Pharmacoeconomics of cardiovascular disease prevention

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Chapter 5

Budget impact of increasing market-share of patient self-testing and patient self-management in anticoagulation

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ABSTRACT

Background: Patient self-testing and/or patient self-management (PST and/or PSM) might provide better coagulation care than monitoring at specialised anticoagulation centres. Yet, it remains an underused strategy in the Netherlands.

Methods: Budget impact analyses of current and new market-share scenarios of PST and/or PSM compared to monitoring at specialised centres were performed for a national cohort of 260,338 patients requiring long-term anticoagulation testing. A healthcare payer perspective and one to five year time horizons were applied. The occurrence of thromboembolic and haemorrhagic complications in the aforementioned patient population were assessed in a Markov model. Dutch specific costs were applied, next to effectiveness data derived from a meta-analysis on self-monitoring of oral anticoagulation. Sensitivity and scenario analyses were performed to assess uncertainty on budget impact model results.

Results: Increasing PST and/or PSM usage on a national level from the current 15.4% to 50% was found to be associated with savings ranging from €8 million following the first year to €184 million after 5 years. Further increases in the use of PST and/or PSM produced greater savings up to €450 million by 5 years after a complete replacement of anticoagulation testing with PST and/or PSM. Sensitivity analyses showed robust cost-savings, with the extreme of thromboembolic risk being maximally unfavourable for the budget impact of PST and/or PSM. Results of a scenario analysis exploring a linear increase in the uptake of PST and/or PSM from the current 15.4% to the expected 50% indicated savings from €2 million after the first year to €184 million cumulatively after the fifth year. Finally, potential unfavourable budget impact was found in scenarios exploring an increase in the use of PST alone as well as increase in market shares of PST and/or PSM in patients with atrial fibrillation on long-term oral anticoagulation.

Conclusion: PST and/or PSM was found to be a more favourable alternative to monitoring at specialised centres. However, using PoC devices solely for PST resulted in greater expenditures compared to testing in anticoagulation clinics. Additionally, our study indicated less favourable findings of using PST and/or PSM in patients with atrial fibrillation.

INTRODUCTION

Oral anticoagulation therapy (OAT) with vitamin K antagonists (VKA) has been shown to reduce the risks of thromboembolic events in a number of clinical situations (1). In the Netherlands, indications for OAT include atrial fibrillation (AF), arterial diseases (e.g., cardiomyopathy, coronary syndromes and surgery, vascular surgery, cerebral embolism), heart valve replacement and venous thromboembolism (2). Patients with AF represent the majority of patients requiring OAT (i.e. 62%). Given the increase in numbers of AF patients, it is not surprising that the number of patients requiring OAT has increased as well over the past decades in Western countries (2). Furthermore, the population of patients in need of OAT is projected to increase further in the coming decades (3,4). This is partly due to the aging population in Western countries and the positive association between age and the incidence and prevalence of AF (5).

While warfarin is commonly used worldwide, acenocoumarol and phenprocoumon (to a lesser extent) are the VKAs of first choice in the Netherlands. Prophylaxis with VKA is considered an effective strategy but it has some shortcomings, including multiple interactions with food and other drugs as well as inter-individual and intra-individual variability in pharmacodynamics (6,7). As a result, regular monitoring is required to maintain the international normalized ratio (INR) within the therapeutic range. INR-testing is typically performed at specialised anticoagulation testing centres, adding to the cumbersomeness of VKA use for the patients. Notably, Point-of-Care (PoC) devices allow for patient self-testing (PST), where trained patients can perform the INR-test but still inform his/her healthcare provider for subsequent advice on anticoagulant dosing, or even patient self-management (PSM), with trained patients performing the INR testing, interpreting the results, and adjusting dosing accordingly.

In agreement with the increasing number of patients with indications for OAT, the number of patients using INR-testing in the Netherlands has increased from approximately 320,000 in 2002 to 430,000 in 2012 (2). Again, this trend is expected to continue in the coming years with the aging population. Also, between 2007 and 2011 annual incidence for AF has steadily increased from under 40,000 in 2008 to 56,000 in 2012 (2).

These figures, however, may still underrepresent the actual number of patients in need of OAT as many eligible patients do not receive anticoagulation because of concerns of the patients or concerns of their physicians of being outside the INR range (8-12). PoC testing may also address this issue. As supported by international findings (13,14), PST and/or PSM can lead to better coagulation care in the Netherlands compared to regular monitoring in specialized anticoagulation centres (2). This may be due in part to the convenience of use, resulting in more frequent testing, which is associated with greater time in therapeutic range (TTR) (15). Also, findings from meta-analytical studies suggest that PST and/or PSM compared to regular monitoring has similar risks of bleedings but

reduced risks of thromboembolic events and all-cause mortality (13). Finally, it has been reported that the patient empowerment inherent in PoC-strategies in itself already directly reduces the risks of complications and death even in the absence of any measurable increase in the quality of anticoagulation control (16). Despite these positive results, PST and/or PSM remains an underused strategy in the Netherlands.
Eligible patients for PST and/or PSM include all those on long-term OAT (regardless of indication), who have passed the required training. To date, the estimated number of patients on long-term OAT in the Netherlands is approaching 260,338. In the current situation, 15.4% of this population utilizes PST and/or PSM (2). In this study, we will assess the budget impact of the current situation and new scenarios where PST and/or PSM represents 50%, 75% and 100% of INR monitoring in the Netherlands.

METHODS

A budget impact analysis (BIA) was performed, using a patient cohort approach. Patients in the cohort exit the model after death, but no new patients enter the model (closed model). The perspective of the study is that of a healthcare payer. In the present analysis, the patient cohort includes all patients, who require anticoagulation monitoring for OAT for any clinical indication.
The design and reporting of study outcomes followed the recommendations of International Society for Pharmacoeconomics and Outcomes Research for BIAs (ISPOR) Task Force (17)(18).

Model structure

Patients indicated for OAT are at risk of haemorrhagic and thromboembolic events. To incorporate the course of disease in the BIA, a Markov model was developed. This model includes the following health states: no complications, thromboembolic complications, haemorrhagic complications, and death (Figure 1). A cycle length of one year was used. The cumulative budget impact of the cohort was assessed each year up to 5 years. Patients enter the model in the “no complications” health state.

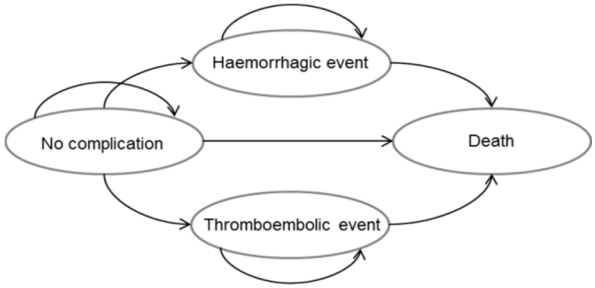

Figure 1 Markov model structure.
Patients enter the model in the “No complication” health state. Possible transitions are defined by the arrows.

In the base-case analysis, transition probabilities for thromboembolic and haemorrhagic complications and death were based on a systematic review and meta-analysis of individual patient data on self-monitoring of oral anticoagulation by Heneghan et al. (14). This study estimated the relative risks (RR) of thromboembolic and haemorrhagic complications and death between testing at anticoagulation centres and PST and/or PSM for all indications of OAT (Table 1). To assign transition probabilities for each testing strategy, baseline risks for patients visiting anticoagulation centres/clinics were also needed. Data on the number of thromboembolic and haemorrhagic complications and death, and duration of follow-up for this group were taken from studies by Menendez-Jandula et al., Fitzmaurice et al., Matchar et al., and Siebenfofer et al. (Table 2 (19-22). These studies were selected because they were included in the study by Heneghan et al. and hence provide internal validity to our study (14). To estimate baseline risks of complications and death, we conducted a meta-analysis on the aforementioned studies in the statistical program R 3.0.2, using the "metafor" package (Table 1)(19-24). Because the study populations are not homogeneous across the studies and do not fit the assumption of a fixed-effect meta-analysis, a random-effect meta-analysis was applied.
Annual risks of complications and death for the PST and/or PSM group were calculated by taking the product of the RRs reported by Heneghan et al. and the baseline risks estimated through a random-effect meta-analysis (Table 1)(14). In addition, age-specific background mortality rates for the Netherlands for 2012 were used to estimate transition from no complications to death (25).

Cost parameters

Costs associated with thromboembolic and haemorrhagic complications were collected from published Dutch studies. All costs were inflated to 2013 levels using the harmonised index for consumer product (HICP) for the health sector for the Netherlands (26). Costs for thromboembolic events were derived from costs of ischemic stroke (27), myocardial infarction (28), and pulmonary embolism (29) with contributions of 71.43%, 24.32%, and 4.25%, respectively, to the overall estimate (30). Cerebral haemorrhage (31), gastrointestinal bleeding (32), and other bleedings (32) were assumed to represent 10.66%, 30.46%, and 58.88% of the costs associated with haemorrhagic complications (30). For each complication, costs were differentiated between first and subsequent years in the analysis, given the differences in the nature of complications between these years. No subsequent year cost was assumed for pulmonary embolism and bleeding events though. Furthermore, death was not associated with any additional cost. The weighted costs of thromboembolic complications were €41,866 for the first year and €8,750 for subsequent years. For haemorrhagic complications, the weighted averages were €9,748 and €1,263 for first and subsequent years, respectively (Table 3).

Table 1 Annual risks of clinical events for use in the Markov model – base-case analysis.

	Specialized Centre	PST and/or PSM	
	Annual baseline risk[a], %	Relative risk[b]	Annual risk[c], %
Thromboembolic Event	3.22 (1.50-4.94)	0.44 (0.17-1.14)	1.42 (0.26-5.63)
Haemorrhagic Event	2.84 (1.16-4.52)	0.91 (0.74-1.12)	2.58 (0.86-5.06)
Death	2.87 (1.01-4.74)	0.82 (0.52-1.28)	2.35 (0.53-6.07)

PST, patient self-testing; PSM, patient self-management.
[a]Estimated through a random-effects meta-analysis of annual risks for patients using anticoagulation testing centre.
[b]Adapted from the meta-analysis of individual patient data on self-monitoring of oral anticoagulation by Heneghan et al.(14).
[c]Estimated by taking the product of the relative risks reported by Heneghan et al. (14) and the baseline annual risks estimated by the authors' random-effects meta-analysis of annual risks for patients using anticoagulation testing centre.
95% confidence intervals of risk estimates are showed in parentheses.

Table 2 Studies used to estimate annual risks of complications for patients using testing centres.

Study	Country	Open RCT design	Events	Patient-years	Proportion	SE
Menendez-Jandula (2005)(19)	Spain	Single-centre				
Thromboembolic events			20	363	0.055	0.012
Haemorrhagic events			7	363	0.019	0.007
Death			15	363	0.041	0.010
Fitzmaurice (2005)(20)	UK	Multi-centre				
Thromboembolic events			4	264	0.015	0.008
Haemorrhagic events			3	264	0.011	0.007
Death			1	264	0.004	0.004
Matchar (2010)(21)	USA	Multi-centre				
Thromboembolic events			101	4235	0.024	0.002
Haemorrhagic events			199	4235	0.047	0.003
Death			157	4235	0.037	0.003
Siebenhofer (2008)(22)	Germany	Multi-centre				
Thromboembolic events			13	290	0.045	0.012
Haemorrhagic events			10	290	0.034	0.011
Death			11	290	0.038	0.011

RCT, randomised clinical trial; SE, standard error.

Table 3 Costs parameters applied in the model (€2013 per patient).

	First Year	Subsequent Years
Stroke(27)	50,828	11,800
Myocardial infarction(28)	22.015	1.338
Pulmonary embolism(29)[a]	5.244	0
Weighted Average Thromboembolic Event [b]	41,866	8,750
Cerebral haemorrhage(27)(31)[c]	38,417	11,800
Gastrointestinal bleeding(32)	7,120	0
Other major bleeding(32)	5,884	0
Weighted Average Haemorrhagic event[d]	9,748	1,263
Testing strategy		
VKA(33)	16	16
Specialized Centres	248	248
Blood sampling & INR-measurements at centres(34)[e]	181	181
Additional tariff for blood sampling at home(34)[f]	67	67
PST and/or PSM	958	749
Initial training & instruction(34)	396	0
Monitoring & supervision (34)[g]	562	749
Additional tariff for phone consultation for PST only (32)[h]	210	210

VKA, vitamin K antagonists; PST, patient self-testing; PSM, patient self-management.
[a]Cost estimate of pulmonary embolism from the original source was corrected to exclude the cost of INR testing and coumarines.
[b]On the basis of the assumption that the cost of a thromboembolic event will be a composite of the costs related to stroke, myocardial infarction and pulmonary embolism with contributions of 71.4%, 24.3%, and 4.2%, respectively, to the overall estimate.
[c]Cost estimate of cerebral haemorrhage from the original source was corrected to exclude the costs of home help and private transportation costs.
[d]On the basis of the assumption that the cost of a haemorrhagic event will be a composite of the costs related to cerebral haemorrhage, gastrointestinal bleeding bleeding and other major bleeding with contributions of 10.7%, 30.5%, and 58.9%, respectively, to the overall estimate.
[e]Assuming 21.1 tests per year(2).
[f]Assuming 8.6 home blood samplings per year(2).
[g]Assuming 3 supervision sessions in the first year and 4 supervision sessions in the subsequent years.
[h]Assuming 12 phone consultations on dosing per year for patients who only self-test.

Acquisition cost of VKA and anticoagulation monitoring are presented in Table 3. Cost of VKA was estimated as a weighted average cost of acenocoumarol and phenprocoumon based on their usage in the Netherlands (i.e. 80%:20%, respectively). The annual cost of VKA was estimated at €16.06 (33). Anticoagulation testing at centres may involve blood sampling at the centres or at home. For blood sampling and measurement at testing centres, 21.1 INR-testings per patient per year was assumed (2). In addition, there were

8.6 home blood samplings per patient per year for the same patient group as those tested in the centre (2). The annual cost of monitoring at testing centres is the same for each year and estimated to be €248 (34).
The first year cost of PST and/or PSM consisted of the costs of the device and one initial training session and 3 supervision sessions. Subsequent years of use required quarterly supervision sessions. The costs of the first and subsequent years were estimated to be €958 and €749, respectively (34). While these patients receive information for possible adjustments in their VKA dose by e-mail or specific software, no additional costs were added for dosing adjustments.

Budget impact analysis
In the analysis, a cohort population size was evaluated at 260,338. This cohort size represents an estimate of all patients requiring long-term anticoagulation testing for OAT for any indication on a national level for the Netherlands. Using estimates from the Federation of Dutch Thrombosis Services ("Federatie Nederlandse Trombosediensten"; FNT) Report 2012, the current share of PST and/or PSM among patients on long-term monitoring was assumed to be 15.4% (2). This current situation was evaluated against potential new market penetration scenarios of 50%, 75%, and 100% for PST and/or PSM. The BIA was evaluated for each year up to 5 years. Costs were not discounted as recommended by the ISPOR Task Force for BIAs (17).

Sensitivity analysis
To examine the impact of uncertainty in key model parameters (i.e. baseline and relative risks of complications and death and cost parameters) univariate sensitivity analyses were performed on the 5-year BIA results considering a market penetration scenario of 50% in Dutch patients on long-term OAT. Here each parameter was varied over the 95% confidence interval (CI) while holding all other parameters constant. Where CI or standard deviation (SD) was unavailable, the SD was assumed to be 25% of the mean.

Scenario analyses
Three scenario analyses were conducted to investigate the impact of increasing the market share of PST and/or PSM up to 50% under different decision analytic settings. The first scenario explored a linear increase in the uptake of PST and/or PSM from the current 15.4% to the expected 50% in 5 years. In the second scenario, an increase in the market share of PST alone from the current 6.16% (i.e. 40% of all patients with PoC devices) to 50% was explored. Here, transition probabilities for thromboembolic and haemorrhagic complications in the Markov model were based on the RRs of utilizing PST alone compared to testing at specialized centres as reported by Heneghan et al. while the baseline risks were estimated through a random-effect model (Table 4). The costs of PST alone were assumed to be associated with additional €210 per year, reflecting consultations for dosing regime adjustments. In the third scenario, the BIA of increasing the market share of

PST and/or PSM from the assumed 15.4% to 50% in patients with AF was explored in scenario 3. In this analysis, it was assumed that 62% of patients on long-term OAT are affected with AF, thus a cohort population size was evaluated at 161,410 patients. Transition probabilities in the Markov model were based on the RRs assessed in AF patients (Table 4).

Table 4 Annual risks of clinical events for use in the Markov model – scenario analyses

	Specialized centre	PST		AF	
	Annual baseline risk[a]	Relative risk[b]	Annual risk[c]	Relative risk[b]	Annual risk[c]
Thromboembolic Event					
Mean	3.22%	0.74	2.38%	0.67	2.16%
Low 95% CI	1.50%	0.3	0.45%	0.28	0.42%
High 95% CI	4.94%	1.82	8.99%	1.57	7.76%
Haemorrhagic Events					
Mean	2.84%	0.84	2.39%	1.04	2.95%
Low 95% CI	1.16%	0.64	0.74%	0.81	0.94%
High 95% CI	4.52%	1.12	5.06%	1.34	6.06%
Death					
Mean	2.87%	0.91	2.61%	0.72	2.07%
Low 95% CI	1.01%	0.75	0.76%	0.43	0.43%
High 95% CI	4.74%	1.11	5.26%	1.2	5.69%

PST, patient self-testing; AF, atrial fibrilation.
[a]Estimated through a random-effects meta-analysis of annual risks for patients using anticoagulation testing centre.
[b]Adapted from the meta-analysis of individual patient data on self-monitoring of oral anticoagulation by Heneghan et al.(14).
[c]Estimated by taking the product of the relative risks reported by Heneghan et al. (14) and the baseline annual risks estimated by the authors' random-effects meta-analysis of annual risks for patients using anticoagulation testing centre.
95% confidence intervals of risk estimates are showed in parentheses.

RESULTS

Base-case results

The estimation of total costs per patient associated with INR monitoring in specialized anticoagulation centres and with PoC-devices for a time horizon of one to five years is detailed in Table 5. Monitoring related costs were higher than event related costs only in the first year in patients conducting INR-testing with PoC-devices. Costs associated with thromboembolic and haemorrhagic events were responsible for the vast majority part of total costs with PoC-devices in the longer time horizons and in all time horizons in patients conducting testing in specialized centres. Expanding the aforementioned findings to the

Dutch national cohort of 260,338 patients who are using long-term anticoagulation testing, a current situation of 15.4% using PST and/or PSM with PoC-devices resulted in cumulative costs of €486 million, €1.00 billion, €1.54 billion, €2.11 billion, and €2.70 billion in the first, second, third, fourth, and fifth year, respectively (Figure 2). Increasing the use of PST and/or PSM to 50% in the first year resulted in cost-saving of €8 million from the healthcare budget. The savings increased exponentially each year, reaching estimated savings of €184 million after the fifth year. Similarly, increasing PST and/or PSM market penetration to 75% and 100% produced correspondingly greater 5-year cumulative savings of €317 and €450 million, respectively. While it is not likely that PST and/or PSM will completely replace INR-testing at specialised anticoagulation centres, this latter scenario illustrates the potential maximum savings in long-term utilization.

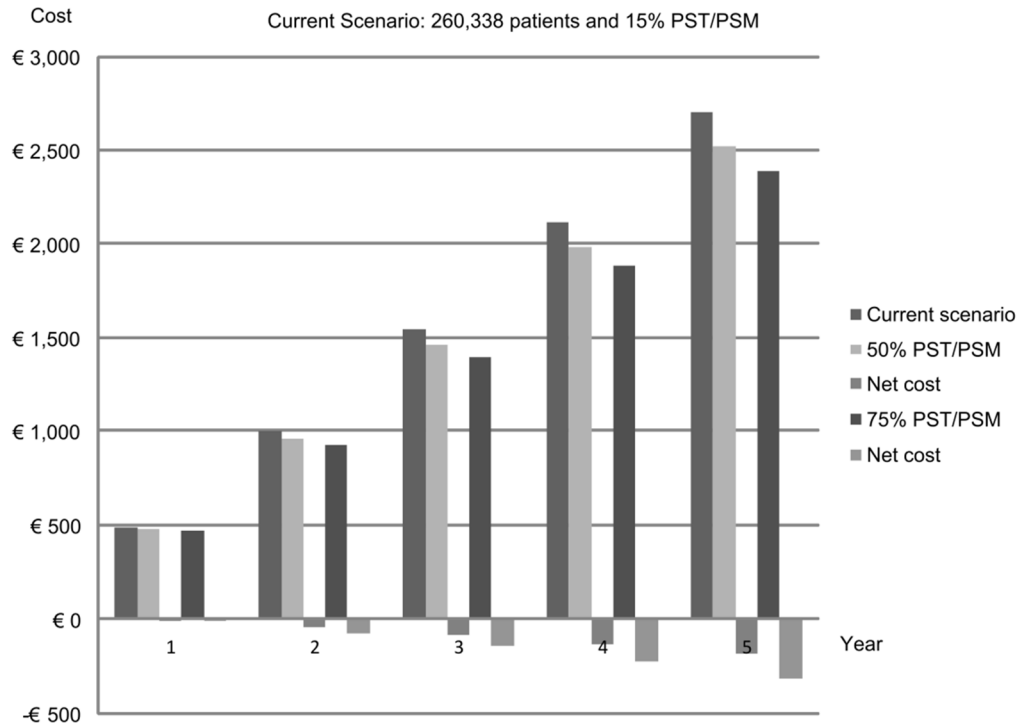

Figure 2 Budget impact analysis from year 1 to year 5 of current and new market share scenarios for PST and/or PSM (in millions).
PST, patient self-testing; PSM, patient self-management.

Table 5 Cost allocation of overall medical costs associated with anticoagulation monitoring with PST and/or PSM and within specialized anticoagulation centres (€, per patient). Current situation.

	PST/PSM			Specialised centre		
Year	Total	Monitoring	Events	Total	Monitoring	Events
1	1,796	951	845	1,881	256	1,628
2	3,444	1,651	1,793	3,912	490	3,422
3	5,140	2,306	2,834	6,071	703	5,368
4	6,877	2,919	3,958	8,336	897	7,439
5	8,647	3,492	5,155	10,690	1,073	9,617

PST, Patient self-testing; PSM, patient self-management

Sensitivity analysis

The results of the univariate sensitivity analyses show the impact of uncertainty surrounding the key model parameters, illustrating that the relative and baseline risk of thromboembolic complications had the highest impact on the BIA results (Figure 3). Specifically, when the relative risk of thromboembolic complications would drop to the lower limit of the 95% CI, BIA results would indicate total health care expenditures of €302 million. At risks increasing to the upper limits of 95% CIs, a cost-saving of €382 million would be observed. The univariate sensitivity analyses also showed the BIA results were sensitive to the uncertainty around the cost parameters. Yet, these results generally favored an increasing market penetration of PST and/or PSM. Notably, cost savings were robust over the whole range of variations except at the extreme for thromboembolic risk, reflecting a situation with this risk at its lower limit that is maximally unfavourable for our BIA.

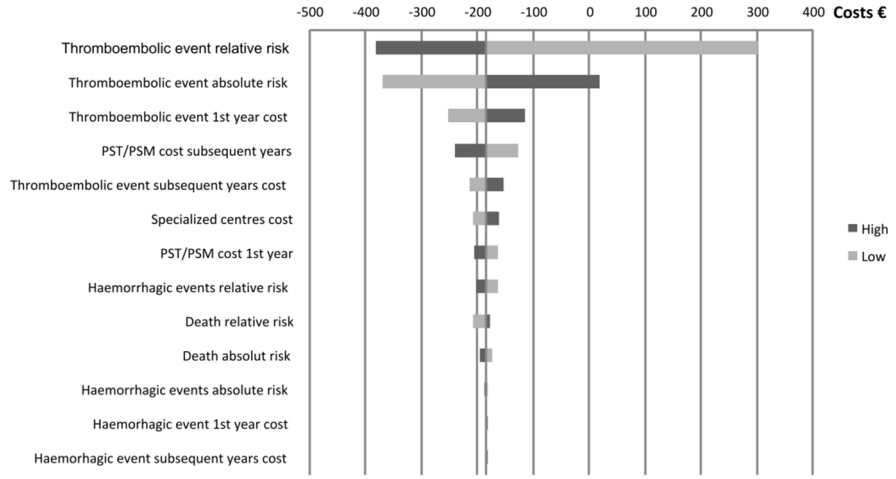

Figure 3 Tornado diagram illustrating results from sensitivity analyses for budget impact analysis in a 5 year horizon considering a market penetration scenario of 50% for PST and/or PSM in a Dutch cohort of 260,338 patients (in millions).

Grey bars denote influence of the low value of the 95% confidence interval range and black bars denote influence of the high value for parameters investigated.

PST, patient self-testing; PSM, patient self-management.

Scenario analyses

The results of scenario analyses are presented in Table 6. A linear increase in the uptake of PST and/or PSM from the current 15.4% to the expected 50% indicated savings from € 2 million after the first year to €184 million cumulatively after the fifth year (scenario 1). Increasing the market share of PST alone from the current 6.16% to 50% resulted in expenditures from €57 million after the first year to €123 million cumulatively after the fifth year (scenario 2). Finally, increasing the market share of PST and/or PSM in a cohort of 161,410 AF patients indicated an expenditure of €15 million after the first year but resulted in cumulative savings of €2 million after 5 years (scenario 3).

Table 6 Results of scenario analyses on uptake of PST and/or PSM (€, in millions)

	New scenario	Current scenario	Difference
Scenario 1: 260,338 patients and 15.4% PST and/or PSM			
1	485	486	-2
2	983	1,000	-17
3	1,493	1,543	-50
4	2,007	2,112	-105
5	2,517	2,701	-184
Scenario 2: 260,338 patients and 6.16% PST			
1	555	497	57
2	1,113	1,030	83
3	1,697	1,595	102
4	2,301	2,186	115
5	2,923	2,800	123
Scenario 3: 161,410 AF patients and 15.4% PST and/or PSM			
1	325	310	15
2	652	638	15
3	996	985	11
4	1,354	1,348	6
5	1,723	1,725	-2

*values are rounded

Scenario 1 explores a linear increase in the uptake of PST and/or PSM from the current 15.4% to the expected 50% in 5 years.

Scenario 2 explores an increase of market share of PST alone from 6.16% to 50%.

Scenario 3 explores an increase of market share of PST and/or PSM in AF patients from 15.4% to 50%.

DISCUSSION

Our study presents a BIA of the current practice as well as new varying market penetration scenarios of anticoagulation monitoring with PST and/or PSM compared to monitoring at specialised anticoagulation centres in the Netherlands. Our findings in the base-case analysis indicated that increasing PST and/or PSM usage for anticoagulation testing from the current 15.4% to 50%, 75% and 100%, would lead to significant savings in all analysed scenarios. Even though INR testing is 3.9 times and 3.0 times more costly for PST and/or

PSM compared to specialised anticoagulation centres during the first year and subsequent years, cost-saving was still observed when considering total direct medical costs due to considerably higher event-related costs. This is due to the greater risk reductions of thromboembolic and haemorrhagic complications, associated with high medical costs. In fact, increasing the number of patients switching from conventional testing to PST and/or PSM by increasing market penetration, produced even greater savings in the time horizon of five years. For example, considering a national-level cohort population, potential maximum savings over the current situation of €450 million may be observed in 5 years. However, this is under the unlikely scenario of 100% adoption of PST and/or PSM. Yet, even if PST and/or PSM would be adopted by 50% of all patients requiring long-term INR testing – a figure that is quite attainable in the coming years – would result in a savings range from €8 million following the first year to €184 million after 5 years. These analyses clearly demonstrated the value of PST and/or PSM strategy with PoC-devices in the Netherlands. Univariate sensitivity analyses revealed the major impact of uncertainty in baseline thromboembolic risk on the BIA results. The impact of the uncertainty in the baseline thromboembolic risk can be directly attributed to its impact on the occurrence of stroke, myocardial infarction and pulmonary embolism events and their related costs of treatment reaching in the first year and follow-up years a weighted average cost of €41,866 and €8,750 per patient respectively. Overall, univariate sensitivity analysis showed robust cost savings, with the extreme of thromboembolic relative and absolute risk being maximally unfavourable for the BIA of PST and/or PSM at the relatively unlikely exception.

Finally, this study observed potential unfavourable budget impact of increasing market shares of PST alone as well as increasing market shares of PST and/or PSM in AF patients on long-term OAT (scenarios 2 and 3). Greater expenditures associated with increasing market shares of PST alone in scenario 2 are due to not only the higher cost of PST strategy compared to PST and PSM combined but also costs associated with lower number of prevented complications in comparison to the base-case scenario. The findings in scenario 3 may be attributed to lower number of thromboembolic complications prevented in comparison to the base-case scenario with a corresponding greater number of haemorrhagic complications with PST and/or PSM compared to monitoring in specialized centers, which are associated with high costs.

Comparison with other studies

To our knowledge, published economic evaluations of PST and/or PSM compared to monitoring at specialised anticoagulation centres or to routine clinic-based care are all cost-effectiveness analyses (CEA). This hampers a direct comparison of our study findings with the ones from these other studies. Yet, there is a general agreement in the conclusions of the available CEAs with our study results regarding the preference for PST and/or PSM for long-term use. Specifically, Regier et al. found the self-managed

anticoagulation to be a more cost-effective alternative compared to physician-managed anticoagulation from the Canadian healthcare payer perspective in a 5-year time horizon with an incremental cost-effectiveness ratio (ICER) of CAD14,129 per quality-adjusted life year (QALY) (35). In the same study, when use of self-management was limited to a 1-year time horizon, an ICER of CAD236,667 per QALY was estimated (35). Furthermore, in the study by Lafata et al., self-testing in a US setting was found to be a cost-effective alternative to testing in anticoagulation clinics with an ICER of $24,818 per event avoided in a 5-year time horizon (36). Finally, Jowett et al. found PSM compared to routine clinic-based monitoring unlikely to be cost-effective from the UK healthcare system perspective in a 1-year time horizon (i.e. ICER of £32,716 per QALY) (37). These findings may be mainly attributed to greater local costs of PST/PSM compared to alternative testing strategy and sources of effectiveness data. Across all the aforementioned studies, the cost of testing with PST and/or PSM outweighed the cost of alternative strategy. The costs associated with thromboembolic and haemorrhagic complications were greater with PST and/or PSM strategy compared to alternative testing. This was mainly driven by the effectiveness data used in those studies. In particular, Jowett et al. utilized patient-level data from a randomised clinical trial (RCT) by Fitzmaurice et al. which indicate greater number of thromboembolic and haemorrhagic events with PST and/or PSM compared to alternative testing strategy (20). In the studies by Regier et al. and Lafata et al., the number of thromboembolic and haemorrhagic events was estimated based on the TTR achieved while using investigated testing strategies (i.e. 71.8% vs. 63.2% and 89% vs. 65%, respectively) and risk of those events conditional on the TTR. This estimation resulted in a relatively low number of events avoided with PST and/or PSM compared to alternative testing strategy. Regier et al. found only 0.72 thrombotic and 0.17 haemorrhagic events avoided per 100 patients with PST and/or PSM in the first year, and after five years this summed up to 3.5 and 0.79 events avoided, respectively. Similarly, Lafata et al. observed in total 4.9 events avoided per 100 patients with PST and/or PSM over a five year time horizon.

Strengths and limitations

Inferences drawn from BIAs are related to the quality of the evidence that goes into the model. One point of strength of the current analysis is that effectiveness inputs are based on a synthesis of evidence (14). In the hierarchy of evidence pyramid, evidence synthesis of multiple trials resides above evidence from a single RCT (38,39). Yet, it must be pointed out that no studies investigating the effectiveness of PST and/or PSM have been conducted in the Netherlands. In the present analysis, effectiveness measures were derived from studies investigating PST and/or PSM versus specialized testing centres for all OAT indications (19-22). Because of the heterogeneity between the studies, a random-effect model was used to establish baseline risks for thromboembolic and haemorrhagic complications for patients using anticoagulation testing centres. To estimate risks of

complications for PST and/or PSM patients, relative risk reductions were applied as reported by Heneghan et al. (14). In addition to possibly providing some external validity, an advantage of this approach over relying on data from a single RCT is that all indications for OAT were considered. This reflects a more complete assessment of the impact of different strategies on costs of anticoagulation testing. Finally, we examined the impact of uncertainty surrounding the key model parameters on BIA results.

Our study has several limitations. Firstly, only direct medical costs were considered in our analyses and no costs related to productivity loss were included. Costs related to productivity loss may be reduced for PST and/or PSM patients because they may spend less time away from work as a result of greater effectiveness in prevention of complications (Table 1). Also, testing at home with a PoC-device avoids work time lost because it eliminates the need for travel and waiting time at testing centres. Yet, one caveat in considering productivity loss among patients indicated for OAT is that many are elderly patients, such as those with AF, may already be retired. Notably, although the current estimates on cost-savings in the 5-year time horizon applied are substantial, they may still reflect an underestimation of the true savings in the patient groups where accounting for productivity loss is considered to be appropriate (i.e. patients <65 years of age). Secondly, our model design may also be a factor for underestimation. In this analysis, clinical events and associated costs were followed for a cohort of patients for up to 5 years. An alternative approach is to dynamically add new patients each year as estimated by annual incidence rates (i.e. assume an open cohort). Such an approach would include more patients in the analysis because the incidence rates are expected to continue to rise in the coming decades (3). Thirdly, the recent introduction of novel oral anticoagulants (NOACs), such as dabigatran, rivaroxaban and apixaban, on the Dutch market for use in patients with some of the indications for OAT, was not accounted for in our study (40,41). Currently, such a comparison between NOACs and the VKAs managed with PST and/or PSM is hampered given the lack of RCTs between the two comparators as well as data on the current use of NOACs in clinical practice in the Netherlands. Fourthly, future uptake of PST and/or PSM strategy (i.e. 50, 75 and 100%) in this study was based on an assumption. Yet, it may be more informative to estimate this in relation to the factors influencing its current low market share, for example due to patients' preferences. In particular, there are indications by some Dutch experts that some patients prefer to have more regular contact with hospitals/anticoagulation centres rather than to self-manage. Additionally, they indicate that an increase in the uptake of PoC strategies could be achieved if these strategies would be actively offered to patients as an alternative to management in the clinics what currently is not the case. Finally, estimates of the baseline risks used in this study were not supported by local real-life data. Such information unavailable and is duly needed given that the baseline information used from the RCTs is commonly based on

highly selected patient populations with characteristics that may deviate from the usual practice.

In conclusion, compared to regular anticoagulation testing at specialised centres, PST and/or PSM with PoC-devices resulted in cost-savings. However, using PoC devices solely for PST resulted in greater expenditures compared to testing in anticoagulation clinics. Hence, this strategy may need to be disregarded. Additionally, our study indicated less favourable findings of using PST and/or PSM in patients with AF. Further research is needed to explore this strategy in other indications and confirm the aforementioned findings with local real-life data.

Given the increasing number of patients with indications for OAT and high treatment costs of thromboembolic events, the choice of the optimal monitoring and managing strategy is of high importance, both regarding the costs considered here and the health effects as well. Further research should be directed to perform formal CEAs comparing the two strategies. This would provide the additional insights of both societal costs and long-term effects of those strategies on health, such as expressed in terms of QALYs.

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