Gebruik van point-of care systemen bij patiënten met orale anticoagulatie: een Health Technology Assesment

KCE reports 117A

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

Een belangrijk aantal patiënten neemt orale anticoagulatie medicatie, meestal gedurende zeer lange periodes of zelfs levenslang. Deze behandeling verhoogt hun levensverwachting en vermindert het risico op thrombo-embolische accidenten, maar maakt een rigoureuze opvolging noodzakelijk. Diverse factoren, waaronder voeding en de inname van andere medicatie, kunnen de antistolling beïnvloeden waardoor de dosis regelmatig aangepast moet worden om bloedklonters of een bloeding te vermijden.

Bij deze patiënten wordt dan ook regelmatig, minstens een keer per maand, bloed geprikt om een correctie dosisaanpassing te kunnen doen. Deze opvolging neemt tijd en geld in beslag; daarbij zijn er niet veel mensen die het leuk vinden om regelmatig bloed te laten nemen. Het beschikbaar worden van draagbare coagulometers, bruikbaar op eender welke plaats, hetzij door de behandelende arts hetzij door de patiënt zelf, kunnen de last van deze opvolging in belangrijke mate verminderen.

Vooraleer het gebruik van een dergelijk instrument op grote schaal te introduceren, is het belangrijk de technische waarde, de precisie van de diagnostiek en het voordeel voor de patiënt te verifiëren. Het mogelijke gebruik van de coagulometer door de patiënt doet ook nadenken over eventuele veranderingen aan de organisatie van de zorg. Tenslotte moeten ook de gevolgen voor het budget van de gezondheidszorg bestudeerd worden.

Het is op al deze vragen dat dit rapport een antwoord biedt. Het werd volledig intern door het KCE gerealiseerd maar zoals steeds onderworpen aan een kritische evaluatie door externe experten die we dan ook hartelijk wensen te bedanken,

Jean-Pierre CLOSON

Algemeen Directeur a.i.

Samenvatting en toelichtingen

INLEIDING

In België gebruiken meer dan 100 000 patiënten orale antistollingstherapie met vitamine K antagonisten, meestal voor atriumfibrillatie, hartklepprothese, diepe veneuze trombose, longembolie of beroerte. Een regelmatige controle van de behandeling, waarbij meestal de International Normalised Ratio (INR) wordt gemeten, is essentieel: door een hoge antistollingswaarde kunnen bloedingen optreden, terwijl een lage waarde bloedklonters kan veroorzaken. In de huidige zorg wordt door middel van een veneuze punctie een bloedstaal genomen, meestal door een huisarts. Dit wordt dan naar een laboratorium gezonden waar de INR-waarde wordt bepaald met een gekalibreerd laboratoriumtoestel. Het laboratorium deelt dan het INR-resultaat mee aan de huisarts die de patiënt contacteert en, indien nodig, de behandelingsdosis aanpast.

In de nabije toekomst zouden drie ontwikkelingen de opvolging van de orale stollingstherapie kunnen beïnvloeden:

- In de eerste plaats werden in België antistollingsklinieken opgericht waar een professionele zorgverlener de INR-test uitvoert en de behandelingsdosis aanpast.
- Ten tweede kwamen draagbare apparaten ter beschikking voor point-of-care meting (POC), d.w.z. in aanwezigheid van de patiënt. Met deze apparaten kunnen patiënten of artsen de INR-waarde onmiddellijk bepalen met een druppel bloed. Deze technologie zou de INR-test in het laboratorium kunnen vervangen. Dank zij deze technologie kunnen bovendien nieuwe vormen van zorgorganisatie ontstaan, zoals patiëntzelfmanagement (PZM, de patiënt test zichzelf thuis en past ook de behandelingsdosis aan) en patiëntzelfcontrole (PZC, de patiënt test zichzelf, maar de behandelingsdosis wordt door een professionele zorgverlener aangepast).
- Ten derde worden nieuwe anticoagulantia (inhibitoren van Xa factoren) ontwikkeld en getest waardoor de INR-controle overbodig zou kunnen worden. Hoewel de resultaten van de eerste studies veelbelovend zijn, zal de juiste plaats van deze nieuwe geneesmiddelen in de behandeling nog moeten worden bepaald.

DOEL

Deze health technology assessment (HTA) over POC testen van orale antistollingstherapie wil 4 vragen beantwoorden:

1. Wat is de klinische doeltreffendheid van POC stollingscontrole?
2. Wat zijn de noden en voorkeuren van patiënten met betrekking tot POC stollingscontrole?
3. Wat is de kosten-effectiviteit van POC stollingscontrole?
4. Hoe moet POC controle worden georganiseerd om tot een optimale zorgverlening te komen?

Dit onderwerp werd door het Belgische comité voor klinische biologie naar voren gebracht en omvatte verschillende gezondheidszorggerelateerde onderzoeksvragen: een met betrekking tot de algemene implementatie van antistollingsklinieken in België, een over de waarde van POC testen en een over de organisatie van POC testen. Door een gebrek aan gegevens over huidige antistollingsklinieken werd besloten om de studie te beperken tot de waarde en organisatie van POC apparaten in vier verschillende situaties: nl. patiëntzelfmanagement (PZM), patiëntzelfcontrole (PZC), POC in de huisartspraktijk en POC in de antistollingskliniek.

METHODEN

De resultaten over klinische doeltreffendheid, kwaliteitscontrole en de noden en voorkeuren van patiënten zijn gebaseerd op een systematische literatuurreview. Deze review werd in twee fasen uitgevoerd: eerst werden HTA rapporten gezocht in de CRD-databank, gevolgd door een zoektocht naar systematische reviews en primaire studies in Medline, Embase en CENTRAL. Bestaande HTA rapporten en systematische reviews werden gebruikt als referentiebron. Studies werden geselecteerd indien ze POC-apparaten en laboratoriumtesten bij patiënten met vitamine K antagonisten antistollingstherapie vergeleken. Geen enkele studie werd uitgesloten op basis van deze kritische beoordeling. Om de invloed op patiëntenuitkomsten te evalueren, voerden we een meta-analyse uit. Gegevens uit de gerandomiseerde gecontroleerde onderzoeken werden gepooled voor de volgende uitkomsten: ernstige bloedingen, trombo-embolische accidenten en totale mortaliteit. Om de invloed van de testfrequentie, de setting van de controlegroep (huisarts of antistollingskliniek) en de duur van de studie te beoordelen, werd een meta-regressie uitgevoerd. Funnel plots werden gemaakt om de kans op publicatiebias in te schatten.

De beschrijving van de huidige zorgorganisatie in andere Europese landen was gebaseerd op informatie van contacten met nationale officiële instellingen en uit grijze literatuur. Er werd een cross-check uitgevoerd met informatie van de bedrijven die actief zijn in deze sector.

Een systematische literatuurreview voor economische studies werd uitgevoerd in Medline, Psychinfo, Econlit, Embase, en de Cochrane databanken (waaronder de NHS Economic Evaluation Database (NHS EED)).

Vanuit het perspectief van de Belgische gezondheidszorgbetaler werd een Belgische kosten/batenanalyse gemaakt die zowel de kosten betaald door de RIZIV, als de door de patiënt zelf betaalde kosten, in rekening bracht. POC-strategieën, d.w.z. het gebruik van POC door de huisarts, in antistollingsklinieken, PZM en PZC werden vergeleken met de gewone zorg in België, gedefinieerd als follow-up door de huisarts met standaard laboratoriumtesten. De uiteindelijke uitkomst was het aantal gewonnen levensjaren. Levenskwaliteit werd niet in aanmerking genomen omdat hiervoor geen betrouwbare gegevens beschikbaar waren. De kosten/batenanalyse concentreert zich op de PZM-strategie omdat alleen voor PZM een significante invloed van POC op totale mortaliteit werd vastgesteld. Een dergelijke analyse gaat na of deze strategie al dan niet kosten-effectief is onder verschillende hypothesen. Voor andere strategieën werd de analyse beperkt tot een kostenvergelijking.

Voor de analyse werden twee Belgische gegevensbronnen gebruikt: de Minimale Klinische Gegevens en de Minimale Financiële Gegevens om de gemiddelde kosten van grote trombo-embolische accidenten te bepalen, en de databank van het IMA om het aantal INR-testen per patiënt en per jaar te bepalen, het aantal INR-bepalingen geassocieerd met andere laboratoriumtesten en het gewogen gemiddelde honorarium per consultatie. Alle patiënten die gedurende minstens 6 maanden orale antistollingstherapie gebruikten en die tussen 2002 en 2006 gemiddeld tussen 6 en 52 INR-testen per jaar kregen, werden in de steekproef voor de studie geïncludeerd.

Gegevens inzake doeltreffendeid waren gebaseerd op de resultaten van de meta-analyse.

Voor de analyse werden verschillende hypothesen gehanteerd. Hun invloed op de resultaten werd getest in een probabilistische analyse en verschillende scenario's werden geanalyseerd. Dit laatste betrof het aantal testen (aantal testen blijft gelijk = 15 testen/ jaar; 26 testen/ jaar; 52 testen/jaar), en het aantal huisarts-contacten dat werd gehandhaafd bij het gebruik van POC door patiënten of in antistollingsklinieken (24%, 50%, 100%). De impact van een verschillend aantal patiënten per professionele zorgverlener werd ook getest.

RESULTATEN

KLINISCHE DOELTREFFENDHEID

Technische en diagnostische nauwkeurigheid

Twee HTA-rapporten en 34 primaire studies werden geselecteerd. De kwaliteit van de studies was slechts redelijk zodat een bias van de resultaten niet kan worden uitgesloten.

Op gebied van technische nauwkeurigheid stelde een studie een goede test-retest betrouwbaarheid en inter-rater betrouwbaarheid voor het geteste POC-apparaat (Coagucheck S®) vast.

Wat de diagnostische nauwkeurigheid betreft, is de Pearson's correlatie coëfficiënt tussen POC INR-resultaten en laboratorium INR-resultaten aanvaardbaar tot goed met de meeste resultaten ≥0,85. Op individueel niveau scoort de overeenkomst tussen POC INR-waarden en laboratorium INR-waarden goed op therapeutisch vlak (INR tussen 2 en 3,5), maar het verschil tussen POC en laboratoriumwaarden stijgt naarmate de waarden stijgen.

Falen van de test of niet-interpreteerbare resultaten met POC-apparaten kunnen te wijten zijn aan een interne kwaliteitsfunctie die slechte testresultaten, onvoldoende bloed, subcutane weefseldikte en defect van het instrument of problemen met de teststrips, elimineert. Dit kan leiden tot het gebruik van meer dan een strip per test, vooral bij het starten met zelfcontrole. Vergeleken met de gebruikelijke venepunctie zijn er geen extra veiligheidsproblemen met POC capillaire staalname.

Invloed op patiëntenuitkomsten

Twintig gerandomiseerde gecontroleerde studies werden geselecteerd en een meta-analyse werd uitgevoerd. De kwaliteit van de studies was matig. Twee funnel plots (trombo-emobolie en totale mortaliteit) vertoonden een mogelijke publicatiebias.

Meta-analyse van alle studies

Point-of-care testen leidt tot minder trombo-embolische accidenten (odds ratio 0,43; 95% BI 0,32, 0,58) en een lagere totale mortaliteit (odds ratio 0,59; 95% BI 0,46, 0,74), en heeft geen invloed op het aantal majeure bloedingen, vergeleken met de gebruikelijke laboratorium INR-testen. Wanneer deze resultaten worden toegepast op een mediane risicopopulatie komt dit overeen met 13/1000 minder trombo-embolische accidenten, en 1/1000 minder overlijdens. Sensitiviteits analyses toonden geen significante invloed van de setting van de controlegroep (huisartspraktijk of antistollingskliniek), de duur van de studie of de testfrequentie in de POC-groep vergeleken met de controlegroep. Het gemiddelde aantal INR-testen in de POC-groep bedroeg 41,1 testen/patiënt/jaar (bereik 12-89) vergeleken met 18,1 (bereik 7-40) in de controlegroep.

Meta-analyse per zorgorganisatiemodel

Voor PZM bedraagt de odds ratio 0,39 (95% BI 0,27, 0,56) voor trombo-embolische accidenten en 0,55 (95% BI 0,42, 0,72) voor totale mortaliteit vergeleken met laboratorium INR-testen, ofwel door een huisarts ofwel in een antistollingskliniek.

Voor PZC bedraagt de odds ratio 0,54 (95% BI 0,30, 0,97) voor trombo-embolische accidenten en is niet significant voor totale mortaliteit, vergeleken met gewone zorg.

Voor huisartsen die POC-apparaten gebruiken werd geen significant verschil gezien in vergelijking met laboratoriumtesten, maar voor deze vergelijking was slechts één studie beschikbaar.

Voor verpleegkundigen die POC-apparaten gebruiken in een antistollingskliniek werd geen significant verschil gezien in vergelijking met de gewone zorg in een antistollingskliniek, maar ook hier was slechts één studie beschikbaar.

KWALITEITSCONTROLE

Twee HTA-rapporten en 7 primaire studies werden geselecteerd. De studies waren zeer heterogeen en een rechtstreekse vergelijking was niet mogelijk.

Ondanks de kalibratie van POC-apparaten en de beschikbaarheid van interne kwaliteitsprocessen, kunnen tegenstrijdigheden in de resultaten bestaan die een invloed kunnen hebben op klinische beslissingen. Voor POC-apparaten is externe kwaliteitscontrole noodzakelijk. Vier externe kwaliteitsbeoordelingsmethoden worden beschreven, maar er is geen bewijs dat de ene methode beter is dan de andere. De frequentie van de controles varieert van 2 tot 6 per jaar.

NODEN EN VOORKEUREN VAN DE PATIËNT

Twaalf studies werden geselecteerd; Het bewijsmateriaal dat deze rubriek ondersteunt, is erg beperkt.

De totale tevredenheid is hoger met POC-testen; er is minder pijn en ongemak. Scores werden echter gemeten met verschillende ziektespecifieke tools, die vaak slecht beschreven werden.

Criteria om kandidaten te selecteren voor patiëntzelfmanagement of patiëntzelfcontrole zijn onder andere persoonlijke bereidheid, fysiek in staat zijn tot zelftesten, en de bekwaamheid om een training te volgen en te voltooien. Gestructureerde trainingsprogramma's omvatten het uitvoeren van POC INR-testen, instructies om bloedingen en trombo-embolische complicaties te voorkomen, het effect van dieet en bijkomende medicatie op antistollingscontrole, voorbeelden van de aanpassing van de geneesmiddelendosering, mogelijke problemen die kunnen voorkomen bij operaties, ziekte, inspanningen, zwangerschap en reizen. Schattingen van het percentage patiënten dat in staat is om PZT of PZM uit te voeren, variëren van 14% (VK) tot 24% (Canada).

HUIDIGE ZORGORGANISATIE

De Belgische praktijk werd vergeleken met de Europese buurlanden, nl. Frankrijk, Nederland, Duitsland, Luxemburg, Verenigd Koninkrijk (VK) en Zwitserland.

De mate waarin POC-testen worden terugbetaald door de publieke gezondheidszorg verschilt van land tot land, gaande van geen terugbetaling (België) tot volledige terugbetaling (Nederland).

Voorwaarden om terugbetaling te bekomen zijn o.a. verplichte succesvolle training, die gewoonlijk wordt gegeven door een officiële organisatie, en regelmatige kwaliteitscontroles. Voor patiëntzelfmanagement en patiëntzelfcontrole worden bijkomende criteria aan de patiënt opgelegd, waaronder voldoende fysiek en cognitief vermogen om het POC-apparaat te gebruiken en de antistollingstherapie te beheren, en langetermijn antistollingstherapie (> 1 jaar of levenslang).

ECONOMISCH LITERATUURREVIEW

Drie reviews en 6 primaire economische evaluaties werden geselecteerd.

De literatuurreview toonde dat de kosten/batenanalyse van POC-strategieën in vergelijking met de gewone verzorging onzeker is en afhangt van verschillende factoren. Resultaten werden meest beïnvloed door de doeltreffendheid van de gewone zorg, de populatiekenmerken, het aantal uitgevoerde testen, het standpunt van de economische analyse en de studieperiode.

BELGISCHE KOSTEN EN KOSTEN/BATENANALYSE

Kosten analyse

In de geselecteerde studiepopulatie (IMA dataset, n=2046) waren mannen en vrouwen bijna gelijk vertegenwoordigd. Gemiddelde leeftijd was 76 jaar voor vrouwelijke patiënten en 73 jaar voor mannelijke patiënten. Een mediaan aantal van 15 INR laboratorium testen worden elk jaar uitgevoerd en patiënten hebben gemiddeld 18 huisartscontacten (consultaties en bezoeken – niet noodzakelijk met betrekking tot hun antistollingsbehandeling) per jaar. Bovendien bevat 24% van de INR-test voorschriften andere laboratoriumtesten.

Invloed van het aantal INR-testen per jaar

Bij een gelijk aantal testen als in de studiepopulatie was het gebruik van POC meestal een kostenbesparende strategie vergeleken met de gewone zorg voor alle POC-strategieën (probabiliteit > 70 %). De gemiddelde kostenbesparing varieerde van € 161.18 voor het gebruik van POC door de huisarts tot € 429.34 voor patiëntzelfmanagement.

Indien het aantal testen per jaar met het gebruik van POC-apparaten zou stijgen tot 26, zou patiëntzelfmanagement de hoogste probabiliteit hebben om kostenbesparend te zijn (85%, gemiddelde kostenbesparing van € 367) vergeleken met huidige gewone zorg gevolgd door patientzelfcontrole (60%; gemiddelde kostenbesparing van € 202) en het gebruik van POC in de antistollingskliniek (60%, gemiddelde kostenbesparing: van € 160). Het gebruik van POC door de huisarts zou gemiddeld niet langer kostenbesparend zijn in vergelijking met de huidige gewone zorg (probabiliteit om kostenbesparend te blijven = 31 %).

Indien het aantal testen per jaar stijgt tot 52, zou alleen patiëntzelfmangement een probabiliteit hebben om kostenbesparend te blijven boven 50% (d.w.z. 67%, gemiddelde kostenbesparing van € 220) en het gebruik van POC door de huisarts zou duurder worden dan de gewone zorg (probabiliteit = 97%).

Opgemerkt moet worden dat tijdens de eerste maanden van patiëntzelfmanagement de kosten zouden kunnen stijgen tot het niveau van de kosten van patiëntzelfcontrole indien de patiënten regelmatig advies nodig hebben van een professionele zorgverlener.

Invloed van het aantal contacten met de huisarts

De analyse toonde dat de kosten van POC-strategieën afhangen van het aantal contacten met de huisarts die worden gehandhaafd. Indien alle contacten worden gehandhaafd, zijn de financieel resultaten minder goed.

Invloed van het aantal patiënten door professionele zorgverleners

Uitgaande van de basisveronderstelling van 15 testen per jaar, wordt POC door de huisarts duurder dan de gewone zorg wanneer de huisarts minder dan 2 patiënten per jaar opvolgt, en POC in de antistollingskliniek wordt duurder dan gewone zorg wanneer de kliniek minder dan 173 patiënten per jaar opvolgt.

Kosten/batenanalyse

Met 26 testen per jaar en 24% gehandhaafde huisartsbezoeken wordt ervan uitgegaan dat patiënten in zelfmanagement 0.64 levensjaren winnen (95% BI 0.35-0.93) in vergelijking met patiënten in de gewone zorg, met een toenemende besparing van € 2 964 (95% BI-€ 10 181 - € 1 125) voor een periode van 10 jaar.

In elk onderzocht scenario resulteert zelfmanagement in significant meer ‘gewonnen levensjaren” dan gewone verzorging en is doorgaans kostenbesparend, behalve indien 100% van de huisarts consultaties behouden blijven en ≥ 52 testen per jaar worden uitgevoerd (toenemende kosten van € 984 per gewonnen levensjaar).

BESLUIT

In het algemeen hebben point-of-care testen een positieve invloed op patiëntenuitkomsten, vooral bij patiëntzelfmanagement. Patiëntzelfmanagement is daarom de eerste keuze met betrekking tot klinische uitkomsten (minder trombo-embolische accidenten en lagere totale mortaliteit), en vanuit het standpunt van de betaler aangezien het een kostenbesparende strategie is vergeleken met de gewone zorg. Het kan echter slechts toegepast worden door een klein percentage patiënten.

Patiëntzelfcontrole komt op de tweede plaats. Het vermindert het aantal trombo-embolische accidenten, maar niet de totale mortaliteit. Vanuit het standpunt van de betaler kan patiëntzelfcontrole kostenbesparend zijn in vergelijking met de gewone zorg afhankelijk van het aantal INR-testen en het aantal huisartsraadplegingen dat gehandhaafd blijft.

Wat betreft het gebruik van POC door de huisarts is er geen bewijs dat dit de klinische patiëntenuitkomsten beïnvloedt in vergelijking met de gewone verzorging. Vanuit het standpunt van de betaler is een dergelijke strategie kostenbesparend in vergelijking met hetzelfde aantal laboratorium INR-testen. De toename van het aantal POC-testen gaat echter altijd samen met een toename van het aantal huisartscontacten waardoor deze strategie niet kostenbesparend is in een scenario van 26 testen/patiënten/jaar.

Wat betreft het gebruik van POC-apparaten door professionele zorgverleners in antistollingsklinieken, is er geen bewijs dat dit de klinische patiëntenuitkomsten beïnvloedt in vergelijking met de gewone zorg. In deze strategie hangen de incrementele kosten af van verschillende parameters: het aantal openingsuren van de kliniek, het aantal patiënten, het aantal INR-testen per patiënt en per jaar, en vooral het aantal gehandhaafde consultaties of bezoeken van de huisarts, wat momenteel niet bekend is.

AANBEVELINGEN

Het KCE raadt aan om de organisatie van orale antistollingstherapie op lange termijn monitoring te richten op patiëntzelfmanagement en, in mindere mate, op patiëntzelfcontrole.

Momenteel zijn veel gegevens echter niet beschikbaar in België en zijn de economische conclusies gebaseerd op hypothetische scenario's. Een pilootstudie kan worden opgezet om het aantal en de kenmerken van patiënten die geselecteerd kunnen worden voor patiëntzelfmanagement of patiëntzelfcontrole te bepalen, de echte kosten te berekenen (aantal testen per jaar, aantal contacten met professionele zorgverleners) en om de financiële impact te beoordelen. Gegevens van deze pilootstudie kunnen ook worden gebruikt wanneer de kosten vergeleken moeten worden met toekomstige antistollingsmiddelen.

In elk geval moet met volgende aspecten rekening worden gehouden:

- Selectie van patiënten is gebaseerd op persoonlijke bereidwilligheid en bekwaamheid. Naaste verwanten kunnen ook geselecteerd worden (bijvoorbeeld voor kinderen of patiënten met een visuele handicap).
- Training van de patiënt is verplicht en moet gestandaardiseerd worden. Indien de patiënt slaagt in de praktijktest wordt certificatie verkregen voor patiëntzelfmanagement. Voor patiëntzelfcontrole kan deze test minder veeleisend zijn en zich concentreren op de bekwaamheid om de test uit te voeren.
- Bijstand en follow-up moeten beschikbaar zijn voor het oplossen van problemen met het testen of de aanpassing van de doses.
- Een externe kwaliteitscontrole van de POC-apparaten is nodig.

Bij patiëntzelfmanagement of patiëntzelfcontrole raadt het KCE aan om terugbetaling van volgende kostenelementen te overwegen: patiënttraining, het POC-apparaat, strips en kwaliteitscontrole, en advies van een professionele zorgverlener.

Voor het gebruik van POC-apparaten door een huisarts of in een antistollingskliniek is er momenteel onvoldoende sterk bewijs om het gebruik ervan aan te raden.

Ongeacht het gebruik van POC-apparaten is de ontwikkeling van richtlijnen en training van professionele zorgverleners betrokken bij controle van orale antistollingsbehandeling essentieel.

Een nieuwe evaluatie van deze aanbevelingen is zal nodig zijn wanneer nieuwe antistollingsmiddelen standaard worden voor patiënten met een lange termijn orale antistollingsbehandeling.

Scientific summary

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ABBREVIATIONS

AC	Anticoagulation clinic
ACCP:	American College of Chest physicians
AST	Alternative site testing
CI	Credibility interval or confidence interval
CNK	Code national / nationale code
CRD	Centre for reviews and dissemination
DARE	Database of abstracts of reviews of effects
DDD	Defined daily dose
ECAA	European concerted action on anticoagulation
EQA	External quality assessment
FTE	Full time equivalent
GP	General Practitioner
HTA	Health technology assessment
ICD-9-CM	Internal classification of diseases, 9th revision, clinical modification
IMA-AIM	Common sickness funds agency
INAHTA	International network of agencies for health technology assessment
INR	International Normalized Ratio
IQC	Internal quality control
IRP	International reference preparation
ISI	International Sensitivity Index
ISMAAP	International Self Monitoring Association of oral Anticoagulated Patients
KCE	Kenniscentrum/ Centre d'expertise
LoS	Length of stay
MBDS	Minimum basic dataset
MCD	Minimal clinical data
MesH	Medical subject headings (NML)
MFD	Minimal financial data
NEQAS	National external quality assessment scheme (UK)
NICE	National Institute for Clinical Excellence
NIHDI	National institute for health and disability insurance
NHS	National Health System (UK)
NHS EED	National Health System Economic Evaluation database
NLM	National Library of medicine (US)
NPT	Near patient testing
OAT	Oral anticoagulant therapy
PCT	Primary care trust

POC	Point-of-care
PSM	Patient self management
PST	Patient self testing
PT	Prothrombin time
RCT	Randomized Controlled trial
QUADAS	Quality assessment of studies of diagnostic accuracy
QALY	Quality adjusted life-year
QC	Quality control
UCL	Université catholique de Louvain
UK	United Kingdom
US	United States
VAT	Value added tax
WHO	World Health Organization

1 INTRODUCTION

1.1 ORAL ANTICOAGULATION WITH VITAMIN K ANTAGONISTS

Oral anticoagulants are drugs to prevent thromboembolic events in patients that are at increased risk of forming blood clots. Vitamin K is essential for the synthesis of several blood-clotting factors and vitamin K antagonists prevent blood clots by suppressing the body's production of the vitamin K dependent factors that are essential in the coagulation process. Three vitamin K antagonists (acenocoumarol, phenprocoumon and warfarin) with different pharmacokinetic characteristics are currently used in Belgium.

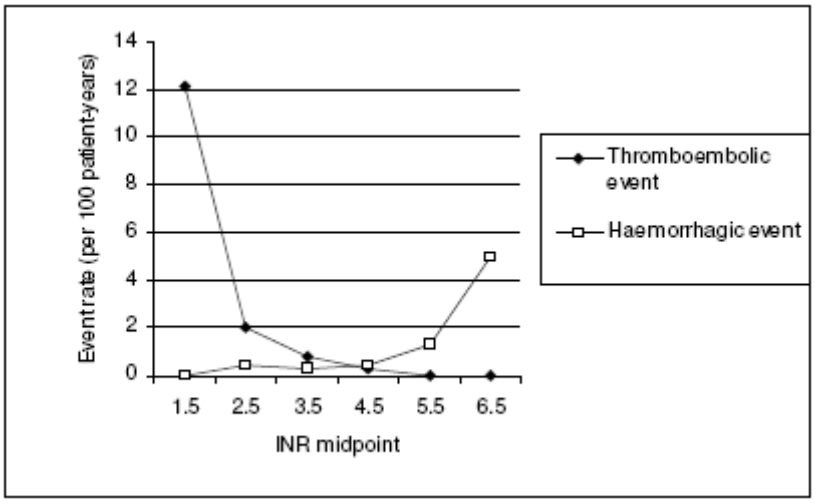
Oral anticoagulant therapy (OAT) using vitamin K antagonists are the standard of care for patients scheduled for long term OAT. They are indicated for patients with atrial fibrillation, prosthetic heart valve, deep vein thrombosis, pulmonary embolism and stroke. Patients with atrial fibrillation, mechanical heart valves, recurrence of deep vein thrombosis or pulmonary embolism often require life-long OAT [1 2 3 4 5].

The International Self Monitoring Association of oral Anticoagulated Patients (ISMAAP) calculated that more than 4 million patients in Europe are living on long-term oral anticoagulation, of which 100.000 in Belgium[6]. Because of the ageing of the population and associated increase in the prevalence of atrial fibrillation and venous thromboembolism, it is expected that more patients may need vitamin k antagonists in the future[7].

1.2 INTERNATIONAL NORMALIZED RATIO (INR)

Frequent monitoring is crucial to ensure an appropriate level of OAT, because of a narrow therapeutic window, a large variation in dose response in individual patients, and fluctuations in individual response over time (caused by food or drugs intake, etc.). The test used worldwide to indicate the intensity or degree of anticoagulation is the International Normalized Ratio (INR), a standardized method for the prothrombin time (PT), which is the time in seconds needed for citrate plasma to clot upon addition of tissue thromboplastin and calcium ions. A too high INR value can lead to bleeding; a too low value may cause clots (figure 1.1). The optimal target range for the INR is however not the same for all indications, and is likely to be influenced by patient characteristics such as co-morbid conditions[8].

Figure 1.1:Relationship between INR level and clinical event rate[9]



Traditionally, the test is performed in a laboratory on a blood sample obtained by venous puncture and collected in a tube containing sodium citrate anticoagulant. The INR is determined using a calibrated laboratory device with appropriate quality controls.

The PT varies with the type of thromboplastin used. To standardise PT tests, the World Health Organization (WHO) adopted in 1982 a means for calibrating thromboplastins by introducing the International Sensitivity Index (ISI). Commercial assays systems (defined as the combination of thromboplastin and instrument) are calibrated against the International reference preparation (IRP) accepted by the WHO. The first WHO IRP was assigned an ISI of 1.0 and it is against this (and subsequent references preparations) that all other thromboplastins are calibrated. The INR (figure 1.2) is the PT ratio of a test sample compared to a normal PT (derived from the mean normal PT of 20 normal donors) corrected for the thromboplastin used in the test, i.e. the value for the PT ratio (ISI) which has been obtained using the WHO reference thromboplastin with an ISI of 1.0 [10 11].

Despite the standardization of INR, however, variability still exists, with instrument variability being a particular issue[9]. For this reason, a local calibration of thromboplastins is recommended. The quality control involves testing of a set of plasma samples with known INRs with the laboratory-specific thromboplastin and on the coagulometers which will be used to derive the PT. In Belgium is the standardization however not optimal [12].

Figure 1.2. Formula for calculating the INR[11]

$$INR = \left(\frac{PT(sec)patient}{MNPT(sec)} \right)^{ISI}$$

INR = International Normalised Ratio

PT = Prothrombin time

MNPT = Mean Normal PT

ISI = International Sensitivity Index

1.3 POINT OF CARE TESTING, SELF TESTING, SELF MANAGEMENT

Since the 1990s, point-of-care (POC) technology has become available for the monitoring of oral anticoagulant therapy (OAT). Portable point-of-care stands for testing where the patient is located, rather than the patient (or the blood sample) traveling to a laboratory. Hereby, patients or physicians use a portable device to determine the INR instantly by using a drop of blood (venous or capillary), instead of sending a venous blood sample to the laboratory and waiting for the result. After a lancet puncture of the finger, the blood is introduced in the POC device which determines the INR value. A result is obtained within three minutes for all devices. POC INR testing in general practice allows direct discussion about the INR level, including the need for any change in management. POC may also be advantageous in rural settings due to improved access. It may also be a good alternative in paediatric populations or in adults with difficulties to prick, because of the increased ease of obtaining a sample.

POC can be performed by a physician or by a health professional which is called alternative site testing (AST). The physician can be the usual family doctor of the patient or someone (doctor or nurse) of a special "anticoagulation clinic" such as in the Netherlands or the United Kingdom. POC can also be performed by the patient. In some cases the patient himself (or a member of the family) tests at home and contacts a professional for dose-adjusting, this is called patient self-testing (PST); in other cases the patient also determines the appropriate dose of OAT (patient self-management or PSM).

1.4 POINT OF CARE DEVICES

Three POC devices are potentially available in Belgium: Coagucheck® (Roche diagnostics), Protime® (Intrumentation Laboratory) and INRatio® (Hemosense).

The first model of Coagucheck® was introduced in 1994, followed in 2000 by the Coagucheck S® and in 2006 by the Coagucheck XS®. The oldest device (a reflectance photometer) measures PT/INR values in capillary whole blood, based on an electrochemical detection. The strip contains reagents and iron particles, which mix with the blood sample when applied. The monitor then starts to measure coagulation time by photometric determination. The iron oxide particles move in response to an oscillating magnetic field. As the blood starts to coagulate, the movement of the iron oxide particles becomes impeded. The monitor then stops the time measurement and displays the result. The recent CoaguChek XS performs an electrochemical measurement of prothrombin time (PT) test using a recombinant human thromboplastin reagent and a peptide substrate, known as Electrocyme TH, which can be used for the determination of serine proteases such as thrombin. Application of the sample leads to the activation of coagulation by the thromboplastin and results in thrombin generation. Thrombin cleaves Electrocyme TH into a residual peptide and electrochemically active phenylenediamine thereby generating an electrochemical signal. The time elapsed from addition of sample to signal generation is used to calculate the INR value. Therefore, one drop of 10 microliters is needed. All the information needed to calibrate the monitor is contained on a code chip. There is internal quality control on each measured strip. Strips can be stored at room temperature. The operating conditions are the following: for temperature: + 18 up to +32°C; for humidity: 10-85%; for height: 4300m; for measuring range: INR from 0.8 up to 8.0. International sensitivity index (ISI) of strips is approximately 1,0. (http://www.coaguchek.com/)

ProTime® Microcoagulation System consists of the Protime instrument (a portable photometer), the reagent cuvette which built –in quality control and the tenderlett® plus sample collection system. A plastic cartridge contains an enclosed capillary channel leading to a chamber with dry rabbit brain thromboplastin. This cartridge is inserted into the instrument. Capillary whole blood form a finger stick flows by capillary action to mix with the thromboplastin. As the blood clots, the light source detects cessation of flow by sensing variation in light scatter from the red blood cells. The time elapsed is converted into PT and INR.

The self-check at start-up checks temperature, timing function, battery level and optical, electrical and mechanical functions. No additional calibration is required. The cuvettes must be refrigerated (2-8°C) to be stable until the date printed on the pouch. The operating temperature is 15-30°C. The sample size is minimum 50 microliters. External direct check whole blood controls are available. (http://www.protimesystem.com/)

INRatio® is a third point of care system using fresh capillary whole blood from a fingerstick. The sample size is 15 microliters and the test results are displayed in less than 2 minutes. The monitor uses the test strip's channel technology to perform the PT test by electric impedance and 2 quality control tests (normal and therapeutic) simultaneously, and determines whether the controls are within the preset limits. No refrigeration is required. (http://www.hemosense.com/patient/inratio.shtml)

1.5 OTHER ANTICOAGULANT TREATMENTS

This report focuses on patients treated with vitamin K antagonists. The advantage of vitamine K antagonists is that the treatment is cheap and effective; the disadvantage is the safety problem and the need of a regular INR follow-up. According to guidelines previously cited, vitamine K antagonist is the standard of care for patients on long term oral anticoagulation therapy.

There are other treatments for anticoagulation. Heparin and low molecular weight heparin are injection treatments to prevent or cure blood clots. Heparin is used in hospitalized patients. The management of the treatment is difficult. A regular follow up of aPTT is needed in patients treated with heparin. Low molecular weight heparins are effective for short term treatments in hospitalized and ambulatory patients. These drugs are expensive but there is in most patients no need for control of coagulation. At the useful doses, there is no risk of bleeding.

New oral antithrombotic agents are arriving, such as the oral direct thrombin or factors Xa inhibitors. The European Medicines Agency (http://www.emea.europa.eu) has accepted the marketing authorization for the active substances dabigatran etexilate (Pradaxa) and rivaroxaban (Xarelto). An unexpected hepatic toxicity was the downfall for ximelagatran [13]. Studies about other substances (such apixaban) are now in process.

The two drugs (dabigatran and rivaroxaban) are indicated in the primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip or knee replacement surgery. These indications need short term treatments and are currently not treated with vitamin K antagonists. These recommendations do thus not influence the conclusions of our report.

Further in process phase III trials of new antithrombotics agents involve not only patient for the prevention following surgical interventions but also for secondary prevention after acute coronary syndromes and prevention of stroke in patients with non valvular atrial fibrillation. These potential indications concern long term anticoagulation, currently treated with vitamin K antagonists. The marketing of new drugs in such indications may interfere with the conclusions of this report. New oral antithrombotic drugs do not need biological controls of INR, which is more comfortable for the patient. The price of such drugs may, however, be higher.

2 SCOPE

This health technology assessment (HTA) report on the point of care (POC) testing of oral anticoagulation therapy (OAT) aims to answer 4 questions.

2.1 FIRST RESEARCH QUESTION

What is the clinical efficay of POC monitoring of OAT? Evaluation of benefit against risk, using established outcome measures like death, haemorrhages, and thrombo-embolic events.

2.2 SECOND RESEARCH QUESTION

What is the cost effectiveness of POC monitoring of OAT? How much will it cost and what are the benefits in the long term?

2.3 THIRD RESEARCH QUESTION

What are the needs and preferences of patients in relation to POC monitoring of OAT? How about patient information, compliance, obstacles and fears related to the use of the technology?

2.4 FOURTH RESEARCH QUESTION

How should POC monitoring be organized to deliver optimal care? Which models exist and which professional requirements are needed?

3 CLINICAL EFFICACY

3.1 INTRODUCTION

With respect to the first question about clinical efficacy (see 2.1), several questions have been considered:

1. What is the place of POC INR devices in the clinical pathway?
2. What is the technical accuracy of the POC INR devices?
3. What is the diagnostic value of POC devices in the INR value detection?
4. How should the quality control of the POC devices be performed?
5. What is the impact on patient outcome of POC INR devices?

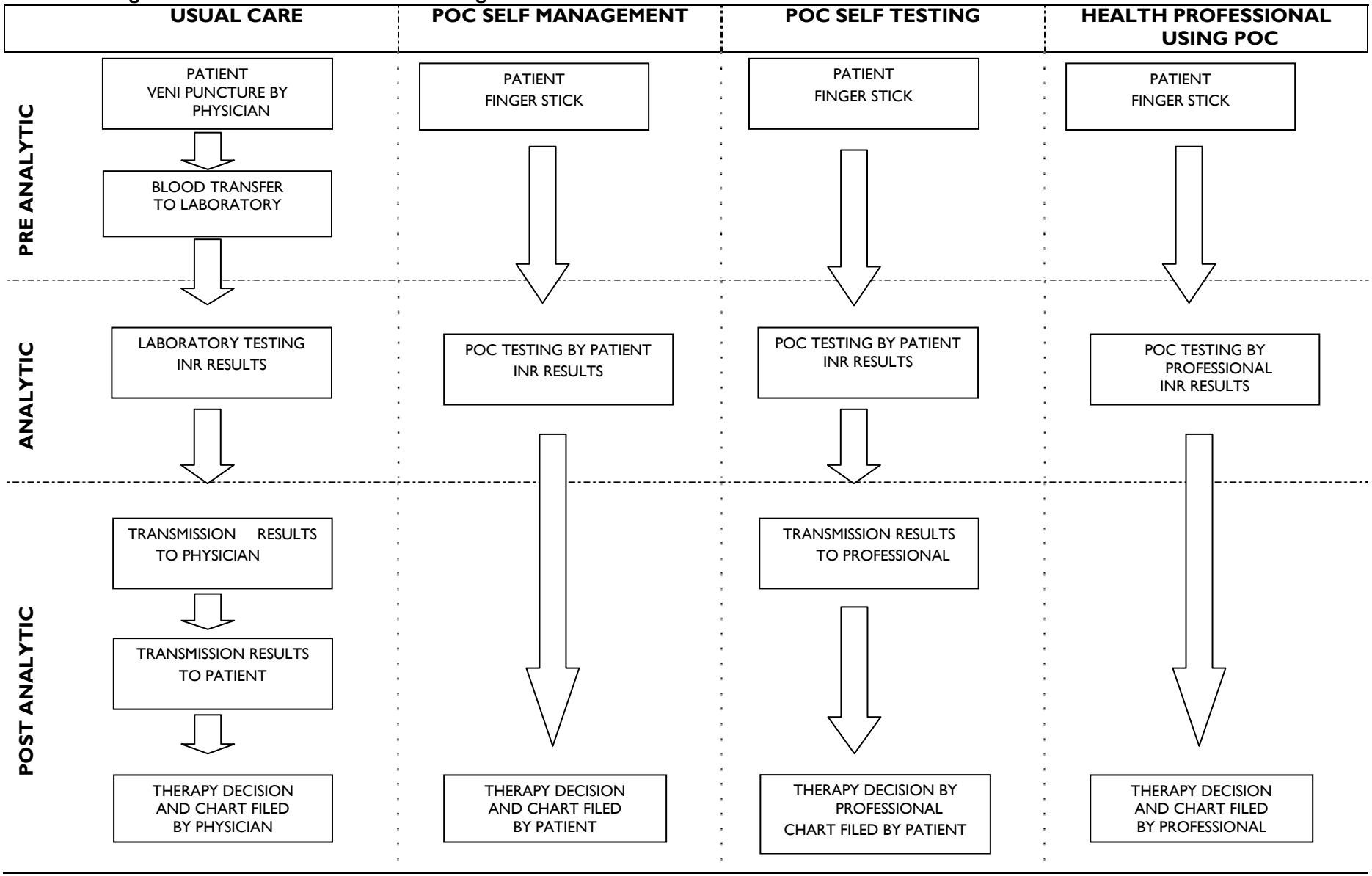
3.2 CLINICAL PATHWAY

The point of care device, also known as "bedside testing" or "near patient testing", is used to test the INR where the patient stays. It gives the result in less than 3 minutes. Its use replaces the INR test usually done in laboratory. According to expert opinion, the use of POC devices simplifies the management of INR testing compared with usual care (figure 3.1), with respect to the way the sample is taken and transferred (pre-analytical phase) and to the way the information is transmitted until the therapy decision is established (post-analytical phase). Several variables may interfere at the pre-analytical phase such an under filling of the citrated tube or the storage of blood[11]. In the post-analytical phase, there is a potential for dosing errors due to the transfer of information by phone from the laboratory to the physician, and, subsequently, from the physician to the patient, or due to delays in contacting patients. However, if the patient tests himself and phones the result to the physician or to another health professional, there are also potentials errors of transmission or of understanding.

On the other hand, the simplification of the management does not lead per se to better outcomes for the patient. As the POC test will be used in replacement of another test, diagnostic accuracy should be at least comparable to the current test[14]. In addition, in case diagnostic accuracy would be better, evidence on the impact on patient outcome is needed[15].

- **Compared with usual care, the use POC device simplifies the pre analytical and the post analytical phases of INR monitoring.**

Figure 3.1: usual care versus POC management



3.3 TECHNICAL AND DIAGNOSTIC ACCURACY

3.3.1 Methods

3.3.1.1 Research question

This chapter focused on the accuracy of POC devices in patients with OAT. What is the technical accuracy in experimental conditions? What is the diagnostic value compared with laboratory INR testing?

3.3.1.2 Search strategy

The search was done in two steps: first a search of HTA reports, secondly a specific search for systematic reviews and primary studies.

HTA reports of point of care devices for anticoagulation testing were searched in the CRD database (DARE, NHS EED, INAHTA) with the following terms: anticoagulants, blood coagulation tests, International Normalized Ratio, INR, Point-of-Care Systems.

The specific search for primary studies was done on the accuracy of the POC INR devices (January 2009) in Pubmed and in Embase. The search strategy is described in table 3.1.

Table 3.1: Search strategy for POC accuracy

Data base	Term	Number
Medline via Pubmed	Coagucheck	18
	Protime AND "Point-of-Care Systems"[Mesh]	91
	inr ratio AND "Point-of-Care Systems"[Mesh]	73
	(("Observer Variation"[Mesh] OR accuracy) AND (INR OR "International Normalized Ratio"[Mesh])) AND "Point-of-Care Systems"[Mesh]	20
	INRatio	5
Embase	Coagucheck	38
	Protime	67
	inr OR 'international normalized ratio'/exp/mj AND 'diagnostic accuracy'/exp/mj	1
	inr OR 'international normalized ratio'/exp/mj AND 'reliability'/exp/mj	0
	INRatio	17

3.3.1.3 Inclusion and exclusion criteria

Studies were included if the studied intervention was POC testing INR for oral anticoagulation with vitamin K antagonists, if the comparison was classical INR (laboratory) and if the outcomes were accuracy, interobserver variation, reliability or quality control. Clinical or experimental studies were included. Case series and retrospective design were excluded. Studies on other devices than Coagucheck, Protime or INRratio (the three potentially available in Belgium) or on other measures than INR were also excluded.

3.3.1.4 Critical appraisal

The quality of HTA reports was appraised with the INAHTA check list available at http://www.inahta.org/upload/HTA_resources/Checklist_instructions_2007.doc

The quality of primary studies was appraised with 7 items of the QUADAS check list[16]:

- spectrum of samples or subjects representative of the patients who will receive the test in practice, i.e. a large range of INR values tested such as in reality,
- selection of samples or subjects clearly described, i.e. consecutive patients such as coming in clinical practice,
- reference standard independent form the index test,

- execution of the index tests described in sufficient details,
- blinding,
- intermediate or uninterpretable results reported in the study,
- and test failures reported.

No study was excluded based on critical appraisal.

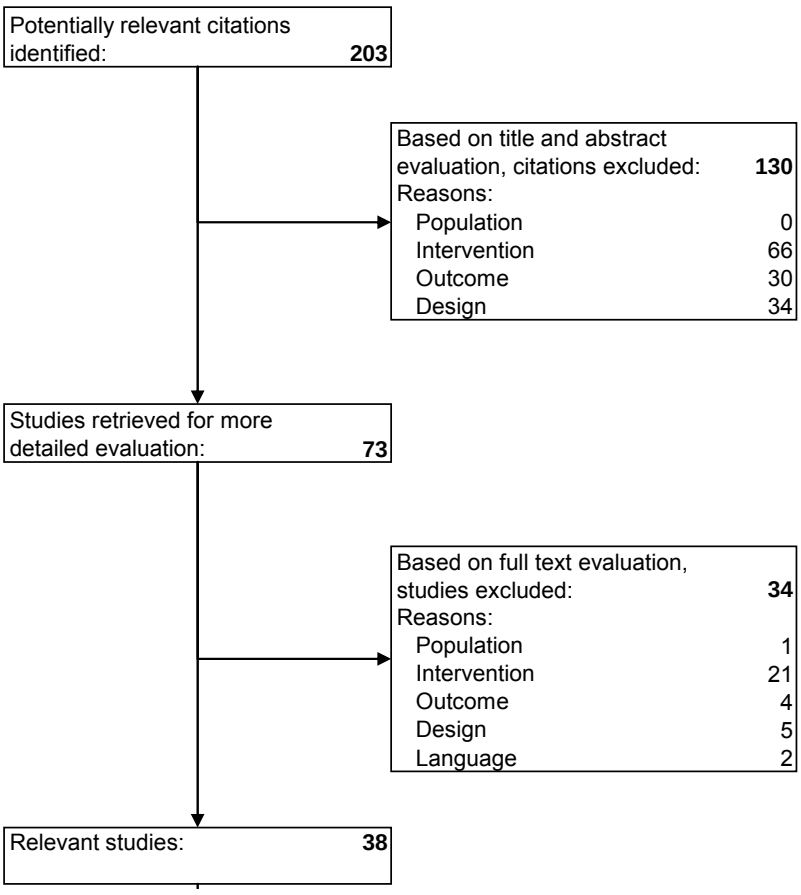
3.3.2 Results

3.3.2.1 Literature search

HTA: After discarding duplicates, 12 potentially relevant HTA reports remained. Two HTAs [7 9] were relevant for the accuracy and the safety of the POC devices.

Primary studies: After discarding duplicates 203 references remained. After applying inclusion criteria on titles and abstracts by two independent persons, 73 publications remained. Full texts were then searched and inclusion/exclusion criteria were applied on full texts. One full text was not found [17] and 34 were excluded (Figure 3.2).

Figure 3.2. Selection of primary studies about POC accuracy



3.3.2.2 Characteristics of the studies

The HTA of the Canadian agency for drugs and technologies in health (CADTH) was published in 2007 and was of very high methodological quality [7]. The second HTA, realized by the medical advisory committee (MSAC) of Commonwealth of Australia in 2005, focused on the use of INR point-of-care testing in general practice. Its quality was acceptable to good[9].

Thirty-three of 38 selected primary studies concerned the technical or diagnostic accuracy (table 4. 2). The five remaining studies were included in the specific section of quality control. One recent study[18] was added by an external expert.

The results of the critical appraisal are summarized in table 3.2. All studies performed an independent verification of the INR in a laboratory, using venous blood. The most studies included a spectrum representative including subjects with a large range of INR results. No study mentioned a procedure of blinding. No study was excluded based on quality assessment.

Table 3.2: Evidence table technical and diagnostic accuracy

Reference	Population	Index test	Linear regression analysis	Mean difference	Agreement between individual INR results	Quality appraisal
Andrews 2001[19] USA	N = 386 1-85 years In clinic	Protime	r = 0.92 (CI not available)	Average mean difference = 0.03 (graphical figure)	77% of POC results within the 0.4 INR 93% within the 0.7 INR	QUADAS 5Y 2N
Bauman 2008[20] Canada	N = 62 Children Clinic	Coagucheck XS (t1 health prof, t2 parent)	NA	Average mean difference 0.11 (-0.20; 0.42) (t1) 0.13 (-0.22; 0.48) (t2)	95% of differences within the range of –0.2 to 0.4 INR units (t1) and –0.2 to 0.5 INR units (t2)	QUADAS 3Y 1U 3N
Bereznicki 2007[21] Australia	N = 17 (n = 59) Primary care	Coagucheck XS	(r2=0.91, p=0.01) (CI not available)	Mean difference in INR values: 0.07 (p=0.01).	3 of 59 (5.1%) POC tests differed by >15% No paired INR >20%. No paired >0.5 INR units.	QUADAS 3Y, 1U, 3N
Chapman 1999[22] USA	(n=30) Clinic	Coagucheck Protime	Coagucheck: r = 0.93 Protime: r = 0.93	mean ±SD Coagucheck: 0.28 ±0.23 (p = 0.96) Protime: 0.56 ±0.34 (p < 0.001).)	NA	QUADAS 5Y, 1U, 1N
Cosmi 2000[23] Italy	N= 78 Adults OAT Antico clinic	Coagucheck	NA	Mean difference: - 0.025 :(LA)-0.84/ +0.81).	NA	QUADAS 4Y, 1U, 2N
Daly 2003[24] Ireland	N = 122 (n = 185) Primary care	Coagucheck	r2 = O.11 [95% CI -0.19 to 0.50]	Mean difference: -0.061 (95% CI -1.14, 1.02).	NA	QUADAS 4Y, 1U, 2N
Dorfman 2005[25] USA	N = 52 Adults laboratory	Coagucheck S Protime	Coagucheck r= 0.90 (p <0.0001) Protime r= 0.90 (p <0.0001)	Mean difference: CoaguChek: +0.24 (-0.63, 1.23) Protime: +0.35 (-0.53, 1.23)	For most specimens, INR results differed -0.3 to +0.6 (CoaguChek) and by -0.3 to +0.8 (Protime) INR units.	QUADAS 4Y, 3N
Finck 2001[26] USA	N = 46 (versus 3 different labos)	Coagucheck Protime	Coagucheck: r = 0.92 to 0.95 Protime: r = 0.87	NA	Percentage within 0.3 INR Coagucheck 78, 80 and 85% Protime: 34, 46 and 51%	QUADAS 3Y, 1U,

Reference	Population	Index test	Linear regression analysis	Mean difference	Agreement between individual INR results	Quality appraisal
			to 0.90 (CI not available)		(versus 3 labos)	
Gardiner 2005[27] England	N = 84 (n = 234) Adults Antico clinic	Coagucheck S Self testing	r = 0.95 (CI not available)	Mean difference: -0.04 (95% CI -0.80, 0.70)	85% of CoaguChek results within 0.5 INR units of the laboratory method. On 4 occasions, differences of >1 unit INR	QUADAS 3Y, 2U, 2N
Gosselin 2000[28] USA/ Canada	N = 100 OAT and healthy Clinic	Coagucheck Coagucheck Plus Protime	Coagucheck r=0.97 Coagucheck Plus r >0.900 Protime r >0.900	NA	All POC methods demonstrated a significant (p <0.05) difference in INR values, when compared with Innovin or TPC generated INRs. (absolute value not described)	QUADAS 3Y, 1U, 3N
Ignjatovic 2004[29] Australia	N= 18 children Hospital	Coagucheck	r = 0.885 (CI not available)	NA	In 88% of the CoaguChek cases, the difference from the venous result was < 0.5.INR unit.	QUADAS 4Y, 3N
Jackson 2004[30] Australia	N = 169 adults (n = 401) Rural practice	Coagucheck S	r = 0.89 (p<0.001)(CI not available)	Mean difference: - 0.08 (±0.42)	88% of results within 0.5 INR For laboratory INR ≤1.9: , 2.0–3.5 and ≥3.6, 97%, 90% and 57% within 0.5 INR respectively.	QUADAS 4Y, 3N
Jonsson 2004[31] Sweden	N = 351 Antico unit	Coagucheck S	r = 0.81 (CI not available)	Mean difference (S.D.): 0.23 (0.50) (p < 0.001).	NA	QUADAS 4Y, 3N
Karon 2008[32] USA	N = 98 Clinic INR > 6 = exclusion	Coagucheck S Coagucheck XS	NA	Median bias Coagucheck S: -0.2 Coagucheck XS: 0.0 (SD not available)	CoaguChek S 88% of within 0.4 INR and 8% >0.5 INR CoaguChek XS > 90% within 0.4 INR and 2% >0.5 INR	QUADAS 3Y, 1U, 3N
Kemme 2001[33] Netherlands	N = 12 Warfarin Laboratory	Coagucheck Plus	NA	Mean difference 0.36 (-0.25, 0.96)	INR values were overestimated Increase in the difference was observed with increasing magnitude (slope = 0.33, P <	QUADAS 3Y, 1U, 3N

Reference	Population	Index test	Linear regression analysis	Mean difference	Agreement between individual INR results	Quality appraisal
					0.001).	
Kitchen 2006[34] UK	N = 276	Coagucheck Coagucheck S	Coagucheck: r = 0.95 (p = 0.0002) Coagucheck S: r = 0.96 (p = 0.003) (CI not available)	Mean difference for Coagucheck: 0.0 (graphical figure)	NA	QUADAS 2Y, 3U, 2N
Koerner 1998[35] USA	N=101 healthy and OAT Clinic	Coagucheck	r = 0.97 (CI not available)	NA	71.3% results within 0.1 INR, 83.2 % within 0.2, 86.1% within 0.3 and 90.1% within 0.5 units.	QUADAS 4Y, 3N
Kong 2008[36] Singapore	N = 230 (n = 253) tertiary hospital	Coagucheck XS	r =0.945 (CI not available)	Mean difference: graphical figure	Variations increased with INR readings above 3.5	QUADAS 4Y, 1U, 2N
Lizotte 2002[37] Canada	N = 100 OAT antico clinic	Coagucheck S	Test-retest reliability: 0.98 (CI 95% 0.98-0.99) Inter rater reliability: 0.97 (0.95-0.98)	NA	The mean real difference did not vary significantly according to the INR ranges.	QUADAS 6Y, 1N
McBane 2005[38] USA	N = 94 OAT Anticoagulation clinic	Coagucheck Protime 3	CoaguChek (r2=0.90) ProTime 3 device (r2=0.73) (CI not available)	Mean ±SD: CoaguChek - 0.2 ±0.31 units ProTime 3: + 0.8 ±0.68 units	Agreement ±0.4 INR unit: 82% (CoaguChek) and 39% (ProTime 3 devices) of INR results	QUADAS 5Y, 2N
Moore 2007[39] UK	N = 186 OAT Anticoagulant clinic	Coagucheck S Protime INRatio	CoaguChek S: r^2 = 0.96 ProTime: r^2 = 0.96 INRatio: r^2 = 0.80 (CI not available)	NA	Percentages of paired results within 0.5 INR units: 77.1% (Coagucheck S), 92.0% (Protime) 54.2 %(INRatio). All POC: greater variation at INR values above 3.0.	QUADAS 4Y, 3N
Murray 1999[40]	N = 19 (n = 62)	Coagucheck	Coagucheck: r =0.96	Mean difference Coagucheck: -0.10	NA	QUADAS 5Y, 2N

Reference	Population	Index test	Linear regression analysis	Mean difference	Agreement between individual INR results	Quality appraisal
UK	G P	Protime	Protime: r= 0.92	Protime: -0.28 (SD in graphical figure)		
Nowatzke 2003[41] USA	N = 19 children (n = 30) Hospital OAT	Coagucheck Protime	Coagucheck: r2 = 0.877 Protime: r2 = 0.885 (CI not available)	NA	NA	QUADAS 2Y, 2U, 3N
Orellana 2003[42] Spain	N= 155 OAT laboratory	Coagucheck S	r = 0.912. (CI not available)	Mean difference: 0.309 (0.202-0.417).	NA	QUADAS 3Y, 1U, 3N
Ruzicka 1997[43] Austria	N= 134 (65 OAT) Hospital	Coagucheck Plus	r =0.997 (p<0.001) (CI not available)	NA	NA	QUADAS 4Y, 3N
Shiach 2002[44] England	N = 46 (n = 465) community clinic	Coagucheck	NA	Mean relative deviation <10% for INR < 4.0 and 12.6% for INR > 4.0.	NA	QUADAS 3Y, 1U, 3N
Stoysich 2001[45] USA	N = 23 OAT Hospital	Coagucheck Protime	Coagucheck: r = 0.928 (p <0.001) Protime: r = 0.953 (p <0.001) (CI not available)	Mean difference: Coagucheck: -0.22 (±0.242) Protime: +0.32 (±0.285)	Difference > 0.5 INR: Coagucheck: 9.8% Protime: 3.9%	QUADAS 3Y, 2U, 2N
Sunderij 2005[46] Canada	N = 55 (n = 114) self testing	Protime Microcoagulation system	r = 0.62. (CI not available)	Mean (SD) difference: 0.44 (0.61).	within 0.5 INR : 76% within 0.7 INR: 86%	QUADAS 4Y, 1U, 2N
Taborski 2004[47] Germany	N = 5 healthy + 77 OAT Clinic	Coagucheck S INRatio	Coaguchek S: r = 0.937 INRatio: r = 0.954 (CI not available)	Mean relative deviation Coagucheck S: 9.72% INRatio: 6.87%	NA	QUADAS 4Y, 2U, 1N
Tay 2002[48] Malaysia	N = 50 antico clinic	Protime analyser	r = 0.940. (CI not available)	Mean difference: 0.123 (-0.344 to +0.680) (p=0.061)	NA	QUADAS 4Y, 1U, 2N

Reference	Population	Index test	Linear regression analysis	Mean difference	Agreement between individual INR results	Quality appraisal
Torreiro 2009[18] Spain	N= 41 n= 218 PSM	Coagucheck XS	r = 0.95 (CI not available)	Mean difference: 0.1 (-0.47 to +0.67)	NA	QUADAS 3Y, 2U, 2N
Van den Besselaar 2000[49] Netherlands	N= 20 healthy + 60 OAT Antico clinic	Coagucheck Venous blood	NA	Mean relative deviation: 5.8% (strips with ISI 1.5) 2.8% (strips with ISI 1.1)	Statistically significant INR differences (p <0.001),	QUADAS 1Y, 3U, 3N
Van de Ven 2005[50] Netherlands	N = 111 OAT Antico clinic	Protime	R = 0.87 (graphical method for CI)	Mean difference in a graphical figure	NA	QUADAS 2Y, 1U, 4N
Williams 2007[51] Australia	N = 80 (n = 184)	Coagucheck S Coagucheck XS	NA	NA	INR difference of ≤0.5 INR units: 57% of the CoaguChek S 81% of the CoaguChek XS.	QUADAS 2Y, 3U, 2N

NA Not available

3.3.2.3 Technical accuracy

Technical accuracy aims to evaluate the test in experimental conditions. One study [37] showed experimental results.

The test-retest reliability is defined as the capacity of the method to produce similar INRs when the measurements are repeated with the same patients under similar conditions. The test-retest reliability has been studied with the CoaguCheck S®. The intra class (INR <2, ≥2-≤3, >3) coefficient was 0.98 (CI 95% 0.98-0.99). For the inter rater reliability, defined as the capacity of the device to produce similar results when measurement is repeated for the same patient under similar conditions, but by different operators, the intra class coefficient was 0.97 (0.95-0.98)[37].

- **One study shows good test-retest reliability and good inter-rater reliability for one POC device (Coagucheck S®).**

3.3.2.4 Diagnosis accuracy

HTA

One HTA report[9] is based on two studies[44] [24] in general practice and concluded that there was no significant difference in diagnostic performance between POC testing and laboratory testing, with a remark about accuracy at higher INR levels. Diagnostic performance was not discussed in the other HTA report[7].

Primary studies

In this review, 34 studies were found about the diagnosis accuracy of POC INR devices (table 3.2). The results of INR are measured as a continuous variable. There were no data included in the studies allowing the estimation of sensibility and specificity of the POC INR testing. The result is compared with the laboratory INR result which is considered as the gold standard.

Correlation coefficient

The Pearson's correlation coefficient (r) between POC INR results and laboratory INR results was acceptable to good in most studies, whatever the site (hospital, anticoagulation clinic, local laboratory, primary care practice or at home), the actor of the test (health care professional or patient itself) or the patient (child or adult). Table 3.3 illustrates the correlation coefficient (r) according to the type of POC device. In 21 out of 31 comparisons, r was ≥ 0.90; in 27 out of 31 comparisons, r was ≥ 0.85. The Pearson's correlation coefficient for INR results between local laboratories was described in one study[26] and it was good (r = 0.93 to 0.97). The limits of the correlation coefficient to measure agreement have been described by Bland and Altman [52]. Moreover, no study mentioned a confidence interval for the r, except one[50] which mentioned it in a graphical figure.

Mean difference

The mean difference between the results of INR obtained by POC device and by laboratory varies from -0.29 to 0.80 INR units, according to the selected studies (table 3.2).

Agreement at individual level

Between studies, there is a great disparity of reference values (such as 0.2, or 0.4, or 0.5, or 0.6, or 0.7 INR units differences between the POC and the laboratory INR results) to evaluate the agreement at individual INR results level. A difference of ± 0.5 INR units between the two systems was considered as clinically acceptable in a previous guideline[53]. In the studies, considering this kind of difference, the results with ± 0.5 INR units varied from 54 to 100%. Six of 12 studies related results with ± 0.5 INR difference in 85 and 92% of the samples (Table 3.4.).

Table 3.3: Pearson's correlation coefficient between POC results and laboratory results

POC device	Correlation coefficient (r)
Coagucheck	0.885 (Ignjatovic 2004)[29] 0.877 (Nowaztke 2003)[41] 0.90 (McBane 2005)[38] > 0.90 (Gosselin 2000)[28] 0.928 (Stoysich 2001)[45] 0.92 to 0.95 (Finck 2001)[26] 0.95 (Kitchen 2006)[34] 0.97 (Koerner 1998)[35]
Coagucheck Plus	0.90 (Gosselin 2000)[28] 0.997 (Ruzicka 1997)[43]
Coagucheck S	0.81 (Jonsson 2004)[31] 0.89 (Jackson 2004)[30] 0.912 (Orellana 2003)[42] 0.937 (Taborski 2004)[47] 0.95 (Gardiner 2005)[27] 0.96 (Moore 2007)[39] 0.96 (Kitchen 2006)[34]
Coagucheck XS	0.91 (Bereznicki 2007) [21] 0.945 (Kong 2008)[36] 0.95 (Torreiro 2009)[18]
Protime microcoagulation system	0.62 (Sunderij 2005)[46] 0.87 (Van de Ven 2005)[50] 0.87 to 0.90 (Finck 2001)[26] 0.885 (Nowaztke 2003)[41] > 0.90 (Gosselin 2000)[28] 0.92 (Andrews 2001) [19] 0.940 (Tay 2002)[48] 0.953 (Stoysich 2001)[45] 0.96 (Moore 2007)[39]
Protime 3	0.73 (McBane 2005)[38]
INRatio	0.80 (Moore 2007)[39] 0.954 (Taborski 2004)[47]

Table 3.4: POC INR results in relation to laboratory INR results

POC device	Within ± 0.4 INR unit	Within ± 0.5 INR unit	Other
Coagucheck	82% (McBane 2005)[38]	88% (Ignjatovic 2004)[29] 90.1% (Koerner 1998)[35]	71.3% within 0.1 INR unit (Koerner 1998)[35]
Coagucheck Plus	NA	NA	NA
Coagucheck S	NA	57% (Williams 2007)[51] 77.1% (Moore 2007)[39] 85% (Gardiner 2005)[27] 88% (Jackson 2004)[30] 88% (Karon 2008)[32]	NA
Coagucheck XS	> 90% (Karon 2008)[32]	81% (Williams 2007)[51] 100% (Bereznicki 2007)[21]	95% between -0.2 to + 0.4 INR unit (Bauman 2008)[20]
Protime microcoagulation system	77% (Andrews 2001)[19]	92.0% (Moore 2007)[39] 76% (Sunderij 2005)[46]	86% within 0.7 INR unit (Sunderij 2005)[46]
Protime 3	39% (McBane 2005)[38]	NA	NA
INRatio	NA	54.2% (Moore 2007)[39]	NA

NA: Not available

Agreement with respect to the range of INR value

Several studies showed that the difference between POC INR values and laboratory INR values changed in relation with the range of INR values.

- Most studies related that this difference increases with the increase of INR value[30 44 54 18 36 51]. POC INR results are more imprecise when the laboratory INR value of the sample analyzed is above the therapeutic range. For example, in the study by Jackson, for 3 different ranges laboratory INR values (one range ≤1.9, one range between 2.0 and 3.5 and one range ≥3.6), 97%, 90% and 57% of readings with POC device were within 0.5 INR units, respectively. In the study by Shiach, the mean relative deviation (MRD), calculated across 0.5 INR unit intervals, was less than 10% for laboratory INR results < 4.0 and 12.6% for laboratory INR results > 4.0 and the Bland Altman curve showed evidence of positive bias: the difference in INR increased as the average INR increased.
- One study (Cosmi) described also small divergences in results for INR values below the therapeutic range. For laboratory INR values in the range <2.0 the mean INR value was -0.0675 (limits agreement LA: -0.37/ +0.23). For the INR values in the range between 2.0 and 3.0, the mean INR value was +0.018 (LA: -0.39/ +0.35) and for the range of INR >3.0, it was + 0.039 (LA: -0.49/ +0.55).
- In the study by Lizotte[37], however, the mean real difference did not vary significantly according to the INR ranges.

- **All studies compare the results of INR with a POC device on capillary blood with the results of INR performed with a laboratory coagulometer on venous blood sample.**
- **The Pearson's correlation coefficient (r) between POC INR results and laboratory INR results is acceptable to good. The clinical relevance of this correlation is however discutable.**
- **The percentage of samples in a range of difference of ± 0.5 INR units between the results of INR obtained by POC device and by laboratory varied from 54 to 100% depending on the studies, with most studies having results between 85 and 92%.**
- **There is however an uncertainty about the diagnostic performance of POC testing at higher INR levels. The difference between POC INR values and laboratory INR values increases as the average INR increases.**

3.3.2.5 Tests failure and un-interpretable results

Tests failure and un-interpretable results are reported in a few studies.

In the study by Andrews[19] with the Protime ®, the no test result (due to an on board quality function that eliminates bad tests results) dropped from approximately 10% (at start) to 4 to 8% across the individual sites. During the study by Tay[48], who also used Protime ®, insufficient blood sample collection was observed in about 4% of the participants. This was due to the fact that the Tenderlett Plus fingerstick device owns a rather shallow puncture needle with a puncture depth of 1.75 mm which could be an important problem for blood collection especially in patients with more subcutaneous tissue.

Gardiner[27] performed 234 tests with the CoaguCheck S®. He encountered one defect instrument defect and one test-strip problem. On each occasion, both the patient's sample and the quality control gave unexpected abnormal results and the problem, once identified, was easily corrected. In the study by Lizotte[37] who also used the CoaguCheck S®, in 13 out of 393 tests (3.3%) no result could be obtained after four finger pricks. For the remaining 380 INR test results, a total of 478 finger pricks had to be performed; this represents 25.8% extra finger pricks. The reasons for using additional finger pricks were: an insufficient quantity of blood (16.1%), the drop of blood sliding out of the sample target area of the test-strip (7.9%) and an error message or outlier value (1.8%).

The percentage of extra finger pricks did not vary with the investigator or pharmacist who conducted the test (p = 0.338).

In the study by Stoysich[45], one out of 44 samples using the CoaguCheck S® reported an error (because of an air bubble in the sample). Twenty one out of the 75 samples using the Protime®; reported an error of reading. Four errors occurred during the quality control check; 10 were caused by battery malfunction and seven by sample size error. Taborski[47] showed that there was no malfunction or problem with CoaguCheck S® and INRatio® during the study.

- **Tests failure or un-interpretable results with POC devices may be due to internal quality function eliminating bad tests results, insufficient blood sample, subcutaneous tissue thick, and defect of instrument or test-strip problems. This may result in a use of more than one strip per test, essentially at the start of self testing (4 to 25% extra finger pricks).**

3.3.2.6 Safety

The only risks or adverse reactions are those associated with obtaining the capillary sample, such as localised bleeding, bruising or a vaso-vagal episode. There is a risk of needle stick injury when obtaining the sample, which could potentially result in infection with a blood-borne virus to the operator. There are no excess safety concerns with capillary sampling when compared with veni-puncture for laboratory-based INR testing[9].

- **There are no excess safety concerns with POC capillary sampling compared with veni-puncture.**

3.3.3 Discussion

A major problem of comparative studies is that similar lack of correlation of INR results exits when anticoagulated plasmas are simultaneously compared using different instrument/ thromboplastin combinations[8]. Several parameters may influence the results in studies about the diagnosis accuracy of the POC devices: the differences in ranges of INR values of the patients included in the studies, to the calibration and the ISI value of reference laboratory coagulometers used as gold standard, and to the calibration and the ISI value of the POC device tested. Moreover, the quality of the studies is globally not very high and methodological biases are not excluded.

3.4 QUALITY CONTROL

Quality assurance of POC monitors is required to ensure that results are reliable. Both internal quality control (IQC) and also external quality assessment (EQA) are recommended by guidelines [53]. IQC is available for each POC device. The quality control agents are included in the strip for CoaguCheck® and INRatio® devices and in the cuvette for Protime® devices. Health professionals and patients should realize IQC regularly. Recommendations on IQC modalities are published based on a low level of evidence[53].

However, despite the integration of quality processes in the POC devices by the firma, limitations to accuracy and precision have been documented. Problems identified with POC instruments include incorrect calibration of the ISI of the POC instruments, the inability to calculate a mean normal PT, inaccuracies in INR determination in patients with antiphospholipid antibodies with certain instruments [8], inappropriately handled proficiency testing material, inaccuracies in the calibration of the system by the manufacturer or deterioration during transport/storage of the test strips[34].

External quality assessment (EQA) is considered to be necessary for laboratory INR in Europa, in America and elsewhere, but for POC devices, the use of external quality assessment is sometimes questioned in the literature. In 2006, Kitchen stated that it was not known whether EQA is also required for INRs determined with POC monitors, although guidelines[53] have recommended it[34]. ACCP guidelines recommends for POC devices to participate in proficiency schemes available through professional or national quality assurance organizations[8].

3.4.1 Methods

3.4.1.1 Research question

How should the EQA of the POC devices be performed?

Population: patients with OAT

Index test: INR from POC device

Comparison: INR from EQA process

O: Accuracy, clinical outcomes

Comparison between two EQA processes was also considered.

3.4.1.2 Search

HTA: See above (technical and diagnostic accuracy)

Primary studies: A specific search was done on the quality control of POC INR devices (March 2009) in Pubmed and in Embase. The search strategy is described in table 3.5.

Table 3.5: Search strategy for quality control

Data base	Term	Number
Medline via Pubmed	"Quality Control"[Mesh] AND "Point-of-Care Systems"[Mesh]	123
	"Quality Control"[Mesh] AND Coagucheck	0
	"Quality Control"[Mesh] AND CoaguCheck	0
	"Quality Control"[Mesh] AND Protime	159
	"Quality Control"[Mesh] AND INRatio	0
	"Quality Control"[Mesh] AND "International Normalized Ratio"[Mesh]	39
Embase	'quality control*'/exp/mj AND 'international normalized ratio'/exp/mj	3
	'quality control'/exp/mj AND 'point of care testing'/exp/mj	2
	'quality control'/exp/mj AND CoaguCheck	0
	'quality control'/exp/mj AND protime	0
	'quality control'/exp/mj AND INRatio	0
Other	Previous search about accuracy	5

* Emtree term for "quality assessment" and for "quality assurance"

3.4.1.3 Selection of studies

Studies were included if an external quality control process was the studied intervention for a POC INR device (CoaguCheck, Protime or INRatio) used in patients with OAT. In addition, the study had to relate clinical outcomes or impact to the accuracy of the test. Clinical and experimental studies were included if there was a control group. Letters, editorials, review without systematic search were excluded.

3.4.1.4 Quality assessment

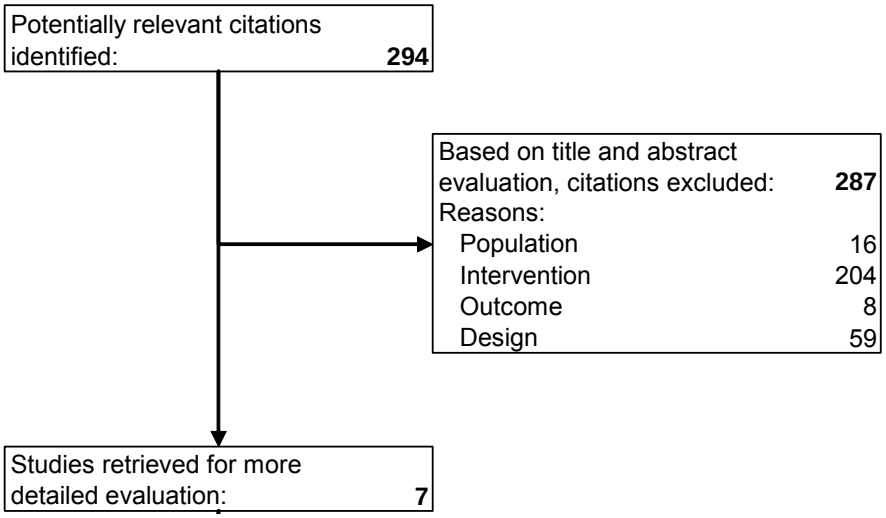
For the critical appraisal of primary studies, 7 items of the QUADAS check list were used as for the diagnosis studies (see section 3.3.1.3). The quality assessment of HTA reports is described in the same section.

3.4.2 Results

3.4.2.1 Literature search

After removal of duplicates, 294 publications remained. After application of inclusion/exclusion criteria (figure 3.3), 7 publications remained.

Figure 3.3: Selection of studies for quality control



3.4.2.2 Quality assessment

The quality assessment of HTA reports is described in section 3.3.2. The results of quality assessment of primary studies are summarized in table 3.6. All studies included a large spectrum of INR ranges. None study related a blinding process.

3.4.2.3 Review

HTA

In the 2 HTA reports, the recommendations about quality controls remain undefined. One mentioned that some researchers have recommended periodic internal or external accuracy checks to ensure that results are reliable[7]. And for the other HTA report, laboratory testing may still be used, for example, to check some abnormal INR levels and as a check of concordance between POC and laboratory testing after initiating OAT[9].

Primary studies

Seven primary studies were selected (table 3.6). All devices tested were Coagucheck® or Coagucheck S®. Several external quality assessment (EQA) methods were studied:

- comparison with simultaneous INR results on venous blood tested with a reference coagulometer in laboratory [55 56 57 58],
- assessment with the percentage difference of the POC device INR results from the median INR of all devices of a centrum (conventional EQA)[57],
- comparison with INR of two lyophilised certified plasmas samples as recommended in the UK NEQAS programme[34 59 58],
- comparison with 5 certified INR ranges quality control plasma as recommended by the ECAA (European concerted action on anticoagulation)[55 60 57].

Five studies compared the value of POC INR results with the EQA INR value[55 34 60 56 58]. One study compared the results of conventional EQA and ECAA EQA with similar results for the proportion of unsatisfactory performances indicated by a 15% deviation with each method[57]. One study compared the ability of patients and health care professionals to use UK NEQAS programmes, with no significant difference in the median results[59].

None study related clinical outcomes. Five studies evaluated the difference between the INR result of the POC and the external quality control by a deviation of ±15%[34 59 60 57 56]. One study used the criterion of ±0.5 INR units[55] such as in the guideline of the British society of haematology taskforce for haemostasis and thrombosis[53].

One study used other criteria (14.8 and 12.7% of deviation)[56]. The frequency of controls ranges from 2 to 6 controls/ year.

Each EQA methods showed divergences between POC INR results and the external quality controls (table 3.6.). By reason of a gap of direct comparative studies between most EQA methods, a gap of studies evaluating an impact on patients' outcomes and the great heterogeneity of selected studies, there is not evidence in our literature review that an EQA method is superior to another with respect to the accuracy of POC devices.

3.4.3 Discussion

The heterogeneity of the studies is an obstacle to fimr conclusion. A comparison between results of selected studies is perilous. There is indeed a great disparity between studies with respect to EQA methods, criteria to assess a deviation, comparisons of INR either at POC device level or either with a mean of results of a centrum.

The need for EQA may however be justified by divergences in results that may have an impact on clinical decisions. The advantage of an EQA method using certified plasmas is the accuracy of the reference test. A comparison with a parallel venous blood testing requires necessary confidence in the accuracy (and the quality controls) of the coagulometer used in the laboratory as reference for quality control of POC devices, the two methods (POC and laboratory coagulometers) having some potential imprecision.

- **Despite the calibration of POC devices and the availability of internal quality process, divergences in results may exist which can have an impact on clinical decisions.**
- **External quality control, though even asked in the literature, is recommended for POC devices.**
- **Four processes are described: comparison with a reference laboratory, conventional EQA (median of all results), UK NEQAS programme (2 lyophilised certified plasmas) or ECAA quality control (5 certified ranges plasmas).**
- **There is no evidence in the literature that an EQA method is superior to another.**

Table 3.6: Quality control studies

Reference	Population	Index test	Comparator EQA	Results	Critical appraisal
Barcellona 2008[55]	99 patients OAT at home (95 devices)	INR results of Coagucheck S	1. INR results of reference coagulometer in laboratory (venous blood) 2. ECAA: 5 certified INR ranges quality control (QC) plasmas	1. INR value difference > ± 0.5: 1% (quarterly one), 7.5% (Q2), 11.5% (Q3) (Chi-Square: 8.315, p=0.0156) Lots with differences higher than 10% in terms of ± 0.5 INR at the first, second and third controls were 16%, 20.8% and 61%, respectively. 2. Six monitors (6.3%) failed (result not in the range) with one or two of the QC plasmas but performed well at the second measurement using the same vial. Five monitors (5.2%) failed with one or two of the QC plasmas of one vial but performed well using a new vial. Two monitors (2%) failed with two vials of plasmas but performed well using a different lot of strips. One monitor (1%) gave unsatisfactory results with repeated test on the plasmas and with different lots of test strips.	QUADAS technical 4Y, 2U, 1N
Kitchen 2006[34]	POC devices used by > 10 centers	Coagucheck Coagucheck S Hospital laboratories with INR conventional techniques	UK NEQAS programme: one or two lyophilised plasma samples (six surveys per annum)	Results of centres in consensus if less than 15% difference between medium peer groups. In each survey 10–11% of centres using POC monitors obtained INR results which were >15% different from those in other centres using the same monitors. For hospital laboratories using conventional INR techniques this figure was 12%.	QUADAS technical 3Y, 2U, 2N
Meijer 2006[60]	Thrombosis centers 523 devices	Coagucheck	5 certified INR plasma samples ECAA	20.3% (106/523) of devices showed a ≥15% deviation from the certified INR on at least 1 of the 5 QA plasma samples (from which 76.4% with 1; 7.9% with 2; 4.7% with 3, and one device with 4 of the 5 plasma samples). Of the 106 monitors with significant INR deviations, 71 (67.0%) used lot 965, but only 35 (33.0%) used other lots of strips. This difference was significant at the 5% level (P = 0.007).	QUADAS technical 4Y, 1U, 2N
Murray 2003[59]	General practice Coagucheck S 23 patients 75 professionals	EQA (UK NEQAS) realized by patient	EQA (UK NEQAS) realized by health care professionals	**There was no significant difference in the median results on NEQAS samples obtained by the patients and those obtained by professionals. Three patients were outwith consensus (results > 15% from the median INR) on more than one occasion.** **Good agreement can be achieved between patients analysing the same EQA samples, with coefficients of variation ranging from 22.3% to as low as 5.4%.**	QUADAS technical 5Y, 1U, 1N

Poller 2006 [57]	Thrombosis centers 523 devices Coagucheck	Conventional external quality assessment: percentage difference of the device from the median INR of all data from all devices	5 certified INR plasma samples ECAA tested on individual monitors by the trained staff	15% deviation from the ECAA set was compared with 15% deviation from overall median INR. The results were similar (20.3% and 18.5%, respectively). Interlot differences of CoaguChek test strips were detected, but the incidence of unsatisfactory performance was similar with both analyses, from 6.5% to 37.5% at the 9 centres with the certified INR method and from 5.9% to 33.3% with the overall median analysis.	QUADAS technical 4Y, 1U, 2N
SØLVIK 2006[58]	205 paired measures	Coagucheck S INR results	1. Traditional EQA (NEQAS UK) plasmas at 2 INR levels Result acceptable if ≤±12.7% 2. Split-Sample survey: venous blood laboratory Result acceptable if ≤±14.8%	Two parallel independent survey: No direct comparison Traditional EQA: the total imprecision was 8.0 % at the low level (1.6 INR) and 10.5 % at the therapeutic level (3.4 INR). Split-sample survey: the total imprecision was 12.3 % at the low level (2.1 INR) and 10.7 % at the high level (3.0 INR).	QUADAS technical 3Y, 2U, 2N
Tripodi 2004[56]	N = 14 patients Contorl at 3 times	INR self-testing Coagucheck Coagucheck S	Laboratory INR (venous blood).	Majority of measurements lying within 15% of the consensus values. 3 INR values with a deviation >15% at each control time	QUADAS technical 3Y, 2U, 2N

3.5 IMPACT ON PATIENT OUTCOME

Next to the technical and diagnostic accuracy, a monitoring strategy can impact patient outcome, either in a positive or negative direction. The impact on patient outcome is typically evaluated in a randomised controlled trial, in which the independent effect of the new monitoring strategy is compared to the usual strategy.

3.5.1 Methods

3.5.1.1 Research question

What is the impact of point-of-care anticoagulation monitoring on patient-centred outcomes such as major haemorrhages, major thromboembolic events, and death?

P patients taking oral anticoagulants for at least three months

I point-of-care monitoring: by physician or paramedic, patient self-testing, patient self-management

C usual care

O thrombo-embolic events, major bleeding episodes, and death from all causes

3.5.1.2 Literature search

To summarise the evidence of impact on patient outcome, a two staged approach was followed. First, evidence synthesis such as HTA reports and systematic reviews was searched and appraised for quality. Good quality studies were included in our review. Second, updates of these studies were made by searching for original studies published after the most recent search date of the included HTA reports and systematic reviews.

HTA reports

See above (chapter on technical and diagnostic accuracy)

Systematic reviews and meta-analyses

Electronic databases were searched with a combination of terms relating to anticoagulant therapy and point-of-care testing.

Medline: (("Anticoagulants"[Mesh] OR "Vitamin K"[Mesh] OR "coumarin "[Substance Name]) AND ("Self Care"[Mesh] OR "Self Administration"[Mesh] OR "Consumer Participation"[Mesh])) AND systematic[sb], search date 20/01/2009.

Embase: ('anticoagulant agent'/exp OR 'antivitamin k'/exp OR 'coumarin'/exp) AND ('drug self administration'/exp OR 'self care'/exp OR 'consumer'/exp) AND ([meta analysis]/lim OR [systematic review]/lim) AND [embase]/lim, search date 30/03/2009.

Primary studies

Original randomised controlled trials, published after the last comprehensive literature search of one of the HTA reports or systematic reviews included above, were searched in the following electronic databases: Medline, Embase, CENTRAL. A sensitive search strategy was used, as described by Brown et al[7]. See appendix 1 for details on terms used.

3.5.1.3 Selection of studies

HTA reports and systematic reviews

HTA reports and systematic reviews were selected for possible inclusion in our review when a systematic and transparent literature search had been conducted for randomised controlled trials including patients taking at least 3 months of oral anticoagulants and comparing a point-of-care monitoring strategy with usual care on patient-centred outcomes.

Primary studies

Studies were selected in a first round based on title only, selecting all articles on anticoagulation in general. In a second round, based on title and abstract, all studies that were possible randomised controlled trials including patients taking oral anticoagulants and compared a point-of-care monitoring strategy with usual care were included. Letters, editorials, reviews, guidelines were excluded. This selection was done in duplicate by two independent reviewers. Discrepancies were resolved by consensus.

Final selection for inclusion in KCE meta-analyses

All studies included in at least one of the HTA reports or systematic reviews, or identified in the update were retrieved in full text, and selected based on the following selection criteria:

Design: randomised controlled trials

Population: patients taking oral anticoagulants for at least 3 months during the study

Intervention: POC monitoring of oral anticoagulants by health professionals or patients

Comparison: usual care: anticoagulation clinics, hospital clinics, primary care

Outcome: thrombo-embolic events, major haemorrhages, or death.

3.5.1.4 Quality assessment

All randomised controlled trials were assessed for quality using the tool described by the Cochrane Handbook of Systematic Reviews[61]. Studies were not excluded based on quality.

3.5.1.5 Analyses

Data were extracted from all the articles, and entered in Review Manager 5[62] for analyses. Intention-to-treat analyses were performed as much as possible, by using the number of randomised patients of each group as denominator. Haemorrhages were considered major in case they resulted in death, or were clinically overt and showed one of the following: critical site involvement (intra-cranial, retroperitoneal, intra-ocular, intra-spinal, or pericardial), drop in haemoglobin of ≥2.0 grams per decilitre, need for transfusion of >2 units of packed red blood cells, or a bleeding index of >2.0. Thrombo-embolic events were considered major if they were venous and arterial thrombo-embolic complications of stroke and valve thrombosis. Transient ischemic attacks were considered to be minor thrombo-embolic events. In case it was not possible to evaluate whether the adverse events reported complied with these definitions, the definition of the authors was used.

Meta-analyses were performed using the fixed effects model in case no or limited heterogeneity was present (I^2 ≤25%). When I^2 lied between 25-75%, a random effects model was chosen. When I^2>75%, data were not pooled but reasons for heterogeneity were explored[61]. The outcome measure reported is the odds ratio, which is the ratio of the odds of the intervention group over the control group. The odds of an event, understood best by those who enjoy wagers, is the number of times it occurred (a) divided by the number of times it did not (b), or a/b. For example, if the event rate for a disease is 0.2 (10%), its non-event rate is 0.8 and therefore its odds are 2/8. Funnel plots were constructed when five or more studies were available for one specific comparison and one specific outcome. The Egger's statistical test for publication bias was applied when 10 or more studies were available[61]. Sensitivity analyses were planned on frequency of testing, setting of the control group and duration of the study.

3.5.2 Results

3.5.2.1 Literature search

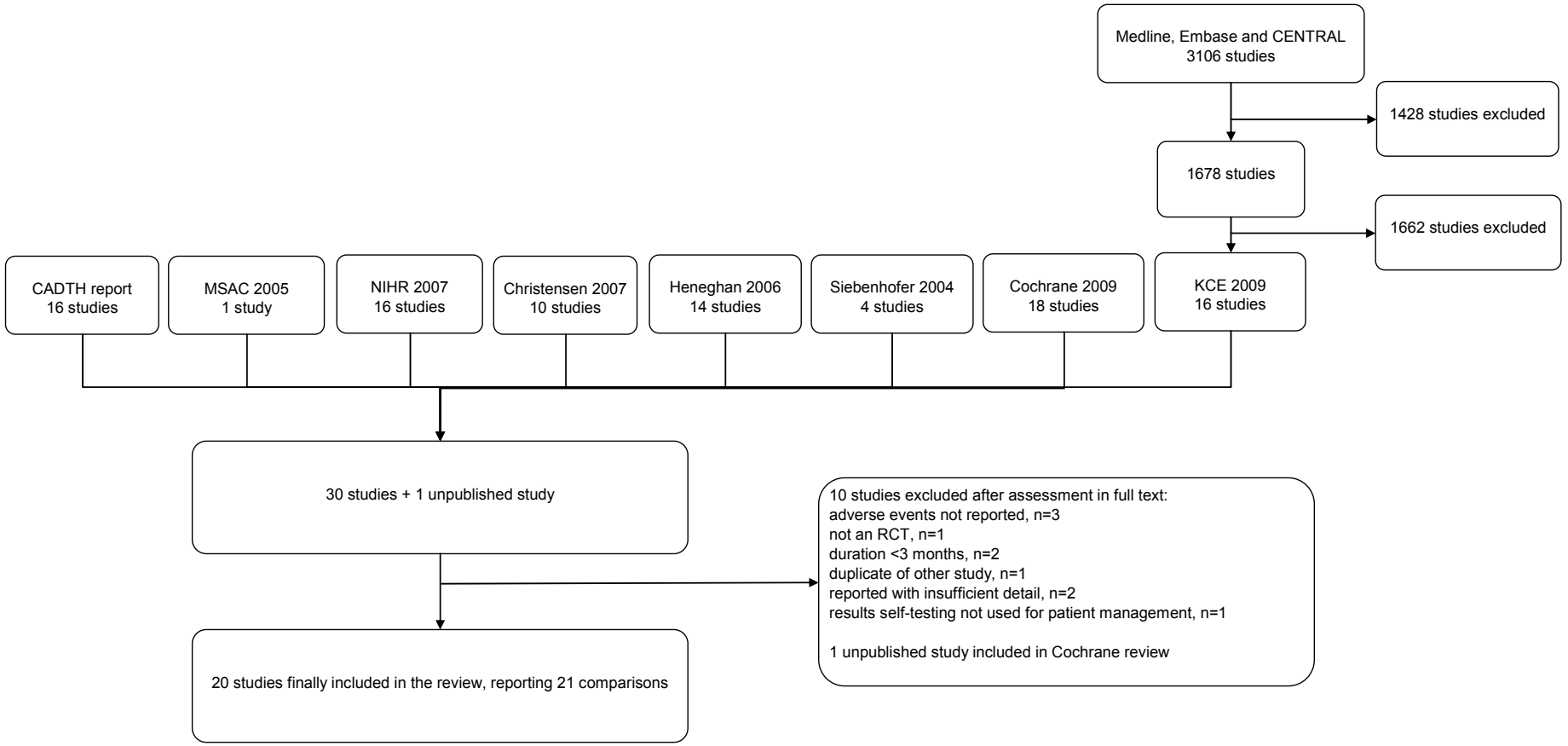
From the 12 possible HTA reports that were identified in the previous chapter, three were relevant for the evaluation of impact on patient outcome: the Canadian HTA report by Brown et al. (2007)[7], the HTA report by Hayes Inc. (2006)[63] and the Australian HTA report by MSAC (2005)[9]. The report by Hayes Inc. was not available at our institution, by which we included only the Canadian and the Australian report.

The search for systematic reviews in Medline yielded 23 articles, that in Embase 24 articles, totalling 43 articles after discarding duplicates. After applying inclusion and exclusion criteria, 7 possibly eligible systematic reviews were selected for assessment in full text. Of these, one article was in Spanish[64] and another in Norwegian[65], both were subsequently excluded; another article did not report explicit selection criteria and searched in only one database[53] and was excluded as well. Finally, one article proved to be a HTA report not captured in the search for HTA reports[66]. As a result, three systematic reviews were included for further review[67-69]. An as yet unpublished Cochrane review on the efficacy of self-testing and self-management was presented at the South West Society of Academic Primary Care Conference (Winchester March 7th, 2009)[70]. We received the list of included studies by personal communication (R. Perera, University of Oxford). Details on the respective HTA reports and systematic reviews are summarised in appendix 2.

The literature search for original studies was limited to the most recent search date of a HTA report or systematic review included above, which was 2005. We identified 1804 potentially relevant articles in Medline, 1437 in Embase and 171 in CENTRAL, totalling 3106 articles after duplicates were discarded. In the first round, 1428 articles were excluded as they did not relate to anticoagulation, judged on title and abstract. In a second round, an additional 1662 studies were excluded, based on our selection criteria, leaving 16 articles. The interrater agreement of the two independent reviewers performing the selection was good: kappa 0.707 (0.524-0.890).

Ultimately, 31 studies were identified in the HTA reports, systematic reviews and update (Table 9.1). Of these 31 studies, 10 studies were excluded after assessment in full text, and one was excluded because full text could not be obtained. We excluded one study by Koertke et al. (2001)[71] that was a duplicate of another study, Koertke et al. 2007[72]. However, in the more recent study, no data on major thrombo-embolism and major haemorrhages were reported, which were reported in the older study. Thus, the data of the older study were used for these outcomes, and included under Koertke 2007. In conclusion, 20 studies were finally included in our review, reporting 22 comparisons. One comparison included trained patients versus untrained patients in an anticoagulation clinic, which was subsequently excluded as it did not involve a point-of-care test[73]. See Figure 3.4 for the flow chart of the literature search.

Figure 3.4: flow chart of literature search



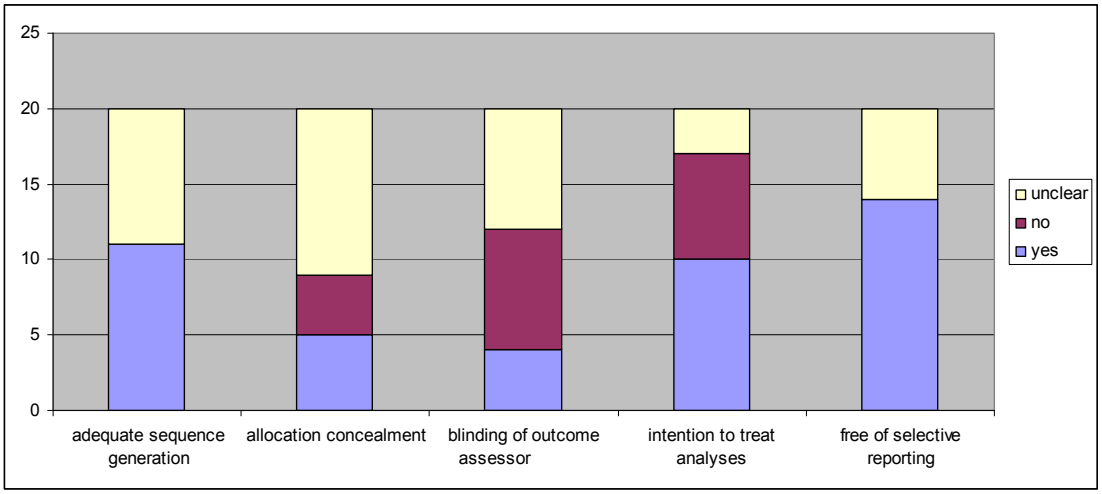
3.5.2.2 *Characteristics of included studies*

The quality assessment of the included studies is presented in Figure 3.5. Allocation concealment and blinded assessment of the outcome were poorly reported or not performed.

The indication for anticoagulation was not specified in 13 studies, in five studies patients received anticoagulation for heart valves[74 75 72 76 77] and in two for atrial fibrillation[78 79]. Most studies used the Coaguchek® (Roche Diagnostics) as point-of-care device, one study used Pro Time (Int Technidyne Corporation)[80], one study used Coumatrak Protime system (Biotrack)[81], and one study used Thrombotrak (Nycomed)[82]; one study did not specify which device was used . Eight studies had a duration of 6 months[81 83 84 85 86 73 78 87], one study of eight months[80], four studies of 12 months[82 88 89 77] and one study of nine years[72]. The duration was not specified in one study[75].

Seven studies reported having received a research grant from the manufacturer of the point-of-care device used in the study[86 73 89 87 90 80 79], and two received material support[84 76].

Figure 3.5: quality assessment of included studies

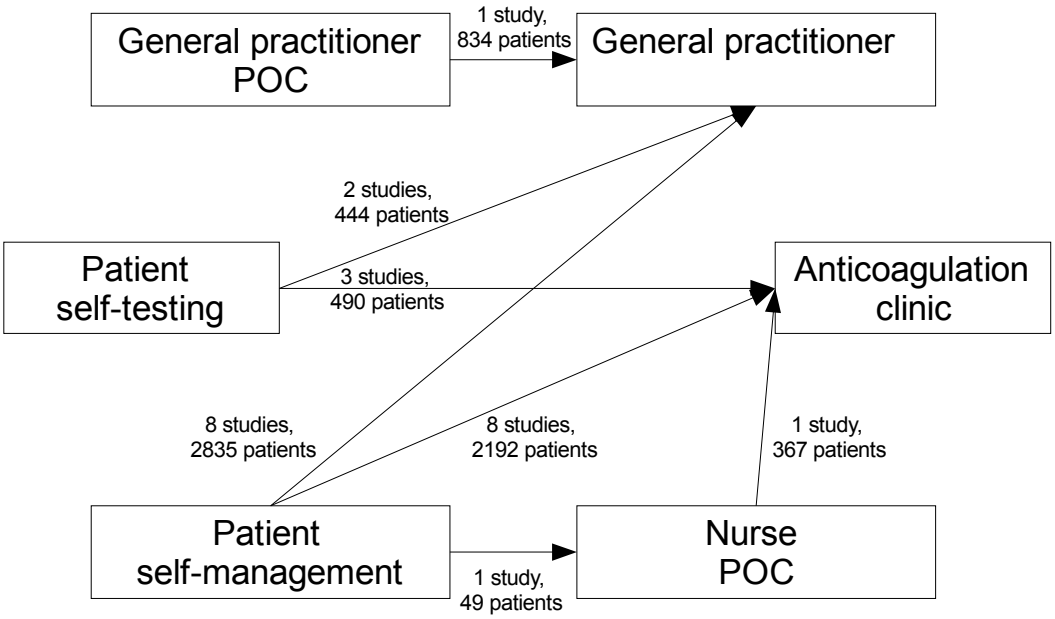


3.5.2.3 *Meta-analyses*

Comparisons were then categorised in intervention-control pairs, as represented in Figure 3.6.

Anticoagulation clinics are the most commonly used control group, with 12 comparisons in total, followed by the general practitioner with 11 comparisons. One study compared patient self-management to nurse-led point-of-care testing. Four studies reported a control group consisting of monitoring by either a GP or an anticoagulation clinic.

Figure 3.6: comparisons included in the review



POC: point-of-care testing

The meta-analyses were performed for the subgroups patient self-management, patient self-testing, general practitioner POC and nurse-led POC, combining all control groups. The effect of the control groups on the effect estimate was tested in sensitivity analyses.

Table 3.7: characteristics of included studies

Study	Population	Intervention/ Device	Control	Duration	Mean age (range or SD)	Anticoagulant agent
Beyth 2000[81]	Inclusion criteria: ≥65 years, warfarin planned for ≥10 days. Exclusion criteria: warfarin at any time during the previous 6 months, admitted from a nursing home, enrolled in another clinical trial, too ill to give consent and no available surrogate, discharged prematurely, did not speak English; private physician refused to participate; no random allocation was taking place.	Patient self-testing Coumatrak Protime Test System	Usual care, provided by their personal physician	6 months	75 (65-94)	Warfarin 100%
Christensen 2006[83]	Inclusion criteria: oral anticoagulation for ≥ 8 months, > 18 years, and willingness to be randomized. Exclusion criteria: previous use of patient self-management and residence/travel abroad.	Patient self-management CoaguChek S	Usual care, provided in hospital or by a physician	24 weeks	Intervention: 45.5 (13.3) Control: 51.6 (14.0)	Warfarin 70%; phenprocoumon 30%
Claes 2005[84]	Inclusion criteria: Patients treated with oral anticoagulation for at least 28 days (steady state).	General practitioner POC testing CoaguChek	GP usual care; GP bimonthly feedback; GP computer assisted dosing	6 months	70.2 (11.9)	Acenocoumarol 9%, phenprocoumon 85%, warfarin 6%
Cromheecke 2000[85]	Inclusion criteria: Patients on chronic anticoagulant therapy with oral agents	Patient self-management CoaguChek	Anticoagulation clinic	6 months	42 (22-71)	Acenocoumarol 64%; phenprocoumon 36%
Eitz 2008[74]	Inclusion criteria: indication for implantation of mechanical heart valve prostheses in any position, the availability of INR values, and complete information on adverse events.	Patient self-management CoaguChek	Usual care provided by GP	24 months	Intervention 56.4 (11.0) Control 62.4 (7.8)	Warfarin 100%

Fitzmaurice 2002[86]	Inclusion criteria: Patients attending the clinic, > 18 years, anticoagulation treatment ≥6 months, with sufficient vision and manual dexterity to operate a Coaguchek system, and with satisfactory INR control (=INR within 0.5 of the target value for at least 60% of the time in the previous 12 months). From this list, the practice nurse selected patients who would be capable of performing patient self management, following the criteria of previous treatment adherence, physical well being, anxiety, cognitive ability, visual acuity, and ability to follow simple instructions	Patient self-management CoaguChek	Nurse-led POC testing	6 months	Intervention 63.0 Control 69.0	Warfarin 100%
Fitzmaurice 2000[82]	Inclusion criteria: Patients taking warfarin	Nurse-led POC testing Thrombotrak	Usual care provided in hospital	12 months	Not given	Warfarin 100%
Fitzmaurice 2005[88]	Inclusion criteria: Patients ≥18 years, >12 months indication for oral anticoagulation, who had taken warfarin for at least six months with a target INR of 2.5 or 3.5.	Patient self-management CoaguChek S	Hospital or practice based anticoagulant clinics	12 months	65 (18-87)	Warfarin 100%
Gadisseur 2003[73]	Inclusion criteria: Need for long-term OAT, ≥3 months of OAT experience, age between 18-75 years. Exclusion criteria: antiphospholipid syndrome, a life-threatening illness, life expectancy <1 year, diminished understanding, physical limitations making successful implementation impossible	Patient self-testing CoaguChek Patient self-management CoaguChek	Anticoagulation clinic	26 weeks	Intervention 54.8 (25-74) Control 62.0 (32-75) Intervention 53.9 (24-75) Control 62.0 (32-75)	Phenprocoumon 65%, Acenocoumarol 35%
Horstkotte 1998[75]	Inclusion criteria: St. Jude Medical aortic or mitral valve prostheses	Patient self-testing CoaguChek R	Routine care by private physician	Approx 40000 follow-up days	Not stated	Not stated
Khan 2004[78]	Inclusion criteria: Atrial fibrillation with target INR range of 2–3, warfarin ≥12 months, INR SD ≥0.5 over the previous 6 months and aged ≥65 years. Exclusions: general frailty, poor hearing or eyesight, impairment of hand functioncaused by disabling arthritis, stroke or tremor, dementia, or living in institutional care which precluded the use of a coaguchek System, or when the cause of instability of anticoagulation control was apparent and would not be altered by access to the coaguchek System.	Patient self-testing Coaguchek	Anticoagulation clinic	24 weeks	Intervention 75 (65-87) Control group 71 (65-91)	Warfarin 100%

Koertke 2007[72]	Inclusion criteria: Undergone a mechanical aortic, mitral, or double heart valve replacement.	Patient self-management CoaguChek Plus	Usual care by GP	9.3 (2.8) years	70 (28-87)	Phenprocoumon 100%
Menendez-Jandula 2005[89]	Inclusion criteria: Ambulatory patient ≥18 years, anticoagulant therapy ≥3 months before entering the study. Exclusion criteria: severe physical or mental illness without a responsible caregiver, of foreign origin and unable to understand Spanish.	Patient self-management CoaguChek S	Anticoagulation clinic	11.8 months	Intervention: men 64 (13), women 65 (15); Control: men 64 (12), women 67 (11)	Acenocoumarol 100%
Sawicki 1999[87]	Inclusion criteria: disease or condition expected to require life-long anticoagulantion Exclusion criteria: previously treated in these centers	Patient self-management CoaguChek	Usual care by GP or outpatient clinic	6 months	55 (12)	Phenprocoumon 100%
Sidhu 2001[76]	Inclusion criteria: Previously had heart valve operations, life-long anticoagulation therapy with warfarin. Exclusion criteria: >85 years, visual difficulties.	Patient self-management CoaguChek	Usual care by GP or anticoagulation clinic	2 years	Intervention 61 (32-85) Control 60.8 (26-81)	Warfarin 100%
Siebenhofer 2008[90]	Inclusion criteria: Long-term anticoagulation either with phenprocoumon or acenocoumarol and aged ≥60 years. Exclusion criteria: previous participation in a self-management OAC program, severe cognitive impairment (assessed informally by study personnel) or terminal illness.	Patient self-management CoaguChek S	Education and usual care by GP or anticoagulation clinic	2 years	Intervention: 69 (6.1); control 69 (6.4)	Phenprocoumon 91 and 89%; Acencoumarol 9% and 11%
Soliman Hamad 2009[77]	Inclusion criteria: Elective mechanical aortic valve replacement, informed consent, enough knowledge of computers and use of Internet. Exclusion criteria: already using anticoagulants before the operation, chronic bleeding diathesis, chronic liver disease, chronic alcoholism, neurological deficits which interfere with the self-measurement method, severe operative or postoperative complications that can prolong the hospital stay or any other complications that, according to the investigator, can influence the postoperative course.	Patient self-management CoaguChek	Anticoagulation clinic	1 year	Intervention: 55.7 (9.3) Control 56.3 (8.6)	Not stated

Staresinic 2006[91]	Inclusion criteria: ≥18 years, indefinite warfarin therapy, ≥ 3 months of warfarin therapy before the screening visit, and telephone availability. Exclusion criteria: declined or unable to provide written informed consent, planned absences from the state, planned interruptions of warfarin therapy within 2 weeks of study enrollment, no suitable caregiver for participants requiring assistance for cognitive or physical deficiencies, or enrolled in other VA-Madison investigational protocols.	Patient self-testing Device not specified	Anticoagulation clinic	24 months	Intervention 68.2 (10.1) Control 70.4 (8.1)	Warfarin 100%
Sunderji 2004[80]	Inclusion criteria: Planned warfarin therapy for at least 1 year, receiving warfarin at least 1 month before the study, at least 18 years of age. Exclusion criteria: known hypercoagulable disorders, mental incompetence, language barrier, unable to attend training sessions	Patient self-management Pro Time	Routine care by GP	Not stated (8 months according to Heneghan et al.)	Intervention 62.3 (24-85); Control 57.6 (20-79)	Warfarin 100%
Voller 2005[79]	Inclusion criteria: Long-term anticoagulation because of permanent nonvalvular atrial fibrillation. Exclusion criteria: lack of suitability for INR self-management, participation in another study, alcohol or another addiction, a mechanical heart valve replacement or anticoagulant treatment already administered for another indication and diseases such as AIDS or carcinomas.	Patient self-management CoaguChek	Routine care by GP or specialist	2 years	64.3 (9.2)	Not stated

Results on major thrombo-embolism

Overall, 19 studies were available on 6688 patients, with 13 comparisons on patient self-management, five comparisons on patient self-testing, one comparison on GP POC use and one comparison on nurse POC use (one study provided two comparisons). Combining all studies yields a pooled odds ratio of 0.43 (95% CI 0.32, 0.58), with no apparent heterogeneity (I^2 0%). (Figure 3.7)

For patient self-management, the pooled odds ratio is 0.39 (95% CI 0.27, 0.56), again with no apparent heterogeneity (I^2 0%).

For patient self-testing, the pooled odds ratio is 0.54 (95% CI 0.30, 0.97), with no heterogeneity.

One study reported the efficacy of GPs using a POC device, and found no statistically significant difference (OR 0.61; 95% CI 0.20, 1.89).

Likewise, the one study reporting the efficacy of nurses using a POC device found a non-significant odds ratio of 0.33 (95% CI 0.04, 2.77).

A funnel plot was constructed, showing possible asymmetry (Figure 3.8). The Egger's test was statistically significant combining all studies (p=0.003).

Figure 3.7: forest plot on major thrombo-embolism

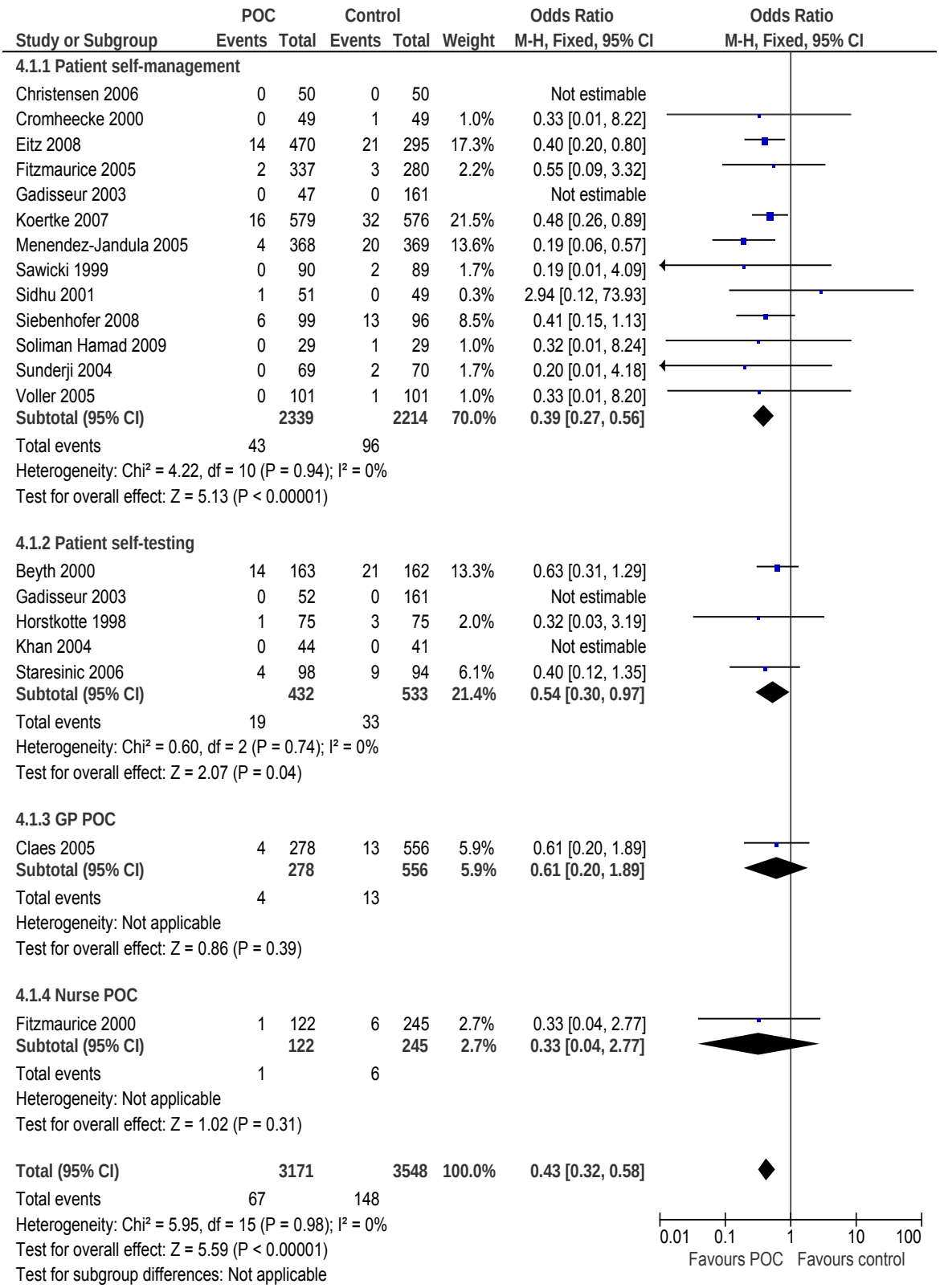
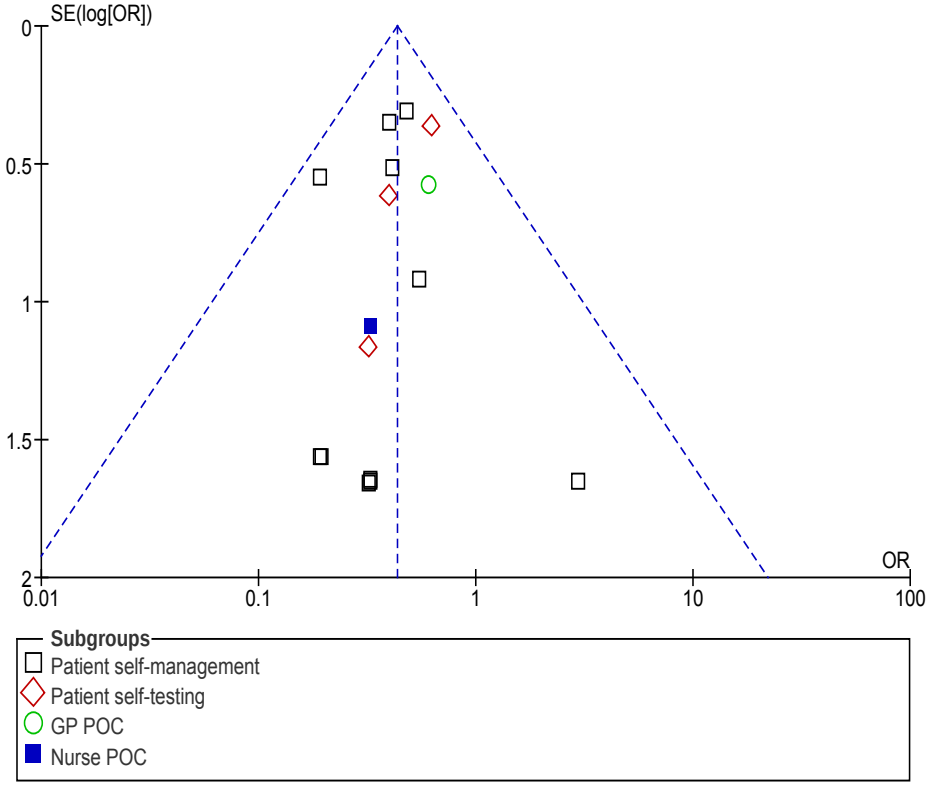


Figure 3.8: funnel plot on major thrombo-embolism



Results on major haemorrhage

Overall, 19 studies were available on 6688 patients, with 13 comparisons on patient self-management, five comparisons on patient self-testing, one comparison on GPs using the POC device and one comparison on nurses using the POC device (one study reported two comparisons). (Figure 3.9)

The pooled odds ratio of all studies is 0.99 (95% CI 0.76, 1.29), with no apparent heterogeneity (I^2 0%).

The subgroup of patient self-management yields a pooled odds ratio of 1.08 (95% CI 0.80, 1.47), the subgroup of patient self-testing 0.60 (95% CI 0.32, 1.13). The study evaluating GP POC use reports an OR of 1.11 (95% CI 0.37, 3.35) and the study evaluating nurse POC use reports an OR of 6.06 (95% CI 0.25, 149.0). No heterogeneity was apparent in any of the subgroups.

The funnel plot does not clearly show asymmetry

Figure 3.10), and the Egger's test for publication bias was not statistically significant (p=0.069).

Figure 3.9: forest plot on major haemorrhage

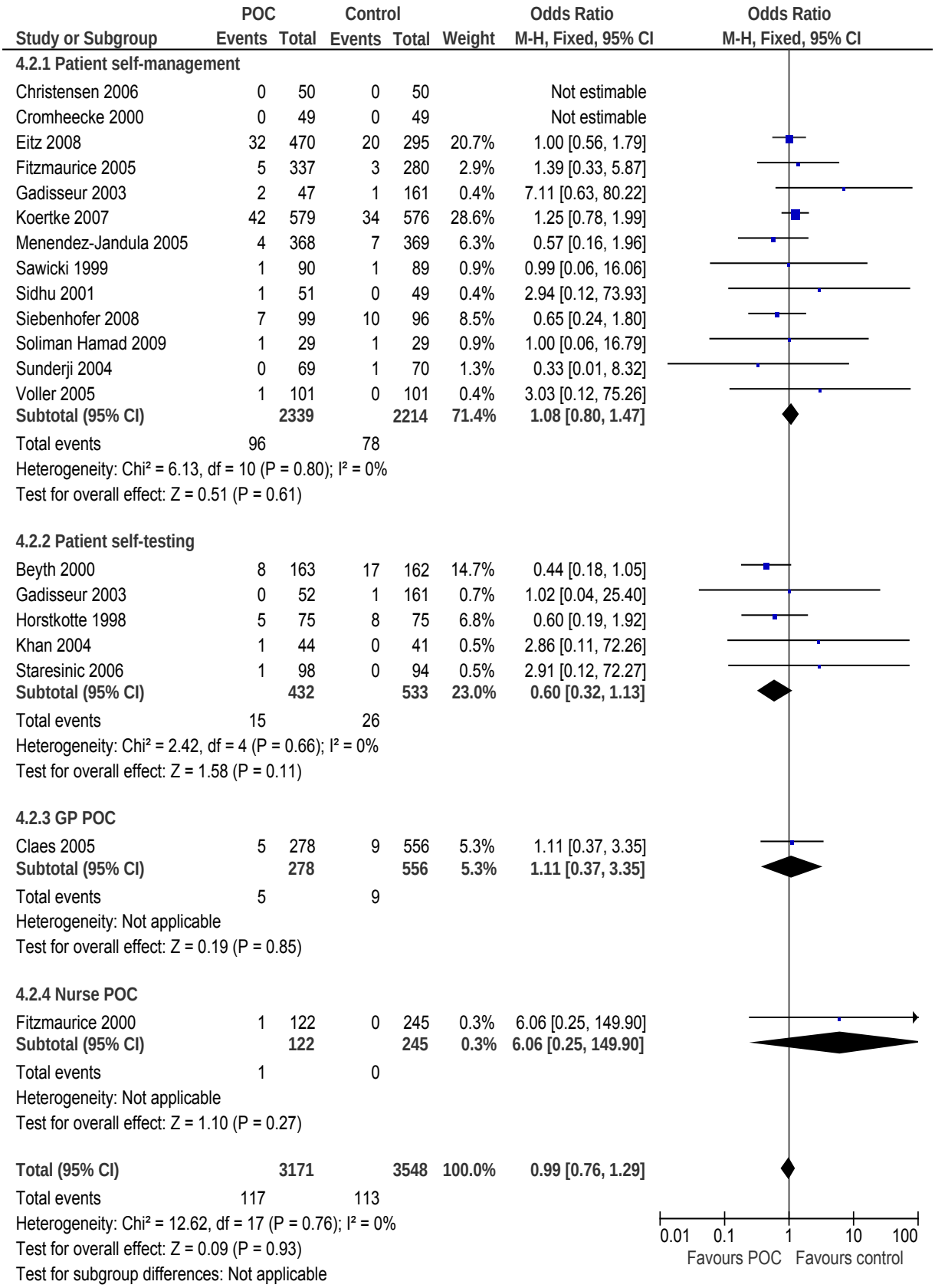
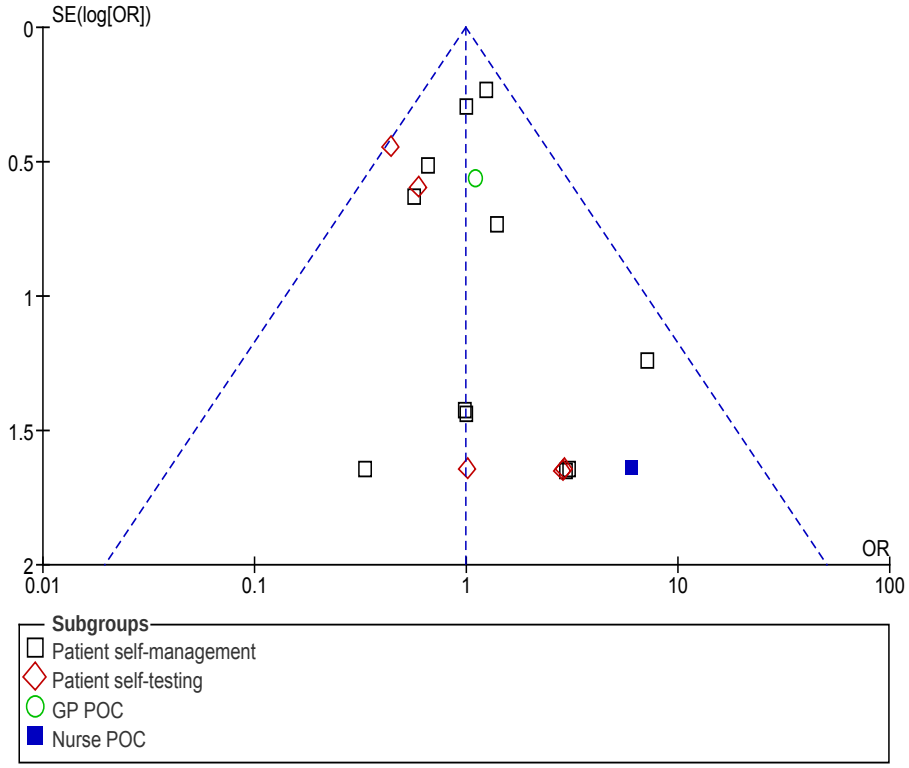


Figure 3.10: funnel plot on major haemorrhage



All cause mortality

Again, 19 studies were available, but reporting data on less patients than the previous outcomes (n=6463), because one study reports long-term follow-up data in which not all patients were included[72].

Overall, the pooled odds ratio is 0.59 (95% CI 0.46, 0.74), with little heterogeneity (I^2 6%). (Figure 3.11) As this does not exceed our predefined threshold of 25%, a fixed effects model was applied.

In the subgroup of patient self-management, the odds ratio is 0.55 (95% CI 0.42, 0.72), with limited heterogeneity (I^2 24%). The results for this subgroup are mainly driven by the study by Koertke et al. (2007), accounting for 79% of the weight of the subgroup and 67% of the weight overall. In this study, patients who had undergone heart valve replacement (mean age 70 years, ranging from 28-87) were followed up for a mean of 9.3 years after randomisation. The randomisation procedure, however, is not clear and allocation concealment is not described. Additionally, the mortality rates in the control group are highly variable: six studies did not report any deaths either in the POC group or the control group, mortality rates in the control group vary between 0.36 and 11.46, the latter the study by Koertke et al.

In the subgroup of patient self-testing, the odds ratio is 0.74 (5% CI 0.41, 1.37). The study on GP POC use did not report any deaths; the study on nurse POC use has an odds ratio of 1.00 (95% CI 0.25, 4.09).

The funnel plot shows possible asymmetry (figure 3.12), and the Egger's test is statistically significant (p=0.001).

Patient self-management versus nurse-led POC

One study reported the comparison of two types of point-of-care testing, being patient self-management with nurse-led POC (Fitzmaurice 2002). In this study, 23 patients were randomised to patient self-management, and 26 to nurse-led POC testing. There were no major haemorrhages reported in either group, by which this outcome is not estimable.

Identical results were obtained for major thrombo-embolism and mortality: no events in the patient self-management group and one event for each outcome in the nurse-led POC group. This yields a non-significant odds ratio of 0.36 (95% CI 0.01, 9.32) for both outcomes.

Figure 3.11: forest plot on all cause mortality

Study or Subgroup	POC Events	POC Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
4.3.1 Patient self-management						
Christensen 2006	0	50	0	50		Not estimable
Cromheecke 2000	0	49	0	49		Not estimable
Eitz 2008	0	470	0	295		Not estimable
Fitzmaurice 2005	2	337	1	280	0.6%	1.67 [0.15, 18.47]
Gadisseur 2003	0	47	0	161		Not estimable
Koertke 2007	94	488	142	442	66.7%	0.50 [0.37, 0.68]
Menendez-Jandula 2005	6	368	15	369	8.2%	0.39 [0.15, 1.02]
Sawicki 1999	1	90	1	89	0.6%	0.99 [0.06, 16.06]
Sidhu 2001	0	51	4	49	2.5%	0.10 [0.01, 1.87]
Siebenhofer 2008	15	99	11	96	5.3%	1.38 [0.60, 3.18]
Soliman Hamad 2009	1	29	1	29	0.5%	1.00 [0.06, 16.79]
Sunderji 2004	0	69	0	70		Not estimable
Voller 2005	0	101	0	101		Not estimable
Subtotal (95% CI)		**2248**		**2080**	**84.4%**	**0.55 [0.42, 0.72]**
Total events	119		175			
Heterogeneity: Chi² = 7.95, df = 6 (P = 0.24); I² = 24%						
Test for overall effect: Z = 4.47 (P < 0.00001)						
4.3.2 Patient self-testing						
Beyth 2000	21	163	26	162	12.6%	0.77 [0.42, 1.44]
Gadisseur 2003	0	52	0	161		Not estimable
Horstkotte 1998	0	75	0	75		Not estimable
Khan 2004	0	44	0	41		Not estimable
Staresinic 2006	0	98	1	94	0.8%	0.32 [0.01, 7.86]
Subtotal (95% CI)		**432**		**533**	**13.4%**	**0.74 [0.41, 1.37]**
Total events	21		27			
Heterogeneity: Chi² = 0.29, df = 1 (P = 0.59); I² = 0%						
Test for overall effect: Z = 0.95 (P = 0.34)						
4.3.3 GP POC						
Claes 2005	0	278	0	556		Not estimable
Subtotal (95% CI)		**278**		**556**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
4.3.4 Nurse POC						
Fitzmaurice 2000	3	122	6	245	2.2%	1.00 [0.25, 4.09]
Subtotal (95% CI)		**122**		**245**	**2.2%**	**1.00 [0.25, 4.09]**
Total events	3		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.01 (P = 1.00)						
Total (95% CI)		**3080**		**3414**	**100.0%**	**0.59 [0.46, 0.74]**
Total events	143		208			
Heterogeneity: Chi² = 9.58, df = 9 (P = 0.39); I² = 6%						
Test for overall effect: Z = 4.41 (P < 0.0001)						

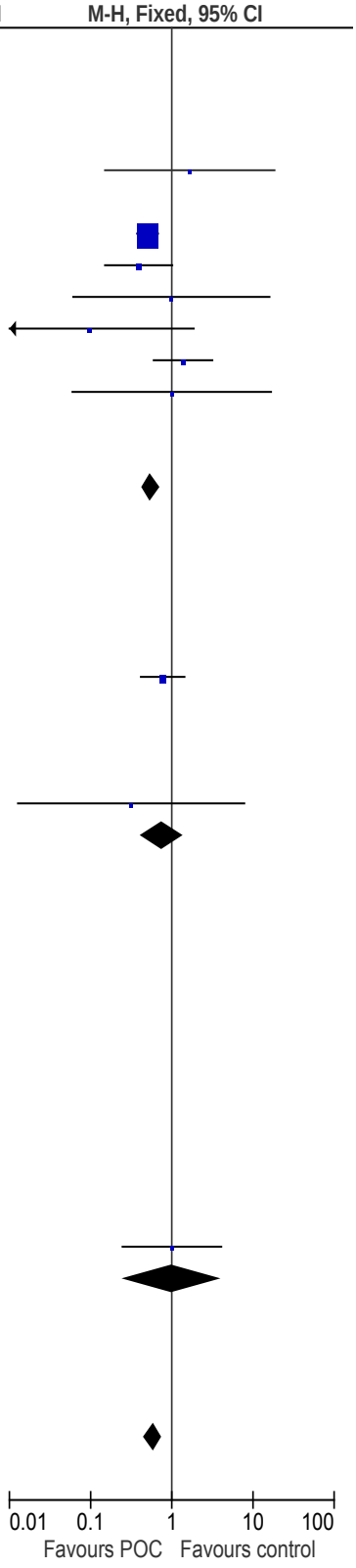
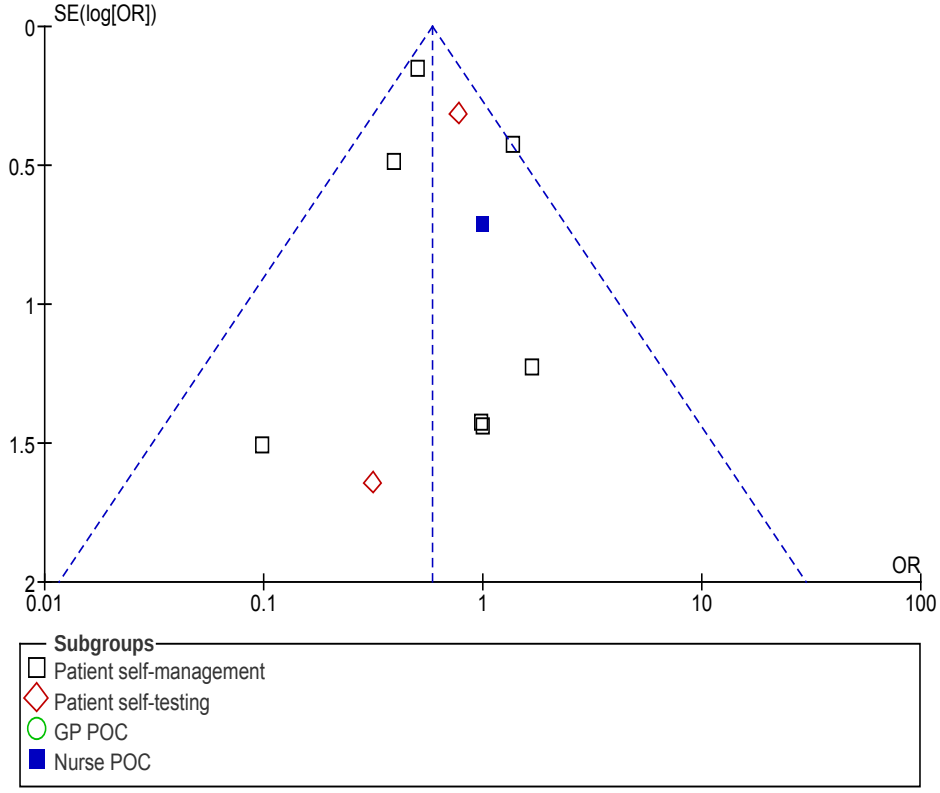


Figure 3.12: funnel plot on all cause mortality



3.5.2.4 *Sensitivity analyses*

Setting of the control group

Setting of the control group was defined as an anticoagulation clinic or general practice. Three studies used a mixed control group: Sawicki[87], Sidhu[76, 90]. Therefore, two metaregressions were performed by placing them in the anticoagulation clinic setting in the first metaregression and in the general practice setting in the second metaregression.

For the outcome of thrombo-embolic events, there was no significant interaction for setting combining all studies (p=0.805 and 0.993) for the two regressions respectively. In addition, no significant interaction was found for the subgroup of patient self-management (p=0.923 and 0.959), or for patient self-testing (p=0.959), for both regressions.

For the outcome major haemorrhages, no significant interaction was found combining all studies (p=0.347 and 0.439) nor for patient self-management (p=0.483 and 0.692), nor for patient self-testing (p=0.374 for both regressions).

For the outcome all cause mortality, no significant interaction was found combining all studies (p=0.315 and 0.243), nor for patient self-management only (p=0.465 and 0.299). For this outcome, metaregression was not possible for patient self-testing as only two studies reported deaths.

Duration of the study

The study duration was used in a metaregression as a continuous outcome. There was no significant effect for any of the three outcomes: major haemorrhage (p=0.490), major thrombo-embolism (p=0.547), all cause mortality (p=0.870).

Frequency of testing

The frequency of INR testing might influence the results, as many studies report higher frequencies in the point-of-care group. The mean number of INR tests in the point-of-care group was 41.1 tests/patient year, ranging from 12.2-89.7/patient year. In the control group, the mean number of tests/patient year was 18.1, ranging from 7.7 to 40.5/patient year (Table 3.8).

The influence of test frequency on the efficacy of POC testing was tested in a metaregression, using the frequency ratio. This ratio was calculated as the mean number of tests per patient year in the intervention group over the mean number of tests per patient year in the control group. The metaregression was not significant for either three of the outcomes: major haemorrhage (p=0.513), major thrombo-embolism (p=0.797) and all cause mortality (p=0.365).

Table 3.8: mean number of INR tests

Study	Intervention group (per patient year)	Control group (per patient year)	Frequency ratio
Beyth 2000	34	21	1.62
Christensen 2006	12.2	13.2	0.92
Claes 2005	20.4	Group 1: 20.4 Group 2: 20.4 Group 3: 19.2	1
Cromheecke 2000	42.4	40.5	1.05
Eitz 2008	41.4	13.6	3.04
Fitzmaurice 2002	29.2	10.6	2.75
Fitzmaurice 2000	Not available	Not available	
Fitzmaurice 2005	29.4	9.6	3.06
Gadisseur 2003a	54.0	20.1	2.69
Gadisseur 2003b	54.1	20.1	2.69
Khan 2004	Not available	Not available	
Koertke 2007	36.1	7.7	4.69
Menendez-Jandula 2005	41.9	12.8	3.27
Sawicki 1999	Not available	Not available	
Sidhu 2001	46.8	12.5	3.74
Siebenhofer 2008	60.5	19.2	3.15
Soliman Hamad 2009	61.0	23.8	2.56
Staresinic 2006	Not available	Not available	
Voller 2005	55.5	19.7	2.82
Horstkotte 1998	89.7	19.7	4.55
Sunderji 2004	41.8	24.8	1.69

3.5.3 Discussion

The results of this meta-analysis show that point-of-care testing leads to less thrombo-embolic events and deaths, and has no impact on the number of major bleeding events. Applying the main results to a median risk population, this corresponds to 13/1000 less thrombo-embolic events, and 1/1000 less deaths (Table 3.9). Sensitivity analyses did not show a significant effect of the setting of the control group, duration of the study or the ratio of frequency of testing.

However, the quality of the underlying evidence is moderate, as many studies do not provide information on the concealment of allocation or blinding of the outcome assessors. In addition, many studies were relatively small reporting only a few events. In total, 170 thrombo-embolic events, 154 events of major bleeding and 351 deaths were reported in both intervention and control groups.

Thirteen studies reported null event in either the intervention or control group for at least one of the three outcomes. Furthermore, we found evidence of possible publication bias, although this may also be caused by the large number of small studies included in the meta-analyses.

Most studies compared patient self-management to usual care in anticoagulation clinics or in general practice. Fewer studies evaluated patient self-testing and only one study was available on GP point-of-care testing and nurse-led point-of-care testing respectively. For the latter, outcomes were non-significant. For patient self-testing, only the odds ratio on thrombo-embolic events was significant.

- **Point-of-care testing leads to less thrombo-embolic events (pooled odds ratio 0.43; 95% CI 0.32, 0.58) and less all cause mortality (pooled odds ratio 0.59; 95% CI 0.46, 0.74), and has no impact on the number of major bleeding events.**
- **Applying the main results to a median risk population, this corresponds to 13/1000 less thrombo-embolic events, and 1/1000 less deaths.**
- **Sensitivity analyses did not show a significant effect of the setting of the control group, duration of the study or the ratio of frequency of testing.**
- **For patient self-management, the pooled odds ratio is 0.39 (95% CI 0.27, 0.56) in favour of a reduction of thrombo-embolics events and 0.55 (95% CI 0.42, 0.72) for all cause mortality.**
- **For patient self-testing, the pooled odds ratio is 0.54 (95% CI 0.30, 0.97) in favour of a reduction of thrombo-embolics events and is not significant for all cause mortality.**
- **No significant difference was found for GP and nurses using POC devices, but only one study was available for each of these comparisons.**
- **There is some evidence of publication bias.**

Table 3.9: summary of findings table

Outcomes	Assumed risk Control group1	Corresponding risk point-of-care testing (95% CI)	Relative risk (95% CI)	Quality of the evidence
Major thrombo-embolic event	24 per 1000	11 per 1000 (8-14)	0.45 (0.34-0.60)	●●●○ Moderate[2]
Major haemorrhage	11 per 1000	11 per 1000 (8-14)	0.99 (0.77-1.27)	●●●○ Moderate[2]
All cause mortality	2 per 1000	1 per 1000 (1-2)	0.65 (0.54-0.79)	●●●○ Moderate[2]

1 Assumed risk control group based on median risk of all control groups in meta-analysis; [2] Quality of evidence moderate because of flaws in design: absence of information on concealment of allocation and blinding, few number of events and possible publication bias; CI: confidence interval

Quality of evidence based on the categories of the GRADE Working Group grades of evidence:

●●●● High quality: further research is very unlikely to change our confidence in the estimate of effect

●●●○ Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

●●○○ Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

●○○○ Very low quality: we are very uncertain about the estimate.

4 PATIENT ISSUES

The objective of this chapter is to define, from the available literature, the needs and preferences of patients with respect to POC monitoring of OAT.

4.1 METHODS

4.1.1 Research question

The search question was formulated as follows:

What are the needs and preferences of OAT patients with respect to patient information, compliance, obstacles and fears related to the use of the POC technology?

The PICO was defined as follows:

- Patients: patients treated with chronic oral anticoagulation
- Intervention: POC
- Comparison: standard management (laboratory) or previous situation
- 0utcome: needs, preferences, fears, satisfaction, training, education, obstacles, compliance.

4.1.2 Search strategy

Three databases were searched (Medline, Embase and Psychinfo) as described in table 4.1.

Table 4.1. Description of the search strategy for patients' issues.

Date	Database	Search	Final nbr of retrieved articles
10/3/09	Medline	Database: Ovid MEDLINE(R) 1950 to Present with Daily Update Search Strategy: 1 Anticoagulants/ (39167) 2 Point-of-Care Systems/ (3694) 3 coagucheck.mp. (19) 4 Protime.mp. (33) 5 INRatio.mp. (5) 6 consumer satisfaction/ or patient satisfaction/ (53381) 7 Fear/ (16293) 8 "Quality of Life"/ (72759) 9 Patient Education as Topic/ (54279) 10 Patient Compliance/ (35890) 11 4 or 3 or 2 or 5 (3728) 12 8 or 6 or 7 or 10 or 9 (216709) 13 11 and 1 and 12 (16)	16
10/3/09	Embase	1. 'anticoagulant therapy'/mj AND 'point of care testing '/mj (5) 2. coagucheck (39) 3. protime (67) 4. inratio (17) 5. #1 OR #2 OR #3 OR #4 (111) 6. 'patient satisfaction'/de (52,644) 7. 'fear'/de (20,225) 8. 'quality of life'/de (123,838) 9. 'patient education'/de (62,591) 10. 'patient compliance'/de (60,464) 11. #6 OR #7 OR #8 OR #9 OR #10 (296,850) 12. #5 AND #11 (16)	16

10/3/09	Psychinfo	Database: PsycINFO <1806 to March Week 1 2009> Search Strategy: 1 anticoagulant drugs/ (73) 2 exp "Quality of Life"/ (15490) 3 exp Client Satisfaction/ (2738) 4 exp Fear/ (11689) 5 exp Client Education/ (2351) 6 exp Client Attitudes/ or exp Treatment Compliance/ (19433) 7 6 or 4 or 3 or 2 or 5 (47698) 8 1 and 7 (10)	10

4.1.3 Inclusion criteria

Studies were included

1. if patients were treated with OAT and managed with POC devices for dosing INR and
2. if the outcomes were patients' issues such as needs, preferences, fears, quality of life, impact of training, education, obstacles, compliance, capacity.

Publications such as letters, reviews and studies without inclusion of patients were excluded.

4.1.4 Critical assessment

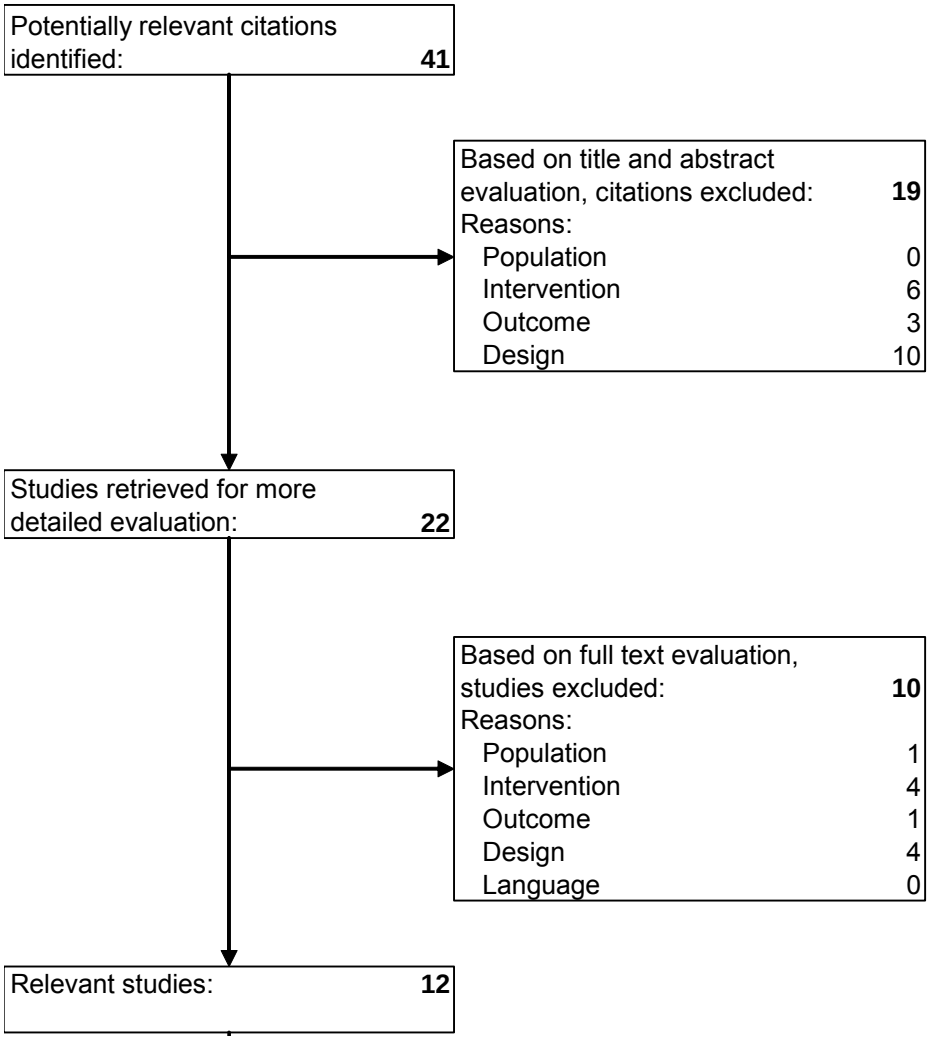
Checklists of the Dutch Cochrane, in relation with the corresponding study (RCT, case control, observational), were used.

4.2 RESULTS

4.2.1 Literature search

After discarding duplicates, 41 publications remained. Finally, twelve publications were selected (see figure 4.1).

Figure 4.1: Studies selection for patients' issues



4.2.2 Characteristics of the studies

All 12 primary studies showed quantitative results. Several types of design were found:

- Two publications were randomized controlled trials, one with single blinding for the evaluator[87] and the other without blinding[92].
- One was a case control study[23].
- Six studies were evaluations or questionnaires before and after one intervention[93 94 95 96 97 98].
- Three studies were descriptive trials without control [27 99 100]. In two cases [27 99], the questionnaire was included in a RCT, testing only the population of the intervention group.

None study was excluded based on quality assessment score. Table 4.2 provides details about critical appraisal and a summary of the included studies. The HTA reports previously described in the section about clinical efficacy [7 9 66] were also considered.

4.2.3 Patient satisfaction

Each study showed an overall satisfaction of the patient in favour of POC testing [94 95 27 87 92]. Evaluation of pain was also in favour of POC testing. PSM reduced distress and perceived daily hassles. Most patients (87%) are confident in the result that they obtained by PST [27]. Time spent in therapeutic range is as good in home management by family for children [93] or PSM for adults [23] as in hospital management, and even better [96]. Moreover, as seen in the meta-analysis in chapter 3, the clinical impact on patient outcomes is improved.

4.2.4 Selection of patients for patient self-management or self-testing

The selection criteria in trials resulted in the exclusion of many patients before randomization and many patients did not complete training. Pooling data from all trials suggested that, on average, 33% of patients agreed to participate in the trials; 80% of patients randomised to PSM were successfully trained and/or able to conduct self monitoring, and 87% of those who started PSM continue to the end of the study. The population able to conduct PSM in UK was estimated at 14% [66]. Brown et al. estimated the self testing and self monitoring capacity was 24% of patients (Canada) [7].

Criteria to select patients include personal willingness, capacity of self testing and capacity to complete and succeed the training for self management. In the HTA by Brown, if self testing is considered, informed decision needs to be made at the individual health provider and patient level to ensure that appropriate candidates are selected: a willingness to learn, the incentive to perform the test as required, adequate motor skills, adequate eyesight to see the screen, or a willing caregiver who will take the responsibility for monitoring. Patients must then be educated about anticoagulation and be trained in the use of the monitor. A testing schedule can be given to the patient for recording results. Instructions can be reinforced at follow-up visits, with an opportunity for the patient to ask questions and express concerns [7].

4.2.5 Patient training

All studies about PST or PSM required that patients included take part in training.

One study described the training for PST [100]. An education program with an average of 3.5 sessions of 20 minutes was necessary to obtain the manual ability in patients hospitalized after mechanical heart valve replacement, followed by one month of close monitoring by a professional. This program was done in addition to the standard anticoagulation education provided to all patients. Most patients (84%) scheduled for PST initially have some difficulties to obtain an adequate sample, but subsequently it became easier.

The training for PSM is described in 3 studies [87 99 98]. The structured programme consists of several teaching sessions (3 weekly sessions of 90 minutes) in small groups (3 to 6 patients) with practical exercises and problem solving. Nurses and physicians were trained beforehand to ensure standards and consistency.

The content of the training included the following items: instructions to prevent bleeding and thromboembolic complications; the effect of diet and additional medication on anticoagulation control; examples of adapting drug dosage; possible problems that might be encountered with operations, illness, exercise, pregnancy, and travelling.

Finally, the aptitude of the patient to perform PSM is tested by a professional. In the study by Sawicki, the quality of INR value self-monitoring was checked by the training nurse at the end of the first and at the beginning of session two and three. The patients had to estimate their INR value with an absolute deviation of less than 0.4 from the reference value. If they failed, the training was repeated [87]. Völler showed that there were significant improvements in knowledge post training ($p<0.001$) and in retention of the acquired information (p=NS vs. post-training; N=45) after 6 months. The INR results were equivalent to professional operators (r=0.92) with little or no bias across all clinic visits. Compliance with weekly testing, which was an objective of the training, improved from the first month to the third months ($p = 0.03$), and remained at the required weekly frequency through 6 months [98]. Murray specified that patients should be able to the following in order to be selected for self management: accurately perform an INR test (by using the point of care system), management of quality control issues, use of algorithm and adjustment of dosage, and document INR results and adverse events. In the study evaluating the ability to realize self management, 26% (85/327) of patients did not complete training. Among these, 79% were excluded because they had difficulties with the manual act of POC testing. The remaining 21% were excluded because they could not accurately realize an INR or adjust the dose. Patients who completed training were younger (61 v 71 years, P = 0001) and had a higher than average education level ($P = 0.003$) [99].

4.3 DISCUSSION

Despite the absence of conflict between results about patient satisfaction, limits may be present. Scores about needs and preferences were measured with different tools, often poorly described. Only two studies included really a comparative group and blinding was only present in one study, for the evaluation.

The evidence supporting this section is low. Methodological biases are not yet excluded about patient selection and training, with respect to the design of included studies.

- **Overall satisfaction, pain and distress are in favour of POC. Scores were, however, measured with different tools, often poorly described.**
- **Criteria to select candidates for POC devices include personal willingness; physical capacity of self testing, and capacity to complete and succeed training.**
- **Structured training programmes include the performance of POC INR tests, instructions to prevent bleeding and thromboembolic complications; effect of diet and additional medication on anticoagulation control; examples of adapting drug dosage; possible problems that might be encountered with operations, illness, exercise, pregnancy, and travelling.**
- **The percentage of patients able to carry out PST or PSM has been estimated at 14 and 24 %.**

Table 4.2: Description of the studies selected for patients' issues.

Reference	Population	Interventions in the study	Comparison used for patients issues	Methods and results	Critical appraisal
Bradbury 2008[93] UK	37 children	POC at home management by family	Previous hospital management	Time spent in therapeutic range Hospital monitoring: median 70.0 (inter-quartile range 34.5) Home monitoring: median 75.0 (inter-quartile range 44.5). 2.3 tests with INR > 6.0 (no statistical differences)	Randomisation: no Comparative: same group before/ after Blinding no Selection described Intervention described Retrospective assessment
Chaudry 2004[94] USA	216 patients Mayo clinic	Nurse managed POC INR system and face to face counseling	Previous traditional venipuncture and telephone follow up	Satisfaction due to POC Questionnaire (87% responses: n=187): 79% overall satisfaction ($p < 0.001$) (time spent, pain, time to receive results) Questionnaire not available in the publication	Randomisation: no Comparative: same group before/ after Blinding no Selection poorly described Intervention poorly described prospective
Cosmi 2000[23] Italy	78 patients in each group	Self management 3 instruction sessions	Previous antico clinic	Time spent in therapeutic range Equal in the 2 groups (80%)	Case control study Randomisation: no Comparative groups: similar Blinding no Selection clearly described Intervention clearly described prospective
Gadisseur 2004[95] Netherlands Belgium	Population within a RCT Routine care PST PSM	Management and education program after 26 weeks: 118 responses	At baseline (usual care): 163 responses	General treatment satisfaction: High under routine care (5.11 on a scale of 1–6); PST increased (+0.19) and PSM (+0.32). PSM: reduced distress (-0.44), perceived daily hassles (-0.31) strain on the social network (-0.21).	Randomisation: no Comparative: same group before/ after Blinding no Selection clearly described Intervention clearly

Reference	Population	Interventions in the study	Comparison used for patients issues	Methods and results	Critical appraisal
				Education: increased distress (+0.33) and perceived daily hassles (+0.23). Similar for PST, PSM and routine care.	described Prospective
Gardiner 2004[27] UK	44 patients included in one RCT	After 3 month PST (31 questionnaires completed):	No comparison	Acceptability of PST 84% initially difficult to obtain an adequate sample, but subsequently very easy (55%) of the 84% or quite easy (32%). One patient found the CoaguChek S difficult to use. Most patients (87%) confident in the result that they obtained. Most (77%) preferred self-testing. None of the patients experienced difficulty using the internal QC procedure.	RCT study that included observational part about quality of life Prospective design Single group considered Questionnaire not available in the publication
Murray 2004[99] UK	327 patients included in a RCT	PSM group and training (at least 2 sessions)	No comparison	Acceptability of PSM and training Between unselected patients, 26% (85/327) did not complete training. 79% excluded themselves for manual difficulty with the procedure and 21% for incapacity of accurately realized an INR and adjust the dose. Patients who completed training were younger (61 v 71 years, P = 0001) and educated above standard (P = 0.003).	RCT study that included observational part about quality of life Prospective design Single group considered Questionnaire not available in the publication
O'Shea 2008[96] USA	60 patients	Internet-PSM with daily review by the supervising physician	Previous anticoagulation clinic	Mean time in therapeutic range: Increased from 63% (antico) to 74.4% (Internet) Mean difference: 11.4% (P = 0.004, 95% confidence interval 5.5–17.3%).	Randomisation: no Comparative: same group before/ after Blinding no Selection clearly described Intervention clearly described Prospective
Sawicki	179 patients in 5	Structured	Conventional	Satisfaction at baseline and at 6-month follow-	Randomisation: yes

Reference	Population	Interventions in the study	Comparison used for patients issues	Methods and results	Critical appraisal
1999[87] Germany	referral centers	treatment and teaching programme PSM	care (family physician including referral to specialists)	up. General treatment satisfaction: PSM: +1.54 (SD 1.38) Routine care: +0.24 (1.48) p<0.001) Daily hassles: PSM + 0.83 (0.92) Routine care: +0.35 (0.96) p=0.003. Scores of self-efficacy and distress improved in both group. No significant effect on the strained social network scores.	Blinding inclusion: no Patient blind: no Evaluator blind: yes Similar groups: yes % follow up: yes Intention to treat analysis: yes Similar cointervention?
Thompson 2008[100] USA	55 patients after mechanical heart valve implantation	Self testing Education program (average of 3.5 sessions of 20 minutes) + 1 month monitoring	No comparison	Capacity of self test testing 5 refused to be included All 50 patients (but 1) were able to self test (98%)	observational Randomisation: no Comparative: no Blinding no Selection clearly described Intervention clearly described Prospective
Völler 2004[97] Germany	76 patients who started OAC	PSM Structured education program for 2 days (T1, T2)	Prior to start (T0) T3 = 6 weeks after training	Knowledge test: 74/76 patients gave at least 50% correct answers at T3 (97.4% IC95%: 90.8-99.7%) Average rates of correct answers: from 40% (T0) to 96% (T3). All patients reported less fear of complications an less limitations in their daily life	Randomisation: no Comparative: same group before/ after Blinding no Selection poorly described Intervention poorly described prospective
Völler 2007[98] Germany	107 patients	Training programme PSM	Before to 6 months after training	Significant improvements in knowledge post training (p<0.001) and in retention of acquired information (p=NS vs. post-training; N=45) after 6 months. Equivalent INR results to professional operators (r=0.92) with little or no bias across all clinic visits.	Randomisation: no Comparative: same group before/ after Blinding no Selection clearly described Intervention clearly described

Reference	Population	Interventions in the study	Comparison used for patients issues	Methods and results	Critical appraisal
				Compliance with weekly testing improved from1 to 3 months (p = 0.03), remaining at the required weekly frequency through 6 months. Average patient satisfaction improved significantly during the first month and remained constant thereafter. Statistically significant improvement in the Physical Component Summary of SF12.	Prospective
Woods 2004[92] Canada	60 patients	POC	Venous INR	Using a 10-point visual analogue scale: Patient satisfaction very strong for POC(1.64 vs. 4.45; P < 0.001) Pain results in favor of POC (0.83 vs. 2.23; P V 0.004). Patients spent, on average, 33 fewer minutes in the clinic with POC (P < 0.001).	Randomisation: yes Blinding inclusion: no Patient blind: no Evaluator blind: no Similar groups: yes % follow up: yes Intention to treat analysis: yes Similar cointervention?

5 CARE ORGANISATION IN BELGIUM AND IN EUROPEAN COUNTRIES

5.1 INTRODUCTION AND METHODS

The purpose of this chapter is to compare management schemes to monitor patients on long term anticoagulation therapy among European Countries. We focus on the description of usual care for each country, on reimbursement conditions for POC systems, and on training and quality control aspects. We are also interested in which trademark is most present in European country. Belgian practices are compared to neighbouring or Dutch and French speaking European countries, i.e. France, the Netherlands, Germany, Luxembourg, United Kingdom (UK) and Switzerland. Information came from the following sources:

- National official websites related to health care and personal contacts
- Specialized literature
- Websites specific to long term anticoagulation therapy and personal contacts (e.g. anticoagulation clinics or patients' associations websites)
- POC device manufacturers' websites and personal contacts (Roche diagnostics)

When sources were contradictory, we only selected the most reliable (i.e. official sources) and most recent information. Our results were then compared with information provided by the companies who are active in this sector to cross-check our findings.

5.2 BELGIUM

5.2.1 Usual care

In Belgium, most patients on long term anticoagulation therapy are currently managed by their general practitioner, with blood testing in laboratory (see clinical pathway). Recently, a few number anticoagulation clinics have been created. These clinics carry out the follow-up of patients on anticoagulation therapy. With respect to clinical advantage in patients with specific conditions (child, congenital cardiology), some health care units have furnished a POC device for self management to some patients waiting for Belgian reimbursment conditions.

To discuss the quality of the current management of anticoagulation in Belgium and the training of health professionals is out of the scope of this report. Some initiatives to improve global quality are currently in progress. For example, a guideline about "Aanbeveling orale anticoagulantietherapie door de huisarts", based on an evidence based medecine methodology, is to be published and implemented by Domus Medica. This guideline should be later translated and implemented by the Société Scientifique de Médecine Générale (SSMG) for the french-speaking GP.

5.2.2 The use of POC systems and reimbursement conditions

Currently, neither the POC devices nor the consumables (test strips, lancets, etc.) associated with POC testing are reimbursed by the Belgian National Institute for Health and Disability Insurance (NIHDI). This applies to the GPs, the patients and the clinics using the device.

5.2.3 Patient training and quality control

No formal guidelines for quality control of POC devices or patient training exist in Belgium. Some Belgian anticoagulation clinics provide patient training about anticoagulation. Moreover, patients have the possibility to follow a course organized by the patient association Vibast/Girtac. This course focuses more on precautions and lifestyle for patients on long term anticoagulation therapy than on the use of POC devices itself.[101]

5.3 UNITED KINGDOM

5.3.1 The NHS system

In the UK, every legal resident is covered by the National Health Service (NHS). Health services are provided by local NHS organizations and have two levels, i.e. primary care and secondary care.

Primary care consists of everyday health services delivered by general practitioners, dentists or opticians, and are managed by Primary Care Trusts (PCTs)[a]. PCTs control 80% of the NHS budget. They are responsible for the efficiency of health care in their area and for decisions on the provision of health care services. Choices are based on guidelines provided by other national organizations such as the National Institute for Clinical Excellence (NICE) or the Department of Health. PCTs also have a major role in commissioning secondary care. Secondary care consists of acute health care regrouping both emergency care and elective care, i.e. planned specialist medical care or surgery.[102]

5.3.2 Usual care and NICE guidelines

The international self-monitoring association of oral anticoagulated patients (ISMAAP) estimated that more than 1 000 000 patients are currently on long term oral anticoagulation therapy in the UK.[6] In the past, monitoring was traditionally done in hospitals with blood laboratory testing. However, an increase in the indications (e.g. inclusion of patients with atrial fibrillation) and thus of the number of patients on long term anticoagulation therapy implied the development of alternative models such as primary care-based clinics. To help PCTs to reduce the demand on secondary care, enhanced services for anticoagulation monitoring were created. The requirements for an anticoagulation service are specified within the General Medical Services contract, of which a description is publicly available on the website of the National Department of Health.[103] The objective was to increase the number of local services to meet local need, to improve patient convenience and choices, and to ensure value for money.[103]

In these clinics, blood samples are either sent to a laboratory for testing, or the testing is done directly by means of the POC system. The management of patients in these clinics will depend on the decision of the local PCT. With laboratory testing there is a delay between the blood sampling and the availability of the results. In this case, results are usually written in a national record booklet which is sent to the patient by post.[104, 105]

An international study estimated that in the UK, 80% of patients on long term anticoagulation therapy were managed in anticoagulation clinics.[106]

5.3.3 The use of POC systems and reimbursement conditions

Since 2005, the Department of Health promotes strategies based on patient choice and patient self-care and developed the idea that treatment and care should take into account patients' individual needs and preferences. According to this philosophy, it is stated that patients with indications for long term (> 1 year) anticoagulation therapy should be considered for patient self-management.[107] Besides this, NICE provided in 2006 new national guidance for patients on atrial fibrillation. In this guidance, they recommended that patients on long term anticoagulation therapy for atrial fibrillation should have access to patient self-management if they prefer and if the following conditions are met:[108]

- The patient has the physical and cognitive capacities to perform the self-monitoring test, or if not, a designated carer is able to do it;
- The patient and/or the carer follows a training programme;
- The patient's ability is regularly reviewed;
- The equipment is regularly checked by a quality control programme.

[a] PCT are responsible for funding healthcare products and services in England. Corresponding organizations in other regions of the UK are Local Health Boards (LHB) in Wales, Area Health Boards (AHB) in Scotland, and Health and Social Services (HSS) Boards in Northern Ireland. For simplicity, these organizations are often referred to as "PCT" in the literature.

More detailed guidelines developed by the British Society of Haematology Taskforce for haemostasis and Thrombosis can be found in an article by Fitzmaurice *et al*.[53]

Two POC systems received satisfactory evaluations by the UK Medicines and Healthcare Products Regulatory Agency (MHRA) Coagulation Evaluation Centre, i.e. the CoaguChek and ProTime.[53] Other devices are under evaluation.

Currently, the device is not included in the basic health care package and is at the patient charge in UK. Concerning test strips, the decision depends on the local PCT. Even if the Department of Health encourages the delivery of test trips, they are not provided by every PCT and their costs fall sometimes to the patient charge.[109] According to Roche Diagnostic, no more than 24 test strips per year are reimbursed.

5.3.4 Patient training and quality control

Training is recommended in NICE guidelines but no official rules determine how training should be carried out. NICE only suggested two sessions of three hours to cover both theoretical and practical aspects of self-management.[104] There are also no formal rules on how quality control for self-management strategies should be carried out. As a suggestion, the example of Germany is often cited.[53, 104]

5.4 GERMANY

5.4.1 Usual care

According to the ISMAAP, 600 000 patients are currently on long term anticoagulation therapy in Germany.[6] In this country, patients on long term anticoagulation therapy are usually managed by general practitioners with standard laboratory testing. Once the general practitioner receives the results, he contacts the patient and adapts his therapy if necessary.[110]

5.4.2 The use of POC systems and reimbursement conditions

In Germany, self-management of anticoagulation therapy exists since 1987. Consequently, a high number of patients manage their anticoagulation therapy by themselves (PSM or PST) in this country. For patients on lifelong anticoagulation therapy which have adequate physical and cognitive capacity to self-manage their therapy, both the devices and test strips are usually reimbursed by the health insurances.[111] ISMAAP identified major conditions for which devices and test strips were usually reimbursed by health insurances in Germany:[6]

- "Patients wit mechanical heart valve replacement;
- Children on anticoagulation;
- Patients on lifelong anticoagulation because of atrial fibrillation, recurrent thromboembolism etc. and at least one of the following indications;
    - Difficult peripheral veins;
    - Complications during treatment with a vitamin-k-antagonist like bleeding or thromboembolism;
    - Inability to get to the general practitioner because of immobility."
    - Two kinds of devices can be reimbursed by the health insurances, i.e. CoaguChek and INRatio. The CoaguChek seems to be the most used device.[110, 112] The Association of Self Management (Arbeitsgemeinschaft Selbstkontrolle der Antikoagulation e.V. = ASA) advises to perform one test a week (or more frequently in some situation such as with the concomitant use of other medicines with a possible interaction).[112]

5.4.3 Patient training and quality control

Nationally approved, formalized training programs are organized by the ASA. They organize seminars to train doctors or nurses who will train their patients. They also train patients directly. Both theoretical and practical aspects of anticoagulation are investigated in the sessions. A complete description of the training can be found on the ASA website (http://www.asaev.de/). The training is usually funded totally or partially by the health insurers. Quality controls are usually managed by the GP and are mandatory.[112] No official information on the frequency of quality control was found but the study by Taborski *et al*,[110] estimated that four quality controls were performed per year by sending blood sample in laboratory.

5.5 THE NETHERLANDS

5.5.1 Usual care

ISMAAP estimated that about 140.000 patients were currently on long term anticoagulation therapy in the Netherlands.[6] Each of these patients is managed in a structured thrombotic service, called "*Trombosediensten*".

In the Netherlands, health care is financed by a mix of public and private health insurance, and health policy decisions are taken by the ministry of Health (i.e. Ministerie van Volksgezondheid, Welzijn en Sport (VWS)).

Trombosediensten are included in the basic health care package covered by the public health insurance.[113, 114] A list of *Trombosediensten* can be found on internet (http://www.fnt.nl/patienten/trombosediensten).

5.5.2 The use of POC systems and reimbursement conditions

An increasing demand of patients for self-management implied the question of reimbursement of POC systems in the Netherlands. Consequently, the ministry of Health accepted to consider self-management for reimbursement, especially for young patients under long term anticoagulation therapy. Patient selection for self management therapies is the responsibility of the *Trombosediensten*. They are also responsible for the provision of POC devices, consumables (test strips), training and quality controls. All of this is covered by the public health insurance.[6, 113, 114] It seems that CoaguChek is the most frequently used device in the Netherlands.[6, 113, 114]

5.5.3 Patient training and quality control

Patient training and quality controls are organized and financed by the *Trombosediensten*. Training for self-testing usually consists of four sessions of two hours. Patients are then followed during a 3 month period. They usually perform a test each week and send the results to a *Trombosedienst* which controls and adapts the therapy. After three months, patients have the possibility to follow training for self-management. Then, they usually perform a test one time every two weeks and they log the results in a logbook. They are controlled by the trombosediensten every 3-5 months.[6, 113, 114] According to Roche Diagnostics, an amount of €250 per year is forseen for test strips (= +/- 45 tests per year).

5.6 SWITZERLAND

5.6.1 Usual care

According to the ISMAAP, 50 000 patients are currently on long term anticoagulation therapy in Switzerland.[6] These patients are usually managed by their general practitioner using POC systems (source: personal contact with *CoagulationCare*) or with blood testing in the laboratory.[115]

5.6.2 The use of POC systems and reimbursement conditions

Since 1998, patients have the possibility to manage their anticoagulation therapy by themselves. In Switzerland, a list of medical devices included in the basic coverage of health insurers (i.e. the "liste des moyens et appareils (LIMA)") has been created. However, POC systems are not included in the list. The reimbursement is thus not mandatory but health insurers usually accept to cover part of the costs, for a range between 50 to 90%. Depending on the health insurer, this coverage includes either everything, only the POC device or only the consumables.[115] Moreover, a specific foundation in charge of patient training has been created, i.e. the *CoagulationCare* foundation. This foundation is sponsored by pharmaceutical companies, including Roche Diagnostics. POC system used during the training is the CoaguChek. To obtain reimbursement, patients must be trained by this foundation.[115]

5.6.3 Patient training and quality control

A one day training about the theoretical and practical aspects of anticoagulation therapy similar to the German training of the ASA is managed by the *CoagulationCare* foundation. The training is provided for free to the patients. These trainings are organized in four cities, i.e. Lucerne, Berne, Olten and Zurich. The general practitioner stays the privileged contact during and after the training.

No formal rules on the frequency of quality controls exist in Switzerland (sources: personal contact with *CoagulationCare*).

5.7 GRAND DUCHY OF LUXEMBOURG

5.7.1 Usual care

Patients are traditionally followed by the general practitioner in Luxembourg. In 2001 the "Centre Hospitalier de Luxembourg" set up an anticoagulation clinic. The objective was to improve the follow-up, the training, the compliance and the patient involvement. A full-time nurse has been attributed to the anticoagulation clinic. In this clinic, a test is usually performed one time every two weeks except if the INR becomes unstable.[116]

5.7.2 The use of POC systems and reimbursement conditions

Since 2002 the use of POC systems is reimbursed for patients on long term anticoagulation therapy with adequate physical and cognitive capacity to self-manage their therapy. To obtain a reimbursement, the prescribing physician must certify that the patient or the carer succeeded training and is able to manage correctly the device. He is also responsible for the patient follow-up. The device is wholly reimbursed and can be renewed every 5 years. Test strips are also reimbursed (12 tests/year). The anticoagulation clinic analyzed the consumption of test strips and estimated that on average patients performed about 1 test per week.[117] However, only one test per month is reimbursed (sources: Roche Diagnostics).

5.7.3 Patient training and quality control

The anticoagulation clinic organizes patient training about the use of CoaguChek in 4 sessions. After the training, the anticoagulation clinic evaluates the patient knowledge and provides them a certificate. After the training, the follow-up and control of the patient is usually done by the prescribing physician.[116, 117] No formal rule for quality controls were found in the statute of the national health institute.[117]

5.8 FRANCE

5.8.1 Usual care

In France, the standard of care to control patients on long term anticoagulation therapy is blood sampling in the local laboratory of the patient. Results are then transmitted to the GP who adapts the therapy if necessary and schedules the next test. Anticoagulation clinics have also been created but the GP remains the final responsible for the patients' therapy management. Anticoagulation clinics can provide patient's education and can give advices on therapy management by using a computer assisted dosing software. For instance, results of the INR tests performed in laboratory could be sent to the anticoagulation clinic, which determines the posolgy of the oral anticoagulant and the date of the next test through the computer assisted dosing software, and which sends these results to the general practitioner. The general practitioner remains responsible of the patient and is free to follow or not the advices of the anticoagulation clinic.

5.8.2 The use of POC systems and reimbursement conditions

For adults, the use of POC systems is not reimbursed. On the other hand, since 2008, self-testing is wholly reimbursed for children on long term anticoagulation therapy (< 18 years old). To obtain the reimbursement, the child and/or family member must be trained and followed by a public or private hospital, specialized in treating children with congenital heart diseases (for children with cardiologic indication). This specialized structure must have been educated to patient self-testing management and must be available 24h/24h.[118-120]

The reimbursement includes the devices, consumables (test strips and lancets), quality control and training. They can renew the device every 2 years.[118-120]

Two trademarks are reimbursed for children, i.e. CoaguChek and INRatio.[118-120]

5.8.3 Patient training and quality control

The training provided to the child and/or a family member must include both theoretical and practical aspects of anticoagulation therapy and self-testing. At the end of this training and before providing the device, a check must be carried out by the specialized structure on the theoretical and practical knowledge acquired. This check must verify that the family and/or child has clearly understood the principles behind anticoagulant treatment, such as how the POC device works, the need for a good quality blood sample and the possibility to contact the centre in case of emergency. If any aspect of this training is not successful, the trainer must once again go over the information which has not been understood well and must then reassess the child's and/or family's knowledge. A continuous assessment of this knowledge, which is required for renewal of the prescription for test strips, must be carried out 12 weeks after the first delivery and then be repeated every 6 months. This check must be carried out by the specialized structure which gave the initial training.

The scheduling of tests and quality controls is described in Table 5.1. The INR results are transmitted to the specialized structure, which adjust the treatment and tell the patient the date of the next test. They also inform the child's general practitioner.[118-120]

Table 5.1: Quality control

Period	Self-testing	Quality control in laboratory
0-3 weeks	1x per day	1x per week
4-15 weeks	1x per week	1x per month
16-27 weeks	1x per 2 weeks	1x per month
≥28 weeks	1x per 2 weeks	1x per 6 months

5.9 PRICE COMPARISON

Currently, Roche Diagnostics was the only firm active on the Belgian market. The price comparison was thus limited to the CoaguChek XS. In Belgium, the CoaguChek XS end user price is €1054.30. In other countries, prices vary from €620 in the Luxembourg to €1136 in France (see Table 5.2). The price in France corresponds to the tariff fixed by the list of products and services reimbursed (LPP). Prices in other countries are supposed to depend mainly of the sales volume and of negotiations. According to Roche Diagnostics, the low price of the CoaguChek in the Luxemburg was based on an agreement with local authorities regarding education and other costs (sources: communication with Roche Diagnostics).

Table 5.2: Price comparison

Country	Coaguchek XS price
France	€1136
Germany	around €750
Luxembourg	around €620
The Netherlands	around €650
Switzerland	FrS 1259.45 (€782)* (6 test strips included)**
UK	around £550 (€736)* (6 test strips included)**

*Conversion rate: 31 January 2008. ** Around €5.55 per test strip

5.10 DISCUSSION

Even after the diffusion of POC systems for follow-up of oral anticoagulation therapy, the follow-up of patients remains predominantly done by the general practitioner with classical blood testing in the laboratory in most selected countries. Exceptions are found in the UK and the Netherlands, where patients are usually followed-up in anticoagulation clinics. In other countries, some anticoagulation clinics are also set up but their role and number is limited, precluding the follow-up of every patient on long term anticoagulation therapy.

Our overview shows that the coverage of self-testing systems varies between countries. POC are currently not reimbursed in Belgium while the Netherlands and the Luxembourg offer a total coverage of patient self-testing, if prescribed and followed by a *Trombosedienst* (The Netherlands), or by the general practitioner (Luxembourg). Most countries reimburse the self-testing partially. In the UK, the POC device is not reimbursed but some PCTs provide the test strips for free to the patients. In France, self-testing is reimbursed for children up to 18 years old but not for adults. In other selected countries (Germany and Switzerland), reimbursement was not systematic and depended on the patient's health insurer. If reimbursed, the coverage usually included the device and the test strips (totally or only partially) but also training and quality control. A summary of the comparison can be found in Table 5.3.

Most countries specify eligibility criteria for reimbursement. Criteria to obtain reimbursement for self-testing include:

- clinical indication for long term or lifelong anticoagulation therapy such as mechanical heart valve replacement (e.g. almost every country);
- clinical indication for long term anticoagulation therapy and at least one of the following indication: difficult peripheral veins, complications (bleeding or thromboembolims) or inability to get the GP (e.g. Germany);
- children with a clinical indication for long term anticoagulation therapy (e.g. Germany, France);
- prescription by a specialized structure or by the GP, which is responsible of the patient training and follow-up and who certifies that the patient is able to self-manage his therapy (e.g. the Netherlands and Luxembourg);

- patients or carers must follow and succeed an official training organized by a specialized structure (which provides a certificate) (e.g. Germany, Switzerland, France);
- quality control must be performed by a specialized structure or by the general practitioner (parallel determination of the INR by blood sample analysis in laboratory) (e.g. Germany, France);
- for self-management, patients or carers must have adequate physical and cognitive capacities to manage their anticoagulation therapy by themselves (certified by the prescriber) (e.g. almost every country).

Moreover, the price comparison shows that the CoaguChek XS prices varied from €620 (Luxembourg) to €1136 (France).

The example of these countries could be of interest for Belgian policy makers.

Key points

- **The extent of coverage of POC testing from public health care resources varies between countries, going from no public coverage (Belgium) to complete coverage (the Netherlands).**
- **Conditions to obtain reimbursement include mandatory successful training usually given by an official organization and regular quality controls (parallel determination of the INR by blood sample analysis in laboratory).**
- **For PST or PSM additional criteria are imposed on the patient, including adequate physical and cognitive capacities to use the POC device and to manage the anticoagulation therapy and being on long-term anticoagulation therapy (>1 year or lifelong).**
- **CoaguChek XS prices vary from €620 (Luxembourg) to €1136 (France) and is around €1054 in Belgium.**

Table 5.3: Summary of the international comparison

Country	Usual care	Self-testing reimbursement	Training	Quality control
Belgium	GP (Blood testing in laboratory)	No	No formal rules	No formal rules
UK	Anticoagulation clinics (Blood testing in laboratory and POC systems)	Test strips (maximum 24/year) (Not systematic, depending of PCT)	No formal rules	No formal rules
Germany	GP (Blood testing in laboratory)	Device, test strips, training and quality control (Not systematic and not wholly covered, depending of the health insurer)	Mandatory – National training program given by the ASA	Mandatory follow-up by the GP. (No formal rules on the number of quality control)
The Netherlands	Anticoagulation clinics (Trombosediensten)	100% coverage of device, test strips, training and quality control (+/- 45 tests/year) (If prescribed by a Trombosedienste)	Mandatory – Management by the Trombosedienste	The *Trombosedienst* is responsible of the patient follow-up (quality control on average every 3-5 months)
Switzerland	GP (Blood testing in laboratory and POC system)	Device, test strips, training and quality control (Not systematic and not wholly covered, depending of the health insurer)	Mandatory – Management by the Coagulationcare foundation (program based on the ASA training)	Follow-p by the GP. (No formal rules on the number of quality control)
Luxembourg	GP (Blood testing in laboratory)	Device (If prescribed by a physician) Renewal of the device every 5 years (12 tests per year)	Mandatory – Certify by the prescribing physician	The prescribing physician is responsible of the patient follow-up (No formal rules on the number of quality control)
France	GP (Blood testing in laboratory)	For adults: no reimbursement For children (<18 years old): 100% coverage of device, test strips, training and quality control (from 16 weeks, 1 test every 2 weeks) (If prescribed and followed by a specialized structure) – Renewal of the device every 2 years	For adults: no formal rules For children: Mandatory – Management by the specialized structure	For adults: no formal rules For children: Mandatory – Management by the specialized structure – From 28 weeks: every 6 months

6 ECONOMIC LITERATURE REVIEW

6.1 INTRODUCTION

In Belgium, the number of patients on long term anticoagulation therapy is substantial (see chapter 7). Before a decision on the reimbursement of point-of-care (POC) systems is taken, decision makers might wish to know whether the device offers 'value for money'. Value for money is typically assessed in economic evaluations. In this chapter we review the literature on economic evaluations of POC systems compared to usual care. We restricted our review to full economic evaluations, defined as analyses comparing both costs and outcomes of at least two health care programs (definition Drummond *et al*).[121]

6.2 METHODS

6.2.1 Literature search strategy

Economic evaluations were sought from four sources:

- A search on MEDLINE, Psychinfo, and Econlit via "Ovid"
- A search on Embase
- A search via the "Cochrane Library" on the following databases: Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, Database of Abstracts of Reviews of Effects (DARE), NHS Economic Evaluation Database (NHS EED) and Health Technology Assessment (HTA) database
- Identification of studies from the bibliography of selected studies

The keywords used and the results are detailed in the appendix.

6.2.2 Selection criteria and method

This review focused on POC systems available in our country, i.e. CoaguChek, ProTime microcoagulation, or INRatio. Thus, studies that did not consider at least one of these POC systems were excluded.

Only full economic evaluations having a defined primary outcome and reviews of economic evaluations were retained. Cost-outcome descriptions with multiple outcomes were excluded. Partial analyses which focused only on the cost were also excluded. Before exclusion, a rapid assessment showed that these rejected studies did not give enough information to assess their quality or had a poor quality.

The search was limited to papers written in English, Dutch, French, Spanish, or German. A first selection was based on titles and abstracts. Two health economists (SG-IC) assessed abstracts for relevance. Full papers were obtained and assessed for all potentially relevant studies.

6.2.3 Data extraction and quality assessment strategies

Data were extracted using a structured data extraction form and quality was assessed by a single economist using a standard quality assessment checklist for economic evaluations (see appendix to this chapter). The quality of studies was discussed narratively.

6.2.4 Conversion in Euro 2007

Costs were transformed into 2007 prices for each country using Consumer Price Indices available on the OCDE website. Then we applied the Purchasing Power Parities (PPP) index to obtain comparable costs in Euro across the different countries. These PPP index were obtained from the websites of Eurostat and of the International Monetary Fund. The PPPs used correspond to 2007 Euro for the 27 member states of the European Union. If the year of costs was not reported, we used the year of publication minus 2 years. The original cost figures (i.e. before conversion) are presented in appendix.

6.3 RESULTS

6.3.1 Quantity of research available

Of the 34 studies selected on the abstract, 1 study duplicated findings of another included trial,[122] 7 studies were cost or cost minimization analyses,[9, 110, 123-127] 7 studies were cost-outcome descriptions,[86; 36; 128; 129; 130; 45; 131] 2 studies were cost-outcome descriptions assessing a POC system not available in our country,[132, 133] and 10 studies were reviews of the literature with insufficient information to assess their quality and with no additional information compared to selected reviews.[134-143]

Finally, 7 studies were eligible for inclusion in our literature review: 4 primary full economic evaluations,[144-147] 2 studies which included both a full economic evaluation and a review of existing cost-effectiveness studies,[7, 66] and 1 review of cost-effectiveness studies.[120] The flow diagram is described in the appendix to this chapter.

6.3.2 Description of economic evaluation reviews

Three reviews of economic evaluations were identified.[7, 66, 120]

Brown et al

Brown *et al*[7] assessed economic evaluations that compared the use of POC systems to the use of routine INR laboratory tests for the control of adult patients on long term anticoagulation therapy. They included both full economic evaluations and partial comparisons such as cost studies. The research was performed in July 2005 with no year or language restrictions. Only two full economic evaluations were identified in this review, i.e. Lafata *et al* 2000[146] and de Solà-Morales *et al* 2003.[148]

The study of Lafata *et al*[146] is described in the next section. The study of de Solà-Morales *et al*[148] was not selected in our literature review because it was written in Catalan. Therefore a brief description of the study is given here. This cost-effectiveness study compared standard laboratory tests to different POC management strategies using the CoaguChek (in hospital, in the general practitioner's office, for patient self-testing (PST), and for patient self-management (PSM)). They adopted the Spanish health insurer perspective and used a Markov model for a 5-year period. They assumed that the efficacy in terms of life expectancy between all four POC management strategies was equivalent. Life expectancy for the control group (i.e. standard laboratory tests), however, was estimated to be inferior. The authors concluded that POC management strategies were less costly compared to standard laboratory tests and were thus dominant strategies. Furthermore, comparing the different POC strategies, POC management in hospital appeared less expensive than POC at the GP and PST/PSM. The authors thus concluded that this strategy was the most cost-effective approach from the health insurer's perspective. Results of this study were summarized in table 1.

Table 6.1 : Cost-effectiveness of POC management strategies: Results of de Solà-Morales et al

Intervention	Time frame	Effectiveness (life expectancy)	Direct health care costs
Laboratory INR	5 years	4.234	€11 805
POC in hospital		4.665	€4 337
POC in GP practice		4.665	€4 542
PST		4.665	€5 864
PSM		4.665	€6 808

INR = International normalized ratio
POC = Point-of-Care
PST = Patient self-testing
PSM = Patient self-management

In addition to the two full economic evaluations, Brown *et al* also identified 4 cost studies.[110, 123, 124, 126] They concluded that the selected studies were favorable to POC management strategies compared to standard laboratory testing. Major reasons were the adoption of the societal perspective and the assumptions about the reduced incidence of complications in case of PST or PSM. Because no studies were done in the Canadian setting, they also conducted their own economic evaluation. This primary economic evaluation is described in the next section.

Connock et al

Connock *et al* reviewed economic evaluations comparing different management models for patients on long term oral anticoagulation therapy. They focused on patient self-testing and self-management compared to a management in anticoagulation clinics. The research was performed in September 2005 with no year or language restrictions. This review identified three cost-utility studies,[145-147] one cost-effectiveness study[148], one cost-outcome description[129] and two cost studies.[110] From these studies, they concluded that when only direct health care costs were included (e.g. cost for testing, follow-up and complications), PSM was more costly than anticoagulation clinics. However, from the societal perspective, which includes indirect costs such as time and productivity losses and transport costs, PST/PSM costs were lower than anticoagulation clinics in one study[146] and higher in another study[145]. Moreover, at a threshold of £30 000 per QALY (as determined by NICE), most identified studies favored PSM strategies compared to usual management by a general practitioner,[110, 127, 129, 147] or compared to usual management in anticoagulation clinics.[127, 146] According to the authors, these results were influenced by the inclusion of complication costs due to major bleeding or thromboembolic events, and especially by the assumption of reduced complications due to the increasing number of tests in the PSM strategy.

The results of the study of Jowett *et al*[145] were less favorable. In this study, PSM was not a cost-effective strategy compared to usual care in hospital or anticoagulation clinics at a threshold value of £30 000/QALY. Connock *et al*[66] put most emphasis on these results because of its UK setting. Additionally, the authors conducted their own study in the UK setting. This primary economic evaluation is described in the next section.

Haute Autorité de Santé

Finally, the "Haute Autorité de Santé" (HAS) conducted a review of economic evaluations analyzing self-testing and self-management compared to standard laboratory testing or to management by anticoagulation clinics for adults on long term oral anticoagulation therapy.[120] They selected studies from January 1995 to April 2008 with no language restrictions and identified six full economic evaluations[66, 129, 144-147] and eight partial comparisons.[86, 110, 123, 124, 128, 131, 133, 140] They concluded that globally, the selected studies were of poor methodological quality. According to the authors, not enough evidence existed to determine if self-management was a cost-effective strategy compared to standard laboratory testing in France.

For self-testing, there was also not enough evidence to determine if such a strategy was cost-effective compared to standard laboratory testing or compared to a management by anticoagulation clinics. They only concluded that compared to these latter strategies, self-testing was more costly. Finally, they also concluded that not enough evidence existed on the use of POC systems by a health care professional in France.

6.3.3 Description of primary economic evaluations

Among the six primary full economic evaluations, one study was a cost-effectiveness analysis[144] and five were cost-utility analyses.[7, 66, 145-147] Cost-effectiveness analyses and cost-utility analyses differ in the way they express the outcomes of compared programs. In cost-utility analyses, outcome data are measured in terms of quality-adjusted life years (QALYs). Thus, this kind of analysis takes both morbidity and mortality into account. Cost-effectiveness analyses often only take mortality into account as outcome of an intervention or some kind of surrogate outcome parameter. The use of surrogate outcome parameters is to be avoided, as they preclude comparisons between cost-effectiveness analyses of interventions for different diseases. The cost-effectiveness analysis identified in this study used an intermediary outcome parameter: the number of days within a 0.5 range from the INR target.

Key data extraction for each selected economic evaluation is provided in the appendix to this chapter. The quality of the evaluations was assessed following a quality assessment checklist and is described in the appendix to this chapter.

Comparators

Three economic evaluations compared patient self-management (PSM) using POC systems to usual care in the studied country.[66, 145, 147] In the study of Regier *et al*, usual care was defined as management by the general practitioner (GP) with laboratory testing. In the other studies,[66, 145] the definition of usual care was somehow ambiguous and seemed not only to include standard laboratory testing but also some use of POC systems (see table 2).

Two studies compared patient self-testing (PST) with using POC systems in anticoagulation clinics. In addition, these two strategies were compared to standard laboratory testing.[7, 146]

Finally, one study assessed different management strategies by general practitioners (see table 2).[144]

Table 6.2 : Comparators of primary economic evaluations

		(Anticoagulation) clinic		GP	
	PSM/PST	POC	lab	POC	lab
Connock	V	Usual care*			
Jowett.	V	Usual care*			
Regier	V				Usual care
Lafata	V	V***			Usual care**
Brown	V	V			Usual care§
Claes				V§§§	V§§ (incl. usual care)

* Usual care in UK studies (Connock and Jowett) defined as primary or secondary clinic-based anticoagulation management. It is not clear from the studies whether usual care comprises only laboratory tests or also some near-patient testing.
** Usual care in US study (Lafata) defined as "blood sample in laboratory". Usual care consists in "management at traditional non organized center" with blood testing in laboratory.
*** Defined as "anticoagulation clinic with in-clinic capillary monitors for an INR with immediate test results".
§ Usual care in Brown defined as "monitoring achieved through regular visits to a laboratory or hospital where blood is taken and tested to determine the international normalized ratio (INR)".
§§ In Claes, 4 laboratory testing scenarios are analysed: 1) Without education of GP and patients; 2) With education of GP and patients; 3) With education of GP and patients and feedback on results; 4) With education of GP and patients and use of a Dawn AC computer assisted.
§§§ One POC scenario is analysed: use of POC at a GP with education of GP and patients.

POC device

Even if the POC device used in the analysis was not always clearly specified, an examination of the sources showed that CoaguChek was analyzed in four studies[7, 66, 144, 145] and ProTime was assessed in two studies.[7, 147] In the study of Lafata *et al*, not enough data were given to determine which POC device was analyzed.[146]

6.3.3.1 *Studies comparing PSM/PST to laboratory testing (either at clinic or at GP's office)*

Connock et al

In a first study, Connock *et al*[66] compared patient self-monitoring to usual care in the UK. Usual care consists of primary or secondary clinic-based AC management. The precise definition of usual care however was ambiguous. Both standard laboratory testing and POC testing seemed to be considered as part of the usual care strategy. The authors furthermore used the term self-monitoring to regroup both patient self-management (PSM) and PST. They constructed a Markov model to assess both direct health care costs and outcomes from the UK NHS perspective for a 10-year period. The POC device tested was the CoaguChek. The cost associated to patient self-monitoring was found to be higher than the cost of usual care while the difference in QALYs was not statistically significant. The authors concluded that from the NHS perspective, PSM with CoaguChek was not a cost-effective strategy compared to UK usual care at a threshold of £30 000/QALY (as determined by NICE). The number of tests performed in each strategy was not explicitly mentioned in the article. Following the guidelines for economic evaluations in the UK, the evaluation was performed from the perspective of the NHS. If a societal perspective had been taken, and consequently productivity losses and transportation costs for patients and relatives had been taken into account, the ICER would likely have improved. Finally, we should note that this study is specific to the UK setting and that results can not be generalized to the Belgian setting.

Jowett et al

Jowett *et al*[145] compared PSM using CoaguChek to usual care in the UK setting. This cost-utility study was performed alongside a randomized clinical trial for a 1 year period. Two perspectives were assessed, i.e. the NHS and the societal perspective. Usual care was defined as primary or secondary clinic-based AC management with laboratory testing or near-patient INR testing strategies. Both standard laboratory testing and tests performed by POC systems seemed to be considered in the usual care strategy. The number of tests performed in each strategy was also not clearly specified. The results showed that the costs were significantly higher in case of a PSM strategy than in case of usual care, even from the societal point of view (i.e. with the inclusion of transportation time and cost, and productivity losses in the cost estimate). Moreover, no significant differences in terms of QALYs were found between the two strategies. So, even from the societal perspective, the authors concluded that PSM was not a cost-effective strategy at a threshold of £30 000/QALY (as determined by NICE). Again, given the specificity of this study to the UK setting, it is uncertain whether the results can be generalized to the Belgian situation.

Regier et al

Regier *et al*[147] compared PSM to management by the GP with blood testing in a laboratory. The analysis was performed from the Canadian health insurer's perspective. The POC device studied was not specified but based on the sources presented it seems that ProTime was considered. A Markov model for a 5-year period was used. The model only included direct health care costs for the insurer. In the PSM group, it was assumed that 52 tests were performed per year while only 14 tests per year were performed in the control group. Moreover, the authors assumed that a higher frequency of tests reduced the number of complications.

Concerning the results, even if the additional cost of the PSM strategy ranged from €232 to €1 238, such a strategy gained between 0.056 and 0.084 additional QALYs, and was considered by the authors as cost-effective compared to GP management (ICERs ranged from €2900 to €20 633). It should be noted that this analysis was specific to patients with atrial fibrillation or with a mechanical heart valve, with adequate manual dexterity and able to manage their coagulation therapy by themselves. Moreover, the method to estimate cost and outcome data was not clear and costs were specific to the Canadian setting. Generalizability of such results to our country is thus difficult. It should also be noted that the incremental QALYs found in this study were significantly higher than in other studies. The reasons for this are uncertain. The fact that only patients able to use POC devices and with adequate dexterity were considered in the analysis could partially explain these results.

Lafata et al

Lafata *et al*[146] analysed the cost-effectiveness of moving from usual care, which consists in a management by a traditional non organized centre with blood testing in laboratory, to POC management at an organized anticoagulation clinic, and of moving from the anticoagulation clinic to a PST strategy (with a follow-up by an organized anticoagulation clinic). Organized clinics were defined as clinics which do have dedicated nurses who use explicit treatment protocols and processes. The study was conducted in the United States. A Markov model was constructed for a 5-year period.

Two perspectives were assessed, the medical care provider's and the societal perspective. The POC system used was not specified. In the PST group, it was assumed that 52 tests were performed per year while only 14 tests per year were performed in the usual care group. Even from the societal perspective, costs were higher in the PST group than in the control group (incremental cost: €1 001) and the number of QALYs gained by this strategy was relatively low (incremental QALY: 0.01). The authors concluded that with an ICER of €77 962/QALY PST was not a cost-effective strategy compared to management in a non-organized anticoagulation clinic. The estimates were based on a population that might not be representative for the general population on long-term anticoagulation therapy, as it included only few patients with atrial fibrillation.

Moreover, the methods to estimate the costs and outcomes were not transparent and the generalizability of these results to our setting is difficult. The costs of patient education were also not taken into account in the estimates. Finally, it should be noted that according to the sensitivity analysis, the higher frequency of tests in the PST group had an important impact on such a result.

Brown et al

Brown *et al*[7] performed a similar study in the Canadian setting. They compared PST with the CoaguChek (52 tests/year) to usual care in Canada (visit to laboratory or hospital with laboratory blood testing) (20 tests/years) using a Markov model for a 5-year period. From the societal perspective, with the inclusion of nursing home costs, transportation time and cost, and productivity losses in the cost estimate, PST costs less (-€135) and offers more QALYs (+0.03) than the laboratory testing strategy. Consequently, from this perspective, PST was a dominant strategy. Probabilistic sensitivity analysis showed that PST was a dominant strategy in 52% of the simulations.

This result contrasts with the result of the study by Lafata *et al*. A reason for this difference might be the higher number of tests in the usual care group in the study by Brown et al. than in the study by Lafata *et al* (20 versus 14 respectively for usual care and 52 in both studies for PST).

From the medical care provider perspective, i.e. when transportation time and costs, and productivity losses were included in the cost estimate, the ICER was €52 419/QALY. The authors concluded that PST was not a cost-effective strategy, because its ICER exceeded the assumed threshold value of $50 000/QALY. It should be noted that even if most parameters of the model and their sources were given, methods used to estimate them were sometimes unclear.

Studies comparing PST or PSM to laboratory testing (either at clinic or GP's office) are summarized in table 3.

Table 6.3: PSM or PST compared to laboratory testing (either at clinic or at GPs office)

Authors (Country-design)	Interventions	Perspective	Time frame	Incremental QALYs	Incremental cost	Incremental cost-effectiveness ratio	Authors' conclusions
Connock *et al.* (UK - Markov model-patients on LT AOT)	PST/PSM CoaguChek; 30 tests/year) vs usual clinic management§(10 tests/year)	NHS	10 years	0.016 (95%CI: -0.13- 0.18)	€1348 (95%CI: 956-1772)	€85 452/QALY (95%CI not specified)	Probability that PSM is cost-effective (up tot £30 000/QALY) is 44% over a 10-year period. Therefore, PSM is unlikely to be more cost-effective than usual care in the UK.
Jowett *et al.* (UK- RCT- patients on LT AOT)	PSM (CoaguChek; 30 tests/year) vs usual clinic management§ (10 tests/year)	NHS	1 year	Complete data: 0.001 (95%CI: -0.03-0.03) Imputed data**: 0.009 (95%CI: -0.01-0.03)	€409	Complete data: €408 787/QALY Imputed data : €45 421/QALY	PSM does not appear to be cost-effective compared with usual care in the UK.
		Societal			€393	Complete data: €392 807/QALY Imputed data : €43 646/QALY	
Regier *et al.* (Canada – Markov model – patients on LT AOT for atrial fibrillation or mechanical heart valve + adequate dexterity*)	PSM (ProTime; 52 tests/year) vs laboratory test at GPs office (14 tests/year)	Health care payer	5 years	0.07 (95%CI: 0.06-0.08)	€740 (95%CI: 232-1238)	€10 569/QALY	PSM is a cost-effective strategy compared to usual care in Canada.
Lafata *et al.* (US – Markov model – patients on LT AOT)	PST (52 tests/year) vs laboratory test at a GPs office (14 tests/year)	Medical care provider	5 years	0.0128 (95%CI not given)	€1146 (95%CI not given)	€89 289/QALY (95%CI not given)	Authors concluded that in the societal perspective, PST was the most cost-effective alternative.
		Societal			€1,001 (95%CI not given)	€77 962/QALY	
Brown *et al.* (Canada – Markov model – patients on LT AOT)	PST (CoaguChek; 52 tests/year) vs laboratory test (20 tests/year)	Medical care provider	5 years	0.0264 (95%CI not given)	€1386 (95%CI not given)	€52 419/QALY (<50 000$ in 2% of the simulations of the probabilistic sensitivity analysis)	From medical provider perspective, PST is not a cost-effective strategy compared to usual care. From societal perspective, PST is a cost-saving strategy.
		Societal			-€135*** (95%CI not given)	Dominant strategy (in 52% of the simulations of the probabilistic sensitivity analysis)	

§ Usual clinic management in the studies of Connock et al. and Jowett et al. may also include use of near patient testing at the clinic. *Able to manage CoaguChek by themselves; ** missing data for QALYs were estimated using a simulation based technique ***Nursing home cost included (without inclusion of nursing home cost: + €157). PSM = patient self-management; PST = Patient self-testing; GP = General Practitioner; QALY = Quality adjusted life-year; RCT = Randomized Controlled Trial; LT AOT = Long Term Anticoagulation Therapy; UK = United Kingdom; USA = United States.

6.3.3.2 *Studies comparing POC in anticoagulation clinics to usual care (laboratory testing either at clinic or GP's office)*

Economic evaluations comparing the use of POC in anticoagulation clinics with usual care practices are summarized in table 4.

Lafata

The study by Lafata *et al*[146] and the study by Brown *et al*[7] described above also compared the use of POC (CoaguChek and ProTime) in anticoagulation clinics compared to standard laboratory testing. From the perspective of the medical care provider, the use of POC devices in anticoagulation clinics was found to be a dominant strategy compared to usual care. The savings resulting from avoided complications in anticoagulation clinics was the major determinant for this result. Probabilistic sensitivity analysis showed that from the medical care perspective, the use of POC devices in anticoagulation clinics was a dominant strategy compared to usual care in 63% of the simulations in the study of Brown *et al* and in 80% of cases in the study of Lafata *et al.*

From the societal perspective, results were less clear. In the study by Lafata *et al*,[146] the number of QALYs gained was 0.005 and the incremental costs were €1 248, resulting in a cost-effectiveness ratio of €249 976/QALY. The major cause of this high cost-effectiveness ratio from the societal perspective was the higher number of tests performed in anticoagulation clinics (i.e. 23 compared to 14 in the usual care group) which increased the transportation time and costs, and the productivity losses for patients and relatives. It should be noted that results of the probabilistic sensitivity analysis for this comparison (i.e. use of POC in anticoagulation clinic compared to usual care from the societal perspective) were not reported and that the 95% confidence intervals for costs and outcomes were not specified.

Brown

In the study by Brown *et al*,[7] the number of tests did not differ significantly between anticoagulation clinics and usual care (20 versus 23 respectively). This resulted in a reduction in the incremental cost and a subsequent reduction in the cost-effectiveness ration from the societal perspective to €7 766/QALY with the CoaguChek device and €11 472/QALY with the ProTime device. The authors concluded that from the societal perspective the use of POC in anticoagulation clinics was a cost-effective strategy compared to usual care.

The number of QALYs gained with POC management in anticoagulation clinics was assumed to be equal to the number of QALYs gained with PST in the study by Brown et al. The numbers were superior to those of Lafata *et al* (0.026 vs 0.005), which had an important impact on the ICER estimates. We could not find a clear explanation for these differences because the methods used to value outcomes in these studies were not clear. Sensitivity analyses showed that the ICER estimate was most sensitive to assumptions regarding the time spent below or above therapeutic range, the related impact on complications (based on the assumption that time spent below or above therapeutic range had a significant impact on complication), and the number of tests performed.

Table 6.4: POC in anticoagulation clinics compared to usual care (laboratory testing at clinic or GP's office)

Authors (Country-design)	Interventions	Perspective	Time frame	Incremental QALYs	Incremental cost	Incremental cost-effectiveness ratio	Authors' conclusions
Lafata *et al.* (US – Markov model – patients on LT AOT)	Organized anticoagulation clinics (23 tests/year) vs standard laboratory testing (14 tests/year)	Medical care provider	5 years	0.005*	-€150*	Dominant strategy (80%)**	From the medical care provider perspective, POC in anticoagulation clinics is a dominant strategy. compared to usual care.
		Societal			€1248*	€249 976/QALY*	
Brown *et al.* (Canada – Markov model – patients on LT AOT)	Organized anticoagulation clinics (CoaguChek and ProTime; 23 tests/year) vs standard laboratory testing in non organized clinics (20 tests/year)	Medical care provider	5 years	0.0264*	CoaguChek:-€52* ProTime: €46*	CoaguChek: Dominant strategy (63%)** ProTime: €1751/QALY* (<$50 000 = 100%)**	From health care provider perspective, POC in ACC is cost-saving (CoaguChek) or cost-effective (ProTime). From societal perspective, POC in ACC is cost-effective (for both CoaguChek and ProTime) compared to usual care.
		Societal			CoaguChek: €205* ProTime: €303*	CoaguChek: €7766/QALY* (<$50 000 = 86%)** ProTime: €11 472/QALY* (<$50 000 = 82%)**	

*95%CI not given; **Results of the probabilistic sensitivity analysis; PST = Patient self-testing; QALY = Quality adjusted life-year; LT AOT = Long Term Anticoagulation Therapy; US = United States; ACC = anticoagulation clinic.

6.3.3.3 *Studies comparing POC management strategies: PST versus anticoagulation clinics*

Studies comparing POC management strategies are summarized in table 5.

Lafata *et al*[146] and Brown *et al*[7] compared two POC management strategies, i.e. patient self-testing (PST) and management in anticoagulation clinics with POC systems. According to results of Lafata *et al*,[146] PST allowed to gain more QALYs compared to anticoagulation clinics while no difference in QALYs was assumed in the model of Brown *et al*. With the inclusion of cost results, analyses showed that from the societal perspective, PST was a cost saving [7] or dominant strategy [146] compared to anticoagulation clinics. The inclusion of transportation time and costs had a determinant impact on the results.

From the medical care provider perspective PST was no longer cost-effective according to the authors, using a threshold value for the cost-effectiveness ratio of $50 000/QALY.

However, not enough statistical information was provided. Confidence intervals for both incremental costs and outcomes were not given and we had no information to determine if the differences were statistically significant. In the study of Lafata *et al*[146], probabilistic sensitivity analysis showed that from the societal point of view, PST was a dominant strategy in only 48% of the model simulations.

Table 6.5: Comparison of POC management strategies: PST versus anticoagulation clinics

Authors (Country-design)	Interventions	Perspective	Time frame	Incremental QALY	Incremental cost	Incremental cost-effectiveness ratio	Authors' conclusions
Lafata *et al.* (US – Markov model – patients on LT AOT)	PST (52 tests/year) vs organized anticoagulation clinics (23 tests/year)	Medical care provider	5 years	0.008	€1297	€165 237/QALY	From societal perspective, PST is cost-saving compared to POC at ACC.
		Societal			-€247	Dominant strategy	
Brown *et al.* (Canada – Markov model – patients on LT AOT)	PST (CoaguChek; 52 tests/year) vs organized anticoagulation clinics (CoaguChek and ProTime; 23 tests/year)	Medical care provider	5 years	0 (assumption)	CoaguChek: €1437 ProTime: €1339	Anticoagulation clinics = cost-saving	From medical care provider, PST is not cost-effective compared to POC at ACC's. From societal perspective, PST is cost-saving.
		Societal			CoaguChek: -€340 ProTime: -€438	PST = cost-saving	

PST = Patient self-testing; QALY = Quality adjusted life-year; LT AOT = Long Term Anticoagulation Therapy; US = United States; ACC = anticoagulation clinic.

6.3.3.4 *Studies comparing management by a GP: POC versus laboratory testing*

Claes *et al*[144] assessed the impact on both costs and outcomes of various management strategies by GP in Belgium. This study is summarized in table 6. They adopted the health care payers' perspective and conducted a randomized clinical trial for a 6-month period. Five strategies were compared:

- Usual care by a GP with standard laboratory testing (control group).
- Management by a GP with standard laboratory testing associated with patients' and GP education.
- Management by a GP with standard laboratory testing associated with patients' and GP education, and with a feedback of GP results.
- Management by a GP with POC system (CoaguChek) associated with patients' and GP education.
- Management by a GP with standard laboratory testing associated with patients' and GP education and with a GP assistance using a Dawn AC computer (D).

The measure for efficacy was the number of days per GP within a 0.5 range from the INR target. Final outcomes, such as life years gained, QALYs or complications, were not measured. A statistically significant improvement in the surrogate outcome measure was observed between all the intervention groups and the control group (usual care). Between the intervention groups, however, no difference in effectiveness was observed. According to the authors, this result highlighted the fact that patient and GP education could have a favorable impact.

The study also showed that fewer tests were performed in most intervention groups, especially when the computer assisted advices were used (1.9 versus 2.6). This observation did not apply to the strategy where POC systems were used. In this case, the number of tests remained stable (2.6).

Cost analyses showed that the use of POC systems led to fewer direct health care costs than other strategies. Therefore the authors concluded that, compared to usual care, the use of the POC system was a dominant strategy. However, the 95%CI of costs data were not specified and we had no information to determine whether costs differences were statistically significant. Moreover, sensitivity analysis showed that results were mostly influenced by the overhead laboratory costs (i.e. a rough and uncertain parameter) in the standard laboratory testing strategy. By decreasing overhead laboratory costs, POC was not anymore a dominant strategy. On the other hand, as highlighted by the authors, except if laboratory structures were reorganized consequently, overhead costs cannot be retrieved totally.

It should also be noted that the period of the study was limited to six months and costs due to adverse events were not included. Additionally, direct non health care costs, indirect costs, and final end-point such as QALY were not measured. The study therefore did not allow the calculation of a meaningful ICER.

Table 6.6: Management by GP: Comparison of various strategies

Authors (Country-design)	Interventions	Perspective	Time frame	Additional days per GP within a 0.5 range from the INR target	Incremental cost per GP	Incremental cost-effectiveness ratio	Authors' conclusions
Claes *et al.* (Belgium – RCT – patients on LT AOT)	GP management (laboratory testing:2.2 tests/month)+ education vs GP management (standard laboratory testing: 2.6 tests/month)	Health care payer	6 Months	185 (95%CI: 46-311)	€962	€5.21/day	POC at GP in combination with multifaceted education is cost-effective compared to usual care GP management.
	GP management (laboratory testing:2.2 tests/month)+ education + feedback vs GP management (standard laboratory testing: 2.6 tests/month)			208(95%CI: 92-311)	€1,042	€5.00/day	
	GP management (laboratory testing: 1.9 tests/month)+ education + Dawn AC computer assisted advice vs GP management (standard laboratory testing: 2.6 tests/month)			254 (95%CI: 127-381)	€1,243	€4.88/day	
	GP management (POC: CoaguChek: 2.6 tests/month)+ education vs GP management (standard laboratory testing: 2.6 tests/month)			254 (95%CI: 138-381)	-€87	Dominant strategy	

GP = General Practitioner; QALY = Quality adjusted life-year; RCT = Randomized Clinical Trial; LT AOT = Long Term Anticoagulation Therapy.

6.3.3.5 Cost of different anticoagulation management strategies

Throughout the analyzed primary economic evaluations, costs of management strategies differ considerably, not only in absolute but also in relative terms. Table 6.7 illustrates this variation. It shows the average cost of anticoagulation monitoring per patient per year. In the UK and US studies (Connock, Regier and Lafata), the cost of PSM/PST appears considerably higher than usual care (which consists in laboratory testing either at a GP's office or at a clinic). In the studies of Connock and Jowett for instance, usual care only costs respectively £98.47 and £89.89 per year per patient, whereas PSM costs 4 to 7 times as much. Especially the cost of usual care seems considerably low in these studies compared to the cost of usual care in Belgium (€646 in the study of Claes and €745 in the cost analysis of this report: see chapter 7). In the Canadian study (Brown), costs of PSM/PST and POC at anticoagulation clinics are closer to usual care even though far more tests per year are considered in the PSM/PST approach. Given the large variations in these cost calculations, the conclusions cannot be extrapolated as such to the Belgian situation and therefore an economic evaluation adapted to the Belgian setting is required.

Table 6.7: Mean anticoagulation monitoring cost per patient per year - comparison of literature

		(Anticoagulation) clinic		GP			
	PSM/PST	POC	lab	POC	lab	Cost perspective	Currency and year
Connock	£705.51 (30 tests/yr)	£98.47 (10 tests/yr)				NHS	UK£ 2005
Jowett	£381.53 (30 test/yr)	£89.89 (10 tests/yr)				NHS	UK£ 2003
Regier	unknown				unknown	health care payer	CAN$ 2003
Lafata	$860 (52 tests/yr)	$753 (23 tests/yr)			$396 (14 tests/yr)	societal	US$ 1997
Brown	$1 081 (52 tests/yr)	$1 223 - $1 254 (23 tests/yr)			$1 008 (20 tests/yr)	societal	CAN$ 2005
Claes				€632 (31.2 tests/yr)	– Usual care: no education GP: €646 (31.2 tests/yr) – Education GP: €798 (26.4 tests/yr) – Education GP + feedback: €810 (26.4 tests/yr) – With DAWN: €842 (22.8 tests/yr)	health care payers	€ 2005(?)

6.4 DISCUSSION

This literature review showed that the cost-effectiveness of PST or PSM strategies compared to usual care is uncertain and depends of various factors.

Firstly, the effectiveness of usual care influences the results. In the UK, where usual care seemed to be more effective than in other countries, PST and PSM were not considered cost-effective strategies.[66, 145] In Canadian studies,[7, 147] where the effectiveness of usual care was inferior to that of the UK, the ICERs of PST and PSM were more favorable. In the Canadian study of Regier *et al*,[147] PSM was considered to be a cost-effective strategy compared to usual care defined as GP management and standard laboratory testing from the Canadian health care payer's perspective.

Secondly, the definition of the patient population impacts upon the results. Indeed, in the Canadian study of Regier *et al*,[147] where PSM was considered as a cost-effective strategy, only patients with adequate dexterity to manage their anticoagulation therapy by themselves were selected. Thus, these patients were not representative for the entire patient population on long-term oral anticoagulation therapy, which may have influenced the effectiveness data.

Thirdly, the perspective of the analysis influences the results of the economic evaluation. When a societal perspective is taken, productivity losses and transportation costs for patients and their relatives are included. This usually favors PSM or PST strategies as they require less GP visits. The Canadian study performed by Brown *et al*,[7] for instance, concluded that PST was a dominant strategy compared to standard laboratory testing in an anticoagulation clinic, but this only from the societal perspective. From the medical care provider perspective, this strategy was not considered cost-effective.

Fourthly, the number of tests considered influences the results. The higher the number of tests in the control group (i.e. standard laboratory testing) is, the higher the impact of transportation costs and productivity losses will be, which goes in favor of PST and PSM strategies. Moreover, most studies assumed a lower complication risk in case of PST and PSM due to a higher number of tests, which has also a positive impact on the ICER through a better incremental effectiveness compared to usual care.

Finally, the study period might also impact upon the economic results. The sensitivity analysis performed by Regier *et al* showed that the longer the period was, the lower the ICER of PST strategies was.

Some countries have organized anticoagulation clinics, defined as dedicated nursing or pharmacy staff who uses explicit protocols and processes to monitor and adjust dosages of patients on anticoagulation therapy and to seek physician consult. The use of POC systems in these anticoagulation clinics was assessed in two studies. Results showed that the use of POC systems was a cost-effective strategy and even a dominant strategy compared to standard laboratory testing in non organized clinics from the medical care provider's point of view. From the societal perspective, however, results were uncertain and depended mainly on the differences in the number of tests between the two strategies. If this difference was minor, the impact of the inclusion of transportation costs and productivity losses was reduced. So, as highlighted above, both the inclusion of transportation and productivity costs, and assumptions on the number of tests influenced results.

The use of POC systems in anticoagulation clinics was also compared to PST and results were mostly influenced by the perspective adopted. From the societal perspective, PST was preferred but from the medical care provider's perspective, results were more in favor of anticoagulation clinics. The difference in QALYs gained between these two strategies has also an important impact and estimates were based on assumptions. More studies on this topic are thus needed.

Finally, concerning GP management strategies, a Belgian study showed that education of patients and the GP could enhance the effectiveness of usual care in terms of time within the INR target. However, not enough information on cost variations was given and not enough clinical effectiveness data were collected to determine if the use of POC systems by the GP was a cost-effective strategy compared to standard laboratory testing.

In conclusion, results were mostly influenced by the following parameters:

- Effectiveness of usual care in the country
- Characteristics of the target population
- The perspective of the economic analysis
- The number of tests performed and the assumption of a decreasing of complication due to an increasing in the number of tests
- The study period

An evaluation of these parameters for the Belgian setting is thus important before an evidence-based decision on the use of POC systems can be taken.

Key points

The literature review showed that the cost-effectiveness of POC strategies compared to usual care is uncertain and depends of various factors. Results were mostly influenced by:

- **Effectiveness of usual care in the country setting**
- **Cost differences between the care strategies**
- **Population characteristics**
- **The number of tests performed**
- **The perspective of the economic analysis**
- **The study period**

More data specific to the Belgian setting are needed before taking any evidence based decision on the routine use of POC systems.

7 BELGIAN COST-EFFECTIVENESS ANALYSIS

7.1 INTRODUCTION

The purpose of this chapter is to assess the cost-effectiveness of relevant management strategies for patients on long term anticoagulation therapy from the Belgian health care payer perspective. The literature review has shown that current studies are not sufficient to conclude on the cost-effectiveness of the different management strategies in a Belgian setting. A new model was therefore developed.

7.2 METHOD

7.2.1 Description of data sources

Two Belgian health care data sources were used for the analysis. The data obtained from the IMA-AIM (Common Sickness Funds Agency) are described in section 7.2.1.1. The data from the MBDS (Minimum Basic Data Set) are described in section 7.2.1.2.

7.2.1.1 IMA-AIM databases

Databases of the IMA-AIM contain information on the consumption of reimbursed medical interventions and their corresponding level of reimbursement, co-payments and supplements. In this analysis, the following data were available:

- data on reimbursement of pharmaceutical products dispensed by public and in hospital pharmacies
- data on reimbursement of all non-pharmaceutical reimbursed health care
- population characteristics of patients such as age, gender

In this report, only the IMA-AIM sample of the Belgian population was analyzed. It has drawn a sample from the total sickness funds' database: 1 out of 40 (2.5%) of the Belgian population younger than 64 years and 1 out of 20 (5%) of the Belgian population over 65. This population sample (IMA-AIM) is a permanent sample created to furnish Belgian health care data. (for a detailed description of the sampling procedure see Sectorale comite van sociale zekerheid) Of this sample of the Belgian population, all patients with at least one prescription for one of the vitamin K antagonists (see Table 7.1) dispensed in a public pharmacy between 2002 and 2006 were included.

These datasets were used to define the anticoagulation drugs used in Belgium and their defined daily doses, as well as to determine the mean number of tests per patient per year, the percentage of prescription for an INR test without other laboratory tests, and the weighted average fee per GP consultation.

Table 7.1: Vitamin K antagonists

ATC level 5	ATC label	Commercial label	CNK public pharmacy[a]	DDD[b] per package
B01AA03	Warfarin	marevan	55699	16.66
B01AA04	phenprocoumon	marcoumar	119065	25
B01AA07	acenocoumarol	sintrom	129908	20
			129890	6

[a] Code used to identify the package form of a drug by the National Institute for Health and Disability Insurance (NIHDI)
[b] Daily Defined Dose

7.2.1.2 Hospital databases

Two other databases specific to Belgian hospitals were also investigated, i.e. the Minimal Clinical Data (MCD) database (as part of the Minimum Basic Data Set (MBDS)) and the Minimal Financial Data (MFD) database. The MCD database contained medical information, such as principal diagnosis, secondary diagnoses, and procedures. Administrative data, such as length of stay (LOS), status at discharge (including death), and demographic information (such as age and sex) were also included. Diagnoses and procedures were coded using the International Classification of Diseases, 9th revision, Clinical Modification (ICD-9-CM). The MFD database contained information on resource use of all performed procedures and pharmacological products given to the patient.

This database was used to determine the mean cost of major complications defined as major thromboembolic events and major bleedings requiring a hospitalization (see section 7.2.5.4).

7.2.2 Study perspective

In accordance with the Belgian pharmacoeconomic guidelines,[149] the analysis was conducted from the Belgian health care payer perspective, including both costs paid by the national health insurer (the National Institute for Health and Disability Insurance (NIHDI)) and patients' out-of-pocket payments. Productivity losses were not taken into account. The impact of transportation costs was examined in a separate sensitivity analysis.

7.2.3 Intervention and comparators

In Belgium, the standard of care for the management of patients on long term anticoagulation therapy consists of a follow-up by the general practitioner (GP) with an analysis of the blood sample by a laboratory using standard coagulometers. INR results are then sent back to the GP who contacts the patient and adapts his therapy if necessary.

With the emergence of Point-of-Care (POC) systems, the following new strategies can now be considered in Belgium:

- Management by a GP using POC systems with a direct adaptation of the patient therapy. With this strategy, dose changes may be determined in different ways. One option is that the GP uses a treatment algorithm. An example of treatment algorithm can be found in the literature.[76, 80] The GP may also determine the dose intuitively based on his experience. Another way is that the GP obtains dose recommendations through computer assisted dosing software (such as Dawn clinical software, Milnthorpe, Cumbria) that calculates the recommended anticoagulant dose for the patient and the date of the next blood analysis. The fact that this software is expensive (roughly estimated at €15 000 - source: personal communication from UCL) definitely inhibits large distribution of this software. Instead, it can be imagined that the GP logs on to central software through the web. However, as there is no information available on the cost of such a centralized software system, it was assumed in this analysis that the GP defined dose adjustments using a treatment algorithm;
- Management by an anticoagulation clinic (AC) with the use of POC systems and computer assisted dosing software;
- Management by an AC with the use of POC systems and a treatment algorithm;
- Patient self-testing (PST) using POC systems, with a call to a health professional who adapts the therapy according to INR results and fixes the date of the next check;
- Patient self-management (PSM) using POC systems. In this strategy, there are also different options for determining the dose adjustments. One option is that the patient determines the dose adjustment by himself, using a treatment

algorithm. The treatment algorithm also includes instructions on the next test and when to contact the GP or the AC. Another option could be that the patient logs on to a central system for dose adjustment instructions. In this analysis, it was assumed that the patient used a treatment algorithm.

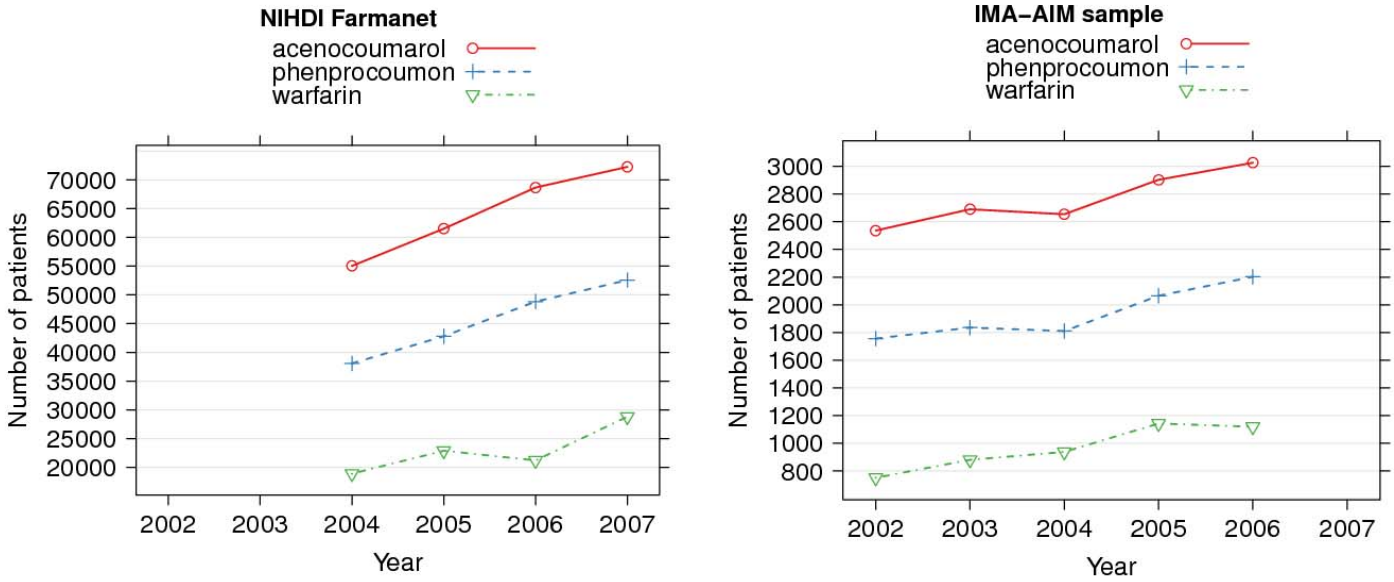
These five strategies were compared to usual care (i.e. follow-up by the GP with standard laboratory testing) in the Belgian setting. All oral anticoagulation drugs available in Belgium were investigated, i.e. phenprocoumone, warfarin, and acenocoumarol.

7.2.4 Population

7.2.4.1 Comparison of IMA-AIM sample with nationwide data

From the Belgian National Institute for Health and Disability Insurance (NIHDI), we retrieved the number of patients and the number of DDD by age and gender for 2004 to 2007 for the studied vitamin K antagonists. These data represent the nationwide reimbursement of the retained drugs. Figure 7.1 shows the evolution of number of patients both for the NIHDI Farmanet data and for the IMA-AIM sample.

Figure 7.1 : Number of patients nationwide (left panel; NIHDI Farmanet) and in the IMA-AIM sample (right panel) by vitamin K antagonist between 2002 and 2007.

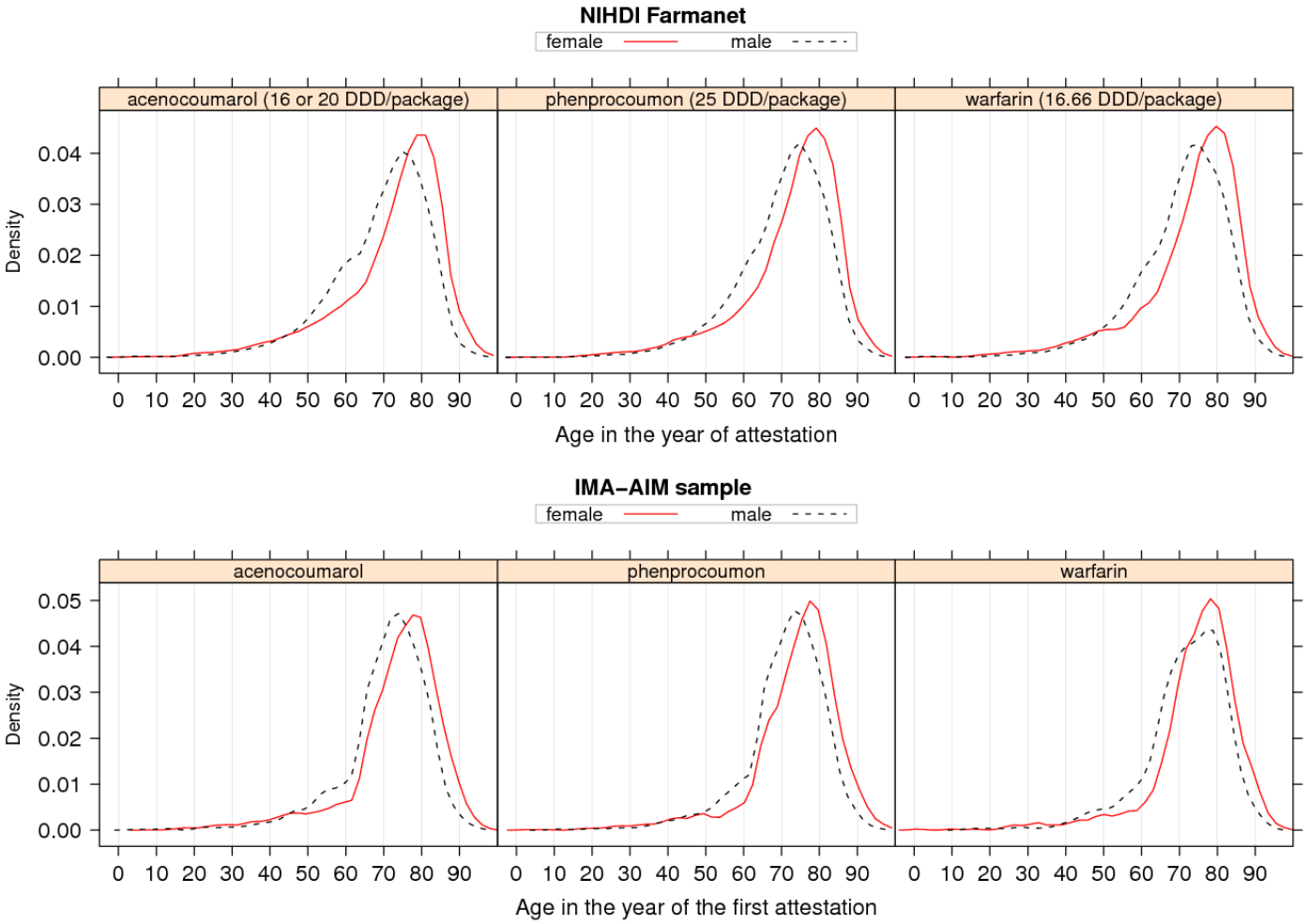


The number of patients using one or more of the vitamin K antagonists in IMA-AIM sample corresponds to 4.8% of the NIHDI Farmanet number of patients in 2004, 4.8% in 2005, and 4.6% in 2006. This corresponds reasonably well to the fact that the IMA-AIM sample is 5% of the general population over 65.

The distribution of age in the IMA-AIM sample is fairly similar to that of the NIHDI Farmanet data (see Figure 7.2). The overrepresentation of patients aged 65 or more in the IMA-AIM sample shows up in the figure by the larger left tail of the NIHDI Farmanet distribution: relatively speaking, there are more patients younger than 65 in the NIHDI Farmanet data than in the IMA-AIM sample.

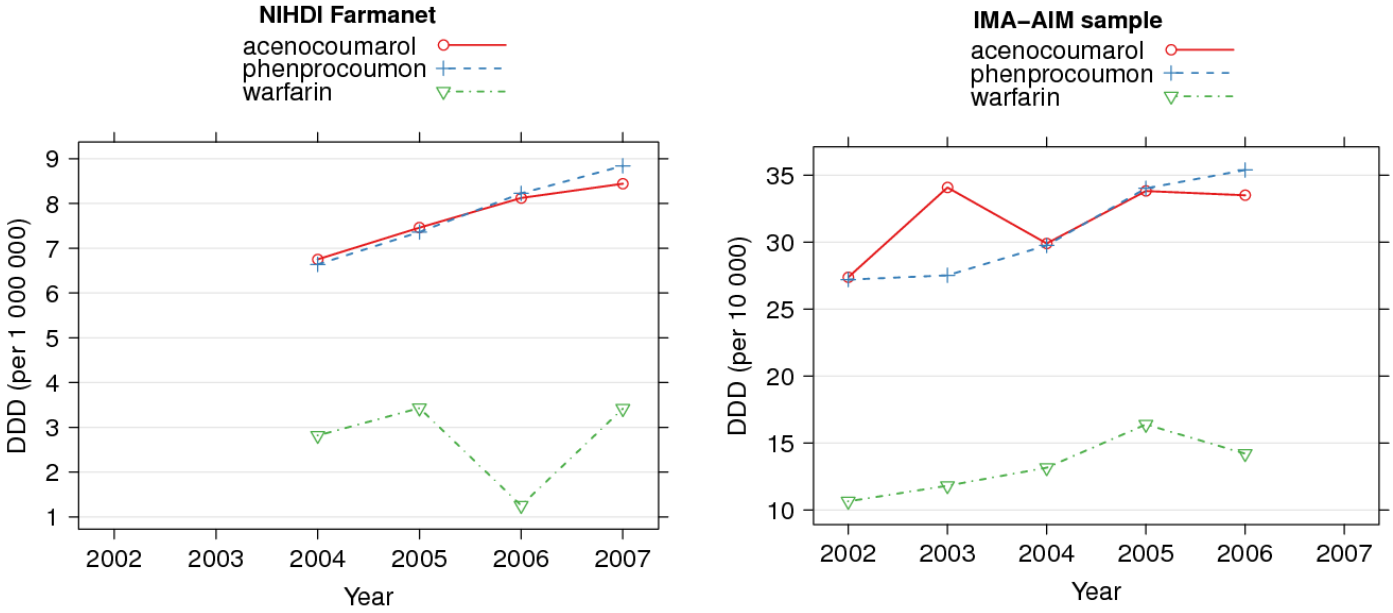
There are about an equal number of men in our sample as women (49.40% versus 50.60%). On average, the women are a few years older. The distribution of age and gender does not differ fundamentally in function of the vitamin K antagonists (see Figure 7.2). As for age, the gender distribution of the IMA-AIM sample is fairly similar to the NIHDI Farmanet data. Overall, the median age at attestation in the NIHDI farmanet data is 76 years for female patients (Q1=67, Q3=82) and 72 years for male patients (Q1=63, Q3=78). Similarly, the median age at the first attestation in the IMA-AIM sample is 76 years for female patients (Q1=69,Q3=81) and 73 years for male patients (Q1=66,Q3=78).

Figure 7.2 : Age by gender distribution in function of the vitamin K antagonists (top panel: NIHDI Farmanet; bottom panel: IMA-AIM sample).



In line with the increase of number of patients, the number of DDD reimbursed per year show a steady increase both in the NIHDI Farmanet data between 2004 and 2007 as well as in the IMA-AIM sample between 2002 and 2006 (see Figure 7.3). In both datasets, a temporary decrease in 2006 is observed for warfarin.

Figure 7.3 : DDD per year in function of the vitamin K antagonists (left panel: NIHDI Farmanet; right panel: IMA-AIM sample).

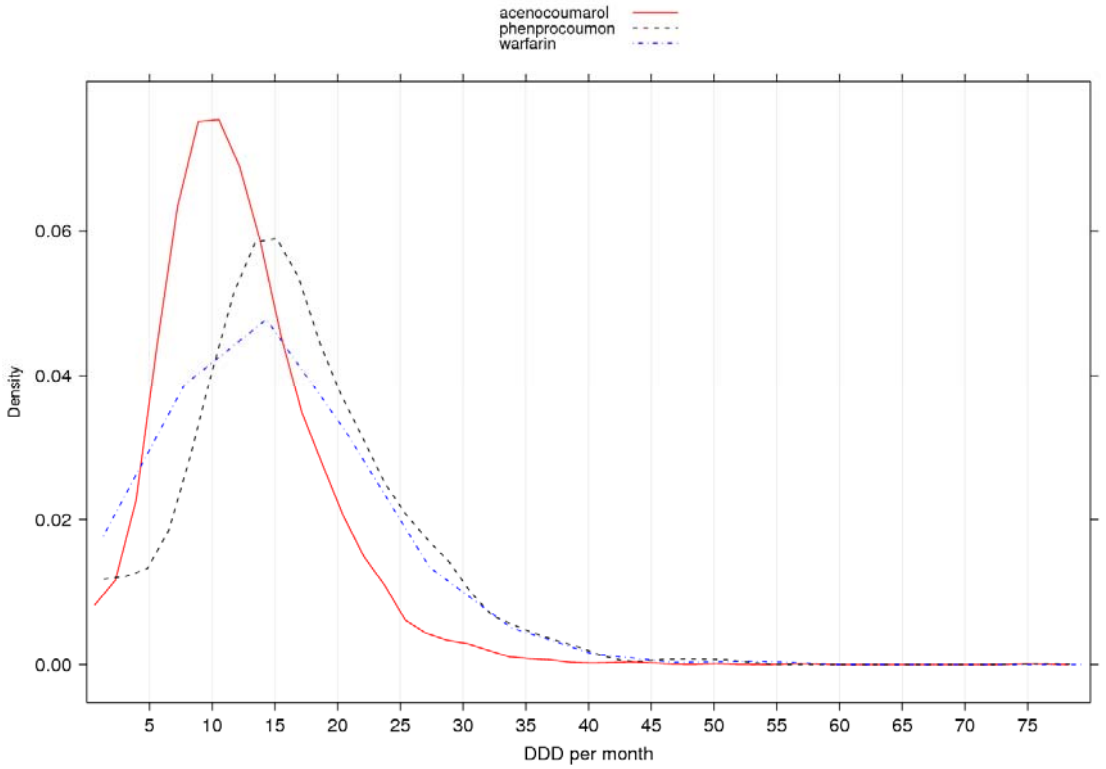


7.2.4.2 The IMA-AIM sample revisited

For the remainder of this chapter, we do not consider patients on short term treatment with oral anticoagulation. We restricted the IMA-AIM sample to patients on long term oral anticoagulation therapy for at least 6 months and which had on average between 6 and 52 INR test per year. To this extent, the number of patients in our sample was reduced from 11 769 to 5 907. However these 50.73% of patients represent 79.81% of the total DDD use in the sample in the available time frame.

In this restricted IMA-AIM sample, we found a large variation in the delivery of vitamin K antagonists between patients as could be expected on clinical grounds (see Figure 7.4). Both warfarin and phenprocoumon show a slightly larger spread in delivery of number of DDD's per month than acenocoumarol.

Figure 7.4 : The average number of DDD (defined daily dose) per month in function of vitamin K antagonists.



7.2.5 The cost-effectiveness analysis

The clinical literature review found evidences for a significant impact of POC on mortality for PSM but not for other strategies. Therefore, a cost-effectiveness analysis was performed for PSM. For other strategies, not enough reliable evidence on the impact of POC on mortality was identified from the literature review. For these strategies, the analysis was therefore limited to a cost comparison.

7.2.5.1 Structure

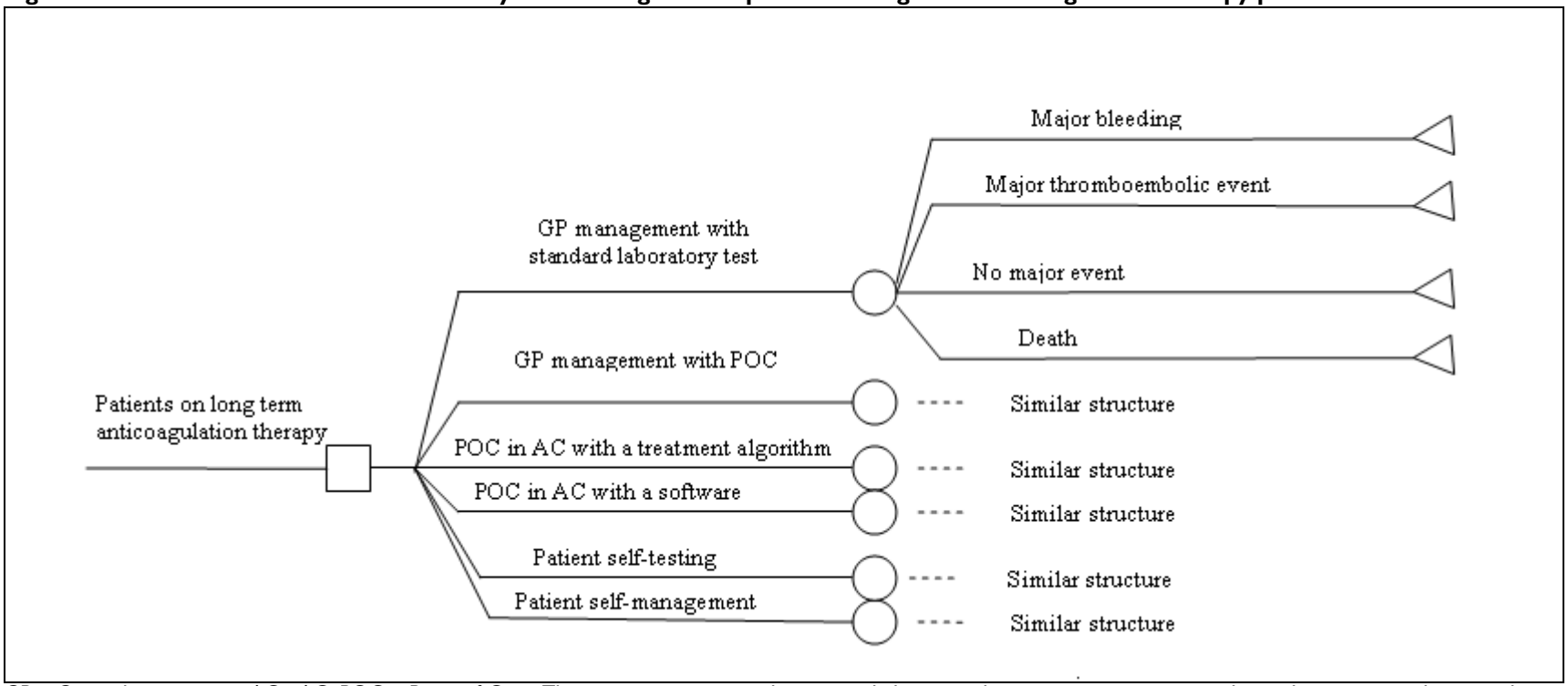
A decision tree model was constructed with a structure based on studies identified in the literature research and on expert opinion (See figure 7.5). The first node indicates the choice between the relevant strategies. For each strategy, the structure of the model was similar. During one year, patients could have a major bleeding complication, a major thromboembolic event, no major event, or could die.

Major bleeding and major thromboembolic events were included in the model as events that influenced health care costs. Incremental costs were hence determined by the cost of patients' testing and follow-up, and the costs of complications. Outcomes were expressed in terms of life years gained. Quality of life impairment due to major bleeding or thromboembolic complications was not taken into account.

Because of a lack of Belgian cost data, minor events, recurrence of events in the same year, and long term disabilities were not taken into account in the analysis. The risk of minor events, recurrence of events, and long term disabilities is expected to be similar between groups or even to be reduced with the use of POC. The non inclusion of these costs is thus a conservative approach which goes in favour of standard laboratory testing.

- **Cost-effectiveness was only investigated for PSM compared to usual care. For other strategies, the research was limited to a cost analysis.**

Figure 7.6 : Decision tree for economic analysis of management options for long term anticoagulation therapy patients



GP = General practitioner; AC= AC; POC = Point-of-Care. The square represents a decision node between the management strategies, the circles represent chance nodes and triangles correspond to costs and outcomes in term of mortality. Probabilities, costs, and outcomes are described in the sections "outcome data" and "cost data".

7.2.5.2 *Time window and discounting*

In the clinical literature research the study with the longest follow-up provided mortality data for a 10 year period. In this study, a timeframe of 10 years was thus chosen for the cost-effectiveness analysis. As advised in the Belgian pharmacoeconomic guidelines,[149] costs were discounted at an interest rate of 3% and outcomes were discounted at an interest rate of 1.5%.

7.2.5.3 *Outcome data*

The final outcome considered in this study was the number of life years gained. Because no reliable data were found, the impact on the quality of life in terms of quality-adjusted life year (QALY) measured by a generic instrument was not assessed. Mortality rates used in this study were derived from the study of Koertke *et al*,[72] i.e. the study with the longest follow-up and the highest weight in the meta analysis. In the study of Koerkte *et al*, the 10-year survival was 67.7% in the usual care group and 80.6% in the PSM group. These data were then transformed in annual transition probabilities using the formula of Miller and Homan (1994), i.e. $1-(1-P(t_0,t_j))^{1/j}$, with $P(t_0,t_j)$ being the cumulative probability between t_0 and t_j (see Table 7.2).[150]

The complications (thromboembolic events and major bleeding) were taken into account for the costs calculation in the analysis (see section 7.2.5.1). For none of the strategies, a significant difference in terms of major bleeding was found and the difference in the number of major thromboembolic events was only significant for PST and PSM (see the meta-analysis in the chapter on clinical effectiveness). For PSM, the clinical literature review also found evidences for a significant impact of POC on mortality. Therefore, only the impact of major thromboembolic events on costs for PST and both the impact of major bleeding and major thromboembolic events on costs for PSM should be assessed. However, the definition of major bleeding varies in the literature and the estimation of its cost depends of this definition. Moreover, according to data of the clinical literature review, the impact of major bleeding would be limited (1% difference for a 10 year-period).[71] It was therefore decided to only assess the impact of major thromboembolic events on costs for PST and PSM.

In the cost-effectiveness model comparing PSM to usual care, annual transition probabilities for major thromboembolic events came from the study of Kroekte *et al* (see Table 7.2).[71]

Table 7.2 : Outcome data for the cost-effectiveness model

	Standard laboratory testing	PSM
Annual probability of death	0.038	0.021
Annual probability of major thromboembolic event	0.028	0.014

7.2.5.4 *Cost data*

In accordance with the Belgian pharmacoeconomic guidelines,[149] the cost analysis was conducted from the Belgian health care payer perspective, including both health care payments by the national health insurer (NIHDI) and patients' out-of-pocket payments. Productivity losses were not assessed. The impact of transportation costs was assessed separately in a sensitivity analysis. Assumptions made in this analysis were submitted to the experts committee of the study. All costs are expressed in 2008 Belgian tariffs (Source NIHDI). For the use of POC at AC, no specific nomenclature codes existed. We thus assessed a real cost instead of using tariffs as it was done for the other strategies. Moreover, for the POC device and consumables (test strips and lancets), the 2008 Belgian prices provided by Roche Diagnostics were used. Table 7.4 to Table 7.12 summarize the cost items for each strategy and the sources they are based upon.

Number of tests

The number of tests was based on IMA-AIM data. Patients having less than 6 tests/year or with ≥ 53 tests/year were excluded of the analysis (not clinically relevant; n=12% of patients excluded). In this dataset, the median number of tests per patient per year was 15 and 75% of Belgian patients had less than 22 tests per year (see Table 7.3).

It was therefore assumed that patients on long term anticoagulation therapy and followed by standard laboratory testing performed a median number of 15 tests per year.

Table 7.3 : Number of tests/year

	N	Min	Q1	Median	Q3	Max	Mean	SD
Number of tests/year	5907	6.01	11.97	15.30	21.64	52.88	17.61	8.48

For the POC strategies, no data were available. Obviously the number of tests has an important impact on results (as shown in the review of the literature on economic evaluations). The impact of the number of tests was therefore analyzed by a sensitivity analysis.

Number of GP consultations

According to experts, the number of GP consultations due to INR testing in usual care may differ to the number of tests. However, IMA/AIM data showed that 98% of patients received no more than one INR prescription per day they consulted their GP. A number of GP consultations due to INR testing inferior to the number of laboratory tests was thus not analyzed. It could also happen that patients return to their GP to obtain their INR results and hence have two GP consultations per INR test. Nevertheless, in the IMA/AIM data, the median number of consultations was 18 and the median number of tests was 15. Therefore, patients usually do not consult their GP two times per INR tests. It was thus assumed that the number of GP consultations due to INR testing in usual care equalled the number of INR tests.

For the strategy "POC by the GP", it was also assumed that the number of GP consultations equalled the number of tests.

Moreover, the analysis of IMA/AIM data showed that 24% of INR tests prescriptions included other laboratory examinations. It was thus assumed that for the use of POC in AC, for PST, and for PSM, 24% of the GP visits in usual care were maintained. The impact of a variation of this number (50% and 100%) was also tested in the sensitivity analysis.

Usual care cost items

The cost of INR testing in the laboratory is split into a fee per INR testing and a lump sum per patient per day covering the overhead laboratory costs. The level of these fees and lump sum payments are specified in the Belgian nomenclature. The corresponding NIHDI codes are 592852, 592874[2] and 554573[3] respectively.

For the analysis of the cost avoided by POC compared to standard laboratory testing, information is needed on the proportion of laboratory prescriptions solely for INR determination. Indeed, if INR is the only test on the prescription, replacing this test by POC would imply a saving for the NIHDI of both the test fee and the lump sum fee. However, if other blood tests than INR are prescribed, replacing INR in laboratory by POC would not permit to save the lump sum fee. The NIHDI would still have to pay the lump sum to the laboratory to cover the overhead costs associated with the other tests. Therefore, it would not be correct to assume that the lump sum fee could be avoided each time the INR determination is replaced by the POC test. In fact the lump sum would be avoided only in cases where INR was the only test on the prescription.

2 Lump sum for a total amount of prescription under B 700
3 Thromboplastine time

The proportion of prescriptions with INR test only is obtained from the IMA-AIM database. This proportion is then used to estimate the total volume of lump sums avoided by replacing standard laboratory testing of INR by POC.

The cost of the GP consists of a fee per consultation. A weighted average fee per consultation was calculated according to the distribution of NIHDI codes for different types of GP consultations in the IMA/AIM data (see Table 7.4).

Table 7.4 : Distribution and average fee of NIHDI codes for GP consultations at the GP office and for home consultations

	NIHDI codes	Distribution	Fee
GP consultations at the GP office:			
Unlicensed general practitioner	101010	0.24%	€13.28
Licensed general practitioner	101032	2.86%	€18.39
Accredited general practitioner	101076	42.84%	€21.53
Home consultations:			
Unlicensed general practitioner	103110	0.25%	€26.40
Licensed general practitioner	103132	53.82%	€32.32
Average fee			€27.24

The numbers of INR tests and the percentage of home consultations were estimated from IMA-AIM data (see Table 7.5).

Table 7.5 : Prices (€2008 – Belgian tariffs), quantities, and sources of cost items for usual care (base case scenario)

Cost items	Total	Sources
INR test fees	€ 0.59	NIHDI
INR test lump sum	€ 20.56*	NIHDI
INR test fees + lump sum	€ 21.15*	NIHDI
% of prescriptions with INR only	76%	IMA-AIM data.
GP consultation	€ 27.24	NIHDI
Median number of GP consultations per year	Equal to the number of tests (15)	Expert opinion and IMA-AIM data
Median number of tests per year	15	IMA-AIM data

* Amounts for accredited clinical biologists. For non accredited clinical biologists, the sum of the lump sum and the fees for the INR act is €20,72 (NIHDI codes 592815, 592830 and 554573).

Cost items of PSM, PST and POC by GP

In the POC management strategies, the costs of POC devices (i.e. CoaguChek XS for patients and CoaguChek XS Plus for GP) and consumables (lancets and test strips) were provided by Roche Diagnostics Groups, the market leader in Belgium. Other firms are currently not active on the Belgian market. The prices mentioned by the distributor of the Protime device are, however, similar to those of the CoaguChek. For the INRatio device, no information from the distributor could be obtained.

For the PSM and PST strategies (but not for the POC management by a GP), a cost for patient training was included. No nationally approved programmes organized by a specialized structure such as in Germany exist in Belgium. To estimate the costs of such a program for the patients, fees determined by the NIHDI for the training of diabetic patients were used, i.e. €171.88 for PST and PSM (NIHDI codes 423135 – 423150 – 423172 – 423194). This amount is similar to the estimation of a German study in which the cost of an official training program for PST was around € 200.[110]. For none of the strategies, a cost for training of the GP or the nurse was included.

In terms of quality control, there are two types of control. On one hand the investigated device (CoaguChek) allows the patient to do an internal quality control at each test without cost. On the other hand, an external quality control is needed to check whether the device is still appropriately calibrated. In some countries, like France,

external quality controls are mandatory. Following the example of this country, the cost of external quality controls was included in the analysis with the assumption of two quality controls per year.[120].

It was also assumed that this external quality control was performed by a parallel determination of the INR with standard laboratory tests. The cost taken into account for this control was thus the cost of a standard laboratory test (comprising the INR testing fee plus the lump sum for the overhead costs).

The POC device and the training were depreciated over a 5-year period using an interest rate of 3% as advised in the Belgian pharmacoeconomic guidelines.[149] It was assumed that POC devices should be renewed every 5 years and that training must be performed at each renewal.

As in the usual care group, the cost of the GP consultation consists in a fee per consultation (see Table 7.7 to Table 7.9).

For PST, a cost for the telephonic consultation on dose management was assessed. Because no specific nomenclature code existed, this cost was estimated by a prowy, i. e. 5 minutes of the time of a specialist in haematology. This cost was estimated based on the average yearly cost in the Saint-Luc university hospital (i.e. FTE €138 708), which gives a cost of €7.68 for 5 minutes (See Table 7.6). This proxy-cost was used for a telephonic consultation by GP, specialists or other health professionnals.

Table 7.6 : Number of FTE requirements for one telephonic consultation on dose management in the PST strategy

Working hours / week / FTE	38
Working weeks / year / FTE (Taking into account vacation)	45
% productive hours / total working hours / FTE (Taking into account sickness leave and other service related duties)	88%
Phone time	5 min
FTE requirement for one 5-minute telephonic consultation	0.0000554

In 2005, 12 470 active GPs were identified in Belgium[151] and 153 634[4] patients on oral anticoagulation therapy were identified in the farmanet dataset. An average of 12.32 patients per GP was therefore assumed. This number was similar to the estimate of the Belgian study of Claes *et al,* [144] where the average number of patients by GP was 12.6.

Table 7.7 : Prices (€2008 – Belgian tariffs), quantities and sources of cost items for the management by the GP with POC (Base case scenario)

Cost items	Total	Sources
POC device - professional	€1151.1	Roche Diagnostics*
Average number of patients per GP	12.32	Pharmanet and Literature research[151]
External quality control	€ 21.15	NIHDI (INR test fees and lump sum)
Frequency quality control, per year	2	Literature research[120]
Lancing device	€ 0.11	Roche Diagnostics (21.18 for 200)*
Test strip	€ 5.55	Roche Diagnostics (133.10 for 24)*
Lancet	€ 0.11	Roche Diagnostics (21.39 for 200)*
GP consultation	€ 27.24	NIHDI
Median number of GP consultations per year	Equal to the number of tests (15)	Expert opinion and IMA-AIM data
Median number of tests per year	15	Expert opinion and IMA-AIM data

*VAT included

4 This number also includes patients on short term anticoagulation therapy and is thus an upper estimate of the number of patients on long term anticoagulation therapy. More precise data could not be obtained.

Table 7.8: Prices (€2008 – Belgian tariffs), quantities and sources of cost items for PST (Base case scenario)

	Total	Sources
POC device - patient	€ 1054.3	Roche Diagnostics*
Training, per 5 years	€ 171.88	NIHDI (proxy)
External quality control	€ 21.15	NIHDI (INR test fees and lump sum)
Frequency quality control, per year	2	Literature research[120]
Test strip	€ 5.5	Roche Diagnostics (133.10 for 24)*
Lancet	€ 0.1	Roche Diagnostics (20.82 for 200)*
GP consultation	€ 27.24	NIHDI
Telephone costs patient-> health professional	€ 0.62	Belgacom*
Health professional time (for each test 5 min.)	€7.68	Saint-Luc hospital
Median number of GP consultations per year	24% of consultations in usual care	Expert opinion and IMA-AIM data
Median number of tests per year	15	Expert opinion and IMA-AIM data

*VAT included

Table 7.9 : Prices (€2008 – Belgian tariffs), quantities and sources of cost items for PSM (Base case scenario)

	Total	Sources
POC device - patient	€ 1054.3	Roche Diagnostics*
Training, per 5 years	€ 171.88	NIHDI (proxy)
External quality control	€ 21.15	NIHDI (INR test fees and lump sum)
Frequency quality control, per year	2	Literature research[120]
Test strip	€ 5.5	Roche Diagnostics (133.10 for 24)*
Lancet	€ 0.1	Roche Diagnostics (20.82 for 200)*
GP consultation	€ 27.24	NIHDI
Median number of GP consultations per year	24% of consultations in usual care	Expert opinion and IMA-AIM data
Median number of tests per year	15	Expert opinion and IMA-AIM data

*VAT included

Cost of anticoagulation clinics

Scale of anticoagulation clinics

Based on the experience of the "cliniques universitaires Saint-Luc", it was assumed that on average 240 patients per year could be followed by an AC[152] if the opening hours of this clinic were 8h–12h on Monday, Tuesday and Friday. If this clinic was open 40 hours per week, 800 patients could be followed per year. Extrapolating this patient number to the total patient base in Belgium (i.e. 153 634, theoretically assuming that all patients are treated in ACs), this translates into 192 ACs in total.

Furthermore, because the follow-up of patients with POC system does not require a large space, it was assumed that the room space was around 20 m².

Investment costs

Investment costs included the cost of the POC device (CoaguChek XS Plus) and the cost of a computer assisted dosing software. The cost of the software was estimated at €15 000 (Source: personal communication from the "cliniques universitaires Saint-Luc"). These investments were depreciated over a 5-year period using an interest rate of 3%. Investment costs for the building space were included as part of the overhead costs.

Operational cost

Operational costs included the costs for consumables (i.e. the lancing devices, test strips, and lancets), for the external quality controls, for patient training, and for the personnel. The cost for consumables and external quality control were estimated in the same way as for the management by a GP. No cost for patient or personnel training was included.

For the personnel cost, assumptions were based on the working of the AC in the "Saint-Luc" hospital. During the opening hours, one secretary and one nurse were needed. The number of nursing and secretary full time equivalent (FTE) was calculated according to the opening hours with a correction for vacation and for the percentage of productive hours, i.e. 0.41 FTEs (see Table 7.10).

It was also assumed that the intervention of a specialist in haematology was needed for 30% of time during the opening hours (= 0.12 FTEs).

Table 7.10 : Number of FTEs required running an AC (treating 240 patients):

	Nurse	Secretary	Specialist
Working hours / week / FTE	38	38	38
Working weeks / year / FTE (Taking into account vacation)	45	45	45
% productive hours / total working hours / FTE (Taking into account other service related duties and sickness leave)	88%	88%	88%
Opening hours / week	12	12	12
Presence during the opening hours	100%	100%	30%
Opening weeks / year	52	52	52
Number of FTEs	0.415	0.415	0.124

In a previous report of the Belgian Health Care Knowledge Centre (KCE), the average cost per nursing FTE at the radiology department was estimated at around €60 000 in 2008.[153] This estimate was made based on the Finhosta database, which regroups yearly data on detailed accounting, statistical (number of admissions, discharges, deaths …) and personnel data of every Belgian hospital. In this analysis, it was therefore assumed that the cost per nursing FTE was €60 000.

The cost per secretary FTE is based on wage scales at Belgian private hospitals (for January 2008). The selected wage basis concerned a secretary with the grade B110 and with 7 years seniority, i.e. €13 845.15.[154] This wage basis was multiplied by an indexation coefficient of 1.4282 to calculate the actual gross wage. This gross wage was in turn multiplied by 1.62 to calculate the cost per FTE, taking into account other costs such as employer's contribution or holiday pays (35% for employer's contribution and 27% for holiday pays and other). The cost per secretary FTE was thus estimated at €32 033.30.

The cost per specialist in haematology (FTE) was estimated based on the average yearly cost in the Saint-Luc university hospital, i.e. €138 708. This proxy-cost could also be used for another specialist or health professional which may be responsible for the AC.

Overhead costs

Items included in overhead costs were indirect amortization costs covering the amortization of the hospital building, the financial charges of the hospital loans, indirect maintenance costs covering cleaning personnel, cleaning products, general technical maintenance and security and utilities (water, gas and electricity), indirect heating costs covering cost of fuel and cost of personnel for heating, indirect administrative costs, and other general costs.

Indirect amortization, financial charges, general costs, general maintenance and heating costs were estimated based on a cost per m^2.

Indirect administrative costs were estimated based on a cost per FTE employed, i.e. 0.95 FTE for the AC.

Estimations of the overhead costs came from a previous KCE report and were retrieved from Finhosta data 2005.[153]. To obtain 2008 Belgian costs, the consumer price index was used (See Table 7.11).

Table 7.11 : Overhead costs.

Item (cost allocation base)	2005 (Consumer price index : 111.0358)	2008 (Consumer price index : 120.2513	m² / FTE	Total cost
Amortization costs (m²)	€14.40	€15.60	20 m²	€311.90
General costs (m²)	€30.00	€32.49	20 m²	€649.80
Financial costs (m²)	€9.50	€10.29	20 m²	€205.77
Maintenance costs (m²)	€89.50	€96.93	20 m²	€1938.56
Heating costs (m²)	€11.90	€12.89	20 m²	€257.75
Administrative costs (FTE)	€9213.00	€9977.64	0.95 FTE	€9516.5
Total overhead costs				€12 879.94

Total costs of anticoagulation clinics

Table 7.12 summarizes the cost items for the management by POC at ACs and the sources they are based upon.

Table 7.12 : Prices (€2008 – Belgian tariffs), quantities, and sources of cost items for the management in ACs with POC (Base case scenario).

	Total	Sources
POC device - professional	€1151.1	Roche Diagnostics*
Computer assisted dosing software	€15 000	Oral communication with Saint-Luc*
Average number of patients per year	240	Grey literature
External quality control	€21.15	NIHDI (INR test fees and lump sum)
Frequency quality control, per year	2	Literature research[120]
Lancing device	€0.11	Roche Diagnostics (21.18 for 200)*
Test strip	€5.55	Roche Diagnostics (133.10 for 24)*
Lancet	€0.11	Roche Diagnostics (21.39 for 200)*
Annual nursing cost	€24 880.38	Finhosta data [153] -0.41 FTE
Annual secretary cost	€13 283.35	Private Belgian hospitals .[154] – 0.41 FTE
Annual specialist or internal GP cost	€17 255.54	University hospital (“Saint-Luc”) – 0.12 FTE
Overhead costs	€12 879.94	Finhosta data
Median number of GP consultations per year	24% of consultations in usual care	Expert opinion and IMA-AIM data
Median number of tests per year	15	Expert opinion and IMA-AIM data

*VAT included

Cost of complications

For PST and PSM, cost savings related to the reduction of major thromboembolic events were also analyzed. From the MBDS database, all in-hospital stays for which a major thromboembolic event was the reason for hospitalization (i.e. events coded as principal diagnosis) were selected. These events were identified using the ICD-9-CM diagnosis codes detailed in the appendix to this chapter. For the selected in-hospital stays, a median hospitalization cost was measured using the MFD database. 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. Additional remuneration consists of a lump sum billed per admission and a lump sum billed per day of hospital stay. Therefore, the average 100% cost per day of stay was recalculated based on the 100% per diem costs per hospital and per type of stay, published by NIHDI[5], and weighted for hospital stay volume.

The in-hospital stays were then split into two subgroups, notably patients who died versus patients who survived. As a result two costs were obtained, i.e. the median cost of a major thromboembolic event not followed by death (€4 176.98) and the median cost of a major thromboembolic event followed by death (€4 182.21). However, no data on the risk of death after a major thromboembolic event could be retrieved from the clinical literature research of this report. Therefore, because the median cost of a major thromboembolic event did not differ significantly if a patient died or not (similar median cost), the two subgroups were grouped in one group, i.e. patients that had a major thromboembolic event (regardless of whether they died or not after the event), with a median cost of €4 177.88.

7.2.5.5 Sensitivity analysis

Probabilistic analysis

For the cost-effectiveness model of PSM compared to standard laboratory testing, uncertainty of the results, i.e. incremental effectiveness, incremental cost, and incremental cost-effectiveness (ICER) was handled by applying probability distributions on major input variables for which the distribution was available. The distribution of these parameters is described in Table 7.13.

Table 7.13 : Distribution of uncertain parameters for the cost-effectiveness model of PSM compared to usual care

Uncertain input values	Point estimate	Distribution
Standard Laboratory test		
Number of tests	Mean: 17.6 Median: 15.3	Gamma(1.46;8.22;shift: 6.01) (source = IMA-AIM data)
Cost of a major thromboembolic event	Mean: €5765 Median: €4 178	Gamma(1.127557;5112.8) (source = MKG data)
2-year incidence of thromboembolic events	0.056	Beta(32;544) (source = Koertke *et al*)
10-year mortality	0.323	Beta(142;300) (source = Koertke *et al*)
PSM		
Cost of a major thromboembolic event	Mean: €5765 Median: €4 178	Gamma(1.127557;5112.8) (source = MKG data)
2-year incidence of thromboembolic events	0.028	Beta(16;563) (source = Koertke *et al*)
10-year mortality	0.194	Beta(94;394) (source = Koertke *et al*)

5 http://www.inami.fgov.be/care/fr/hospitals/specific-information/prices-day/index.htm

For the probability cost analysis of POC strategies compared to usual care, the probability distributions of the major input variables for which the distribution was available are described in Table 7.14.

Latin hypercube simulations were then performed and allowed us to obtain the 95% credibility interval of the ICER after 5 000 simulations.

Table 7.14 : Distribution of uncertain parameters for the cost analysis of POC systems used by the GP compared to usual care

Uncertain input values	Point estimate	Distribution
Number of tests in usual care	Mean: 17.6 Median: 15.3	Gamma(1.46;8.22;shift: 6.01) (source = IMA-AIM data)
Cost of a major thromboembolic event	Mean: €5765 Median: €4 178	Gamma(1.127557;5112.8) (source = MKG data)
Risk difference in major thromboembolic event for PST compared to usual care	0.03	EXP(Normal(LN(0.03);(0 to LN(0.06))/(1.96*2))*(source = Koertke *et al*)
Risk difference in major thromboembolic event for PSM compared to usual care	0.03	EXP(Normal(LN(0.03);(LN(0.02) to LN(0.04))/(1.96*2))** (source = Koertke *et al*)

PST = patient self-testing; PSM = patient self-management
*A log transformation of the risk difference of 0.03 (CI95% 0-0.06) was done to obtain the parameters of the normal distribution μ = LN(0.03) and σ = (0 to LN(0.06))/1.96*2 on log scale. The resulting variable was then exponentiated.
**A log transformation of the risk difference of 0.03 (CI95% 0.02-0.04) was done to obtain the parameters of the normal distribution μ = LN(0.03) and σ = ((LN(0.02) to LN(0.04))/1.96*2 on log scale. The resulting variable was then exponentiated.

Scenario analysis on the number of INR tests in POC strategies

For the number of tests in the PSM and PST groups, no data were available. Different scenarios were thus analysed, i.e. 15 (current Belgian median), 26 (1 time every two weeks) and 52 tests per year (= 1 time per week).

For the number of tests in other POC strategies (use by the GP or at ACs), it was firstly assumed that the number of tests did not differ from the current number of laboratory tests. Then, because practices could change with the reimbursement of POC systems, the impact of performing 26 and 52 tests was also analyzed.

Scenario analysis on the number of GP consultations in POC strategies

In the base case scenario, the assumption was made that 24% of GP visits due to INR tests in usual care were maintained for PST, PSM, and the use of POC by GP. Two other scenarios were also tested:

- 50% of GP consultations due to INR testing in usual care were maintained with the use of POC at AC and with PST and PSM.
- 100% of GP consultations due to INR testing in usual care were maintained with the use of POC at AC and with PST and PSM.

Threshold analysis

Uncertainty concerning the number of patients per GP or per ACs was also analyzed and threshold values from which the POC strategies became more costly than usual care were determined. These threshold analyses were done based on deterministic (instead of probabilistic) results. In these analyses, the number of tests was 15 (= Belgian median), and for the use of POC in AC, 4 GP visits were maintained (=25% of 15).

7.3 RESULTS

7.3.1 Cost analysis

7.3.1.1 Cost of testing and follow-up

The probabilistic analysis shows that if current practices are maintained with the use of POC by GP and at ACs, average savings for these strategies will range from €161.18 to €221.73 compared to standard laboratory testing. The probability that these POC strategies remain cost-saving will be superior to 70% (see Table 7.15).

However, if 26 tests per year are performed, the use of POC by GP will on average no longer remain cost-saving (probability <€0 = 31%). Moreover, without the inclusion of savings due to the reduction of thromboembolic complications, the probability that PST (with 26 tests per year and with 24% of GP contacts maintained) remains cost-saving is inferior to 50% (probability <€0 = 38%) (see Table 7.15).

If 26 tests per year are performed, only PSM (probability <€0 = 65%) and the use of POC at AC (probability <€0 = 60-62%) will on average be cost saving strategies.

If 52 tests per year are performed, the use of POC by GP and PST will usually be more expensive than current usual care (probability >€0 = 97% and 87% respectively) and the probability that PSM and the use of POC at AC remains cost saving will be inferior to 50%.

Total cost for each strategy is detailed in the appendix to this chapter.

Table 7.15 : Probabilistic cost analysis without complication – Base case scenario (24% of GP consultations in usual care maintained for PST-PSM and AC)

Strategies	Number of tests/year	Number of GP consultations	Incremental cost		Probability <€0
			Average	95% CI	
POC by GP	IMA/AIM data distribution*	Equal to the number of tests	-€ 161.18	(-408.20 to -47.81)	100.00%
	26	Equal to the number of tests	€ 115.55	(-907.51 to 585.06)	30.60%
	52	Equal to the number of tests	€ 973.50	(-49.55 to 1443.02)	2.96%
POC at AC (software)	IMA/AIM data distribution*	24%**	-€ 208.09	(-941.97 to 128.72)	73.72%
	26	24%**	-€ 159.79	(-1029.11 to 239.16)	60.26%
	52	24%**	-€ 10.07	(-879.38 to 388.89)	41.10%
POC at AC (algorithm)	IMA/AIM data distribution*	24%**	-€ 221.73	(-955.62 to 115.07)	76.36%
	26	24%**	-€ 173.44	(-1042.75 to 225.51)	62.28%
	52	24%**	-€ 23.72	(-893.03 to 375.24)	42.62%
PST	15	24%**	-€ 131.90	(-1001.22 to 267.05)	56.28%
	26	24%**	€ 21.47	(-847.84 to 420.43)	37.78%
	52	24%**	€ 384.00	(-485.32 to 782.95)	13.26%
PSM	15	24%**	-€ 256.37	(-1125.68 to 142.59)	75.34%
	26	24%**	-€ 194.26	(-1063.57 to 204.70)	65.42%
	52	24%**	-€ 47.47	(-916.78 to 351.49)	45.36%

* Distribution = gamma(1.46;8.22;shift: 6.01). In the IMA/AIM data, the mean number of test was 17.6 and the median number of tests was 15.3; **24% of GP visits in usual care are maintained; POC = Point of care; CI = credibility interval; GP = general practitioner; AC = Anticoagulation clinic; PST = patient self-testing; PSM = patient self-management

7.3.1.2 Total cost including complications

As mentioned in the methodology section (7.2.5.4 Cost data – Cost of complications), only savings due to the reduction of major thromboembolic events in PST and PSM are taken into account in this analysis (no savings in other POC strategies).

With the inclusion of complication costs, cost-savings for PSM and PST increase. The probability that PSM remains cost-saving is 85% with 26 tests/year and 67% with 52 tests/ year. The probability that PST with 26 tests/ year remains cost-saving increases to 60%. However, with 52 tests/ year, the probability that PST remains cost-saving is inferior to 30% (see Table 7.16).

Therefore, if 26 tests/year are performed and if complications are taken into account, PSM (-€367; probability <€0 = 85%) will be the strategy with the highest average cost-saving, followed by PST (-€202; probability <€0 = 60%) and by the use of POC at AC (-€160 (software) and -€173 (algorithm); probability <€0 = 60-62%). However, the use of POC by GP will on average no longer be a cost-saving strategy in these assumptions (probability <€0 = 31%).

Table 7.16 : Probabilistic cost analysis taking into account reduced risk of thromboembolic complications for PST and PSM – Base case scenario (24% of GP consultations in usual care maintained for PST-PSM and AC)

Strategies	Number of tests/year	Number of GP consultations	Incremental cost		Probability <€0
			Average	95% CI	
POC by GP	IMA/AIM data distribution*	Equal to the number of tests	-€ 161.18	(-408.20 to -47.81)	100.00%
	26	Equal to the number of tests	€ 115.55	(-907.51 to 585.06)	30.60%
	52	Equal to the number of tests	€ 973.50	(-49.55 to 1443.02)	2.96%
POC at AC (software)	IMA/AIM data distribution*	24%**	-€ 208.09	(-941.97 to 128.72)	73.72%
	26	24%**	-€ 159.79	(-1029.11 to 239.16)	60.26%
	52	24%**	-€ 10.07	(-879.38 to 388.89)	41.10%
POC at AC (algorithm)	IMA/AIM data distribution*	24%**	-€ 221.73	(-955.62 to 115.07)	76.36%
	26	24%**	-€ 173.44	(-1042.75 to 225.51)	62.28%
	52	24%**	-€ 23.72	(-893.03 to 375.24)	42.62%
PST	15	24%**	-€ 355.58	(-1459.55 to 204.75)	77.58%
	26	24%**	-€ 202.20	(-1306.17 to 358.13)	60.00%
	52	24%**	€ 160.32	(-943.65 to 720.65)	28.88%
PSM	15	24%**	-€ 429.34	(-1359.28 to 72.39)	91.74%
	26	24%**	-€ 367.23	(-1297.17 to 134.49)	85.06%
	52	24%**	-€ 220.44	(-1150.38 to 281.28)	67.24%

* Distribution = gamma(1.46;8.22;shift: 6.01). In the IMA/AIM data, the mean number of test was 17.6 and the median number of tests was 15.3; **24% of GP visits in usual care are maintained; POC = Point of care; CI = credibility interval; GP = general practitioner; AC = Anticoagulation clinic; PST = patient self-testing; PSM = patient self-management

By taking into account a reduced cost of complications for PSM and PST:

- **In the scenario of 26 tests/year, PSM is the strategy with the highest average cost-saving (-€367; probability <€0 = 85%), followed by PST (-€202; probability <€0 = 60%) and the use of POC at AC (-€160 (software) and -€173 (algorithm); probability <€0 = 60-62%).**
- **The use of POC by GP is on average no longer cost-saving compared to usual care with 26 tests/year (probability <€0 = 31%). With 52 tests/year, this strategy is more expensive than usual care (probability >€0 = 97%);**
- **PST and the use of POC at AC are on average no longer cost-saving compared to usual care with 52 tests/year (probability <€0 is inferior to 50%)**
- **Even with 52 tests/year, PSM is on average a cost-saving strategy compared to usual care (probability <€0 = 67%).**

7.3.1.3 Scenarios on GP consultations or visits

In the first scenario, it was assumed that 24% of GP consultations or visits in usual care due to INR testing were maintained for PST, PSM and the use of POC at ACs. In this section, the impact of maintaining 50% and 100% of GP consultations is tested.

If 50% of the GP consultations or visits are maintained and if 26 tests per year are performed, the probability that the use of POC at AC and by PST is cost-saving will be inferior to 50% (See Table 7.17).

If 100% of the GP consultations or visits are maintained and if 26 tests per year are performed, the probability to remain cost-saving strategies will be inferior to 25% for the use of POC at AC and by PST and inferior to 50% for PSM (See Table 7.17).

Table 7.17 : Probabilistic cost analysis with complications – Second scenario (50% of GP consultations in usual care maintained)

Strategies	Number of tests/year	Number of GP consultations	Incremental cost		Probability <€0
			Average	95% CI	
POC by GP	IMA/AIM data distribution*	Equal to the number of tests	-€ 161.18	(-408.20 to -47.81)	100.00%
	26	Equal to the number of tests	€ 115.55	(-907.51 to 585.06)	30.60%
	52	Equal to the number of tests	€ 973.50	(-49.55 to 1443.02)	2.96%
POC at AC (software)	IMA/AIM data distribution*	50%**	-€ 83.34	(-650.67 to 177.03)	55.68%
	26	50%**	-€ 35.05	(-737.80 to 287.47)	44.88%
	52	50%**	€ 114.68	(-588.08 to 437.20)	27.06%
POC at AC (algorithm)	IMA/AIM data distribution*	50%**	-€ 96.99	(-664.31 to 163.38)	58.64%
	26	50%**	-€ 48.69	(-751.45 to 273.82)	46.90%
	52	50%**	€ 101.03	(-601.72 to 423.55)	28.38%
PST	15	50%**	-€ 228.71	(-1208.73 to 258.62)	67.26%
	26	50%**	-€ 75.33	(-1055.36 to 412.00)	47.92%
	52	50%**	€ 287.20	(-692.83 to 774.52)	18.50%
PSM	15	50%**	-€ 304.59	(-1086.30 to 127.34)	83.64%
	26	50%**	-€ 242.49	(-1024.20 to 189.45)	75.10%
	52	50%**	-€ 95.70	(-877.41 to 336.24)	54.58%

* Distribution = gamma(1.46;8.22;shift: 6.01). In the IMA/AIM data, the mean number of test was 17.6 and the median number of tests was 15.3; **50% of GP visits in usual care are maintained; POC = Point of care; CI = credibility interval; GP = general practitioner; AC = Anticoagulation clinic; PST = patient self-testing; PSM = patient self-management

Table 7.18 : Probabilistic cost analysis with complications – Third scenario (100% of GP consultations in usual care maintained)

Strategies	Number of tests/year	Number of GP consultations	Incremental cost		Probability <€0
			Average	95% CI	
POC by GP	IMA/AIM data distribution*	Equal to the number of tests	-€ 161.18	(-408.20 to -47.81)	100.00%
	26	Equal to the number of tests	€ 115.55	(-907.51 to 585.06)	30.60%
	52	Equal to the number of tests	€ 973.50	(-49.55 to 1443.02)	2.96%
POC at AC (software)	IMA/AIM data distribution*	100%**	€ 156.56	(-90.46 to 269.93)	7.82%
	26	100%**	€ 204.85	(-177.60 to 380.37)	10.30%
	52	100%**	€ 354.58	(-27.87 to 530.10)	3.20%
POC at AC (algorithm)	IMA/AIM data distribution*	100%**	€ 142.91	(-104.11 to 256.28)	9.14%
	26	100%**	€ 191.21	(-191.25 to 366.73)	11.34%
	52	100%**	€ 340.93	(-41.52 to 516.45)	3.60%
PST	15	100%**	€ 8.39	(-877.96 to 363.73)	36.04%
	26	100%**	€ 161.76	(-724.59 to 517.11)	20.84%
	52	100%**	€ 524.29	(-362.06 to 879.63)	6.64%
PSM	15	100%**	-€ 64.70	(-597.85 to 235.49)	54.42%
	26	100%**	-€ 2.59	(-535.75 to 297.60)	43.64%
	52	100%**	€ 144.20	(-388.96 to 444.39)	22.62%

* Distribution = gamma(1.46;8.22;shift: 6.01). In the IMA/AIM data, the mean number of test was 17.6 and the median number of tests was 15.3; **100% of GP visits in usual care are maintained; POC = Point of care; CI = credibility interval; GP = general practitioner; AC = Anticoagulation clinic; PST = patient self-testing; PSM = patient self-management

The scenario analysis on the number of GP consultations or visits shows that:

- **if 50% of GP consultations or visits in usual care are maintained and 26 tests per year are performed, the probability that POC at AC and by PST remains cost-saving will be inferior to 50%.**
- **if 100% of GP consultations or visits in usual care are maintained and 26 tests per year are performed, the use of POC at AC and by PST will usually be more expensive than standard laboratory testing (probability <€0 inferior to 25%)**
- **if 100% of GP consultations or visits in usual care are maintained, the probability that PSM remains cost-saving will be inferior to 50% with 26 tests per year and inferior to 25% with 52 tests per year.**

7.3.1.4 Variation of the number of patients treated per GP or AC

Concerning the management by a GP or in ACs, the mean number of patients had also an important impact on the results.

If it is assumed that 15 tests are performed in each strategy, and that 4 GP consultations (24%) are maintained with the use of POC at ACs, the use of POC by the GP or the use of POC at ACs (with a computer assisted dosing software) will remain cost-saving above 2 (=GP) and 173 (=AC with software) patients per year respectively.

If 26 tests per year are performed, POC by GP will no longer be cost-saving and POC at AC will remain cost-saving above 204 patients per year (and 355 patients with 52 tests/year).

In ACs, the impact of the number of patients was also tested with the assumptions of five day opening (instead of 3 half days) and 26 tests/week. Under these assumptions, the management in an AC with a POC system and a computer assisted dosing software is not anymore a cost saving strategy below 605 patients.

In the assumption of an equal number of tests between strategies (= 15 tests/year):

- **POC by GP becomes more expensive than usual care when less than 2 patients are followed per year;**
- **POC at AC (with software) becomes more expensive than usual care when less than 173 patients are followed per year (3 half days opening/week).**

In the assumption of 26 tests/year in AC:

- **POC at AC (with software) becomes more expensive than usual care when less than 204 patients per year are followed by the AC with 3 half days opening/week, and when less than 605 patients per year are followed for 5 days opening/week.**

7.3.1.5 Inclusion of transportation cost

In the base case analysis, transportation costs were not included. In Belgium, the GP office is usually close to the patients' home. Inclusion of transportation costs for the management by the GP is thus expected not having an important cost impact. For ACs, however, the impact of transportation costs may be more important. It was thus tested from how many kilometres the management in ACs would become more expensive than usual care. The fiscally deductible rate per kilometre was used, i.e. €0.15/km. Assuming 15 tests/year in each strategy and 4 GP consultations maintained (=24%), the use of POC at AC is not anymore a cost-saving strategy from a distance between the AC and the patient of 385 km for ACs using a computer assisted dosing software and of 431 km for ACs using an algorithm. Consequently, the inclusion of transportation cost does not influence the relative cost position of ACs compared to usual care.

- **The inclusion of transportation costs is expected to have little impact on results**

7.3.2 Cost-effectiveness analysis

The cost-effectiveness of PSM compared to usual care (standard laboratory testing and follow-up by the GP) in Belgium was assessed for a 10 year period (= the longest follow-up time in the literature on clinical effectiveness).

Results of the probabilistic analysis for the three investigated scenarios on the number of tests/year (15 tests, 26 tests and 52 tests in the PSM strategy) and the scenarios on the number of GP consultations or visits (24%, 50% and 100% of GP consultations or visits in usual care due to INR tests maintained) are described in Table 7.19 and Figure 7.7 to Figure 7.13.

In all scenario investigated, the ICER of PSM compared to usual care is on average a dominant strategy compared to usual care, except in the scenario of 100% of GP consultations maintained and 52 tests/year. In the worst case scenario investigated, the ICER is usually inferior to €7 000 per life year saved.

However, if 100% of GP consultations or visits are maintained, and from 26 tests per year, the probability that PSM remains a dominant strategy will be inferior to 50%.

Table 7.19 : Results of the probabilistic analysis for the cost-effectiveness model (10-year period)

Sc.	N° of test	N° of GP consultations	Incremental life year gained	Incremental cost	Incremental cost-effectiveness	Probability <€0
	(PSM)	(PSM)	Mean (CI 95%)*	Mean (CI 95%)	Mean (CI 95%)*	
1	15	24%**	0.64 (0.35 to 0.93)	€-3443.67 (-10 659.02 to 641.71)	Dominant strategy (Dominant to €965/LY)	91.24%
2	26	24%**	0.64 (0.35 to 0.93)	€-2964.26 (-10 181.36 to 1124.73)	Dominant strategy (Dominant to €1727/LY)	84.96%
3	52	24%**	0.64 (0.35 to 0.93)	€-1831.12 (-9052.36 to 2263.70)	Dominant strategy (Dominant to €3677/LY)	68.02%
4	15	50%**	0.64 (0.35 to 0.93)	€-2480.75 (-8692.16 to 1073.34)	Dominant strategy (Dominant to €1684/LY)	83.26%
5	26	50%**	0.64 (0.35 to 0.93)	€-2001.35 (-8212.43 to 1554.87)	Dominant strategy (Dominant to €2515/LY)	75.28%
6	52	50%**	0.64 (0.35 to 0.93)	€-868.2 (-7076.04 to 2692.74)	Dominant strategy (Dominant to €4536/LY)	56.10%
7	15	100%**	0.64 (0.35 to 0.93)	€-629.00 (-5900.02 to 1970.68)	Dominant strategy (Dominant to €3283/LY)	54.08%
8	26	100%**	0.64 (0.35 to 0.93)	€-149.59 (-5426.91 to 2452.95)	Dominant strategy (Dominant to €4199/LY)	44.02%
9	52	100%**	0.64 (0.35 to 0.93)	€983.55 (-4282.92 to 3586.03)	€1757.4 (Dominant to €6521/LY)	25.18%

*It was assumed that the number of tests had no impact on effectiveness criteria
**24% and ***100% of GP consultations in usual care due to INR tests were maintained in PSM
UC= Usual care: follow-up by the GP with standard laboratory testing; PSM = patient self-management; CI = credibility interval.

Figure 7.7 : Acceptibility curves. The curves represent, for each scenario, the probability that PSM is cost-effective for various threshold values of the cost per life-year gained.

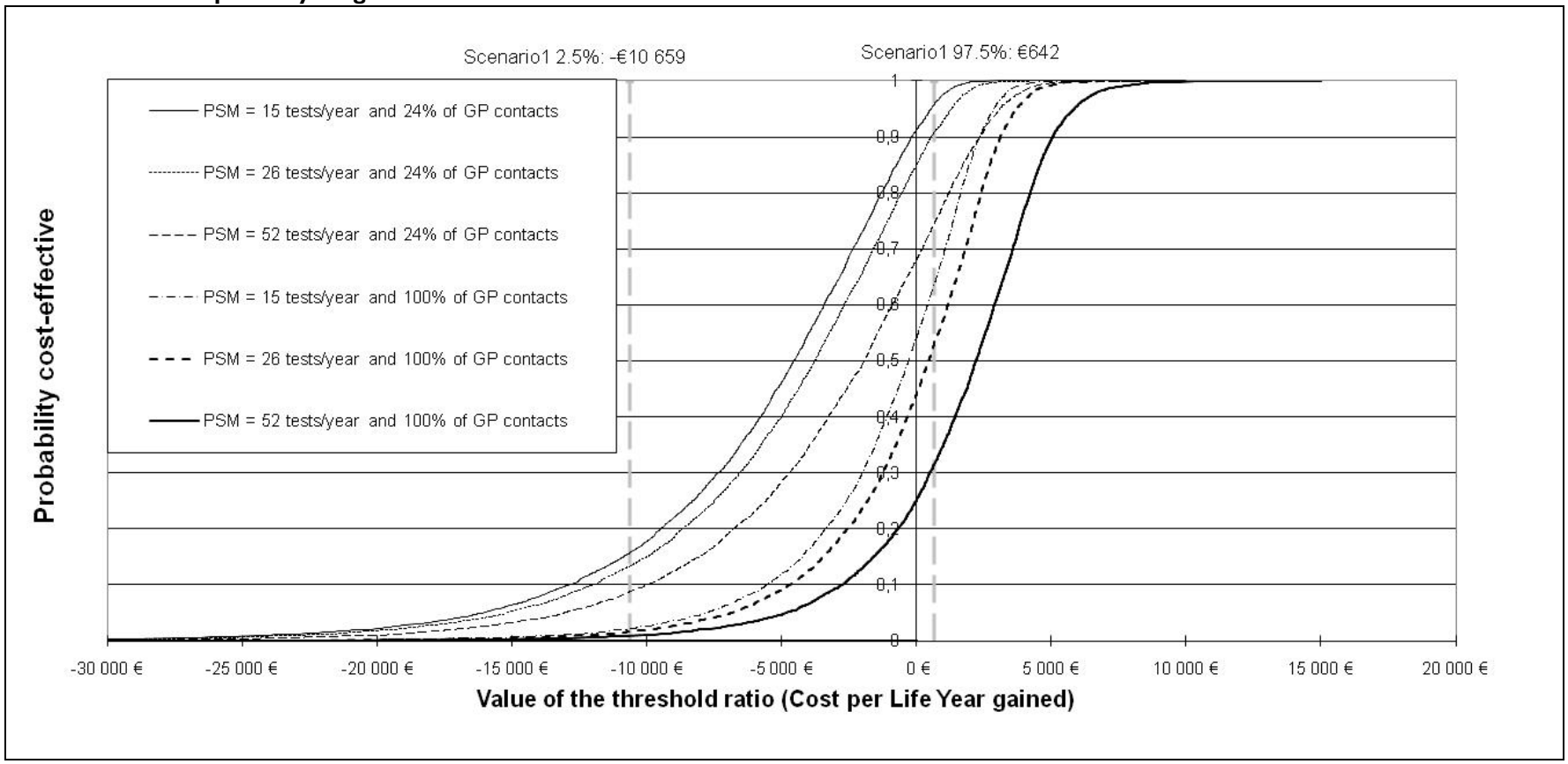


Figure 7.8: Probabilistic analysis – Scenario 1

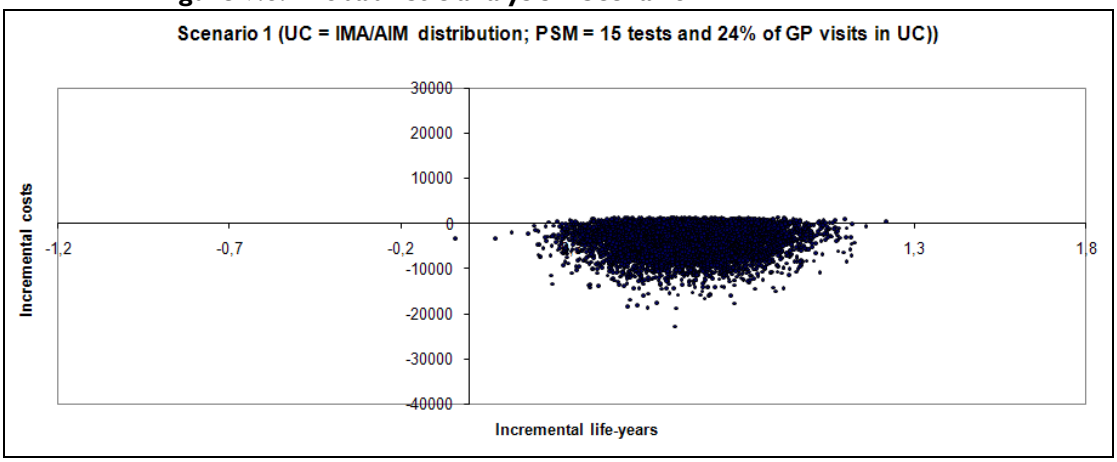


Figure 7.9: Probabilistic analysis – Scenario 2

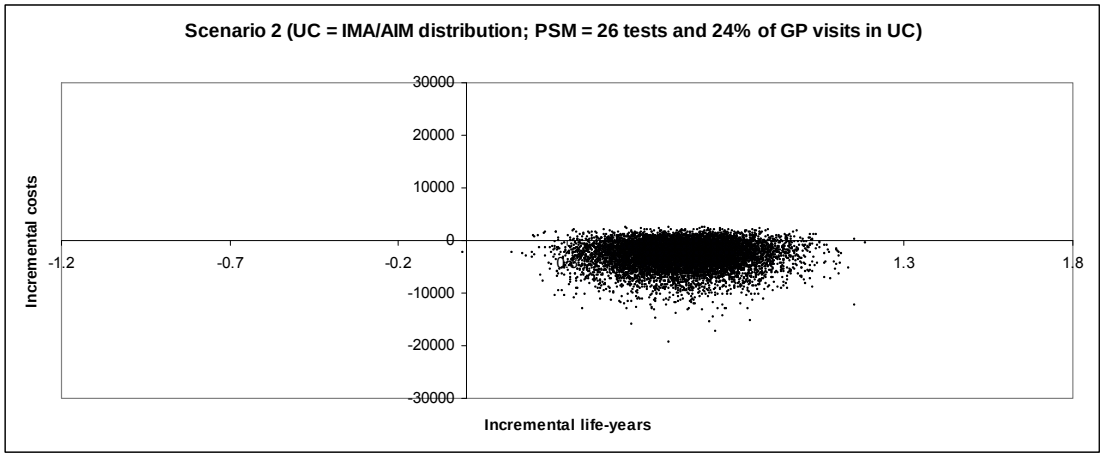


Figure 7.10 : Probabilistic analysis – Scenario 3

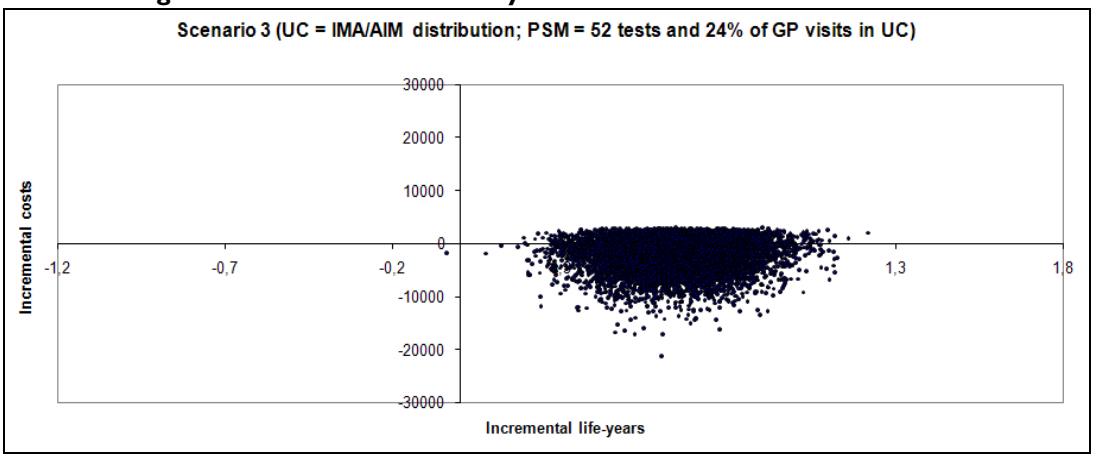


Figure 7.11 : Probabilistic analysis – Scenario 7

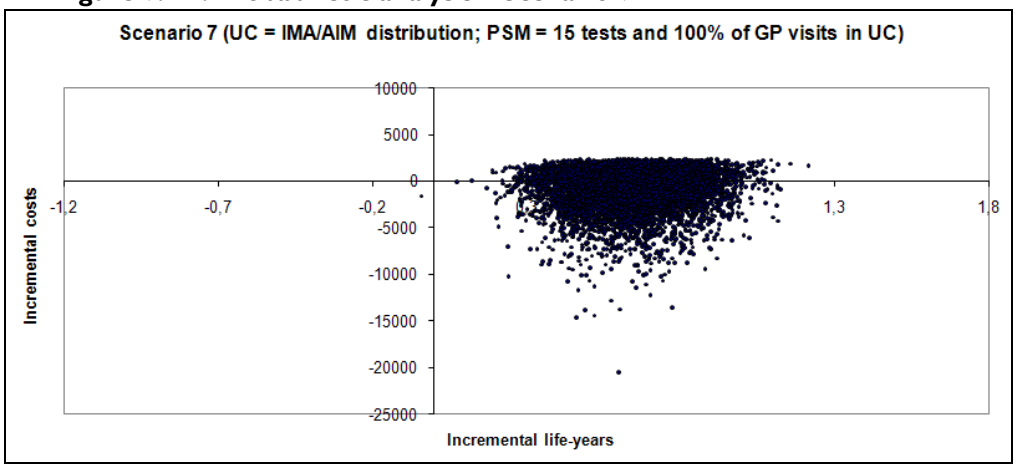


Figure 7.12 : Probabilistic analysis – Scenario 8

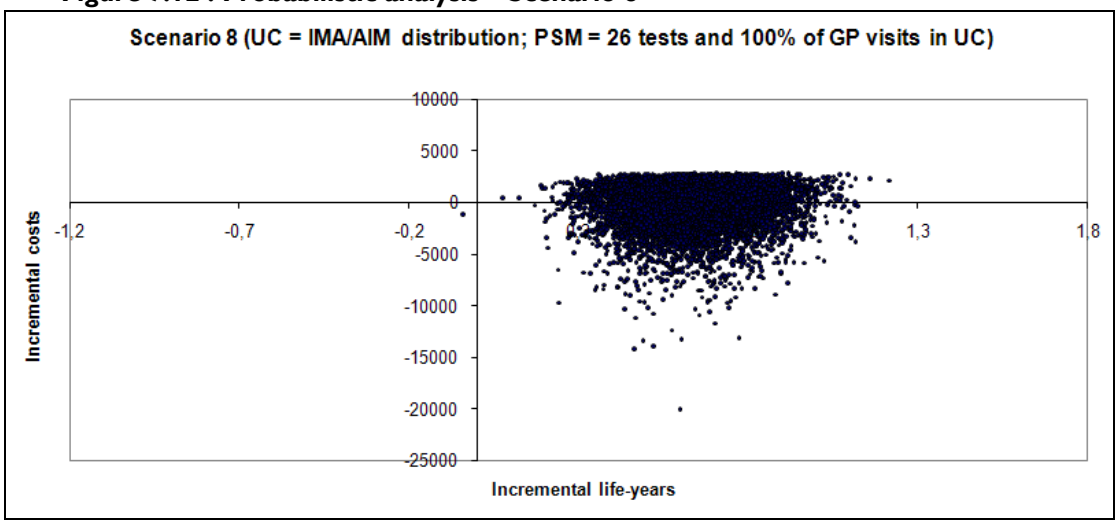
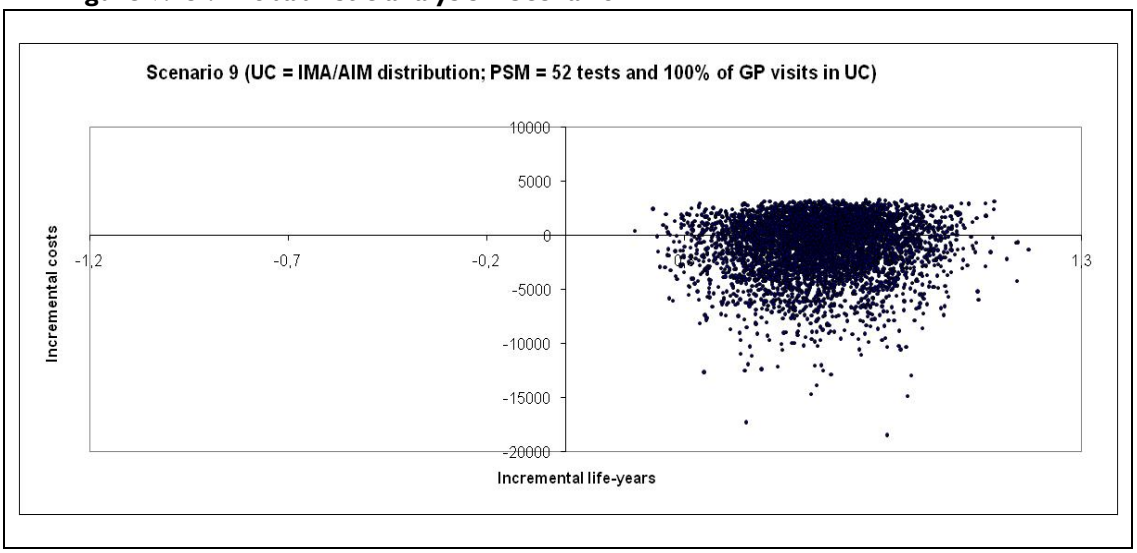


Figure 7.13 : Probabilistic analysis – Scenario 9



- **On a 10-year period, PSM is on average a dominant strategy compared to usual care, except if 100% of GP consultations are maintained and if 52 tests/year are performed**

7.4 DISCUSSION

This analysis consisted of two parts. In a first part, a cost analysis was done comparing all strategies. In a second part, a cost-effectiveness analysis was done for the PSM strategy compared to usual care. For the other strategies, no cost-effectiveness ratio was calculated as there was not sufficient comparative outcome data available.

The cost analysis shows that if an equal number of tests between strategies was performed and if current practices are not changed (median number of tests/year = 15), the use of POC by the GP, by the patient, or in ACs will on average by cost saving compared to usual care (i.e. follow-up by the GP with standard laboratory testing). It is not known however whether the assumption of an equal number of tests between strategies is valid, as the literature research showed that usually, with the use of POC, the number of tests increased.

The impact of a variation in number of tests on the costs was thus assessed in probabilistic analyses. In the scenario of 26 tests per year, the probabilistic cost analysis shows that PSM is the strategy with the highest average cost-saving compared to usual care, followed respectively by PST, and the use of POC at AC. However, with 26 tests/year, the use of POC by GP is on average no longer cost-saving. If 52 tests/year are performed, only PSM has a probability to remain cost-saving superior to 50% (i.e. 67%) and the use of POC by the GP will usually be more expensive compared to usual care.

In the base case, it was also assumed that 24 % of GP consultations or visits in usual care due to INR were maintained in PST, PSM and AC strategies because IMA/AIM data showed that 24% of INR tests were combined with other laboratory examinations. Because this assumption is not always realistic, almost for old patients with comorbidities, other scenarios were also investigated (50% and 100% of GP visits maintained). The probabilistic analysis for these scenarios shows that the probability to remain cost-saving will be inferior to 50% for the use of POC at AC and by PST if 50% of GP consultations or visits in usual care due to INR tests are maintained and if 26 tests/ year are performed. If 100% of GP consultations or visits are maintained, the use of POC at AC and by PST will usually be more expensive than current usual care, and the probability that PSM remains cost saving will be inferior to 50%.

Moreover, the probabilistic cost-effectiveness analysis shows that PSM is on average a dominant strategy compared to usual care, which means that PSM resulted in significantly more "life years gained" than usual care and is on average cost-saving. In the worst case scenario investigated (52 tests/year and 100% of GP consultations in usual care due to INR tests maintained), PSM is on average not anymore a dominant strategy but the ICER remains usually inferior to €7 000 per life year saved. However, if 100% of GP consultations or visits in ususal care are maintained, and from 26 tests per year, the probability that PSM remains a dominant strategy will be inferior to 50%. The impact on QALY was not investigated (as no data was available on this) but with the inclusion of the quality of life, the ICER of PSM compared to usual care would be expected to improve (not evidence based). It should also be noted that effectiveness estimates (mortality rates) came from a study where the difference in the number of tests between PSM and standard laboratory tests was important (36 versus 8). Metaregression analyses performed in the chapter on clinical effectiveness showed that the difference in the number of tests between POC strategies and usual care had no significant impact on all cause mortality. If future studies showed that the number of tests could influence the results, new assessment should be done.

The mean number of patients per GP or in ACs also has an impact on results. An increasing number of patients obviously has a downward impact on costs, showing the advantage of grouping the follow-up of patients on long term anticoagulation therapy. The threshold deterministic analysis shows that a minimum of 605 patients should be followed in AC to remain cost-saving compared to usual care (in the scenario of 5 days opening per week).

With a total number of 153 634 Belgian patients on oral anticoagulation therapy (including patients on short term therapy) and assuming that 50% of these patients would be followed in ACs, no more than 127 ACs should be created. If only 25% of these patients were followed at AC (such as in USA and in Italy[106]), the maximal number of AC would be 63.

The conducted cost- and cost-effectiveness analysis is subject to a number of limitations. First of all, transportation costs were not taken into account in the base case analysis. A threshold analysis has shown that the inclusion of transportation costs in the AC strategy had no major impact on its cost position relative to usual care. The impact of these transportation costs on the cost position relative to other strategies (POC by GP, PST, PSM), however, was not examined (but was expected to be minor in Belgium). The cost of POC management at ACs for patients who are not able to move towards the clinics was also not assessed. For these patients (about 54% of home consultations in IMA/AIM data), the nurse could for example moves towards the patient residence or specific transports in ambulance could be organized. The additional cost of these strategies was however not assessed.

Beside the transportation cost, the impact of productivity and time losses was also not examined. Time losses include travelling, waiting and testing time for the patient and its caregiver, such as a family member. The impact of these elements is difficult to assess. Although all these elements are also to be considered in policy-making, they were not included in the cost analysis given the lack of supporting data.

Furthermore, no training cost of the GP or the nurse was included and the cost of patients' training was based on a proxy. Nevertheless, the influence of this cost on results would be minor, as this cost would be allocated over a large number of years and/or patients.

The cost of PSM strategy could also be underestimated at the beginning of the treatment. Indeed, if patients contact regularly a health professional at the beginning of their treatment, the cost of PSM could approach the cost of PST.

It should also be noted that the cost linked to the waste management concerning the lancets was not included in this analysis. Lancets are hazardous waste and according to the law (e.g. AGF 2003-12-05/82 art. 5.5.2.1), it is forbidden to throw them in traditional garbage can. As for diabetics patients, these lancets must be collected in specific container (usually yellow) available in pharmacy and must be thrown in the local container park or given during the collecting of hazardous waste organized by local authorities. According to the association for patients on long term anticoagulation therapy, a container of 0.5 litters cost around €2.5[101].

Finally, it should be noted that not enough information was available neither on the number of patients eligible for PST or PSM or for follow-up at anticoagulation clinics in Belgium nor on the number of GP contacts maintained. Therefore, a budget impact analysis was not performed. However, this chapter gives an idea of the average cost-savings per patient for each strategy. In the future, a pilot study to determine these parameters could be performed in Belgium, which could allow us to determine the budgetary impact of POC management.

If current practices are not changed for the number of INR tests (Belgian median = 15 tests/year),

by taking into account a reduced cost of complications (for PSM and PST),

and if the number of GP contacts (linked to INR tests) is reduced to 24% of the current number for PST, PSM and POC at AC:

- **The use of POC is usually a cost-saving strategy (probability >70%) compared to usual care for each strategy (PSM, PST, POC at GP and POC at AC)**

In the scenario of 26 tests/year in each strategy,

by taking into account a reduced cost of complications (for PSM and PST),

and if the number of GP contacts (linked to INR tests) is reduced to 24% of the current number for PST, PSM and POC at AC:

- **PSM is the strategy with the highest average cost-saving compared to current usual care, followed respectively by PST and the use of POC at AC;**
- **The use of POC by GP is on average no longer cost-saving compared with current usual care (median of 15 tests/ year) (probability to remain cost-saving = 31%)**

In the scenario of 52 tests/year,

by taking into account a reduced cost of complications (for PSM and PST),

and if the number of GP contacts (linked to INR tests) is reduced to 24% of the current number for PST, PSM and POC at AC:

- **Only PSM has a probability to remain cost-saving superior to 50% (i.e.67%);**
- **The use of POC by GP is usually more expensive than current usual care (median of 15 test/year) (probability = 97%).**

If 50 % of GP contacts in usual care are maintained

and if 26 tests per year are performed,

- **The probability that the use of POC at AC and by PST remains cost-saving will be inferior to 50%**

If 100 % of GP contacts in usual care are maintained,

and from 26 tests per year,

- **The use of POC at AC and by PST will usually be more expensive than usual care (probability to remain cost-saving <25%),**
- **PSM will on average no longer be cost-saving (probability to remain cost-saving <50%)**

8 CONCLUSIONS

The scope of this report included four topics about the monitoring of INR by POC devices in patients with long term oral anticoagulation with vitamin K antagonists: clinical effectiveness, patient issues, organisation model and economic analysis

8.1 CLINICAL EFFICACY

Several clinical questions about the clinical efficacy of monitoring with POC devices have been developed in this report. The responses are shortly presented here. The methodological quality of supporting evidence used is described by the GRADE working group [155] and presented in table 8.1.

- In the clinical pathway, the POC device replaces laboratory INR testing and thereby simplifies the pre analytical and the post analytical phases of INR monitoring, especially in case of PSM and if a health professional uses a POC compared with usual care (low quality of evidence).
- Technical accuracy is good but only one study was identified (low quality of evidence).
- Several technical problems may cause uninterpretable INR results; essentially the first months, at the start of self testing with 4 to 25% extra finger pricks (low quality of evidence).
- The diagnostic performances of POC devices are acceptable to good, with limitations described in the report (moderate quality of evidence).
- There are no additional safety problems due to POC devices compared with veni-puncture (low quality of evidence)
- External quality control is recommended for POC devices with a range of 2 to 6 controls per year (low quality of evidence). Four processes are studied: comparison with a reference laboratory, conventional EQA (overall median), UK NEQAS programme (2 lyophilised certified plasmas) or ECAA quality control (5 certified ranges plasmas).

With respect to the impact on patients' outcomes, our meta-analysis shows that

- Point-of-care testing leads to less thrombo-embolic events (pooled odds ratio of 0.43; 95% CI 0.32, 0.58) and less all cause mortality (pooled odds ratio is 0.59; 95% CI 0.46, 0.74), and has no impact on the number of major bleeding events (moderate quality evidence).
- For patient self-management, the pooled odds ratio for major thrombo-embolism is 0.39 (95% CI 0.27, 0.56) and 0.55 (95% CI 0.42, 0.72) for all cause mortality (moderate quality evidence).
- For patient self-testing, the pooled odds ratio for major thrombo-embolism is 0.54 (95% CI 0.30, 0.97), but is not significant for all cause mortality (moderate quality evidence).
- No significant difference for major thrombo-embolism or mortality was found for GP and nurses using POC devices, but only one study was available for each of these comparisons (moderate quality of evidence).
- Sensitivity analyses did not show a significant effect of the setting of the control group, duration of the study or the ratio of frequency of testing.

These clinical conclusions are concordant with those of recent HTA reports [7 66 9].

8.2 PATIENT ISSUES

Three aspects were mainly developed in the literature: changes in quality of life, criteria to select candidates to PSM or PST, and patients' training.

- Patient satisfaction scores, such as overall satisfaction, pain, distress, are in favour of POC, compared with previous usual care with venous punction (low quality of evidence)
- Criteria to select candidates to POC devices include personal willingness; physical capacity of self testing (motor skills, eyesight) and capacity to complete training and succeed in accurately perform an INR test, manage of quality control issues, use of algorithm and adjustment of dosage, and document INR results and adverse events (low quality of evidence).
- The percentage of patients able to carry out PST or PSM was estimated to 24% in Canada[7] and to 14% in UK[66] .

8.3 ORGANISATION MODEL

The organisation of INR testing in patients with long term oral anticoagulation varies between countries in Europe such as the extent coverage of POC testing, going from no public coverage (Belgium) to complete coverage (Netherlands).

Conditions to obtain reimbursement include mandatory successful training usually given by an official organization and regular external quality controls such as parallel determination of the INR by blood sample analysis in laboratory.

For PST or PSM additional criteria are imposed on the patient, including adequate physical and cognitive capacities to use the POC device and to manage the anticoagulation therapy and being on long-term anticoagulation therapy (>1 year or lifelong).

A CoaguChek XS price varies from €620 (Luxembourg) to €1136 (France) and is around €1054 in Belgium.

Table 8.1: GRADE CLASSIFICATION

Grade of Recommendation/ Description	Benefit vs. Risk and Burdens	Methodological Quality of Supporting Evidence	Implications
1A/ Strong recommendation, high quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	RCTs without important limitations or overwhelming evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
1B/ Strong recommendation, moderate quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
1C/ Strong recommendation, low quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	Observational studies or case series	Strong recommendation, but may change when higher quality evidence becomes available
2A/ Weak recommendation, high quality evidence	Benefits closely balanced with risks and burden	RCTs without important limitations or overwhelming evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients' or societal values
2B/ Weak recommendation, moderate quality evidence	Benefits closely balanced with risks and burden	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients' or societal values
2C/ Weak recommendation, low quality evidence	Benefits closely balanced with risks and burden	Observational studies or case series	Very weak recommendation, other alternatives may be equally reasonable

8.4 ECONOMIC CONCLUSIONS

The literature review has shown that the cost-effectiveness of POC strategies compared to usual care depends on various factors (effectiveness of usual care, number of tests, etc.) and current studies are not sufficient to conclude on the cost-effectiveness of the different POC management strategies in a Belgian setting. A new model was therefore developed.

The analysis shows that if current practices are maintained, POC strategies will on average be cost-saving compared to a follow-up by the GP with standard laboratory testing (probability >70%) (see Table 8.2).

In a scenario with 24% of GP consultations or visists maintained for PSM, PST and POC at AC, a variation of the number of tests shows that if one test every two weeks is performed (i.e. 26 tests per year) in POC strategies, PSM will be the strategy with the highest average cost-saving compared to usual care, followed respectively by PST and the use of POC at AC. The analysis also shows that with 26 tests/year, the use of POC by GP will on average no longer be cost-effective compared with current usual care (median of 15 tests/ year) (probability to remain cost-saving = 31%).

With one test per week (52 tests/year), only PSM has a probability to remain cost-saving superior to 50% (i.e.67%) and the use of POC by GP will become more expensive than usual care (probability = 97%).

Moreover, if 50 % of GP consultations or visits in usual care are maintained and if 26 tests per year are performed, the probability that the use of POC at AC and by PST remains cost-saving will be inferior to 50%. If 100 % of GP consultations or visits in usual care are maintained and if 26 tests per year are performed, the use of POC at AC and by PST will usually be more expensive than usual care (probability to remain cost saving <25%) and the probability that PSM (from 26 tests/year) remains a cost-saving strategy will be inferior to 50%.

The probabilistic cost-effectiveness analysis also shows that PSM is usually on average a dominant strategy compared to usual care. On a 10-year period, PSM results in significantly more "life years gained" than usual care and is usually on average cost-saving. However, if 100% GP consultations or visists in usual care are maintained, and from 26 tests per year, the probability that PSM remains a dominant strategy will be inferior to 50%.

Table 8.2 : Probabilistic cost analysis taking into account reduced risk of thromboembolic complications for PST and PSM – Base case scenario (24% of GP consultations in usual care maintained for PST-PSM and AC)

Strategies	Number of tests/year	Number of GP consultations	Incremental cost		Probability <€0
			Average	95% CI	
POC by GP	IMA/AIM data distribution*	Equal to the number of tests	-€ 161.18	(-408.20 to -47.81)	100.00%
	26	Equal to the number of tests	€ 115.55	(-907.51 to 585.06)	30.60%
	52	Equal to the number of tests	€ 973.50	(-49.55 to 1443.02)	2.96%
POC at AC (software)	IMA/AIM data distribution*	24%**	-€ 208.09	(-941.97 to 128.72)	73.72%
	26	24%**	-€ 159.79	(-1029.11 to 239.16)	60.26%
	52	24%**	-€ 10.07	(-879.38 to 388.89)	41.10%
POC at AC (algorithm)	IMA/AIM data distribution*	24%**	-€ 221.73	(-955.62 to 115.07)	76.36%
	26	24%**	-€ 173.44	(-1042.75 to 225.51)	62.28%
	52	24%**	-€ 23.72	(-893.03 to 375.24)	42.62%

PST	15	24%**	-€ 355.58	(-1459.55 to 204.75)	77.58%
	26	24%**	-€ 202.20	(-1306.17 to 358.13)	60.00%
	52	24%**	€ 160.32	(-943.65 to 720.65)	28.88%
PSM	15	24%**	-€ 429.34	(-1359.28 to 72.39)	91.74%
	26	24%**	-€ 367.23	(-1297.17 to 134.49)	85.06%
	52	24%**	-€ 220.44	(-1150.38 to 281.28)	67.24%

* Distribution = gamma(1.46;8.22;shift: 6.01). In the IMA/AIM data, the mean number of test was 17.6 and the median number of tests was 15.3; **24% of GP visits in usual care are maintained; POC = Point of care; CI = credibility interval; GP = general practitioner; AC = Anticoagulation clinic; PST = patient self-testing; PSM = patient self-management

8.5 GLOBAL CONCLUSION

Compared with laboratory INR testing, the testing of INR with point-of-care devices is a good option for patients with long term anticoagulation with vitamine K antagonists. Globally, POC testings increase patient' satisfaction, lead to less thrombo-embolic events and less all cause mortality but have no impact on the number of major bleeding events.

Four potential organisation models are compared: two at patient level (PSM and PST) and two at health professional level (POC by GP and POC in AC). PSM and PST strategies need patient selection and training. In specific situations (such as child), PSM or PST may be done by a close relative. External quality control is needed for POC devices in each strategy.

- Patient self monitoring (PSM) is the first choice organisation at the patient level with respect to clinical outcomes (less thrombo-embolic events and less all causes mortality), and also at the payer level, because it is the dominant strategy with the highest cost-savings.
- Compared with PSM, patient self-testing (PST) is the second choice at patient level. PST improves thrombo-embolic events but not all causes mortality. For the payer perspective the cost-savings are also lower and depend of the number of INR tests and essentially of the number of GP visits maintained.
- Considering the use of POC by GP, there is not evidence that it improves (or damages) the clinical outcomes of patients compared with usual care. From the payer perspective, such strategy is cost saving compared with the same number of laboratory INR testing. The increase of the number of POC tests goes however always with an increase of the number of GP contacts and this strategy is not yet cost-saving in a scenario of 26 tests/ patient/ year.
- Considering the use of POC devices by health professionals in anticoagulation clinics, there is also not evidence that it improves (or damages) the clinical outcomes of patients compared with usual care. In this strategy, the incremental costs depends on several parameters: the number of opening hours of the AC, the number of patients followed, the number of INR tests per patient and per year, and especially the number of remaining GP consultations or visits.

In conclusion, for patients who have the willingness and the ability to do it, PSM is the best strategy. Patients scheduled to long term oral anticoagulation (or close relative of such patients) should be encouraged and trained for PSM. For others patients who need help for testing and/or management, several POC strategies (PST, POC at GP, and POC at AC) were available, near usual care with laboratory INR testing, with advantages and limits described in this report.

9 APPENDICES

9.1 APPENDIX : IMPACT ON PATIENT OUTCOME

9.1.1 Appendix: search terms used for update

Medline

1	exp anticoagulants/	148703
2	(warfarin or coumadin or coumarin).mp. [mp=title, original title, abstract, name of substance word, subject heading word]	19942
3	(oral adj anticoagul$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]	4838
4	1 or 3 or 2	154338
5	Self Administration/	6838
6	Drug Administration Schedule/	66244
7	International Normalized Ratio/	2025
8	Point-of-Care Systems/	3623
9	near patient test$.mp.	199
10	self test$.mp.	428
11	self manage$.mp.	4122
12	Drug Monitoring/	9192
13	Primary Health Care/	37864
14	(primary care or general practice or general practitioner$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]	87315
15	6 or 11 or 7 or 9 or 12 or 14 or 8 or 10 or 13 or 5	195294
16	4 and 15	4239
17	limit 16 to yr="2004 - 2009"	1804

Embase

1	warfarin OR coumadin OR coumarin AND [2004-2009]/py	18,625
2	oral AND anticoagul* AND [2004-2009]/py	7,694
3	'anticoagulant agent'/exp AND [2004-2009]/py	94,949
4	#1 OR #2 OR #3 AND [embase]/lim	89,263
5	'drug self administration'/exp OR 'drug administration'/exp OR 'international normalized ratio'/exp AND [embase]/lim AND [2004-2009]/py	12,436
6	point AND of AND care AND systems AND [embase]/lim AND [2004-2009]/py	693
7	near AND 'patient'/exp AND test AND [embase]/lim AND [2004-2009]/py	101
8	'self'/exp AND test* AND [embase]/lim AND [2004-2009]/py	3,033
9	'self'/exp AND manage* AND [embase]/lim AND [2004-2009]/py	1,809
10	'drug monitoring'/exp AND [embase]/lim AND [2004-2009]/py	5,802
11	'primary health care'/exp AND [embase]/lim AND [2004-2009]/py	20,151
12	'primary care' OR 'general practice' OR 'general practitioner' AND [embase]/lim AND [2004-2009]/py	36,063
13	#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12	65,494
14	#4 AND #13	4,772
15	'randomized controlled trial'/exp OR 'clinical trial'/exp OR 'controlled clinical trial'/exp OR 'double blind procedure'/exp OR 'randomization'/exp OR 'placebo'/exp AND [embase]/lim AND [2004-2009]/py	231,562
16	#15 AND #14	1,437

CENTRAL

#1	MeSH descriptor Anticoagulants, this term only	2591
#2	warfarin or coumarin or coumadin in Clinical Trials	1452
#3	oral anticoagul* in Clinical Trials	890
#4	(#1 OR #2 OR #3), from 2004 to 2009	837
#5	MeSH descriptor Self Administration explode all trees	536
#6	MeSH descriptor Drug Monitoring explode all trees	787
#7	(international normalised ratio):ti,ab,kw, from 2004 to 2009 in Clinical Trials	187
#8	(point of care):ti,ab,kw, from 2004 to 2009 in Clinical Trials	997
#9	(#5 OR #6 OR #7 OR #8), from 2004 to 2009	1459
#10	(#4 AND #9), from 2004 to 2009	171

9.1.2 appendix: hta reports and systematic reviews

9.1.2.1 Canadian Agency for Drugs and Technologies in Health

The literature was searched in multiple databases (Medline, Embase, BIOSIS, PASCAL and DIALOG databases, Cochrane Library, CRD, LILACS), using a sensitive search strategy. Included studies were RCTs only, with patients taking oral anticoagulants for at least 3 months after the start of the trial, comparing POC testing at an anticoagulation clinic, POC self-testing by the patient, POC self-testing plus self-management and control, or any other POC management strategy with usual care (venipuncture blood draw for an INR lab test and management provided by an anticoagulation clinic or individual practitioner). The outcomes were rates of major haemorrhage, major thromboembolic event rates and time in range.

The report included 16 RCTs, which are listed in table 9.1.

9.1.2.2 MSAC 2005

This report is limited to the use of INR point-of-care testing in the general practice setting. Multiple electronic databases were searched: Medline, Embase, Cochrane Controlled Trials Register (now CENTRAL), Current Contents, Science Citation Index, Cochrane Database of Systematic Reviews, Evidence Based Reviews and CRD Database. In addition, other sources of information were consulted. A sensitive search string was used; search date October 2004.

Outcomes considered were time in therapeutic range, major bleeding and thromboembolic events.

Two studies were included in the report, of which one was a cross-over RCT and the other was a case series. The RCT is listed in table 9.1.

9.1.2.3 NIHR 2007

This report was identified in the search for systematic reviews, but was essentially a HTA report by the Health Technology Assessment Programme of the National Institute for Health Research (UK)[66].

Literature was searched in Medline, Embase, CENTRAL and CINAHL using a sensitive search string. In addition, reference lists were scanned and ongoing or unpublished studies were searched in trial registries. Search date was September 2005. The scope of the report included near patient testing in primary care, patient self-testing and patient self-management.

The report included 16 RCTs, listed in table 9.1.

9.1.2.4 Christensen 2007

The databases Cochrane Controlled Trial Register and Medline were searched using a sensitive search string, supplemented by hand searching, reference tracking and personal files. Search date was December 2005. All RCTs including patient ≥ 18 years of age with an expected duration of oral anticoagulant treatment of ≥6 months and comparing POC self-management or self-testing with usual care were included. Outcomes were death, major complications including major thromboembolic events or major bleeding events, and minor complications.

Ten studies were included in the systematic review, listed in table 9.1.

9.1.2.5 Heneghan 2006

The following databases were searched: Medline, Embase, CENTRAL, trials registries. In addition, references lists were checked, manufacturers approached and experts consulted. Search date was 2005. Studies were eligible if they were RCTs comparing patient self-testing or self-management to usual care, and reporting the clinical outcomes major bleeding and thromboembolic events.

The review included 14 RCTs, listed in table 9.1.

9.1.2.6 Siebenhofer 2004

The authors searched Medline, Embase, the Cochrane Library and the Cochrane Controlled Trials Register, using a sensitive search string. Search date was January 2003. Studies were eligible in case they were randomised controlled trials, compared self-management control versus routine care in oral anticoagulation patients. Outcomes included anticoagulation control, major bleeding, recurrent thromboembolism, all-cause mortality and treatment-related quality of life.

Four studies were included, listed in table 9.1.

9.1.2.7 Cochrane systematic review by Garcia-Alamino et al.

Based on the information available, 18 studies were included (table 9.1), of which one unpublished (Kaatz). As additional information on the design and data of this unpublished study by Kaatz et al. was not yet available, it was not included in our review.

Table 9.1: studies included in previous HTA reports and systematic reviews, and found in KCE update

	CADTH 2007	MSAC 2005	NIHR 2007	Christensen 2007	Heneghan 2006	Siebenhofer 2004	Cochrane 2009	KCE update 2009
Beyth 2000	x		x		x		x	
Claes 2005	x							
Cromheecke 2000	x		x	x	x	x	x	
Fitzmaurice 2005	x		x	x			x	
Fitzmaurice 2002			x	x	x		x	
Fitzmaurice 2000	x							
Gadisseur 2003	x		x	x	x		x	
Gardiner 2005			x		x		x	
Gardiner 2006			x					
Horstkotte 1998	x		x		x		x	
Khan 2004	x		x		x		x	
Koertke 2000	x							
Koertke 2001	x		x	x	x	x	x	
Menendez-Jandula 2005	x		x	x	x		x	
Sawicki 1999	x		x	x	x	x	x	
Shiach 2002	x	x						
Sidhu 2001	x		x	x	x		x	
Sunderji 2004	x		x	x	x		x	
Voller 2005	x		x	x	x		x	
Watzke 2000						x		
White 1989			x		x		x	
Christensen 2006							x	x
Christensen 2007								x
Eitz 2008								x
Jackson 2004								x
Koertke 2007								x
Siebenhofer 2007							x	x
Siebenhofer 2008								x
Soliman Hamad 2009								x
Staresinic 2006								x
Kaatz (unpublished)							x	

9.2 APPENDIX: SOURCES FOR THE REIMBURSEMENT CONDITIONS COMPARISON

Belgium	1) Contact with Roche Diagnostic (Dominique Bolain) 2) Contact with the « Cliniques universitaires Saint-Luc » 3) Website: http://www.girtac.be (Lucio Scanu) 4) Specialized literature : [84]
UK	1) Official websites : http://www.dh.gov.uk/ http://www.nhs.uk http://www.nice.org.uk 2) Other websites : http://www.ismaap.org/ http://www.anticoagulationeurope.org/ 3) Specialized literature : [53, 102, 103, 105-109, 156]
Germany	1) Websites : http://www.ismaap.org/ http://www.asaev.de/ 2) Specialized literature : [110-112]
The Netherlands	1) Official website: http://www.fnt.nl 2) Other websites : http://www.ismaap.org/ http://www.trombosedienstfrieslandnoord.nl/ http://www.trombosedienst-leiden.nl/
Switzerland	1) Official website : http://www.bag.admin.ch/ 2) Other web site : http://www.ismaap.org/ http://www.coagulationcare.ch/ (Contact with Walter Wuillemin)
Luxembourg	1) Official website : http://www.secu.lu/ http://www.cns.lu/ http://www.legilux.public.lu/ 2) Other web site : http://www.ismaap.org/ 3) Specialized literature : [116, 117]
France	1) Official website : http://www.legifrance.gouv.fr/ 2) Other web site : http://www.ismaap.org/ http://www.has-sante.fr/ (Contact with Dr Catherine Denis) 3) Specialized literature : [118-120]

9.3 APPENDIXES ECONOMIC LITERATURE RESEARCH

9.3.1 Appendix : Literature search strategy

Date	January, 09 2009
Database	Ovid MEDLINE(R)
Date covered	1950 to Present with Daily Update
Search Strategy	1 exp "costs and cost analysis"/ (142811) 2 cost of illness/ (11316) 3 exp health care costs/ (32513) 4 exp economics/ (406956) 5 value of life/ (5096) 6 exp "economics, dental"/ (3748) 7 exp "economics, hospital"/ (15983) 8 exp "economics, medical"/ (12227) 9 exp "economics, nursing"/ (3862) 10 exp "economics, Pharmaceutical"/ (2018) 11 quality-adjusted life years/ (3732) 12 models, economic/ (3362) 13 markov chains/ (5289) 14 monte carlo method/ (11953) 15 decision tree/ (6754) 16 6 or 11 or 3 or 7 or 9 or 12 or 2 or 15 or 14 or 8 or 1 or 4 or 13 or 10 or 5 (431936) 17 econom$.tw. (98011) 18 cost$.tw. (220977) 19 (price? or pricing?).tw. (15395) 20 (pharmacoeconomic? or (pharmaco adj economic?)).tw. (2128) 21 budget$.tw. (12069) 22 expenditure$.tw. (24341) 23 cea.tw. (12622) 24 cua.tw. (622) 25 cba.tw. (7984) 26 25 or 21 or 17 or 20 or 22 or 18 or 24 or 16 or 19 or 23 (668427) 27 exp anticoagulants/ (152548) 28 exp 4-Hydroxycoumarins/ (14170) 29 (oral adj anticoagul$).tw. (4789) 30 international normalized ratio/ (2079) 31 point of care systems/ (3683) 32 drug monitoring/ (9362) 33 blood coagulation tests/ (15299) 34 27 or 28 or 29 (153469) 35 33 or 32 or 30 or 31 (29780) 36 35 and 34 (6857) 37 36 and 26 (217)
Note	

Date	January, 13 2009
Database	Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations
Date covered	January 12, 2009
Search Strategy	1 econom$.tw. (11264) 2 cost$.tw. (23662) 3 (price? or pricing?).tw. (1537) 4 (pharmacoeconomic? or (pharmaco adj economic?)).tw. (207) 5 budget$.tw. (1188) 6 expenditure$.tw. (2226) 7 cea.tw. (804) 8 cua.tw. (33) 9 cba.tw. (259) 10 (oral adj anticoagul$).tw. (366) 11 Point-of-Care Systems.mp. [mp=title, original title, abstract, name of substance word, subject heading word] (6) 12 inr.mp. [mp=title, original title, abstract, name of substance word, subject heading word] (393) 13 self test$.mp. [mp=title, original title, abstract, name of substance word, subject heading word] (50) 14 International Normalized Ratio.mp. [mp=title, original title, abstract, name of substance word, subject heading word] (292) 15 blood coagulation test$.mp. (8) 16 (Acenocoumarol or Dicumarol or Ethyl Biscoumacetate or Phenprocoumon or Warfarin).mp. (964) 17 anticoagul$.mp. (3095) 18 6 or 3 or 7 or 9 or 2 or 8 or 1 or 4 or 5 (36352) 19 16 or 10 or 17 (3611) 20 11 or 13 or 12 or 15 or 14 (562) 21 19 and 20 (332) 22 21 and 18 (18)
Note	

Date	January, 09 2009
Database	Ovid Econlit
Date covered	1969 to December 2008
Search Strategy	1 econom$.tw. (228653) 2 cost$.tw. (70244) 3 (price? or pricing?).tw. (81693) 4 (pharmacoeconomic? or (pharmaco adj economic?)).tw. (227) 5 budget$.tw. (12296) 6 expenditure$.tw. (14736) 7 cea.tw. (80) 8 cua.tw. (12) 9 cba.tw. (109) 10 inr.mp. [mp=heading words, abstract, title, country as subject] (1) 11 self test$.mp. [mp=heading words, abstract, title, country as subject] (14) 12 International Normalized Ratio.mp. [mp=heading words, abstract, title, country as subject] (0) 13 point-of-care.mp. [mp=heading words, abstract, title, country as subject] (2) 14 blood coagulation test$.mp. [mp=heading words, abstract, title, country as subject] (0) 15 6 or 3 or 7 or 9 or 2 or 8 or 1 or 4 or 5 (336810)

	16 anticoagulant$.mp. [mp=heading words, abstract, title, country as subject] (2) 17 (oral adj anticoagul$).mp. [mp=heading words, abstract, title, country as subject] (1) 18 16 or 17 (2) 19 11 or 13 or 10 or 12 or 14 (17) 20 18 and 19 (0) 21 19 and 15 (12)
Note	

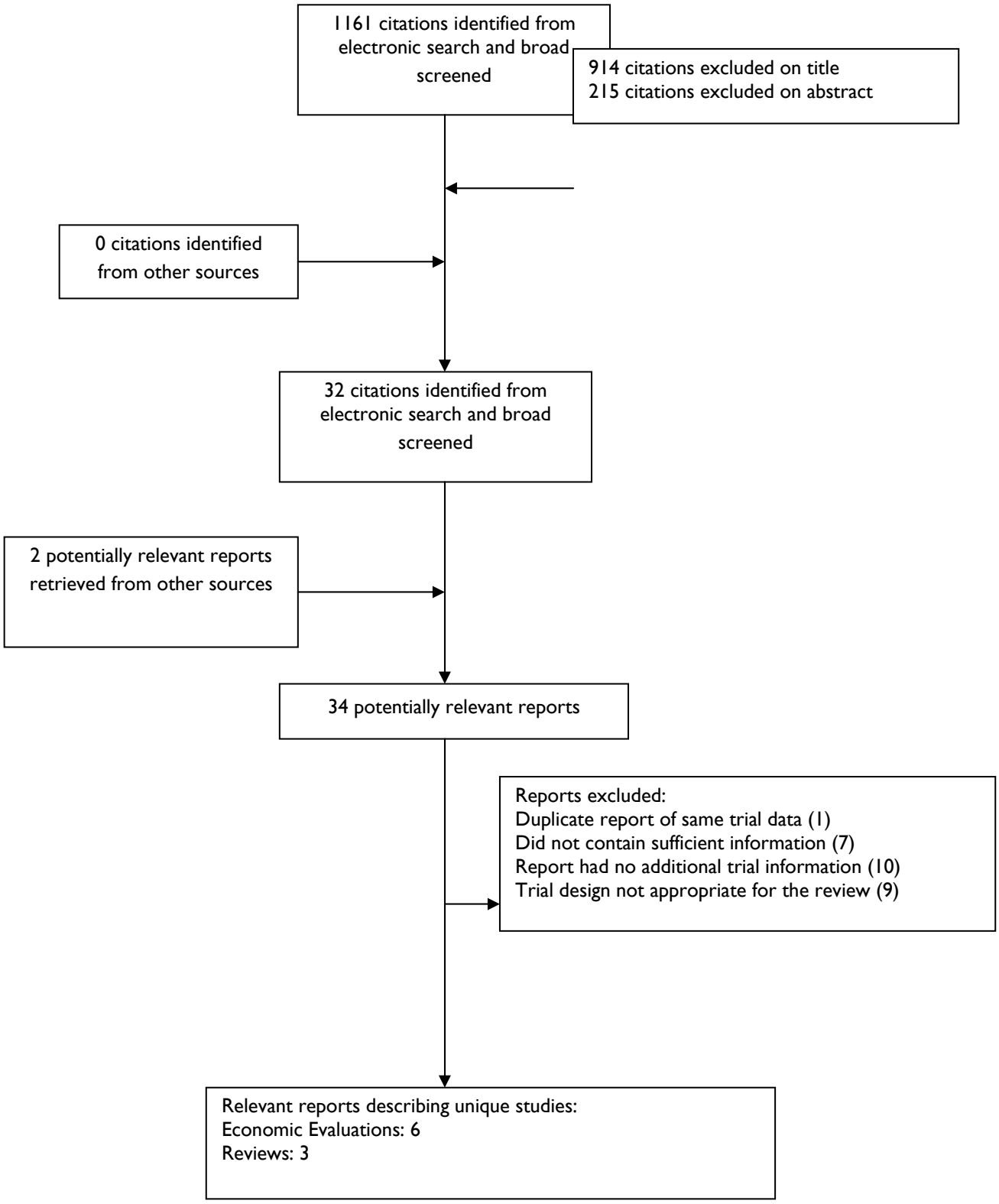
Date	January,09 2009
Database	Ovid PsycINFO
Date covered	1806 to January Week 1 2009
Search Strategy	1 econom$.tw. (52461) 2 cost$.tw. (39812) 3 (price? or pricing?).tw. (6454) 4 (pharmacoeconomic? or (pharmaco adj economic?)).tw. (211) 5 budget$.tw. (3371) 6 expenditure$.tw. (4114) 7 cea.tw. (304) 8 cua.tw. (15) 9 cba.tw. (414) 10 inr.mp. [mp=title, abstract, heading word, table of contents, key concepts] (41) 11 self test$.mp. [mp=title, abstract, heading word, table of contents, key concepts] (237) 12 International Normalized Ratio.mp. [mp=title, abstract, heading word, table of contents, key concepts] (12) 13 point-of-care.mp. [mp=title, abstract, heading word, table of contents, key concepts] (59) 14 blood coagulation test$.mp. [mp=title, abstract, heading word, table of contents, key concepts] (1) 15 6 or 3 or 7 or 9 or 2 or 8 or 1 or 4 or 5 (97924) 16 anticoagulant$.mp. [mp=title, abstract, heading word, table of contents, key concepts] (179) 17 (oral adj anticoagul$).mp. [mp=title, abstract, heading word, table of contents, key concepts] (32) 18 16 or 17 (186) 19 11 or 13 or 10 or 12 or 14 (343) 20 18 and 19 (12) 21 20 and 15 (0) 22 18 and 19 (12)
Note	

Date	January, 13 2009
Database	Cochrane Library: Cochrane Database of systematic reviews, DARE, Cochrane Central Register of Controlled Trials, HTA, NHS EED, Cochrane groups and Methods studies.
Date covered	1993 to Present
Search Strategy	#1 MeSH descriptor Economics explode all trees 27625 #2 MeSH descriptor Costs and Cost Analysis explode all trees 25894 #3 cost or costs or costing 43481 #4 economic* or pharmacoeconomic* 36109 #5 (#1 OR #2 OR #3 OR #4) 48566 #6 MeSH descriptor Anticoagulants explode all trees 6633 #7 MeSH descriptor 4-Hydroxycoumarins explode all trees 1015 edit delete #8 anticoagul* 4777 #9 MeSH descriptor International Normalized Ratio explode all trees 249 #10 MeSH descriptor Blood Coagulation Tests explode all trees 1413 #11 MeSH descriptor Point-of-Care Systems, this term only 200 #12 MeSH descriptor Drug Monitoring explode all trees 775 #13 international normalized ratio or international normalised ratio or inr 824 #14 (#6 OR #7 OR #8) 8314 #15 (#9 OR #10 OR #11 OR #12 OR #13) 2818 #16 (#14 AND #15) 1307 #17 (#16 AND #5) 135
Note	Cochrane Database of Systematic Reviews [13] | Database of Abstracts of Reviews of Effects [4] | Cochrane Central Register of Controlled Trials [41] | Methods Studies [0] | Health Technology Assessment Database [5] | NHS Economic Evaluation [72] | Cochrane Groups [0].

Date	January, 13 2009
Database	Embase
Date covered	1974 to present
Search Strategy	#1. 'health economics'/exp OR 'health economics' 431,365 #3. 'health care cost'/exp OR 'health care cost' 136,298 #4. 'economic evaluation'/exp OR 'economic evaluation' 142,216 #7. 'pharmacoeconomics'/exp OR 'pharmacoeconomics' 139,701 #8. 'health care cost'/exp OR 'health care cost' 136,298 #12. expenditure*:ab,ti NOT energy:ab,ti 15,106 #13. econom*:ab,ti OR cost:ab,ti OR costs:ab,ti OR cost 361,686 ly:ab,ti OR costing:ab,ti OR price:ab,ti OR prices :ab,ti OR pricing:ab,ti OR pharmacoeconomic*:ab,ti #14. budget*:ab,ti 15,846 #15. 'value *2 money' 713 #16. #1 OR #3 OR #4 OR #7 OR #8 OR #12 OR #13 OR #14 OR 672,275 #15 #17. 'anticoagulant agent'/exp 336,273 #18. 'international normalized ratio'/exp 2,535 #19. 'blood clotting test'/exp 10,194 #20. 'point of care testing'/exp 804 #21. 'drug monitoring'/exp 31,871 #22. 'self test':ab,ti 267

	#23. 'international normalized ratio':ab,ti OR 'interna tional normalised ratio':ab,ti OR 'inr':ab,ti	4,655
	#24. #18 OR #19 OR #20 OR #21 OR #22 OR #23	48,584
	#25. #17 AND #24	10,082
	#26. #16 AND #25	785
Note		

9.3.2 Appendix : Flow diagram For cost-effectiveness studies



9.3.3 Appendix : data extraction form

Authors (Year)	Connock M, Stevens C, Fry-Smith A, Jowett S, Fitzmaurice D, Moore D, Song F (2007).
Funding	NHS R&D HTA Programme.
Country	UK.
Design	CUA, Markov Model (based on a previous RCT). [*Fitzmaurice 2005 self …*]
Perspective	NHS.
Time window	5 and 10 years
Interventions	Patient self-testing and patient self monitoring (PST/PSM) versus current routine care in the UK (clinic-based monitoring with blood sample sent to laboratory). Instrument: Roche CoaguChek S.
Population	Patients aged 65 years and on long term oral anticoagulation therapy.
Assumptions	1) The risk of haemorrhagic and thrombotic complications was determined by the quality of anticoagulation control (percentage of INR time in, below or above the therapeutic range). 2) 50% of patients disabled due to major haemorrhagic events stopped oral anticoagulation therapy. Thus, the risk of complication for these patients was assumed to increase (RR: +1.0). 3) The risk of death compared with the general population of the same age was assumed to be higher (Risk ratio = 1.2). 4) The risk of death in patients with minor haemorrhagic or thrombotic events was also assumed to be higher (RR: +1.0, +1.75, +2.5). 5) The risk of complications in PSM patients was assumed to be reduced by 5% (range tested: 0-10%). The reduction of complication risk in PSM patients due to training, etc. was assumed to be 2,5% (0-5%). 6) Utility associated with minor haemorrhagic events was assumed to be 0.72 (0.70-0.74). 7) The GP consultation time was estimated to be 10 minutes. 8) 40% of patients who received PSM training did not perform PSM. 9) The cost due to patient training and CoaguChek machine were applied only to the first year and the machine was used by other patients in three-quarters of PSM cases after patients stop performing PSM. 9) In sensitivity analysis, a range of values 25% smaller and greater than some point estimate was tested if no other data were available. For risk ratio and utility values, a range of 0.5 smaller or greater was tested. In stochastic simulations, beta distribution was used for categorical data, triangular distribution for risk ratios, utility values and procedures weightings, and normal distribution for cost input values.
Data source for costs	Fitzmaurice 2005[88]; Jowett 2006[145]; Curtis 2005[157], Department of health[158]; Chambers 1999[159]; Youman 2003[160]
Cost items included	[2005 UK £] Direct NHS health care costs for anticoagulation testing, monitoring, training and costs associated with adverse events. Transportation time and costs, and productivity losses were not included.
Data source for outcomes	The proportion of time in, below or above the INR therapeutic range : Fitzmaurice 2005[88]; Risk of haemorrhagic and thrombotoc events: Palareti 1996[161]; Cannegieter 1995[162], EAFTSG 1995[163], Tangelder 2001[164]; Risk of death after an acute event: Regier 2006[147], Sundberg 2003[165]; Risk of disability in patients who survived an acute event: Gage 1995[166]; utility values: Regier 2006[147], Thomson 2000[167], Fitzmaurice 2002 [88], Post 2001[168]
Discounting	Both costs and outcomes : 3.5% (0-6%)
Costs	Incremental NHS cost: £901.04 (95%CI: £705 to £1,105) over a 5-year period and £1,003.93 (95%CI: £712 to £1,320) over a 10-year period.
Outcomes	Incremental QALY : 0.00736 (IC 95%: -0.079 to 0.103) over a 5-year period and 0.01577 (IC 95%: -0.132 to 0.179) over a 10-year period.
Cost-effectiveness	5 years : £122,365/QALY ; 10 years : £63,655/QALY: ICER < £30,000/QALY : 44%.
Sensitivity analysis	ICER < £30,000/QALY : 44%.

Conclusions	According to the UK setting, PSM is not cost-effective for a willingness-to-pay threshold of £30,000 in comparison with the current specialized anticoagulation clinics in the UK. However, for some patients who are frequently away from home, who are in employment or education, or those who find it difficult to travel to clinics, their quality of life may be enhanced by PSM.
Remarks	1) Patients characteristics were not clearly described. Moreover, the definition of usual care was not clear. Effectiveness and cost data came mostly from a study where usual care was not clearly described (usual care = hospital outpatient clinics or primary care-based clinics; with blood sample sent to the laboratory or near-patient INR testing). Furthermore, the number of tests performed in each groups was not specified. 2) No distinction was made between patient self-testing and patient self-management. 3) Quantities of resources and their unit costs were only partially reported. The generalisability to other settings is thus more difficult. 4) Only direct NHS health care costs were included. Transportation costs and productivity losses were not included. Even if the assessment of such costs is difficult, their inclusion could reduce the cost differences. On the other hand, the impact of transportation cost on the total cost is expected by authors to be negligible (in the UK setting). 5) According to the authors, the cost-effectiveness of patient education and training in long term oral anticoagulation therapy need to be investigated. 6) Sensitivity analysis did not cover the number of tests performed and the impact on complications. 7) The analysis is only specific to the UK setting and generalisability is difficult.

Authors (Year)	Jowett S, Bryan S, Murray E, McCahon D, Raftery J, Hobbs R, Fitzmaurice D (2006).
Funding	Medical Research Council, NHS career scientist award, and MRC health services research fellowship.
Country	UK.
Design	CUA, randomized controlled trial.
Perspective	NHS and societal perspective.
Time window	12 months
Interventions	Patients self-management (PSM) (337 patients; complete data for 326 patients / number of tests/year: 12.4) versus current routine care in UK (hospital outpatient clinics or primary care-based clinics; with blood sample sent to the laboratory or POC systems) (280 patients; complete data for 265 patients / number of tests/year: 37.9). Instrument not clearly specified: expected CoaguChek.
Population	617 patients on long term oral anticoagulation therapy. (209 for patients' private costs). The mean age was 64 years old in the PSM group and 66 years old in the control group.
Assumptions	1) If a machine was not used for a full year, it could be used by another patient. The cost of the machine was amortized over 3 years. 2) Productivity lost was valued as the mean gross weakly wage and for unemployed patients, leisure time lost was valued at 40% of the mean average wage.
Data source for costs	Study data, Roche, BNF, NHS diagnostics, Netten and Curtis 2003[169], NHS reference costs 2003 and National Tariffs 2004[170].
Cost items included	(£ 2003) Direct health care costs (including anticoagulation testing, monitoring, training and costs due to adverse events): Labor, consumable, capital and overheads. Transportation time and costs, and productivity losses for patients and relatives were also included.
Data source for outcomes	Study data. QALY: EQ-5D questionnaire. Utility values were derived from a UK general population survey: Dolan 1995[171].
Discounting	Not appropriate (1 year).

Costs	1) Total NHS cost: PSM group: £416.76 (95%CI: £393.95 to £441.81) / Control group: £122.32 (95%CI: £103.48 to £143.90) / Incremental cost: £294.44 2) 1) Total societal cost: PSM group: £462.73 (95%CI: £439.28 to £489.15) / Control group: £179.80 (95%CI: £160.09 to £202.58) / Incremental cost: £282.93 => Significant differences (p<0.001).
Outcomes	1) No significant differences in INR percentage time in range. 2) Incremental QALY: for complete data: 0.001 (95%CI: -0.027 to 0.032) / for imputed data : 0.009 (95%CI: -0.012 to 0.030) => Not Significant.
Cost-effectiveness	1) In the NHS perspective: for the complete analysis: £294,440/QALY / for the imputed data : £32,716/QALY 2) In the societal perspective: for the complete analysis: £282,930/QALY / for the imputed data : £31,437/QALY
Sensitivity analysis	ICER < £30,000/QALY : 1) In the NHS perspective: for the complete analysis: 26% / for the imputed data : 46% 2) In the societal perspective: for the complete analysis: not specified / for the imputed data : 49%
Conclusions	According to the UK setting, PSM is not a cost-effective strategy for a willingness-to-pay threshold of £30,000 in comparison with the current routine care (hospital or practice-based clinics).
Remarks	1) The definition of usual care was not clear. 2) The instrument's brand tested was not specified. 3) Costs were based on a randomized clinical trial and thus did not reflect real life practice. 4) Even if unit costs were specified, quantities of resources were not reported separately from their unit costs. The generalisability to other settings is thus more difficult. Moreover, cost calculations linked to complications due to adverse events were not clear. 5) The follow-up was too short (1 year). 6) Sensitivity analysis did not cover the number of tests performed and the impact on complications. 7) The analysis was only specific to the UK setting and generalisability is difficult.

Authors (Year)	Regier DA, Sunderij R, Lynd LD, Gin K, Marra CA (2006).
Funding	Grant-in-Aid from the Heart and Stroke Foundation of British Columbia and Yukon, and the Michael Smith Foundation for Health Research Scholar Awards.
Country	Canada.
Design	CUA, Markov model.
Perspective	Canadian health care payer.
Time window	5 years.
Interventions	Patient self-management (PSM) (52 tests) versus clinical standard of practice in Canada (Primary care physician management; 14 tests). Instrument was not clearly specified: expected ProTime Microcogulation System.
Population	Patients on long term oral anticoagulation therapy for atrial fibrillation or for a mechanical heart valve, with adequate manual dexterity and able to be in the PSM group (criteria not clearly specified).

Assumptions	1) It was assumed that one pharmacist conducted 2 training sessions lasting for a total of 5 hours, that 3 patients attended each session and that the pharmacist needed one full work day to develop sufficient training expertise. 2) In the physician management group, 14 laboratory tests per year were assumed and each test was followed by a telephone consult. In the PSM group, Patients conducted their test weekly and contacted a pharmacist after each test during the first month and once a month thereafter. 3) 10% of patients received tissue plasminogen activator. In the probabilistic sensitivity analysis, Dirichlet distribution was used for transition probabilities and triangular distribution for costs (with a variation of +/- 25%). 4) Reduction of complications compared to usual care (for 5 years and 100 patients): 3.5 thromboembolic events, 0.79 bleedings and 0.12 deaths.
Data source for costs	Sunderij 2004[80], Adams 2003[172], Canadian Institute for Health Information[173], Health Funding and Costing Branch.[174]
Cost items included	(Canadian $ 2003) Direct NHS health care costs for anticoagulation testing, monitoring, training and costs associated with adverse events. Transportation time and costs, and productivity losses were not included.
Data source for outcomes	Heneghan 2006[68], Sunderij 2004[80], Palareti 1996[161], Cannegieter 1995[162], Weimar 2002[175], Mayo 1999[176], Hankey 2002[177], White 1996.[178] QALY (using EQ-5D): Post 2001[168], Glick 1999[179], Van Exel 2004[180].
Discounting	Both costs and outcomes: 3%.
Costs	1) PSM : $6,116 (95%CI: $5,426 to $6,830) 2) Pysician management: $5,127 (95%CI: $4,390 to $5,894) 3) Incremental cost: $989 (95%CI: $310 to $1,655).
Outcomes	1) PSM : 4.28 (95%CI: 4.24 to 4.30) 2) Pysician management: 4.21 (95%CI: 4.19 to 4.25) 3) Incremental QALY: 0.07 (95%CI: 0.056-0.084).
Cost-effectiveness	$14,129/QALY.
Sensitivity analysis	ICER < $23,800/QALY : 95%. With varying assumptions of resource utilization, of the discount rate, and of utility values, the ICER remained inferior to $20,000/QALY. Various timeframe were also tested: the ICER was $236,667/QALY for 1 year, $75,882/QALY for 2 years, $34,484/QALY for 3 years, and $2,995/QALY for 10 years.
Conclusions	Compared to physician management, PSM is a cost-effective strategy for patients on long term oral anticoagulation therapy for atrial fibrillation or for a mechanical heart valve.
Remarks	1) Patients characteristics were not clearly described. 2) Methods to estimate the model parameters were not clear. Outcomes valuations and Costs calculations were not clear. 3) Quantities of resources were not reported separately from their unit costs. The generalisability to other settings is thus more difficult. 4) Only direct health care costs were included. Transportation costs and productivity losses were not included. Even if the assessment of such costs is difficult, their inclusion could reduce the cost differences. 5) The analysis was specific to patients with atrial fibrillation or with a mechanical heart valve, with adequate manual dexterity and able to be in the PSM group (criteria not clearly specified).

Authors (Year)	Lafata JE, Martin SA, Kaatz S, Ward RE (2000).
Funding	Boehringer Mannheim Corp.
Country	United States.
Design	CUA, Markov model.
Perspective	Medical care provider and societal perspecitive.
Time window	5 years.
Interventions	1) Usual care: management in a non organized anticoagulation clinic with laboratory tests (14 tests/year). 2) Management in an organized anticoagulation clinic with POC system (23 tests/year). 3) Patient self-testing (PST) with POC system and call to an organized anticoagulation clinic (52 tests/year). Instrument not specified.
Population	Patients aged 57 years and on long term oral anticoagulation therapy.
Assumptions	1) 50% of patient discontinued therapy after becoming permanently disabled. 2) 30% of patients were accompanied by a family member for clinic-based testing. 3) Reduction of complications compared to usual care (for 5 years and 100 patients): for PST with POC: 8.8; and for POC in anticoagulation clinics: 3.7.
Data source for costs	Ansell 1995[181], Bernardo 1996[182], Gottlieb 1994[183], Ansell 1989[123], US Bureau of the Census, Current Population Reports 1997[184], Murphy 1994[185], Mitchell 1996[186], Holloway 1996[187], Health Insurance Association of America 1997[188].
Cost items included	($ 1997). Direct health care costs for anticoagulation testing, monitoring, and costs associated with adverse events: Labor, consumable, and capital. Transportation time and cost, and productivity losses for patients and relatives were also included. Time lost for training was also measured (but not the direct cost of the training).
Data source for outcomes	Chiquette 1995[189], White 1996[178], Ansell 1995[181], Hasenkam 1997[190], Anderson 1993[191], Fihn 1993[192], Fihn 1996[183], Gottlieb 1994[183], The Boston Area Anticoagulation Trial 1990[193], Connolly 1991[194], European Atrial Fibrillation Trial Study Group 1993[195], The European Atrial Fibrillation Trial Study Group 1995[196], Ezekowitz 1992[197], Petersen 1989[198], Stroke Prevention in Atrial Fibrillation Investigators 1991[199], Stroke Prevention in Atrial Fibrillation Investigators 1994[200], Palaretti 1996[161], van der Meer 1993[201], White 1989[202], Wilkinson 1997[203], Bonita 1997[204], Dorman 1997[205], Tennant 1997[206], Dighe 1997[207], Naglie 1992[208], Disch 1994[209], Tsevat 1989[210], Seto 1997[211], Gage 1995[166].
Discounting	Costs and outcomes: 3%.
Costs	Medical care costs: (1): $4,195.14 / (2): $4,055.60 / (3): $5,260.14 / Societal costs: (1) : $5,297.37 / (2): $6,456.71 / (3): $6,227.27.
Outcomes	Incremental QALY: (2) versus (1): 0.005 / (3) versus (1) : 0.0128 / (3) versus (2) : 0.008.
Cost-effectiveness	1) Medical care costs: (2) versus (1): Dominant strategy / (3) versus (1): $82,949/QALY / (3) versus (2): $153,504/QALY. 2) Societal perspective: (2) versus (1): $232,226/QALY / (3) versus (1): $72,426/QALY / (3) versus (2): Dominant strategy.
Sensitivity analysis	When only medical care costs are considered, (2) is a dominant strategy compared to (1) in 80% of cases. In the societal perspective, (3) is a dominant strategy compared to (2) in 48% of cases. Results are very sensitive to time spent below and above therapeutic range and to the number of tests.
Conclusions	From the medical care provider perspective, anticoagulation clinic is a dominant strategy compared to usual care. In the societal perspective, PST becomes the most cost-effective alternative.

Remarks	1) Except for the age, patients' characteristics were not clearly described. 2) The instrument's brand tested was not specified. 3) Estimates were based on populations including few patients with atrial fibrillation and thus did not reflect the general population on long-term anticoagulation therapy. 4) Methods to estimate the model parameters were not clear. Outcomes valuations and Costs calculations were not clear. The cost linked to the patient formation seems not to be taken into account. 5) Quantities of resources were not reported separately from their unit costs. The generalisability to other settings is thus more difficult. 6) Authors concluded that in the societal perspective, PST was the most cost-effective alternative. However, compared to usual care the ICER was $72,426/QALY. Thus, PST was not a cost-effective strategy compared to usual care at a threshold of $50,000/QALY. Moreover, the sensitivity analysis showed that compared to anticoagulation clinics, PST was a dominant strategy only in 48% of cases. 7) The 95% CI for costs, outcomes and the resulting ICER should have been specified. 8) Results of the probabilistic sensitivity analysis were not fully specified.

Authors (Year)	Brown A, Wells P, Jaffey J, McGahan L, Poon M-C, Cimon K, Campbell K (2007). The Canadian Agency for Drugs and Technologies in Health (CADTH).
Funding	Health Canada, and the governments of Alberta, British Columbia, Manitoba, New Brunswick, Newfoundland and Labrador, Northwest Territories, Nova Scotia, Nunavut, Ontario, Prince Edward Island, Saskatchewan, and Yukon.
Country	Canada.
Design	CUA, Markov model.
Perspective	Medical care provider and societal perspectives.
Time window	5 years.
Interventions	(1) Usual care (standard laboratory test with a venipuncture blood draw for an INR; 20 tests/year) (2) Anticoagulation clinic using the POC monitor for INRs (CoaguChek; 23 tests/year) (3) Anticoagulation clinic using the POC monitor for INRs (ProTime; 23 tests/year) (4) Patient self-testing (PST) using the POC monitor for INRs (CoaguChek; 52 tests/year) + call of results to an anticoagulation clinic or a family doctor.
Population	Patients on long term oral anticoagulation therapy (> 3 months).
Assumptions	1) 50% of patient discontinued therapy after becoming permanently disabled. 2) Effectiveness parameters are assumed to be the same for POC testing in anticoagulation clinic or for POC use by a patient (PST group). 3) For CoaguChek and ProTime, parameter values are assumed to be the same except for the cost of the device and the related equipment. 4) Time for caregivers is assumed to be equal to time for the patient. 5) Caregiver is assumed to travel with the patient. 6) 30% of patients were accompanied by a family member for clinic-based testing and 9% received help with home testing.
Data source for costs	Ansell 1989[123], Ansell 1995[181], Bernardo 1996[182], Murphy 1994[185], Lathe 2003[212], Labor force survey 2005[213], National Joint Council 2005, Ontario Ministry of Health and Long-Term Care 2005[214], Health costing in Alberta: 2005 annual report[215], Health costing in Alberta: 2003 annual report[174], Government of Alberta (Long-term care accommodation charges 2001).
Cost items included	($ 2005). Direct health care costs for anticoagulation testing, monitoring, and costs associated with adverse events: Labor, consumable, and capital. Transportation time and cost, and productivity losses for patients and relatives were also included.

Data source for outcomes	Meta-analysis performed in this study. Lafata 2000[122, 146], Wilkinson 1997[203], Bonita 1997[204], Dorman 1997[205], Tennant 199[2067], Dighe 1997[207], White 1996[178], EAFT study group 1993[195], Naglie 1992[208], Seto 1997[211], Tsevat 1989[210], Disch 1994[209], Gage 1995[166], Fihn 1993[192], Mitchell 1996[186], Holloway 1996[187], Abridged life table, Ontario 2005[216].
Discounting	Both costs and outcomes: 5% (0-3% in the sensitivity analysis).
Costs	Nursing home cost excluded: Medical care costs: (1) $6,282.76 (2) $6,210.85 (3) $6,347.19 (4) $8,211.16 / Societal costs: (1) $9,246.09 (2) $9,937.81 (3) $10,074.14 (4) $9,464.35. Nursing home cost included: Medical care costs: (1) $12,101.34 (2) $11,623.40 (3) $11,759.74 (4) $13,623.71 / Societal costs: (1) $15,064.67 (2) $15,350.36 (3) $15,486.70 (4) $14,876.90.
Outcomes	QALY: (1) 3.8797 (2) 3.9061 (3) 3.9061 (4) 3.9061
Cost-effectiveness	Medical care costs : Nursing home cost excluded: (2) versus (1) : (2) dominant strategy / (3) versus (1):$2,437/QALY/ (4) versus (1) $72,955/QALY / Nursing home cost included: (2) versus (1): (2) dominant strategy / (3) versus (1): (3) dominant strategy / (4) versus (1): $57,595/QALY / Societal costs: Nursing home cost excluded: (2) versus (1) $26,201.52/QALY / (3) versus (1): $31,365.53 / (4) versus (1): $8,267.42. / Nursing home cost included: (2) versus (1) $10,808/QALY / (3) versus (1): $15,966/QALY / (4) versus (1): (4) dominant strategy.
Sensitivity analysis	Medical care costs : Nursing home cost excluded: (2) versus (1) : < $0 = 63% / (3) versus (1): <$50,000/QALY= 100% / (4) versus (1): <$50,000/QALY= 2% / Nursing home cost included: (2) versus (1): <$0 = 99% / (3) versus (1): <$0 = 94% / (4) versus (1): <$50,000/QALY= 26% / Societal costs (Nursing home cost included): (2) versus (1): <$50,000/QALY= 86% / (3) versus (1): <$50,000/QALY= 82% / (4) versus (1): <$0 = 52%.
Conclusions	From the medical care provider perspective, an anticoagulation clinic using CoaguChek is a dominant strategy compared to usual care. With ProTime, results are also favorable. On the other hand, PST is not a cost-effective strategy compared to usual care from this perspective. From the societal perspective and compared to usual care, an anticoagulation clinic is a cost-effective strategy and PST is a dominant strategy.
Remarks	1) Patients characteristics were not clearly described. 2) Methods to estimate the model parameters were sometimes not clear. 3) Costs calculations linked to complications due to adverse events were not clear. 4) Cost and impact of patient training was not analyzed 5) Authors concluded that in the societal perspective, PST was a dominant strategy compared to usual care. However, the sensitivity analysis showed that compared to usual care, PST was a dominant strategy only in 52% of cases and the probability to be under $50,000/QALY was not specified. 6) The 95% CI for costs, outcomes and the resulting ICER should have been specified. 7) The probabilistic sensitivity analysis did not seem to take into account all uncertain parameters (e.g. cost data?).

Authors (Year)	Claes N, Moeremans K, Buntinx F, Arnout J, Vermylen J, Van Loon H, Annemans L (2006).
Funding	No funding.
Country	Belgium.
Design	CEA, RCT BISOAT (+retrospective analysis for usual care).
Perspective	Health care payer.
Time window	6 months.
Interventions	Usual care : Management by a GP (2.6 tests/month) versus : (1) Management by a General Practitioner (GP) + patient and GP education on oral anticoagulation (2.2 tests/month). (2) Management by a GP + patient and GP education on oral anticoagulation + feedback on coagulation performance every 2 months (comparison of GP practice performance with the mean clinical performance of the group) (2.2 tests/month). (3) Management by a GP using POC device (CoaguChek) + patient and GP education on oral anticoagulation (2.6 tests/month). (4) Management by a GP + use of a Dawn AC computer assisted advice + patient and GP education on oral anticoagulation (1.9 tests/month). NB: The proportion of patient visits at home was 30% and at the GP office was 70%.
Population	834 patients on Oral anticoagulation therapy for at least 28 days and 66 GP.
Assumptions	/
Data source for costs	Interviews and RCT [Claes 2005][84].
Cost items included	(Activity-based costing method). Direct health care costs for anticoagulation testing, monitoring, and training (Labor, consumable, capital and overheads). Patients' transportation time and costs; and productivity losses are excluded. For laboratory tests, a lump-sum is foreseen to represent overhead costs.
Data source for outcomes	RCT [Claes 2005][84].
Discounting	Not appropriate.
Costs. NB: Cost over 6 months per GP.	Usual care : €4,080 / (1): €5,046 (Incremental cost: €966) / (2): €5,122 (Incremental cost: €1,042) / (3): € 3,993 (Incremental cost: -€87) / (4. €5,323 (Incremental cost: €1,243).
Outcomes. NB: Outcomes over 6 months per GP.	Absolute number of additional days within a 0.5 range from the INR target: (1): 185 (95%CI: 46 to 311) / (2): 208 (95%CI: 92 to 311) / (3) 254 (95%CI: 138 to 381) / (4) 254 (95%CI: 127 to 381).
Cost-effectiveness	Incremental cost per additional day within a 0.5 range from the INR target. Compared to usual care: (1) €5.23/day / (2) €5.02/day / (3) Dominant strategy / (4) €4.90/day.
Sensitivity analysis	If the limits of the 95%CI of outcomes were tested, the ICER of the strategy (1) was the most unstable (from €3.1/day to €20.93/day) because the range of CI outcome values for this group was large. If equal amount of tests were used between the strategies, the ICERs for (1), (2) and almost (4) get worse. Inclusion of overhead costs for laboratory test has an important impact on the strategy (3); By reducing these costs, the strategy (3) is not anymore a cost-effective strategy. Finally, increasing the timeframe, the number of GP or the number of patients per GP improved the ICER.
Conclusions	A GP management using the CoaguChek device in combination with a multifaceted education is a cost-saving alternative for usual care and the Belgian health-care payers have to consider reimbursement for this strategy.

Remarks	1) The number of tests between strategies differed. The strategy D led to fewer tests than usual care (1.9 versus 2.6), which improved the ICER. Strategy A and B also (2.19 tests). Only strategy C had the same number of tests (2.6). 2) Costs were based on interviews through a randomized clinical trial. They were thus only estimates and did not reflect real cost in daily practice. 3) Cost items included in the study were not clear. Quantities of resources were not reported separately from their unit costs. Moreover the year of costs was not specified. 4) Overhead costs represented 50% of the total cost and had an important impact on result. By decreasing these costs, strategy C was not anymore a dominant strategy. Moreover, the real overhead cost instead of a lump sum should have been measured. 5) Costs associated with adverse events were not included. 6) The 95% CI for costs should have been specified. We have no information on cost variations. 7) The follow-up is too short (6 months). On the other hand, more the period is long, more the ICER is improved. 8) Outcomes were measured by the number of additional days within a 0.5 range from the INR target, which was not a final end-point outcome. QALYs should have been measured. 9) Probabilistic sensitivity analysis was not performed and the 95%CI of the ICERs were not specified.

9.3.4 Appendix: quality assessment checklist

Study design	Connock	Jowett	Regier	Claes	Lafata	Brown
The research question is stated	Partially	Partially	Partially	Partially	Partially	Partially
The economic importance of the research question is stated	Yes	Yes	Yes	No	Yes	Yes
The viewpoints of the analysis are clearly stated and justified	Not justified	Yes	Yes	Not justified	Yes	Yes
The rationale for choosing the alternative programmes or interventions compared is stated	Yes	Yes	Yes	No	Yes	Yes
The alternatives being compared are clearly described	No	No	Partially	Yes	Partially	Partially
The form of economic evaluation used is stated	Yes	Yes	Yes	Yes	Yes	Yes
The choice of form of economic evaluation is justified in relation to the questions addressed	Yes	Yes	Yes	No	Yes	Yes

Data collection	Connock	Jowett	Regier	Claes	Lafata	Brown
The sources of effectiveness estimates used are stated	Yes	Yes	Yes	Yes	Yes	Yes
Details of the design and results of effectiveness study are given (if based on a single study)	NA	Yes	NA	Yes	NA	NA
Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)	Partially	NA	No	NA	No	Partially
The primary outcome measure(s) for the economic evaluation are clearly stated	Yes	Yes	Yes	Yes	Yes	Yes
Methods to value health states and other benefits are stated	Sources given	Yes	Partially	Yes	No	No
Details of the subjects from whom evaluations were obtained are given	No	Partially	Partially	Yes, in the BISOAT study	Partially	No
Productivity changes (if included) are reported separately	NA	Yes	NA	NA	Yes	Yes
The relevance of productivity changes to the study question is discussed	No	Yes	No	No	Yes	Yes
Quantities of resources are reported separately from their unit costs	No	No	No	No	No	Partially
Methods for the estimation of quantities and unit costs are described	Not clearly	Yes	Not clearly	Not clearly	No	Not clearly
Currency and price data are recorded	Yes	Yes	Yes	No	Yes	Yes
Details of currency or price adjustments for inflation or currency conversion are given	Yes	Yes	Yes	No	Yes	Yes
Details of any model used are given	Yes	NA	Partially	NA	Yes	Yes
The choice of model used and the key parameters on which it is based are justified	Partially	NA	No	NA	No	Partially

NA = Not appropriate

Analysis and interpretation of results	Connock	Jowett	Regier	Claes	Lafata	Brown
Time horizon of costs and benefits is stated	Yes	Yes	Yes	Yes	Yes	Yes
The discount rate(s) is stated	Yes	NA	Yes	NA	Yes	Yes
The choice of rate(s) is justified	according to NHS guidelines	NA	Yes	NA	Yes	Yes
An explanation is given if costs or benefits are not discounted	NA	Yes	NA	No	NA	NA
Details of statistical tests and confidence intervals are given for stochastic data	Yes	Yes	Yes	Partially	No	No
The approach to sensitivity analysis is given	Yes	Yes	Yes	Yes	Yes	Yes
The choice of variables for sensitivity analysis is justified	Yes	Partially	No	No	Yes	No
The ranges over which the variables are varied are stated	Yes	Partially	Yes	Yes	Partially	Yes
Relevant alternatives are compared	Yes	Yes	Yes	Yes	Yes	Yes
Incremental analysis is reported	Yes	Yes	Yes	Yes	Yes	Yes
Major outcomes are presented in a disaggregated as well as aggregated form	Yes	Yes	Yes	Yes	No	Yes
The answer to the study question is given	Yes	Yes	Yes	Yes	Yes	Yes
Conclusion follow from the data reported	Yes	Yes	Yes	Partially	No	Partially
Conclusions are accompanied by the appropriate caveats	Yes	Yes	No	No	No	No

NA = Not appropriate

9.4 APPENDIXES COST-EFFECTIVENESS ANALYSIS

9.4.1 NIHDI Nomenclature laboratory tests

Cluster	Subcluster	Code	Description
allergy	RAST	438115	Bepalen van specifieke IgE per antigeen (Maximum 6) (Cumulregel 47) Klasse 13
allergy	RAST	556275	Bepalen van specifieke IgE per antigeen (Maximum 6)(Cumulregel 47) Klasse 13
allergy	total IgE	438093	Doseren van IgE totaal (Maximum 1) (Cumulregel 46) Klasse 13
allergy	total IgE	556253	Doseren van IgE totaal (Maximum 1)(Cumulregel 46) Klasse 13\midrule
anemia	Folic acid	433053	Doseren van foliumzuur in het serum (Maximum 1) (Cumulregel 303) Klasse 13
anemia	Folic acid	541435	Doseren van foliumzuur in het serum met niet isotopen-methode (Maximum 1) (Cumulregel 303) Klasse 13
anemia	Folic acid eryhtrocytes	433075	Doseren van foliumzuur in de erythrocyten (Maximum 1) (Cumulregel 304) Klasse 14
anemia	Folic acid eryhtrocytes	541450	Doseren van foliumzuur in de erythrocyten met niet isotopenmethode (Maximum 1) (Cumulregel 304) Klasse 14
anemia	Iron	540551	Doseren van ijzer (Maximum 1) (Cumulregel 15) Klasse 9
anemia	Iron + RBC	540573	Doseren van ijzer en bepalen van het ijzerbindend vermogen (Maximum 1) (Cumulregel 15, 16) Klasse 11
anemia	Vit B12	433112	Doseren van vitamine B12 (Maximum 1) (Cumulregel 303) Klasse 13
anemia	Vit B12	541494	Doseren van vitamine B12 met niet isotopen-methode (Maximum 1) (Cumulregel 303) Klasse 13
anemia	Vit B12 + folic acid	433134	Doseren van vitamine B12 en foliumzuur (Maximum 1) (Cumulregel 303) Klasse 16
anemia	Vit B12 + folic acid	541391	Doseren van vitamine B12 en foliumzuur, met niet isotopenmethode (Maximum 1) (Cumulregel 303) Klasse 16
anemia	ferritin	433090	Doseren van ferritine (Maximum 1) (Cumulregel 305) Klasse 13
anemia	ferritin	541472	Doseren van ferritine met niet isotopen-methode (Maximum 1) (Cumulregel 305) Klasse 13
anemia	transferrin	541030	Doseren van transferrine met een immunologische methode (Maximum 1) (Cumulregel 16) Klasse 9\midrule
cardiovascular	HDL-cholesterol	540293	Doseren van HDL-cholesterol (Maximum 1) (Cumulregel 13) Klasse 10
cardiovascular	LDL-cholesterol	542231	Doseren van LDL-cholesterol, met uitsluiting van berekeningsmethoden (Maximum 1)(Cumulregel 13) (Diagnoseregel 54) Klasse 14
cardiovascular	Total cholesterolerol	540271	Doseren van totale cholesterol (Maximum 1) Klasse 6
cardiovascular	triglycerides	541376	Doseren van triglyceriden (Maximum 1) Klasse 8\midrule
diabetes	C-peptide	434173	Doseren van C-peptide (Maximum 1) (Cumulregel 322, 89) Klasse 16

diabetes	C-peptide	559134	Doseren van C-peptide (Maximum 1)(Cumulregel 89, 322) Klasse 16
diabetes	Glucose (+4)	120190	Glucosedagcurve (minimum 4 doseringen), inclusief de eventuele doseringen van de glucosurie (Maximum 1) (Cumulregel 1) Klasse 18
diabetes	Glucose (+4)	125193	Glucosedagcurve (minimum 4 doseringen), inclusief de eventuele doseringen van de glucosurie (Maximum 1) (Cumulregel 3) Klasse 18
diabetes	Hb gly	540750	Doseren van glycohemoglobine in hemolysaat (Maximum 1) (Cumulregel 18) (Diagnoseregel 56) Klasse 13
diabetes	Hyperglycemia curve	120153	Curve van verwekte hyper- of hypoglycemie (minimum vier doseringen), inclusief de eventuele doseringen van de glucosurie. De hiervoor gebruikte produkten zijn begrepen in de honoraria van deze verstrekking (Maximum 1) (Cumulregel 1) Klasse 18
diabetes	Hyperglycemia curve	125156	Curve van verwekte hyper- of hypoglycemie (minimum 4 doseringen), inclusief de eventuele doseringen van de glucosurie. De hiervoor gebruikte produkten zijn begrepen in de honoraria van deze verstrekking (Maximum 1) (Cumulregel 3) Klasse 18
diabetes	glucose	120050	Doseren van glucose (Maximum 1) (Cumulregel 1) Klasse 3
diabetes	glucose	125053	Doseren van glucose (Maximum 1) (Cumulregel 3) Klasse 3
diabetes	insuline	434210	Doseren van insuline (Maximum 1) (Cumulregel 221, 322) Klasse 14
diabetes	insuline	546092	Doseren van insuline (Maximum 1) (Cumulregel 221, 322) Klasse 14\midrule
full blood count	erythrocytes / hematocrite	123034	Tellen van de erythrocyten en/of hematocriet (Maximum 1) Klasse 2
full blood count	erythrocytes / hematocrite	127035	Tellen van de erythrocyten en/of hematocriet (Maximum 1) Klasse 2
full blood count	formula	123071	Leucocytenformule vastgesteld met microscoop op minimum 100 cellen (Maximum 1) (Cumulregel 100) Klasse 6
full blood count	formula	123174	Vereenvoudigde leucocytenformule (lymfocyten, monocyten en granulocyten), afgeleid van de analyse van een differentieel volumetrisch histogram, verkregen na lytische reactie (Maximum 1) (Cumulregel 100) Klasse 2
full blood count	formula	123196	Leucocytenformule (ten minste vijf populaties), vastgesteld met cellenteller en gebaseerd op criteria die niet alleen de celgrootte omvatten, inclusief de controles door microscopie (Maximum 1) (Cumulregel 100) Klasse 6
full blood count	formula	127072	Leucocytenformule vastgesteld met microscoop op minimum 100 cellen (Maximum 1) (Cumulregel 102) Klasse 6
full blood count	formula	127175	Vereenvoudigde leucocytenformule (lymfocyten, monocyten en granulocyten), afgeleid van de analyse van een differentieel volumetrisch histogram, verkregen na lytische reactie (Maximum 1) (Cumulregel 102) Klasse 2
full blood count	formula	127190	Leucocytenformule (ten minste vijf populaties), vastgesteld met cellenteller en gebaseerd op criteria die niet alleen de celgrootte omvatten, inclusief de

			controles door microscopie (Maximum 1) (Cumulregel 102) Klasse 6
full blood count	hemoglobin	123012	Doseren van hemoglobine door elektrofotometrische methode (Maximum 1) Klasse 2
full blood count	hemoglobin	127013	Doseren van hemoglobine door elektrofotometrische methode (Maximum 1) Klasse 2
full blood count	leucocytes	123056	Tellen van de leucocyten (Maximum 1) Klasse 2
full blood count	leucocytes	127050	Tellen van de leucocyten (Maximum 1) Klasse 2
full blood count	thrombocytes	123115	Tellen van de thrombocyten (Maximum 1) Klasse 2
full blood count	thrombocytes	127116	Tellen van de thrombocyten (Maximum 1) Klasse 2\midrule
hormonology	FSH	434593	Doseren van follikel stimulerend hormoon (FSH) (Maximum 1) (Cumulregel 309, 322) Klasse 14
hormonology	FSH	546136	Doseren van follikelstimulerend hormoon (FSH) (Maximum 1) (Cumulregel 309, 322) Klasse 14
hormonology	LH	434571	Doseren van luteniserend hormoon(LH) (Maximum 1) (Cumulregel 123, 322) Klasse 14
hormonology	LH	546114	Doseren van luteniserend hormoon (L.H.) (Maximum 1) (Cumulregel 123, 322) Klasse 14
hormonology	Oestradiol	434652	Doseren van oestradiol (Maximum 1) (Cumulregel 212, 313, 322) Klasse 18
hormonology	Oestradiol	546210	Doseren van oestradiol (Maximum 1) (Cumulregel 212, 313, 322) Klasse 18
hormonology	Progest	434674	Doseren van progesteron (Maximum 1) (Cumulregel 314, 322) Klasse 17
hormonology	Progest	546232	Doseren van progesteron (Maximum 1) (Cumulregel 314, 322) Klasse 17
hormonology	Prolactine	434615	Doseren van prolactine (Maximum 1) (Cumulregel 310, 322) Klasse 15
hormonology	Prolactine	546151	Doseren van prolactine (Maximum 1) (Cumulregel 310, 322) Klasse 15
hormonology	Testosterone	434895	Doseren van testosteron (Maximum 1) (Cumulregel 322, 110) Klasse 17
hormonology	Testosterone	559613	Doseren van testosteron (Maximum 1)(Cumulregel 110, 322) Klasse 17\midrule
inflammation	CRP	541052	Doseren van CRP met een immunologische methode (Maximum 1) (Cumulregel 35) Klasse 9
inflammation	Fibrinogen	554610	Doseren van fibrinogeen (Maximum 1) (Cumulregel 101) Klasse 6
inflammation	sedimentation rate	123152	Meten van de snelheid van de globulaire sedimentatie (Maximum 1) Klasse 2
inflammation	sedimentation rate	127153	Meten van de snelheid van de globulaire sedimentatie (Maximum 1) (Cumulregel 101) Klasse 2\midrule
ions	Ca	540190	Doseren van calcium (Maximum 1) (Cumulregel 12) Klasse 6
ions	Cl	540256	Doseren van chloriden (Maximum 1) Klasse 4
ions	K	540934	Doseren van kalium (Maximum 1) Klasse 6

ions	Mg	540794	Doseren van magnesium (Maximum 1) Klasse 7
ions	Na	541354	Doseren van natrium (Maximum 1) Klasse 5
ions	Na bicarbonates	540492	Doseren van de bicarbonaten in het plasma of het serum, met uitsluiting van de berekeningsresultaten die zijn verkregen uitgaande van de gegevens betreffende het zuur-base evenwicht (Maximum 1) (Cumulregel 57) Klasse 4\midrule
kidney	Urea	120072	Doseren van ureum (Maximum 1) Klasse 3
kidney	Urea	125075	Doseren van ureum (Maximum 1) Klasse 3
kidney	Uric acid	120013	Doseren van urinezuur (Maximum 1) Klasse 4
kidney	Uric acid	125016	Doseren van urinezuur (Maximum 1) Klasse 4
kidney	creatinine	540330	Doseren van creatinine (Maximum 1) (Cumulregel 8) Klasse 5\midrule
liver	Anti HCV	551154	Diagnose en controle van de evolutie van virale hepatitis C, door aantonen van anti-HC antilichamen (Maximum 1) (Cumulregel 328) Klasse 13
liver	Anti-HAV	551375	Opsporen van specifieke IgG- of totale antilichamen tegen Hepatitis A (Maximum 1) (Cumulregel 328) Klasse 13
liver	Anti-HBc	437113	Diagnose en controle van de evolutie van virale hepatitis B : door aantonen van HBc antilichaam (Cumulregel 234, 328) (Maximum 1) Klasse 13
liver	Anti-HBc	551471	Diagnose en controle van de evolutie van virale hepatitis B door aantonen van anti HBc antilichamen met niet isotopenmethode (Maximum 1) (Cumulregel 234, 328) Klasse 13
liver	Anti-HBe	437091	Diagnose en controle van de evolutie van virale hepatitis B : door aantonen van HBe antilichaam (Cumulregel 233, 328) (Maximum 1) Klasse 13
liver	Anti-HBe	551456	Diagnose en controle van de evolutie van virale hepatitis B door aantonen van anti HBe antilichamen met niet isotopenmethode (Maximum 1) (Cumulregel 233, 328) Klasse 13
liver	Anti-HBs	437076	Diagnose en controle van de evolutie van virale hepatitis B : door aantonen van HBs antilichaam (Cumulregel 232, 328) (Maximum 1) Klasse 13
liver	Anti-HBs	551434	Diagnose en controle van de evolutie van virale hepatitis B door aantonen van anti HBs antilichamen met niet isotopenmethode (Maximum 1) (Cumulregel 232, 328) Klasse 13
liver	GOT, ASAT	120094	Doseren van aspartaat aminotransferasen (Maximum 1) (Cumulregel 2) Klasse 6
liver	GOT, ASAT	125090	Doseren van aspartaat aminotransferasen (Maximum 1) (Cumulregel 4) Klasse 6
liver	GOT,ASAT + GPT, ALAT	120131	Doseren van aspartaat aminotransferasen en alanine aminotransferasen (Maximum 1) (Cumulregel 2) Klasse 10
liver	GOT,ASAT + GPT, ALAT	125134	Doseren van aspartaat aminotransferasen en alanine aminotransferasen (Maximum 1) (Cumulregel 4) Klasse 10
liver	GPT, ALAT	120116	Doseren van alanine aminotransferasen (Maximum 1) (Cumulregel 2) Klasse 6

liver	GPT, ALAT	125112	Doseren van alanine aminotransferasen (Maximum 1) (Cumulregel 4) Klasse 6
liver	HBe Ag	437054	Diagnose en controle van de evolutie van virale hepatitis B : door aantonen van HBe antigeen (Cumulregel 231, 328) (Maximum 1) Klasse 13
liver	HBe Ag	551412	Diagnose en controle van de evolutie van virale hepatitis B door aantonen van HBe antigeen met niet isotopen-methode (Maximum 1) (Cumulregel 231, 328) Klasse 13
liver	HBs Ag	437032	Diagnose en controle van de evolutie van virale hepatitis B : door aantonen van HBs antigeen (Maximum 1)(Cumulregel 230, 328) Klasse 13
liver	HBs Ag	551390	Diagnose en controle van de evolutie van virale hepatitis B door aantonen van HBs antigeen met niet isotopen-methode (Maximum 1) (Cumulregel 230, 328) Klasse 13
liver	IgM anti-HAV	437010	Aantonen van recente infectie door hepatitis A-virus door het opzoeken van de IgM-antilichamen (Maximum 1)(Cumulregel 229, 328) Klasse 14
liver	IgM anti-HAV	551353	Diagnose van een recente hepatitis A virus-infectie door opzoeken van IgM antilichamen met niet isotopen-methode (Maximum 1) (Cumulregel 229, 328) Klasse 14
liver	LDH	541774	Doseren van melkzuurdehydrogenasen (Maximum 1) (Cumulregel 10) Klasse 6
liver	Phos alc	541914	Doseren van de alkalische fosfatasen (Maximum 1) Klasse 6
liver	T-BIL/D-BIL	120035	Doseren van bilirubine (Maximum 1) Klasse 5
liver	T-BIL/D-BIL	125031	Doseren van bilirubine (Maximum 1) (Cumulregel 5) Klasse 5
liver	T-BIL/D-BIL	540175	Doseren van totale bilirubine en van de fracties ervan (Maximum 1) (Cumulregel 5) Klasse 8
liver	gamma GT	541892	Doseren van de gammaglutamyltransferasen (Maximum 1) (Cumulregel 23) Klasse 6\midrule
pancreas	amylase	541612	Doseren van amylasen (Maximum 1) (Cumulregel 21) Klasse 9
pancreas	lipase	541833	Doseren van lipasen (Maximum 1) Klasse 9\midrule
protein	electro	540455	Electroforese van protenen met curve en berekening (Maximum 1) (Cumulregel 11) Klasse 12
protein	protein tot	125532	Doseren van totale protenen (Maximum 1) (Diagnoseregel 1) Klasse 3
protein	protein tot	540956	Doseren van totale protenen (Maximum 1) Klasse 3\midrule
rheumatism	Waaler Rose	124530	Test van Waaler Rose op plaatje (Maximum 1) Klasse 3
rheumatism	Waaler Rose	128531	Test van Waaler Rose op plaatje (Maximum 1) (Cumulregel 109) Klasse 3\midrule
thyriod	Antimicrosomial antibodies	438056	Doseren van thyroperoxydase antilichamen (anti-TPO) (Maximum 1) (Cumulregel 330) Klasse 13
thyriod	Antimicrosomial antibodies	556091	Opzoeken en titreren van anti-thyroied microsomen of anti-thyroperoxidase antilichamen (Maximum 1) (Cumulregel 330) Klasse 13
thyriod	Antithyroglobul antibodies	438071	Doseren van anti-thyroglobuline antilichamen (Maximum 1) (Cumulregel 331) Klasse 13
thyriod	Antithyroglobul antibodies	556076	Opzoeken en titreren van antithyroglobuline-antilichamen (Maximum 1) (Cumulregel 331) Klasse 13

thyriod	T3 free	434394	Doseren van vrije T3 (Maximum 1) (Cumulregel 218, 220) Klasse 15
thyriod	T3 free	546291	Doseren van vrije T3 (Maximum 1)(Cumulregel 218, 220) Klasse 15
thyriod	T3 total	435013	Doseren van totaal triiodothyronine (T3) of van thyroxine bindend globuline (TBG) of de saturatiecapaciteit van thyroxine bindend globuline (Maximum 1) (Cumulregel 218,220) Klasse 15
thyriod	T3 total	559252	Doseren van totaal triiodothyronine (T3) en van thyroxine bindend globuline (TBG) of van de saturatiecapaciteit van het thyroxine bindend globuline (TBG) (Maximum 1)(Cumulregel 218, 220) Klasse 15
thyriod	T4 free	434335	Doseren van vrije T4 (Maximum 1) (Cumulregel 218, 219) Klasse 15
thyriod	T4 free	546276	Doseren van vrije T4 (Maximum 1)(Cumulregel 218, 219) Klasse 15
thyriod	T4 total	434991	Doseren van totale thyroxine (T4) en van het thyroxine bindend globuline (TBG) of de saturatiecapaciteit van thyroxine bindend globuline (Maximum 1) (Cumulregel 218, 219) Klasse 15
thyriod	T4 total	546070	Doseren van totale thyroxine (T4) en van het thyroxine bindend globuline (TBG) of de saturatiecapaciteit van thyroxine bindend globuline(TBG) (Maximum 1)(Cumulregel 218, 219) Klasse 15
thyriod	TSH	434313	Doseren van schildklier-stimulerend hormoon (TSH) (Maximum 1) (Cumulregel 218, 311, 322) Klasse 13
thyriod	TSH	546173	Doseren van schildklier stimulerend hormoon (TSH) (Maximum 1) (Cumulregel 218, 311, 322) Klasse 13
thyriod	Thyroglobul.	434291	Doseren van thyroglobuline (Maximum 1) (cumulregel 94) Klasse 14
thyriod	Thyroglobul.	559230	Doseren van thyroglobuline (Maximum 1)(Cumulregel 94) Klasse 14\midrule
tumour markers	C.E.A.	436192	Doseren van C.E.A. (Maximum 1) (Cumulregel 201, 317) (Diagnoseregel 46) Klasse 15
tumour markers	C.E.A.	548332	Doseren van C.E.A. met niet isotopen-methode (Maximum 1) (Cumulregel 201, 317) (Diagnoseregel 46) Klasse 15
tumour markers	CA 15.3	436170	Doseren van CA 15.3 (Maximum 1)(Cumulregel 201, 315) (Diagnoseregel 46) Klasse 20
tumour markers	CA 15.3	548310	Doseren van CA 15.3 met niet isotopen-methode (Maximum 1) (Cumulregel 201, 315) (Diagnoseregel 46) Klasse 20
tumour markers	CA 19-10	548354	Doseren van carbohydrate antigen 19-9 (CA 19-9) (Maximum 1)(Cumulregel 201)(Diagnoseregel 46) Klasse 20
tumour markers	CA 19-9	436214	Doseren van carbohydrate antigen 19-9 (CA 19-9) (Maximum 1) (Cumulregel 201) (Diagnoseregel 46) Klasse 20

9.4.2 NIHDI nomenclature codes GP visits

Code	Description group	Description detail
101010	Consultation at the GP practice	Raadpleging in de spreekkamer van de algemeen geneeskundige met verworven rechten
101032	Consultation at the GP practice	Raadpleging in de spreekkamer van de erkende huisarts
101076	Consultation at the GP practice	Raadpleging in de spreekkamer van de geaccrediteerde erkende huisarts
103110	GP visit at the patients home	Bezoek, bij de zieke thuis, door de algemeen geneeskundige met verworven rechten
103132	GP visit at the patients home	Bezoek, bij de zieke thuis, door de erkende huisarts
103213	GP visit at the patients home at increased fee	Bezoek door de algemeen geneeskundige met verworven rechten bij verscheidene rechthebbenden in hun gemeenschappelijke woonplaats of gemeenschappelijk huis, bij eenzelfde reis : twee rechthebbenden, per rechthebbende
103235	GP visit at the patients home at increased fee	Bezoek door de algemeen geneeskundige met verworven rechten bij verscheidene rechthebbenden in hun gemeenschappelijke woonplaats of gemeenschappelijk huis, bij eenzelfde reis : drie rechthebbenden of meer, per rechthebbende
103316	GP visit at the patients home at increased fee	Bezoek door de algemeen geneeskundige met verworven rechten in een instelling waar kinderen, herstellenden of gehandicapten verblijven (dagverblijf, overnachting, dagverblijf en overnachting) : bij één rechthebbende
103331	GP visit at the patients home at increased fee	Bezoek door de algemeen geneeskundige met verworven rechten in een instelling waar kinderen, herstellenden of gehandicapten verblijven (dagverblijf, overnachting, dagverblijf en overnachting) : bij twee rechthebbenden, bij eenzelfde reis, per rechthebbende
103353	GP visit at the patients home at increased fee	Bezoek door de algemeen geneeskundige met verworven rechten in een instelling waar kinderen, herstellenden of gehandicapten verblijven (dagverblijf, overnachting, dagverblijf en overnachting) : bij drie rechthebbenden of meer, bij eenzelfde reis, per rechthebbende
103412	GP visit at the patients home at increased fee	Bezoek door de erkende huisarts bij verscheidene rechthebbenden in hun gemeenschappelijke woonplaats of gemeenschappelijk huis, naar aanleiding van een zelfde reis : twee rechthebbenden, per rechthebbende
103434	GP visit at the patients home at increased fee	Bezoek door de erkende huisarts bij verscheidene rechthebbenden in hun gemeenschappelijke woonplaats of gemeenschappelijk huis, naar aanleiding van een zelfde reis : drie rechthebbenden of meer, per rechthebbende
103515	GP visit at the patients home at increased fee	Bezoek door de erkende huisarts in een instelling waar kinderen, herstellenden of mindervaliden verblijven (verblijf overdag, verblijf 's nachts, verblijf overdag en 's nachts) : bij één rechthebbende
103530	GP visit at the patients home at increased fee	Bezoek door de erkende huisarts in een instelling waar kinderen, herstellenden of mindervaliden verblijven (verblijf overdag, verblijf 's nachts, verblijf overdag en 's nachts) : bij twee rechthebbenden, naar aanleiding van een zelfde reis, per rechthebbende
103552	GP visit at the patients home at increased fee	Bezoek door de erkende huisarts in een instelling waar kinderen, herstellenden of mindervaliden verblijven (verblijf overdag, verblijf 's nachts, verblijf overdag en 's nachts) : bij drie

		rechthebbenden of meer, naar aanleiding van een zelfde reis, per rechthebbende
103611	GP visit at the patients home at increased fee	Bezoek, tussen 18 en 21 uur afgelegd bij de zieke thuis
103913	GP visit at the patients home at increased fee	Bezoek door de erkende huisarts, bij de zieke in een inrichting die een forfaitaire tegemoetkoming zoals voorzien in de ministriële besluiten van 19 mei 1992 en 5 april 1995 met betrekking tot respectievelijk de rust- en verzorgingstehuizen en de rustoorden voor bejaarden, in rekening kan brengen : bij één rechthebbende
103935	GP visit at the patients home at increased fee	Bezoek door de erkende huisarts, bij de zieke in een inrichting die een forfaitaire tegemoetkoming zoals voorzien in de ministriële besluiten van 19 mei 1992 en 5 april 1995 met betrekking tot respectievelijk de rust- en verzorgingstehuizen en de rustoorden voor bejaarden, in rekening kan brengen : bij twee rechthebbenden, bij eenzelfde reis, per rechthebbende
103950	GP visit at the patients home at increased fee	Bezoek door de erkende huisarts, bij de zieke in een inrichting die een forfaitaire tegemoetkoming zoals voorzien in de ministriële besluiten van 19 mei 1992 en 5 april 1995 met betrekking tot respectievelijk de rust- en verzorgingstehuizen en de rustoorden voor bejaarden, in rekening kan brengen : bij drie rechthebbenden of meer, bij eenzelfde reis, per rechthebbende
104112	GP visit at the patients home at increased fee	Bezoek door de algemeen geneeskundige met verworven rechten bij de zieke in een inrichting die een forfaitaire tegemoetkoming zoals voorzien in de ministriële besluiten van 19 mei 1992 en 5 april 1995 met betrekking tot respectievelijk de rust- en verzorgingstehuizen en de rustoorden voor bejaarden in rekening kan brengen : bij één rechthebbende
104134	GP visit at the patients home at increased fee	Bezoek door de algemeen geneeskundige met verworven rechten bij de zieke in een inrichting die een forfaitaire tegemoetkoming zoals voorzien in de ministriële besluiten van 19 mei 1992 en 5 april 1995 met betrekking tot respectievelijk de rust- en verzorgingstehuizen en de rustoorden voor bejaarden in rekening kan brengen : bij twee rechthebbenden, bij eenzelfde reis, per rechthebbende
104156	GP visit at the patients home at increased fee	Bezoek door de algemeen geneeskundige met verworven rechten bij de zieke in een inrichting die een forfaitaire tegemoetkoming zoals voorzien in de ministriële besluiten van 19 mei 1992 en 5 april 1995 met betrekking tot respectievelijk de rust- en verzorgingstehuizen en de rustoorden voor bejaarden in rekening kan brengen : bij drie rechthebbenden of meer, bij eenzelfde reis, per rechthebbende
104215	GP visit at the patients home at increased fee	Bezoek door de erkende huisarts tussen 18 en 21 uur afgelegd bij de zieke thuis
104370	GP visit at the patients home	Bezoek door de erkende huisarts thuis bij een palliatieve patiënt
104392	GP visit at the patients home at increased fee	Bezoek door de erkende huisarts tussen 18 en 21 uur thuis bij een palliatieve patiënt
104510	GP visit at the patients home at increased fee	Bezoek door de algemeen geneeskundige met verworven rechten tussen 18 en 21 uur afgelegd bij de zieke thuis
104672	GP visit at the patients home	Bezoek door de algemeen geneeskundige met verworven rechten, thuis bij een palliatieve patiënt
104694	GP visit at the patients home at increased fee	Bezoek door de algemeen geneeskundige met verworven rechten, tussen 18 en 21 uur thuis bij een palliatieve patiënt

9.4.3 Appendix: ICD-9-CM codes for Major thromboembolic events

41511	Iatrogenic pulmonary embolism and infarction
41519	Other pulmonary embolism and infarction
41001	Acute myocardial infarction - Of anterolateral wall - initial episode of care
41011	Acute myocardial infarction - Of other anterior wall - initial episode of care
41021	Acute myocardial infarction - Of inferolateral wall - initial episode of care
41031	Acute myocardial infarction - Of inferoposterior wall - initial episode of care
41041	Acute myocardial infarction - Of other inferior wall - initial episode of care
41051	Acute myocardial infarction - Of other lateral wall - initial episode of care
41061	Acute myocardial infarction - True posterior wall infarction - initial episode of care
41071	Acute myocardial infarction - Subendocardial infarction - initial episode of care
41081	Acute myocardial infarction - Of other specified sites - initial episode of care
41091	Acute myocardial infarction - Unspecified site - initial episode of care
43300	Occlusion and stenosis of precerebral arteries - Basilar artery - without mention of cerebral infarction
43301	Occlusion and stenosis of precerebral arteries - Basilar artery - with cerebral infarction
43310	Occlusion and stenosis of precerebral arteries - Carotid artery - without mention of cerebral infarction
43311	Occlusion and stenosis of precerebral arteries - Carotid artery - with cerebral infarction
43320	Occlusion and stenosis of precerebral arteries - Vertebral artery - without mention of cerebral infarction
43321	Occlusion and stenosis of precerebral arteries - Vertebral artery - with cerebral infarction
43330	Occlusion and stenosis of precerebral arteries - Multiple and bilateral - without mention of cerebral infarction
43331	Occlusion and stenosis of precerebral arteries - Multiple and bilateral - with cerebral infarction
43400	Occlusion of cerebral arteries - Cerebral thrombosis - without mention of cerebral infarction
43401	Occlusion of cerebral arteries - Cerebral thrombosis - with cerebral infarction
43410	Occlusion of cerebral arteries - Cerebral embolism - without mention of cerebral infarction
43411	Occlusion of cerebral arteries - Cerebral embolism - with cerebral infarction
43490	Occlusion of cerebral arteries - Cerebral artery occlusion, unspecified - without mention of cerebral infarction
43491	Occlusion of cerebral arteries - Cerebral artery occlusion, unspecified - with cerebral infarction
4358	Other specified transient cerebral ischemias
4359	Unspecified transient cerebral ischemia
4440	Arterial embolism and thrombosis - Of abdominal aorta
4441	Arterial embolism and thrombosis - Of thoracic aorta
44421	Arterial embolism and thrombosis - Of arteries of the extremities - upper
44422	Arterial embolism and thrombosis - Of arteries of the extremities - lower
44481	Arterial embolism and thrombosis - Of other specified artery - Iliac artery
44489	Arterial embolism and thrombosis - Of other specified artery - Other
4449	Arterial embolism and thrombosis - Of unspecified artery

452	Portal vein thrombosis
4532	Other venous embolism and thrombosis - Of vena cava
4533	Other venous embolism and thrombosis - Of renal vein
45340	Other venous embolism and thrombosis - Venous embolism and thrombosis of unspecified deep vessels of lower extremity
45341	Other venous embolism and thrombosis - Venous embolism and thrombosis of deep vessels of proximal lower extremity
45342	Other venous embolism and thrombosis - Venous embolism and thrombosis of deep vessels of distal lower extremity
4538	Other venous embolism and thrombosis - Of other specified veins
4539	Other venous embolism and thrombosis - Of unspecified site

9.4.4 Results of the probabilistic cost analysis for each strategy and scenario

Strategies	Number of tests/year	Number of GP consultations	Total cost	
			Average	90% CI
Standard laboratory testing	IMA/AIM data distribution*	Equal to the number of tests	€766.25	€319.57 to €1569.72
POC by GP	IMA/AIM data distribution*	Equal to the number of tests	€605.07	€266.25 to €1214.54
	26	Equal to the number of tests	€881.79	€881.79 to €881.79
	52	Equal to the number of tests	€1739.75	€1739.75 to €1739.75
POC at AC (algorithm)	IMA/AIM data distribution*	24%**	€544.51	€418.26 to €771.62
	26	24%**	€592.8	€525.68 to €713.55
	52	24%**	€742.53	€675.4 to €863.28
POC at AC (software)	IMA/AIM data distribution*	24%**	€558.16	€431.9 to €785.27
	26	24%**	€606.45	€539.33 to €727.2
	52	24%**	€756.18	€689.05 to €876.92
PST (without complication)	15	24%**	€634.34	€567.22 to €755.09
	26	24%**	€787.72	€720.59 to €908.46
	52	24%**	€1150.24	€1083.12 to €1270.99
PST (with complications)	15	24%**	€410.67	€-149.68 to €672.81
	26	24%**	€564.05	€3.7 to €826.18
	52	24%**	€926.57	€366.22 to €1188.71
PSM (without complication)	15	24%**	€509.88	€442.76 to €630.63
	26	24%**	€571.99	€504.86 to €692.73
	52	24%**	€718.78	€651.65 to €839.52
PSM (with complications)	15	24%**	€336.91	€0.28 to €546.61
	26	24%**	€399.01	€62.39 to €608.71
	52	24%**	€545.81	€209.18 to €755.51
Standard laboratory testing	IMA/AIM data distribution*	Equal to the number of tests	€766.25	€319.57 to €1569.72
POC by GP	IMA/AIM data distribution*	Equal to the number of tests	€605.07	€266.25 to €1214.54
	26	Equal to the number of tests	€881.79	€881.79 to €881.79
	52	Equal to the number of tests	€1739.75	€1739.75 to €1739.75
POC at AC (algorithm)	IMA/AIM data distribution*	50%**	€669.26	€470.28 to €1027.18
	26	50%**	€717.55	€577.71 to €969.11
	52	50%**	€867.28	€727.43 to €1118.83
POC at AC (software)	IMA/AIM data distribution*	50%**	€682.91	€483.93 to €1040.82
	26	50%**	€731.2	€591.35 to €982.75
	52	50%**	€880.93	€741.08 to €1132.48

PST (without complication)	15	50%**	€759.09	€619.24 to €1010.65
	26	50%**	€912.47	€772.62 to €1164.02
	52	50%**	€1274.99	€1135.15 to €1526.55
PST (with complications)	15	50%**	€537.54	€-22.75 to €903.3
	26	50%**	€690.92	€130.62 to €1056.68
	52	50%**	€1053.44	€493.15 to €1419.2
PSM (without complication)	15	50%**	€634.63	€494.78 to €886.18
	26	50%**	€696.73	€556.89 to €948.29
	52	50%**	€843.53	€703.68 to €1095.08
PSM (with complications)	15	50%**	€461.65	€102.72 to €773.63
	26	50%**	€523.76	€164.83 to €835.74
	52	50%**	€670.55	€311.62 to €982.53
Standard laboratory testing	IMA/AIM data distribution*	Equal to the number of tests	€766.25	€319.57 to €1569.72
POC by GP	IMA/AIM data distribution*	Equal to the number of tests	€605.07	€266.25 to €1214.54
	26	Equal to the number of tests	€881.79	€881.79 to €881.79
	52	Equal to the number of tests	€1739.75	€1739.75 to €1739.75
POC at AC (algorithm)	IMA/AIM data distribution*	100%**	€909.16	€570.34 to €1518.63
	26	100%**	€957.45	€677.76 to €1460.56
	52	100%**	€1107.18	€827.48 to €1610.29
POC at AC (software)	IMA/AIM data distribution*	100%**	€922.81	€583.98 to €1532.28
	26	100%**	€971.1	€691.41 to €1474.21
	52	100%**	€1120.83	€841.13 to €1623.93
PST (without complication)	15	100%**	€998.99	€719.3 to €1502.1
	26	100%**	€1152.37	€872.67 to €1655.47
	52	100%**	€1514.89	€1235.2 to €2018
PST (with complications)	15	100%**	€774.63	€130.09 to €1356.31
	26	100%**	€928.01	€283.47 to €1509.68
	52	100%**	€1290.53	€645.99 to €1872.21
PSM (without complication)	15	100%**	€874.53	€594.84 to €1377.64
	26	100%**	€936.63	€656.94 to €1439.74
	52	100%**	€1083.43	€803.73 to €1586.53
PSM (with complications)	15	100%**	€701.55	€272.66 to €1228.54
	26	100%**	€763.65	€334.77 to €1290.64
	52	100%**	€910.44	€481.56 to €1437.43

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Wettelijk depot : D/2008/10.273/47

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.
33. Effecten en kosten van de vaccinatie van Belgische kinderen met geconjugeerd pneumokokkenvaccin. D/2006/10.273/21.
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.
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