9, -€13, and -€15.8 million for the first three years, respectively). Secondly, less antibiotics and oral corticosteroids would be used (-€0.7, -€1.1, and -€1.4 million for the first three years, respectively). This time, the decision of both the Minister of Health and the Minister of Budgets was positive. This decision was published on February 19, 2004 and took effect on March 1, 2004 (source: www.riziv.fgov.be).

In the reimbursement modalities, the diagnostic criteria for COPD were mentioned, being the following: 1) symptoms of shortness of breath, expectoration or cough; 2) history of smoking (at least ten pack years) or professional exposition to toxic particles or gasses; FRV1/VC < 0.7 or FEV_1/FVC < 0.7. The number of reimbursable packages was restricted to 13 per patient per year. The reimbursement was granted without prior agreement of the insurance organisation, under the condition that the attending physician adds "third-party payer regimen applicable" on the prescription and keeps the data that prove the above mentioned conditions at the disposal of the advisory physician of the insurance organisation. (Reimbursement chapter IV) As of the 1st of November 2008, reimbursement is no longer subject to this a posteriori control by the insurance organisation, but to the adherence to the clinical practice guideline published in the Moniteur Belge/Belgisch Staatsblad. (Reimbursement chapter II) The RIZIV/INAMI can audit adherence to this guideline.

Attending physicians are expected to keep the necessary information in their medical records, such as diagnostic criteria and staging, for potential control directly by the RIZIV/INAMI.

Being a Class I drug, i.e. a drug with a therapeutic added value in comparison towards existing alternatives, a revision of the reimbursement decision was demanded within 36 months. The following data were required: 1) data on monthly sales numbers; 2) data from an observational study including 1000 COPD patients visiting pulmonologists and general practitioners, and covering the whole country, with collected data at the beginning and after one and two years. These data include the use of tiotropium, long-acting beta-2-mimetics (with or without corticoids), short-acting medication (antibiotics and oral corticoids), occurrence of exacerbations, severity based on GOLD stages, and age.

Based on this revision, the conclusions of the Ministerial Decision indicated that 1) there was no benefit of using tiotropium in comparison to long-acting B2-agonists, 2) that the price of tiotropium was 33% higher in comparison to these alternatives, and 3) that the introduction of tiotropium, in contrast to what was announced, did not decrease treatment costs related to other drugs. Nevertheless, reimbursement modalities were unchanged after this revision (December 12, 2007).

1.6.2 Economic impact

The public price of Sprivia (RIZIV/INAMI code 00470448) for 30 units is €51.75. The patient's co-payment is €10.80 or €7.20 for persons with a preferential reimbursement status.[a] For ambulatory and hospitalized patient, the price is €1.5963 and €1.3593 per unit, respectively. For the ambulatory patient, the co-payment is calculated per pharmaceutical specialty and is based on the reimbursement category. For hospitalized patients, a fixed lump sum of €0.62 is taken into account no matter how many units of this or other specialties are received (source: www.riziv.fgov.be).

The cost to the health care payer (both patient co-payment and NIHDI expenditure) for one patient to take tiotropium for one month is €51.75. In contrast, for an alternative such as salmeterol this is much less, i.e. €31.24 per month.

[a] Tiotropium is placed in reimbursement category B. This means that for non-hospitalised patients, 15% is not reimbursed with a maximum of €7.2 for preferential reimbursed patients and 25% with a maximum of €10.8 for non-preferential reimbursed patients. (source: http://www.riziv.fgov.be/drug/nl/drugs/general-information/refunding/index.htm, accessed December 2, 2008)

Tiotropium is part of the anatomical group R (Respiratory system). In 2006, this anatomical group accounted for a net expenditure for the National Institute of Health and Disability Insurance (RIZIV/INAMI) of € 188 603 037. This is about 8.7% of the total net expenditures of about €2.16 billion. The co-payments were €68 886 464 representing about 12.9% of total co-payments (about €534 million). In total, health care payers had a total expenditure of about €257 million for the anatomical group R (9.6% of €2.7 billion for all anatomical groups).[23] In 2007 tiotropium stood at number 22 in the top-25 of expenditures per active substance for the RIZIV/INAMI (Table 8).[24] In that same year, the number of patients for whom at least one package was dispensed was 86 686.

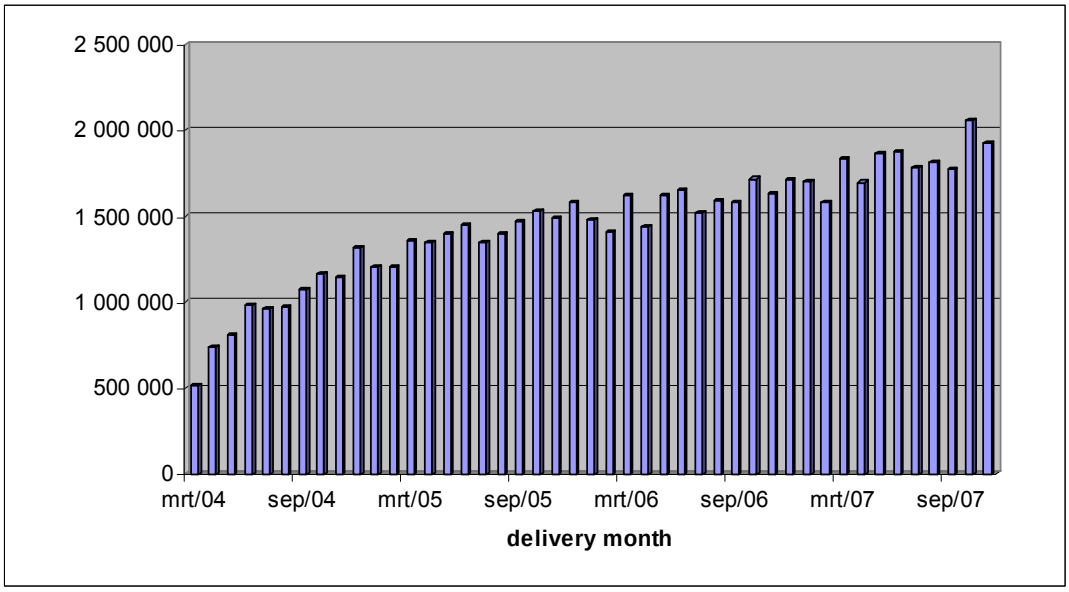
Table 8: TOP-25 of expenditures (in €) for RIZIV/INAMI by active substance in 2007

Ranking	active substance	net amount (€)	patients
1	ATORVASTATINE	85 561 314	259 787
2	OMEPRAZOL	52 538 689	612 45
3	SIMVASTATINE	47 666 132	516 779
4	CLOPIDOGREL	47 486 130	117 883
5	SALMETEROL MET EEN CORTICOSTEROID	45 200 481	211 191
6	ETANERCEPT	38 436 521	3 98
7	PANTOPRAZOL	37 409 165	177 765
8	BLOEDSTOLLINGSFACTOR VIII (ANTIHEMOFILIE-FACTOR A)	36 453 099	224
9	VENLAFAXINE	34 506 172	129 329
10	INTERFERON BETA-1A	31 446 952	3 168
11	MOLSIDOMINE	30 811 130	135 963
12	ROSUVASTATINE	30 339 318	148 279
13	ADALIMUMAB	29 644 396	2 875
14	ESCITALOPRAM	29 497 917	218 61
15	RISPERIDON	27 155 334	80 024
16	FORMOTEROL MET EEN CORTICOSTEROID	26 731 392	152 682
17	PERINDOPRIL	26 426 913	199 011
18	OLANZAPINE	24 775 795	42 589
19	AMOXICILLINE MET ENZYMREMMER	24 135 844	1 370 085
20	AMLODIPINE	22 491 579	299 638
21	ZUURSTOF	22 179 153	24 651
22	**TIOTROPIUM BROMIDE**	**21 752 113**	**86 686**
23	IMATINIB	20 269 441	768
24	NADROPARINE	19 841 100	164 141
25	BISOPROLOL	19 326 497	510 349

http://www.riziv.fgov.be/drug/nl/statistics-scientific-information/pharmanet/info-spot/2008-10-03/index.htm[24] (accessed December 2, 2008)

The RIZIV/INAMI expenditures on tiotropium have increased very fast the first months after this drug was reimbursed (Figure 5). The first month after reimbursement, expenditures were only slightly above €500.000. In January 2005, this was already more than €1.2 million per month, one year later almost €1.5 million, at the beginning of 2007 more than €1.7 million, and at the end of 2008 almost €2 million per month.

Figure 5: Evolution of the RIZIV/INAMI expenditures (in €) on tiotropium (March 2004 – November 2007)



Source: Pharmanet data

Key points

- **The GOLD guideline recommends long-acting bronchodilating agents to patients with stage II COPD or higher.**
- **According to GOLD, there is insufficient evidence to recommend one long-acting bronchodilator over another.**
- **Tiotropium is reimbursed in Belgium for the treatment of COPD since March 2004.**
- **At the reimbursement revision in December 2007, tiotropium was found to have no benefit over long-acting B2-agonists, was more expensive than these alternatives, and did not decrease treatment costs related to other drugs. In contrast, reimbursement rules were not changed.**
- **The number of patients being treated with tiotropium was already more than 86 000 in 2007.**
- **End 2008, the NIHDI expenditures for tiotropium were about €2 million per month.**

2 THE ISSUE

Since the reimbursement of tiotropium, new data were published that demonstrate an effect on important patient-related outcomes, such as the number of exacerbations and hospitalisations. Based on these data, the manufacturer calculated that reimbursing this drug would result in cost savings for the RIZIV/INAMI, despite the relative high charge for this drug. Although the reimbursement of tiotropium remained unchanged during its revision, this reasoning (and thus its relative higher price) has been questioned.

Furthermore, there are few data available on the effectiveness of tiotropium treatment in real-world practice. Decision makers questioned whether the positive effects from trials could also be observed in Belgian patients, outside the environment of a controlled clinical study. Secondly, it was questioned whether the extra expenses for tiotropium were recovered due to less expenditures for other COPD-related interventions.

3 OBJECTIVES

3.1 INITIAL OBJECTIVES

Starting up this Health Technology Assessment (HTA) report, our initial research questions were the following:

- What is the health care consumption (medication, consultations, and hospitalisation) of patients with COPD taking tiotropium in comparison with those not taking this medication?
- What are the factors that can explain these observed differences?
- To what extent do these data deviate from data based on RCTs?
- Taking into account this information, what is the effect on total costs for the RIZIV/INAMI?

3.2 ADJUSTED (REALISTIC) OBJECTIVES

One of the research questions suggested at the beginning of this HTA report concerned the effectiveness of tiotropium: is this product really better than its alternatives in real-world conditions?

Available databases were critically appraised to see whether this research question could be answered. Being aware of the limitations of available data, initial objectives were reformulated to be able to provide correct and objective policy recommendations.

3.2.1 Limitations of observational data

Randomised controlled trials (RCT) are widely acknowledged as the best available tool for evaluating the risks and benefits of medical interventions.[25] RCTs, however, also have their known limitations such as the extrapolation of findings to larger real world populations, which may not fulfil strict inclusion criteria. Observational real-world data may not provide a solution because of several reasons.

The main problem is that it is difficult (or even impossible) to create a well-defined control group. This control group would consist of COPD patients that do not take tiotropium with similar patient characteristics (age, sex, COPD stadium, and other co-morbidities). Identifying COPD patients not taking tiotropium was not possible. No Belgian database included this kind of information. Using other variables as a proxy (such as the use of antibiotics, steroids, etc.) could not provide a solution since this would provide a mixture of COPD and asthmatic patients.

A possible solution for this problem was to use patients taking tiotropium as their own control in a before/after analysis. Tiotropium is reimbursed since March 1, 2004 and (in theory) only used for COPD patients (see reimbursement modalities part 1.6.1). The number of exacerbations and hospitalisations could be compared with their situation before taking tiotropium. Nevertheless, other factors, such as the progression of the disease or changes in smoking behaviour, could also have an influence on differences observed. As mentioned by Lewsey et al.[25] routine data sets have generally been assembled for other purposes and may omit potentially confounding variables. The 'allocation' of patients to treatments will tend to reflect other factors whose effects cannot be fully captured in a covariate adjustment.[26] Risk or severity adjustments are obviously restricted to information recorded in the database and COPD stadium or smoking behaviour, for example, are not included in the Belgian databases. As a result, every seemingly plausible explanation for differences between the treatment and control group may be questioned. Finally, the observational data were not intended to analyse treatment effects. As a result, the quality of the data may lead to questions about the validity of findings.[25]

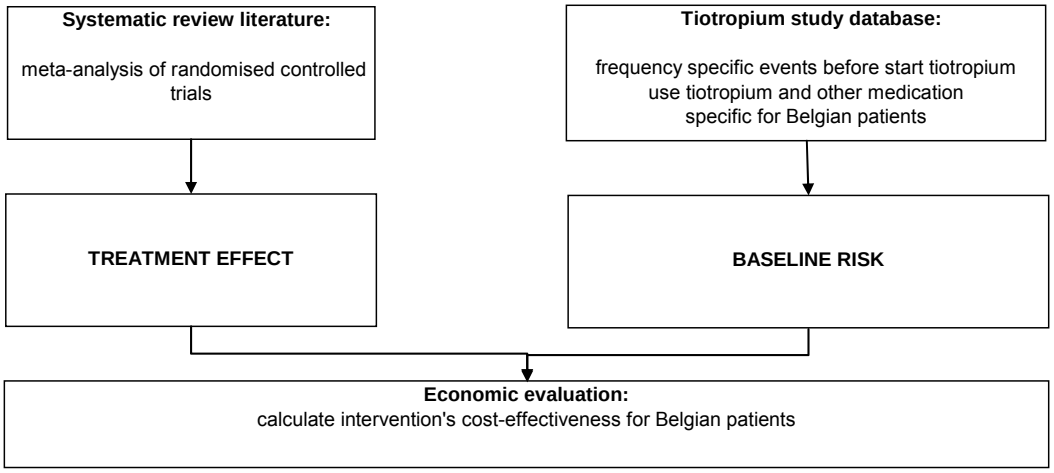
In summary, it is clear that the effectiveness of tiotropium can not be estimated reliably based on the administrative data we have at our disposal.

3.2.2 Opportunities of observational data

Nevertheless, the analysis of observational data is not worthless. In the first place, our large database is an ideal source for a descriptive analysis of the Belgian situation: how many patients use tiotropium, what is the real-world budget impact, are there geographical differences, which other medication is used together with tiotropium, etc.

Secondly, the observational data provide input for a "what-if" cost-effectiveness analysis. In a first step, in the "before" group, the real-world situation is reproduced based on the observational database. In a second step, relying on data from RCTs and/or meta-analysis, the hypothetical situation is set up "as if" tiotropium would have been used. This combines both strengths of data obtained from observational databases (reproducing the real-world base case) and RCTs (providing the treatment effect). As such, the real-world cost effectiveness can be calculated. The following figure shows for which analysis the different sources were used.

Figure 6: Use of specific sources for different goals



Key points

Final research questions for this HTA report:

- **What is the efficacy of tiotropium in COPD patients for patient-centered outcomes?**
- **What is the cost-effectiveness of tiotropium in real-world conditions (taking into account the baseline risk of Belgian patients for certain events and the treatment effect based on RCTs)?**

4 GUIDELINES

The treatment with tiotropium is embedded in the global treatment of the COPD patient. Clinical practice guidelines were used to describe the place of tiotropium in the treatment of a COPD patient.

4.1 METHODS

The following guideline developers or guideline databases and search engines were consulted for clinical practice guidelines on COPD:

- National Institute of Health and Clinical Excellence (NICE)
- Scottish Intercollegiate Guidelines Network (SIGN)
- American Thoracic Society (ATS)
- European Respiratory Society (ERS)
- Global Initiative for Chronic Obstructive Lung Disease (GOLD)
- British Thoracic Society
- Agency for Health Research and Quality (AHRQ)
- National Guideline Clearinghouse
- TRIP database

Search terms used were 'COPD OR Chronic Obstructive Pulmonary Disease OR tiotropium' (March 2008).

Guidelines were selected according to the following criteria.

- Clinical practice guideline
- Management of patients suffering from COPD
- Based on a systematic review of the available evidence
- Published maximum 5 years ago (2003 included)

All guidelines were subsequently assessed for quality, using the AGREE instrument. In case the guideline document did not include details on the methods used, the website of origin was searched for possible descriptions on methodology. The AGREE score was calculated by summing up the scores for all 23 items (strongly agree=4 points, strongly disagree=1 point), by which the maximum score is 92 points and the minimum score is 23 points. Guidelines with a score of less than 50 were excluded.[27]

4.2 RESULTS

Details on the quality assessment for each item are provided in appendix, Table 44.

4.2.1 NICE

196 documents were found, of which one clinical practice guideline on COPD, published in 2004: "Chronic obstructive pulmonary disease. Management of chronic obstructive pulmonary disease in adults in primary and secondary care."[3] The Agree score was 82.

Short-acting bronchodilators, as necessary, should be the initial empirical treatment for the relief of breathlessness and exercise limitation (Grade B). Patients who remain symptomatic should have their inhaled treatment intensified to include long-acting bronchodilators or combined therapy with a short-acting beta2-agonist and a short-acting anticholinergic (Grade A). Long-acting bronchodilators should be used in patients who remain symptomatic despite treatment with short-acting bronchodilators because these drugs appear to have additional benefits over combinations of short-acting drugs (Grade A). Long-acting bronchodilators should also be used in patients who have two or more exacerbations per year (Grade D).

The choice of drug(s) should take into account the patient's response to a trial of the drug, the drug's side effects, patient preference and cost (Grade D). Combining long-acting Beta2-agonists with long-acting anticholinergics is not recommended. Information on the meaning of the grades of recommendation used by NICE in this guideline is given in appendix (Table 45).

4.2.2 SIGN

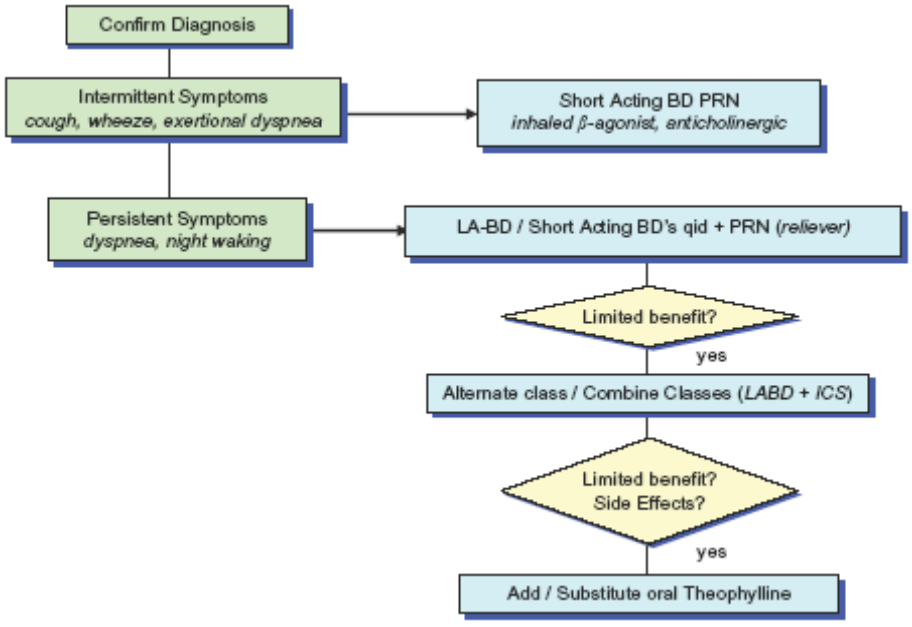
26 documents were found, of which one document was potentially relevant. However, this document[28] is part of the clinical guideline on community management of lower respiratory tract infections in adults, and covers only the treatment of acute exacerbation of COPD. Tiotropium has no role in the treatment of acute exacerbations.

4.2.3 American Thoracic Society/ European Respiratory Society

309 documents were found, of which one was a practice guideline developed by the American Thoracic Society and European Respiratory Society: "Standards for the diagnosis and treatment of patients with chronic obstructive pulmonary disease."[22] The Agree score was 56.

A flow algorithm is provided for the management of patients (Figure 7), which indicates that long-acting bronchodilators can be prescribed in patients with persistent symptoms such as dyspnoea and night waking, after prescribing short-acting bronchodilating therapy. The guideline does not recommend a choice between long-acting inhaled Beta-agonists and tiotropium: both improve health status and reduce exacerbations and hospitalisations compared with placebo and regular ipratropium. The guideline states that in one clinical trial, tiotropium appeared to be superior to salmeterol.[29] This trial, however, was labelled as one part of the Brusasco 2003 study[30] in the Cochrane review, which did not find tiotropium to be superior to salmeterol. Combination therapy is recommended in case of limited benefit with long-acting bronchodilator therapy, and consists of a long-acting bronchodilator and inhaled corticosteroids.

Figure 7: Algorithm for the management of COPD patients



Source: American Thoracic Society, 2004[22]
SA-BD: short-acting bronchodilator; LA-BD: long-acting bronchodilator; ICS: inhaled corticosteroids

The most commonly reported adverse events of anticholinergics are as follows:

- Dry mouth, which is most marked with tiotropium.
- Metallic taste after inhalation (mainly with ipratropium)
- Closed angle glaucoma, a very rare complication that has only been reported in individuals using a high dose of treatment with a nebuliser and face mask.
- Paradoxical bronchoconstriction has been reported in asthmatics but not confirmed in COPD.

4.2.4 GOLD

When the Global Initiative for Chronic Obstructive Lung Disease (GOLD) program was initiated in 1998, one goal was to produce recommendations for management of COPD. The first report, 'Global Strategy for Diagnosis, Management and Prevention of COPD' was issued in 2001, and in 2006 a complete revision was prepared based on research published through June, 2006. The first update of the 2006 report (published in 2007) includes the impact of publications from July 1, 2006 through June 30, 2007.[1] The Agree score was 60.

None of the existing medications for COPD have been shown to modify the long-term decline in lung function that is the hallmark of this disease (Evidence A). Therefore, pharmacotherapy for COPD is used to decrease symptoms and/or complications.

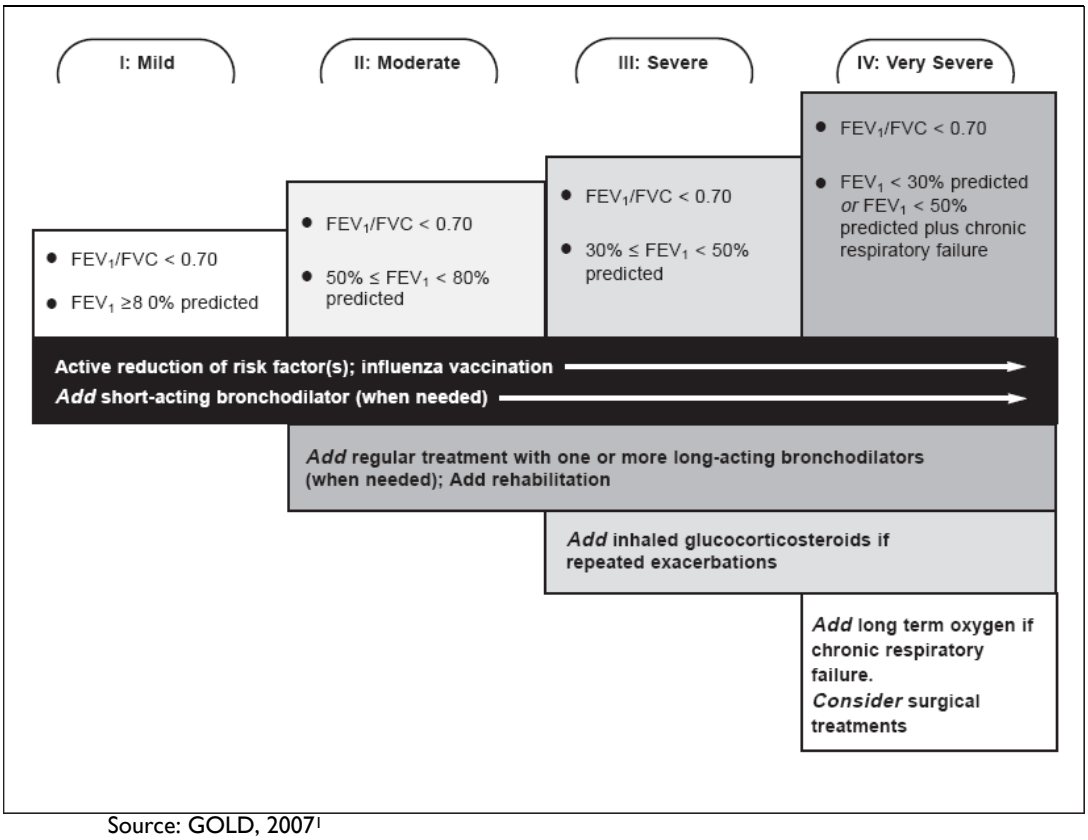
Bronchodilator medications are central to the symptomatic management of COPD (Evidence A). They are given on an as-needed basis or on a regular basis to prevent or reduce symptoms and exacerbations. Regular treatment with long-acting bronchodilators is more effective and convenient than treatment with short-acting bronchodilators (Evidence A).

The principal bronchodilator treatments are β2-agonists, anticholinergics, and methylxanthines used singly or in combination (Evidence A). The choice between β2-agonists, anticholinergics, methylxanthines, or combination therapy depends on availability and individual response in terms of symptom relief and side effects. There is insufficient evidence to favour one long-acting bronchodilator over others.

An inhaled glucocortico-steroid combined with a long-acting β2-agonist is more effective than the individual components in reducing exacerbations and improving lung function and health status (Evidence A).

Therapy at each GOLD stage of COPD is represented in the following figure.

Figure 8: Therapy at each stage of COPD



Source: GOLD, 2007[1]

4.2.5 British Thoracic Society

62 documents were found, of which one was potentially relevant. This was, however, the NICE guideline, which is already included in this summary.

4.2.6 AHRQ

489 documents were found with the term COPD. However, no clinical practice guideline was identified.

4.2.7 National Guideline Clearinghouse

122 documents found, of which three guidelines were relevant and subsequently assessed for quality, and included in this report: guidelines produced by Institute for Clinical Systems Improvement (ICSI),[31] the Singapore Ministry of Health[32] and the American College of Physicians.[33]

4.2.7.1 ICSI

Health Care Guideline: Chronic Obstructive Pulmonary Disease, 6th Edition, January 2007.[31] Agree score 58.

In this guideline, a stepped therapy regimen is recommended, with the first step consisting of short-acting bronchodilators as needed and in the second step adding scheduled dosing of bronchodilators. Among the bronchodilators, tiotropium is the preferred treatment, because of the benefit over salmeterol as shown in the Donohue study.[29]

4.2.7.2 *Singapore Ministry of Health*

Clinical Practice Guidelines: Chronic Obstructive Pulmonary Disease, published in 2006.[32] Agree score 55. Treatment recommendation in this guideline are summarised in Table 9. Tiotropium is recommended in patients with persistent symptoms and/or frequent exacerbation and a spirometry of FEV1 > 50% predicted.

Table 9: recommendations of the Singapore Ministry of Health guideline

Symptoms	Exacerbations	Spirometry	Recommended pharmacotherapy
Intermittent AND	Few exacerbations	Regardless of FEV1	SABA or Combination SABA/SAAC inhaler as needed for symptom relief
Persistent AND/OR	Frequent exacerbations† AND	FEV1 > 50% predicted	SABA as needed for symptom relief With one of the following: 1) SAAC 4 to 6 hourly or 2) Combination SABA/SAAC inhaler 4 to 6 hourly or 3) Long-acting anticholinergic (LAAC) once daily to which may be added: Long-acting beta2-agonist (LABA) 12 hourly AND/OR Sustained-release theophylline 12 hourly or once daily
Intermittent or Persistent AND	Frequent exacerbations AND	FEV1 < 50% predicted	As above AND Inhaled corticosteroids

Source: Singapore Ministry of Health
FEV1: forced expiratory volume in one second; SABA: short-acting β2-agonists; LABA: long-acting β2-agonists; SAAC: short-acting anticholinergics; LAAC: long-acting anticholinergics

4.2.7.3 *American College of Physicians*

Diagnosis and Management of Stable Chronic Obstructive Pulmonary Disease: A Clinical Practice Guideline from the American College of Physicians.[33] Agree score 66.

Treatment for stable COPD should be reserved for patients who have respiratory symptoms and FEV_1 less than 60% predicted as documented by spirometry (Grade: strong recommendation, moderate-quality evidence). No evidence supports treating asymptomatic patients, because treatment does not improve outcomes. This recommendation does not address the occasional use of bronchodilators for acute symptomatic relief.

Clinicians should prescribe one of the following maintenance monotherapies for symptomatic patients with COPD and FEV_1 less than 60% predicted: long-acting inhaled β-agonists, long-acting inhaled anticholinergics, or inhaled corticosteroids (Grade: strong recommendation, high-quality evidence). Monotherapy with a long-acting inhaled β-agonist, a long-acting inhaled anticholinergic, or an inhaled corticosteroid is beneficial in reducing exacerbations. Inhaled corticosteroids and long-acting inhaled bronchodilators have similar effectiveness but differ in adverse effects, reductions in deaths, and hospitalizations. The review did not systematically evaluate all other outcomes. Evidence is insufficient to recommend one monotherapy over another.

4.2.8 TRIP database

36 guidelines were found, among which several guidelines already identified in previous sources, such as the GOLD guideline, the NICE guideline and the ATS/ERS guideline. One additional guideline was identified, the COPD-X Plan: Australian and New Zealand Guidelines for the management of Chronic Obstructive Pulmonary Disease.[34] However, the AGREE score was 48, mainly caused by an unclear methodology for searching, selecting and appraising the evidence. The guideline was consequently not included in this review.

Key points

- **Long-acting bronchodilators are recommended in patients who remain symptomatic despite adequate treatment with short-acting bronchodilators.**
- **Most guidelines do not recommend one long-acting bronchodilator over another.**

5 CLINICAL EFFECTIVENESS

In this systematic review, the available evidence is summarised on the efficacy of tiotropium on patient-centred outcomes. These outcomes include exacerbations, hospitalisations, mortality, quality of life (QoL) and dyspnoea. The results of this review will subsequently be used as input for an economic evaluation.

5.1 METHODS

The systematic review had an iterative approach: good-quality synthesis was searched first, and complemented by original studies published later.

5.1.1 Search strategy

5.1.1.1 Evidence synthesis

The search for evidence synthesis was focused on HTA reports and systematic reviews (search date July 2007, update in November 2008). Databases used were INAHTA, CRD HTA, NICE, the Cochrane Database of Systematic Reviews (CDSR), Medline and CRD DARE. The search terms used in each database are listed in appendix (Table 46).

5.1.1.2 Original studies

Systematic reviews identified in the previous section were subsequently updated with original studies published in Medline or Embase, after the last literature search. Search terms are also listed in appendix (Table 46). The date of search was July 2007 and an update was performed in November 2008.

In addition to published studies, attempts were made to identify unpublished studies by searching the FDA (http://www.fda.gov/cder/index.html) and EMEA websites (http://www.emea.europa.eu/htms/human/epar/s.htm), clinical trial registries and contacting known experts in the field.

5.1.2 Selection of studies

Evidence synthesis studies were eligible if they reviewed the literature systematically on the clinical efficacy of tiotropium in patients with stable COPD, on clinically relevant outcomes such as exacerbations, COPD-related hospitalisations, mortality, dyspnoea and quality of life.

Original studies were eligible if they included a population with stable COPD, with no exacerbation one month prior to study entry, were randomised controlled trials with a follow-up of at least 12 weeks after randomisation, and compared tiotropium to placebo, ipratropium bromide or LABA. Eligibility of studies was assessed by two researchers independently. Disagreement was resolved by consensus.

5.1.3 Quality appraisal

Systematic reviews were assessed for quality using the checklist for systematic reviews of the Dutch Cochrane Centre (www.cochrane.nl). Inclusion criteria based on quality were: the use of a sensitive search strategy in several databases, explicit criteria for inclusion and exclusion, and the application of quality assessment on the included studies.

Likewise, original studies were assessed on quality using the tool described in the Cochrane Handbook of Systematic Reviews. No studies were excluded based on quality assessment.

5.1.4 Analysis

The results of the studies were extracted from the papers and pooled where appropriate.

Primary outcome was the proportion of patients experiencing at least one exacerbation, the exacerbation frequency, the proportion experiencing at least one exacerbation related hospitalisation, the hospitalisation frequency, and mortality. Secondary outcomes were the St George's Respiratory Questionnaire (SGRQ), and the Transitional Dyspnoea Index (TDI).

All data were extracted by two independent researchers. Pooling was done using the fixed effects model in case heterogeneity as assessed with I^2 was ≤ 25%.[35] In all other cases, a random effects model was used.

Funnel plots were constructed when five or more studies were available for one specific comparison and one particular outcome. A funnel plot is a simple scatter plot of the intervention effect estimates from individual studies against some measure of each study's size or precision. Effect estimates from small studies will scatter more widely at the bottom of the graph, with the spread narrowing among larger studies. In the absence of bias the plot should approximately resemble a symmetrical (inverted) funnel. Although funnel plot asymmetry has long been equated with publication bias[36] the funnel plot should be seen as a generic means of displaying small-study effects.[37] Small-study effects may be due to publication bias, differences in methodological quality and true heterogeneity. Finally, it is of course possible that an asymmetrical funnel plot arises merely by the play of chance.[38]

All analyses were performed with Review Manager version 4.2.[39]

5.2 RESULTS

5.2.1 Search results

5.2.1.1 Evidence synthesis

Six reports were identified in the search for HTA reports, of which one was potentially relevant based on title and abstract. This one report, however, was a rapid review of emerging drugs.[40] and was therefore not included.

The search for systematic reviews and meta-analyses identified five studies in the CDSR database, 11 studies in Medline and six in DARE. Of these studies, four were potentially relevant.[41-44] No additional potentially relevant studies were identified in the 2008 update.

One review by Barr et al. is a Cochrane review published in the Cochrane Library in April 2005,[41] and the other is an update of this review published in Thorax in 2006.[42] The same methodology was used in both reviews, although the Thorax review used more stringent inclusion criteria. A comparison of the criteria used in both reviews is shown in Table 11.

Quality assessment of all systematic reviews is summarised in Table 10. Overall, the quality of the Barr reviews and the Rodrigo review were very good. The review by Kesten al.[43] consisted of a pooled analysis of all trials in the manufacturer's (Boehringer Ingelheim) database. The quality of this study was rather low, judging by the criteria for a systematic review. The study was not intended to be a systematic review, and, therefore, is not eligible for this part of our report. Nevertheless, as it is a comprehensive report on adverse events, the Kesten study will be included in the chapter on safety.

Table 10: Quality assessment of systematic reviews

	Barr (Cochrane)[41]	Barr (Thorax)[42]	Kesten[43]	Rodrigo[44]
Adequate research question	Yes	Yes	Yes	Yes
Adequate search strategy	Yes	Yes	No	Yes
Adequate selection of studies	Yes	Yes	No	Unclear
Adequate quality assessment	Yes	Yes	No	Yes
Adequate description of data extraction	Yes	Yes	Unclear	Yes
Description of characteristics of included studies	Yes	Yes	Insufficient	Yes
Handling of clinical and statistical heterogeneity	Yes	Yes	Unclear	Yes
Correct methods of statistical pooling	Yes	Yes	Unclear	Yes

The inclusion criteria of the systematic reviews are summarised in Table 11. Overall, the Barr review published in Thorax is the most applicable for our research question, as it summarises the evidence of trials with a minimum duration of 12 weeks, whereas the Cochrane review and the Rodrigo review included all trials with a minimum of 1 month and 1 week respectively. Therefore, the Barr review published in Thorax was chosen as the starting point of our review.

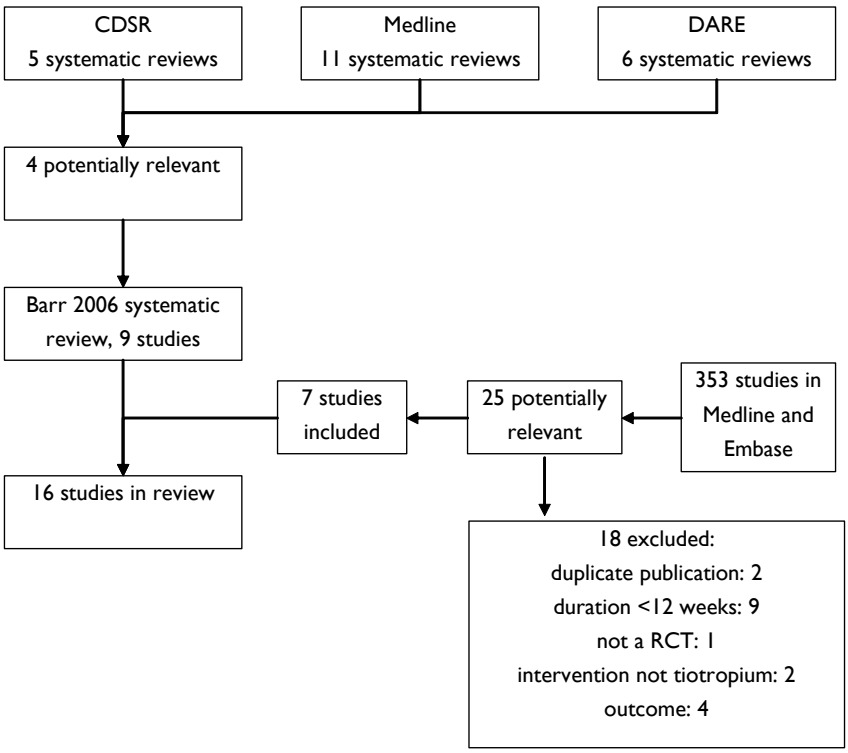
Table 11: Inclusion criteria of the systematic reviews

	Barr (Cochrane)[41]	Barr (Thorax)[42]	Rodrigo[44]	KCE
P	>35 years, stable COPD (ATS/ERS/GOLD) No exacerbation <1 month prior to study No significant other diseases, asthma, cystic fibrosis, bronchiectasis, other lung diseases	Stable COPD (ATS/ERS) No exacerbation <1 month prior to study	>35 years stable COPD (ATS/ERS/GOLD)	Stable COPD (ATS/ERS/GOLD) No exacerbation <1 month prior to study
I	Tiotropium	Tiotropium	Tiotropium	Tiotropium
C	Placebo Ipratropium bromide LABA (salmeterol or formoterol)	Placebo Ipratropium bromide LABA	Placebo Ipratropium bromide LABA	Placebo Ipratropium bromide LABA
O	Primary outcome: clinical endpoints = exacerbations, hospitalizations, mortality Secondary outcome: quality of life, pulmonary function, exercise performance, adverse events	Primary outcome: clinical endpoints = exacerbations, hospitalizations, mortality Secondary outcome: quality of life, pulmonary function, adverse events	Primary outcome: COPD exacerbations, hospitalizations, and mortality. Secondary outcome measures: health status, symptoms, spirometric measures, static lung volumes, exercise performance, inhaled rescue medication, and side-effects.	Primary outcome: clinical endpoints = exacerbations, hospitalizations, mortality Secondary outcome: quality of life, pulmonary function, adverse events
D	RCT Follow-up ≥1 month after randomization	RCT Follow-up ≥12 weeks after randomization	RCT Follow-up ≥1 week after randomization	RCT Follow-up ≥12 weeks after randomization
	Net number of 9 studies included	Net number of 9 studies included	Net number of 13 studies included	Net number of 16 studies included

5.2.1.2 *Original studies*

The search for original studies was limited to studies published after the Barr 2006 literature review. Consequently, only studies published in 2006 or thereafter were eligible. Discarding duplicates, a total of 353 studies were thus identified in Medline and Embase. After applying inclusion and exclusion criteria on title and abstract, 25 studies were potentially relevant. After assessing these studies in full text, seven studies were included in the final review.[45-51] Adding these studies to those already included in the review by Barr et al., 16 studies were included in our meta-analysis (see Figure 9).

Figure 9: Identification and selection of systematic reviews and meta-analyses



CDSR: Cochrane Database of Systematic Reviews; DARE: Database of Abstracts of Reviews of Effects

5.2.1.3 *Supplemental information*

No report on tiotropium was found on the EMEA site, whereas the FDA published an approval review in 2004 available on http://www.fda.gov/cder/foi/nda/2004/21-395_Spiriva.htm.

Six phase 3 clinical trials were considered before approval by the FDA, including 2663 patients. Studies are identified by means of a number. The six studies consist of three replicate pairs: one year versus placebo, one year versus ipatropium and six months versus placebo and salmeterol. The methods and sample sizes of these three replicate pairs correspond to three published studies, already captured by our literature search. The studies 205-114/ 205.117 and 205-115/ 205.128 correspond to the study of Casaburi, published in 2002.[52] The studies 205.122A/ 205.126A and 205.122B/ 205.126B correspond to the study of Vincken, published in 2002.[53] The studies 205.130 and 205.137 correspond to the study of Brusasco, published in 2003.[30] Only the three aggregated studies were incorporated in our review.

5.2.2 Characteristics of included studies

A description of the characteristics of each study is provided in Table 12, and quality assessment is summarised in Table 13.

Overall, studies were very alike with similar inclusion and exclusion criteria. Patients were eligible for the studies if they were at least 40 years old, had smoked at least 10 pack years and suffered from COPD GOLD stage II-III. The mean age of patients ultimately included ranged from 59.1 to 76.3 years, the baseline FEV_1 ranged from 34.4% predicted to 53.3% predicted.

Duration ranged from three months (n=5), six months (n=3), nine months (n=1), 12 months (n=5), 24 months (n=1) and 48 months (n=1).

Concomitant medication permitted during the trial was specified in all studies except in one.[30] All studies allowed short-acting beta-agonist medication, no study allowed the use of other anticholinergic medication. Long-acting beta-agonists were not allowed in seven studies. Inhalant glucocorticosteroids were allowed in 12 studies, oral glucocorticosteroids were allowed in 11 studies, albeit that a maximum dose was specified in most cases.

Only three trials[48, 50, 54] reported adequate concealment of allocation and most studies did not perform an intention to treat analysis for all outcomes reported. Although all studies reported to be double blind, implying blinding of both patient and treating physician, not one study described blinded assessment of the outcome. All studies were at least sponsored by a pharmaceutical company manufacturing tiotropium or the comparator drug, and analyses were performed by the pharmaceutical company in three cases.

Table 12 : characteristics of included studies

Study	Methods	Participants	Interventions	Outcomes	Notes
Beeh 2006[55]	one week run-in 12 weeks	>=40 years, Stable COPD, FEV1<=70% and FEV1/FVC<0.7, >= 10 pack years	Tiotropium 18 µg Placebo	Exacerbations FEV1 FVC	Permitted: shortacting beta-mimetica (fenoterol) Not permitted: Long-acting and short-acting anticholinergics
Briggs 2005[56]	2-week run-in 12 weeks	>=40 years, FEV1 <=60% pred and FVC <=70%, >=10 pack years.	Tiotropium 18 µg Salmeterol 50 µg	Exacerbations Hospitalisation Mortality FEV1 FVC	Permitted: rescue salbutamol, previously prescribed theophylline compounds, inhaled steroids, and modest doses of oral steroids. Not permitted: anticholinergic agents or long-acting beta-agonists other than study medication
Brusasco 2003[30]	2-week baseline 6 months	>40 years, FEV1 <=65% and FVC <=70%, >10 pack years	Tiotropium 18 µg Salmeterol 50 µg Placebo	Exacerbations Hospitalisation Mortality SGRQ TDI FEV1 FVC	Permitted: not stated Not permitted: not stated
Casaburi 2002[52]	Combined results of 2 RCT 2-week baseline 1 year	>=40 years, stable COPD, FEV1 <=65%, FVC <=70% >=10 pack years,	Tiotropium 18 µg Placebo	Exacerbations Hospitalisation Mortality SGRQ TDI FEV1 FVC	Permitted: albuterol as needed, stable doses of theophylline, inhaled glucocorticosteroids and the equivalent of 10 mg oral prednisone/day, Not permitted: anticholinergics and LABA
Casaburi 2005[57]	one week run-in 25 weeks	>=40 years, FEV1 <=60% and FEV1/FVC <=0.70, >10 pack years, candidates for pulmonary rehabilitation	Tiotropium 18 µg Placebo	Mortality	Permitted: albuterol as needed, previously prescribed inhaled steroids, theophylline and oral steroids, Not permitted: Other ß-agonists (short and longacting) and anticholinergics No intention to treat analysis

Chan 2007[46]	2 weeks run-in 1 year	>=40 years, FEV1 <=60% and FEV1/FVC <=0.70, >10 pack years, >=1 exacerbation in the past 2 years but not within 6 weeks before entering the study	Tiotropium 18 µg Placebo	Exacerbations Hospitalisation Mortality SGRQ	Permitted: oral steroids at stable dose <= 10 mg prednisone/day, stable doses of inhaled steroids, theophylline, mucolytic, LABA; salbutamol for acute relief Not permitted: inhaled anticholinergics or oral ß-agonists
Dusser 2006[58]	48 weeks	>=40 years, pre-bronchodilator FEV1 30-65% pred and FEV1/SVC <=70% pred, >=10 pack years, one or more exacerbations in the last year but not within 6 weeks prior to the study	Tiotropium 18 µg Placebo	Exacerbations Hospitalisation Mortality FEV1 FVC	Permitted: short-acting betagonists, concomitant use of inhaled or oral steroids (<10 mg prednisone equivalent) at stable dosages, treatment of COPD exacerbations as deemed necessary (excluding anticholinergics and long acting beta-agonists) Not permitted: Longacting beta-agonists, inhaled anticholinergics other than the study drug and theophylline
Freeman 2007[47]	12 weeks	>=40 years, stable COPD, FEV1 <=65% and FEV1/FVC <=0.70, >10 pack years, short-acting ß-agonists as rescue medication	Tiotropium 18 µg Placebo	Exacerbations FEV1	Not stated
Magnussen 2008[51]	2 weeks run-in 12 weeks	>=40 years, stable COPD + physician diagnosis of asthma before the age of 30, FEV1 <=80%, FVC <=70% >=10 pack years, ICS treatment >=1 year before the study, acute bronchodilator response >=200 ml and >=12% of prebronchodilator FEV1	Tiotropium 18 µg Placebo	Exacerbations Mortality	Permitted: LABA, inhaled steroids, oral steroids <=10 mg prednisone/day, theophyllines, leukotriene antagonists, cromones; salbutamol for acute relief Not permitted: anticholinergic therapy

Niewoehner 2005[54]	6 months	>= 40 years diagnosis of COPD, FEV1 <= 60% predicted FVC <= 70% >= 10 pack-years	Tiotropium 18 µg Placebo	Exacerbations Hospitalisation Mortality	Permitted: Usual care authorized (including inhaled corticosteroids and long-acting ß-agonists), antibiotics and systemic steroids for exacerbations. Not permitted: other anticholinergic bronchodilators
Powrie 2007[45]	2-week run in 1 year	COPD FEV1 <80% pred and FEV1/FVC <70%, >=10 pack years	Tiotropium 18 µg Placebo	Exacerbations Hospitalisation	Permited: usual medication Not permitted: Anticholinergics other than the study drug
Tashkin 2008[48]	at least 2-week run-in 4 years	>=40 years, Stable COPD, FEV1<=70% and FEV1/FVC<0.7, and perform satisfactory spirometry >= 10 pack years	Tiotropium 18 µg Placebo	Lung function decline Exacerbations Hospitalisations Mortality SGRQ	Permitted: usual medication Not permitted: anticholinergics other than study drug unless for the treatment of exacerbations
Tonnel 2008[49]	2 weeks run-in 9 months	>=40 years, Stable COPD, FEV1<=70% and FEV1/SVC<0.7, > 10 pack years	Tiotropium 18 µg Placebo	Exacerbations SGRQ	Permitted: salbutamol, stable dosage of theophylline, mucolytics, ICS and oral steroids (<10 mg of prednisone) Not permitted: ß-blockers, antileukotrienes, oral or inhaled LABA, short-acting anticholinergics, or any other investigational drug
Verkindre 2006[59]	2-week run-in 12 weeks	>= 40 years, FEV1<=50% pred, and FEV1 /SVC <=70%, with lung hyperinflation (RV>=125% of predicted) >=10 pack-years	Tiotropium 18 µg Placebo	Mortality SGRQ FEV1 FVC	Permitted: oral corticosteroids (at a dose of <=10 mg/day prednisone or equivalent), inhaled corticosteroids, theophylline preparations, mucolyticagents and salbutamol metered-dose inhaler as needed. Not permitted: short-acting anticholinergics, oral ß 2 -agonists, or long-acting ß 2 -agonists

Vincken 2002[53]	2 RCTs, 2 weeks baseline 52 weeks	>= 40 years, clinical diagnosis of COPD, FEV1<=65% pred and FVC <=70% >=10 pack-years.	Tiotropium 18 µg Ipratropium 40 mg	Exacerbations Hospitalisation Mortality SGRQ TDI FEV1 FVC	Permitted: salbutamol as needed; theophyllines, inhaled steroids and oral steroids (at a dose of <=10 mg/day prednisolone or equivalent) if stable dosage. Not permitted: other ß agonists (long or short acting) and inhaled anticholinergic medications (other than study drugs)
Wedzicha 2008[50]	2 weeks run-in with oral corticosteroids and inhaled salmeterol 2 years	40-80 years clinical history of COPD exacerbations post-bronchodilator FEV1<50% pred + reversibility to 400 µg salbutamol <=10% of FEV1 pred + >=2 on modified MRC dyspnoea scale >=10 pack-years.	Tiotropium 18 µg Salmeterol 50 µg + fluticasone 500 µg	Exacerbations Hospitalisation Mortality SGRQ	Permitted: short acting inhaled ß-agonists, and standardised short courses of oral steroids and/or antibiotics for exacerbations

Table 13: Quality assessment of included studies

Study	Adequate sequence generation?	Allocation concealment?	Blinding?	Incomplete outcome data addressed?	Free of selective reporting?	Free of other bias?
Beeh 2006[55]	Unclear	Unclear	Patient: Yes Personnel: Yes Assessors: Unclear	Intention to treat analysis, except for lung function and exacerbations in which only treated patients were analysed Dropout tiotropium 8.8%, placebo 13.6%	Yes	Initiated and sponsored by Boehringer Ingelheim
Briggs 2005[56]	Unclear	Unclear	Patient: Yes Personnel: Yes Assessors: Unclear	Analyses based on population with at least one dose of study medication and one post-dose spirometry Imputation using least favourable method and last observation carried forward Dropout tiotropium 8.8%, salmeterol 12.6%	Results on exacerbation frequency and hospitalisation frequency not adequately reported	Funded by Boehringer Ingelheim and Pfizer

Brusasco 2003[30]	Unclear	Unclear	Patient: Yes Personnel: Yes Assessors: Unclear	Analyses adjusted for length of exposure. Imputation using last observation carried forward and other values for that patient on the same day for spirometry. Dropout tiotropium 15.4%, salmeterol 18.7%, placebo 25.8%	No standard errors reported for hospitalisation frequency	Initiated and sponsored by Boehringer Ingelheim
Casaburi 2002[52]	Unclear	Unclear	Patient: Yes Personnel: Yes Assessors: Unclear	Analyses based on population with at least 2 weeks of data for that particular endpoint Imputation based on least favourable method and last observation carried forward Dropout tiotropium 18.7%, placebo 27.8%	Yes	Initiated and sponsored by Boehringer Ingelheim
Casaburi 2005[57]	Unclear	Unclear	Patient: Yes Personnel: Yes Assessors: Unclear	Analysed based on population with adequate data following multiple administration of study medication Dropout tiotropium unclear, placebo unclear	Yes	Initiated and sponsored by Boehringer Ingelheim
Chan 2007[46]	Unclear	Unclear	Patient: Yes Personnel: Yes Assessors: Unclear	Analyses based on full analysis set Imputation using last observation carried forward and least favourable Dropout tiotropium 7.4%, placebo 12.5%	Yes	Initiated and sponsored by Boehringer Ingelheim
Dusser 2006[58]	Unclear	Unclear	Patient: Yes Personnel: Yes Assessors: Unclear	Analysed based on patients with at least one postrandomisation measurement. Impuatation using last observation carried forward and least favourable method Dropout tiotropium 23.4%, placebo 28.8%	Yes	Initiated and sponsored by Boehringer Ingelheim

Freeman 2007[47]	Unclear	Unclear	Patient: Yes Personnel: Yes Assessors: Unclear	Analyses based on full analysis set (=patients randomised and received multiple doses of study drug) Imputation using least favourable model Dropout tiotropium 9.0%, placebo 16.9%	Yes	Initiated and sponsored by Boehringer Ingelheim
Magnussen 2008[51]	Unclear	Unclear	Patient: Yes Personnel: Yes Assessors: Unclear	Imputation using last observation carried forward and least favourable Dropout tiotropium 2.2%, placebo 4.5%	Yes	Initiated and sponsored by Boehringer Ingelheim
Niewoehner 2005[54]	Yes	Yes	Patient: Yes Personnel: Yes Assessors: Unclear	Analyses based on patients who took at least one dose of study medication Imputation based on longitudinal data analysis methods for spirometry. Dropouts tiotropium 16%, placebo 27%	Yes	Initiated, sponsored and analysed by Boehringer Ingelheim
Powrie 2007[45]	Unclear	Unclear	Patient: Yes Personnel: Yes Assessors: Unclear	Analyses based on full analysis set (=all randomised and treated patients with efficacy data) Imputation based on interpolation of last observation carried forward Dropout tiotropium 30.4%, placebo 28.7%	Yes	Sponsored by Boehringer Ingelheim
Tashkin 2008[48]	Yes	Yes	Patient: Yes Personnel: Yes Assessors: Unclear	Analyses based on population with at least 3 postrandomisation data points Dropout tiotropium 36.2%, placebo 44.6%	Yes	Initiated, sponsored and analysed by Boehringer Ingelheim
Tonnel 2008[49]	Yes	Unclear	Patient: Yes Personnel: Yes Assessors: Unclear	Analyses based on full analysis set (=patients randomised, received study drug and had at least one valid posttreatment measurement) Imputation using last observation carried forward Dropout tiotropium 14.7%, placebo 25.7%	Yes	Initiated and sponsored by Boehringer Ingelheim

Verkindre 2006[59]	Unclear	Unclear	Patient: Yes Personnel: Yes Assessors: Unclear	Analyses based on patients with patients with efficacy data Imputation based on last observation carried forward or least favourable method. Dropout tiotropium unclear, placebo unclear	Yes	Initiated and sponsored by Boehringer Ingelheim
Vincken 2002[53]	Unclear	Unclear	Patient: Yes Personnel: Yes Assessors: Unclear	Analyses based on population with multiple administration of study medication Imputation using last observation carried forward or least favourable method. Dropout tiotropium 15.2%, ipratropium 11.2%	Yes	Initiated and sponsored by Boehringer Ingelheim
Wedzicha 2008[50]	Yes	Yes	Patient: Yes Personnel: Yes Assessors: Unclear	Analyses based on population with at least one dose of study medication Dropout tiotropium 41.7%, salmeterol/fluticasone 34.5%	Yes	Initiated, sponsored and analysed by Glaxo Smith Kline

5.2.3 Meta-analyses

Meta-analyses were performed for exacerbations, COPD-related hospitalisations, mortality, St George's Respiratory Questionnaire, and Transition Dyspnoea Index.

5.2.3.1 Exacerbations

In the studies, exacerbations were mainly defined as at least one or two new or increased respiratory symptoms, such as cough, wheeze, dyspnoea, chest congestion, shortness of breath or sputum production, necessitating a change in treatment. Two studies used a purely symptom-based definition.[45, 53]

Proportion of patients experiencing at least one exacerbation

Fourteen studies reported 11 comparisons for placebo, one for ipratropium, two for salmeterol and one for salmeterol/fluticasone. A random effects model was used as heterogeneity was observed for the comparison with placebo (Figure 10).

A significant difference was found for the comparison with placebo, with an odds ratio of 0.77 (95% CI 0.67 to 0.88). Using the absolute risk difference, tiotropium reduces the proportion of patients experiencing at least one exacerbation by 5% (95% CI 3 to 8), compared to placebo. This corresponds to a number needed to treat of 20 (95% CI 12 to 33), in other words 20 patients need to be treated with tiotropium to prevent one patient of experiencing at least one exacerbation. One study found contradictory results.[46] The study protocol and patient population are not markedly different from the other studies. Excluding this study by Chan et al. did not significantly affect the heterogeneity (I^2 56.6%) nor the effect measure (odds ratio 0.74, 95% CI 0.64-0.85).

Stratifying the studies according to study duration shows a gradient of lesser effect in longer studies (Figure 11): the odds ratio in studies of 3 months duration is 0.62 (95% CI 0.49-0.80) whereas in the study of 48 months, the odds ratio is 0.95 (95% CI 0.85-1.06). The difference in summary estimate between these subgroups was tested statistically using metaregression, with duration of follow-up as covariate (restricted maximum likelihood method in STATA). Duration of follow-up was found to be a statistically significant covariate (p=0.003) with a coefficient of 0.0056 (95% CI 0.0019-0.0092), indicating lower effect with longer duration.

Compared to ipratropium, the odds ratio is significant in favour of tiotropium: 0.64 (95% CI 0.44 to 0.92), corresponding to an absolute difference of 11% (95% CI 2-20).

The odds ratios for the comparisons of tiotropium with salmeterol and salmeterol/fluticasone were not significant: 0.86 (95% CI 0.67 to 1.11), corresponding to a risk difference of 2% (95% CI 1 to 6) for salmeterol; and 0.88 (95% CI 0.71-1.10) corresponding to a risk difference of 3% (95% CI 2-8) for salmeterol/fluticasone respectively.

Figure 10: Meta analyses on proportion of patients experiencing at least one exacerbation

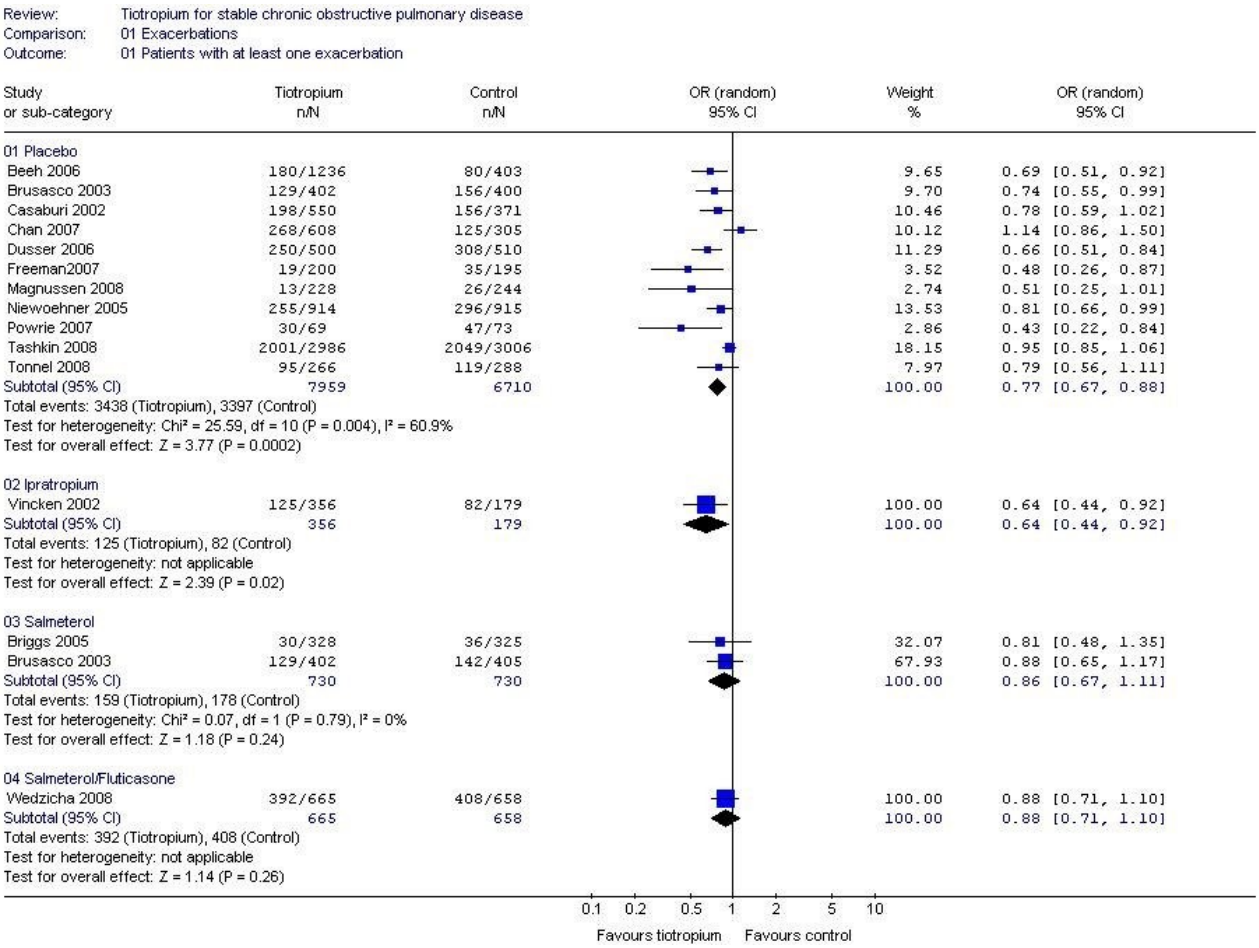
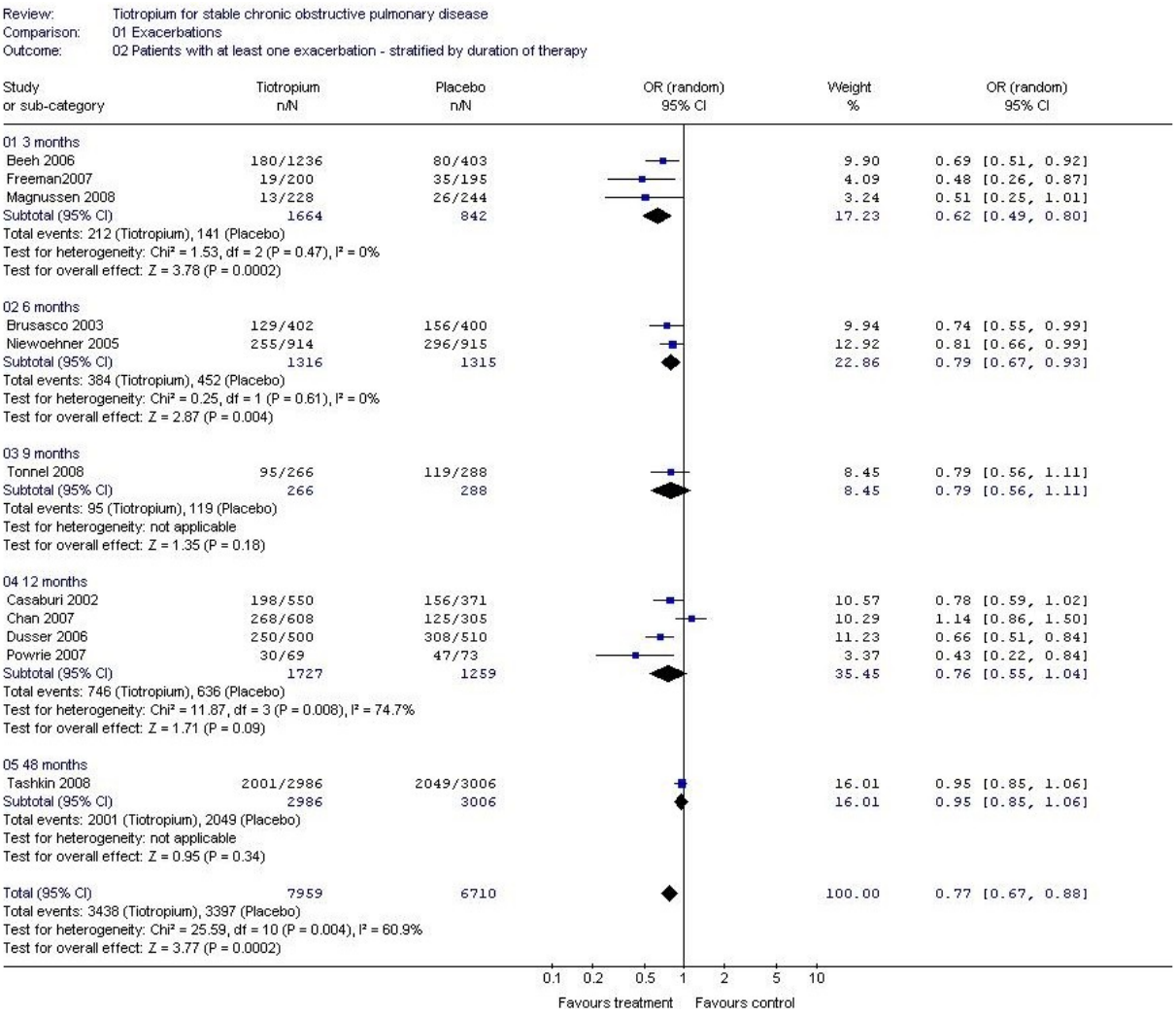


Figure 11: Meta analyses on proportion of patients experiencing at least one exacerbation, placebo controlled stratified by duration



Exacerbation frequency

The second outcome is exacerbation frequency, expressed as the number of exacerbations per patient per year. Results were available from nine studies, of which seven compared to placebo and one compared to ipratropium and salmeterol respectively.

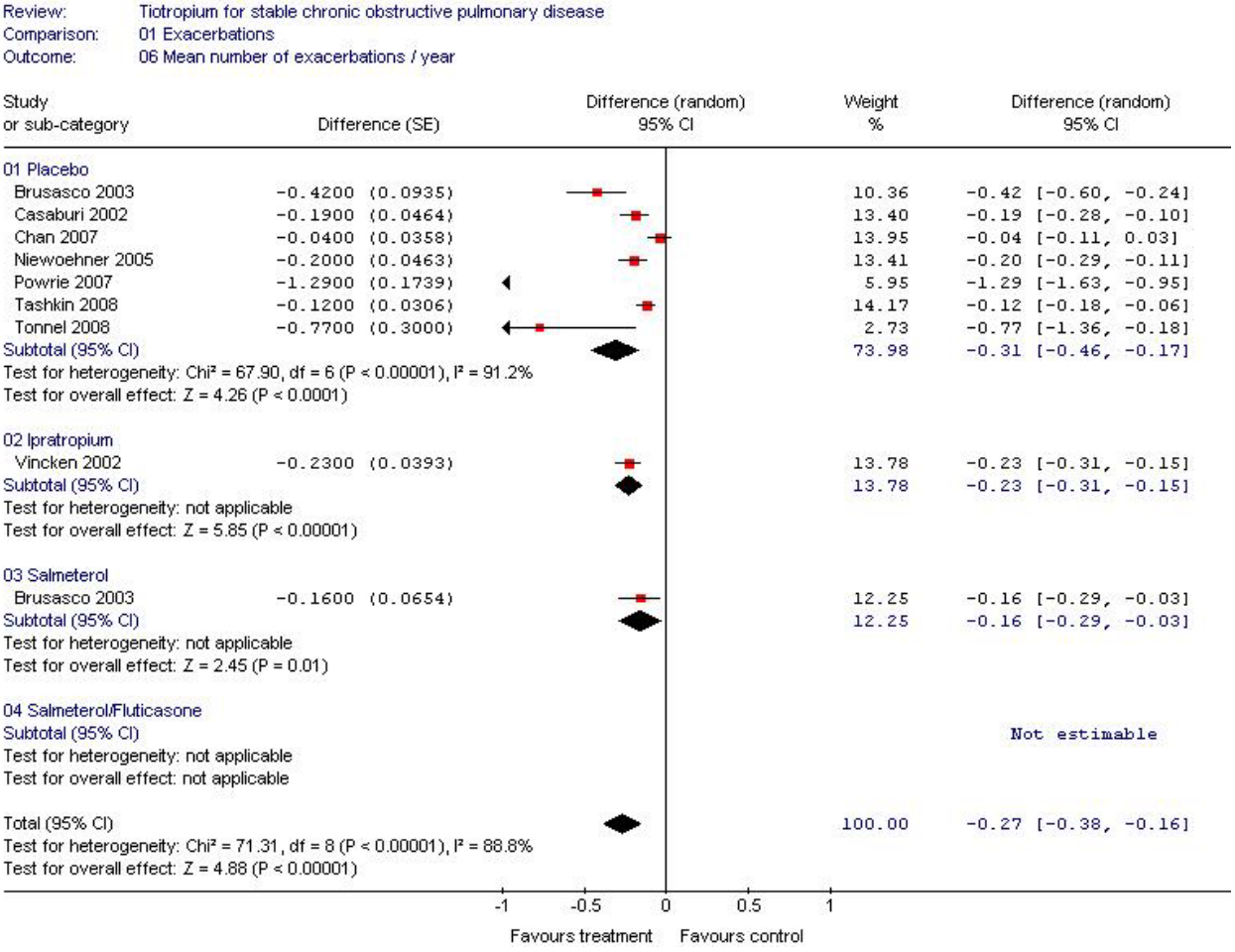
Because not all studies reported frequencies for both groups with their variance, the inverse variance method was used to pool results. The pooled mean difference between tiotropium and placebo is -0.31 exacerbations/patient year (95% CI -0.46 – -0.17). However, heterogeneity was substantial (I^2 91.2%), mainly caused by one study[45] (Figure 12). This study has a markedly higher exacerbation frequency in the control group than the other studies, namely 2.46 exacerbations/patient years whereas the other studies reported frequencies between 0.83-1.05 exacerbations/patient years.

The higher frequency in the Powrie study can be explained by the fact that it used a symptom-based definition of an exacerbation (not necessarily involving a change in treatment, as the other studies). Sensitivity analysis excluding this study decreases heterogeneity (I^2=79%), with a pooled mean difference of -0.19 (95% CI -0.28 – -0.09).

Compared to ipratropium, tiotropium reduces the exacerbation frequency with 0.23 (95% CI -0.31 – -0.15).

Of note, of the two studies comparing tiotropium with salmeterol, both studies report non-significant p-values for the difference in exacerbation frequency. However, one study[56] does not detail the exact results. In addition, results were not retrieved after contact with the corresponding author. Consequently, only one study is included in the meta-analysis, resulting in a mean difference of -0.16 exacerbations/patient year (95% CI -0.29 – -0.03). This result, however, is influenced by publication bias.

Figure 12: exacerbation frequency



Time to first exacerbation

Time to first exacerbation was analysed in 10 studies. Tiotropium was compared to placebo in eight studies[30, 45, 48, 49, 52, 54, 55, 58] which all found a significant result in favour of tiotropium. Most studies only reported a p-value ranging from 0.011 to <0.001. Only Niewoehner reported a hazard ratio of 0.83 (95% CI 0.70-0.98), Dusser reported a delay of approximately 100 days in experiencing the first exacerbation and Tashkin reported a median of 16.7 months (95% CI 14.9-17.9) for tiotropium compared to 12.5 months (95% CI 11.5-13.8) for placebo.

Tiotropium was compared to salmeterol in two studies.[30, 56] Briggs et al. and Brusasco et al. found similar results for tiotropium as for salmeterol without specifying the exact results.

Finally, tiotropium was compared to ipratropium in one study,[53] which found that the time to first exacerbation was significantly longer (p=0.008) in patients receiving tiotropium.

5.2.3.2 Hospitalisations for COPD exacerbation

Proportion of patients with at least one hospitalisation

The proportion of patients with at least one hospitalisation for COPD exacerbations was pooled using a fixed effects model (Figure 13): seven comparisons were available for placebo,[30, 45, 46, 48, 52, 54, 58] one for ipratropium,[53] two for salmeterol[30, 56] and one for salmeterol/fluticasone.[50]

Only the comparison with placebo was statistically significant, with an odds ratio of 0.88 (95% CI 0.79-0.97). This corresponds to an absolute risk difference of 2% (95% CI 0 - 3), and a number needed to treat of 50 (95% CI 33-∞). A similar gradient for study duration was found as for exacerbations: studies of 6 months duration had an odds ratio of 0.69 (95% CI 0.51-0.94), 12 months 0.79 (95% CI 0.59-1.05) and 48 months 0.93 (95% CI 0.82-1.04). However, this gradient was not statistically significant (p=0.064) in a metaregression with duration of follow-up as covariate.

The odds ratio for ipratropium was 0.59 (95% CI 0.32-1.09), for salmeterol 0.54 (95% CI 0.29-1.01), and for salmeterol/fluticasone 0.78 (95% CI 0.57-1.06); neither were statistically significant.

Hospitalisation frequency

Six studies reported sufficient information on hospitalisation frequency to be included in the meta-analysis, five comparing with placebo[46, 48, 52, 54, 58] and one with ipratropium.[53] As for the outcome exacerbation frequency, the inverse generic variance method was chosen, because not all studies reported frequencies and their variances for all groups.

The difference in hospitalisation frequency with placebo is -0.04/patient year (95% CI -0.08 – -0.01), with ipratropium -0.06 (95% CI -0.09 – -0.03) (Figure 14). The frequency in the control group ranged from 0.150-0.250/patient year.

Two studies[30, 56] comparing tiotropium with salmeterol reported non-significant p-values, but no exact results were published.

Figure 13: Proportion of patients with at least one exacerbation related hospitalisation

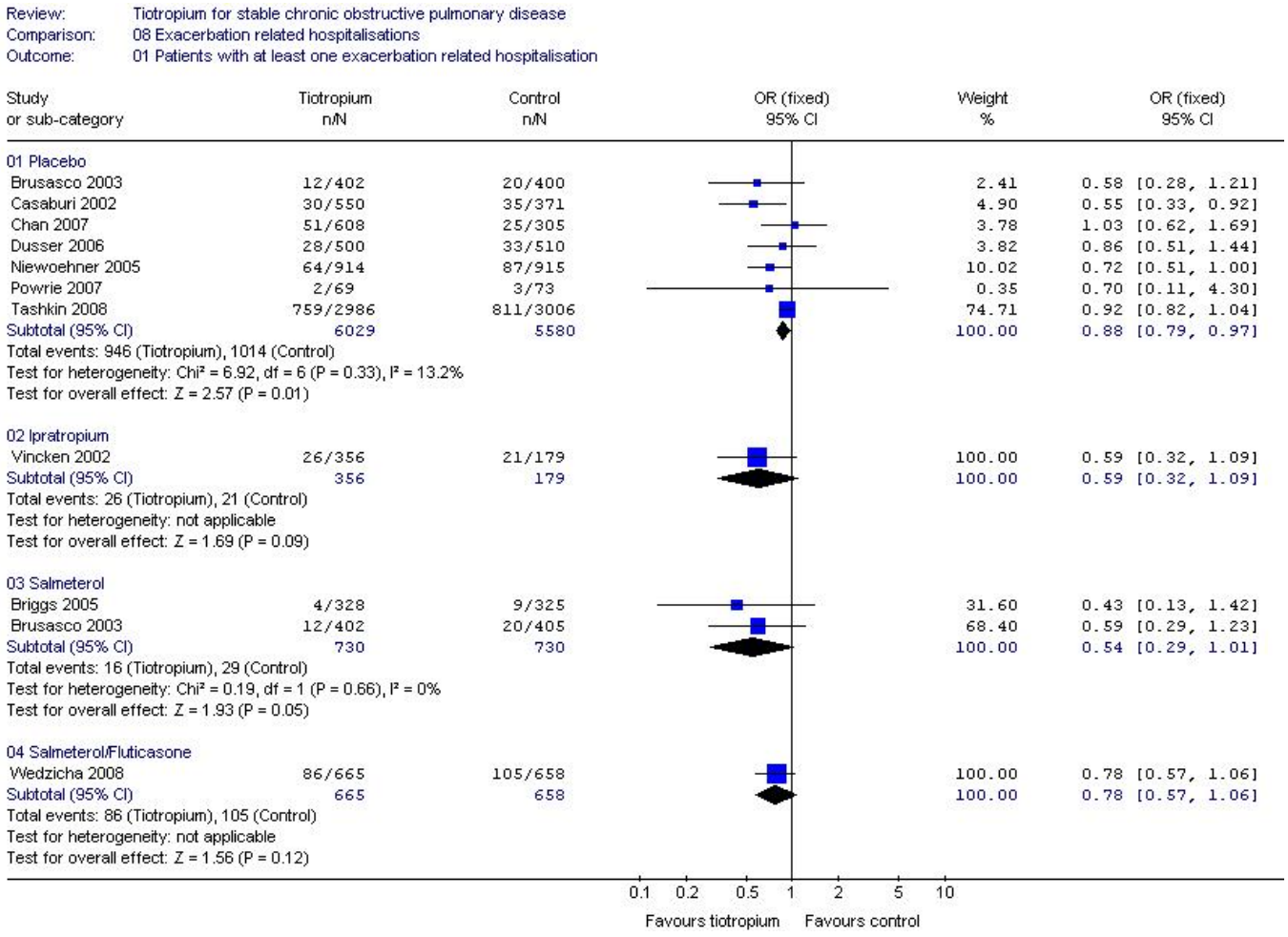
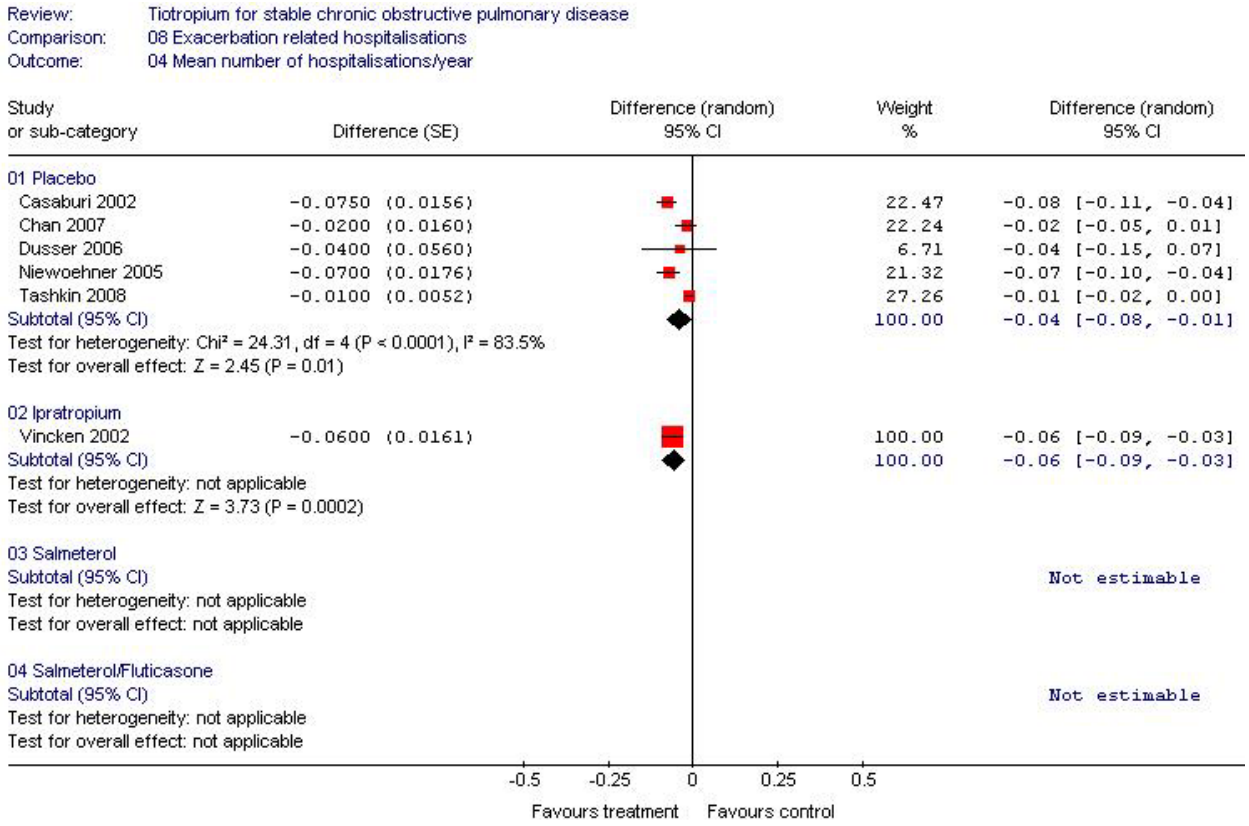


Figure 14: hospitalisation frequency

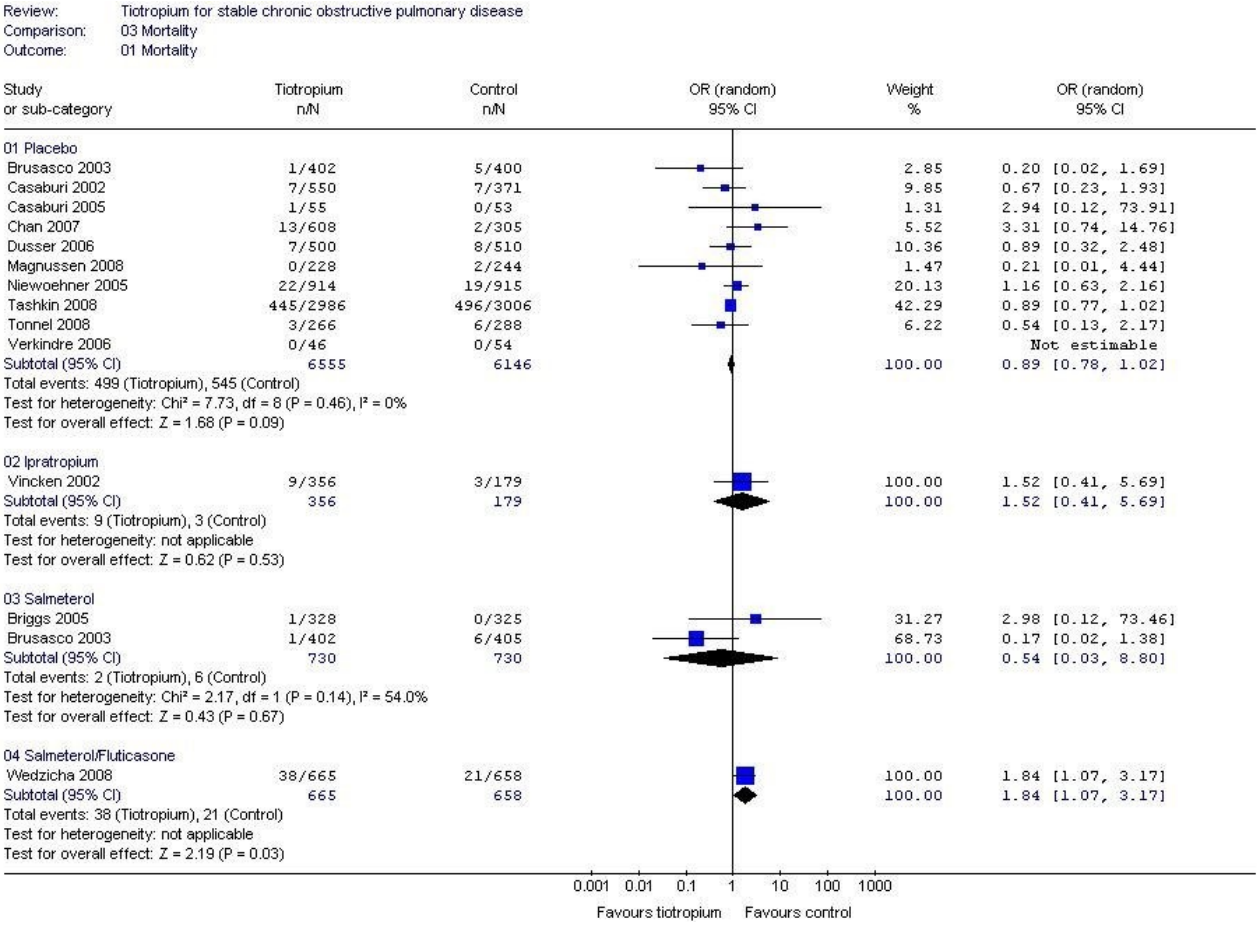


5.2.3.3 *Mortality*

Based on the results of thirteen studies,[30, 46, 48-54, 56-59] all-cause mortality does not differ significantly between tiotropium and placebo, ipratropium or salmeterol (Figure 15), but does differ significantly with salmeterol/fluticasone in favour of the latter: odds ratio 1.84 (95% CI 1.07-3.17).

In general, mortality rates during the trials were markedly lower than the mortality rates in the general population, except for the Niewoehner trial. This may be caused by the stringent exclusion criteria used in the various trials, leading to a relatively lower-risk population in the trials compared to the general population.

Figure 15: Meta-analyses on all cause mortality



5.2.3.4 *Quality of life*

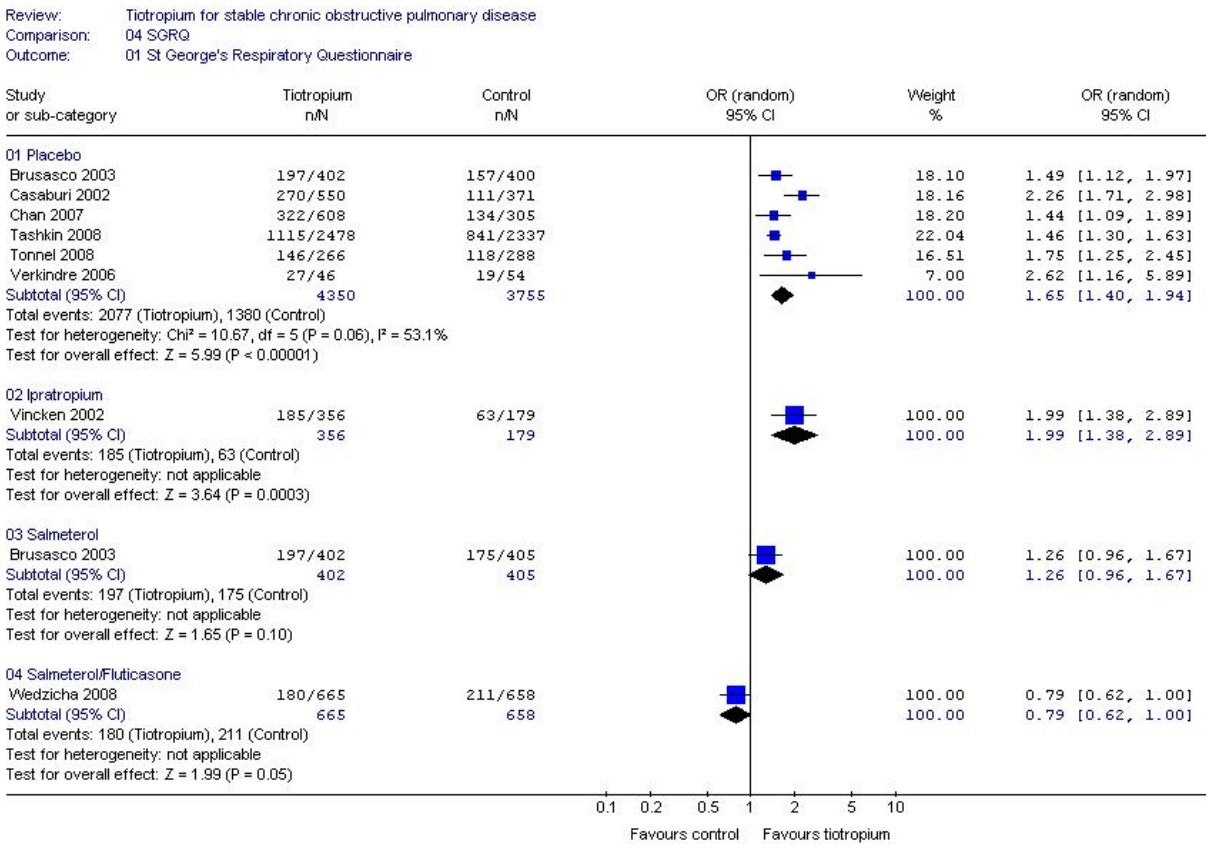
The St George's Respiratory Questionnaire (SGRQ) is a disease specific instrument that contains 76 items in three subscales: symptoms, activity and impact. Each response has an empirically derived weight. The total score is calculated from responses to all items, and range from 0 to 100, with 0 reflecting no impairment and 100 the worst impairment.

Eight studies assessed changes in the SGRQ, with six comparisons with placebo,[30, 46, 48, 49, 52, 59] one with ipratropium,[53] one with salmeterol[30] and one with salmeterol/fluticasone.[50] All studies used a decrease of at least 4 units on the total score as a clinically meaningful result. The proportion of patients attaining this clinically meaningful result was pooled, using a random effects model, as significant heterogeneity was present (I^2=60%) for the placebo controlled studies (Figure 16).

Compared to placebo, the odds ratio was 1.65 (95% CI 1.40-1.94) and for ipratropium 1.99 (95% CI 1.38-2.89). The absolute risk difference was 12% (95% CI 8-16) compared to placebo corresponding to a NNT of 8 (95% CI 6-12) and 17% (95% CI 8-25) compared to ipratropium, with a NNT of 6 (95% CI 4-12).

Compared to salmeterol, the odds ratio was 1.26 (95% CI 0.96-1.67), and compared to salmeterol/fluticasone 0.79 (95% CI 0.62-1.00).

Figure 16: Meta-analyses on health related quality of life



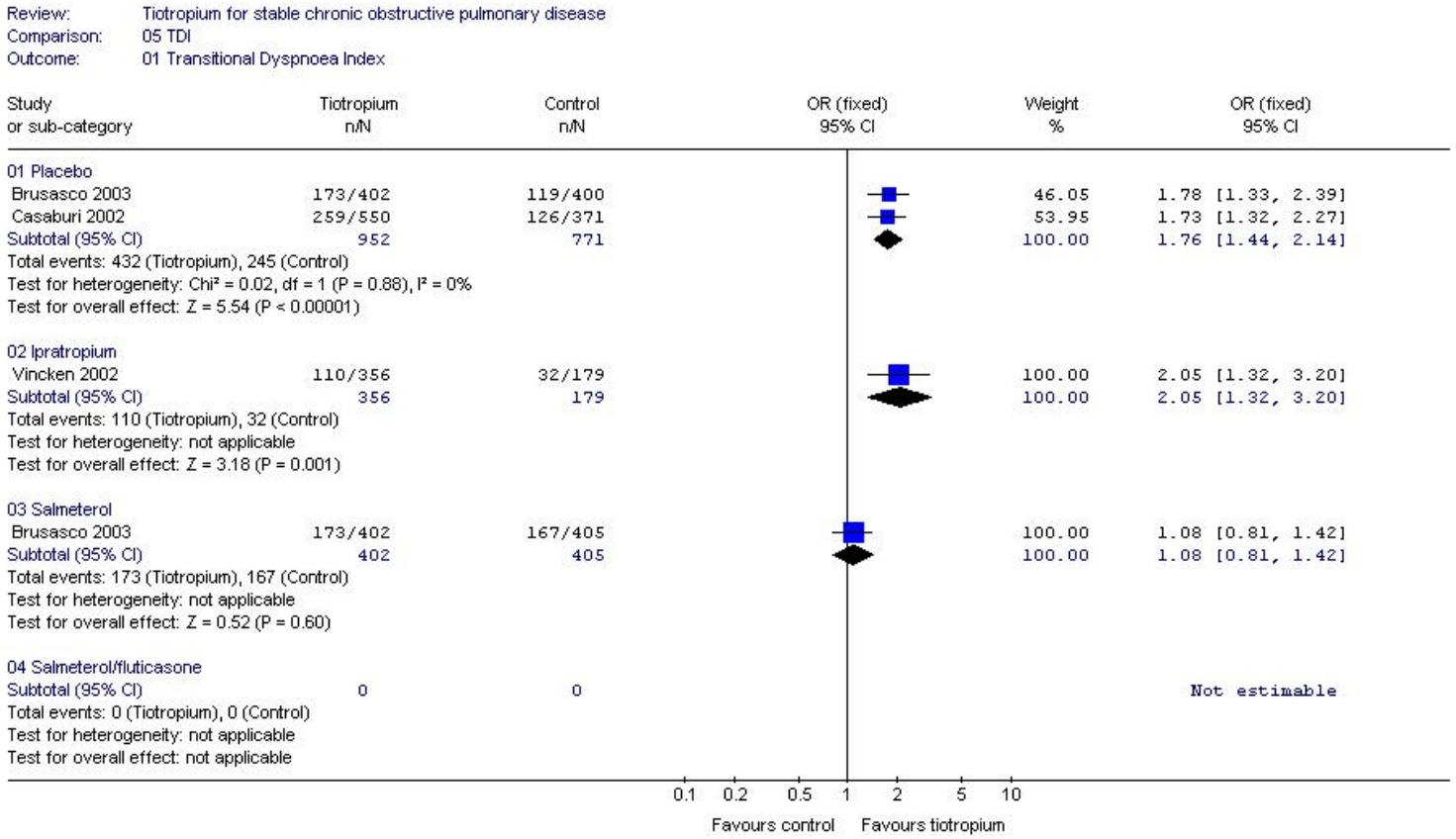
5.2.3.5 Dyspnoea

The Transition Dyspnoea Index (TDI) assesses breathlessness in three domains: functional impairment, magnitude of task, and magnitude of effort, that are summed up to create a focal score. The TDI score ranges from –3 (major deterioration) to +3 (major improvement) for each domain. The sum of all domains yields the TDI focal score (–9 to +9).[60] A change of at least one unit is considered clinically meaningful.

Compared to placebo, the odds ratio for attaining a clinically meaningful change was 1.76 (95% CI 1.44-2.14), and compared to ipratropium, the odds ratio was 2.05 (95% CI 1.32-3.20) (Figure 17). These odds ratios correspond to an absolute difference of 13% in both cases (95% CI 9-18 for placebo, and 6-20 for ipratropium). The number needed to treat for one patient to experience a clinically meaningful change is 8 (95% CI 6-11 for placebo and 5-17 for ipratropium).

Compared to salmeterol, the odds ratio was 1.08 (95% CI 0.81-1.42), which is not significant.

Figure 17: Meta-analysis on dyspnoea



5.2.3.6 *Sensitivity analyses*

Sensitivity analyses were planned for duration of the studies, involvement of the manufacturer of tiotropium and severity of COPD of the patient population (GOLD stage II versus III or higher).

For the outcome 'proportion of patients experiencing at least one exacerbation' and 'proportion of patients with COPD related hospitalisation' stratified analyses have been presented in the previous paragraphs, showing decreasing effect on remaining exacerbation-free in studies with longer duration.

Planned sensitivity analyses according to ties with the manufacturer were not possible, as every study was affiliated with the manufacturer of tiotropium or the comparator drug.

All studies included patients with at least GOLD severity stage II; sensitivity analyses were planned according to baseline FEV1: ≥ 50% predicted or <50%. Only two studies had a baseline FEV_1 ≥50% (GOLD stage II),[45, 51] all other studies had a baseline FEV_1 < 50% (GOLD stage III). However, the Powrie study used a symptom-based definition of exacerbations and the Magnussen study did not define exacerbations. In addition, the Magnussen study did not report hospitalisations, the Powrie study did not report mortality and neither reported the St George's Respiratory Questionnaire. Therefore, a comparison of these two studies to the main results was not meaningful.

5.2.3.7 *Publication bias*

Funnel plots were possible for the placebo controlled comparison on exacerbations and the placebo controlled comparison on exacerbation related hospitalisation (Figure 18 and Figure 19). Both funnel plots showed asymmetry.

A statistical test for funnel asymmetry (Egger's test) was applied for the plot on exacerbations, as it requires at least 10 studies in order for the test to have sufficient power,[38] showing statistical significant publication bias: p=0.008.

Figure 18: Funnel plot of proportion of patients with at least one exacerbation

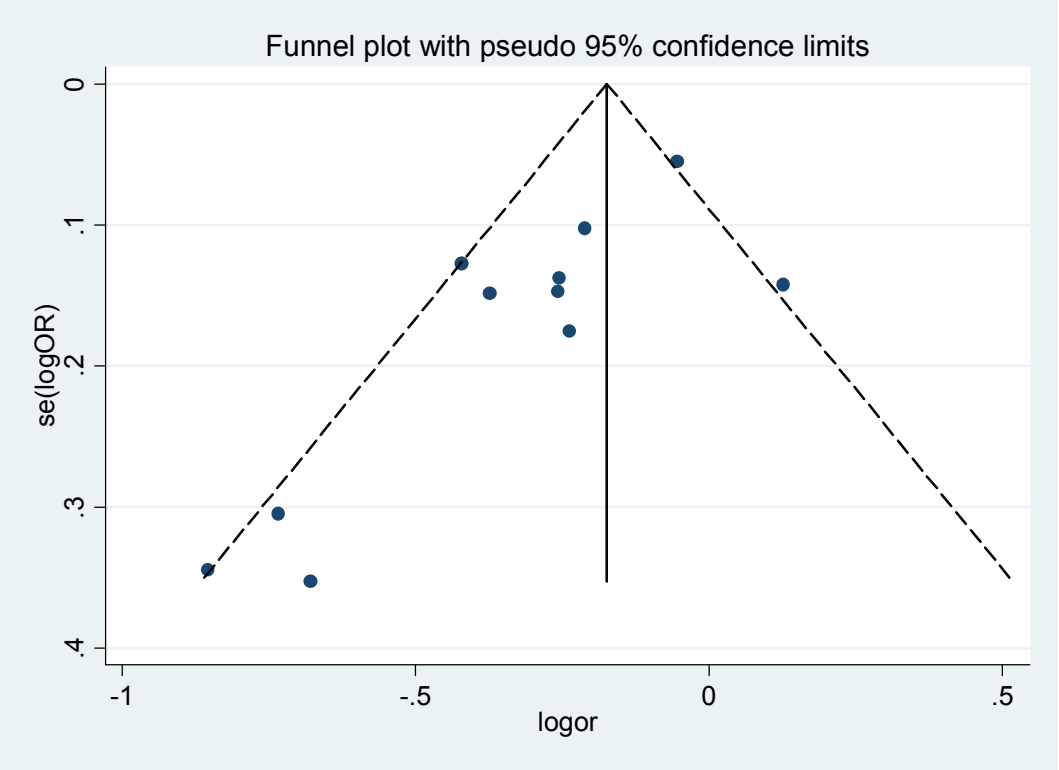
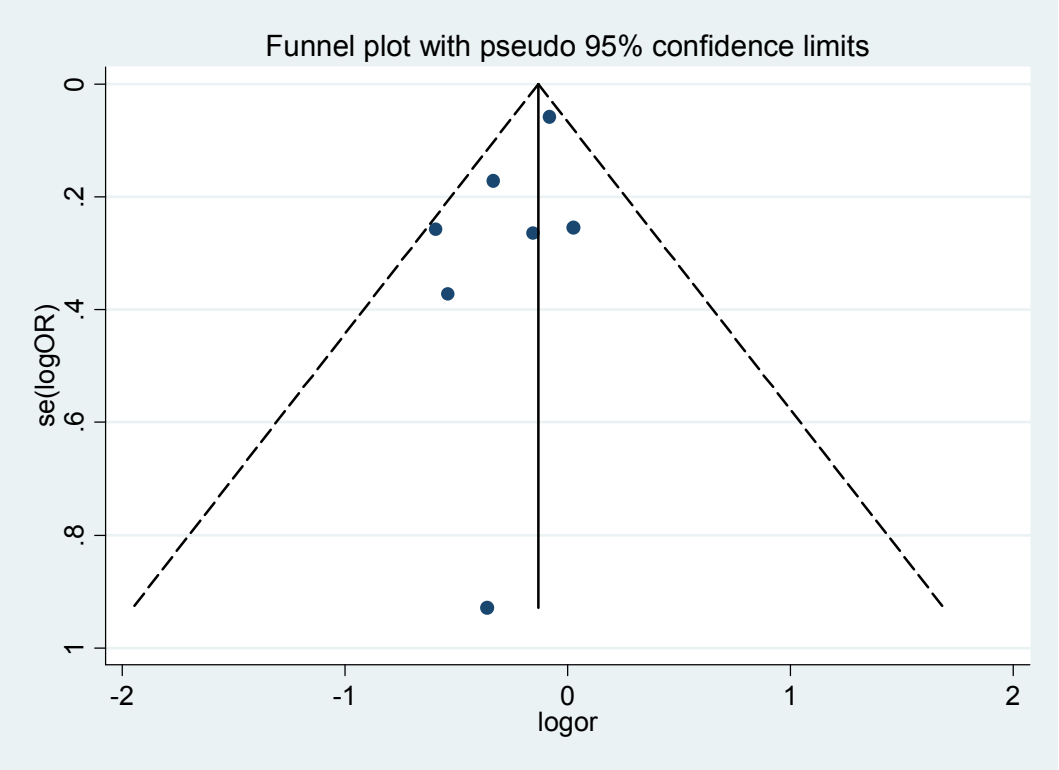


Figure 19: Funnel plot of proportion of patients with at least one COPD related hospitalisation



Key points

- **This meta-analysis was restricted to clinically relevant, patient-centered outcomes**
- **Overall, tiotropium shows similar effects on these outcomes compared to salmeterol**
- **Proportion of patients experiencing at least one exacerbation:**
  - **Significant difference with placebo and ipratropium,**
  - **No significant difference with salmeterol and salmeterol/fluticasone**
- **Exacerbation frequency:**
  - **Significant difference with placebo and ipratropium**
  - **One study showed a significant difference with salmeterol, the other study reports a non-significant difference without detailing the results**
- **Time to first exacerbation:**
  - **Significantly longer compared to placebo and ipratropium**
  - **Not different for salmeterol**
- **Proportion of patients with at least one COPD related hospitalisation:**
  - **Significant difference with placebo**
  - **No significant difference with ipratropium, salmeterol and salmeterol/fluticasone**
- **COPD related hospitalisation frequency:**
  - **Significant difference with placebo and ipratropium**
  - **No significant difference with salmeterol**
- **Mortality:**
  - **No significant difference with placebo, ipratropium and salmeterol**
  - **Significant difference with salmeterol/fluticasone in favour of the comparator drug**
- **Quality of life (St George's respiratory questionnaire):**
  - **Significant difference with placebo and ipratropium**
  - **No significant difference with salmeterol and salmeterol/fluticasone**
- **Dyspnoea:**
  - **Significant difference with placebo and ipratropium**
  - **No significant difference with salmeterol**
- **Publication bias:**

Statistically significant test for publication bias for studies reporting the outcome of proportion of patients with at least one exacerbation. Studies comparing tiotropium and salmeterol report non-significant results for some outcomes, without specifying the exact results. Consequently, these results could not be included in the meta-analyses.

- **Subgroup analyses based on COPD severity were not possible.**

6 HARMS

Any healthcare intervention comes with the risk of harmful or adverse effects. Therefore, a review on the beneficial effects of the intervention should be balanced by a review of the harmful effects.

Many terms are used to describe harms associated with healthcare interventions. Published papers often use terms loosely and interchangeably.

- Adverse event: an unfavourable outcome that occurs during or after the use of a drug or other intervention but is not necessarily caused by it
- Adverse effect: an adverse event for which the causal relation between the intervention and the event is at least a reasonable possibility
- Adverse drug reaction: an adverse effect specific to a drug
- Side effect: any unintended effect, adverse or beneficial, of a drug that occurs at doses normally used for treatment
- Complications: adverse events or effects following surgical and other invasive interventions.[38]

Tiotropium is a quaternary ammonium muscarinic receptor antagonist. In general, muscarinic receptor antagonists prevent the effect of acetylcholine by blocking its binding to muscarinic cholinergic receptors at neuroeffector sites on smooth muscle, cardiac muscle and gland cells, in peripheral ganglia, and in the central nervous system. The quaternary ammonium antagonists exhibit a greater degree of nicotinic blocking activity, and consequently are more likely to interfere with ganglionic or neuromuscular transmission. Since quaternary compounds cross the blood-brain barrier poorly, they have little or no effect on the central nervous system. Common adverse effects of anticholinergics include urinary retention or difficulties in urination, dry mouth, constipation, increased heart rate, palpitations and narrow angle glaucoma.[61] The aim of this chapter is to summarize the evidence on adverse effects of tiotropium specifically. For the long-acting beta-agonist alternatives, salmeterol and formeterol, the most recent review on adverse effects was also included and discussed (see part 6.3 'safety profile of alternative drugs').

6.1 METHODS

Evidence on adverse effects of tiotropium was summarized based on various sources of evidence, in line with current international recommendations.[38] Using the same studies i.e. RCTs, to evaluate beneficial and harmful effects has the advantage that these can be compared directly in the same population and setting. However, trials may be limited in time and population size to accurately demonstrate rare, long-term or previously unrecognised harmful effects. Therefore, combining this type of evidence with studies specifically designed to evaluate harmful effects, such as observational studies and postmarketing surveillance data, will increase the available information.[62]

As stated above, the selected studies for the chapter on clinical efficacy were analysed for adverse effects, together with the systematic reviews summarising the evidence of these trials. In addition, the FDA approval review files were consulted for additional, unpublished information from the trials.

First, the randomized trials included in the chapter on clinical efficacy were analysed on reported adverse effects and withdrawals. Second, a literature search was performed for observational studies on adverse effects.

6.1.1 Search terms used in Medline

The search was performed on July 10, 2008 using the following terms: ("Scopolamine Derivatives/adverse effects"[Mesh] OR "Scopolamine Derivatives/poisoning"[Mesh] OR "Scopolamine Derivatives/toxicity"[Mesh]) OR (tiotropium AND (adverse effects OR toxicity OR adverse events OR complications))

6.1.2 Search terms in Embase

The search was performed on July 10, 2008 using the following terms: tiotropium bromide/exp/dd_adverse drug reaction OR tiotropium bromide/exp/dd/drug toxicity

6.1.3 Selection criteria

Inclusion criteria:

- studies on tiotropium
- reporting any adverse effect
- articles were eligible, regardless of design, patient population or dosage of tiotropium.

Exclusion criteria:

- articles reporting intended, beneficial effects such as differences in exacerbation.
- studies on healthy volunteers

Postmarketing surveillance data were sought from international and national regulatory agencies. The following sites of national and international agencies were searched for reports on adverse effects of tiotropium:

- Europe: European Medicines Agency, www.emea.eu
- US: Food and Drug Administration, www.fda.gov/medwatch
- UK: Medicines and Healthcare Products Regulatory Agency, www.mhra.gov.uk
- Australia: Australian Adverse Drug Reactions Bulletin, www.tga.gov.au/adr/aadrb.htm
- Netherlands: Landelijke Registratie en Evaluatie van Bijwerkingen, www.lareb.nl

6.2 RESULTS

The sixteen RCTs included in the chapter on clinical efficacy were analysed for adverse effects. Nine of the 16 trials were included in the Barr systematic review, published in Thorax. In addition, two reviews were identified in the literature search on clinical efficacy that reported evidence on harms[43, 63] including several of the RCTs cited above.

The search for studies on adverse effects in Medline and Embase yielded 165 and 161 articles respectively, resulting in 279 articles after discarding duplicates. Based on title and abstract, 12 articles were selected for further review. One article was an alert of an FDA warning.[64] The remaining articles included five case reports,[65-69] one analysis of administrative data on hospitalisations,[70] one cohort study comparing safety of long-acting bronchodilators in a morbidity registry,[71] one post-hoc analysis of a randomised controlled trial,[72] one review of drug-induced urinary retention,[73] one review on potential adverse effects of bronchodilators in the treatment of older people,[74] and one trial evaluating electrocardiophysiological changes in patients using tiotropium.[75]

Postmarketing surveillance data were found on the FDA website. No data were found on the EMEA site.

6.2.1 Randomised controlled trials

6.2.1.1 Exclusion criteria used in the trials

Most trials excluded patients with asthma or atopy, with oxygen therapy and 'significant' disease other than COPD. In addition, several trials specifically excluded patients with active cardiac disease, i.e. cardiac arrhythmia requiring drug therapy, myocardial infarction ≤1 year prior to study enrolment and heart failure ≤3 years prior to enrolment. Patients at risk of systemic anticholinergic adverse effects were excluded as well: narrow-angle glaucoma, prostatic hypertrophy or bladder-neck obstruction.

These exclusion criteria are relevant for clinical practice. In a study on COPD patients visiting a general practitioner or specialist outpatient clinic in Norway, only 17% met the criteria used in many RCTs.[76]

6.2.1.2 Reported adverse events

In the systematic review by Barr et al.,[42] summary estimates are provided for eight adverse events: dry mouth, constipation, urinary retention, urinary tract infection, chest pain, myocardial infarction, arrhythmia or atrial fibrillation and congestive heart failure. Two of these were found to be significantly increased in patients taking tiotropium compared to placebo, ipratropium or salmeterol: dry mouth and urinary tract infection. The odds ratio for dry mouth was 3.9 (95% CI 2.8-5.5) based on seven comparisons and 4830 participants. The odds ratio for urinary tract infection was 1.6 (95% CI 1.03-2.6), based on 4 comparisons and 3268 participants. Heterogeneity was evident for arrhythmias or atrial fibrillation overall and in comparison with placebo (p=0.05). This heterogeneity resulted from one trial that reported atrial fibrillation results only.[54] When this trial was excluded, heterogeneity was not evident (p=0.71) and the frequency of arrhythmias was significantly higher with tiotropium than with placebo (OR 2.33, 95% CI 1.11-4.88), based on the four remaining trials.

Seven trials were identified in the previous chapter that were not included in this meta-analysis.[45-51] Chan[46] reported an increased risk of dry mouth, and more serious adverse events for which treatment was necessary compared to placebo. Freeman,[47] Tonnel[49] and Magnussen[51] reported higher risks of dry mouth. In the study of Powrie et al.[45] more cases of hypertension, myocardial infarction and urinary tract infection were reported in the tiotropium group than in the placebo group, but neither result was statistically significant, mainly because of the small sample size of the study (total number of participants 142). Wedzicha[50] reported more cardiac disorders associated with death in the tiotropium group, and mortality was also higher among patients with cardiovascular disorders at baseline (8% in patients receiving tiotropium and 3% in patients receiving salmeterol/fluticasone). On the other hand, pneumonia and candidiasis were more common in the salmeterol/fluticasone group. Tashkin[48] reports no differences between tiotropium and placebo for a range of adverse events, including atrial fibrillation and stroke. In addition, the relative risk for myocardial infarction was statistically significant in favour of tiotropium (0.71, 95% CI 0.52-0.99).

The systematic review by Singh et al.[63] summarised all randomised controlled trials on anticholinergics ipratropium and tiotropium, to explore the association with serious cardiovascular events, being nonfatal myocardial infarction, nonfatal stroke and cardiovascular death. A thorough and systematic search strategy was used, with duplicate searching, selection, quality assessment and data extraction. 17 RCTs were included totalling 14,783 participants, of which 12 trials and 8628 participants on tiotropium. However, 488 patients were double counted by including studies that were published twice.[29, 77] Tiotropium did not significantly increase the risk of cardiovascular death, MI, or stroke: risk ratio 1.43 (95% CI, 0.95-2.16).

Stratifying results by trial duration, results show a significantly increased risk of major cardiovascular events in trials longer than 6 months: risk ratio 2.12 (95% CI 1.22-3.67), but not for the short-term trials: risk ratio 0.82 (95% CI 0.42-1.58). Data for the individual outcomes are not presented separately for tiotropium. Importantly, the double-counted patients are all included in the short-term trials, by which the result for the long-term trials is unaffected by this error.

Essentially, the study by Kesten et al.[43] is a meta-analysis of all tiotropium trials in the Boehringer Ingelheim database. However, trials are denoted by an internal number without reference to published studies. Some study numbers correspond to those cited at the FDA site in their review before approval, others do not and not all studies cited in the FDA review are cited in the meta-analysis. In addition, two asthma-trials were included. The mean duration of exposure to the drug is 149 and 150 days (SD 106-110) for tiotropium and placebo respectively, but almost 50% of patients were exposed ≤90 days.

The investigators developed their own selected events categories, combining adverse events into medically similar categories: events possibly related to antimuscarinic effects, events related to the administration of an inhaled product, events that appeared to be imbalanced in the phase III program, and events of public health and regulatory importance, such as myocardial infarction and cardiac arrest. The Niewoehner trial[54] had markedly fewer adverse events, because it collected serious adverse events only. Three selected adverse events were significantly more common in the tiotropium group than in the placebo group: other arrhythmias, dry mouth and urinary retention. The relative risk (RR) of other arrhythmias was 2.71 (95% CI 1.10-6.65), of dry mouth RR 3.60 (95% CI 2.56-5.05) and of urinary retention RR 10.93 (95% CI 1.26-94.88). Other arrhythmias was defined as dysrrhythmias that were not analysed as a separate selected event and did not include ventricular tachycardia/fibrillation or atrial fibrillation.

Based on the studies submitted by the manufacturer for approval by the FDA (http://www.fda.gov/cder/foi/nda/2004/21-395_Spiriva.htm), dry mouth was much more common in the tiotropium groups than in the placebo or ipratropium groups. Table 14 summarises the adverse events reported by ≥3% in the tiotropium group and occurring more frequently than in the placebo or comparator group in 1-year COPD clinical trials.(FDA Approved Labeling page 10) In addition, adverse events in the category of "heart and rhythm disorders" were more common in the one year tiotropium group than in the placebo studies (4.4% versus 2.2%). However, this signal was not seen in the ipratropium-controlled studies.(FDA medical review p 11) In addition, the frequency of QTc[b] outliers was increased in the tiotropium group in one study (no. 205.131). This study enrolled 198 patients, and found the number of subjects with changes from baseline corrected QT-interval of 30-60msec to be higher in the tiotropium group. This difference was apparent using both the Bazett (20% versus 12%) and the Fredericia (16% versus 1%) corrections of QT for heart rate. Other clinical studies have not detected an effect of the drug on the QT interval, but the FDA warns that the collection of ECG data in these other studies was insufficient to definitely exclude a possible effect.

Table 14: Adverse events (%) reported by ≥3% in the tiotropium group and occurring more frequently than in the placebo or comparator group in 1-year COPD clinical trials

	Placebo-controlled trials (corresponding to Casaburi 2002)		**Ipratropium-controlled trials (corresponding to Vincken)**	
Events	Tiotropium (n = 550)	Placebo (n = 371)	Tiotropium (n = 356)	Ipatropium (n = 179)
Accidents	13	11	5	8
Chest pain (non specific)	7	5	5	2
Edema, dependent	5	4	3	5
Abdominal pain	5	3	6	6
Constipation	4	2	1	1
Dry mouth	16	3	12	6
Dyspepsia	6	5	1	1
Vomiting	4	2	1	2
Myalgia	4	3	4	3
Infection	4	3	1	3
Moniliasis	4	2	3	2
Epistaxis	4	2	1	1
Pharyngitis	9	7	7	3
Rhinitis	6	5	3	2

[b] The QT interval is a measure of the time between the start of the Q wave and the end of the T wave on the electrocardiogram. The QT interval is dependent on the heart rate and has to be adjusted to aid interpretation by using a simple formula that leads to the heartrate-corrected QT interval or QTc

Sinusitis	11	9	3	2
Upper respiratory tract infection	41	37	43	35
Rash	4	2	2	2
Urinary tract infection	7	5	4	2

Two causes of death were reported to the FDA in the tiotropium group and not in the comparator groups at the time of the approval review (December 2003): myocardial infarction (4 deaths) and arrhythmias (1 death). However, overall mortality was similar between tiotropium and placebo.

In the search for studies on adverse events, one placebo-controlled RCT was identified that specifically evaluated the effect of tiotropium on ECG findings.[75] In this study, funded by the manufacturer of tiotropium, using similar inclusion and exclusion criteria as in the other COPD studies, patients with pre-existing cardiovascular disease were permitted to participate, unless they had experienced a myocardial infarction in the preceding 6 months, were hospitalised for heart failure in the preceding year, or had life-threatening arrhythmias requiring intervention or change in drug therapy within the last year. A 12-lead ECG was performed at the screening visit, at the end of the run-in period. At the baseline evaluation, pre-dose and 5 minutes post-dose ECGs and 24-hour Holter monitoring were performed and repeated after 8 and 12 weeks. The ECGs and Holter monitoring results were centrally read, blinded to treatment allocation. Baseline ECGs were calculated as the means of the screening and run-in ECGs. Abnormal rhythm on ECG was defined as the occurrence of at least two consecutive abnormal heart beats, arrhythmia as any abnormal heart beat, and abnormal conduction as any change in the normal atrioventricular conduction. The study found no differences in the number of patients developing abnormal rhythm, or arrhythmias.

No statistically significant differences were noted in mean change from baseline for the average and maximum values for PR, QRS, QT, QTcB and QTcF intervals[c] during treatment. No patient developed new-onset QT or QRc longer than 500 msec, and no differences were noted in the percentage of patients developing new QT prolongation of less than 30 msec, 30-60 msec, or greater than 60 msec. However, the study included 196 patients and was not powered to detect significant differences in ECG parameters.

Finally, the data of the Niewoehner trial was used to assess the impact of discontinuation from the trial or the study drug on the risk ratio for serious adverse events.[72] For this purpose, the data were analysed for separate periods: from the start of the trial to the end of the trial, from start to discontinuation, from discontinuation to the end of the trial, from start until 30 days after the last treatment and time off treatment starting 31 days after the study drug. The authors conclude that the results show that there was a higher incidence of serious adverse events in the post-treatment period, and the risk was higher in the control group. However, neither result is significant, except for the outcome 'any serious adverse event' in the time off treatment starting 31 days after the study drug. For this outcome, the risk ratio was 2.16 (95% CI 1.00-4.67) in favour of placebo.

[c] Different time intervals measured on the electrocardiogram.

6.2.2 Observational studies

6.2.2.1 Cohort studies

Two cohort studies were available, one cohort study is a population-based study in Denmark and another cohort study was based on a morbidity registry in primary care in the UK.

The first cohort study collected data on residents of three Denmark counties who were hospitalised for COPD between 1977 and 2003.[70] For these patients, data on prescription drugs, hospitalisations and mortality were collected. Endpoints were ascertained for the period of availability of tiotropium only. The analyses were based on 10 603 patients, of which 2 870 were tiotropium users.

The majority of patients (64%) were followed for 18-24 months. There was proportionally more use of respiratory medication in tiotropium users. Events during the exposure time were calculated as incidence rates, and rate ratios were calculated by taking the ratio of the incidence rates in the tiotropium group compared to the non-tiotropium group. These analyses were adjusted for age, gender, and Charlson's comorbidity index. The adjusted rate ratio for COPD-hospitalisation was higher among tiotropium users: RR 1.52 (95% CI 1.29-1.79). The authors found an elevated adjusted rate ratio for hospitalisations for atrial flutter and atrial fibrillation, although the estimate is not statistically significant (RR 1.21, 95% CI 0.87-1.69). There were few cases of supraventricular tachycardia and ventricular arrhythmia, by which the estimates are imprecise: RR 0.65 (95% CI 0.26-1.65) and RR 1.97 (95% CI 0.56-6.88), respectively. In this cohort, all-cause mortality was significantly less in tiotropium users, with an adjusted rate ratio of 0.77 (95% CI 0.65-0.91). Only myocardial infarction mortality was elevated, but not statistically significant (RR 1.25, 95% CI 0.49-3.17). Some of the results in this study, such as the reduced mortality and the elevated COPD-related hospitalisations in tiotropium users, are conflicting with what was found in randomised trials. Although the authors have adjusted the analyses for age, gender, Charlson's comorbidity index, other respiratory medications, nitrates, other cardiovascular medications, and asthma diagnosis, it is likely that confounding by indication is still present, as the severity of the disease is not directly accounted for. In addition, the sample size is relatively small considering the rare occurrence of some adverse events. By comparison, the pooled analyses of the randomised trials included almost twice as many tiotropium patients (4 757) than this study (2 870).

Likewise, the second cohort study included only 1061 tiotropium users.[71] In this study, a primary care registry was used to assess any differences between tiotropium and long-acting beta-agonists in mortality and serious adverse events. Confounding was controlled for by propensity scores based on a long list of covariates relating to the disease, co-morbidities, other medications and history. Hazard ratios for total mortality and cardiac endpoints were similar for tiotropium and salmeterol. Important to note is that the mean follow-up in this study was only 5 months, and the sample size is too small to detect rare adverse events.

6.2.2.2 Narrative reviews

Two narrative reviews were identified, one on drug-induced urinary retention[73] and one on potential adverse effects of bronchodilators in older people.[74]

Gupta et al.[74] report that changes in drug metabolism and co-morbidities put older people more at risk for adverse effects of drugs. In addition, absorption of inhaled drugs may be less optimal in the aging lung. Parasympathetic activity decreases with aging. However, relatively little is known about the effect of aging on anticholinergic responses in humans. In animal models, changes due to reduced receptor numbers or post-receptor coupling were seen. The authors found that older people are underrepresented in RCTs on pulmonary drugs for COPD, with only a few trials recruiting patients >80 years of age. Consequently, adverse effects reported in trials are mainly based on patients with a mean age of approximately 60 years of age. The main adverse effects are dry mouth, cardiac effects, ocular effects, respiratory effects, effects on cognitive function, and falls.

Dry mouth, which is the most frequent adverse effect, can contribute in older people to difficulties in communication, mucosal damage, denture misfit, poor appetite, and risk of malnutrition. The authors warn about the risk of cardiovascular adverse effects. Although trials with tiotropium have not shown statistically significant ECG changes, the Lung Health Study that evaluated ipratropium did find a significant difference in total deaths, and in deaths and hospitalisations caused by cardiovascular and coronary artery disease. The higher incidence of supraventricular tachycardia displayed a dose effect.[78]

The second narrative review summarises evidence on drug-induced urinary retention.[73] In general, inhaled anticholinergics have low systemic effects by which the risk of urinary retention appears lower than in systemic drugs. However, cases of acute drug-induced urinary retention have been described for ipratropium.

6.2.2.3 Case reports

One article reports the case of a patient who, after accidental contact of the right eye with the drug, was diagnosed with one-sided acute angle-closure glaucoma, which was treated successfully.[68] The relation between the drug and the adverse effect is considered as very probable.

A patients with known oral lichen planus developed new lesions after three days of therapy with tiotropium. A previous treatment with tiotropium had resulted in similar ulcerations after three days of therapy.[65] The ulcerations healed after discontinuation of treatment. The relation between the drug and the adverse effect is considered as very probable.

In another case report, the appearance of a photosensitive lichenoid eruption is linked to the use of tiotropium, which was started 22 months earlier.[66] The eruption disappeared gradually after treatment with tiotropium was stopped and topical treatment was applied. Patch testing with tiotropium and other agents was negative. The relation between the drug and the adverse effect is considered as probable.

The fourth case report details the history of a patient who developed skin lesions one week after the introduction of tiotropium.[67] The lesions were diagnosed as subacute cutaneous lupus erythematosus, and were associated with leukopenia. Six weeks later, tiotropium was discontinued and the lesions rapidly resolved. After reintroduction of tiotropium, the lesions reappeared. The relation between the drug and the adverse effect is considered as very probable.

Finally, two cases are reported of postoperative ileus in patients using tiotropium.[69] Both patients experienced five days of intestinal paralysis after abdominal surgery, which necessitated an ileostomy in one case. The authors hypothesize that tiotropium accumulated in the digestive tract due to normal postoperative ileus, and together with the after-effects of anticholinergic anaesthetics, postoperative opioid medication and immobilisation, caused a prolonged postoperative ileus period. The relation between the adverse effect and the drug is considered as uncertain.

6.2.3 Postmarketing surveillance data

On the FDA site,(http://www.fda.gov/cder/foi/label/2006/021395s008s015lbl.pdf) information was found in the warnings and in two audiences.(http://www.fda.gov/medwatch/safety/2008/safety08.htm) The FDA warns that tiotropium is not indicated for the initial treatment of acute episodes of bronchospasm, i.e. rescue therapy. Immediate hypersensitivity reactions, including angio-oedema may occur. Inhaled medicines, including tiotropium, may cause paradoxical bronchospasm.

FDA and the American Association of Poison Control Center's (AAPCC) National Poison Data System have received many reports of patients swallowing Spiriva capsules rather than placing the capsules in the inhalation devices. Healthcare professionals should discuss with patients how to correctly use the Spiriva HandiHaler.[Posted 02/29/2008]

Boehringer Ingelheim and FDA notified healthcare professionals that ongoing safety monitoring has identified a possible increased risk of stroke in patients who take Spiriva.

The preliminary estimates of the risk of stroke are 8 patients per 1000 patients treated for one year with Spiriva, and 6 patients per 1000 patients treated for one year with placebo. This means that the estimated excess risk of any type of stroke due to Spiriva is 2 patients for each 1000 patients using Spiriva over a one year period. FDA has not confirmed these analyses and while pooled analyses can provide early information about potential safety issues, these analyses have inherent limitations and uncertainty that require further investigation using other data sources.[Posted 03/18/2008] on October 7, 2008 the FDA posted that preliminary data from the Uplift trial[48] showed that there was no increased stroke risk compared to placebo.

In the Dutch database on side effects, 105 reports on possible side effects were listed, most of which were reported once or twice (accessed on July 29, 2008). We list those possible side effects that were reported at least 5 times:

- Rash: 16 reports
- Palpitations: 10 reports
- Dry mouth: 10 reports
- Pruritus: 10 reports
- Dyspnoea: 9 reports
- Headache: 8 reports
- Dizziness: 7 reports
- Blurry vision: 6 reports
- Urine retention: 5 reports
- Nose bleed: 5 reports
- Constipation: 5 reports

6.3 SAFETY PROFILE OF ALTERNATIVE DRUGS

6.3.1 Salmeterol

The long-acting beta-agonist salmeterol is one of the alternatives for tiotropium, as recommended by the clinical guidelines. A recent Cochrane systematic review summarized the serious adverse events as reported in patients with asthma.[79] Based on all randomised controlled trials, they concluded that all-cause mortality of salmeterol is not significantly different from placebo or salbutamol: odds ratios 1.33 (95% CI 0.85-2.10) and 1.23 (0.75-2.02) respectively. However, serious adverse events, defined as all cause non-fatal events, were significantly more common in patients taking salmeterol than in patients taking placebo: odds ratio 1.14 (1.01-1.28). Considering the baseline rate of 3.6%, this corresponds to a number needed to harm of 188 (100-3000). The odds ratio for serious adverse events in the cardiovascular system was not statistically significant compared to placebo: 0.98 (95% CI 0.73-1.31). Compared to salbutamol, serious adverse events were not significantly different (odds ratio 0.99; 95% CI 0.84-1.16). Although the review included 32 trials which randomised 62 630 participants, the rarity of mortality and serious adverse events means that there is still considerable uncertainty in relation to the size of the effects being investigated. In addition, it is unclear to what extent these results can be extrapolated to COPD patients, as these tend to be older and have more co-morbidities.

In December 2008, the FDA published a meta-analysis that explores possible associations of four long-acting beta agonists (LABAs) currently marketed in the United States (salmeterol, salmeterol/fluticasone, formoterol and formoterol/budesonide) with asthma-related hospitalization, asthma-related intubation, and asthma-related death in asthmatic patients.[80] The meta-analysis was based on patient-level data from randomized parallel controlled clinical trials available to the sponsors of LABAs. Only data from trials that studied the treatment of asthma were included. FDA provided instructions to the sponsors on the post-hoc adjudication of outcomes and the structure of data to be submitted. The study used data from 110 trials and 60 954 subjects that met the inclusion criteria for the analysis.

Based on the findings from this meta-analysis, LABAs as a group were associated with an increased risk of an asthma composite endpoint consisting of asthma-related hospitalization, asthma-related intubation, and asthma-related death among asthmatic subjects. This overall finding for the asthma composite endpoint was supported both by asthma-related hospitalization and the asthma-related death components. However, findings for individual drugs and subgroups were driven by the asthma-related hospitalization component. The risk difference estimate for the asthma composite endpoint of the LABA rate minus the non-LABA rate was 2.80 (95% CI: 1.11, 4.49) per 1000 subjects. The increased risk was seen in three of the four drugs studied, formoterol, salmeterol, and formoterol/budesonide, but was not apparent in salmeterol/fluticasone. The increased risk was not apparent when the LABA was used in conjunction with an ICS. Youths (age 4 – 11 years) appeared to be at the greatest risk among age groups: risk difference 14.83 (95% CI: 3.24, 26.43) per 1000 subjects.

Blacks/ African Americans had observed elevated risks relative to other race subgroups. Females had observed elevated risks relative to males. Differences in observed risk among the four drugs and in the use of ICS may be an artifact of differences among trials included in the meta-analysis and limitations on the information available for the meta-analysis.

It should be noted, however, that the trials included in the meta-analysis were generally not designed to collect the endpoints considered in the analysis. In addition, information on dropout from the trials was not obtained. Differential dropout patterns may introduce bias. However, information on treatment duration was obtained and found to be similar between the comparison groups. Finally, information on individual subject and trial characteristics were limited. Potential unobserved differences in study populations among the drugs and subgroups may have been associated with the observed effects. This included concomitant ICS use and adverse event information ascertainment.

6.3.2 Inhaled corticosteroids

In 2007, the Cochrane Library published a systematic review on the use of inhaled corticosteroids (ICS) in patients with stable COPD.[81] All-cause mortality was not significantly different in patients taking inhaled corticosteroids than in patients taking placebo, with odds ratios of 0.98 (95% CI 0.83 to 1.16, 8390 participants), as reported in nine long-term studies of more than 6 months duration; and 0.17 (95% CI 0.02 to 1.53; 1171 participants) in four medium term studies of >2 and ≤6 months duration.[81] The risk of oropharyngeal candidiasis was significantly increased with ICS in long-term and medium term studies: OR 2.49 (95% CI 1.78 to 3.49; 4380 participants) and OR 5.74 (95% CI 3.52 to 9.34, 1697 participants), respectively. For participants randomised to less than 1000mcg/d beclomethasone dipropionate equivalent, this corresponded to a number needed to harm of 44 (95% CI 20 to 131). In studies assessing more than 1000mcg/d beclomethasone dipropionate equivalent, there was some variation in baseline risk, leading to a range of number needed to harrm of 13 (95% CI 7 to 34) to 57 (95%CI 29 to 156). There was also an increased risk of hoarseness or dysphonia in the long-term studies (OR 1.95, 95% CI 1.41 to 2.70; 3267 participants), with minimal heterogeneity, implying a consistent effect across the studies; and in the medium-term studies (OR 4.13, 95% CI 1.74 to 9.80). There was no significant difference in throat irritation, although there was much heterogeneity between the two studies that reported this. No significant increased risk of fractures or osteoporosis has been found. Skin bruising has been found to be significantly increased in patients taking inhaled corticosteroids.

In a recent systematic review and meta-analysis, it was confirmed that inhaled corticosteroids do not affect mortality; however, a significant effect on the incidence of pneumonia was found: the relative risk is 1.34 (95% CI, 1.03-1.75), especially in patients with the highest doses, short duration of therapy, low baseline FEV1 and combination with bronchodilator therapy.[82]

Key points

- **The population included in tiotropium trials is highly selective and only represents a small proportion of COPD patients in real life.**
- **Two adverse events were significantly higher with tiotropium versus placebo, ipratropium or salmeterol, i.e. dry mouth and urinary tract infection.**
- **Arrhythmias were significantly increased in tiotropium patients after exclusion of one trial causing heterogeneity. In 2004, the FDA warned about an increased frequency of QTc outliers. Further research on this adverse event is needed.**
- **Based on a systematic review, major cardiovascular outcomes (myocardial infarction, stroke and cardiovascular death) are significantly increased in long-terms tiotropium trials. This was however not demonstrated in the UPLIFT trial.**
- **Salmeterol is associated with an increased risk of asthma-related composite endpoint (death, intubation, hospitalisation) in asthmatic patients.**
- **Inhaled corticosteroids are associated with an increased risk of pneumonia.**

7 COST EFFECTIVENESS OF TIOTROPIUM FOR COPD PATIENTS: A REVIEW OF THE LITERATURE

7.1 METHODS

7.1.1 Literature search strategy

The search for the economic literature about the use of tiotropium in COPD patients was performed by consulting various databases up to mid December 2008. The CRD HTA and CDSR Technology Assessment databases were searched to retrieve HTA reports on this topic. The websites of HTA institutes mentioned on the INAHTA (International Network of Agencies for Health Technology Assessment) website were also consulted. The NHS EED(CRD), Medline(OVID), EMBASE, Econlit(OVID), and CDSR Economic Evaluation databases were searched to retrieve both full economic evaluations and reviews of full economic evaluations of tiotropium. No restrictions on the time period and language were imposed. An overview of the search strategy and results are provided in appendix 4.

7.1.2 Selection criteria

All retrieved references were assessed against pre-defined selection criteria, in terms of population, intervention, comparator, and design (Table 15), in a two-step procedure: initial assessment of the title, abstract, and keywords, followed by a full-text assessment of the selected references. When no abstract was available and the citation was unclear or ambiguous, consideration of the citation was directly made on the basis of full-text assessment. Reference lists of the selected studies were checked for additional relevant citations. This whole literature search and selection procedure was replicated by a second reviewer to assess the quality of this process and approve the literature selection. The selected full economic evaluations, i.e. the studies comparing at least two alternative treatments in terms of costs and outcomes (see classification in appendix, Figure 37), were then summarised in an in-house data extraction form.

Table 15: Economic evaluation selection criteria

	Inclusion criteria	Exclusion criteria
Population	Patients suffering from COPD	Other patient groups
Intervention	Tiotropium	Other interventions
Comparator	Other treatments for COPD such as salmeterol and ipratropium or 'general' treatment.	Placebo
Design	Full economic evaluations (primary or secondary studies)	Cost description, cost comparison, etc.

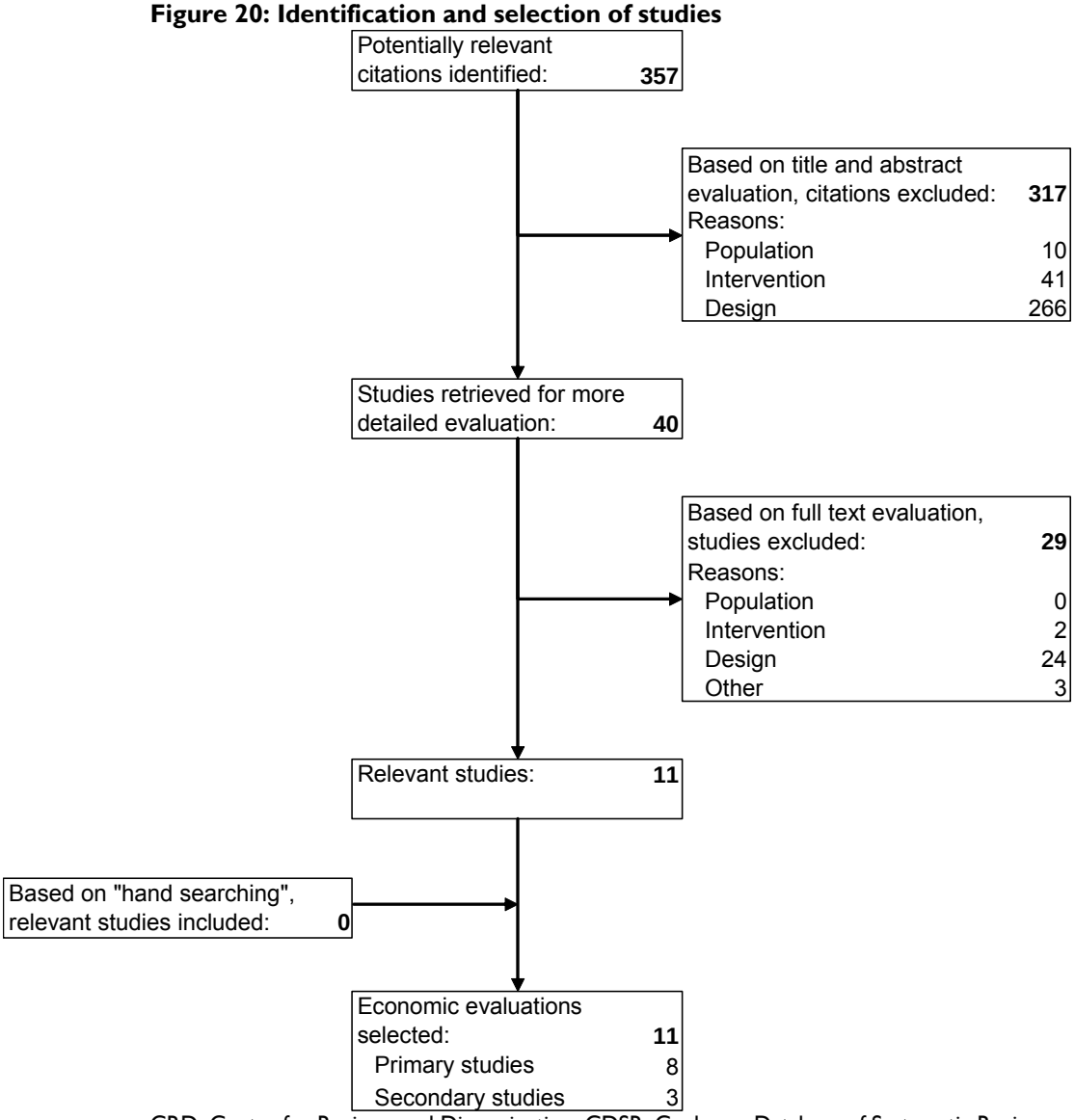
7.1.3 Selection process

After excluding 62 duplicates, 357 unique citations were identified. None of the six HTA citations[83-88] included a chapter on the cost-effectiveness of tiotropium in COPD patients, neither under the form of a literature review, nor as a separate economic evaluation. Beside the six HTA citations identified, the searches on the NHS EED (CRD), Medline(OVID), EMBASE, Econlit(OVID) and CDSR Economic Evaluation databases returned another 351 unique citations which were assessed against our inclusion criteria. Of the pooled 357 references identified, 317 did not meet the inclusion criteria based on title and abstract evaluation.

Of the 40 citations retained for full-text assessment, 29 were excluded: 24 studies had an inappropriate design, two did not meet the intervention criteria and 3 research articles could not be obtained.[89-91] One of the 29 studies excluded during this full-text assessment phase was the recently published 'Expected Value of Perfect Information' study of Oostenbrink et al.[92] This EVPI study was discarded because it was considered to be a methodological paper (rather than a genuine new economic evaluation) built on the model and the results of a previously published economic evaluation of tiotropium, already included in the current review.[93] Eleven studies pertaining to the economic evaluation of tiotropium were thus retained with our search strategy.[93-103]

Further exploration of the references of those articles and of web tools allowed the identification of seven potentially relevant additional citations that, finally, were all discarded. Three citations could not be found (paid access or unanswered requests to the authors),[104-106] two did not meet the inclusion criteria[107, 108] and another two[109, 110] were abstract presentations of the preliminary results of a previously selected full economic evaluation.[100] The flow chart of this selection process is presented in Figure 20.

Figure 20: Identification and selection of studies



CRD: Centre for Reviews and Dissemination; CDSR: Cochrane Database of Systematic Reviews

Altogether, eight out of the eleven studies selected by this iterative search procedure were full economic evaluations (primary studies) of tiotropium.[93, 94, 96, 98-102] Data from these studies were retrieved by using standard extraction sheets.

The remaining three studies were reviews of full economic evaluations (secondary studies) of various COPD maintenance therapies, including the use of tiotropium.[95, 97, 103] The relevant economic evaluations mentioned in these secondary studies were already identified in our search strategy.[96, 99, 100]

7.2 OVERVIEW OF THE ECONOMIC EVALUATIONS

An overview of the general characteristics of the eight economic evaluations is presented in Table 16. All studies were published after the year 2004. They were performed for the Netherlands,[99, 100] Canada,[99, 102] Switzerland,[98] Greece,[96] Spain,[93] and the US.[94, 101] Two studies were trial-based economic evaluations.[100, 102] The US studies were deterministic[94] or probabilistic[101] simulations using aggregated data depicting a typical COPD patient. The remaining four studies were Markov model-based economic evaluations, all built on an initial model developed by Oostenbrink et al.[99] for the Netherlands and Canada.

7.2.1 Analytical technique

Four studies reported their results both in terms of cost-utility ratios, with outcomes expressed as extra costs per quality-adjusted life-years (QALYs) (or months) gained, and cost-effectiveness ratios.[93, 96, 99, 102] Four other studies performed either a cost-utility[94] or a cost-effectiveness analysis (Table 16).[98, 100, 101]

Current pharmacotherapy for the maintenance treatment of COPD patients has not (yet) shown to substantially impact survival. Rather, studies have demonstrated that tiotropium reduces the exacerbations frequency and improves the physiological outcomes (e.g. FEV1), the morbidity, and the general health status of COPD patients.[45] Health-related quality-of-life measures (HRQoL) appear thus to be a relevant outcome for the evaluation of COPD treatments. Such quality-of-life (QoL) measures further facilitate comparison across different diseases and interventions. The studies performing a cost-effectiveness analysis did not use survival (life-years gained (LYG)) as a measure of outcome but rather surrogate measures of the drugs' clinical action: exacerbation-free months gained[93] or exacerbations avoided.[96, 98-102] In those studies, an exacerbation was defined as new onset or worsening of more than one symptom, such as cough, sputum, dyspnoea or wheeze, lasting for at least three days. In Onukwugha et al.,[101] exacerbations further had to give rise to an emergency room visit or to a hospitalisation.

7.2.2 Perspective

All studies adopted about the same Health Care Payer perspective in their base-case analysis. They all considered direct medical costs, defined as payments out of the Government health care budget, excluding the patients' share. A single study explicitly stated that patients' out-of-pocket expenses were also included in their base-case.[100]

Though they refer to this as being a "societal perspective", the patients' costs considered were all related to the health care sector (mainly drugs costs, and no such costs as travel expenses…), i.e. rather being a health care payer perspective (Table 16).

7.2.3 Time horizon and discount rate

The piggy-back trial-based economic evaluations[100, 102] were limited to a 1-year time horizon, which corresponds to the follow-up period of the trials they were based on.[53, 111] The US simulation-based economic evaluations[94, 101] and the three eldest model-based economic evaluations[96, 98, 99] also used a 1-year timeframe. This time horizon appears long enough to capture a significant number of important clinical endpoints such as exacerbations, and to capture seasonal variations. However, due to the progressive and chronic nature of COPD, and since this disease requires long-term maintenance treatment on a daily basis, Rutten-van Molken et al. argue costs and outcomes should be tracked for a longer timeframe, ideally over a patient's lifetime. In their model-based economic evaluation a longer 5-year timeframe was applied (Table 16).[93]

The studies with a one-year timeframe did not apply discounting. Conform to the Spanish guidelines,[112] Rutten-van Molken et al.[93] used a 6% discount rate to present the costs and outcomes of their 5-year model in present values.

Table 16: General characteristics of the economic evaluations

Author	Publication year	Country	Analysis		Time horizon	Discount rate	Costing perspective: cost items included
			CUA	CEA			
Najafzadeh et al.	2008	Canada	X	X	1 year	na	Direct medical costs[a]
Onukwugha et al.	2008	USA		X	1 year	na	Direct medical costs
Rutten-van Molken et al.	2007	Spain	X	X	5 years	6%[b]	Direct medical costs
Oba.	2007	USA	X		1 year	na	Direct medical costs
Maniadakis et al.	2006	Greece	X	X	1 year	na	Direct medical costs
Schramm et al.	2005	Switzerland		X	1 year	na	Direct medical costs
Oostenbrink et al.	2005	Canada The Netherlands	X	X	1 year	na	Direct medical costs
Oostenbrink et al.	2004	The Netherlands		X	1 year	na	Direct medical costs Patients' out-of-pocket costs

a. Direct medical costs are the costs borne by the Government health care budget; b. Discount rate for both costs and outcomes; CUA: cost-utility analysis; CEA: cost-effectiveness analysis.
The studies from Rutten-van Molken, Maniadakis and Oostenbrink were explicitly industry sponsored.

7.2.4 Population

Tiotropium is indicated for the maintenance treatment of COPD patients. In the trial-based economic evaluations,[100, 102] the population considered was more selective compared to the population targeted for routine use of tiotropium. In both studies, patients were included if they had a diagnosis of relatively stable COPD and an FEV1 ≤65% of predicted normal. Patients were also required to have a smoking history of at least 10 pack-years. Patients with a history of asthma, allergic rhinitis or atopy were excluded. In the model-based economic evaluations,[93, 96, 98, 99] the population identified for therapy with tiotropium was less restricted and included patients with a diagnosis of COPD whose disease severity was classified as moderate, severe or very severe (stage II-IV). The disease severity was defined according to the GOLD criteria (see Figure 8).[113]

Patients with mild COPD and patients with asthma or respiratory disorders were thus excluded, either explicitly in the RCT-based studies[100, 102] or implicitly in the modelling studies.[93, 96, 98, 99]

In Oba,[94] the population consisted in moderate (stage II) and severe (stage III) COPD patients, as defined by the GOLD criteria. By contrast with the other studies, the population simulated in Onukwugha et al.[101] included patients with mild COPD, besides those with moderate to very severe COPD (according to the GOLD criteria), on the grounds that such patients would also be offered tiotropium in daily practice.

The extent to which COPD severity impacts the cost-effectiveness of tiotropium was explored by sub-groups analyses in five studies, assuming that (at the start of the model) all patients have either mild,[101] moderate, severe or very severe COPD.[93, 96, 99, 101, 102]

7.2.5 Intervention / comparators

Tiotropium is a long-acting inhaled anticholinergic that provides 24 hours bronchodilation with once-daily dosing. It is used for the maintenance treatment of COPD. In the economic evaluations, alternative active treatments to tiotropium consisted of ipratropium and salmeterol. Ipratropium is a short-acting inhaled anticholinergic, which has to be used four times daily. Salmeterol is a long-acting inhaled beta-2-agonist, which has to be used twice daily.

All but two studies[96, 102] compared tiotropium with ipratropium. Four studies further compared tiotropium with salmeterol[93, 96, 98, 99] and one study with placebo.[94] One study further assessed the impact of administering concomittant medications in COPD.

This study compared tiotropium monotherapy with a combined tiotropium plus salmeterol therapy and with a combined tiotropium plus salmeterol/fluticasone therapy.[102]

The four economic evaluations[93, 96, 98, 99] based upon the Oostenbrink et al.[99] markov probabilistic model used the same clinical trial to derive their transition probabilities: Vincken et al.[53] for tiotropium against ipratropium and Brusasco et al.[30] for tiotropium against salmeterol. In Oba,[94] the Vincken et al.[53] trial was also used for comparing tiotropium with ipratropium, and the results of two placebo-controlled trials[30, 52] were pooled for comparing tiotropium with placebo (Table 17). Since it does not represent the standard of care, placebo is however not considered to be the appropriate comparator and these results will therefore not be discussed. In Onukwugha et al.,[101] the difference in exacerbation-related hospitalisation and ER visit rates between tiotropium and ipratropium was based on the trial of Niewoehner et al.[54] Although this trial was conducted in a population comparable to that in Onukwugha et al.,[101] the comparator to tiotropium in Niewoehner et al.[54] was placebo and not ipratropium.

Table 17: Comparators to tiotropium

Author	Publication year	Tiotropium compared with					
		Ipratropium	Trial source	Salmeterol	Trial source	Other	Trial source
Najafzadeh et al.	2008			X[a]	Aaron et al., 2007	X[b]	Aaron et al., 2007
Onukwugha et al.	2008	X	Niewoehner et al., 2005				
Rutten-van Molken et al.	2007	X	Vincken et al., 2002	X	Brusasco et al., 2003		
Oba.	2007	X	Vincken et al., 2002			X[c]	Casaburi et al., 2002 Brusasco et al., 2003
Maniadakis et al.	2006			X	Brusasco et al., 2003		
Schramm et al.	2005	X	Vincken et al., 2002	X	Brusasco et al., 2003		
Oostenbrink et al.	2005	X	Vincken et al., 2002	X	Brusasco et al., 2003		
Oostenbrink et al.	2004	X	Vincken et al., 2002				

a. Tiotropium monotherapy is compared with a combined tiotropium + salmeterol therapy; b. Tiotropium monotherapy is compared with a combined tiotropium + salmeterol/fluticasone therapy; c. Tiotropium is compared with placebo.

7.2.6 Costs

Whenever possible, the original unit costs of the interventions (tiotropium, ipratropium and salmeterol) and of COPD treatment (maintenance therapy and exacerbation) were reported in tables to allow the comparison between the studies. To improve this comparability, original costs were standardized in common euros of the year 2006 (for Belgium) using Consumer Price Indices and Purchasing Power Parities (Table 18).

Table 18: Correction for price inflation and currency conversion

Author	Publication year	Country	Costing year	Original currency	CPI multiplicator[a]	PPP multiplicator[b]
Najafzadeh et al.	2008	Canada	2006	CAN$	1.00000	0.74667
Onukwugha et al.	2008	USA	2004	$	1.06728	0.89600
Rutten-van Molken et al.	2007	Spain	2005	€	1.03516	1.18206
Oba.	2007	USA	2005	$	1.03226	0.89600
Maniadakis et al.	2006	Greece	2005	€	1.03196	1.27092
Schramm et al.	2005	Switzerland	c	CHF	1.02244	0.52706
Oostenbrink et al.	2005	Canada	2001	€	1.11590	d
		The Netherlands	2001	€	1.09842	1.00112
Oostenbrink et al.	2004	The Netherlands	2001	€	1.09842	1.00112

a. From costing year to 2006; b. To Belgian euro of the year 2006; c. Not mentioned. The year before the publication year was taken (i.e. 2004); d. Costs already converted in euro by Oostenbrink et al.(2005) in the original study (Can$1 = €0.62, exchange rate April 2004); Consumer Price Indices (CPI) and Purchasing Power Parities (PPP) were obtained from the OECD website, accessed on January 17, 2008 (www.stats.oecd.org).

7.2.6.1 Interventions

With the exception of Oba et al.[94] there was no great variability in the reported prices of tiotropium, i.e. from €1.6 to €2.2 per day. In Oba, the price of tiotropium was double the lowest price of this range, with €3.1 per day (Table 19). This discrepancy may be due to several factors such as country differences in drug prices, the bargaining power of local authorities or groups, the costing year, etc.

Compared to tiotropium, ipratropium and salmeterol were less expensive drugs. In all studies, the price of salmeterol was about 60% (€0.88 per day in Greece[96] and Switzerland[98]) to 80% (€1.35 per day in Canada and The Netherlands[99]) of that of tiotropium. There was much more discrepancy in the relative price of ipratropium which was about 11% (€0.23 per day in Spain[93]) to 73% (€2.26 per day in the USA[94]) of the price of tiotropium.

All other things being equal, the higher the differences between the prices of tiotropium and its comparators, the less favourable the study results.

Table 19: Daily cost of tiotropium, salmeterol and ipratropium

Author	Publication year	Country	Original cost per day			Cost in 2006 Belgian euro		
			Tiotropium	Salmeterol	Ipratropium	Tiotropium	Salmeterol	Ipratropium
Najafzadeh et al.[a]	2008	Canada	CAN$2.25	CAN$1.76	-	€1.68	€1.31	-
Onukwugha et al.	2008	USA	$2.28	-	$0.67	€2.18		€0.64
Rutten-van Molken et al.	2007	Spain	€1.80	€1.20	€0.19	€2.20	€1.47	€0.23
Oba.	2007	USA	$3.35	-	$2.44	€3.10	-	€2.26
Maniadakis et al.	2006	Greece	€1.19	€0.67	-	€1.56	€0.88	-
Schramm et al.	2005	Switzerland	CHF2.94	CHF1.64	CHF0.83	€1.58	€0.88	€0.45
Oostenbrink et al.	2005	Canada	€1.51	€1.21	€0.54	€1.69	€1.35	€0.60
		Netherlands	€1.57	€1.24	€0.69	€1.73	€1.36	€0.76
Oostenbrink et al.	2004	Netherlands	€1.57	-	€0.33	€1.73	-	€0.36

a. The original cost of the combined salmeterol/fluticasone treatment in Najafzadeh et al.(2008) was CAN$4.64 per day, corresponding to €3.46 in 2006 Belgian euro.

7.2.6.2 Maintenance therapy and exacerbations

The measurement of the resources used for COPD treatment was derived from (local) literature in three studies[93, 94, 98] and was done by means of observational data in the five other studies. The sources used to obtain observational data were clinical trials,[99, 100, 102] prospective observational studies[99] or databases.[96, 101]

The costs per patient and per year associated with each severity stage of COPD maintenance therapy were rather comparable between studies. These costs (in 2006 euros) ranged from €370[99] to €530[93] for moderate COPD, from €470[99] to €720[93] for severe COPD and from €670[99] to €1000[93] for very severe COPD (Table 20).

Care for COPD exacerbations is the main cost-driver. COPD exacerbations usually require hospitalisations which represents nearly 70% of all direct medical costs associated with this disease.[114] The capacity of tiotropium in reducing those exacerbations and the resulting cost reductions will thus have a large impact on the cost-effectiveness results. There was great variability in the reported treatment costs for exacerbations. A non-severe exacerbation costs between €47 in Canada[99] against nearly €1000 in Greece.[96] Similarly, a severe exacerbation costs €2660 in Spain[93] against €4400 in Greece,[96] and even over €4600 in the US (i.e. €1548 per hospital day with a median length of stay of 3 days).[101] The other US study did not stratify exacerbations according to their severity and a case was assumed to cost €4700 on average.[94] Though these differences certainly reflect national disparities in health practice, the total costs avoided by tiotropium will be higher in countries where exacerbation treatment costs more.

Table 20: Costs of COPD maintenance therapy (per patient per year) and exacerbations (per exacerbation)

Author	Publication year	Country	Original cost					Cost in 2006 Belgian €				
			Maintenance therapy			Exacerbation		Maintenance therapy			Exacerbation	
			Moderate	Severe	Very severe	Non-severe	Severe	Moderate	Severe	Very severe	Non-severe	Severe
Najafzadeh et al.	2008	Canada	[a]	-	-	-	-	-	-	-	-	-
Onukwugha et al.	2008	USA	-	-	-	$277[b]	$1619[c]	-	-	-	€265[b]	€1548[c]
Rutten-van Molken	2007	Spain	€430	€587	€818	€83	€2176	€526	€718	€1001	€102	€2663
Oba.	2007	USA	[d]	-	-	$5100		-	-	-	€4717	
Maniadakis et al.	2006	Greece	€360	€437	€570	€745	€3334	€472	€573	€748	€977	€4373
Schramm et al.	2005	Switzerland	[e]	-	-	-	-	-	-	-	-	-
Oostenbrink et al.	2005	Canada	€329	€421	€602	€42	€2911	€367	€470	€671	€47	€3248
		Netherlands	€409	€533	€663	€316	€3695	€450	€586	€729	€347	€4063
Oostenbrink et al.	2004	Netherlands	[a]	-	-	-	-	-	-	-	-	-

a. Trial-based economic evaluation: unit costs are not reported in this format; b. Cost per exacerbation resulting in an ER visit; c. Cost per per hospital day related to a COPD exacerbation. The median length of stay per hospitalisation is 3 to 4 days for mild, moderate or severe COPD, and 6.25 days for very severe COPD; d. There is no distinction between non-severe and severe COPD exacerbation. Costs for COPD maintenance therapy were either ignored or not reported; e. Unit costs for maintenance therapy and exacerbations are not reported.

7.2.6.3 Indirect (time) costs

The number of days patients were unable to perform most of their usual daily activities, including paid work, was investigated in the Dutch study.[100] It was estimated that, compared to ipratropium, the number of inactivity days was 18% less with tiotropium (24 inactivity days against 29), although this difference was not statistically significant. In this study, inactivity days were not valued since less than 10% of the study population had paid employment. This confirms the argument that the calculation of indirect (productive time) costs is less relevant in a population of moderate and severe COPD patients, because such patients are considered functionally disabled and most of them are early retirees.[97] Time costs outside the labour force (home activities) may however still be relevant to consider.

7.2.7 Outcomes

The utility values used in the five studies performing a cost-utility analysis,[93, 94, 96, 99, 102] together with the instrument used to describe the health states, are reported in Table 21.

Table 21: Utility weights

Author	Publication year	Country	COPD states			Exacerbations		Instrument
			Moderate	Severe	Very severe	Non-severe	Severe	
Najafzadeh et al.	2008	Canada	[a]	-	-	-	-	SGRQ
Rutten-van Molken et al.	2007	Spain	0.81	0.76	0.66	- 15%[b]	- 50%[b]	EQ-5D
Oba.	2007	USA	[a]	-	-	-	-	SGRQ
Maniadakis et al.	2006	Greece	0.76	0.75	0.55	- 15%[b]	- 50%[b]	EQ-5D
Oostenbrink et al.	2005	Canada The Netherlands	0.76	0.75	0.55	- 15%[b]	- 50%[b]	ED-5D

a. No details provided; b. Reduction in utility value during the month following an exacerbation; SGRQ: St George's Respiratory Questionnaire.

In Maniadakis et al.[96] and Oostenbrink et al.,[99] the utility scores of each COPD state were based on the same observational study.[115] This study was performed in COPD patients classified according to their disease severity, and used the generic EQ-5D instrument to obtain the health-related quality of life measures.

Those values were used interchangeably between three different countries (Greece, Canada and The Netherlands) without discussion about potential problems of transferability.

In Rutten-van Molken et al.,[93] generic EQ-5D utility scores were obtained from patients enrolled in a COPD trial (UPLIFT[116]) and were adjusted for the Spanish population.[117] During the month following an exacerbation, it was estimated (or rather assumed, see discussion chapter 9) that utility values would reduce by 15% in case of non-severe exacerbation, and by 50% in case of severe exacerbation.[93, 96, 99]

In Oba,[94] incremental QALYs were calculated based on the improvement in QoL reported in the trials comparing tiotropium with placebo[30, 52] or ipratropium.[53] In those trials, QoL was estimated by the disease-specific St George Respiratory Questionnaire. Based on an algorithm,[118] Oba[94] converted those health-related improvements in EQ-5D scores. In Najafzadeh et al.,[102] utilities were calculated from the SGRQ scores of the patients in each treatment arm of the Optimal Therapy trial,[111] according to the algorithm published by Meguro.[119]

7.2.8 Effectiveness / modelling

Table 22 provides a comparison of the values of the three main health outcomes reported by the studies. For each outcome considered, there was a great level of consistency between the studies, whether model-based,[93, 96, 98, 99] RCT-piggy-backed[100, 102] or simulation-based.[94, 101]

Compared to salmeterol, the gain in QALYs obtained by tiotropium was small and varied between 0.02 (-0.08–0.13) QALYs (7 days) in a 1-year timeframe[96, 99] to 0.14 (-0.16–0.49) QALYs (51 days) in a 5-year timeframe.[93] In Najafzadeh et al.,[102] the addition of salmeterol to the tiotropium monotherapy resulted in a small mean loss of -0.005 (-0.009–0.003) QALYs over a year, and the addition of both salmeterol and fluticasone to tiotropium resulted in a small gain of 0.006 (-0.014–0.025) QALYs.[102] Slightly higher improvements with tiotropium were reported by Oba,[94] with 0.036 (0.006–0.012) QALYs gained (13 days) compared to ipratropium and 0.032 (0.014–0.050) QALYs gained (12 days) compared to placebo in a 1-year timeframe.

The mean number of exacerbations avoided per patient per year varied between 0.17 (-0.02–0.37)[96, 99] to 0.18[98] when tiotropium was compared to salmeterol, and between 0.27 (0.02–0.52)[100] to 0.32[98] when tiotropium was compared to ipratropium.

In Rutten-van Molken et al.,[93] the mean difference in exacerbation-free months was in favour of tiotropium with 1.54 (-2.5–6.8) months gained over salmeterol.

Table 22: Mean and incremental health outcomes

Author	Publication year	Mean health outcomes			Incremental outcomes: Tiotropium versus		
		Tiotropium	Salmeterol	Ipratropium	Salmeterol	Ipratropium	Other
Quality-adjusted life-years							
Najafzadeh et al.	2008	Not reported	Not reported	-	-0.005 (-0.009–0.003)[a]	-	0.006(-0.014–0.025)[b]
Rutten-van Molken et al.	2007	3.15 (2.99–3.31)	3.02 (2.73–3.31)	3.00 (2.61–3.39)	0.14 (-0.16–0.49)	c, d	-
Oba.	2007	Not reported	-	Not reported	-	0.036 (0.012–0.060)	0.032 (0.014–0.050)[e]
Maniadakis et al.	2006	0.70 (0.63–0.77)	0.68 (0.60–0.75)	-	0.02 (-0.08–0.13)	-	-
Oostenbrink et al.	2005	0.70 (0.63–0.77)	0.68 (0.61–0.76)	0.67 (0.59–0.75)	0.02 (-0.08–0.12)	d	-
Exacerbations							
Najafzadeh et al.	2008	1.56 (1.34–1.81)	1.69(1.47–1.94)[a]	-	Not reported	-	No reported[f]
Onukwugha et al.	2008	Not reported	-	Not reported	-	Not reported	-
Rutten-van Molken et al.	2007	3.50 (3.23–3.77)	4.16 (3.38–4.94)	4.71 (3.65–5.77)	Not reported	d	-
Maniadakis et al.	2006	0.85 (0.80–0.91)	1.02 (0.84–1.21)	-	0.17 (-0.02–0.37)	-	-
Schramm et al.	2005	0.89	1.07	1.21	0.18	0.32	-
Oostenbrink et al.	2005	0.85 (0.80–0.91)	1.02 (0.84–1.22)	1.14 (0.92–1.40)	0.17 (-0.02–0.37)	d	-
Oostenbrink et al.	2004	0.74 (0.58–0.90)	-	1.01 (0.81–1.21)	-	0.27 (0.02–0.52)	-
Exacerbation-free months							
Rutten-van Molken et al.	2007	46.83 (44.62–48.98)	45.29 (41.13–49.45)	44.89 (39.28–50.50)	1.54 (-2.5–6.8)	d	-
Maniadakis et al.	2006	11.15 (11.09–11.20)	10.98 (10.79–11.16)	-	Not reported	-	-

a. Combined tiotropium + salmeterol therapy; b. Tiotropium versus a combined tiotropium + salmeterol/fluticasone therapy; c. Each treatment option is compared with the next best alternative in terms of effectiveness. Ipratropium is thus an alternative to salmeterol, not to tiotropium; d. The time horizon in Rutten-van Molken et al.(2007) is 5 years, while it is 1 year in other studies; e. Tiotropium versus placebo; f. The mean number of exacerbations of the combined tiotropium + salmeterol/fluticasone treatment arm was 1.35 (1.16–1.55) for the trial duration.

Although mostly positives, the mean incremental outcomes (whether QALYs gained, exacerbations avoided or exacerbation-free months gained) between tiotropium and salmeterol were associated with large 95% confidence intervals crossing zero.[93, 96, 99, 102] This indicates highly uncertain results since tiotropium may yield similar or even worse health outcomes than this comparator. It is therefore crucial for studies evaluating the cost-effectiveness of COPD treatments to handle the efficacy data's uncertainty via statistical analyses. This is a weakness of the study of Schramm et al.[98] that did not perform such statistical analysis and only reported mean positive results.

7.2.9 Sensitivity analyses

Uncertainty (whether methodological, data or generalizability uncertainty) in economic evaluations of health care interventions is omnipresent and should be properly accounted for and handled in (probabilistic) sensitivity analyses.

With this respect, six studies developed a probabilistic model and performed a probabilistic sensitivity analysis.[93, 96, 99-102] These studies presented their results using cost-effectiveness acceptability curves and the distribution of the simulations over the cost-effectiveness plane. Scenario analyses were also performed to estimate whether some specific parameters were decisive for the cost-effectiveness ratio: subgroup analyses for the distribution of the patients over the disease stages,[93, 96, 99, 101, 102] for Belgian patients and costs,[100] for exacerbation costs[99] and for utility values.[99]

The analysis of uncertainty in Oba[94] was limited to a deterministic sensitivity analysis where the results of a best- and worst-case scenario were presented by varying the amount of QALYs gained and the costs of hospitalizations and scheduled visits. Likewise, Schramm et al.[98] only performed a univariate sensitivity analysis varying the price of tiotropium.

7.3 RESULTS

7.3.1 Base-case results

7.3.1.1 Tiotropium versus ipratropium

The four studies directly assessing the cost-effectiveness of tiotropium compared to ipratropium found that tiotropium resulted in a significant gain in health outcome.[94, 98, 100, 101] Two of those studies further reported that tiotropium was cost-saving since it generated mean savings of €360[94] and €1030[98] per year (see appendix for the mean and incremental total costs reported by the studies). However, both studies did not compute confidence intervals around these mean cost values. In Oostenbrink et al.,[100] tiotropium also significantly reduced exacerbations but at an either lower (in 24% of cases) or higher cost (in 74% of cases) than ipratropium (Table 23). Based on the ratio of the mean incremental costs to the mean incremental effects, they found a cost-effectiveness ratio of €667 per exacerbation avoided. In Onukwugha et al.,[101] the mean ICER per exacerbation avoided was $2280 (284 - 4276).

7.3.1.2 *Tiotropium versus salmeterol*

The cost-effectiveness of tiotropium compared to salmeterol appears more controversial. Two studies found that there was almost neutrality between the two alternatives in terms of incremental costs and QALYs, as the dots simulated were almost evenly scattered around the four quadrants of the cost-effectiveness plane (Table 23).[96, 99] Only the 5-year-long study of Rutten-van Molken et al.[93] demonstrated a clinical advantage (in terms of QALYs gained) for tiotropium since the proportion of simulations in the right quadrants of the cost-effectiveness plane was approximately 80%, compared to about 50% in Greece, Canada and The Netherlands.[96, 99] The gain in QALYs remained however small (0.14) and non-significant (95% CI: -0.16–0.49). Based on the ratio of the mean incremental costs to the mean incremental QALYs, they found a cost-effectiveness ratio of €4120 per QALY gained and further calculated that, for any value of the ceiling ratio above €8160 per QALY gained, tiotropium should be adopted because it resulted in the highest expected net benefit. However, although tiotropium had the highest probability of being optimal above the ceiling of €8160 per QALY gained, this probability was at most 58%.

More favourable results were observed when the cost-effectiveness of tiotropium versus salmeterol was expressed in terms of exacerbations avoided. In Schramm et al.,[98] tiotropium was found to be both less expensive and more clinically effective (i.e. dominant) than salmeterol. However, this study did not perform a statistical analysis of its results. In Greece, Canada and The Netherlands, roughly 95% of the iterations were found in the right-quadrants of the cost-effectiveness plane, demonstrating the large (but non-significant) clinical advantage of tiotropium over salmeterol. In Greece[96] and in The Netherlands,[99] tiotropium further resulted in net savings (lower-right quadrant) in about 64% and 42% of the simulations, respectively. In both countries those favourable results were mainly driven by the large savings due to the reduction in exacerbations since the cost of treating a severe exacerbation was much higher (above €4000) than the cost assumed in other studies (Table 20).

Oostenbrink et al.[99] computed the net benefit of each medical treatment and estimated which option resulted in the highest expected net benefit for various threshold values. The net benefit of an option was calculated as its total costs (C) minus its effects (E) multiplied by the threshold value (C – (E * threshold)). In The Netherlands, the threshold value above which tiotropium resulted in the highest expected net benefit was €0 per exacerbation. In Canada, tiotropium resulted in the highest expected net benefit for any value of the threshold above €10 per exacerbation. Below this threshold, salmeterol was the optimal option.[99]

In the 5-year Spanish model,[93] about 25% of the dots were found in the left-quadrants, signifying worse health outcome (exacerbations-free months) for tiotropium. Therefore, the threshold value above which tiotropium was the optimal option (€640 per exacerbation-free month) was higher than that reported for The Netherlands or Canada.

In Najafzadeh et al.,[102] the effectiveness (in terms of QALYs gained or exacerbations avoided) of adding salmeterol or salmeterol/fluticasone to tiotropium was not found to be significantly different from that of tiotropium monotherapy. In this study the combination of salmeterol plus tiotropium was less effective and more costly (i.e. dominated) than tiotropium monotherapy, and the combination of salmeterol/fluticasone plus tiotropium was associated with an incremental cost of more than $200 000 per QALY compared to tiotropium alone.

Table 23: Results of the studies

Author	Publication year	Country	Results		
			Incremental cost-effectiveness ratio	Cost-effectiveness plane[a]	
Tiotropium versus ipratropium					
Onukwugha et al.	2008	USA	*Outcome: exacerbations avoided*	0%	100%
			$2280 (284–4279) per exacerbation avoided		
Oba.	2007	USA	*Outcome: QALY gained*		
			Tiotropium dominant		-
Schramm et al.	2005	Switzerland	*Outcome: exacerbations avoided*		
			Tiotropium dominant		-
Oostenbrink et al.	2004	Netherlands	*Outcome: exacerbation avoided*		
			€667 per exacerbation avoided[b]	2%	74%
			Prob Tiotropium is cost-effective at €0 threshold: 24%		24%
			Prob Tiotropium is cost-effective at €2000 threshold: 80%		
Tiotropium versus salmeterol					
Rutten-van Molken	2007	Spain	*Outcome: QALY gained*		
			€4118 per QALY gained[b]	15%	68%
			Below €8157 threshold, highest net benefit obtained by Ipratropium	5%	12%
			Above €8157 threshold, highest net benefit obtained by Tiotropium		
			Outcome: exacerbation-free month gained		
			€360 per exacerbation-free month gained[b]	18%	65%
			Below €639 threshold, highest net benefit obtained by Ipratropium	8%	9%
			Above €639 threshold, highest net benefit obtained by Tiotropium		
Maniadakis et al.	2006	Greece	*Outcome: QALY gained*		
			Unconclusive results	Dots evenly distributed across the 4 quadrants	
			Outcome: exacerbation avoided		
			Prob Tiotropium is cost-effective at €0 threshold: 65%	3%	32%
			Prob Tiotropium is cost-effective at €1000 threshold: 77%	1%	64%
			Prob Tiotropium is cost-effective at €20000 threshold: 95%		
Schramm et al.	2005	Switzerland	*Outcome: exacerbations avoided*		
			Tiotropium dominant		-
Oostenbrink et al.	2005	Canada	*Outcome: QALY gained*		
			Unconclusive results	Dots evenly distributed across the 4 quadrants	
			Outcome: exacerbation avoided		
			Below €10 threshold, highest net benefit obtained by Salmeterol	5%	95%
			Above €10 threshold, highest net benefit obtained by Tiotropium		
		Netherlands	*Outcome: QALY gained*		
			Unconclusive results	Dots evenly distributed across the 4 quadrants	
			Outcome: exacerbation avoided		
			Above €0 threshold, highest net benefit obtained by Tiotropium		
			Prob Tiotropium is cost-effective at €0 threshold: 43%	4%	53%
			Prob Tiotropium is cost-effective at €500 threshold: 60%	1%	42%
Tiotropium versus tiotropium + salmeterol					
Najafzadeh et al.	2008	Canada	*Outcome: QALY gained*		
			Tiotropium alone dominant		-
			Outcome: exacerbation avoided		
			Tiotropium alone dominant		-
Tiotropium + salmeterol / fluticasone versus tiotropium					
Najafzadeh et al.	2008	Canada	*Outcome: QALY gained*		
			CAN$243 180 per QALY gained		-
			Prob Tiotropium alone is cost-effective at $50 000 threshold: 80%		
			Outcome: exacerbation avoided		
			CAN$6510 per exacerbation avoided		-

a. The horizontal axis represents the difference in health outcome, the vertical axis represents the difference in costs; b. Ratio of the mean incremental cost to the mean incremental outcome.

7.3.2 Sensitivity analyses

7.3.2.1 Patient sub-groups

Distribution of COPD patients among the disease stages

To reflect the progressive nature of COPD, patients simulated in model-based studies were classified into three (or four[101]) disease states of increasing severity. The baseline distributions of the patients among those disease states are presented in Table 24.

Table 24: Baseline distribution of COPD patients among disease states

Author	Publication year	Country	Distribution of COPD patients		
			Moderate	Severe	Very severe
Najafzadeh et al.	2008	Canada	-	-	-
Onukwugha et al.[a]	2008	USA	41%	40%	11%
Rutten-van Molken et al.	2007	Spain	55%	35%	10%
Oba.	2007	USA	-	-	-
Maniadakis et al.	2006	Greece	20%	50%	30%
Schramm et al.	2005	Switzerland	25%	50%	25%
Oostenbrink et al.	2005	Canada The Netherlands	25%	50%	25%
Oostenbrink et al.	2004	The Netherlands	-	-	-

a. There were also 8% of the COPD patients in the mild disease severity stage.

The impact of COPD disease severity on the cost-effectiveness of tiotropium was investigated in five studies.[93, 96, 99, 101, 102] These studies assumed that, at the start of the model, 100% of the patients had either mild,[101] moderate, severe or very severe COPD, or they restricted their calculations to subgroups of patients defined by COPD severity.[102] In Spain[93] and in Canada,[99] the threshold value above which tiotropium had the highest expected net benefit increased with the severity of COPD. Likewise, in the most recent studies,[101, 102] the ICERs across disease severity groups showed a trend towars more favourable results with the most severe COPD subpopulations. By contrast, in Greece[96] and in the Netherlands,[99] there was no such gradient between the patients' disease severity and the cost-effectiveness of tiotropium since results did not deviate much from those of the baseline scenario.

Belgian patients

The trial-based economic evaluation of Oostenbrink et al.[100] reported the results of a separate analysis only including the subset of Belgian patients enrolled in the trial (representing about 15% of all patients). The resources used by those patients were multiplied by Belgian unit costs, making the results specific for Belgium. The daily prices of tiotropium and ipratropium (metered dose inhaler) were estimated to be €1.80 (€2 in 2006 €) and €0.29 (€0.32 in 2006 €). Compared to ipratropium, tiotropium resulted in 0.43 (-0.57–1.43) exacerbation avoided per patient per year, and in an incremental cost of €159 (-1086–1404). The mean cost per exacerbation avoided was €371. There were large confidence intervals around the mean incremental costs and outcomes, mainly due to the small number of Belgian patients in this sub-study, i.e. 50 patients in the tiotropium group and 25 in the ipratropium group.

7.3.2.2 Exacerbations

Oostenbrink et al.[99] demonstrated that the main driver of cost-effectiveness was the difference in exacerbation rates between the treatment groups rather than the difference in disease-state transition rates. Indeed, applying similar exacerbation rates to treatment groups considerably increased the ceiling ratios above which tiotropium is the optimal treatment, i.e. €8500 per exacerbation avoided in The Netherlands and €11000 in Canada, instead of €0 and €10, respectively, in the base-case.

7.3.2.3 Utility values

One study[99] used alternate utility values in their sensitivity analysis. The weights attributed to the disease states were 0.81, 0.72 and 0.67[120] instead of 0.76, 0.75 and 0.55[115] (base-case) for moderate, severe and very severe COPD, respectively. These alternate utility values did however not change the baseline studies' results.

7.4 DISCUSSION

Based on the results of the studies, compared to ipratropium, tiotropium is found to significantly improve the health gains expressed as QALYs gained or exacerbations avoided. Tiotropium was further estimated to be cost-saving compared to ipratropium in two studies[94, 98] and was associated with a incremental cost of €667 to $2280 (284–4276) per exacerbation avoided.[100, 101] It should be noted however that both studies reporting cost-savings for tiotropium were deterministic and no confidence interval around the total incremental costs were reported. Further, although the ICERs reported by Oostenbrink et al.[100] and Onukwugha et al.[101] were considered to be acceptable (at least in the most severe disease groups) by their authors, the attractiveness of such ICERs expressed as disease specific outcomes are rather hard to appraise.

Compared to salmeterol, tiotropium did not demonstrate a clear and significant clinical improvement in terms of QALYs gained. The mean QALYs gained by tiotropium were extremely small (0.02 to 0.14 QALYs gained) and tiotropium was further found to result in worse health outcomes (left-quadrants of the cost-effectiveness plane) than salmeterol in 20%[93] to 50%[96, 99] of the cases. Results with outcomes expressed in natural units (exacerbation avoided) were more in favour of tiotropium though still not significant. The reported proportions of iterations in the left-quadrants of the cost-effectiveness plane for this outcome were smaller than for QALYs: 4-5% in Greece, Canada and the Netherlands,[96, 99] to 26% in Spain.[93] Based on the results of a deterministic model, tiotropium was found to dominate salmeterol.[98] The threshold values above which tiotropium had the highest probability of being optimal compared to salmeterol were €0 per exacerbation avoided in The Netherlands, €10 per exacerbation avoided in Canada and €640 per exacerbation-free month in Spain. Again such disease specific outcomes are hard to assess.

Based on the results of a single study,[102] combination therapies with tiotropium plus salmeterol or with tiotropium plus salmeterol/fluticasone were not found attractive compared to tiotropium monotherapy.

Given the great uncertainty of the results it appears surprising that not all studies performed an extensive sensitivity analysis on those results. The model-based evaluation of Schram et al.[98] was analysed deterministically and only univariate sensitivity analyses were performed. The model developed by Oba[94] was rather a simulation based on aggregated data and reported only a best- and worst-case scenario analysis. In contrast, the guidelines recommend probabilistic modelling and probabilistic sensitivity analyses.

It may also be noticed that some of the studies were industry sponsored. This may have an influence on the objectivity of the study results. However, there is no hard evidence to prove this.

The severity levels assessed in the economic evaluations were mostly moderate to very severe COPD (moderate to severe in Oba[94] and mild to very severe in Onukwugha et al.[101]). Since moderate to severe COPD patients incur almost two to three times the cost of mild COPD patients, results of the evaluations reviewed here are only generalizable to the moderate to severe COPD population. Further, extrapolation of the study results to the Belgian context could only be done with great caution. The main factors precluding the transferability of the results to Belgium appear to be the relative costs of tiotropium and its comparators, and the costs of COPD treatment (more specifically for exacerbations). These costs are likely to vary between countries, due to differences in price levels and treatment practices. Since it appears to be an influential input on the cost-effectiveness results (at least in some studies,[93, 99]) the initial

distribution of patients among COPD disease stages should also reflect the Belgian COPD population.

With the exception of the longer-term Spanish study,[93] the cost-utility analyses included in this review of the literature did not find that the number of QALYs was different between treatment groups. At present, utility is one of the main drivers in the calculations of QALYs for COPD treatments since they do not generally improve survival. Robust estimates of the utilities attached to each COPD severity stage and exacerbations are therefore crucial. The UPLIFT trial[116] used by Rutten-van Molken et al.[93, 121] paved the way in this direction by eliciting EQ-5D scores per COPD disease severity state in a subset of about 1200 patients. However, accurate utility (or disutility) scores for exacerbations are still lacking. Studies in this review usually document a decrease in utility in case of an exacerbation of minus 15%[122] and minus 50%[123] for a non-severe and a severe exacerbation, respectively. Nevertheless, the referenced papers to support these figures do not mention such data. The need for using QALYs as outcome measure for the economic evaluation of COPD treatments is further reinforced by the fact that ICERs expressed with disease specific outcomes, as currently reported in the current economic evaluations, are difficult to interprete.

7.5 CONCLUSION

Compared to ipratropium, tiotropium significantly improved the health gains and appeared to be cost-effective. By contrast, whether or not tiotropium might be considered as the most optimal option compared to salmeterol is hard to assess. Indeed, tiotropium did not offer any significant health gain in QALYs or disease specific outcomes. Further, the interpretation of the cost-effectiveness results of those studies is hampered by the fact that disease-specific outcomes were used.

The sensitivity analyses of the studies showed that the results were most likely to be sensitive to the initial distribution of patients between the disease severity groups and to the costs and rates of exacerbations. Since these inputs, together with the prices of the interventions, are country-specific, and since the available cost-effectiveness evidence for tiotropium appears controversial, an economic evaluation tailored to the Belgian COPD population would be highly informative.

Key points

- **Based on previous published economic evaluations:**
  - Compared to ipratropium, tiotropium significantly improves the health gains (in terms of QALYs gained or exacerbations avoided), and appears to be cost-effective.
  - Compared to salmeterol, health gains (whether in QALYs or in exacerbations avoided) obtained by tiotropium are associated with non-significant and wide confidence intervals. Due to these large uncertainties, no clear conclusion on its cost effectiveness could be drawn.
  - Therapies combining tiotropium with salmeterol or salmeterol/fluticasone were not found cost-effective compared to monotherapies with tiotropium.
- **The interpretation of the results is hampered by the fact ICERs are mostly expressed in terms of disease-specific outcomes.**
- **The cost-effectiveness of tiotropium is most likely influenced by the prices of the interventions, the patients disease severity and the cost and rates of an exacerbation.**
- **Since patients with mild COPD were generally not considered in the economic evaluations of tiotropium, results are only generalizable to the moderate to severe COPD population.**
- **Transferability of the results to the Belgian context should be done with caution since price levels and the distribution of COPD patients to different disease severities is likely to vary across countries.**

8 BELGIAN DATA

8.1 PHARMANET DATA

Pharmanet collects, per prescriber, data on reimbursed prescription drugs that are delivered by a public pharmacy. The most important goal of Pharmanet is to inform the prescriber about his prescribing behaviour and to give him the possibility to compare his behaviour with that of his colleagues. The data collection started in 1997. Since 2004, Pharmanet data has been extended. The most important addition is an enciphered beneficiary number which allows more extensive analyses.[124]

8.1.1 Tiotropium in relation to ATC level 1 group R

To be able to describe the Belgian situation, Pharmanet data on ATC level 1 group R (Respiratory System) were requested. Data ranging from 1997 to 2007 were gathered on the following items: 1) amount of the insurance contribution, 2) co-payments, and 3) the gross amount (= 1 + 2).

A selection of drugs in the anatomical main group R (respiratory system) for the third therapeutic subgroup (drugs for obstructive airway diseases) is given in Table 25. Details are given up to the 5th level of the Anatomical Therapeutic Chemical (ATC) classification system. Tiotropium has the ATC-code R03BB04.

Table 25: ATC-code for respiratory specific medication

ATC	Denomination
R	RESPIRATORY SYSTEM
R03	DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES
R03A	ADRENERGICS, INHALANTS
R03AC	Selective beta-2-adrenoreceptor agonists
R03AC02	Salbutamol
R03AC03	Terbutaline
R03AC04	Fenoterol
R03AC12	Salmeterol
R03AC13	Formoterol
R03AK	Adrenergics and other drugs for obstructive airway diseases
R03AK03	Fenoterol and other drugs for obstructive airway diseases
R03AK04	Salbutamol and other drugs for obstructive airway diseases
R03AK06	Salmeterol and other drugs for obstructive airway diseases
R03AK07	Formoterol and other drugs for obstructive airway diseases
R03B	OTHER DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES, INHALANTS
R03BA	Glucocorticoids
R03BA01	Beclometasone
R03BA02	Budesonide
R03BA05	Fluticasone
R03BB	Anticholinergics
R03BB01	Ipratropium bromide
R03BB02	Oxitropium bromide

R03BB04	Tiotropium bromide
R03C	ADRENERGICS FOR SYSTEMIC USE
R03CC	Selective beta-2-adrenoreceptor agonists
R03CC02	Salbutamol
R03CC04	Fenoterol
R03CC11	Tulobuterol
R03D	OTHER SYSTEMIC DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES
R03DA	Xanthines
R03DA04	Theophylline

Source: \\srvnas1\KCE_studies\Common Library\Pharmaceuticals\ATC-DDD-DDA & others\WHO ATC_DDD 2008-03.xls
http://www.whocc.no/atcddd/

In the Pharmanet data, more drugs are listed than those in the above table. To be able to represent data, all drugs recorded in the Pharmanet data were subdivided in different categories:

- Inhaled long-acting anticholinergics: a) oxitropium: R03BB02, not in database since 2006 and only a small proportion of this subgroup since the introduction of tiotropium (2.4% in 2004 and <0.001% in 2005); and b) tiotropium: R03BB04, reimbursed since March 2004.
- Inhaled long-acting beta-agonists: a) salmeterol: R03AC12; and b) formoterol: R03AC13, in database since 1998.
- Inhaled combination with long-acting beta-agonists: a) salmeterol and other drugs for obstructive airway disease: R03AK06 (since 2001); and b) formoterol and other drugs for obstructive airway disease: R03AK07 (since 2002).
- Inhaled corticosteroids: a) beclometasone: R03BA01; b) budesonide: R03BA02; c) flunisolide: R03BA03 (not in database since 2004); and d) fluticasone: R03BA05.
- Inhaled non-selective beta-agonists: a) isoprenaline: R03AB02 (not in database since 2000); and b) orciprenaline: R03AB03 (not in database since 2001).
- Inhaled short-acting beta-agonists: a) salbutamol: R03AC02; b) terbutaline: R03AC03 (not in database since 2006); c) fenoterol: R03AC04 (not in database since 2005); d) rimiterol: R03AC05 (not in database since 1999); and e) pirbuterol: R03AC08 (not in database since 2003).
- Inhaled short-acting anticholinergics: ipratropium: R03BB01.
- Inhaled combination with short-acting beta-agonists: a) fenoterol and other drugs for obstructive airway disease: R03AK03; and b) salbutamol and other drugs for obstructive airway disease: R03AK04 (since 1999).
- Systemic short-acting beta-agonists: a) salbutamol: R03CC02; b) terbutaline: R03CC03 (not in database since 2007); c) fenoterol: R03CC04; and d) tulobuterol: R03CC11.
- For astma, not for COPD: a) cromoglycic acid: R03BC01 (inhaled other bronchodilators); b) zafirlukast: R03DC01 (since 1999) and c) montelukast: R03DC03 (since 2001) (both leukotriene receptor antagonists); d) omalizumab: R03DX05 (since 2006) (recombinant monoclonal IgE).
- Xanthines (especially for asthma, less for COPD): a) theophylline: R03DA04; b) aminophylline: R03DA05 (not in database since 2003); and c) bamifylline: R03DA08 (not in database since 2007).
- Respiratory stimulants: almitrine: R07AB07 (not in database since 2004).

- Others: a) nasal preparations: R01; b) cough and cold preparations: R05; and c) antihistamines for systemic use: R06.

Figure 21 shows the net amount or the insurance contribution for the costs of the dispensed product (prescription drug or other).[124] In 1997, the expenditures for group R were slightly over €100 million. Ten years later, this amount has almost doubled (+87%). Between 1997 and 2007, the yearly average growth percentage was 6.49%, with the highest yearly growth percentage at the end of the nineties. The expenditures for tiotropium (inhaled long-acting anticholinergics) are clearly observable since 2004, i.e. €9.66, €16.8, €19.0, and €21.6 million in the period 2004-2007. Tiotropium is responsible for more than 10% of the total expenditures for group R since 2006. The main trend in the expenditures, however, is the decreasing use of inhaled corticosteroids and the increasing use of a combination with long-acting beta-agonists (salmeterol and formoterol) between 2001 and 2003.

Figure 21: Amount of the insurance contribution for the anatomical main group R (respiratory system)

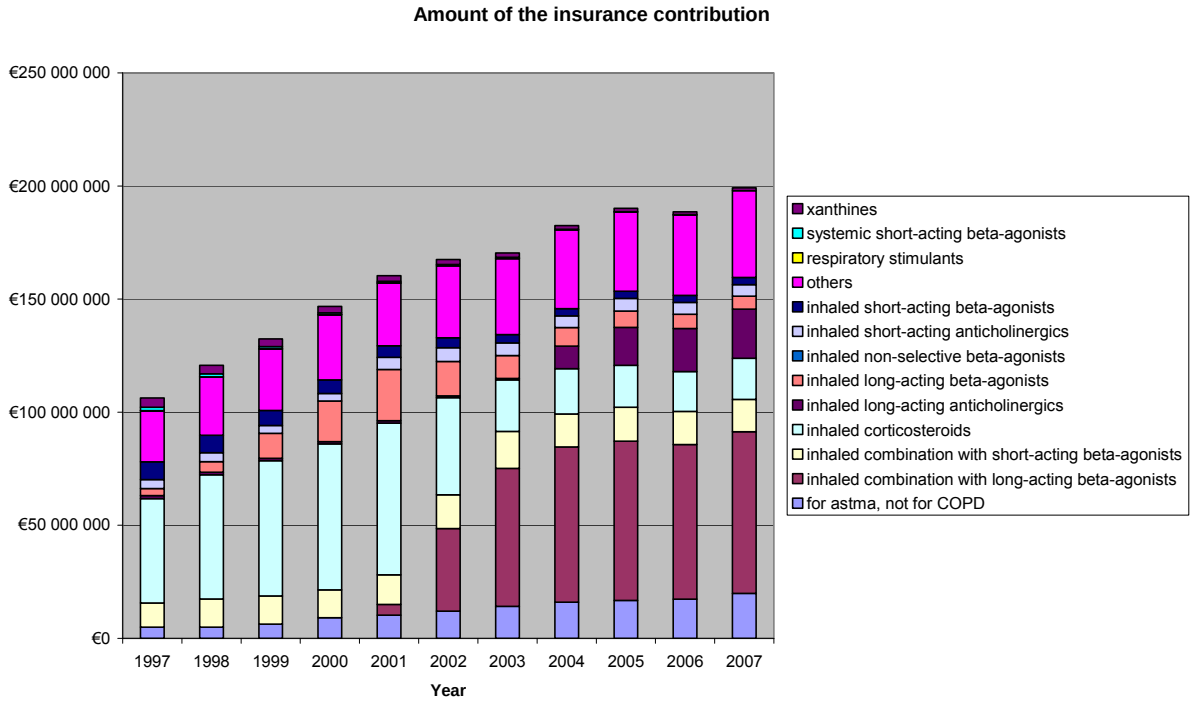


Figure 22 shows the co-payments for group R, which were more than €70 million in 2007 (+93% since 1997 or a yearly average growth percentage of 6.81%). The largest part (range 37.6% – 46.0%) goes to the subgroup 'others'. The co-payments for tiotropium were about €2 million in 2004 and increased further to €3.6, €4.1, and €4.8 million in 2005, 2006, and 2007, respectively. This is more than 6% of total co-payments for group R since 2006.

Figure 22: Co payments for the anatomical main group R (respiratory system)

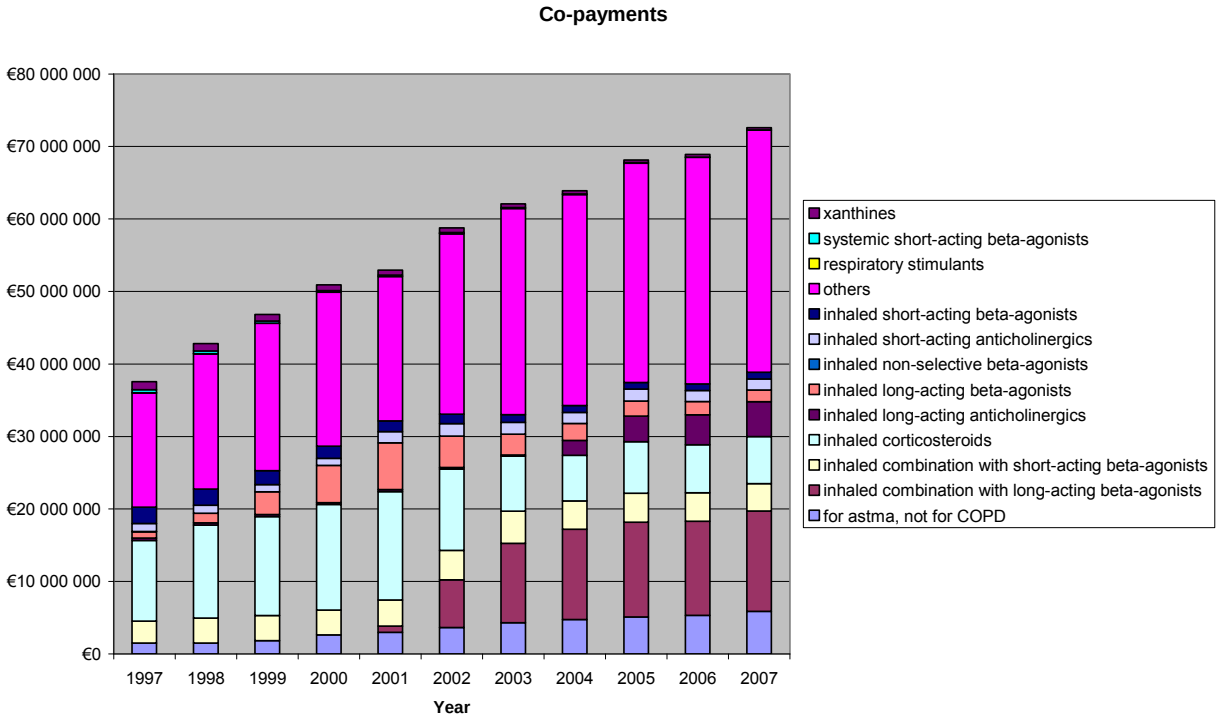
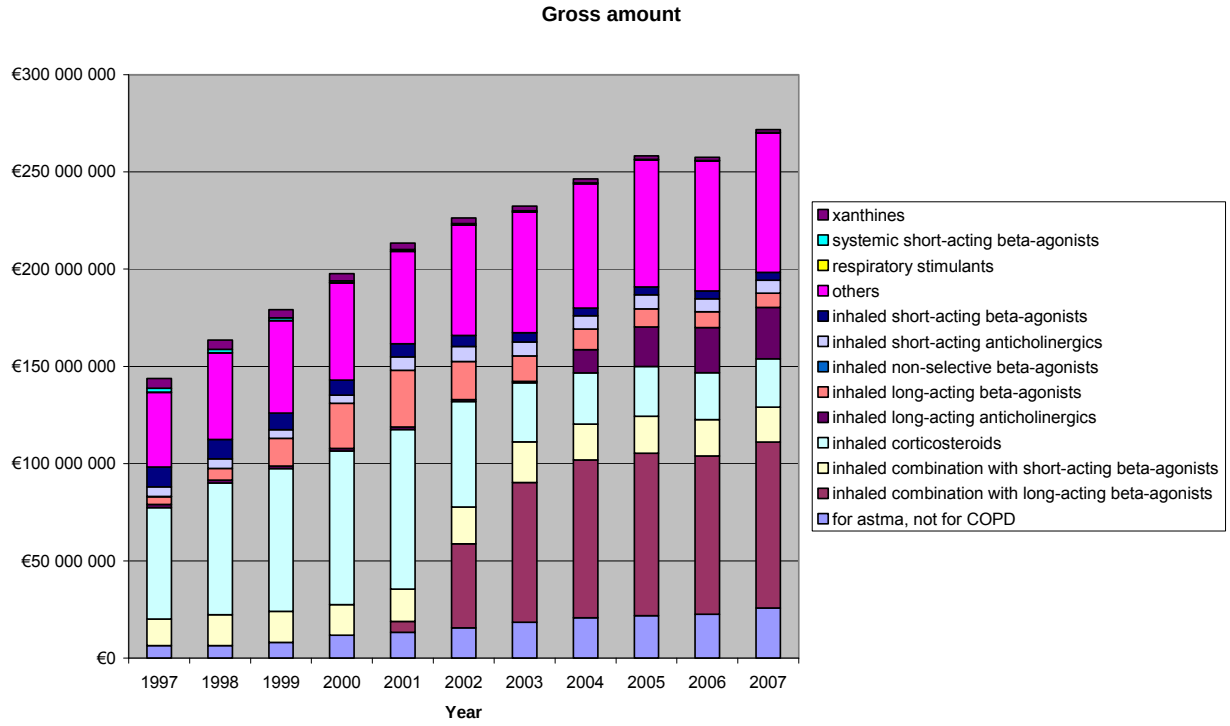


Figure 23 presents the co-payment and the amount of the insurance contribution together, or the gross amount, of the product dispensed. These increased from €144 million in 1997 to €272 million in 2007 (+89% or on average 6.57% yearly). The health care payers' expenditures on tiotropium were €11.7, €20.3, €23.1, and €26.5 million over the period 2004-2007. In comparison to the gross amount spent for group R, tiotropium takes an increasing part which was slightly below 5%, 8%, 9%, and 10% in 2004, 2005, 2006, and 2007, respectively.

Figure 23: Gross amount for the anatomical main group R (respiratory system)



8.1.2 Tiotropium in relation to age, sex and district

The Pharmanet data are also linked to the year of birth, sex and NIS-code of the place of residence. The number of patients taking tiotropium was requested with details according to age, sex, and district. The total number of patients with at least one prescription of tiotropium was about 57 300, 75 400, 77 800, and 86 300 over the period 2004-2007.

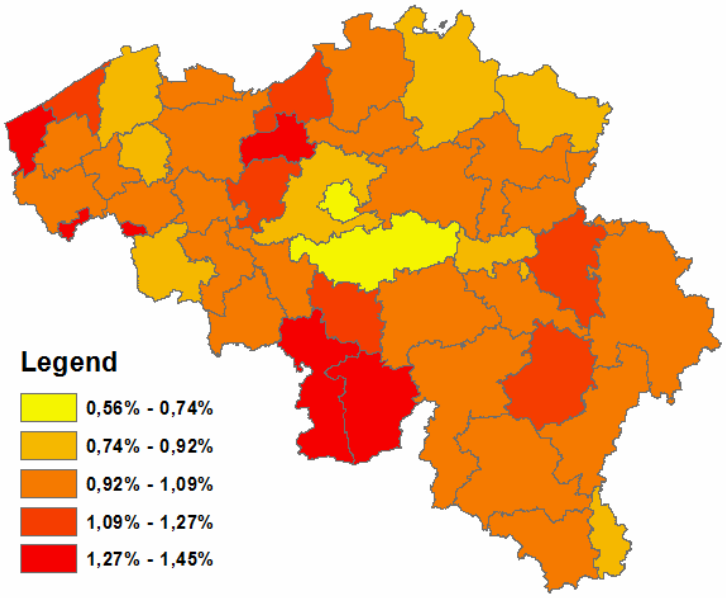
The number and percentage of users is much lower in the female population, i.e. 0.58% versus 1.06% in 2007 (Table 26). Relatively large differences were noticed over the districts, ranging from 0.32% to 0.91% in the female and 0.63% to 1.63% in the male population (Figure 24).

Table 26: Number and percentage of tiotropium users (with at least one prescription) according to sex (period 2004-2007)

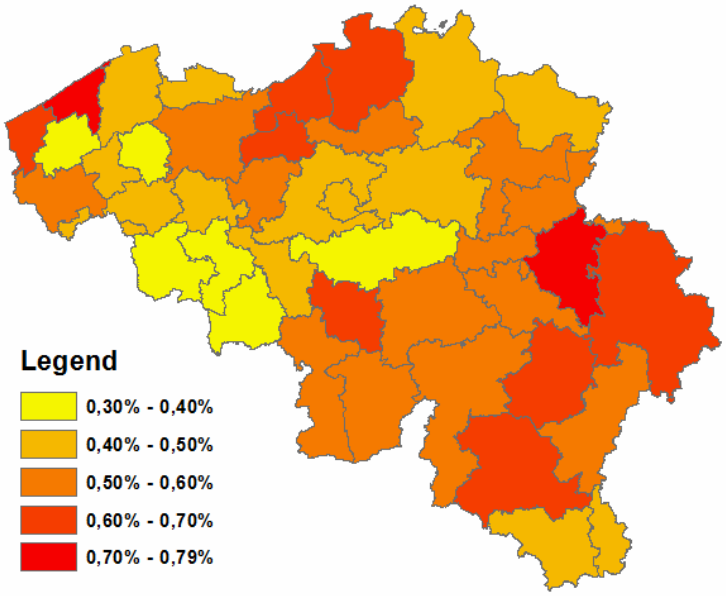
	Total		Male		Female	
	Number	**%**	**Number**	**%**	**Number**	**%**
2004	57 259	0.55%	36 239	0.71%	21 020	0.40%
2005	75 411	0.72%	47 188	0.92%	28 223	0.53%
2006	77 789	0.74%	49 806	0.97%	27 983	0.52%
2007	86 329	0.82%	54 924	1.06%	31 405	0.58%

Figure 24: Percentage of tiotropium users according to sex and district (2007)

Male population



Female population



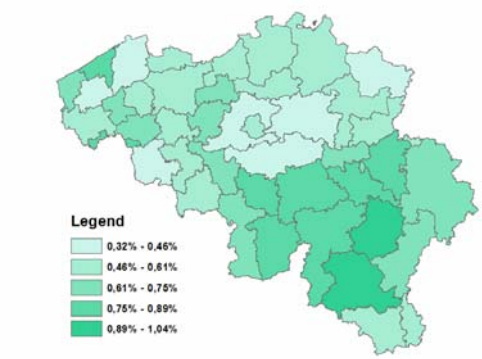
Pharmanet data were requested in five age categories: younger than 45, 45-54, 55-64, 65-74, and 75 years or older. Under the age of 45, tiotropium is scarcely used (Table 27). The number and percentage of users has been increasing slowly over the past three years in the three oldest age categories. Differences are noticed across districts (Figure 25) with a minimum percentage of tiotropium users of 0.02%, 0.32%, 0.93%, 1.8% and 1.9% in 2007 for the five age categories, respectively, and a maximum percentage of 0.13%, 1.04%, 2.86%, 3.95%, and 4.33%, respectively.

Table 27: Number and percentage of tiotropium users according to age (period 2004-2007)

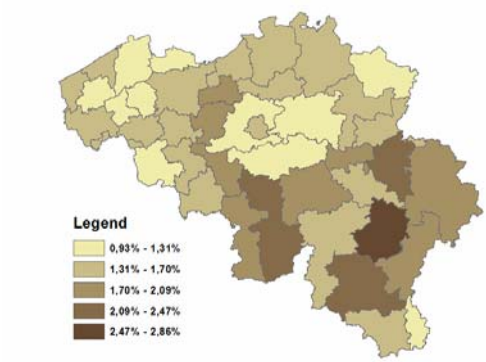
	<45		45-54		55-64		65-74		75+	
	Number	%	Number	%	Number	%	Number	%	Number	%
2004	3 693	0.06%	6 473	0.44%	11 411	1.01%	18 698	1.93%	16 984	2.09%
2005	4 572	0.08%	8 526	0.58%	15 651	1.36%	23 574	2.44%	23 088	2.77%
2006	3 448	0.06%	8 161	0.55%	16 729	1.41%	23 952	2.52%	25 499	2.97%
2007	3 486	0.06%	9 032	0.59%	19 142	1.56%	25 679	2.77%	28 990	3.28%

Figure 25: Percentage of tiotropium users according to age and district (2007)

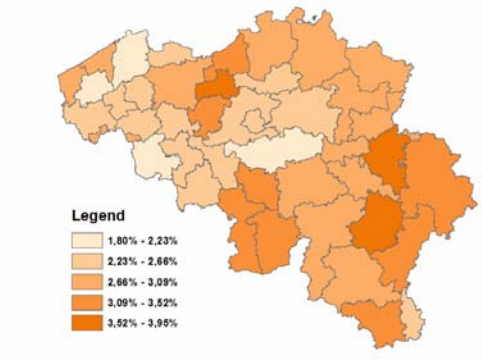
Age 45-54 years



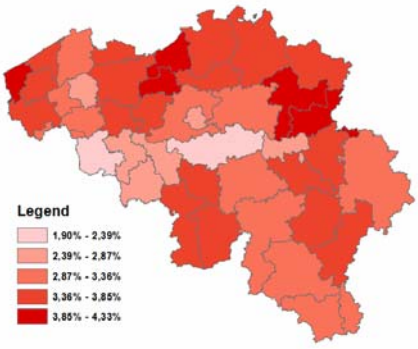
Age 55-64 years



Age 65-74 years

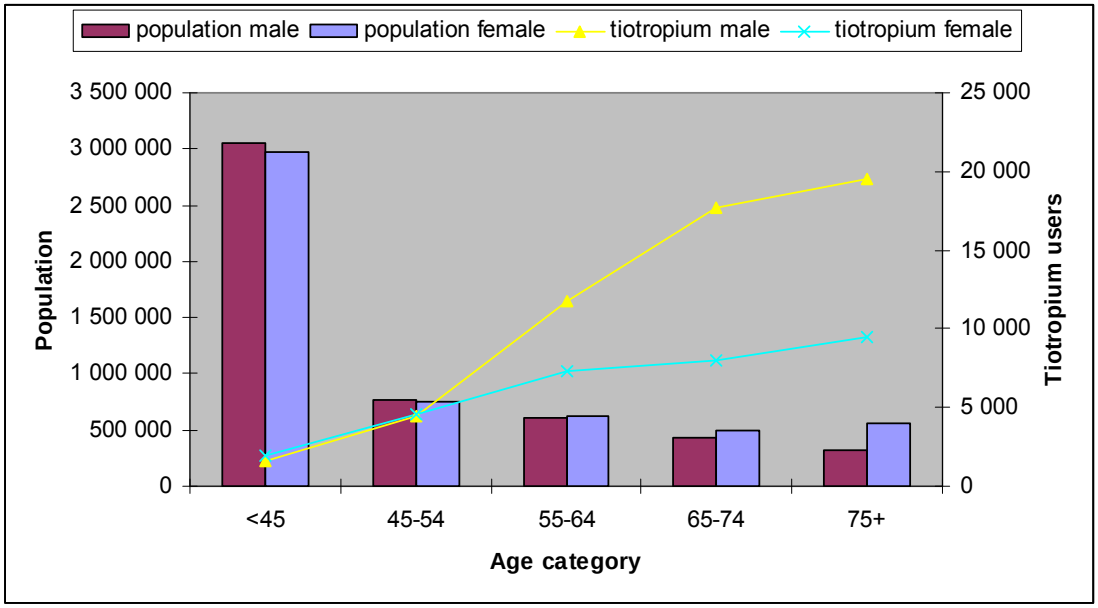


Age 75 and older



The combined influence of both age and sex becomes clearer in Figure 26. While the population size decreases with increasing age, the number of tiotropium users increases. Furthermore, although there are fewer males than females in the older age categories, the number of tiotropium users is about twice as high in the male population.

Figure 26: The population and tiotropium users according to age and sex (2007)



8.2 BCFI/CBIP

The Belgian Center for Pharmacotherapeutical Information (BCFI/CBIP) is a non-profit, non-governmental organisation providing independent information on drugs and promoting rational prescribing. The website of this organisation (www.bcfi.be) was used to find up-to-date prices of tiotropium and other medication of group R (Respiratory System) (accessed December 2008). Table 28 provides price details for tiotropium, ipratropium, salmeterol and formoterol. Comparing the monthly cost, tiotropium is about two thirds more expensive than salmeterol and 60% more expensive than formoterol.

Table 28: Prices (and non-refundable part, i.e. co-payment) for tiotropium and some comparators

Name of substance, brand name (company)	Units	Price	Non-refundable part		Proposed dose	Monthly cost
			Normal	Preference		
tiotropium bromide (18 µg), Spiriva (Boehringer Ingelheim)	30	€ 51.75	€ 10.80	€ 7.20	1 x p.d. 18 µg	€ 51.75
ipratropium bromide (20 µg), Atrovent (Boehringer Ingelheim)	200	€ 10.08	€ 2.52	€ 1.51	3 à 4 x p.d. 40 µg	€ 10.58
salmeterol						
/ (Diskhaler), Serevent (GSK)	/	€ 4.54	€ 4.54	€ 4.54	/	/
25 µg/ 1 dose, Serevent (GSK)	120	€ 31.24	€ 7.81	€ 4.69	2 x p.d. 50 µg	€ 31.24
50 µg/ 1 dose, Serevent (GSK)	60	€ 31.24	€ 7.81	€ 4.69	2 x p.d. 50 µg	€ 31.24
formoterol						
2 H2O 6 µg/ 1 dose, Oxis (AstraZeneca)	60	€ 25.48	€ 25.48	€ 25.48	2 x p.d. 12 µg	€ 50.96
2 H2O 12 µg/ 1 dose, Oxis (AstraZeneca)	60	€ 32.46	€ 8.11	€ 4.87	(max. 48 µg	€ 32.46
2 H2O 12 µg, Foradil (Novartis Pharma)	60	€ 34.66	€ 8.66	€ 5.20	p.d.)	€ 34.66
2 H2O 12 µg, Novolizer Formoterol (Meda Pharma)	60	€ 34.66	€ 8.66	€ 5.20		€ 34.66

p.d.: per day

The following table provides an overview of the price of tiotropium in a selection of other countries, i.e. France, Spain, Italy, the Netherlands, Germany and UK. The initial price and date of reimbursement are indicated, as well as the current price and the date of the last change (if there was a change). The patient co-payment is also indicated, however, we have to remark that payment systems differ across countries (which was not taken into account in this overview).

Table 29: Prices for tiotropium in a selection of countries

Country	Pack size	Price (€)	Date of initial reimburse-ment	Current price (€)*	Date of change	Patient co-payment (€)	part paid by national health insurer	Comment
Belgium	Spiriva 30 caps + HH	51,75	01.03.2004	51,75	-	10,8	40,95	Co-payment is €7,8 for persons with a preferential reimbursement status
France	Spiriva 30 caps + HH	46,17	10.05.2006	40,76	01.08.2008	14,27	26,49	Price change in 2008 due to renegociation with pricing authorities - for patients with recognised chronic treatment: patient co-pay = 0 €
Spain	Spiriva 30 caps + HH	57,44	13.01.2003	52,76	01.02.2006	2,64	50,12	General price decrease for all pharmaceutical products marketed from more than 1 year - pensioner co-payment = 0 €
Italy	Spiriva 30 caps + HH	59,41	13.01.2004	50,8	2006	none	50,8	Linear price decrease of all pharmaceutical products
The Netherlands	(Spiriva 10 caps + HH) price for 30 caps + HH	(14,82) 44,46	01.06.2002	(14,82) 44,46**	-	none	14,82	Price change due to legal price adjustement
Germany	Spiriva 30 caps + HH	65,04	15.06.2002	66,95	15.11.2008	none	66,95	General precription fee for all prescriptions apply (not product-specific)
UK	Spiriva 30 caps + HH	£37,62 / €58,54	03.07.2002	£36,27 / €41,20#	01.02.2009	none	36,27 £/41,20 €	Price change due to legal price adjustement - exchange rate at the corresponding date

HH: handihaler (device); *: If different from the initial one; **: €42,47 without handihaler; #: £33,17 without handihaler.
'Source: personal communication with Boehringer-Ingelheim (March 31, 2009)'

8.3 TIOTROPIUM STUDY DATABASE

The purpose of this part is to present descriptive statistics on COPD patients and their use of tiotropium and other medication, their number of exacerbations and hospitalisations (related to exacerbations), and other health care use. We give a description of the database constructed specifically for this study, and which patients in this database were considered chronic users of tiotropium. A descriptive comparison of the selected with the non-selected patients is provided. Finally, a comparison, observational in nature, of the selected patients the year before and after they started using tiotropium is performed.

8.3.1 General description description of sources of the tiotropium study database

Data on health care use, patient characteristics, and pathology information of tiotropium users was drawn from two existing data sources: the IMA (Common Sickness Funds Agency) health care and patient characteristics database and the MKG-MFG (Minimal Clinical Data; MKG – Minimal Financial Data; MFG) pathology and expenditure database of in hospital stays from the TCT (Technical Cell). IMA expenditure and patient characteristics data for patients for which the NIHDI code 00470448 (Spiriva, tiotropium), and corresponding CNK codes[d], were attested between March 1, 2004 and December 31, 2006, was requested. MKG-MFG hospital stay data from 2002 to 2005 were coupled to the IMA expenditure database. A detailed description of these data sources and the technicalities of the construction of the tiotropium study database can be found in the appendix to this chapter.

8.3.2 Data description

8.3.2.1 Population selection

The initial database of patients with at least one registration of tiotropium included 102 796 patients. From this database, we aimed to select patients that used tiotropium on a regular basis. The following algorithm was used:

1. Calculate the number of days between the first and last attestation for tiotropium.

2. Calculate the sum of all DDDs between first and last attestation date, excluding the number of the DDDs from the last attestation. This was done to have a better match between the number of days between the first and last attestation and the number of DDDs *between* this period.

3. Calculate the DDD ratio: $\frac{\sum_{\text{date first attestation (included)}}^{\text{date last attestation (excluded)}} DDD}{\text{number of days of tiotropium use}}$ excluding patients with all attestations on a single day (first and last attestation date are the same).

4. Based on the previous three and other variables, the following in/exclusion criteria were defined:

- Patients must have more than one attestation (on separate days)
- The total number of DDDs is ≥ 90 in one year.
- The expenditure for tiotropium is more than €120 in one year (in hospital, tiotropium costs €1.3593 for one unit, so 90 DDDs cost more than €120).
- The DDD ratio must be larger than 90/365.

---

[d] CNK codes are codes attributed to a package form of a specific drug. The codes were retrieved from the NIHDI pharmaceutical specialties database (http://www.riziv.fgov.be/inami_prd/ssp/cns2/pages/SpecialityCns.asp) and from the BCFI drug database (http://www.bcfi.be/download/index.cfm?index_lan=2#DB)

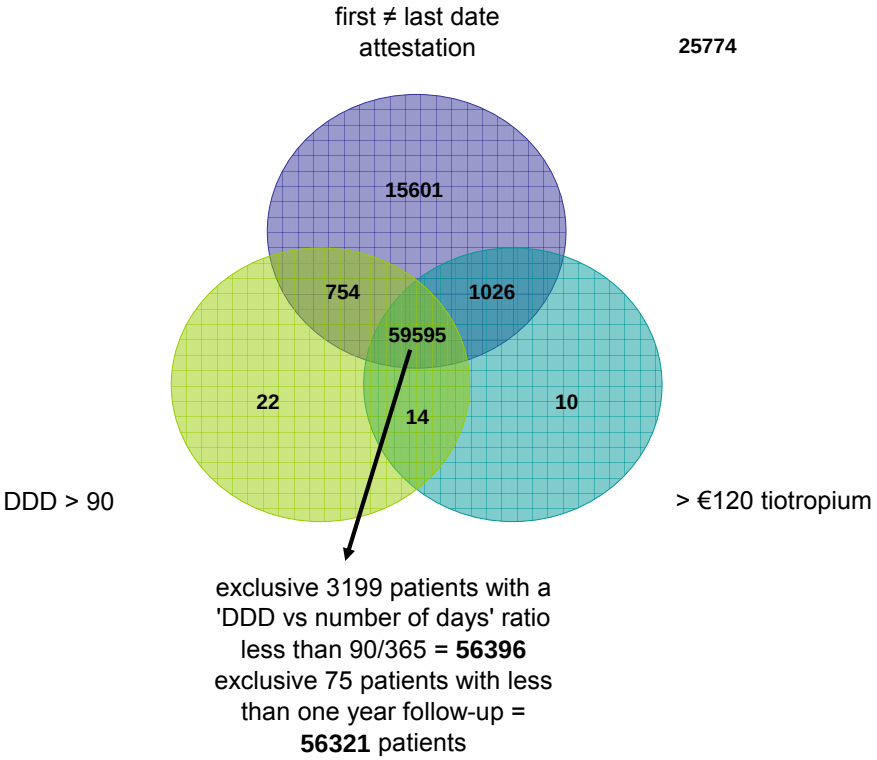
- The patient must have at least one year of data before the first attestation for tiotropium.
- The patients must have at least one year of data after the first attestation for tiotropium. A separate category was made if data was available for less than one year due to death. There was only one patient that fulfilled all other criteria but did not have one year of follow-up due to death.

Figure 27 presents the number of patients fulfilling the inclusion criteria: 25 774 fulfilled none of the first 3 criteria, i.e. having more than one attestation, more than 90 DDDs, and more than €120 expenditures on tiotropium, and 59595 fulfilled all 3 criteria. Another 3199 patients were excluded because they did not have an average DDD above the predetermined ratio and another 75 patients because they had less than one year of follow-up data. Thus, 56 321 patients (54.79%) fulfilled all criteria.

8.3.2.2 Statistical analysis

Differences in characteristics between the selected patients and non-selected patients were tested using the Mann-Whitney test (two unpaired groups for non-normally distributed data) and the Fisher's exact test (unpaired comparison of binomial variables). The analyses were performed with SAS 9.1.3.

Figure 27: Patients selected from original database



DDD: Defined Daily Dose.
Unique exclusion criteria:
1) Patients must have more than one attestation: yes: 76976; no: 25820
2) The total number of DDDs is ≥ 90 during the year after the first attestation: yes: 60385; no: 42411
3) The expenditure for tiotropium is more than €120 during the first year after the first attestation: yes: 60645; no: 42151
4) The ratio of DDDs versus the time between the first and last attestation is larger than 90/365: yes: 65132; no: 37664
5) The patient has at least one year of data before the first attestation for tiotropium: yes: 102796; no: 0
6) The patients has at least one year of follow-up data in the database: yes: 102564; no: 232 (patients with no year of follow-up who died: 19)

8.3.2.3 *Population characteristics*

The population characteristics are summarised in Table 30.

The mean age was calculated at first use of tiotropium and was significantly higher for the selected patients (mean: 68, range (4 - 102)) than for the non-selected patients (mean: 63, range (1 - 103)). Figure 28 shows the age distribution of both patient groups which is more skewed to the left for non-selected patients. Under the age of 55, people had more chance not to fulfil the predefined criteria defining regular tiotropium use.

The percentage of survivors during the follow-up period in our database (i.e. up to December 2006) was significantly different between the two groups, i.e. 83% in selected patients and 85% in non-selected patients.

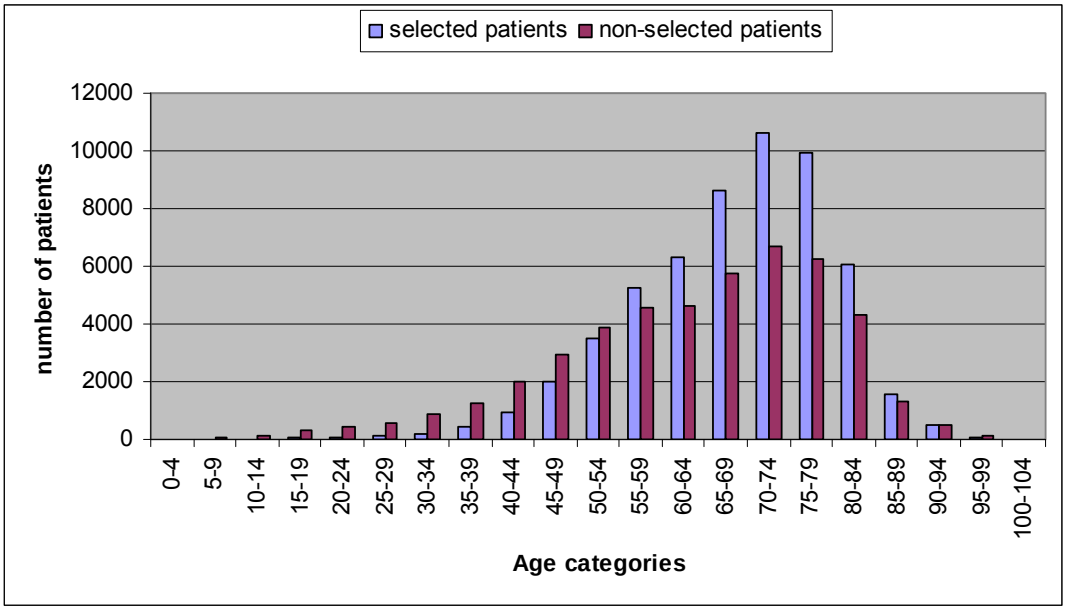
The gender ratio was significantly different between the two groups with 66% being male in the selected group versus 56% in the non-selected group.

Table 30: Population characteristics

	Selected patients	Non-selected patients	p-value
Patients (n, %)	**56321** (54.79%)	**46475** (45.21%)	
Age (mean, SD)	68.05 (11.54)	63.41 (15.49)	<.0001
Alive (%)	83.22%	85.21%	<.0001
Gender (% male)	66.39%	56.43%	<.0001

* Fl & Wal Br & BMR: Flemish and Walloon Brabant and Brussels Metropolitan Region.

Figure 28: The age distribution (in categories) among selected and non-selected patients



8.3.2.4 *Tiotropium use*

The number of days between the first and last attestation was on average 595 in the group of selected patients and 161 days in the non-selected group (Table 31). In the latter, almost 56% (n=25 820) had all tiotropium attestations on the same day. The cost for tiotropium during the first year after the first attestation was obviously much higher in the selected group, i.e. €428 versus €76, taking into account both the NIHDI cost and patient co-payment. The total expenditures during this year was more than €24 million in the selected group versus €3.5 million in the non-selected group.

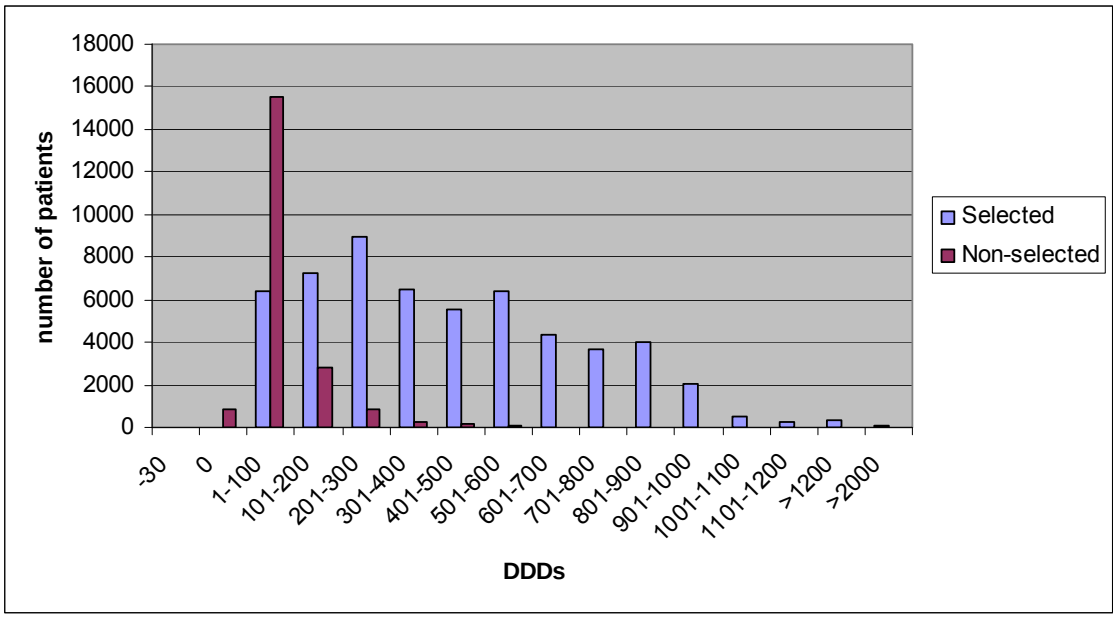
Table 31: tiotropium use

	Selected patients	Non-selected patients	p-value
Patients (n)	**56321 (54.79%)**	**46475 (45.21%)**	
Days between first and last attestation (mean, SD)	594.73 (293.94)	160.76 (275.89)	<.0001
DDDs (mean, SD)	439.19 (305.50)	83.48[a] (368.94)	<.0001
Ratio DDDs vs days (mean, SD)	0.76 (0.65)	0.68[a] (2.80)	<.0001
Cost tiotropium during first year[b] (mean, SD)	427.71 (176.38)	76.08 (56.11)	<.0001
NIHDI	356.24 (148.49)	64.05 (51.18)	<.0001
co-payment	71.47 (33.69)	12.03 (8.06)	<.0001

DDD: Defined Daily Dose; NIHDI: National Institute for Health and Disability Insurance
a: excluding the 25820 observations for which there is no observation. To be in accordance with the number of days between the first and the last attestation, the DDDs of the last attestation were excluded (and for these 25820 patients, all attestations were on the same day)
b: the first year after the first attestation for tiotropium

The average number of DDDs (excluding the DDDs of the last attestation) was 439 in the group of selected patients, more than the fivefold of the 83 DDDs in the non-selected group (not including the 25 820 patients with all attestations on the same day) (Table 31). The total number of DDDs in the selected group accounted for about 24 736 000 DDDs or 93.5% of the total number of DDDs in both groups (26 460 000). Note that the number of DDDs of the last attestation was not taken into account in these calculations (see our formula used to count the number of DDDs). As shown in Figure 29, almost all patients with more than 200 DDDs are selected. Considering a maximum of 13 packages/year is reimbursed by the NIHDI since March 2004 and our database contains data until 2006, a single patient could attain a maximum of 1170 DDDs. 432 (<1%) patients in the selected group exceeded this maximum of 1170 DDDs, with one patient having 14 100 DDDs. In the complete database, 104 (72 selected) patients had more than 2000 DDDs over the whole follow-up period, with an extreme outlier of 28 080 DDDs. These extreme DDDs can be due to registration errors, improper use, loss of medication, increased dosage, use by other persons than the patient, etc.

Figure 29: The number of patients according to the number of DDDs (in categories)



Remark: there were two patients with a negative number of DDDs (-30) in the non-selected group. This probably is due to corrections. The 25820 patients which had only one attestation are not integrated in this figure (due to our formula, which excludes the number of DDDs of the last attestation)

The ratio of the number of DDDs and the number of days between the first and last attestation was on average 0.76 in the selected group versus 0.68 in the non-selected group of patients (again excluding those 25 820 cases, since the denominator was zero, i.e. first and last attestation fall on the same day).

8.3.3 Descriptive statistics for health care use of the selected population

In this section, more details are provided for the group of selected patients. A description of use of other medication, exacerbations and (COPD) hospitalisations is provided. Since tiotropium was reimbursed since March 1, 2004 and our database begins in 2002 and ends in 2006, the number of days prior or post, i.e. how long on average were patients included in the database before or after they had their first attestation for tiotropium, can be very different. To standardise, a description of items is provided exact one year before and/or after the patient's first tiotropium attestation. This means that observations could only be included the earliest on March 1, 2003 up to December 31, 2006 (for a patient that started taking tiotropium on December 31, 2005).

It should be stressed that this is only a descriptive analysis based on observational data and should by no means be interpreted as an analysis of treatment effects. These observational data, however, are essential to describe the medication use of patients and their risk for certain events, which will be used as input for the economic model.

8.3.3.1 Other medication

Tiotropium is one possible treatment for COPD patients, among several others. The following tables show the delivery in ambulatory care of the 19 drugs mentioned in Table 25 at the 5th level of the ATC code. For each of the 19 drugs, the corresponding CNK codes were used to extract the use from the tiotropium study database. Analyses were restricted to ambulatory care because hospital expenditures represented only a very small proportion of expenditures (<0.02%).

For the selected population (n = 56321), the number of DDDs was calculated, for the entire population and for subgroups according to tiotropium use. Results for the entire group are shown in Table 32. Subgroups were determined based on the ratio of the number of days between the first and last attestation (denominator) and the number of DDDs within this time interval (nominator). Those patients with a ratio between 90% and 100%, were considered compliant regular users (n = 8785) and are shown in Table 33.

Table 32: average number of DDDs per patient on other drugs the year before and after the first tiotropium attestation (overall)

n=	56321	prior			post			
		mean	(SD)	# = 0	mean	(SD)	# = 0	difference
	Antibiotics	38,76	(50,99)	12241	40,47	(54,86)	13214	1,71
	Corticosteroids	73,60	(140,12)	31340	85,88	(153,68)	29422	12,28
R03	DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES							
R03A	ADRENERGICS, INHALANTS							
R03AC	Selective beta-2-adrenoreceptor agonists							
R03AC02	Salbutamol	30,61	(127,44)	45439	32,21	(125,25)	44531	1,60
R03AC03	Terbutaline	0,17	(9,51)	56271	0,00	(0,56)	56317	-0,17
R03AC04	Fenoterol	0,65	(22,01)	55964	0,00	(0,00)	56321	-0,65
R03AC12	Salmeterol	8,00	(45,06)	53369	5,72	(39,45)	54300	-2,28
R03AC13	Formoterol	24,01	(85,42)	49400	24,44	(84,46)	49578	0,42
R03AK	Adrenergics and other drugs for obstructive airway diseases							
R03AK03	Fenoterol a.o.*	135,56	(315,29)	30113	120,23	(296,63)	31648	-15,32
R03AK04	Salbutamol a.o.*	18,41	(100,44)	49631	22,46	(111,02)	48587	4,05
R03AK06	Salmeterol a.o.*	91,45	(136,57)	31232	107,95	(145,20)	29044	16,50
R03AK07	Formoterol a.o.*	36,00	(92,50)	43764	50,67	(112,08)	41431	14,67
R03B	OTHER DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES, INHALANTS							
R03BA	Glucocorticoids							
R03BA01	Beclometasone	7,94	(46,37)	53010	6,32	(41,60)	53774	-1,62
R03BA02	Budesonide	14,43	(68,90)	49760	11,65	(49,86)	50964	-2,78
R03BA05	Fluticasone	29,83	(117,80)	49768	20,63	(102,07)	51916	-9,20
R03BB	Anticholinergics							
R03BB01	Ipratropium	28,91	(190,81)	49382	21,50	(111,01)	50574	-7,42
R03BB02	Oxitropium	12,81	(76,90)	53232	0,79	(11,96)	55783	-12,02
R03BB04	Tiotropium	0,01	(0,67)	56309	257,99	(121,80)	390	257,99
R03C	ADRENERGICS FOR SYSTEMIC USE							
R03CC	Selective beta-2-adrenoreceptor agonists							
R03CC02	Salbutamol	0,22	(5,88)	55923	0,21	(5,42)	55901	-0,02
R03CC04	Fenoterol	0,04	(3,12)	56283	0,02	(1,72)	56302	-0,02
R03CC11	Tulobuterol	1,78	(25,83)	55445	1,47	(17,99)	55534	-0,31
R03D	OTHER SYSTEMIC DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES							
R03DA	Xanthines							
R03DA04	Theophylline	69,11	(164,47)	44350	69,20	(163,61)	44076	0,09

*a.o.: and other drugs for obstructive airway diseases: salmeterol + fluticasone; formoterol + beclometasone; fenoterol + ipratropium; salbutamol + ipratropium

In the year preceding their first tiotropium attestation, 19% of patients were delivered salbutamol at least once, 0.08% terbutaline, and 0.63% fenoterol. Combination formulation of salbutamol+ipratropium was delivered to 12% and fenoterol+ipratropium to 47%. Short-acting anticholinergic ipratropium was delivered to 12% of patients, oxitropium to 5.5%. Long-acting beta-agonist salmeterol was delivered to 5.2% of patients and formoterol to 12% of patients. Combination formulation of salmeterol+fluticasone was delivered to 45% and formoterol+beclometasone to 22%. Inhaled corticosteroid beclomethasone was delivered to 5.9% of patients, budesonide to 12% and fluticasone to 12%. Delivery of systemic beta-agonists was low (salbutamol to 0.7%, tulobuterol to 1.6% and fenoterol to 0.07%). 21% of patients had theophylline in the year preceding their first tiotropium attestation. Finally, 78% were prescribed antibiotics and 44% were prescribed systemic corticosteroids.

In the year after their first tiotropium attestation, 21% of patients were delivered salbutamol at least once, 0.007% terbutaline and 0% fenoterol. Combination formulation of salbutamol+ipratropium was delivered to 14% and fenoterol+ipratropium to 44%. Ipratropium was delivered to 10%, and oxitropium to 0.95%. Salmeterol was delivered to 3.6% of patients and formoterol to 12%. Combination formulation of salmeterol+fluticasone was delivered to 48% and formoterol+beclomethasone to 26%. Beclomethasone was delivered to 4.5% of patients, budesonide to 9.5% and fluticasone to 7.8%.

Systemic beta-agonists were little used (salbutamol 0.75%, fenoterol 0.034% and tulobuterol 1.4%). Theophylline was delivered to 22% of patients, antibiotics to 77% and corticosteroids to 48%.

In the year after the first tiotropium attestation, 80% of patients have purchased at least one package of long-acting beta-agonists, salmeterol or formoterol either in individual formulation or in combination with an inhaled corticosteroid. In addition, 82% of patients purchased at least one package of an inhaled corticosteroid, fluticasone, beclomethase or budesonide, again either in individual formulation or combined with a long-acting beta-agonist.

Comparing the year after the first tiotropium attestation to the preceding year, it is difficult to draw conclusions. The proportion of patients that have been delivered at least one prescription of all relevant ATC level 1 group R medications seems to have increased, except for terbutaline, fenoterol, oxitropium and budesonide. From our data of DDDs, it appears that the delivery of single short-acting beta-agonists and anticholinergics declined, but combined treatment with another drug increased. Inhaled corticosteroids appear to have decreased. However, these differences can not be interpreted as treatment effects from our data for several reasons. First of all, the observational design carries the risk of selection by indication. Those patients with more severe disease and consequently higher need for medication were perhaps more likely to be prescribed tiotropium compared to patients with less severe disease. This could lead to a patient population with more severe illness than the general COPD population. Secondly, we do not have a group of non-tiotropium patients to compare our data with. Changes in medication use can be caused in part by progression of disease. Finally, our data are based on the delivery of medication packages in ambulatory care. Packages are then translated into DDDs, which should consequently not be interpreted as consumed doses.

Table 33: average number of DDDs per patient on other drugs the year before and after the first tiotropium attestation (subgroup)

n=	8785	prior		post		
		mean	(SD)	mean	(SD)	difference
	Antibiotics	39,41	(49,34)	39,72	(53,21)	0,31
	Corticosteroids	74,40	(133,83)	83,57	(146,34)	9,17
R03	DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES					
R03A	ADRENERGICS, INHALANTS					
R03AC	Selective beta-2-adrenoreceptor agonists					
R03AC02	Salbutamol	31,76	(133,79)	34,20	(134,75)	2,44
R03AC03	Terbutaline	0,06	(3,37)	0,00	(0,00)	-0,06
R03AC04	Fenoterol	0,58	(10,06)	0,00	(0,00)	-0,58
R03AC12	Salmeterol	9,65	(50,30)	6,89	(43,50)	-2,75
R03AC13	Formoterol	29,67	(90,91)	29,39	(92,95)	-0,29
R03AK	Adrenergics and other drugs for obstructive airway diseases					
R03AK03	Fenoterol a.o.*	145,65	(315,46)	119,12	(280,43)	-26,53
R03AK04	Salbutamol a.o.*	19,05	(83,80)	22,51	(97,35)	3,46
R03AK06	Salmeterol a.o.*	110,27	(148,76)	133,11	(161,76)	22,84
R03AK07	Formoterol a.o.*	43,09	(103,67)	62,79	(127,78)	19,70
R03B	OTHER DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES, INHALANTS					
R03BA	Glucocorticoids					
R03BA01	Beclometasone	10,12	(51,53)	7,43	(46,60)	-2,68
R03BA02	Budesonide	17,72	(63,76)	13,86	(56,64)	-3,85
R03BA05	Fluticasone	38,06	(135,80)	23,97	(110,86)	-14,09
R03BB	Anticholinergics					
R03BB01	Ipratropium	33,16	(142,29)	23,29	(120,80)	-9,87
R03BB02	Oxitropium	17,57	(90,88)	0,95	(14,72)	-16,61
R03BB04	Tiotropium	0,01	(0,45)	331,49	(90,32)	331,48
R03C	ADRENERGICS FOR SYSTEMIC USE					
R03CC	Selective beta-2-adrenoreceptor agonists					
R03CC02	Salbutamol	0,20	(4,89)	0,18	(4,77)	-0,01
R03CC04	Fenoterol	0,04	(2,33)	0,03	(2,07)	-0,01
R03CC11	Tulobuterol	1,93	(21,09)	1,42	(18,42)	-0,51
R03D	OTHER SYSTEMIC DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES					
R03DA	Xanthines					
R03DA04	Theophylline	84,29	(182,77)	83,38	(180,86)	-0,91

*a.o.: and other drugs for obstructive airway diseases: salmeterol + fluticasone; formoterol + beclometasone; fenoterol + ipratropium; salbutamol + ipratropium

In the subgroup of compliant regular tiotropium users, it shows from the DDD analysis that other long-acting drugs are commonly used, both before and after the first tiotropium attestation, with salmeterol + fluticasone accounting for 110-133 DDDs.

8.3.3.2 Exacerbations

An exacerbation is defined as at least one or two new or increased respiratory symptoms, such as cough, wheeze, dyspnoea, chest congestion, shortness of breath or sputum production, necessitating a change in treatment. For the definition of a COPD related exacerbation in our dataset, we had to rely on an approximation based on consumption data, as we did not have ambulatory clinical data.

According to the GOLD guideline, an exacerbation should be treated with increased dosage of bronchodilator therapy, systemic corticosteroids and antibiotics when appropriate.

Evidence shows that in practice, exacerbations are treated with a short course of oral steroids in 30% of cases, antibiotics in 29%, steroids combined with an antibiotic in 23%, and no oral steroid course or antibiotic was prescribed in 18%.[125]

A COPD exacerbation was identified in the tiotropium study database as the occurrence within a seven day interval of both an attestation of an antibiotic and an attestation of a corticosteroid. Two identified exacerbations were counted as one exacerbation when they occurred within seven days of each other. For antibiotics, all public pharmacies CNK codes for ATC level 2 J01 were used, while for corticosteroids, all public pharmacies CNK codes for ATC level 4 H02AB were used. This definition is, although specific, not sensitive as only 1 in 4 exacerbations are treated with this combination. We recognise this limitation fully, and will account for it in the economic model. However, other definitions, such as the delivery of systemic corticosteroids or antibiotics only, would have been more sensitive but very non-specific. As shown in Table 32, antibiotics are prescribed in the vast majority of the population (78% and 76% in the year before and after the first tiotropium attestation, with a mean of 39 and 44 DDDs respectively). From our data, we have no means to determine which antibiotic prescriptions were for a COPD exacerbation and which for another infectious illness. In addition, 44% and 48% of patients were prescribed systemic corticosteroids in the year before and after their first tiotropium attestation, for a mean of 74 and 86 DDDs. Similarly as for antibiotics, systemic corticosteroids can be prescribed for other target conditions than a COPD exacerbations, although probably not as frequent as antibiotics.

Considering that only 23% of all exacerbations is treated with systemic corticosteroids and antibiotics, patients had a mean of 0.8 (SD 0.71) exacerbations per year in the year preceding their first tiotropium attestation. This presumed rate of exacerbations in our population is very close to the rate that was reported in the placebo arm of the Uplift trial[48], which is the largest trial on tiotropium with the longest follow-up.

8.3.3.3 Hospitalisations

As described in our methodology, we disposed of all hospitalisations except for one day admissions, for all tiotropium users in the time frame 2002-2005. To calculate the number of COPD related hospitalisations, only those stays with ICD-9-CM codes (and subcodes) 491 (chronic bronchitis), 492 (emphysema) and 496 (COPD, not otherwise specified) as the primary or secondary diagnosis in any hospital ward during the stay, were retained. As an alternative, a second definition of a COPD related stay retained only those stays with the above ICD-9-CM codes as the primary diagnosis.

The number of hospitalisations per patient was calculated one year before and after the first attestation of tiotropium. However, a number of hospitalisations was excluded because an exact start date of hospitalisation could not be calculated. The date precision of hospitalisation start date in MKG is year/month/day-of-the-week (i.e. 1 to 7). The date precision of attestation in the IMA data is year/month/day. However in the MFG, all attestations have year/month/day precision allowing calculation of a precise start date by finding the first date of attestation. Unfortunately, the date of attestation is available for the MFG only from 2004 onwards.

To calculate the start date for the hospitalisations in 2003, we matched the MKG year/month/day-of-the-week with year/month/day-of-the-week from the IMA attestation date of NIHDI nomenclature codes which are attested for each hospitalisation stay. The corresponding full date was used as the hospitalisation start date. Still, a number of hospitalisations could not be matched because two stays existed for the patient in the same year and month with the same day of the week prohibiting attribution of a correct start date. However, none of these non-matched hospitalisations met our COPD selection criteria. Hence, the reported number of total hospitalisations (irrespective of COPD selection criteria) in the year before tiotropium use will be slightly underestimated (between 13.9% and 16.8%), while the number of hospitalisations with primary and secondary COPD diagnoses, primary COPD diagnosis, and primary COPD diagnosis in one hospital ward are correct.

To calculate the cost of a COPD hospitalisation, an additional, more stringent, selection criterion was used: the hospital stay must be spend either in a single hospital ward, or in two hospital wards of which one was the intensive care unit. This avoided an impact on hospitalisation cost of interventions unrelated to COPD in the same stay in other hospital wards. The cost was calculated as the sum of all expenditures available in the MFG data for the selected stay. In Belgium, hospital per diem costs are covered by 2 distinct systems of public health funding. A major part is covered through fixed monthly hospital payments but these are not registered in the MFG data. Additional remuneration consists of a lump sum billed per admission and a lump sum billed per day of hospital stay, both included in the MFG data. We replaced these lump sums by the 100% hospital per diem costs calculated as the actual per diem prices available per hospital, per year, per semester and per type of stay[e] multiplied by the number of invoiced days for the stay.

As can be expected, the number of hospitalisations decreases with increasing specific definition. Based on the broadest definition, the hospitalisation rate was 0.55/year, whereas the other rates were 0.36, 0.14 and 0.12 hospitalisations/year respectively (Table 34). In the Uplift trial, patients in the placebo arm had a hospitalisation rate of 0.16/year.

A substantial proportion of our population was not hospitalised in the year before the first tiotropium attestation: 67%, 76%, 89% and 90% depending on the definition used (Table 34).

Table 34: average number of hospitalisations per patient (overall and according to subgroups) and the number of patients according to number of hospitalisations (0, 1, 2, 3, or ≥4) the year before the first tiotropium attestation

		hospitalisation							
		all		prim + sec		prim		prim + 1 dep.	
	n	mean	(SD)	mean	(SD)	mean	(SD)	mean	(SD)
Overall	**56321**	**0.55**	**(1.03)**	**0.36**	**(0.82)**	**0.14**	**(0.46)**	**0.12**	**(0.42)**
Number of hospitalisations		**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
0		38010	(67.49)	43064	(76.46)	50156	(89.05)	50929	(90.43)
1		11250	(19.97)	8972	(15.93)	4931	(8.76)	4374	(7.77)
2		4076	(7.24)	2677	(4.75)	887	(1.57)	742	(1.32)
3		1655	(2.94)	917	(1.63)	239	(0.42)	193	(0.34)
≥4		1330	(2.36)	691	(1.23)	108	(0.19)	83	(0.15)

All: all hospitalisations ; prim + sec: hospitalisations with COPD as primary or secondary diagnosis; prim: hospitalisations with COPD as primary diagnosis ; prim + 1 dep.: hospitalisations with COPD as primary diagnosis and stay on only one hospital ward (referral from ICU permitted)

[e] Published by NIHDI (http://www.riziv.be)

Table 35: hospitalisation cost according to selection of hospitalisations and degree of severity (TCT categories)

		cost		LOS	
	number (n)	mean	(SD)	mean	(SD)
All	**204378**	**€2617**	**(3608)**	**11.63**	**(16.11)**
sev 0	3115	€2166	(2743)	17.74	(18.72)
sev 1	48905	€1596	(1565)	5.19	(7.48)
sev 2	84294	€2084	(2475)	8.98	(10.99)
sev 3	51911	€3086	(3435)	15.95	(17.78)
sev 4	16153	€7070	(7792)	29.96	(28.90)
prim. + sec.	**116311**	**€2819**	**(3614)**	**13.38**	**(17.11)**
sev 0	8	€1607	(1323)	8.00	(7.48)
sev 1	13736	€1594	(1452)	6.56	(8.07)
sev 2	52220	€2034	(1854)	9.28	(10.77)
sev 3	38013	€3012	(2975)	16.06	(17.44)
sev 4	12334	€6918	(7600)	30.05	(28.92)
prim.	**39100**	**€2580**	**(3275)**	**14.18**	**(16.01)**
sev 0	1	€4469	/	19.00	/
sev 1	5704	€1456	(1263)	7.70	(6.98)
sev 2	14767	€1882	(1535)	10.65	(9.96)
sev 3	13840	€2581	(2291)	15.28	(14.42)
sev 4	4788	€6074	(6932)	29.61	(28.27)
prim. + 1 dep.	**34033**	**€2282**	**(2551)**	**12.12**	**(10.64)**
sev 0	0	/	/	/	/
sev 1	5323	€1428	(1178)	7.45	(6.28)
sev 2	13251	€1797	(1295)	9.84	(6.94)
sev 3	11843	€2367	(1859)	13.38	(9.48)
sev 4	3616	€5045	(5669)	23.21	(18.93)

LOS: length of stay; All: all hospitalisations ; prim + sec: hospitalisations with COPD as primary or secondary diagnosis ; prim: hospitalisations with COPD as primary diagnosis ; prim + 1 dep.: hospitalisations with COPD as primary diagnosis and stay on only one hospital ward (referral from ICU permitted)

Hospitalisation costs are shown in Table 34. Costs and length of stay vary between hospitalisation definitions. In the MKG registration, a severity score is assigned to the hospitalisation based on comorbidity. Costs increase steeply in the most severe category. Taking into account all the costs related to the hospitalisation, costs vary between €5017 and €5617, with the third definition (hospitalisation with COPD as primary diagnosis) incurring the highest costs.

Table 36: detail of hospitalisation cost according to subcategories and adjusted cost of hospitalisation

	All		prim. + sec.		prim.		prim. + 1 dep.	
	mean	(SD)	mean	(SD)	mean	(SD)	mean	(SD)
Total cost	**€2617**	**(3608)**	**€2819**	**(3614)**	**€2580**	**(3275)**	**€2282**	**(2551)**
clinical biology	€68	(153)	€83	(173)	€89	(174)	€77	(139)
implants	€201	(884)	€169	(849)	€23	(233)	€13	(178)
hospitalisation	€638	(1341)	€670	(1368)	€691	(1279)	€625	(1068)
drugs	€434	(1596)	€521	(1169)	€554	(1184)	€480	(996)
honorarium	€1238	(1378)	€1337	(1477)	€1200	(1336)	€1067	(1017)
blood and others	€38	(241)	€40	(219)	€25	(154)	€21	(149)
adjusted cost	**€5017**	**(6089)**	**€5614**	**(6388)**	**€5617**	**(6023)**	**€5025**	**(4751)**

All: all hospitalisations ; prim + sec: hospitalisations with COPD as primary or secondary diagnosis prim: hospitalisations with COPD as primary diagnosis ; prim + 1 dep.: hospitalisations with COPD as primary diagnosis and stay on only one hospital ward (referral from ICU permitted)

adjusted cost: In Belgium, hospital per diem costs are covered by 2 distinct systems of public health funding. A major part is covered through fixed monthly hospital payments but these are not registered in the MFG data. Additional remuneration consists of a lump sum billed per admission and a lump sum billed per day of hospital stay, both included in the MFG data. In this adjusted cost, these lump sums are replaced by the 100% hospital per diem costs calculated as the actual per diem prices available per hospital, per year, per semester and per type of stay, multiplied by the number of invoiced days for the stay.

8.3.3.4 Exacerbations and hospitalisations

In Table 37, the number of exacerbations and hospitalisations (with COPD as primary diagnosis) are cross-tabulated. From this table, it shows that 84% of the population did not have any exacerbation or hospitalisation in the year preceding the first tiotropium attestation.

Table 37: patients (number and %) according to number of hospitalisations and exacerbations (the year before the first tiotropium attestation)

		Hospitalisations prim						total n
		0	1	2	3	4	≥5	(total %)
Exacerbations	n 0	47393	3096	324	72	15	2	**50902**
	(%)	(84.15)	(5.50)	(0.58)	(0.13)	(0.03)	(0.00)	**(90.39)**
	n 1	1649	1113	141	16	1	0	**2920**
	(%)	(2.93)	(1.98)	(0.25)	(0.03)	(0.00)	(0.00)	**(5.19)**
	n 2	629	409	195	38	8	3	**1282**
	(%)	(1.12)	(0.73)	(0.35)	(0.07)	(0.01)	(0.01)	**(2.29)**
	n 3	270	175	117	39	8	3	**612**
	(%)	(0.48)	(0.31)	(0.21)	(0.07)	(0.01)	(0.01)	**(1.09)**
	n 4	118	77	54	37	13	4	**303**
	(%)	(0.21)	(0.14)	(0.10)	(0.07)	(0.02)	(0.01)	**(0.55)**
	n ≥5	97	61	56	37	29	22	**302**
	(%)	(0.17)	(0.11)	(0.10)	(0.07)	(0.05)	(0.04)	**(0.54)**
total n		**50156**	**4931**	**887**	**239**	**74**	**34**	**56321**
(total %)		**(89.06)**	**(8.77)**	**(1.59)**	**(0.44)**	**(0.12)**	**(0.06)**	**(100.00)**

		Hospitalisations prim + 1 dep.						total n
		0	1	2	3	4	≥5	(total %)
Exacerbations	n 0	47788	2761	290	51	11	1	**50902**
	(%)	(84.85)	(4.90)	(0.51)	(0.09)	(0.02)	(0.00)	**(90.37)**
	n 1	1852	947	107	13	1	0	**2920**
	(%)	(3.29)	(1.68)	(0.19)	(0.02)	(0.00)	(0.00)	**(5.18)**
	n 2	716	361	162	33	8	2	**1282**
	(%)	(1.27)	(0.64)	(0.29)	(0.06)	(0.01)	(0.00)	**(2.27)**
	n 3	313	167	94	32	3	3	**612**
	(%)	(0.56)	(0.30)	(0.17)	(0.06)	(0.01)	(0.01)	**(1.11)**
	n 4	141	70	47	29	12	4	**303**
	(%)	(0.25)	(0.12)	(0.08)	(0.05)	(0.02)	(0.01)	**(0.53)**
	n ≥5	119	68	42	35	25	13	**302**
	(%)	(0.21)	(0.12)	(0.07)	(0.06)	(0.04)	(0.02)	**(0.54)**
total n		**50929**	**4374**	**742**	**193**	**60**	**23**	**56321**
(total %)		**(90.43)**	**(7.76)**	**(1.31)**	**(0.34)**	**(0.10)**	**(0.04)**	**(100.00)**

prim: hospitalisaitons with COPD as primary diagnosis ; prim + 1 dep.: hospitalisations with COPD as primary diagnosis and stay on only one hospital ward.
The percentage of patients with a certain number of exacerbations is based on the use of both antibiotics and corticosteroids within 7 days. As explained in part 8.3.3.2 this is an underestimation. In the economic evaluation, a correction for this underestimation was implemented (see also 8.3.3.2).

Key points

Pharmanet data show that:

- **In 2007, the NIHDI paid more than €21 million for tiotropium. During the same year, the patient's co-payments were almost €5 million. The sum represents about 10% of all expenditures for the anatomical main group R (respiratory system).**
- **In 2007, there were more than 86 000 patients with at least one prescription of tiotropium. More than 60% of patients were male. Since age is one of the determining factors for COPD, tiotropium is taken by a relatively older population.**

BCFI/CBIP data provides prices:

- **One month treatment with tiotropium costs €51.75. For salmeterol, this is €31.24. Tiotropium is about 66% more expensive than salmeterol.**

Based on the tiotropium study database:

- **Over the period March 2004 – December 2005, over 102 000 patients with at least one tiotropium prescription could be identified.**
- **A substantial proportion of patients (>25 000) had all tiotropium attestations on the same day during the observation period.**
- **More than 56 000 'regular' tiotropium users could be selected.**
- **The analyses are based on administrative data that do not contain any clinical information. In addition, they are purely observational by which no estimates on efficacy can be made.**
- **Using a specific but insensitive definition of exacerbations, being the delivery of systemic corticosteroids and antibiotics within 7 days, the exacerbation rate without tiotropium use is estimated at 0.18/patient year. Considering only 23% of exacerbations are treated with this combination, the exacerbation rate corresponds to 0.80/patient year which is very similar to the rate reported in Uplift.**
- **The hospitalization rate for COPD was estimated using different definitions. The definition using all hospitalizations for which COPD was the primary diagnosis was considered most accurate and was subsequently used in the economic model. On average, the selected patients experienced 0.14 hospital admissions the year before the first tiotropium prescription. The cost for this hospital admission was on average €5600.**
- **A large proportion of our population uses other long-acting bronchodilators and inhaled corticosteroids in addition to tiotropium. Approximately 80% purchased at least one package of these treatment modalities, and the mean DDDs are high.**

9 COST EFFECTIVENESS OF TIOTROPIUM FOR COPD PATIENTS IN THE BELGIAN CONTEXT

In this chapter, the cost effectiveness of tiotropium versus relevant comparators is calculated. 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 input parameters (costs, efficacy/effectiveness, QoL). Belgian pharmaco-economic evaluation guidelines have been set up to improve consistency.[126] These guidelines 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. Before discussing these results, the budget impact is calculated.

9.1 METHODS

The basic idea is to use strengths of both observational and RCT data. RCTs are the ideal method for measuring treatment effects. Randomization reduces biases by making treatment and control groups "equal with respect to all features," except the treatment assignment.[127] Nevertheless, the population in trials often does not include a real-world population. An approach to measure the cost effectiveness in a real-world population is to apply the relative treatment effect found in an RCT to the baseline risk for an event calculated from observational data. As such, cost effectiveness, which is driven by absolute benefit, will be lower (i.e. more cost-effective) in subgroups with a higher baseline risk of a certain event (such as exacerbations and exacerbation-related hospitalisations), and vice versa.[128] This is under the assumption that the relative treatment effect is independent from the baseline risk. This may not always be truth. However, in the absence of better data, and because no evidence has been published on a difference in relative treatment effect between subgroups, this may be seen as a realistic assumption allowing the transparent calculation of the intervention's cost effectiveness.

In this approach, the observational data will be used to present the situation 'as it is in real life'. The RCT data will be used to model the relative benefit of tiotropium versus its alternative(s). The following steps are taken:

- What are the events for COPD patients not taking tiotropium, based on observational data?
- What events would have occurred, if they had been treated with tiotropium (applying the relative effect derived from RCTs on these observational data)?
- What is the incremental cost-effectiveness ratio (ICER) comparing these two situations?

9.1.1 Analytic technique

Cost-effectiveness (CEA) or cost-utility analysis (CUA) should be used in the reference case.[126] The review on the efficacy/effectiveness of tiotropium has not shown that tiotropium has an impact on survival. However, avoiding exacerbations and exacerbation-related hospitalisation may influence QoL. Therefore, CUA is applied. An alternative approach used in several studies is to express results in the disease specific outcome such as 'cost per exacerbation-free months' or 'cost per exacerbation avoided'. We believe it is hard to rely on this surrogate measure, which is difficult to interpret by decision makers, and therefore restrict our analysis to 'extra cost per QALY gained'.

9.1.2 Perspective of the evaluation

In accordance with the Belgian pharmaco-economic guidelines, the analysis is performed from the perspective of the health care payer. This includes both costs paid by the standard health insurance and patient co-payment contributions.

9.1.3 Time horizon and discount rate

The time horizon in an economic evaluation should extend far enough into the future to capture the major health and economic outcomes. As a result, the appropriate time horizon depends on the natural course of the disease. Chronic diseases call for a longer time horizon than acute diseases without long-term consequences. The Belgian pharmaco-economic guidelines mention that for chronic diseases and acute diseases with long-term sequelae, a lifetime horizon should be applied.[126] COPD is by definition a chronic disease. Nevertheless, based on published literature, there is no evidence that the long-term course of the disease is altered by using tiotropium in comparison with its relevant comparators, such as salmeterol. Therefore, for this chronic disease, a short-term time horizon of one year is applied. This seems to be justified since it appears to be long enough to capture a significant number of important clinical endpoints such as exacerbations and exacerbation-related hospitalisations, and to capture seasonal variations. Applying a discount rate over such a short period would not influence results drastically, and therefore, no discount rate was applied.

9.1.4 Population

According to the pharmaco-economic guidelines, the patient population to which the pharmaco-economic evaluation applies should be consistent with the patient population defined in the clinical part of the reimbursement request submission. The available observational database does not contain enough clinical data to define the COPD population. In Belgium, however, tiotropium is already reimbursed since March 1, 2004, only for the maintenance treatment of COPD (see part 1.6.1). This allows us to select our population based on the use of tiotropium. By strict application of the reimbursement criteria, this should only contain COPD patients. From this population, a more stringent selection of chronic tiotropium users was selected. The applied criteria are described above (see 8.3.2.1) This group of selected patients will be indicated by mentioning 'All' in the results.

Of this group of tiotropium users, a more selective group was selected, indicated by 'subgroup'. This group consisted of patients taking tiotropium on a very regular basis. Next to fulfilling all previous criteria, these patients had a ratio of DDDs versus number of days between the first and last attestation between 90% and 100%, whereas this was 25% or more for the 'general tiotropium users'.

9.1.5 Intervention / comparators

The intervention under analysis is tiotropium. Previous economic evaluations compared it with placebo, ipratropium or salmeterol. Since it does not represent the standard of care, placebo (in the meaning of no other medication) is however not considered to be the appropriate comparator and therefore will not be included as a relevant comparator. Tiotropium scores better on several outcome measures in comparison to ipratropium, but not in comparison with salmeterol. Salmeterol is less expensive than tiotropium but more expensive than ipratropium. Just like tiotropium, ipratropium is an anticholinergic drug. However, ipratropium is a short-acting bronchodilator for symptomatic treatment. In contrast, tiotropium and salmeterol are long-acting brochodilator medications for maintenance treatment of COPD. Therefore, we only include salmeterol as a valid comparator for tiotropium in our analyses. In the real-world Belgian tiotropium database, it is observed that the real world comparator is more a combination of other drugs, which is also the case in the UPLIFT trial.

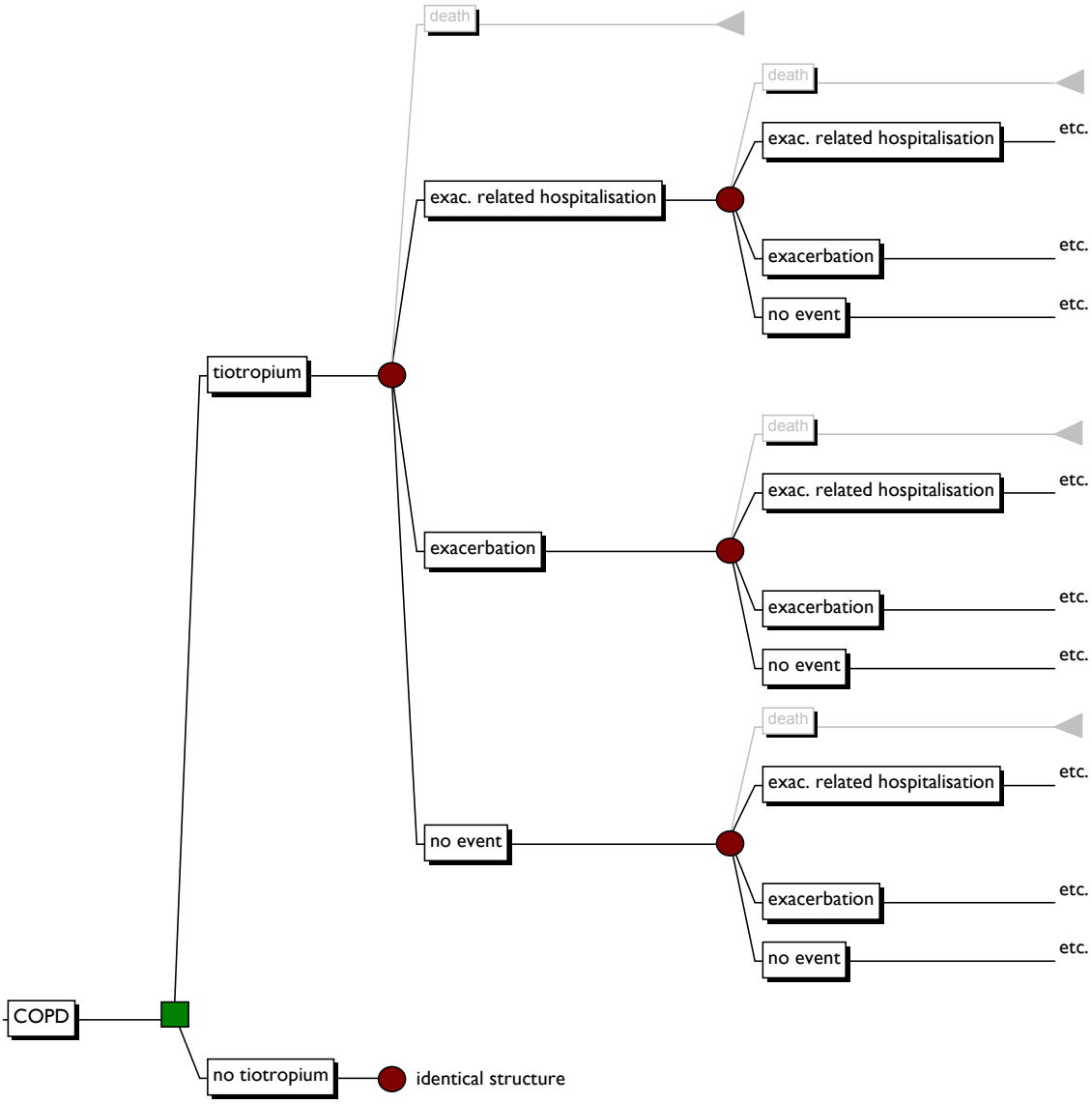
9.1.6 Structure of the model

The structure of the model reflects on which events tiotropium treatment may have an influence. As shown in Figure 30, these are exacerbations and hospitalisations due to exacerbations. It is important to make a distinction in the model between these two variables since both the costs and the influence on these events due to tiotropium versus its comparator differ strongly.

The disease course of COPD is more complex than this model shows. However, to calculate an intervention's cost effectiveness, only incremental costs and effects are of interest. For example, since there is no proven impact on mortality, this event is left out (shown in grey in the figure).

The model does not differentiate during which week or month of the year the events occur. A patient could of course have multiple events during one year, and therefore, the number of events is cumulated over the one year time window.

Figure 30: decision model on tiotropium use for COPD patients



9.1.7 Year of information

In our database, the first attestation for tiotropium can fall between March 1, 2004 and December 31, 2005. As a result, the year before the first attestation can fall between March 1, 2003 and December 31, 2005.

The year after the first attestation can start for some patients on March 1, 2004 up to December 31, 2005 and end somewhere between March 1, 2005 and December 31, 2006. Information on baseline risks for certain events (i.e. exacerbations and exacerbation-related hospitalisations) without tiotropium and costs for other medication will be based on the year before the first tiotropium attestation.

Details on the costs for tiotropium were based on the first year after the first attestation. Information on prices/costs for hospitalisations was based on the complete database (2002-2006).

9.1.8 Costs

The model clearly distinguishes three categories of cost which may influence the incremental cost, i.e. differences due to the use of more or less expensive medication, and due to more or less exacerbations and/or exacerbation-related hospitalisations. An overview of these and other input parameters is provided in the following table.

Table 38: input parameters for the economic evaluation

Input variable		base-case value	Range (95% CI)		Source
Costs (€)					
medication					
tiotropium	real-world all[a]	427,71	426,25	429,17	Belgian database
	theoretical	621,00	/	/	BCFI
	real-world subgr.[c]	565,10	562,15	568,05	Belgian database
salmeterol	real-world[b]	225,46	223,00	227,92	Belgian database
	theoretical	374,88	/	/	BCFI
	real-world subgr.[c]	279,89	272,92	286,86	Belgian database
exacerbation	theoretical	52,72	41,34	64,48	result 1000 simulations
exac.-rel. hosp.					
cost	hosp. prim.	5617	5555	5680	Belgian database
*price**	*hosp. prim.*	*2580*	*2548*	*2613*	Belgian database
Utilities					
exac.-rel. hosp.	QALYgained**	0,013	0,004	0,019	result 1000 simulations
at admission		-0,077	-0,58	0,79	O'Reilly et al., 2007
at discharge		0,58	-0,16	0,98	O'Reilly et al., 2008
LOS		14,18	14,02	14,34	Belgian database
exacerbation	QALYgained**	0,003	0,001	0,005	result 1000 simulations
Events (average per patient)					
exacerbations		0,800	0,775	0,826	Roede et al., 2006 + Belgian database
exac. rel. hosp.		0,141	0,137	0,144	Belgian database
Efficacy/effectiveness					
exacerbation					
base case	relative risk[d]	0,86	0,81	0,91	Tashkin et al., 2008
scenario	relative risk[e]	0,87	0,72	1,05	Brusasco et al., 2003
exac.-rel. hosp.					
base case	relative risk[d]	0,94	0,82	1,07	Tashkin et al., 2008
scenario	relative risk[e]	0,59	0,33	1,05	Brusasco et al., 2003

BCFI: Belgian Centre for Pharmacotherapeutic Information; LOS: length of stay; NIHDI: National Institute for Health and Disability Insurance

*: the (higher) adjusted cost instead of the price was included in the base case analysis (see part 8.3.3.3 for further explanation).

**: average QALY gained per event avoided

Result of 1000 simulations: the uncertainty for these input variables depends on the uncertainty of other variables (as explained in the text). The resulting 95% CI are based on the 1000 simulations.

a: based on the first year of tiotropium use; b: based on the year before the first use of tiotropium; c: subgroup with 'DDD vs number of days' ratio between 90 and 100%; d: using the published 95%CI to define our distibution results in the following mean values in the model: 85.85% instead of 86% and 93.67% instead of 94%. e: exact numbers were not published in the published paper. The calculation of these numbers is explained in part 9.1.10

9.1.8.1 Medication

In the analyses, the real expenditures, including the costs for the NIHDI and patient co-payments, are taken into account. For the general selected population, this cost was on average €427.71 for tiotropium (Table 38). The descriptive part of our observational database showed there is no clear indication for a decrease in the use of salmeterol or other medication when patients started taking tiotropium. Although these are only observational data, with severe limitations as discussed before, these costs were left unchanged in the base case scenario. In a scenario analysis, these costs, which amounted to €225.46 for salmeterol the year before tiotropium was started (Table 38), were subtracted.

In the scenario for the more selective population, the adjusted costs were considered being €565.10 and €279.89 for tiotropium and salmeterol, respectively (Table 38).

Details on the price, including both the cost for the NIHDI and the patient co-payment, were described earlier in this report (see part 8.2). For tiotropium, taking into account the proposed dose of 18µg per day, the monthly cost (30 days) is €51.75. For salmeterol, taking 50µg twice per day, this cost would amount to €31.24 per month. On a yearly basis, the theoretical cost would be €621 for tiotropium and about €375 for salmeterol. A scenario analysis assuming that tiotropium would be taken exactly for 12 months is also considered. In this scenario, the observed salmeterol costs were subtracted.

9.1.8.2 Exacerbation

Exacerbations are defined on the basis of health care resources use. The proxy used was the delivery of oral corticosteroids and antibiotics within 7 days (see 8.3.3.2). As such, the number of exacerbations was underestimated since not all exacerbations are treated as such. As described before, a Dutch study found that steroids combined with an antibiotic were prescribed in 23% of exacerbations. This factor was taken into account in our model resulting in an average number of exacerbations of 0.8 per patient during one year, which was in line with the yearly exacerbation frequency in the UPLIFT trial (0.85 and 0.73 in the placebo and tiotropium group, respectively).

The cost per exacerbation was defined theoretically. The dosis of bronchodilators may be increased and oral steroids (7-10 days 30-40mg prednisolone) and antibiotics (3-7 days in case of certain symptoms) may be prescribed. For our calculation, we included the costs for oral steroids and antibiotics including a uniform distribution on the number of days, i.e. 7-10 days and 3-7 days for both drugs, respectively. The price for prednisolone was €31.5 for 20 units of 32mg, i.e. €1.58 per day. With respect to antibiotics, a daily cost of €1.13 was taken into account (amoxicilline (Docamoxi - 500 mg) taken 3 times a day (1500mg/day) costs €6.02 for 16 units). We also added one to two visits (uniform distribution) to the doctor (€22.46 per visit). As a result, the price for an exacerbation not requiring hospitalisation was on average €52.72 (Table 38).

9.1.8.3 Exacerbation-related hospitalisation

The number of and cost for exacerbation-related hospitalisations were calculated in the previous chapter. Taking all hospitalisations into account or those with a primary or secondary description of COPD would obviously result in a too broad selection. Therefore, two alternative descriptions were set up and analysed, i.e. those with a primary diagnosis of COPD or those with a primary diagnosis and treated in one ward related to COPD (or two if one of these wards was the emergency unit). For our model, the most optimistic scenario for tiotropium was chosen. This resulted in an average of 0.14 hospitalisations per patient (Table 38). With respect to costs, not the price but the adjusted (higher) cost for hospitalisation was taken into account in the base case. Again, the most optimistic cost for tiotropium (i.e. the highest hospitalisation cost) was taken into account being €5617 on average (Table 38). In a scenario analysis, the lower price (not adjusted for the fact that there are 2 distinct systems of public health funding (see 8.3.3.3) of €2580 was considered (Table 38).

9.1.9 Utilities

Tiotropium may avoid exacerbations and exacerbation-related hospitalisations. Next to changes in costs, this also entails changes in utilities. Therefore, for both exacerbations and exacerbation-related hospitalisations QoL data were searched. A quick search for QoL data was performed in PubMed and Embase in January 2009. Details on the followed search string are available in appendix. 67 references were identified in Pubmed, 145 in Embase. 48 duplicates were removed and the remaining 164 references were further selected based on title and abstract. The full text of 14 relevant articles was retrieved.

Only one article explicitly stated general QoL outcomes associated with COPD exacerbation managed in hospital.[129] All others measured QoL for populations as a whole. The latter is less useful in our model since changes in QoL for the population as a whole is linked to several aspects being: a) the number of exacerbations without tiotropium (the baseline risk), b) the treatment effect (the relative risk indicating how many events could be avoided), and c) the changes in QoL by avoiding an event. Transferring the QoL changes in a specific population to another population with for example a very different baseline risk would be incorrect. Therefore, in our model, these three elements are included separately, with the baseline risk for the relevant events based on observational real-world data and the treatment effect on trial results.

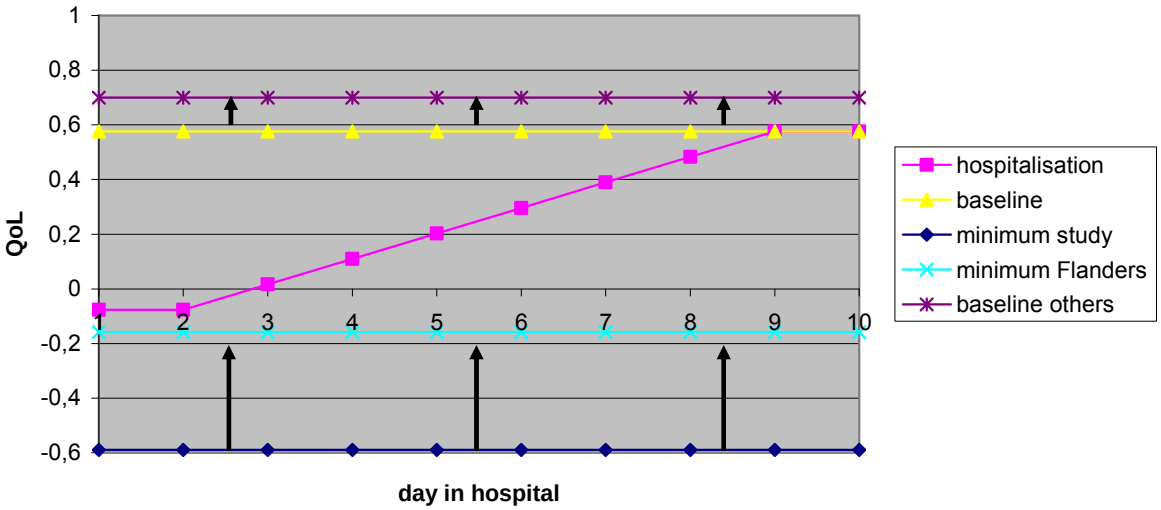
The study of O'Reilly used a preference-based quality of life measure questionnaire (EQ-5D) to evaluate the impact of exacerbation on health status and utility during a patient's admission to hospital and short-term follow-up. 149 patients were included in the study representing 222 admissions to hospital. For each admission, the admission utility value was obtained (if it was within 3 days of being admitted) along with the discharge value (if it was within the 3 days prior to discharge).

At admission patients reported high levels of problems for all dimensions of the EQ-5D. Mean utility (-0.077, SD: 0.397) indicated great impairment, with 61% of patients having a negative utility value representing a health state equivalent to 'worse than death' at admission. Great improvements were reported during admission. At discharge, the mean utility value was increased to 0.576 (SD: 0.317). Three months post-discharge, patients' health status was deteriorated again. In our model, only the loss in QoL during hospitalisation is included. What happens in the months before or after the hospitalisation is assumed not to be influenced by taking tiotropium or one of its alternatives (unless the patient has other exacerbations or exacerbation-related hospitalisation).

The utility scale ranged from -0.59 to 1.00. The weights used to obtain the utility were based on the data collected from a representative survey of the UK general population. In the Belgian pharmaco-economic guidelines, however, the utility scale ranges from -0.1584 to 1.00, relying on Flemish EQ-5D index values (Flanders is a geographical area in the northern part of Belgium).[126] We preferred not to adjust the utility values from O'Reilly's study. The following figure, which shows the example of a 10-day hospitalisation, helps to explain our reasoning. On the one hand, the minimum in the UK study was -0.59 and thus much lower than the minimum value in Flanders (-0.1584). Adjusting minimum values would result in an increased value at admission. On the other hand, at discharge, the mean value was only 0.576, which was assumed to be the baseline value, i.e. the value if there was no hospitalisation. This value, however, was measured when patients were still in hospital. When they are at home, their QoL could be higher. Other studies also indicate higher values for mild, moderate, severe and even very severe COPD. Pickard et al.[130] gathered sufficient studies in COPD to calculate pooled mean utility scores according to GOLD stage, which were the following: stage I = 0.74 (0.62–0.87), stage II = 0.74 (0.66–0.83), stage III = 0.69 (0.60–0.78) and stage IV = 0.61 (0.44–0.77) (most severe). This means that the baseline value could have been higher than the value at discharge in O'Reilly's study. However, we have to take into account that in reality, the comorbidities may be higher than in the selective trial populations.

In the interpretation of the health status data, the authors noted that there was a high level of comorbidity amongst these patients which could affect the findings of the generic measure used. With respect to the gain in QoL, both adjustments (having a higher baseline and having a higher minimum value) could balance out. Therefore, it was preferred to keep the values as they were in O'Reilly's analysis. This means that the value of -0.077 with its uncertainty (SD: 0.397) was taken for the first days in hospital and a value of 0.576 with its uncertainty (SD: 0.317) for the last days. In between, a linear extrapolation was assumed. The loss is indicated by the area between this line ('hospitalisation' in Figure 31) and the baseline ('baseline' in Figure 31). A correlation of 0.9 was implemented between the value at admission and discharge to avoid increases of more than 1.1584 (i.e. the maximum difference according to the Flemish EQ-5D utility scale). This was checked in the output (were applying a correlation of 0.9 resulted in a maximum difference of 1.1539 after 1000 simulations). For the length of stay, similar as for the hospitalisation frequency and cost, the most optimistic scenario (i.e. the longest stay) was taken in to account, being 14.02 days on average (Table 38).

Figure 31: QoI during hospitalisation



With respect to exacerbations, no studies were identified reporting changes in QoL during such an event measured with a generic QoL instrument. All studies made assumptions on the QoL deterioration. During the month following an exacerbation, it was 'estimated' that utility values would reduce by 15% in case of non-severe exacerbation (referring to Paterson et al.[122]), and by 50% in case of severe exacerbation (referring to Spencer et al.[123]) (see Table 21).[93, 96, 99] These values are, however, not mentioned in the referred studies (see further comments in the discussion).

The study of Borg et al.[115] mentioned that at that time, there were no available data on QALY weights during exacerbations. The size of the decrease in QoL was dependent on the severity of the exacerbation, and defined as follows:

- Mild exacerbation, 5% (assumption by expert panel);
- Moderate exacerbation, 15% (assumption by expert panel);
- Severe exacerbation, 70% (derived from asthma data and a severe asthma exacerbation was judged by the expert panel to be equivalent to a severe COPD exacerbation).

In their study they used a resource-driven staging developed from Rodriguez-Roisin:[131]

- Mild, if the patient can manage in his or her normal environment, including phone calls to a doctor that might be followed by a treatment with antibiotics or oral steroids;
- Moderate, if the patient must make an unscheduled visit to the doctor; or
- Severe, if the patient requires hospitalization or emergency room visit.

In our model, only a distinction was made between the first two (mild & moderate) and the latter category (severe). For exacerbation-related hospitalisations, QoL values relied on the previous mentioned O'Reilly study. For exacerbations not requiring hospitalisations, a similar relative proportion in reduction towards the reduction for hospitalisation was taken. In the three economic evaluations,[93, 96, 99] which were all based on the same model, this relative ratio was 50% versus 15% reduction or a relative ratio of 3.33. In Borg et al.[115] this was 70% versus 15% (looking at moderate exacerbations) or a relative ratio of 4.67. The average was taken into account in our model, i.e. a relative ratio of 4, with a minimum of 3.33 and a maximum of 4.67 (uniform distribution). In other words, the QALYs lost due to exacerbations are assumed to be on average one fourth of the QALYs lost due to an exacerbation-related hospitalisation.

9.1.10 Efficacy/effectiveness

Tiotropium may have an influence on the number of exacerbations and exacerbation-related hospitalisations. The treatment effect depends on the comparator taken into consideration. We provide details on two trials, the large UPLIFT trial comparing tiotropium with placebo (indicating 'current treatment'),[48] and a trial comparing tiotropium with salmeterol.[30]

We are interested in the treatment effect of tiotropium versus its comparator on exacerbations and exacerbation-related hospitalisations. In our model, not only the mean treatment effect but also the uncertainty around this mean has to be taken into account. Since one of the trials[30] did not mention these confidence intervals for the events we are interested in, we calculated an approximation of the intervals based on the analysis of rates. "*The analysis of rates is usually done using rate ratios. The rate ratio is defined as:*

$$\frac{\text{rate in exposed}}{\text{rate in unexposed}} = \frac{\lambda_1}{\lambda_0} = \frac{d_1 / T_1}{d_0 / T_0} = \frac{d_1 \times T_0}{d_0 \times T_1}$$,

where λ is the rate per x-year(s) at risk, d is the number of events, and T is the number of years at risk. "*The standard error of the log rate ratio is used to derive confidence intervals, and tests of the null hypothesis of no difference between the rates in the two groups. This is given by:*

$$\text{s.e. of log(rate ratio)} = \sqrt{1/d_1 + 1/d_0}\ .$$

The 95% confidence interval for the rate ratio is:

$$95\%\ \text{CI} = \text{rate ratio} / \text{EF to rate ratio} \times \text{EF},$$

$$\text{where EF} = \exp[1.96 \times \text{s.e. of log(rate ratio)}]$$

A z-test (Wald test) of the null hypothesis that the rates in the two groups are equal is given by:

$$z = \frac{\log(\text{rate ratio})}{\text{s.e. of log(rate ratio)}}$$."[132]

The calculated p-values were compared with the published p-values to see whether this approach resulted in reliable confidence intervals. More details and results of these calculations are given below (9.1.10.1).

9.1.10.1 Tiotropium versus salmeterol: Brusasco et al. trial

The study of Brusasco et al.[30] enrolled patients with COPD in two 6-month randomised, placebo controlled, and double blind studies of tiotropium (n=402) or salmeterol (n=405) or placebo (n=400). The number of exacerbations per patient-year was 1.23 in the salmeterol group and 1.07 for tiotropium. This difference was not significant (p=0.222). For hospital admissions due to exacerbations, expressed as events per patient year, this was 0.17 and 0.10 in the salmeterol and tiotropium group, respectively, which was not statistically different (no p-value given).

No rate ratios and exact confidence intervals were published for these treatment effects. However, in an economic evaluation, uncertainty around input variables should be taken into account. The authors mentioned the Wilcoxon-Mann-Whitney test was used to analyse the number of exacerbations and hospital admissions for an exacerbation. We do not dispose of detailed study results. However, the confidence interval could be approached applying the published event rates and the approximated number of events. The latter is estimated by combining (a) the average number of patients that were enrolled and completed tiotropium (n = 402 and 340, resp.) or salmeterol (n = 405 and 329, resp.), (b) the duration of the trial (6 months), and (c) the number of exacerbations per patient-year or hospital admissions due to exacerbations. As such, the number of events was estimated, i.e. 198.49 and 225.71 exacerbations and 18.55 and 31.20 hospitalisations related to exacerbations, in the tiotropium and salmeterol group, respectively. Together with the number of events per patient-year, a 95% CI around the rate ratio was calculated (see formulas in 9.1.10). This resulted in a relative risk for exacerbations of 86.99% (95% CI: 71.89% - 105.27%), and a relative risk for hospital admissions due to exacerbations of 58.82% (95% CI: 33.11% - 104.50%) with tiotropium versus salmeterol. The published p-value was 0.22 for exacerbations while it was 0.15 with our approximation. In other words, our approximation is not perfect but it results in rather more optimistic (still not significant) results than the correct (unpublished) results. For hospitalisations, there was no p-value published to compare our 0.07 p-value with.

9.1.10.2 Tiotropium versus salmeterol: meta-analysis

As mentioned in the systematic review of the literature, two studies comparing tiotropium with salmeterol reported non-significant p-values for the difference in exacerbation frequency. Since one study[56] did not provide details on the exact results, only one study could be included in the meta-analysis, i.e. the study of Brusasco et al, for which details are described in the previous section. Similar for hospitalisation frequency, these two studies reported non-significant p-values, but no exact results were provided. As a result, no results from a meta-analysis are available, and only the results from the previous section were included in a scenario. It should be remarked that these relative treatment effects are influenced by publication bias (see 5.2.3.1, 5.2.3.2, and 5.2.3.7).

9.1.10.3 Tiotropium versus 'placebo': UPLIFT trial

Recently, results of the UPLIFT trial have been published. In this randomized, double-blind trial, 4 years of tiotropium treatment was compared with placebo in patients with COPD who were permitted to use all respiratory medications except inhaled anticholinergic drugs. The patients were at least 40 years of age, with a postbronchodilator FEV1 of 70% or less than the predicted value and a ratio of FEV1/FVC of 70% or less. In this very large trial, 2987 and 3006 patients were randomly assigned to the tiotropium and placebo group, respectively.[48] In this trial, the hazard ratio for COPD exacerbations was 0.86 (95% CI: 0.81 – 0.91; p-value <0.001). For exacerbations leading to hospitalisations this was 0.94 (95% CI: 0.82 – 1.07; p-value = 0.34).

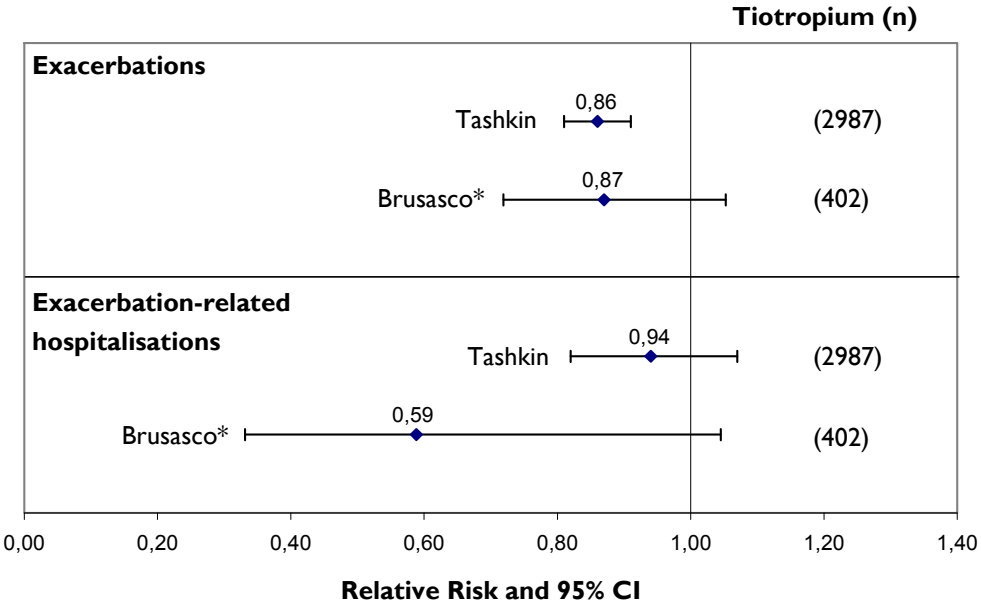
9.1.10.4 Base-case scenario: UPLIFT

In chapter 8, we observed that there was no reduction in the use of other medication. In other words, tiotropium was possibly not (always) replacing other treatments, but probably rather given in addition to other treatments. In the UPLIFT trial, placebo means that patients were permitted to use all respiratory medication except inhaled anticholinergic drugs. A long-acting inhaled β2-agonist was used in 60.1% of both treatment arms.[48] In the Belgian database, it was observed that these drugs were also used for patients that took tiotropium.

Therefore, both because of its size and because it seems to correspond better to what happens in reality, the treatment effects and the surrounding uncertainty from the UPLIFT trial are included in the base case scenario. The relative risks and confidence intervals of the smaller Brusasco trials are considered in a scenario analysis.

As shown in Figure 32, in comparison with the UPLIFT trial, the confidence intervals around the relative risks for the events of interest are much larger in the smaller trial. Moreover, the mean for exacerbation-related hospitalisations of the UPLIFT trial is located in the upper part of the confidence intervals around the relative risks in the smaller trial. In contrast to the non-significant effect on exacerbation frequency from the trials comparing tiotropium with salmeterol, a significant treatment effect was found in the UPLIFT trial. These differences have to be taken into account when comparing the results of the base case and scenario analyses.

Figure 32: Treatment effect for exacerbations and exacerbation-related hospitalisations



* Confidence intervals were not mentioned in the publication but approximated using calculations for rate ratios. The systematic review found indications for publication bias in the comparison of tiotropium versus salmeterol.

9.1.11 Scenario analyses

Some scenarios are already explained in the previous sections. We bring them together in this part, together with some additional scenarios. Table 39 gives an overview of the base case and scenario analyses.

Table 39: overview of base case and scenario analyses

	Base case	Scenario(s)
Population	The base case scenario contains '*general tiotropium users*', defined as follows: 1) Patients must have more than one attestation (on multiple days) 2) The total number of DDDs is ≥ 90 in one year. 3) The expenditure for tiotropium is more than €120 in one year. 4) The DDD average must be larger than 90/365. 5) The patient must have at least one year of data before the first attestation for tiotropium. 6) The patients must have at least one year of follow-up data in the database.	A scenario analysis is performed for '*selected tiotropium users*'. For this category of patients, the fourth item is stricter only selecting patients with a DDD average between 90 and 100%. This scenario is referred to as 'subgroup' (versus 'All').
Medication costs tiotropium and salmeterol	Tiotropium and salmeterol costs observed in our database are taken into account	Costs for salmeterol are left out of consideration in a scenario, i.e. these costs are subtracted from the extra costs for tiotropium as observed in our database. In the result section, this scenario is called scenario 1. Theoretical tiotropium costs for a patient using 12 packages in a year are considered and patients do not take salmeterol anymore. This scenario is called scenario 2.
Treatment effect	The treatment effects as in the *UPLIFT* trial[48] are taken into account.	The *Brusasco*-trial results[30] are taken into account for comparing salmeterol with tiotropium.
Exacerbations and exacerbation-related hosp.	The average number of exacerbations and exacerbation-related hospitalisations are considered.	Scenario analyses are performed depending on the combination of an absolute number of exacerbations and exacerbation-related hospitalisations.
Hospitalisation cost	The 'cost' for a hospitalisation is taken into account, which is an adjustment of the 'price' for a hospitalisation (see 8.3.3.3).	The 'price' for a hospitalisation is taken into account

9.1.12 Probabilistic sensitivity analysis

In an economic evaluation, the uncertainty of the output (IC, IE and ICERs) depends on the uncertainty and relative importance of the input variables. Furthermore, because the output of models (mostly) results from a nonlinear combination of inputs, calculating with deterministic mean values would not provide the correct mean outcome. As mentioned by Briggs et al:[133] $E[g(.)] \neq g(E[.])$ or '*the expectation of the transformation does not equal the transformation of the expectation*'.[134] To capture the parameter uncertainty, input variables in our model are probabilistic values. In contrast to deterministic modelling, multivariable probabilistic modelling takes into account the uncertainty around the values of all input variables at the same time, which is reflected in the uncertainty of the results. This is done by determining probability distributions instead of point estimates for the input variables. Then, simulations are performed. In each iteration, a random draw from the pre-specified probability distributions is made to generate a result. After 1000 simulations, the uncertainty of the result can be measured. Results are presented with 95% credibility intervals.[f]

Performing multivariable probabilistic modelling enables performing probabilistic sensitivity analysis. In contrast to one-way sensitivity analysis, which sets the value of a specific variable at a certain alternative value, probabilistic sensitivity analysis on multiple variables reflects the combined implications of uncertainty in parameters. Using this approach, 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 results. This helps determining the importance of the uncertainty around different input parameters on the result. All modelling is performed in excel and the software package @risk(DecisionTools Suite 4.5, Palisade, London, UK).

Next to the decision of inclusion of probabilistic variables, the choice of distribution has to be determined. This choice depends on the characteristics of the input variables. Due to our large number of observations, the central limit theorem can be applied, which states that the sampling distribution of the mean will be normally distributed irrespective of the underlying distribution of the data with sufficient sample size.[133] All the cost parameters based on the large database are modelled as normal distributions with the appropriate confidence interval around the mean.

The cost for an exacerbation, which was set up theoretically, was calculated by multiplying the cost for antibiotics, steroids and a doctor visit with their specific amounts reflecting the duration of taking medication or the number of doctor visits. These numbers were included as uniform distributions. The relative ratio with a mean value of 4, describing the QALYs lost for an exacerbation versus an exacerbation-related hospitalisation, was also modelled with a uniform distribution varying between 3.33 and 4.67.

For QoL variables at admission and discharge, beta distributions were applied. The normal beta distribution is constrained on the interval 0-1 and is an ideal distribution for QoL values, which normally are situated in this interval. However, the study of O'Reilly provided QoL data during an exacerbation-related hospitalisation with negative values. The minimum of the outcomes could be -0.59 and the maximum remained equal to 1. If the minimum and maximum are equal to 0 and 1, then the parameters of the beta distribution (α_1 and α_2) can be calculated using the method of moments, in which:[133]

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[f] Credibility interval: confidence interval around a cost-effectiveness ratio resulting from an economic model. In contrast to statistical confidence intervals, the values within a credibility interval are not actually observed but result from a mathematical model, making assumptions about the relationships and distributions of input variables.[135]

$$\text{mean} = \frac{\alpha_1}{\alpha_1 + \alpha_2}$$

$$\text{variance} = \frac{\alpha_1 \times \alpha_2}{(\alpha_1 + \alpha_2)^2 \times (\alpha_1 + \alpha_2 + 1)}$$

If the minimum and maximum are not equal to 0 and 1, the parameters for the adjusted beta distribution can be calculated using the following formulas:

$$\text{mean} = \min + \frac{\alpha_1}{\alpha_1 + \alpha_2} \times (\max - \min)$$

$$\text{variance} = \frac{\alpha_1 \times \alpha_2}{(\alpha_1 + \alpha_2)^2 \times (\alpha_1 + \alpha_2 + 1)} \times (\max - \min)^2$$

Finally, the relative risk parameters are modelled using the lognormal distribution, reflecting the published mean values and the (approximated) 95% CI. An overview of the parameters and their surrounding uncertainty is provided in Table 38.

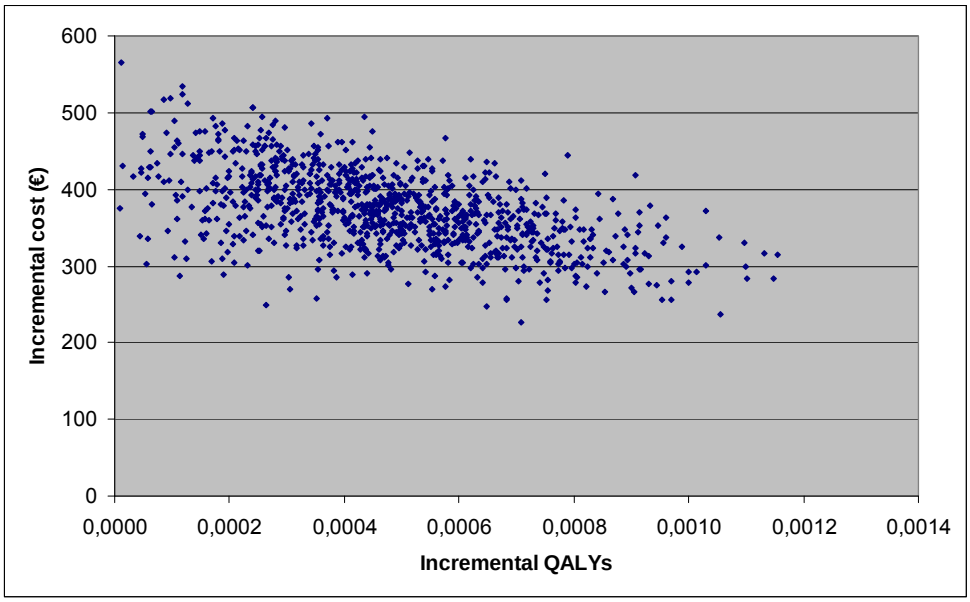
9.2 RESULTS

Results of the economic evaluation are described in this part. First, the base case scenario is presented. Next, the results of the scenario analyses are provided.

9.2.1 Base case

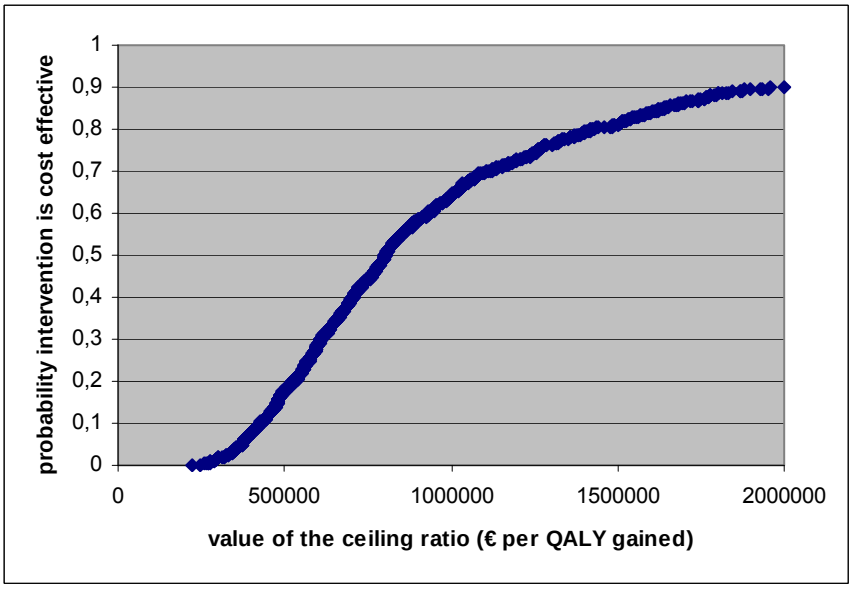
The results of the 1000 simulations are presented in Figure 33. The mean incremental cost is €373 per patient (95% CI 279 – 475). This incremental cost is composed of the following three elements: incremental cost medication: €427.71 (95% CI 426.25 – 429.17), incremental cost related to hospitalisations: -€48.26 (95% CI -143.11 – 55.61), and the incremental cost related to exacerbations: -5.95 (95% CI -8.76 – -3.56). The UPLIFT non-significant treatment effect on hospitalisations and the significant treatment effect on exacerbations are reflected in the confidence interval surrounding the incremental cost for hospitalisations and exacerbations, respectively. The incremental benefit expressed as QALYs gained are on average 0.00048 (95% CI 0.00009 – 0.00092). This is relatively low due to the combination of the following factors: a) a low number of hospitalisations without tiotropium treatment, b) a non-significant treatment effect (on average 0.94) with respect to avoiding exacerbation-related hospitalisations, and c) the relatively short duration that this event influences QoL (probably on average two weeks). In combination with the non-negligible incremental costs, this resulted in an unfavourable ICER of €1 244 023 per QALY gained.

Figure 33: Cost effectiveness plane (base case analysis)



The cost-effectiveness acceptability curve presents the probabilitiy that tiotropium is cost effective, depending on a given threshold value for a QALY. This curve started at a value of about €225 000 and levelled of at values above €2 000 000 per QALY. At a lower willingness to pay for a QALY, the treatment is considered not to be cost effective.

Figure 34: Cost-effectiveness acceptability curve (base case analysis)

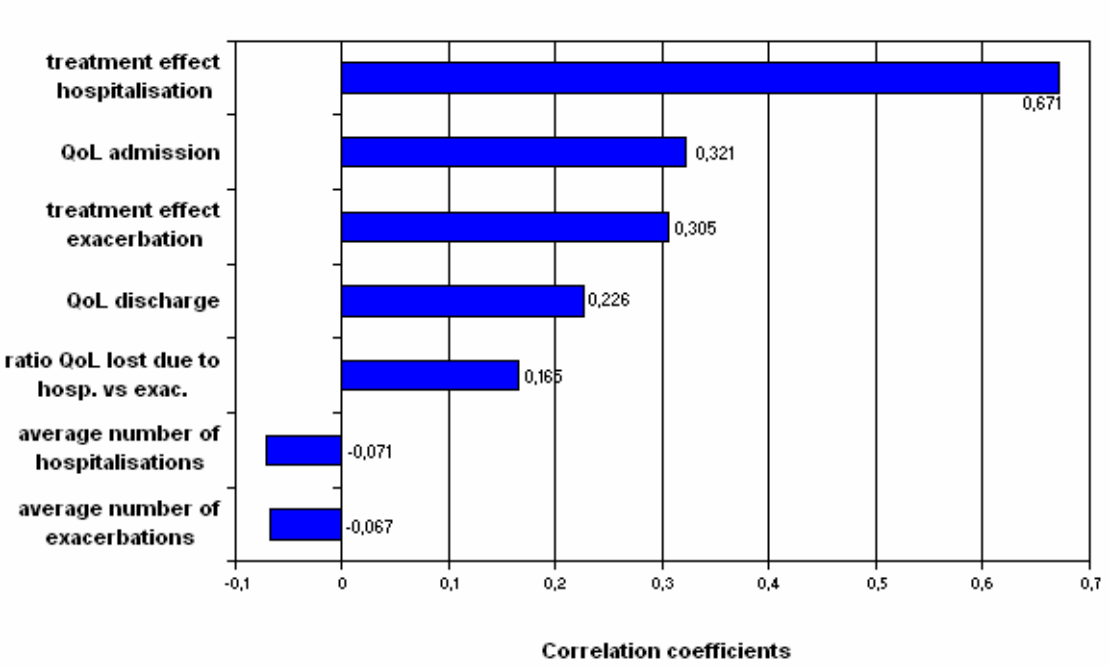


The results of the probabilistic sensitivity analysis are illustrated in Figure 35. It shows which parameters (with their uncertainty) contribute the most to the uncertainty surrounding the ICER. The treatment effect on hospitalisations has the highest correlation coefficient, i.e.0.671. It should be mentioned that the ICER is very dependent on the average number of hospitalisations, which in combination with the treatment effect determines the absolute gain in hospitalisations avoided. However, the number of hospitalisations was based on a very large database, which resulted in a small confidence interval for this input parameter.

As a result, although being a very determinant variable, this input parameter did not have a high correlation coefficient (-0.071) with the uncertainty surrounding the ICER.

In the scenario analysis including the initial number of hospitalisation and/or exacerbation, this large influence will be demonstrated.

Figure 35: Correlation coefficients between uncertainty surrounding input variables and the ICER (base case analysis)



9.2.2 Scenario analyses

All scenarios that apply the treatment effects as published in the UPLIFT trial have rather unfavourable ICERs. Comparing the base case with scenario 1 and 2 shows that the possible cost savings by replacing salmeterol (instead of in addition to as observed in reality) are not enough to provide favourable ICERs (Table 40). Results for the subgroup of intensive tiotropium users are comparable. This is not surprising since this was a scenario in which only the influence on costs was changed. Similar findings are noticed in the scenario changing the cost of hospitalisation (Table 41). With lower hospitalisation costs, the incremental costs are even higher than in the base case scenario. For all scenarios, the incremental benefit is very low due to the low baseline risk for hospitalisation and the relative small and non-significant influence of tiotropium on this event.

Table 40: Incremental cost-effectiveness ratios (ICERs) and 95% CI for several scenarios applying the treatment effects from the UPLIFT trial (All versus subgroup, and base case versus scenario 1 and 2)

		incremental cost (€)		incremental benefit (QALYs)		ICER (€ per QALY gained)	
		2.5%	97.5%	2.5%	97.5%	2.5%	97.5%
UPLIFT							
base case	All	373		0,00048		1244023	
		279	475	0,00009	0,00092	328571	4712704
	subgroup	511		0,00048		1677775	
		415	612	0,00009	0,00092	481885	6038866
scenario 1	All	148		0,00048		532706	
		52	251	0,00009	0,00092	71268	2256191
	subgroup	231		0,00048		795123	
		137	333	0,00009	0,00092	167159	3186211
scenario 2	All	341		0,00048		1142478	
		246	445	0,00009	0,00092	295004	4396273
	subgroup	287		0,00048		971144	
		195	389	0,00009	0,00092	230954	3794068

Table 41: Incremental cost-effectiveness ratios (ICERs) and 95% CI for the scenarios including hospital prices instead of costs (applying the treatment effects from the UPLIFT trial, All, and base case versus scenario 1 and 2)

		incremental cost (€)		incremental benefit (QALYs)		ICER (€ per QALY gained)	
		2.5%	97.5%	2.5%	97.5%	2.5%	97.5%
UPLIFT							
base case	All	400		0,00048		1291069	
		356	446	0,00009	0,00092	397683	4451077
scenario 1	All	174		0,00048		579751	
		130	221	0,00009	0,00092	153781	2192855
scenario 2	All	367		0,00048		1189524	
		323	415	0,00009	0,00092	362411	4101340

In the Brusasco trial, the average treatment effect on avoiding exacerbation-related hospitalisations was more favourable (i.e. being 0.59 versus 0.94 (Table 38)) but still not significant. This is clearly reflected in the lower incremental cost and higher incremental benefit (Table 42). Nevertheless, in the base case (i.e. were the salmeterol costs are not influenced), the ICER remains relatively high. Only when we take into account the extra costs for tiotropium treatment as observed in reality (and not 12 packages a year) and we assume that salmeterol is not taken anymore, and the treatment effect from the Brusasco trial are modelled, then on average there are cost savings. The surrounding 95% CI around the incremental cost is wide due to the high uncertainty surrounding the treatment effect. However, it should be stressed that this scenario, based on the observations, is not realistic and that in the base case, even with the treatment effect from the Brusasco trial, the ICERs are still relatively high.

Table 42: Incremental cost-effectiveness ratios (ICERs) and 95% CI including the treatment effects from the Brusasco trial (All versus subgroup, and base case versus scenario 1 and 2)

		incremental cost (€)		incremental benefit (QALYs)		*deterministic*
		2.5%	97.5%	2.5%	97.5%	
Brusasco						
base case	All	118		0,00101		*116121*
		-108	460	0,00009	0,00209	
	subgroup	255		0,00101		*251527*
		31	595	0,00009	0,00209	
scenario 1	All	-108		0,00101		*cost saving*
		-334	234	0,00009	0,00209	
	subgroup	-25		0,00101		*cost saving*
		-250	313	0,00009	0,00209	
scenario 2	All	86		0,00101		*84414*
		-140	427	0,00009	0,00209	
	subgroup	31		0,00101		*30771*
		-194	371	0,00009	0,00209	

Table 43: IC, IE and ICERs depending on the initial number of hospitalisations and exacerbations (applying the treatment effects from the UPLIFT trial)

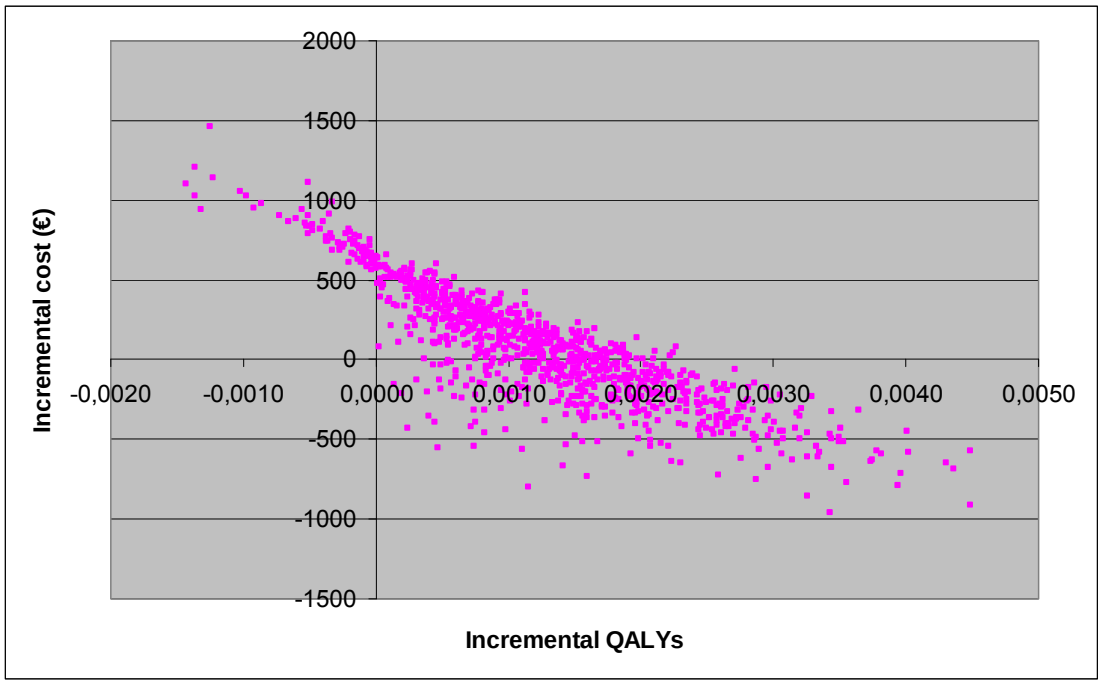
prior number of exacerbations	prior number of hospitalisations: 0			1			2		
	IC	IE	ICER	IC	IE	ICER*	IC	IE	ICER*
0	428 426 429	0,0000 0,0000 0,0000	dominated	84 -581 819	0,0008 -0,0009 0,0027	*107666*	-259 -1589 1211	0,0016 -0,0017 0,0054	*cost saving*
1	420 416 424	0,0005 0,0001 0,0008	1265951 497057 4154369	77 -590 812	0,0012 -0,0004 0,0033	*62094*	-266 -1599 1204	0,0020 -0,0013 0,0061	*cost saving*
2	413 406 419	0,0009 0,0002 0,0017	622357 242740 2049176	70 -599 805	0,0017 0,0000 0,0039	*41019*	-274 -1608 1196	0,0025 -0,0008 0,0066	*cost saving*
3	405 395 415	0,0014 0,0003 0,0025	407826 158255 1338516	62 -608 797	0,0022 0,0002 0,0046	*28873*	-281 -1617 1189	0,0029 -0,0003 0,0072	*cost saving*
4	398 384 410	0,0018 0,0004 0,0034	300561 116258 983186	55 -618 790	0,0026 0,0003 0,0053	*20974*	-289 -1626 1182	0,0034 0,0000 0,0077	*cost saving*
5	391 374 406	0,0023 0,0005 0,0042	236201 90683 769988	47 -627 780	0,0031 0,0005 0,0061	*15425*	-296 -1635 1175	0,0038 0,0003 0,0085	*cost saving*
6	383 363 401	0,0027 0,0006 0,0050	193295 74097 627857	40 -634 770	0,0035 0,0007 0,0068	*11314*	-303 -1645 1167	0,0043 0,0004 0,0092	*cost saving*
7	376 352 397	0,0032 0,0007 0,0059	162648 62023 529076	32 -641 760	0,0040 0,0008 0,0076	*8146*	-311 -1654 1160	0,0048 0,0006 0,0099	*cost saving*
8	368 341 392	0,0036 0,0008 0,0067	139662 52879 456718	25 -650 750	0,0044 0,0010 0,0084	*5630*	-318 -1663 1153	0,0052 0,0007 0,0106	*cost saving*
9	361 330 388	0,0041 0,0009 0,0075	121784 45609 400440	18 -659 740	0,0049 0,0011 0,0092	*3583*	-326 -1672 1143	0,0057 0,0008 0,0114	*cost saving*
10	353 319 383	0,0046 0,0010 0,0084	107482 39741 355417	10 -667 730	0,0053 0,0012 0,0100	*1885*	-333 -1681 1133	0,0061 0,0010 0,0122	*cost saving*

* The ICER of the probabilistic model are not mentioned since simulation results are spread over several quadrants of the cost-effectiveness plane. As an alternative (in italics), the ICER calculated by dividing the mean incremental cost by the mean incremental benefit is presented.

The final scenario analyses modelled the incremental costs, benefits and ICERs in relation to the initial number of exacerbations and exacerbation-related hospitalisations. The UPLIFT-based treatment effects are implemented as before. The results are presented in Table 43 and shows that the initial number of exacerbations does not have a big influence on both incremental costs and incremental effects. The impact on incremental costs is small due to the low cost for treating an exacerbation. An average 14% reduction in combination with an average cost of €53 results in an average decrease in costs of about €7.5 per extra prior exacerbation. The influence on incremental effects is also relatively small. As long as people are not hospitalised for COPD without tiotropium treatment, there is not much to gain.

If on average the population would have one hospitalisation, the average incremental cost would still be positive applying an average treatment effect of 0.94. Due to the uncertainty around this ratio, the confidence interval around the incremental costs varies widely and contains both positive and negative values. Figure 36 shows the cost-effectiveness plane for the scenario with prior one exacerbation and one exacerbation-related hospitalisation. Both incremental costs and benefits cross the x- and y-axis respectively. If the population would have two prior hospitalisations, the average incremental cost would become negative, with a wide confidence interval containing both positive and negative values.

Figure 36: Cost-effectiveness plane (scenario analysis for a population with one prior exacerbation and one prior exacerbation-related hospitalisation)



These scenarios can be applied to the proportion of the real-world population with an observed amount of exacerbation-related hospitalisations. About 90% had no such a hospitalisation prior to being treated with tiotropium. In other words, for this part of the population, there is not much to gain by treating them with tiotropium by way of preventing hospitalisations. The non-negligible extra costs thus make this treatment not cost-effective for the largest part of the population.

9.3 BUDGET IMPACT

A budget impact analysis is normally made at the launch of a new health-care intervention. In contrast, tiotropium is already reimbursed in Belgium since March 2004. In chapter 7, the budget impact of tiotropium was mentioned based on Pharmanet data. In 2007, the NIHDI paid €21.6 million for tiotropium and the patient's co-payments were almost €5 million, i.e. a total of €26.5 million.

Based on the systematic review of the clinical literature, there is no hard evidence that tiotropium is significantly better than salmeterol in preventing exacerbation-related hospitalisations. Furthermore, the observations indicate that there is no clear reduction in the use of other drugs. As a result, a much higher price, as this is currently the case, is hard to defend from a health-care payer's perspective. The conclusions of the Ministerial Decision (December 12, 2007) for the revision of tiotropium reimbursement already indicated that there was no benefit of using tiotropium in comparison to long-acting B2-agonists, that the price of tiotropium was 33% higher in comparison to these alternatives (in fact, currently, it is 66% more expensive), and that the introduction of tiotropium, in contrast to what was announced, did not decrease treatment costs related to other drugs. Despite this, reimbursement rules did not change (see part 1.6.1).

If the tiotropium price would be reduced to €31.24 for 30 units, i.e. the price of salmeterol, than the budget impact for both the NIHDI and the patient's co-payment, based on 2007 data, would decrease to about €16 million, or a cost saving of about €10.5 million a year.

9.4 DISCUSSION

In this part, several aspects about the selected population, time horizon and mortality, effectiveness, and QoL are discussed. Important differences in input variables compared to previous economic evaluations that largely explain differences in the outcomes are also tackled.

9.4.1 Population

One of the strengths of our evaluation is that it considers patients that use tiotropium in their everyday life. In contrast, clinical trials explicitly formulate in- and exclusion criteria. Among those there were variations in these criteria such as different age (e.g. ≥ 40 or 50 years), FEV1 (≤ 50, 60 or 70%), FEV1/FVC (<0.7) or just FVC criteria, and others. In the economic evaluations identified in the systematic review, the population considered was often more selective compared to the population targeted for routine use of tiotropium (see part 7.2.4). All studies, with the exception of one,[101] did not included patients with mild COPD. Nevertheless, these patients are also included in the reimbursement modalities for tiotropium in Belgium. This can be very determining for the results of the economic evaluation, since, the base risk for certain events may be different in comparison to events in trials for a highly selected population. It is the combination of this base risk and the relative treatment effect that determines the absolute reduction in events, which determines the intervention's cost effectiveness. Patients with mild COPD did not participate in clinical trials but probably have a lower base risk, hence, tiotropium's cost effectiveness is probably more unfavourable in this population.

Including patients on the basis of their tiotropium consumption does not necessarily mean that only COPD patients are included. Although reimbursement rules only include COPD as an indication, it is possible that the drug is prescribed to e.g. asthmatic patients. However, including non-COPD patients in our analysis was most likely reduced with our selection criteria (see 8.3.2.1).

One group of patients is excluded in our analysis due to our selection criteria on tiotropium use, i.e. patients that died shortly after starting to take tiotropium. On the other hand, only 19 patients had no one year of follow-up data because they died and only one patient in our database fulfilled the criteria on tiotropium use but did not fulfil the 'one year follow-up' criteria because of death. In other words, in comparison to the selected population, this is a minority of patients. The same criticism holds for data from the year before patients started to take tiotropium. Patients were initially included in the database if they had an attestation for tiotropium for which reimbursement started in March, 2004. Logically, expenditure data from the year before on other medication only included patients that survived that year. As such, some of the most ill people may have been excluded from the observations, which could have an influence on the observed number of exacerbations and exacerbation-related hospitalisations.

In contrast, the advantage is that both the data from the year before and after includes exactly the same time period, i.e. one year, which simplifies comparison of expenditures on other medication.

Another disadvantage of our database is that no parameter was present indicating the COPD stage. As a result, no subgroup analyses could be made according to these stages. In our approach, the population was initially analysed as a whole (i.e. all patients fulfilling our inclusion criteria). In subgroup analyses, the population was divided depending on the number of hospitalisations related to exacerbations (i.e. one, two, three or more exacerbation-related hospitalisations) in combination with the number of exacerbations. This probably is related to COPD severity since exacerbation frequency is positively related to disease severity.[115] These subgroup analyses showed that, in the first place, for a selected group of patients with a relative high base risk on events, the results were more cost effective. On the other hand, it also showed that this is only a minority of the population taking tiotropium on a regular basis. The largest group of patients did not experience any exacerbation or hospitalisation. For this group of patients no events can be avoided because they do not occur without taking tiotropium, no QoL can be gained, no costs will be saved, and tiotropium can only bring on higher costs.

9.4.2 Time horizon and mortality

Most economic evaluations used a 1-year timeframe. This time horizon appears long enough to capture a significant number of important clinical endpoints such as exacerbations, and to capture seasonal variations. It may be argued that due to the progressive and chronic nature of COPD, and since this disease requires long-term maintenance treatment on a daily basis, costs and outcomes should be tracked for a longer timeframe, e.g. over a patient's lifetime. However, based on the results of the review on tiotropium's efficacy/effectiveness, to date no evidence has been found that this drug slows down disease progression or influences mortality. Therefore, a conservative approach in which there is no influence on mortality has been modelled. As a result, extending the time horizon would not have a big influence on results since it would influence costs and effects in about the same way.

One analysis took a 5-year time horizon. In the base case analysis of this study, no backward transitions between the disease states were possible during years 2 to 5, reflecting the progressive nature of COPD.[93] The authors note that no differences between treatments (tiotropium, salmeterol or ipratropium) in terms of mortality risk were assumed. Also the costs per disease severity state and per severe or non-severe exacerbation were mentioned to be equal across treatment groups. In the discussion the authors repeat that the difference between the three treatment groups in terms of QALYs were small, which was expected because treatments do not directly affect survival.[93] However, in their analysis, mortality is influenced when comparing the three treatment arms due to different transition probabilities between the disease states for the different treatments. In other words, the chance of dying when a patient is in a certain disease state is equal over the three groups with the highest probability in the very severe disease state. Nonetheless, the transition probability to go to the more severe disease states was modelled to be higher for salmeterol and ipratropium. As a result, this model implicated an implicit effect on mortality. The model was replicated with the same probabilities as in the published paper. The mortality after 5 years was about 15% with tiotropium and about 20% with salmeterol and ipratropium. Such a large difference is hard to justify in comparison with current evidence and an approach in which there was no influence on mortality was preferred.

'Absence of evidence is not evidence of absence'.[136] Briggs and O'Brien argued that unless a study has been specifically designed to show the equivalence of treatments (in terms of costs or effects), it would be inappropriate to conduct cost-minimization or outcome-maximization type analysis on the basis of an observed lack of significance in either the effect or cost differences between treatments. Instead, analysts should focus their attention on estimation of cost-effectiveness rather than on hypothesis testing of cost or effect differences.[137]

Their contention is that the goal of economic evaluation is the estimation of a parameter – incremental cost-effectiveness – with appropriate representation of uncertainty, rather than hypothesis testing. The point estimates (means) from the cost and effect distributions provide the best estimates of the cost and effect of the alternative treatments and should be used in the primary analysis.[137] Joining this point of view, the treatment effect on for example exacerbation-related hospitalisations has been included in the model, with its non-significant confidence interval. In contrast, including an impact on mortality is not based on evidence and in our opinion thus not appropriate.

9.4.3 Effectiveness

The results are very sensitive to the assumed effectiveness of tiotropium treatment. Greater effectiveness leads to better cost-effectiveness outcomes. In previous economic evaluations, the uncertainty around the treatment effect was very large resulting in wide confidence intervals. One of the main differences compared with previous economic evaluations is the inclusion of the recent published UPLIFT trial results. In part 9.1.10.4 the reasoning is given why the treatment effects versus placebo from the UPLIFT trial were included in the base-case scenario instead of results from a smaller trial in which tiotropium was specifically compared with salmeterol. Trials showed no significant improvement in exacerbations related hospitalisations. The mean effect was very positive, but due to a limited number of events, the confidence intervals were very wide. Furthermore, there is the chance that due to publication bias the treatment effect may be overestimated. For example, one of the publications mentioned the frequency of exacerbations was similar between tiotropium and salmeterol.[56] However, because no further details were provided, the results could not be included in the meta-analysis. The UPLIFT trial is by far the largest trial and showed no significant improvement in exacerbation-related hospitalisation frequencies. Nevertheless, this is the most important determining variable for tiotropium's cost effectiveness. With respect to incremental costs, avoiding hospitalisation entails large cost savings. With respect to effects, QoL is improved by avoiding severe exacerbations needing hospitalisation. The results of the UPLIFT trial show that the treatment effect is less positive, and still not significant, in comparison to previously published results (see Figure 32). Taking into account this treatment effect, instead of the treatment effects from the smaller trials, results in rather unfavourable cost-effectiveness ratios.

9.4.4 Quality of life

Avoiding exacerbations and exacerbation-related hospitalisations should have a positive influence on QoL. How big is this loss in QoL and how long does this effect persist? As mentioned before in the literature review of economic evaluations, three studies estimated that during the month following an exacerbation, EQ-5D utility values would reduce by 15% in case of non-severe exacerbation, and by 50% in case of severe exacerbation.[93, 96, 99] The authors refer to the same two studies from Paterson et al.[122] and Spencer et al.[123] to support the 15% and 50% reduction, respectively. In the original publications, however, no such information is explicitly mentioned.

In the study from Spencer et al.[123] 438 patients with acute exacerbation of chronic bronchitis received gemifloxacin or clarithromycin and were followed up for 26 weeks. This publication did not include measurements based on a generic QoL instrument. Only the St George's Respiratory Questionnaire (SGRQ) was used in this study. SGRQ scores were obtained at baseline and after 4, 12, and 26 weeks. The study was carried out in patients who had previous symptoms of chronic bronchitis and had airflow limitation at the time of presentation with an acute exacerbation. The researchers were unable to make the measurements necessary to confirm airway obstruction at the end of the study, but it was likely that the majority of these patients did have COPD. In the results section of this study, a reduction in SGRQ-scores of 50% was not mentioned. Furthermore, outcomes based on disease specific instruments can not as such be translated to generic QoL outcomes. Therefore, it is not clear why the authors of several studies refer to this study to support the assumption of a 50% reduction in QoL.

In the study of Paterson et al.[122], the 'measure yourself medical outcome profile' (MYMOP), the 'medical outcomes study 6-item general health' survey (MOS-6A), and EuroQoL (EQ-5D) were evaluated in 81 patients with acute exacerbations of type-I chronic bronchitis. This study analysed the responsiveness of these instruments and found that the EQ-5D was overall the least sensitive instrument for distinguishing change in those patients who felt themselves to be `a little better'. No information on a '15% reduction in QoL' was mentioned in this study. Again, it is not clear why these studies refer to this reference to support this assumption. In the absence of studies gathering QoL data with generic instruments, one has to rely on expert opinion, and the potential bias inherent in such information is a methodological concern.[138]

The disease-specific St. George Respiratory Questionnaire (SGRQ) was the most used instrument in clinical studies. However, generic instruments such as the EQ-5D are considered to be useful where measurements of patient utilities are required for economic evaluation. The index-based utility scores can be used to compare burden of disease across different conditions and facilitate the calculation of quality adjusted life years (QALYs) that are incorporated into economic evaluations of health care interventions.[139] In contrast, disease specific instruments may fail to capture all aspects of HRQoL, e.g. co-morbidities and side effects of an intervention. Specifically for COPD patients, van Manen et al.[140] showed that impairments in physical functioning, vitality, and general health are related to COPD and to some extent to comorbidity, while impairments in social and emotional functioning do not seem to be related to COPD, but only to comorbidity.

EQ-5D has gained widespread use for several reasons. It is a brief, simple measure for patients to understand and to complete, imposing minimal respondent burden, and the measure is easy to score and interpret.[130] As mentioned before, the outcomes can be used in economic evaluation. In contrast to the EQ-5D questionnaire, there is no clear economic methodology to value the gain in QoL from disease-specific instruments. Researchers from the UPLIFT trial demonstrated that a generic instrument such as the EQ-5D can be used to assess COPD impact on QoL.[121] A total of 1 235 patients completed this questionnaire. Unfortunately, although the UPLIFT is an RCT, no results comparing QoL for the two patient populations were mentioned. Only results for the SGRQ were published showing a significant improvement in the mean absolute total score on the SGRQ, as compared with the placebo group, at each time point throughout the 4-year period, ranging from 2.3 to 3.3. units.[48] However, only improvements of more than 4 points are considered clinically relevant, which is thus not the case. With respect to EQ-5D values, only mean utility scores for the 4 COPD stages were published. The GOLD staging of COPD severity corresponded to significant differences in generic health-related quality of life, as assessed by the EQ-5D VAS and utility scores.[121] However, the main interest is not in the difference in QoL between the GOLD stages since there is no hard evidence that tiotropium prevents the progression to more severe states in comparison to, for example, salmeterol.

Rutten-van Molken et al. remarked correctly that the EQ-5D has the additional problem of not capturing the impact that COPD exacerbations have on QoL. This problem applies equally to the EQ-5D, the SGRQ, and other generic or COPD-specific quality-of-life instruments. The EQ-5D has no recall period and asks for a description of a patient's health "today."

As noted by the authors, even if there is a recall period, as in the symptoms domain of the SGRQ, these quality-of-life instruments are usually administered during a stable phase of the disease, as a result of which they do not capture the impact of exacerbations. It would be a step forward if utility scores for COPD health profiles could be obtained that combine the description of a patient's underlying COPD severity stage with the description of that patient's exacerbation profile in terms of the frequency, severity, and impact of the exacerbation.[121]

Also other authors already noticed there were no available data on QALY weights during exacerbation.[115] As mentioned by Andersson et al.,[141] it would be interesting to record on a daily basis the development of QoL values over the whole duration of the exacerbation, including a pre- and postexacerbation period of a few days. The study of

O'Reilly, of which the results were included in the economic model, was the first to our knowledge to measure QoL during exacerbation-related hospitalisation. A measure of QoL in the pre-exacerbation period was lacking. However, especially the fact of being hospitalised may influence QoL. In a Swedish study,[142] elderly patients with severe exacerbations of COPD and hypoxaemia were treated with long-term oxygen treatment. Their HRQoL was measured during hospital stay and at follow-up. The SF-36 values were low in patients during the stay in hospital. During the year of observation values improved. The greatest change compared to base line occurred already during the first month of stay at home. The authors remarked that it was possible that the low values reported during the stay in hospital partly constitute an effect of the exacerbation and partly of the hospitalisation. The improving figures after returning home was probably due to a change in both medical status and environment.[142]

In general, generic instruments should be implemented more often in studies to allow inclusion of outcomes in economic evaluations. To be able to translate results to other populations, it would be very interesting not only to measure the average QoL in a specific population but also to measure the influence on QoL due to a certain event. In this case, this would be the exacerbation-related hospitalisations and exacerbations. Towards the future, gathering better evidence on QoL is one of the challenges.

9.5 CONCLUSION

In this economic evaluation a calculation of tiotropium's real-world cost effectiveness was made. Based on our observations discussed in the previous chapter, the treatment effects relying on the large UPLIFT trial seemed the most appropriate. These effects were applied on the baseline risk for exacerbations and exacerbation-related hospitalisations. The cost-effectiveness of tiotropium was unfavourable due to a low average of hospitalisations without tiotropium treatment. Under real-world conditions, it was noticed that the largest part of the population (90%) did not experience an exacerbation-related hospitalisation. As a result, treating this part of the population mainly results in extra costs without relevant benefits. The main cause for tiotropium's unfavourable cost effectiveness ratios are the good results with salmeterol. As shown in the systematic review of the medical literature, tiotropium does not significantly perform better on clinically relevant outcomes. To date, tiotropium has not clearly demonstrated an important effect on quality-adjusted life years nor generates large cost savings by avoiding COPD related events. As a result, from a payer's perspective, the higher price of tiotropium can be questioned. If the price of tiotropium would be lowered to the price of salmeterol, a yearly saving of about €10 million would be generated.

Key points

Estimated real-world cost-effectiveness:

- **Exacerbation-related hospitalisations and the treatment effect on these events were the most determining input variables for tiotropiums cost effectiveness.**
- **The number of exacerbation-related hospitalisations is relatively low and the influence on these events is relatively small and non-significant. As a result, the average incremental benefit is very small.**
- **There is no hard evidence that tiotropium results in cost savings due to less hospitalisations or a reduced consumption of other medication.**
- **Due to the relatively high price for tiotropium, the incremental costs are substantial.**
- **The combination of a substantial incremental cost with a relatively small incremental benefit results in unfavourable incremental cost-effectiveness ratios.**

Budget impact:

- **A lower price for tiotropium, set at about the level of salmeterol, would result in more than €10 million cost savings a year for the health care payer (NIHDI + patient co-payment).**

Further research:

- **More attention should be paid to gathering QoL data using generic instruments from which the results can be used in economic evaluations.**
- **Next to measuring the average QoL in a specific population, measuring the influence of specific events, i.e. exacerbation-related hospitalisations and exacerbations, would be very interesting. This would ease translation of results to other populations.**

10 RECOMMENDATIONS

Tiotropium is reimbursed in Belgium since March 2004. Being a Class I drug, i.e. a drug with a therapeutic added value in comparison towards existing alternatives, a revision of the reimbursement decision was demanded within 36 months. No benefit of using tiotropium in comparison to long-acting B2-agonists was shown, the product has a much higher price than these alternatives, and, in contrast to what was announced, there was no decrease in treatment costs related to other drugs. In contrast, the reimbursement modalities remained unchanged after this revision. No rational arguments for this decision were found.

The authors of this HTA report reach similar conclusions. Based on a systematic review of the literature, the treatment effect was evaluated. No hard evidence is found that tiotropium is significantly better than salmeterol for the following endpoints: proportion of patients experiencing at least one exacerbation, possibly exacerbation frequency, time to first exacerbation, proportion of patients with at least one COPD related hospitalisation, COPD related hospitalisation frequency, mortality, quality of life, and dyspnoea. Furthermore, there is a statistical indication for publication bias and several none significant results were not explicitly mentioned in several studies, excluding their inclusion in the meta-analyses. Based on observational data, no reduction in treatment costs related to other drugs was noticed between the year before and after tiotropium was initiated.

The monthly cost per patient for tiotropium is €51.75. In contrast, this is only €31.24 for salmeterol. If a product costs much more than an alternative, than it should be questioned if these extra expenses are spend wisely. From a health care payer's perspective, it would be rational to pay no more than an alternative if a product has not proven to be better in terms of efficacy/effectiveness or QoL, or does not result in significant cost savings by e.g. preventing other events.

Based on current evidence, being not better on clinically relevant outcomes (but also not being worse), and because no cost savings on e.g. treatment costs for other drugs were found, a price comparable to salmeterol is recommended. With an equal number of patients using tiotropium, this would result in more than €10 million savings for the NIHDI and patient co-payments.

The CTG may propose a new price for tiotropium in a revision. A price around the price of the alternative salmeterol is recommended. If the company does not accept this price, and since there are alternatives to tiotropium treatment, the reimbursement can be rejected. This has never happened before and would create a precedent. In contrast, asking for evidence in a first approval for reimbursement and not changing anything if this proof is not provided is not a healthy situation and gives a wrong signal to different stakeholders. A company that fails to deliver requested evidence for a revision procedure should not be rewarded for doing so.

More in general, the revision procedure should also be critically assessed. If data on effectiveness in real practice are requested for the revision procedure, administrative data analyses can not replace prospective data collection, because of a lack of clinical information. In case a revision depends on real-life effectiveness data, design of the data collection and methods of analyses should be specified beforehand. It should also be clearer from the start what the consequences would be if certain 'promises' are not fulfilled. Will the reimbursement decision for example be cancelled, does the price have to go down, or does the company has to pay back a certain amount?

Finally, towards the future, more research could be performed to identify subgroups of patients that potentially could benefit more from treatment with tiotropium than the general COPD population. Other particular points of interest that further research could focus on are the benefits and risks of combining treatments of different long-acting bronchodilators and the impact of different treatment regimens on quality of life (measured with generic instruments) for specific events such as exacerbations and exacerbation-related hospitalisations.

In summary, the following recommendations are made:

PRICING AND REIMBURSEMENT:

- A price for tiotropium higher than the price of alternative treatments cannot be supported based on current evidence.
- If the company producing tiotropium does not agree to a price reduction, reimbursement of this drug should be stopped. This would clearly not be unethical since there are valid alternatives to tiotropium treatment.

REVISION PROCEDURE

- If data on effectiveness in real practice are requested for the revision procedure, administrative data analyses can not replace prospective data collection, because of a lack of clinical information. In case a revision depends on real-life effectiveness data, design of the data collection and methods of analyses should be specified beforehand.
- Consequences for not fulfilling 'promises' should be specified. These consequences could include cancelling the reimbursement, compulsory price cuts or the obligation to pay back part or all of the previous reimbursement.
- A company that fails to deliver requested evidence for a revision procedure should not be rewarded for doing so.

FURTHER RESEARCH

- Identification of subgroups that potentially could benefit more from treatment with tiotropium than the general COPD population.
- Benefits and risks of combining treatments of different long-acting bronchodilators.
- The impact of treatment with tiotropium on quality of life (measured with generic instruments) per exacerbation or hospitalisation.

11 APPENDICES

APPENDIX 1: GUIDELINES

Table 44: Quality assessment of COPD guidelines.

	NICE	ATS / ERS	GOLD	ICSI	Singapore MoH	ACP	COPD-X
Overall objectives clearly specified	4	4	4	3	3	4	4
Clinical questions specifically described	4	3	3	2	3	4	2
Patients specifically described	4	3	3	4	3	2	2
Relevant professional groups in guideline development group	4	4	3	4	3	2	4
Patients' views and preferences sought	4	4	1	1	1	1	2
Target users are clearly defined	4	3	3	3	4	2	2
Piloted among intended users	1	1	1	1	1	1	1
Systematic methods to search for evidence	4	2	2	2	2	4	2
Criteria for selecting evidence clearly described	4	2	1	1	2	4	2
Methods for formulating recommendations clearly described	3	1	3	3	4	4	3
Health benefits, risks and side effects considered	4	3	3	1	3	3	2
Explicit link between recommendations and evidence	4	1	3	3	4	4	3
External review before publication	4	4	3	3	2	4	1
Procedure for updating is provided	4	1	3	3	3	3	1
Recommendations are specific and unambiguous	3	3	4	3	3	4	2
Different options are clearly presented	3	3	3	2	2	3	2

Key recommendations easily identifiable	4	4	3	3	3	3	3
Supported with tools for application	3	3	3	3	1	2	3
Potential organizational barriers discussed	3	2	2	2	2	2	2
Potential cost implications discussed	4	1	2	2	2	2	2
Key review criteria for monitoring/auditing	4	1	1	3	1	1	1
Editorially independent from funding body	3	2	3	3	2	3	1
Conflicts of interest recorded	3	1	3	3	1	4	1
Overall	**82**	**56**	**60**	**58**	**55**	**66**	**48**

Table 45: NICE grading system

Hierarchy of evidence		**Grading of recommendations**	
Level	**Type of evidence**	**Grade**	**Evidence**
Ia	Evidence from systematic reviews or meta-analysis of randomised controlled trials	A	Based on hierarchy I evidence
Ib	Evidence from at least one randomised controlled trial		
IIa	Evidence from at least one controlled study without randomisation	B	Based on hierarchy II evidence or extrapolated from hierarchy I evidence
IIb	Evidence from at least one other type of quasi-experimental study		
III	Evidence from non-experimental descriptive studies, such as comparative studies, correlation studies and case–control studies	C	Based on hierarchy III evidence or extrapolated from hierarchy I or II evidence
IV	Evidence from expert committee reports or opinions and/or clinical experience of respected authorities	D	Directly based on hierarchy IV evidence or extrapolated from hierarchy I, II or III evidence
NICE	Evidence from NICE guidelines or Health Technology Appraisal programme	NICE	Evidence from NICE guidelines or Health Technology Appraisal programme
HSC	Evidence from Health Service Circulars	HSC	Evidence from Health Service Circulars

APPENDIX 2: CLINICAL EFFECTIVENESS

Table 46: Search terms used for clinical efficacy

	Evidence synthesis	Original studies
CRD HTA	tiotropium OR BA 679 BR OR spiriva OR oxitropium'	
INAHTA	tiotropium OR BA 679 BR OR spiriva OR oxitropium'	
NICE	tiotropium OR BA 679 BR OR spiriva OR oxitropium'	
CDSR	'(("tiotropium "[Substance Name]) OR BA 679 BR OR spiriva OR oxitropium) AND systematic[sb]	
CRD DARE	'(("tiotropium "[Substance Name]) OR BA 679 BR OR spiriva OR oxitropium) AND systematic[sb]	
Medline	'(("tiotropium "[Substance Name]) OR BA 679 BR OR spiriva OR oxitropium) AND systematic[sb]	(("tiotropium "[Substance Name]) OR BA 679 BR OR spiriva OR oxitropium) AND ((clinical[Title/Abstract] AND trial[Title/Abstract]) OR clinical trials[MeSH Terms] OR clinical trial[Publication Type] OR random*[Title/Abstract] OR random allocation[MeSH Terms] OR therapeutic use[MeSH Subheading])
Embase		'tiotropium bromide'/exp OR (BA 679 BR) OR 'spiriva'/exp AND [humans]/lim AND [2006-2007]/py

APPENDIX 3: CLASSIFICATION OF ECONOMIC STUDIES

Figure 37: Classification of economic studies

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

Adapted from Drummond et al.[128]

APPENDIX 4: SEARCH FOR COST-EFFECTIVENESS STUDIES

SEARCH STRATEGY

In March 2008, the websites of HTA institutes (Table 47) and following databases were searched: Medline, Embase, Centre for Reviews and Dissemination (CRD) databases (NHS Economic Evaluation Database (NHS EED) and Health Technology Assessments (HTA)), Cochrane Database of Systematic Reviews (CDSR) (Technology Assessments and Economic Evaluations), and Econlit. The following seven tables (Table 48 to Table 54) provide an overview of the search strategy. In December 2008, the databases were searched again using the same search strategies as those detailed in Table 48 to Table 54, in order to identify the studies during the year 2008. The number of additional citations retrieved during this 1-year period is mentioned in the tables below.

Table 47: List of INAHTA member websites searched for HTA reports

Agency	Country
AETMIS - Agence d´Évaluation des Technologies et des Modes d´Intervention en Santé	Canada
AETS - Agencia de Evaluación de Tecnologias Sanitarias	Spain
AETSA - Andalusian Agency for Health Technology Assessment	Spain
AHRQ - Agency for Healthcare Research and Quality	USA
AHTA - Adelaide Health Technology Assessment	Australia
AHTAPol - Agency for Health Technology Assessment in Poland	Poland
ASERNIP-S - Australian Safety and Efficacy Register of New Interventional Procedures -Surgical	Australia
AVALIA-T - Galician Agency for Health Technology Assessment	Spain
CADTH - Canadian Agency for Drugs and Technologies in Health	Canada
CAHTA - Catalan Agency for Health Technology Assessment and Research	Spain
CEDIT - Comité dÉvaluation et de Diffusion des Innovations Technologiques	France
CENETEC - Centro Nacional de Excelencia Tecnológica en Salud Reforma	Mexico
CMT - Center for Medical Technology Assessment	Sweden
CRD - Centre for Reviews and Dissemination	United Kingdom
CVZ - College voor Zorgverzekeringen	The Netherlands
DACEHTA - Danish Centre for Evaluation and Health Technology Assessment	Denmark
DAHTA @DIMDI - German Agency for HTA at the German Institute for Medical Documentation and Information	Germany
DECIT-CGATS - Secretaria de Ciência, Tecnologia e Insumos Estratégicos, Departamento de Ciência e Tecnologia	Brazil
DSI - Danish Institute for Health Services Research	Denmark
FinOHTA - Finnish Office for Health Care Technology Assessment	Finland
GR - Gezondheidsraad	The Netherlands
HAS - Haute Autorité de Santé	France

HunHTA - Unit of Health Economics and Health Technology Assessment	Hungary
IAHS - Institute of Applied Health Sciences	United Kingdom
ICTAHC - Israel Center for Technology Assessment in Health Care	Israel
IECS - Institute for Clinical Effectiveness and Health Policy	Argentina
IHE - Institute of Health Economics	Canada
IMSS - Mexican Institute of Social Security	Mexico
IQWiG - Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen	Germany
KCE - Belgian Federal Health Care Knowledge Centre	Belgium
LBI of HTA - Ludwig Boltzmann Institut für Health Technonoly Assessment	Austria
MAS - Medical Advisory Secretariat	Canada
MSAC - Medicare Services Advisory Committee	Australia
MTU-SFOPH - Medical Technology Unit - Swiss Federal Office of Public Health	Switzerland
NCCHTA - National Coordinating Centre for Health Technology Assessment	United Kingdom
NHS QIS - Quality Improvement Scotland	United Kingdom
NHSC - National Horizon Scanning Centre	United Kingdom
NOKC - Norwegian Knowledge Centre for Health Services	Norway
NZHTA - New Zealand Health Technology Assessment	New Zealand
OSTEBA - Basque Office for Health Technology Assessment	Spain
SBU - Swedish Council on Technology Assessment in Health Care	Sweden
UETS - Unidad de evaluacíon Technologias Santarias	Spain
VATAP - VA Technology Assessment Program	USA
VSMTVA - Health Statistics and Medical Technologies State Agency	Latvia
ZonMw - The Medical and Health Research Council of The Netherlands	The Netherlands

Table 48: Search strategy and results for CRD: HTA

Date	25/03/2008
Database	CRD HTA
Date covered	No restrictions
Search Strategy	Tiotropium OR "Ba 679 BR" OR Spiriva OR Oxitropium
Note	**6** references found
Update until 15/12/2008	**0** references found

Table 49: Search strategy and results for CRD: NHS EED

Date	25/03/2008
Database	CRD NHS EED
Date covered	No restrictions
Search Strategy	tiotropium OR "Ba 679 BR" OR Spiriva OR oxitropium
Note	**6** references found
Update until 15/12/2008	**0** references found

Table 50: Search strategy and results for Medline (OVID) (part I)

Date	25/03/2008		
Database	Medline (OVID)		
Date covered	1950 to March Week 2 2008		
Search Strategy	**#**	**Search History**	**Results**
	1	economics/	25336
	2	exp "Costs and Cost Analysis"/	135878
	3	"Value of Life"/ec [Economics]	163
	4	Economics, Dental/	1775
	5	exp Economics, Hospital/	15349
	6	Economics, Medical/	6926
	7	Economics, Nursing/	3834
	8	Economics, Pharmaceutical/	1868
	9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8	177432
	10	(econom$ or cost$ or pric$ or pharmacoeconomic$).tw.	291726
	11	(expenditure$ not energy).tw.	11195
	12	(value adj1 money).tw.	10
	13	budget$.tw.	11363
	14	10 or 11 or 12 or 13	303695
	15	9 or 14	395520
	16	letter.pt.	615265
	17	editorial.pt.	216294
	18	historical article.pt.	248057
	19	16 or 17 or 18	1069496
	20	15 not 19	374830
	21	Animals/	4228426
	22	human/	10264750
	23	21 not (21 and 22)	3191592
	24	20 not 23	349964
	25	(metabolic adj cost).ti,ab,sh.	473

	26	((energy or oxygen) adj cost).ti,ab,sh.	1977
	27	24 not (25 or 26)	348095
	28	tiotropium.mp.	304
	29	spiriva.mp,tw,kw.	22
	30	Ba 679 BR.mp.	8
	31	oxitropium.mp.	128
	32	28 or 29 or 30 or 31	425
	33	27 and 32	**33**
Note	No MESH associated with tiotropium in Medline		
Update until 15/12/2008	**5** references found		

Table 51: Search strategy and results for Medline (OVID) (part II)

Date	25/03/2008		
Database	Medline (OVID), non-indexed citations, 1950 - 2d week March 2008		
Date covered	No restrictions		
Search Strategy	**#**	**Search History**	**Results**
	1	cost$.mp. [mp=title, original title, abstract, name of substance word, subject heading word]	9938
	2	economic$.mp. [mp=title, original title, abstract, name of substance word, subject heading word]	4304
	3	budget$.mp. [mp=title, original title, abstract, name of substance word, subject heading word]	570
	4	expenditure$.mp. [mp=title, original title, abstract, name of substance word, subject heading word]	921
	5	1 or 2 or 3 or 4	14229
	6	tiotropium.mp. [mp=title, original title, abstract, name of substance word, subject heading word]	40
	7	spiriva.mp. [mp=title, original title, abstract, name of substance word, subject heading word]	2
	8	Ba 679 BR.mp. [mp=title, original title, abstract, name of substance word, subject heading word]	0
	9	oxitropium.mp. [mp=title, original title, abstract, name of substance word, subject heading word]	1
	10	6 or 7 or 8 or 9	40
	11	5 and 10	2
Update until 15/12/2008	**3** references found		

Table 52: Search strategy and results for EMBASE

Date	26/03/2008		
Database	EMBASE		
Date covered	No restrictions		
Search Strategy	**#**	**Search History**	**Results**
	1	socioeconomics'/exp	105780
	2	'cost benefit analysis'/exp	46837
	3	'cost effectiveness analysis'/exp	54141
	4	'cost of illness'/exp	8517
	5	'cost control'/exp	32242
	6	'economic aspect'/exp	750058
	7	'financial management'/exp	186314
	8	'health care cost'/exp	127769
	9	'health care financing'/exp	9100
	10	'health economics'/exp	408610
	11	'hospital cost'/exp	17479
	12	('finance'/exp) OR ('funding'/exp) OR (fiscal) OR (financial)	123794
	13	'cost minimization analysis'/exp	1306
	14	estimate*:ti,ab,de,cl	351333
	15	cost*:ti,ab,de,cl	393289
	16	variable*:ti,ab,de,cl	347447
	17	unit*:ti,ab,de,cl	1338216
	18	'#15 *4 #14' OR '#14 *4 #15'	261352
	19	'#15 *4 #16' OR '#16 *4 #15'	290398
	20	'#15 *4 #17' OR '#17 *4 #15'	141672
	21	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #18 OR #19 OR #20	1382223
	22	'tiotropium bromide'/exp OR 'tiotropium bromide'	967
	23	'spiriva'/exp OR 'spiriva'	932
	24	'ba 679 br'/exp OR 'ba 679 br'	919
	25	'oxitropium bromide'/exp OR 'oxitropium bromide'	592
	26	tiotropium:ti,ab,de	1056
	27	spiriva:ab,ti,de	39
	28	'ba 679 br':ab,ti,de	9
	29	oxitropium:ab,ti,de	593
	30	#22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29	1561
	31	#21 AND #30	384

	32	editorial:it OR letter:it	946471
	33	#31 NOT #32	359
	34	chronic obstructive lung disease'/exp	40277
	35	#31 AND #34	320
	36	#35 NOT #32	**297**
Note	Tiotropium bromide is an EMTREE index term since 1993. Synonyms: 7beta [hydroxybis (2 thienyl) acetoxy] 9, 9 dimethyl 3 oxa 9 azoniatricyclo [3.3.1.0 2, 4] nonane bromide; ba 679 br; ba679 br; spiriva		
Update until 15/12/2008	**50** references found		

Table 53: Search strategy and results for Econlit

Date	26/03/2008		
Database	Econlit (OVID)		
Date covered	1969 to January 2008		
Search Strategy	**#**	**Search History**	**Results**
	1	tiotropium.mp. [mp=heading words, abstract, title, country as subject]	**3**
	2	spiriva.mp. [mp=heading words, abstract, title, country as subject]	0
	3	Ba 679 BR.mp. [mp=heading words, abstract, title, country as subject]	0
	4	oxitropium.mp. [mp=heading words, abstract, title, country as subject]	0
Update until 15/12/2008	**0** references found		

Table 54: Search strategy and results for CDSR

Date	26/03/2008		
Database	CDSR		
Date covered	No restrictions		
Search Strategy	**#**	**Search History**	**Results**
	1	MeSH descriptor Pulmonary Disease, Chronic Obstructive explode all trees	1217
	2	(tiotropium) or (spiriva) or (ba 679 br) or (oxitropium)	346
	3	(#1 AND #2)	74
Note	Of these 74 references, there were six Technology Assessments and six Economic Evaluations		
Update until 15/12/2008	**2** economic evaluations found		

RESULTS OF SEARCH STRATEGY

A total of 419 papers were identified: 43 with Medline, 347 with Embase, 12 with the CRD NHS EED and HTA databases, 14 from the Cochrane Database of Systematic Reviews (Technology Assessments and Economic Evaluations), and three from Econlit (Table 55). After removing 62 duplicates, 357 articles were left.

Table 55: search for cost-effectiveness studies: summary

	References identified		
Database	**March 2008**	**Update until Dec 2008**	**Total**
MEDLINE	33	5	38
MEDLINE In-Process & Other Non-Indexed Citations	2	3	5
EMBASE	297	50	347
CRD			
NHS EED	6	0	6
HTA	6	0	6
CDSR			
Technology Assessments	6	0	6
Economic Evaluations	6	2	8
Econlit	3	0	3
Total references identified	359	60	419
Duplicates	54	8	62
Total	**305**	**52**	**357**

APPENDIX 5: MEAN AND INCREMENTAL COSTS IN THE ECONOMIC EVALUATIONS OF TIOTROPIUM

Author	Publication year	Country	Mean total direct medical costs			Incremental costs: Tiotropium vs		
			Tiotropium	Salmeterol	Ipratropium	Salmeterol	Ipratropium	Other
Original costs								
Najafzadeh et al.	2008	Canada	2678 (1950–3536)	2810 (2306–3362)[a]	-	Not reported	-	Not reported[b]
Onukwugha et al.	2008	USA	Not reported	-	Not reported	-	Not reported	-
Rutten-van Molken et al.	2007	Spain	6424 (5826–7022)	5869 (4879–6859)	5181 (3844–6518)	555 (-647–1651)	c	-
Oba.	2007	USA	Not reported	-	Not reported	-	-361	835[d]
Maniadakis et al.	2006	Greece	2504 (2122–2965)	2655(2111–3324)	-	-151 (-926–538)	-	-
Schramm et al.	2005	Switzerland	4788	4881	5820	-93	-1032	-
Oostenbrink et al.	2005	Canada	1309 (1222–1408)	1306 (1142–1516)	1307 (1050–1637)	3 (-227–203)	c	-
		Netherlands	1760 (1563–2011)	1802 (1515–2195)	1930 (1503–2525)	-42 (-484–353)	c	-
Oostenbrink et al.	2004	Netherlands	1721 (1407–2035	-	1541 (1222–1860)	-	180 (-268–627)	-
Costs in 2006 Belgian €								
Najafzadeh et al.	2008	Canada	2000 (1456–2640)	2098 (1722–2510)	-	Not reported	-	Not reported
Onukwugha et al.	2008	USA	Not reported	-	Not reported	-	Not reported	-
Rutten-van Molken et al.	2007	Spain	7860 (7129–8592)	7181 (5970–8393)	6340 (4707–7975)	679 (-792–2020)	c	-
Oba.	2007	USA	Not reported	-	Not reported	-	-334	772
Maniadakis et al.	2006	Greece	3284 (2783–3889)	3482 (2769–4360)	-	-198 (-1214–706)	-	-
Schramm et al.	2005	Switzerland	2580	2630	3136	-50	-556	-
Oostenbrink et al.	2005	Canada	1461 (1364–1571)	1457 (1274–1692)	1458 (1172–1827)	3 (-253–227)	c	-
		Netherlands	1935 (1719–2211)	1982 (1666–2414)	2122 (1653–2777)	-46 (-532–388)	c	-
Oostenbrink et al.	2004	Netherlands	1892 (1548–2234)	-	1695 (1343–2046)	-	198 (-295–689)	-

a. Combined tiotropium + salmeterol therapy; b. The mean cost of the combined tiotropium + salmeterol/fluticasone treatment arm was CAN$4042 (3228–4994) for the trial duration, corresponding to €3018 (2410–3729) in 2006 Belgian euro; c. Each treatment option is compared with the next best alternative in terms of effectiveness. Ipratropium is thus an alternative to Salmeterol, not to Tiotropium; d. Tiotropium versus placebo.

APPENDIX 6: INFORMATION ON DATABASES

IMA HEALTH CARE USE AND PATIENT CHARACTERISTICS DATABASE

The purpose of the Common Sickness Funds Agency (IMA) is to organise and manage a common interface to the health care use and patient characteristics data that are collected by the Belgian Sickness Funds. Its mission is to support and improve the Belgian health care system and insurance through registrations, analyses and studies on, among others, the financing, organisation and quality of health care.

The database contains four types of data:

1. Data on all reimbursed health care use per attestation per patient
2. Demographic data: e.g. date of birth, gender, community, if applicable decease date
3. Data on the insurance status, e.g. the right to certain benefits
4. Data on professional status: e.g. unemployment, retirment.

A full description of the layout of the database and available variables can be found in Van de Sande et al .[143]

TCT HOSPITAL STAY DATABASE

The registration of MKG is mandatory for every hospital in Belgium since 1991. This means that for each hospitalized patient, information such as birth date, sex, postal code of domicile and other information such as length of hospital stay (LOS), hospital ward and bed type occupation etc., has to be recorded, along with ICD-9-CM[g] encoding of relevant diagnoses as well as diagnostic and therapeutic procedures performed. Diagnosis and procedure codes are collected per attended hospital department, each coding for one primary and several secondary diagnoses. After stripping of direct patient-identifying information, records have to be sent biannually to the federal Ministry of Health (MoH[h]). Here all department registrations are concatenated with assignment of the primary diagnosis to the whole stay, determinant for the APrDRG-grouper[i] software.

Since 1995 the MKG records are afterwards linked to the Minimal Financial Data (Minimale Financiële gegevens; MFG[j]), yearly transmitted by the sickness funds to the NIHDI[k] and assembling the remuneration costs of each hospital stay. MCD-MFD linkage is performed by the 'Technical Cell' (see above) .

The MKG database also contains records of 'one day' admissions (i.e. patients not staying overnight in the hospital) and outpatients' treatments requiring hospital facilities, however without coupling with billing data yet[l].

A full description of the layout of the database and available variables can be found in Van de Sande et al.[143]

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g International classification of diseases, version 9, clinical modification (WHO)

h Federale Overheidsdienst Volksgezondheid, Veiligheid van de Voedselketen en Leefmilieu / Service Public Fédéral Santé publique, Sécurité de la Chaîne alimentaire et Environnement

i All Patient refined Diagnostic Groups, version 15.0

j MFG = 'Minimale Financiële Gegevens / RFM = Résumé Financier Minimum'

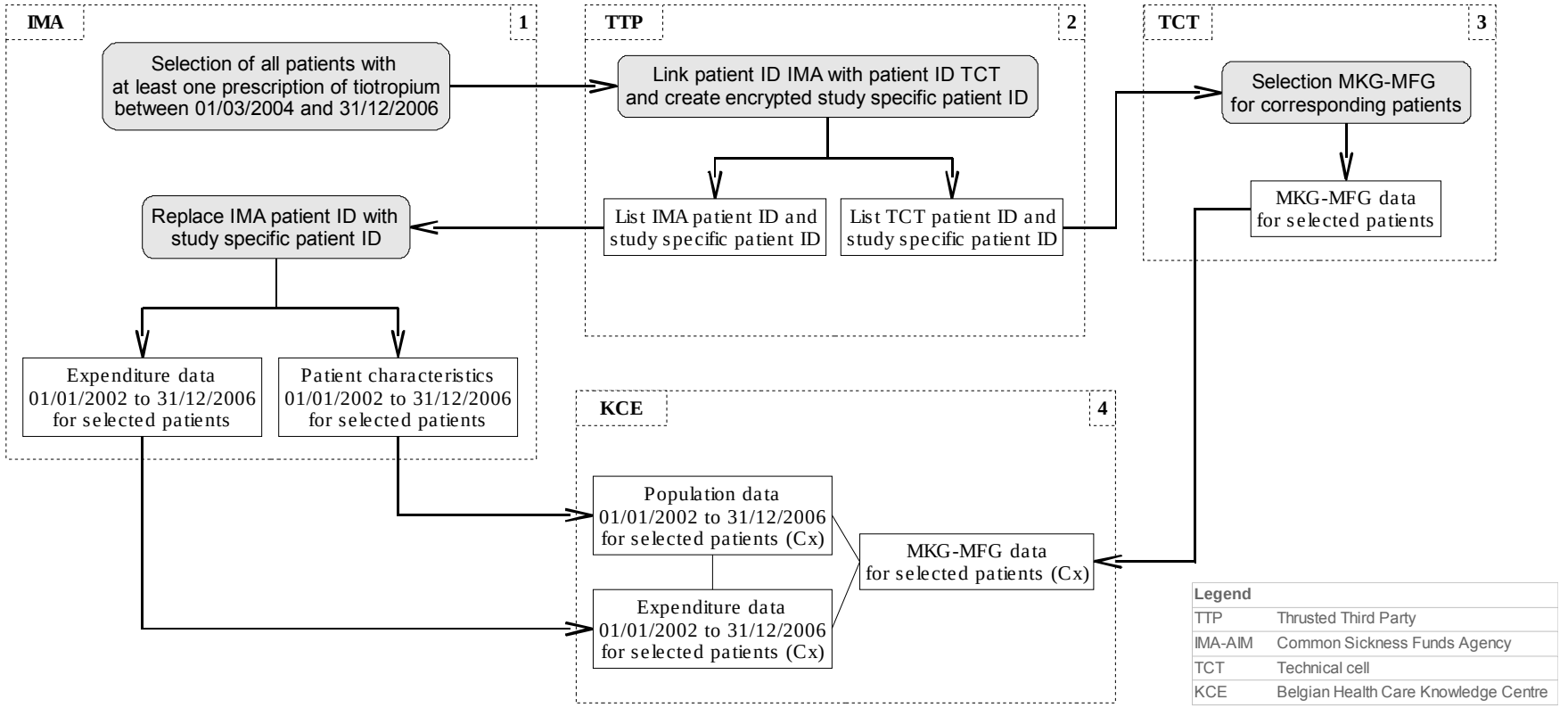
k National Institute for Health care and Disability Insurance

l Planned for data 2006.

CONSTRUCTION OF THE TIOTROPIUM STUDY DATABASE

The tiotropium study database was constructed by extracting all information of patients using tiotropium between 1 March 2004 and 31 December 2006 from the IMA database for the time frame 2002-2006. For these patients all hospital stays between 2002 and 2005 were retrieved from the TCT. The construction of this database was approved by the Sectoral Comitee of Social Security and Health Care which is a part of the Belgian Privacy Comission.[144] The extraction and linkage is shown in Figure 38.

Figure 38: Extraction from and linking of the IMA and TCT databases



APPENDIX 7: SEARCH FOR QUALITY-OF-LIFE DATA

QoL data were searched for both exacerbations and exacerbation-related hospitalisations. In January 2009, a search was performed in PubMed and Embase.

Table 56: Search strategy and results for Medline (PubMed)

Date	09/01/2009		
Database	Medline (Pubmed)		
Date covered	No restrictions		
Search Strategy	#	Search History	Results
	1	"Quality of Life"[Mesh]	70743
	2	"Pulmonary Disease, Chronic Obstructive"[Mesh]	10753
	3	"EQ-5D" or "EQ 5D"	951
	4	"SF-36" or "SF 36"	7067
	5	"Health Utilities Index"	329
	6	"Quality of well-being"	224
	7	#1 and #2	859
	8	#3 or #4 or #5 or #6	8263
	9	#7 and #8	**67**
Note			

Table 57: Search strategy and results for EMBASE

Date	23/01/2009		
Database	EMBASE		
Date covered	No restrictions		
Search Strategy	#	Search History	Results
	1	'quality of life'/exp	127505
	2	'chronic obstructive lung disease'/exp	43067
	3	'eq 5d' or 'eq-5d'	1117
	4	'sf 36' or 'sf-36'	8347
	5	'health utilities index'	369
	6	'quality of well-being'	237
	7	#1 AND #2	2846
	8	#3 OR #4 OR #5 OR #6	9702
	9	#7 AND #8	**145**
Note			

12 REFERENCES

1. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease. 2007. Available from: http://www.goldcopd.org
2. Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention. 2007. Available from: http://www.ginasthma.org
3. National Institute of Health and Clinical Excellence;c 2004. Managing stable COPD. Available from: www.nice.org.uk
4. Chatila WM, Thomashow BM, Minai OA, Criner GJ, Make BJ. Comorbidities in chronic obstructive pulmonary disease. Proc Am Thorac Soc. 2008;5(4):549-55.
5. Mannino DM, Homa DM, Akinbami LJ, Ford ES, Redd SC. Chronic obstructive pulmonary disease surveillance--United States, 1971-2000. MMWR Surveill Summ. 2002;51(6):1-16.
6. Lange P, Groth S, Nyboe J, Appleyard M, Mortensen J, Jensen G, et al. Chronic obstructive lung disease in Copenhagen: cross-sectional epidemiological aspects. J Intern Med. 1989;226(1):25-32.
7. Viegi G, Pedreschi M, Pistelli F, Di Pede F, Baldacci S, Carrozzi L, et al. Prevalence of airways obstruction in a general population: European Respiratory Society vs American Thoracic Society definition. Chest. 2000;117(5 Suppl 2):339S-45S.
8. Halbert RJ, Natoli JL, Gano A, Badamgarav E, Buist AS, Mannino DM. Global burden of COPD: systematic review and meta-analysis. Eur Respir J. 2006;28(3):523-32.
9. Buist AS, McBurnie MA, Vollmer WM, Gillespie S, Burney P, Mannino DM, et al. International variation in the prevalence of COPD (the BOLD Study): a population-based prevalence study. Lancet. 2007;370(9589):741-50.
10. Scientific Institute for Public Health Brussels;c 2004. Health Interview Survey. Available from: http://www.iph.fgov.be
11. Buffels J, Degryse J, Heyrman J, Decramer M, Study D. Office spirometry significantly improves early detection of COPD in general practice: the DIDASCO Study. Chest. 2004;125(4):1394-9.
12. Geijer RMM, Sachs APE, Verheij TJM, Salome PL, Lammers J-WJ, Hoes AW. Incidence and determinants of moderate COPD (GOLD II) in male smokers aged 40-65 years: 5-year follow up. Br J Gen Pract. 2006;56(530):656-61.
13. Johannessen A, Omenaas E, Bakke P, Gulsvik A. Incidence of GOLD-defined chronic obstructive pulmonary disease in a general adult population. Int J Tuberc Lung Dis. 2005;9(8):926-32.
14. Lindberg A, Eriksson B, Larsson L-G, Ronmark E, Sandstrom T, Lundback B. Seven-year cumulative incidence of COPD in an age-stratified general population sample. Chest. 2006;129(4):879-85.
15. Bartholomeeusen S, Kim C-Y, Mertens R, Faes C, Buntinx F. The denominator in general practice, a new approach from the Intego database. Fam Pract. 2005;22(4):442-7.
16. Stang P, Lydick E, Silberman C, Kempel A, Keating ET. The prevalence of COPD: using smoking rates to estimate disease frequency in the general population. Chest. 2000;117(5 Suppl 2):354S-9S.
17. Gan WQ, Man SFP, Postma DS, Camp P, Sin DD. Female smokers beyond the perimenopausal period are at increased risk of chronic obstructive pulmonary disease: a systematic review and meta-analysis. Respir Res. 2006;7:52.
18. Atlas of mortality in Europe. Subnational patterns 1980/1981 and 1990/1991. WHO Reg Publ Eur Ser. 1997;75:1-245.
19. Chapman KR, Mannino DM, Soriano JB, Vermeire PA, Buist AS, Thun MJ, et al. Epidemiology and costs of chronic obstructive pulmonary disease. Eur Respir J. 2006;27(1):188-207.
20. Mathers CD, Lopez AD, Murray CJL. The Burden of Disease and Mortality by Condition: Data, Methods, and Results for 2001. New York: Oxford University Press; 2006.
21. Scientific Institute for Public Health;c 2008. Standardized Procedures for Mortality Analysis - Belgium. Available from: http://www.iph.fgov.be/epidemio/spma/index.htm

22. American Thoracic Society, European Respiratory Society;c 2004. Standards for the diagnosis and management of patients with COPD. Available from: http://www.thoracic.org/
23. RIZIV/INAMI. Statistieken van het RIZIV: Statistieken van de geneeskundige verzorging. In; 2007.
24. RIZIV/INAMI. De TOP 25 van de werkzame bestanddelen in de uitgaven in de ambulante sector van de verzekering voor geneeskundige verzorging in 2007. In; 2008.
25. Lewsey JD, Leyland AH, Murray GD, Boddy FA. Using routine data to complement and enhance the results of randomised controlled trials. Health Technol Assess. 2000;4(22):1-55.
26. Byar D. Why data bases should not replace randomised clinical trials. Biometrics. 1980;36:337-42.
27. The AGREE Collaboration;c 2001 [cited 10/02/2009]. Appraisal of Guidelines for Research & Evaluation (AGREE) Instrument. Available from: www.agreecollaboration.org
28. Scottish Intercollegiate Guidelines Network;c 2002 [cited 10/02/2009]. Community Management of Lower Respiratory Tract Infection in Adults. Available from: http://www.sign.ac.uk/pdf/sign59.pdf
29. Donohue JF, van Noord JA, Bateman ED, Langley SJ, Lee A, Witek TJ, Jr., et al. A 6-month, placebo-controlled study comparing lung function and health status changes in COPD patients treated with tiotropium or salmeterol. Chest. 2002;122(1):47-55.
30. Brusasco V, Hodder R, Miravitlles M, Korducki L, Towse L, Kesten S. Health outcomes following treatment for six months with once daily tiotropium compared with twice daily salmeterol in patients with COPD. Thorax. 2003;58(5):399-404.
31. Institute for Clinical Systems Improvement;c 2007. Health Care Guideline: Chronic Obstructive Pulmonary Disease, 6th edition. Available from: www.icsi.org
32. Singapore Ministry of Health Singapore: Ministry of Health;c 2006. Clinical Practice Guidelines: Chronic Obstructive Pulmonary Disease. Available from: http://www.moh.gov.sg/cpg
33. Qaseem A, Snow V, Shekelle P, Sherif K, Wilt TJ, Weinberger S, et al. Diagnosis and management of stable chronic obstructive pulmonary disease: a clinical practice guideline from the American College of Physicians. Ann Intern Med. 2007;147(9):633-8.
34. Australian Lung Foundation, Thoracic Society of Australia and New Zealand;c 2006. The COPD-X Plan: Australian and New Zealand Guidelines for the management of Chronic Obstructive Pulmonary Disease. Available from: http://www.copdx.org.au/
35. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327(7414):557-60.
36. Begg CB, Berlin JA. Publication bias and dissemination of clinical research. J Natl Cancer Inst. 1989;81(2):107-15.
37. Sterne JA, Gavaghan D, Egger M. Publication and related bias in meta-analysis: power of statistical tests and prevalence in the literature. J Clin Epidemiol. 2000;53(11):1119-29.
38. The Cochrane Collaboration. Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.1. In: Higgins JPT GSe, editor.; 2008.
39. The Nordic Cochrane Centre. Review Manager (RevMan). In. Version 4.2 for Windows ed. Copenhagen: The Cochrane Collaboration.; 2003.
40. Shukla VK. Tiotropium: a potential replacement for ipratropium in patients with COPD. Issues Emerg Health Technol. 2002(35):1-4.
41. Barr RG, Bourbeau J, Camargo CA, Ram FSF. Inhaled tiotropium for stable chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2005(2):CD002876.
42. Barr RG, Bourbeau J, Camargo CA, Ram FSF. Tiotropium for stable chronic obstructive pulmonary disease: A meta-analysis. Thorax. 2006;61(10):854-62.
43. Kesten S, Jara M, Wentworth C, Lanes S. Pooled clinical trial analysis of tiotropium safety. Chest. 2006;130(6):1695-703.
44. Rodrigo GJ, Nannini LJ. Tiotropium for the treatment of stable chronic obstructive pulmonary disease: a systematic review with meta-analysis. Pulm Pharmacol Ther. 2007;20(5):495-502.
45. Powrie DJ, Wilkinson TM, Donaldson GC, Jones P, Scrine K, Viel K, et al. Effect of tiotropium on sputum and serum inflammatory markers and exacerbations in chronic obstructive pulmonary disease. Eur Respir J. 2007;15:15.

46. Chan CK, Maltais F, Sigouin C, Haddon JM, Ford GT, Group SS. A randomized controlled trial to assess the efficacy of tiotropium in Canadian patients with chronic obstructive pulmonary disease. Can Respir J. 2007;14(8):465-72.
47. Freeman D, Lee A, Price D. Efficacy and safety of tiotropium in COPD patients in primary care--the SPiRiva Usual CarE (SPRUCE) study. Respir Res. 2007;8:45.
48. Tashkin DP, Celli B, Senn S, Burkhart D, Kesten S, Menjoge S, et al. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. N Engl J Med. 2008;359(15):1543-54.
49. Tonnel AB, Perez T, Grosbois JM, Verkindre C, Bravo ML, Brun M, et al. Effect of tiotropium on health-related quality of life as a primary efficacy endpoint in COPD. Int J Chron Obstruct Pulmon Dis. 2008;3(2):301-10.
50. Wedzicha JA, Calverley PM, Seemungal TA, Hagan G, Ansari Z, Stockley RA, et al. The prevention of chronic obstructive pulmonary disease exacerbations by salmeterol/fluticasone propionate or tiotropium bromide. Am J Respir Crit Care Med. 2008;177(1):19-26.
51. Magnussen H, Bugnas B, van Noord J, Schmidt P, Gerken F, Kesten S. Improvements with tiotropium in COPD patients with concomitant asthma. Respir Med. 2008;102(1):50-6.
52. Casaburi R, Mahler DA, Jones PW, Wanner A, San PG, ZuWallack RL, et al. A long-term evaluation of once-daily inhaled tiotropium in chronic obstructive pulmonary disease. Eur Respir J. 2002;19(2):217-24.
53. Vincken W, van Noord JA, Greefhorst APM, Bantje TA, Kesten S, Korducki L, et al. Improved health outcomes in patients with COPD during 1 yr's treatment with tiotropium. Eur Respir J. 2002;19(2):209-16.
54. Niewoehner DE, Rice K, Cote C, Paulson D, Cooper JAD, Jr., Korducki L, et al. Prevention of exacerbations of chronic obstructive pulmonary disease with tiotropium, a once-daily inhaled anticholinergic bronchodilator: a randomized trial. Ann Intern Med. 2005;143(5):317-26.
55. Beeh KM, Beier J, Buhl R, Stark-Lorenzen P, Gerken F, Metzdorf N. Efficacy of tiotropium bromide (Spiriva(registered trademark)) in patients with chronic-obstructive pulmonary disease (COPD) of different severities. Pneumologie. 2006;60(6):341-6.
56. Briggs DD, Jr., Covelli H, Lapidus R, Bhattycharya S, Kesten S, Cassino C. Improved daytime spirometric efficacy of tiotropium compared with salmeterol in patients with COPD. Pulm Pharmacol Ther. 2005;18(6):397-404.
57. Casaburi R, Kukafka D, Cooper CB, Witek TJ, Jr., Kesten S. Improvement in exercise tolerance with the combination of tiotropium and pulmonary rehabilitation in patients with COPD. Chest. 2005;127(3):809-17.
58. Dusser D, Bravo ML, Iacono P. The effect of tiotropium on exacerbations and airflow in patients with COPD. Eur Respir J. 2006;27(3):547-55.
59. Verkindre C, Bart F, Aguilaniu B, Fortin F, Guerin JC, Le Merre C, et al. The effect of tiotropium on hyperinflation and exercise capacity in chronic obstructive pulmonary disease. Respiration. 2006;73(4):420-7.
60. Witek TJ, Jr., Mahler DA. Minimal important difference of the transition dyspnoea index in a multinational clinical trial. Eur Respir J. 2003;21(2):267-72.
61. Heller Brown J, Taylor P. Muscarinic receptor agonists and antagonists. In: Brunton L, editor. Goodman and Gilman's The pharmacological basis of therapeutics. eleventh edition ed. New York: The McGraw-Hill Companies; 2006. p. 183-200.
62. Vandenbroucke JP, Psaty BM. Benefits and risks of drug treatments: how to combine the best evidence on benefits with the best data about adverse effects. JAMA. 2008;300(20):2417-9.
63. Singh S, Loke YK, Furberg CD. Inhaled anticholinergics and risk of major adverse cardiovascular events in patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis. JAMA. 2008;300(12):1439-50.
64. Tezky T, Holquist C. FDA Safety Page: Misadministration of capsules for inhalation. Drug Topics. 2005;149(7).
65. Vucicevic Boras V, Savage N, Mohamad Zaini Z. Oral aphthous-like ulceration due to tiotropium bromide. Med Oral Patol Oral Cir Bucal. 2007;12(3):E209-10.
66. Perez-Perez L, Cabanillas M, Pereiro Ferreiros MM, Peteiro C, Toribio J. Photosensitive lichenoid eruption and inhaled tiotropium bromide [1]. Dermatology. 2007;214(1):97-8.

67. Pham HC, Saurat JH. Inhalation route inducing subacute cutaneous lupus erythematosus with tiotropium [8]. Archives of Dermatology. 2005;141(7):911-2.
68. Oksuz H, Tamer C, Akoglu S, Duru M. Acute angle-closure glaucoma precipitated by local tiotropium absorption. Pulmonary Pharmacology and Therapeutics. 2007;20(6):627-8.
69. Praetorius GM. Postoperative intestinal paralysis caused by the muscarinic receptor blocker tiotropium bromide. Urologe - Ausgabe A. 2005;44(4):393-5.
70. de Luise C, Lanes SF, Jacobsen J, Pedersen L, Sorensen HT. Cardiovascular and respiratory hospitalizations and mortality among users of tiotropium in Denmark. Eur J Epidemiol. 2007;22(4):267-72.
71. Jara M, Lanes SF, Wentworth Iii C, May C, Kesten S. Comparative safety of long-acting inhaled bronchodilators: A cohort study using the UK THIN primary care database. Drug Safety. 2007;30(12):1151-60.
72. Kesten S, Plautz M, Piquette CA, Habib MP, Niewoehner DE. Premature discontinuation of patients: A potential bias in COPD clinical trials. European Respiratory Journal. 2007;30(5):898-906.
73. Verhamme KMC, Sturkenboom MCJM, Stricker BHC, Bosch R. Drug-induced urinary retention: Incidence, management and prevention. Drug Safety. 2008;31(5):373-88.
74. Gupta P, O'Mahony MS. Potential adverse effects of bronchodilators in the treatment of airways obstruction in older people: Recommendations for prescribing. Drugs and Aging. 2008;25(5):415-43.
75. Covelli H, Bhattacharya S, Cassino C, Conoscenti C, Kesten S. Absence of electrocardiographic findings and improved function with once-daily tiotropium in patients with chronic obstructive pulmonary disease. Pharmacotherapy. 2005;25(12 I):1708-18.
76. Herland K, Akselsen J-P, Skjonsberg OH, Bjermer L. How representative are clinical study patients with asthma or COPD for a larger "real life" population of patients with obstructive lung disease? Respir Med. 2005;99(1):11-9.
77. Casaburi R, Briggs DD, Jr., Donohue JF, Serby CW, Menjoge SS, Witek TJ, Jr. The spirometric efficacy of once-daily dosing with tiotropium in stable COPD: a 13-week multicenter trial. The US Tiotropium Study Group. Chest. 2000;118(5):1294-302.
78. Anthonisen NR, Connett JE, Enright PL, Manfreda J, Lung Health Study Research G. Hospitalizations and mortality in the Lung Health Study. Am J Respir Crit Care Med. 2002;166(3):333-9.
79. Cates CJ, Cates MJ. Regular treatment with salmeterol for chronic asthma: serious adverse events. Cochrane Database Syst Rev. 2008(3):CD006363.
80. Levenson M. Long-Acting Beta-Agonists and Adverse Asthma Events Meta-Analysis, Statistical Briefing Package for Joint Meeting of the Pulmonary-Allergy Drugs Advisory Committee, Drug Safety and Risk Management Advisory Committee and Pediatric Advisory Committee on December 10-11, 2008. 2008. Available from: http://www.fda.gov/OHRMS/DOCKETS/ac/08/briefing/2008-4398b1-01-FDA.pdf
81. Yang IA, Fong KM, Sim EHA, Black PN, Lasserson TJ. Inhaled corticosteroids for stable chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2007(2):CD002991.
82. Drummond MB, Dasenbrook EC, Pitz MW, Murphy DJ, Fan E. Inhaled corticosteroids in patients with stable chronic obstructive pulmonary disease: a systematic review and meta-analysis. JAMA. 2008;300(20):2407-16.
83. Belgian Health Care Knowledge Centre (KCE). HTA of tiotropium in the treatment of chronic obstructive pulmonary disease (project). Belgian Health Care Knowledge Centre (KCE). Available from: http://www.kce.fgov.be
84. Canadian Coordinating Office for Health Technology Assessment. Tiotropium bromide. Report. Canadian Coordinating Office for Health Technology Assessment (CCOHTA); 2002. Emerging Drug List Issue 24 Available from: https://www.ccohta.ca
85. Canadian Coordinating Office for Health Technology Assessment. Triple therapy for COPD. Review. Canadian Coordinating Office for Health Technology Assessment (CCOHTA); 2005. Emerging Drug List Issue 65 Available from: https://www.ccohta.ca/

86. National Horizon Scanning Centre. Tiotropium for COPD - horizon scanning review. Review. National Horizon Scanning Centre (NHSC); 2001. New and Emerging Technology Briefing Available from: http://www.pcpoh.bham.ac.uk/publichealth/horizon/

87. Shukla VK. Tiotropium: a potential replacement for ipratropium in patients with COPD. Review. Canadian Coordinating Office for Health Technology Assessment (CCOHTA); 2002. Issues in Emerging Health Technologies Issue 35 Available from: https://www.ccohta.ca/

88. Shukla VK, Chen S, Boucher M, Mensinkai S, Dales R. Long-acting beta2 agonists for the maintenance treatment of chronic obstructive pulmonary disease in patients with reversible and non-reversible airflow obstruction: a systematic review of clinical effectiveness. Review. Canadian Coordinating Office for Health Technology Assessment (CCOHTA); 2006. Technology Report Issue 65 Available from: https://www.ccohta.ca/

89. de Lucas Ramos P, Miravitlles M, Rodriguez Gonzalez-Moro J, de Miguel Diez J, Lopez Martin S, Sanchez Munoz G. Cost-effectiveness analysis of the use of tiotropium versus ipratropium for the treatment of chronic obstructive pulmonary disease. Pharmacoeconomics. Spanish Research Articles. 2004;1(3):123-30.

90. Chen AM, Bollmeier SG, Finnegan PM. Long-acting bronchodilator therapy for the treatment of chronic obstructive pulmonary disease. Ann Pharmacother. 2008;42(12):1832-42.

91. Rice KL, Kunisaki KM, Niewoehner DE. Role of tiotropium in the treatment of COPD. Int J Chron Obstruct Pulmon Dis. 2007;2(2):95-105.

92. Oostenbrink JB, Al MJ, Oppe M, Rutten-Van Molken MPMH. Expected value of perfect information: An empirical example of reducing decision uncertainty by conducting additional research. Value in Health. 2008;11(7):1070-80.

93. Rutten-van Molken M, Oostenbrink JB, Miravitlles M, Monz BU. Modelling the 5-year cost effectiveness of tiotropium, salmeterol and ipratropium for the treatment of chronic obstructive pulmonary disease in Spain. Eur J Health Econ. 2007;8(2):123-35.

94. Oba Y. Cost-effectiveness of long-acting bronchodilators for chronic obstructive pulmonary disease. Mayo Clin Proc. 2007;82(5):575-82.

95. Rutten-van Molken M, Lee TA. Economic modeling in chronic obstructive pulmonary disease. Proceedings of the American Thoracic Society. 2006;3(7):630-4.

96. Maniadakis N, Tzanakis N, Fragoulakis V, Hatzikou M, Siafakas N. Economic evaluation of tiotropium and salmeterol in the treatment of chronic obstructive pulmonary disease (COPD) in Greece. Curr Med Res Opin. 2006;22(8):1599-607.

97. D'Souza AO, Smith MJ, Miller LA, Kavookjian J. An appraisal of pharmacoeconomic evidence of maintenance therapy for COPD. Chest. 2006;129(6):1693-708.

98. Schramm W, Haake D, Brandt A. Economic value of tiotropium in the treatment of chronic obstructive pulmonary disease. Schweiz Rundsch Med Prax. 2005;94(46):1803-10.

99. Oostenbrink JB, Rutten-van Molken M, Monz BU, FitzGerald JM. Probabilistic Markov model to assess the cost-effectiveness of bronchodilator therapy in COPD patients in different countries.[see comment]. Value Health. 2005;8(1):32-46.

100. Oostenbrink JB, Rutten-van Molken M, Al MJ, Van Noord JA, Vincken W. One-year cost-effectiveness of tiotropium versus ipratropium to treat chronic obstructive pulmonary disease. Eur Respir J. 2004;23(2):241-9.

101. Onukwugha E, Mullins CD, DeLisle S. Using cost-effectiveness analysis to sharpen formulary decision-making: The example of tiotropium at the veterans affairs health care system. Value in Health. 2008;11(5):980-8.

102. Najafzadeh M, Marra CA, Sadatsafavi M, Aaron SD, Sullivan SD, Vandemheen KL, et al. Cost effectiveness of therapy with combinations of long acting bronchodilators and inhaled steroids for treatment of COPD. Thorax. 2008;63(11):962-7.

103. Starkie HJ, Briggs AH, Chambers MG. Pharmacoeconomics in COPD: Lessons for the future. International Journal of COPD. 2008;3(1):71-88.

104. Bell T, Backhouse ME. An economic evaluation of tiotropium plus existing therapy versus placebo plus existing therapy in the treatment of COP in the USA. Research triangle park: RTI Health Solutions, editors. . 2001.

105. Boehringer Ingelheim Corporation. A six month prospective cost-effectiveness analysis of Spiriva vs Salmeterol in the treatment of COPD 2001.

106. Hilleman DE. Pharmacoeconomic evaluation of tiotropium in COPD. Poster presented at ASHP Midyear Clinical Meeting; December 5-9, 2004; Orlando; Flo.

107. Nowak D, Berger K, Lippert B, Kilgert K, Caeser M, R. S. Epidemiology and health economics of COPD across Europe: a critical analysis. Treat Respir Med 2005;4(6):381-95.

108. Rutten-van Molken. Costs and effects of pharmacotherapy in asthma and COPD. Proefschrift, 24 november 1994, Universitaire Pers Maastricht.

109. Rutten-van Molken M, Oostenbrink J, Koch P. Cost-consequence analysis of tiotropium versus ipratropium for the treatment of chronic obstructive pulmonary disease (COPD). ISPOR European Congress, Cannes, 2001. Value in Health 2001;4(6):461-2.

110. Oostenbrink J, Rutten-van Molken M. Cost-consequence analysis of tiotropium versus ipratropium for the treatment of chronic obstructive pulmonary disease (COPD). . Chest 2001;120 (4 Suppl):148.

111. Aaron SD, Vandemheen KL, Fergusson D, Maltais F, Bourbeau J, Goldstein R, et al. Tiotropium in combination with placebo, salmeterol, or fluticasone-salmeterol for treatment of chronic obstructive pulmonary disease: a randomized trial. Ann Intern Med. 2007;146(8):545-55.

112. Rovira J, Antonanzas F. Economic analysis of health technologies and programmes. A Spanish proposal for methodological standardisation. Pharmacoeconomics. 1995;8(3):245-52.

113. Global Initiative for Chronic Obstructive Lung Disease (GOLD);c 2007. Global Strategy for the Diagnosis, Management and Prevention of COPD. Available from: http://www.goldcopd.org.

114. Ramsey SD, Sullivan SD. The burden of illness and economic evaluation for COPD. Eur Respir J Suppl. 2003;41:29s-35s.

115. Borg S, Ericsson A, Wedzicha J, Gulsvik A, Lundback B, Donaldson GC, et al. A computer simulation model of the natural history and economic impact of chronic obstructive pulmonary disease. Value Health. 2004;7(2):153-67.

116. Decramer M, Celli B, Tashkin DP, Pauwels RA, Burkhart D, Cassino C, et al. Clinical trial design considerations in assessing long-term functional impacts of tiotropium in COPD: the UPLIFT trial. COPD. 2004;1(2):303-12.

117. Badia X, Roset M, Herdman M, Kind P. A comparison of United Kingdom and Spanish general population time trade-off values for EQ-5D health states. Med Decis Making. 2001;21(1):7-16.

118. Stahl E, Lindberg A, Jansson S-A, Ronmark E, Svensson K, Andersson F, et al. Health-related quality of life is related to COPD disease severity. Health Qual Life Outcomes. 2005;3:56.

119. Meguro M JP. Elicitation of utility weights for a copd specific preference measure. Am J Respir Crit Care Med. 2006;3(A488).

120. Kind P, Macran S, Spencer MD. The Quality of Life Deficit in COPD: Evidence from a National Population Survey. Poster presentation. In: ERS. Stockholm; 2002.

121. Rutten-van Molken MPMH, Oostenbrink JB, Tashkin DP, Burkhart D, Monz BU. Does quality of life of COPD patients as measured by the generic EuroQol five-dimension questionnaire differentiate between COPD severity stages? Chest. 2006;130(4):1117-28.

122. Paterson C, Langan CE, McKaig GA, Anderson PM, Maclaine GD, Rose LB, et al. Assessing patient outcomes in acute exacerbations of chronic bronchitis: the measure your medical outcome profile (MYMOP), medical outcomes study 6-item general health survey (MOS-6A) and EuroQol (EQ-5D). Qual Life Res. 2000;9(5):521-7.

123. Spencer S, Jones PW, Group GS. Time course of recovery of health status following an infective exacerbation of chronic bronchitis. Thorax. 2003;58(7):589-93.

124. Pharmaceutical Policy Management Unit, Healthcare Department. Global analytical report on the content of Pharmanet – singular pathway. 2006.

125. Roede BM, Bindels PJ, Brouwer HJ, Bresser P, de Borgie CA, Prins JM. Antibiotics and steroids for exacerbations of COPD in primary care: compliance with Dutch guidelines. Br J Gen Pract. 2006;56(530):662-5.

126. Cleemput I, Van Wilder P, Vrijens F, Huybrechts M, Ramaekers D. Guidelines for pharmaco-economic evaluations in Belgium. Brussels: Belgian Health Care Knowledge Centre (KCE); 2008. Health Technology Assessment (HTA) (KCE Reports 78A (D/2008/10.273/23))

127. D'Agostino RB, Jr., D'Agostino RB, Sr. Estimating treatment effects using observational data. JAMA. 2007;297(3):314-6.

128. Drummond M, Sculpher M, Torrance G, O'Brien B, Stoddart G. Methods for the economic evaluation of health care programmes. Oxford University Press, editor.; 2005.

129. O'Reilly JF, Williams AE, Rice L. Health status impairment and costs associated with COPD exacerbation managed in hospital. Int J Clin Pract. 2007;61(7):1112-20.

130. Pickard AS, Wilke C, Jung E, Patel S, Stavem K, Lee TA. Use of a preference-based measure of health (EQ-5D) in COPD and asthma. Respir Med. 2008;102(4):519-36.

131. Rodriguez-Roisin R. Toward a consensus definition for COPD exacerbations. Chest. 2000;117(5 Suppl 2):398S-401S.

132. Kirkwood B, Sterne A. Essential Medical Statistics. Oxford: Blackwell Publishing; 2003.

133. Briggs AH, Claxton K, Sculpher MJ. Decision modelling for health economic evaluation. Oxford: Oxford University Press; 2006.

134. Rice J. Mathematical statistics and data analysis. 2nd edition ed. Belmont: Duxbury Press; 1995.

135. Cleemput I, Neyt M, Thiry N, De Laet C, Leys M. Threshold values for cost-effectiveness in health care Health Technology Assessment (HTA). Brussels: Belgian Health Care Knowledge Centre (KCE); 2008. (KCE reports 100C (D/2008/10.273/96))

136. Altman DG, Bland JM. Absence of evidence is not evidence of absence. BMJ. 1995;311(7003):485.

137. Briggs AH, O'Brien BJ. The death of cost-minimization analysis? Health Econ. 2001;10(2):179-84.

138. Ruchlin HS, Dasbach EJ. An economic overview of chronic obstructive pulmonary disease. Pharmacoeconomics. 2001;19(6):623-42.

139. Gold M, Siegel J, Russell L, Weinstein M. Cost-effectiveness in health and medicine. New York: Oxford University Press; 1996.

140. van Manen JG, Bindels PJ, Dekker FW, Bottema BJ, van der Zee JS, Ijzermans CJ, et al. The influence of COPD on health-related quality of life independent of the influence of comorbidity. J Clin Epidemiol. 2003;56(12):1177-84.

141. Andersson F, Borg S, Stahl E. The impact of exacerbations on the asthmatic patient's preference scores. J Asthma. 2003;40(6):615-23.

142. Andersson I, Johansson K, Larsson S, Pehrsson K. Long-term oxygen therapy and quality of life in elderly patients hospitalised due to severe exacerbation of COPD. A 1 year follow-up study. Respir Med. 2002;96(11):944-9.

143. Van de Sande S, De Wachter D, Swartenbroeckx N, Peers J, Debruyne H, Moldenaers I, et al. Inventaris van databanken gezondheidszorg - Supplement. KCE Reports vol.30. 2006. (D/2006/10.273/16)

144. Sectoraal Comité van de Sociale Zekerheid en van de Gezondheid - Afdeling Sociale Zekerheid. Beraadslaging nr. 08/011 van 5 februari 2008 met betrekking tot de mededeling van persoonsgegevens aan het Federaal Kenniscentrum voor de Gezondheidszorg in het kader van studie nr 2007-14 "Het gebruik van tiotropium in belgië, en het effect ervan op patiënt gerelateerde uitkomsten". 2008. (SCSZ/08/030) Available from: http://www.privacycommission.be/nl/docs/SZ-SS/2008/beraadslaging_SZ_011_2008.pdf

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Wettelijk depot : D/2008/10.273/18

KCE reports

1. Effectiviteit en kosten-effectiviteit van behandelingen voor rookstop. D/2004/10.273/1.
2. Studie naar de mogelijke kosten van een eventuele wijziging van de rechtsregels inzake medische aansprakelijkheid (fase 1). D/2004/10.273/2.
3. Antibioticagebruik in ziekenhuizen bij acute pyelonefritis. D/2004/10.273/5.
4. Leukoreductie. Een mogelijke maatregel in het kader van een nationaal beleid voor bloedtransfusieveiligheid. D/2004/10.273/7.
5. Het preoperatief onderzoek. D/2004/10.273/9.
6. Validatie van het rapport van de Onderzoekscommissie over de onderfinanciering van de ziekenhuizen. D/2004/10.273/11.
7. Nationale richtlijn prenatale zorg. Een basis voor een klinisch pad voor de opvolging van zwangerschappen. D/2004/10.273/13.
8. Financieringssystemen van ziekenhuisgeneesmiddelen: een beschrijvende studie van een aantal Europese landen en Canada. D/2004/10.273/15.
9. Feedback: onderzoek naar de impact en barrières bij implementatie – Onderzoeksrapport: deel 1. D/2005/10.273/01.
10. De kost van tandprothesen. D/2005/10.273/03.
11. Borstkankerscreening. D/2005/10.273/05.
12. Studie naar een alternatieve financiering van bloed en labiele bloedderivaten in de ziekenhuizen. D/2005/10.273/07.
13. Endovasculaire behandeling van Carotisstenose. D/2005/10.273/09.
14. Variaties in de ziekenhuispraktijk bij acuut myocardinfarct in België. D/2005/10.273/11.
15. Evolutie van de uitgaven voor gezondheidszorg. D/2005/10.273/13.
16. Studie naar de mogelijke kosten van een eventuele wijziging van de rechtsregels inzake medische aansprakelijkheid. Fase II : ontwikkeling van een actuarieel model en eerste schattingen. D/2005/10.273/15.
17. Evaluatie van de referentiebedragen. D/2005/10.273/17.
18. Prospectief bepalen van de honoraria van ziekenhuisartsen op basis van klinische paden en guidelines: makkelijker gezegd dan gedaan.. D/2005/10.273/19.
19. Evaluatie van forfaitaire persoonlijk bijdrage op het gebruik van spoedgevallendienst. D/2005/10.273/21.
20. HTA Moleculaire Diagnostiek in België. D/2005/10.273/23, D/2005/10.273/25.
21. HTA Stomamateriaal in België. D/2005/10.273/27.
22. HTA Positronen Emissie Tomografie in België. D/2005/10.273/29.
23. HTA De electieve endovasculaire behandeling van het abdominale aorta aneurysma (AAA). D/2005/10.273/32.
24. Het gebruik van natriuretische peptides in de diagnostische aanpak van patiënten met vermoeden van hartfalen. D/2005/10.273/34.
25. Capsule endoscopie. D/2006/10.273/01.
26. Medico–legale aspecten van klinische praktijkrichtlijnen. D2006/10.273/05.
27. De kwaliteit en de organisatie van type 2 diabeteszorg. D2006/10.273/07.
28. Voorlopige richtlijnen voor farmaco-economisch onderzoek in België. D2006/10.273/10.
29. Nationale Richtlijnen College voor Oncologie: A. algemeen kader oncologisch kwaliteitshandboek B. wetenschappelijke basis voor klinische paden voor diagnose en behandeling colorectale kanker en testiskanker. D2006/10.273/12.
30. Inventaris van databanken gezondheidszorg. D2006/10.273/14.
31. Health Technology Assessment prostate-specific-antigen (PSA) voor prostaatkankerscreening. D2006/10.273/17.
32. Feedback : onderzoek naar de impact en barrières bij implementatie – Onderzoeksrapport : deel II. D/2006/10.273/19.
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34. Trastuzumab bij vroegtijdige stadia van borstkanker. D/2006/10.273/23.
35. Studie naar de mogelijke kosten van een eventuele wijziging van de rechtsregels inzake medische aansprakelijkheid (fase III)- precisering van de kostenraming. D/2006/10.273/26.
36. Farmacologische en chirurgische behandeling van obesitas. Residentiële zorg voor ernstig obese kinderen in België. D/2006/10.273/28.

37. HTA Magnetische Resonantie Beeldvorming. D/2006/10.273/32.
38. Baarmoederhalskankerscreening en testen op Human Papillomavirus (HPV). D/2006/10.273/35
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44. Een procedure voor de beoordeling van nieuwe medische hulpmiddelen. D/2006/10.273/50.
45. HTA Colorectale Kankerscreening: wetenschappelijke stand van zaken en budgetimpact voor België. D/2006/10.273/53.
46. Health Technology Assessment. Polysomnografie en thuismonitoring van zuigelingen voor de preventie van wiegendood. D/2006/10.273/59.
47. Geneesmiddelengebruik in de belgische rusthuizen en rust- en verzorgingstehuizen. D/2006/10.273/61
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49. Antivirale middelen bij seizoensgriep en grieppandemie. Literatuurstudie en ontwikkeling van praktijkrichtlijnen. D/2006/10.273/65.
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52. Rapid Assessment: Cardiovasculaire Primaire Preventie in de Belgische Huisartspraktijk. D/2007/10.273/03.
53. Financiering van verpleegkundige zorg in ziekenhuizen. D/2007/10 273/06
54. Kosten-effectiviteitsanalyse van rotavirus vaccinatie van zuigelingen in België
55. Evidence-based inhoud van geschreven informatie vanuit de farmaceutische industrie aan huisartsen. D/2007/10.273/12.
56. Orthopedisch Materiaal in België: Health Technology Assessment. D/2007/10.273/14.
57. Organisatie en Financiering van Musculoskeletale en Neurologische Revalidatie in België. D/2007/10.273/18.
58. De Implanteerbare Defibrillator: een Health Technology Assessment. D/2007/10.273/21.
59. Laboratoriumtesten in de huisartsgeneeskunde. D2007/10.273/24.
60. Longfunctie testen bij volwassenen. D/2007/10.273/27.
61. Vacuümgeassisteerde Wondbehandeling: een Rapid Assessment. D/2007/10.273/30
62. Intensiteitsgemoduleerde Radiotherapie (IMRT). D/2007/10.273/32.
63. Wetenschappelijke ondersteuning van het College voor Oncologie: een nationale praktijkrichtlijn voor de aanpak van borstkanker. D/2007/10.273/35.
64. HPV Vaccinatie ter Preventie van Baarmoederhalskanker in België: Health Technology Assessment. D/2007/10.273/41.
65. Organisatie en financiering van genetische diagnostiek in België. D/2007/10.273/44.
66. Health Technology Assessment: Drug-Eluting Stents in België. D/2007/10.273/47
67. Hadrontherapie. D/2007/10.273/50.
68. Vergoeding van schade als gevolg van gezondheidszorg – Fase IV : Verdeelsleutel tussen het Fonds en de verzekeraars. D/2007/10.273/52.
69. Kwaliteit van rectale kankerzorg – Fase 1: een praktijkrichtlijn voor rectale kanker D/2007/10.273/54.
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71. Aanbevelingen voor het gebruik van vijf oftalmologische testen in de klinische praktijk .D/2008/10.273/04
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74. Hyperbare Zuurstoftherapie: Rapid Assessment. D/2008/10.273/13.
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76. Kwaliteitsbevordering in de huisartsenpraktijk in België: status quo of quo vadis? D/2008/10.273/18.
77. Orthodontie bij kinderen en adolescenten. D/2008/10.273/20.
78. Richtlijnen voor farmaco-economische evaluaties in België. D/2008/10.273/23.
79. Terugbetaling van radioisotopen in België. D/2008/10.273/26
80. Evaluatie van de effecten van de maximumfactuur op de consumptie en financiële toegankelijkheid van gezondheidszorg. D/2008/10.273/35.
81. Kwaliteit van rectale kankerzorg – phase 2: ontwikkeling en test van een set van kwaliteitsindicatoren. D/2008/10.273/38
82. 64-Slice computertomografie van de kransslagaders bij patiënten met vermoeden van coronaire hartziekte. D/2008/10.273/40
83. Internationale vergelijking van terugbetalingsregels en juridische aspecten van plastische heelkunde. D/200810.273/43
84. Langverblijvende psychiatrische patiënten in T-bedden. D/2008/10.273/46
85. Vergelijking van twee financieringssystemen voor de eerstelijnszorg in België. D/2008/10.273/49.
86. Functiedifferentiatie in de verpleegkundige zorg: mogelijkheden en beperkingen. D/2008/10.273/52.
87. Het gebruik van kinesitherapie en van fysische geneeskunde en revalidatie in België. D/2008/10.273/54.
88. Chronisch Vermoeidheidssyndroom: diagnose, behandeling en zorgorganisatie. D/2008/10.273/58.
89. Rapid assessment van enkele nieuwe behandelingen voor prostaatkanker en goedaardige prostaathypertrofie. D/2008/10.273/61
90. Huisartsgeneeskunde: aantrekkingskracht en beroepstrouw bevorderen. D/2008/10.273/63
91. Hoorapparaten in België: health technology assessment. D/2008/10.273/67
92. Nosocomiale infecties in België, deel 1: nationale prevalentiestudie. D/2008/10.273/70.
93. Detectie van adverse events in administratieve databanken. D/2008/10.273/73.
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