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Pharmacoeconomics of cardiovascular disease prevention

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Document Version

Publisher's PDF, also known as Version of record

Publication date:

2015

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Stevanovic, J. (2015). *Pharmacoeconomics of cardiovascular disease prevention*. [Thesis fully internal (DIV), University of Groningen]. University of Groningen.

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Chapter 8

General discussion

In the last decades, a decline in cardiovascular diseases (CVD) mortality was observed across most of the developed countries (1). This can likely be attributed to a broad application of prevention strategies (2). In clinical practice, CVD prevention strategies aim at identifying individuals at high CVD risk followed by enhancing risk factor(s) modification (e.g. lifestyle changes and/or pharmacological interventions). This approach was shown to successfully reduce the risk of CVD (3). However, the rate of CVD-related hospital admission and mortality, as well as CVD attributable costs of acute treatment, long-term management and rehabilitation care, all indicate that further spread of CVD prevention approaches and interventions have the potential to be beneficial and further reduce the disease burden (1)(4).

Pharmacological innovations open new opportunities to prevent or delay the onset of CVD. Yet, innovative interventions often come at a higher cost what may be seen as a burden to the healthcare budget and possibly a limitation to patient access. Because of healthcare budget constraints, the decisions to implement innovative interventions in clinical practice have to be made with respect to both health and economic consequences associated with their use.

This thesis deals with pharmacoeconomic issues that relate to pharmacological preventive interventions in CVD. In particular, it addresses challenges in simulating and synthesizing pharmacoeconomic evidence in (primary) CVD prevention, and proposes potential solutions to those challenges. Moreover, it derives pharmacoeconomic evidence on the use of oral anticoagulants (i.e. vitamin K antagonists (VKAs) and novel oral anticoagulants (NOACs)) for secondary CVD prevention. This chapter summarizes and discusses the main results, findings, and ideas described in the previous chapters, including some future perspectives. Lastly, to assess the main implications of this thesis, this chapter discusses methods for providing robust pharmacoeconomic evidence in CVD prevention, and direct implications of pharmacoeconomic evidence on the use of VKAs and NOACs for current practice.

PRINCIPLE FINDINGS AND FUTURE PERSPECTIVES

Part I: Simulating and synthesizing health and economic evidence in (primary) cardiovascular disease prevention

Part I of this thesis examined some of the challenging issues on simulating and synthesizing health and economic evidence in (primary) CVD prevention. In Chapter 2, a systematic literature review on the application of CVD risk prediction models in pharmacoeconomic studies for primary CVD prevention in high income countries was described. This review aimed at understanding the extent that methods for incorporating CVD risk models in pharmacoeconomic studies are being used and assesses their quality. Through a systematic search, 12 eligible pharmacoeconomic studies were identified. The quality assessment indicated disagreement between the characteristics of populations of

the intended population(s) of the risk model, frequent disagreement between risk model- and study time horizons and a general lack of proper consideration of the uncertainty surrounding risk predictions. Based on the findings in Chapter 2, it was concluded that projecting intermediate effectiveness/efficacy evidence to long-term health and economic benefits is possible and useful but careful characterization of the uncertainty should be pursued as well as the limitations of this approach should be acknowledged. To assist in the design of future pharmacoeconomic studies, Chapter 2 proposed a set of recommendations for the appropriate use of a CVD risk model in pharmacoeconomic analysis.

The knowledge and recommendations from Chapter 2 were utilized for designing a pharmacoeconomic model in **Chapter 3**. This model explored the cost-effectiveness of primary CVD prevention with antihypertensive treatment compared to no treatment in patients with mild hypertension, ineligible for treatment according to the Dutch guidelines. Surrogate endpoints on lowering systolic blood pressure (SBP) were projected to hard CVD endpoints with the use of the modified SCORE CVD risk model. It was shown that, the cost-effectiveness of antihypertensive treatment was highly influenced by the model's time horizon. In a lifetime horizon, significant health and economic benefits were observed in all scenarios for both genders and ages when SBP reduction was assumed to be achieved with the use of hydrochlorothiazide (HCT) 25 mg. However, in a 10-year horizon, SBP reductions were more favourable when targeted to older patients and more in men than in women. In scenarios assuming fixed-dose combination HCT 12.5 mg/Losartan 50 mg, long-term health and economic benefits were even more favourable in both time horizons investigated. In the same chapter, a 10-year treatment with HCT 25 mg vs. no treatment was examined in male and female smokers. This analysis indicated more favourable cost-effectiveness for applying antihypertensive treatment compared to no treatment in smokers than the ones estimated for patients with comparable age-, gender- characteristics but with the average prevalence of smoking as representative the for Dutch population. This was due to the higher levels of CVD risk estimated for male and female smokers as well as the greater benefits of risk reduction in this patient population. The aforementioned findings suggest more aggressive SBP reductions in patients with mild hypertension and in smokers, however, uncertainty in the results should be noted. Notably, a relatively large overall uncertainty was observed surrounding the estimated values in the analysis regardless of the applied time horizon. As expected from our previous work, the largest contribution to the overall uncertainty came from the uncertainty surrounding the risk prediction.

The model in Chapter 3 was informed with various published Dutch cost estimates such as cost of heart failure (HF), angina, stroke, etc. Given the major changes in the clinical practice and treatment of HF in the last decade, and the fact that hospitalization costs substantially contribute to the total health care expenditures in HF patients, **Annex 1**

aimed to provide up-to-date information on the characteristics and use of hospital care resources associated with HF in the Netherlands. Notably, given that HF hospitalizations might occur due to the new onset of HF ('*de novo*') or deterioration of chronic HF with symptoms that warrant hospitalization, these are labelled acute heart failure (AHF) hospitalizations. This study identified 31,248 HF hospitalizations in the 2011 Dutch National Medical Registration (LMR) data. Based on the hospital resource use associated with the hospitalisations in 2011 and under the assumption that the resource use of inpatient care was associated only with the costs of stay in general hospital wards, the minimum total hospital costs were estimated to be €3,902 and €4,044 for women and men, respectively. When the cost of stay in emergency wards was assumed to plausibly significantly contribute as well to the cost of inpatient care, the aforementioned total cost estimates almost doubled. Due to the limitations of the LMR data to provide information on medication use, further analysis should be directed to linking the available LMR data with hospital claims data which could indicate the cost of medication use and, therefore, provide more comprehensive AHF cost estimates.

Chapter 4 describes an evidence synthesis (a multivariate meta-analysis) of instrument-specific preference-based health-related quality of life (HRQoL) values in coronary heart disease (CHD) and its underlying disease-forms (i.e. stable angina, post-acute coronary syndrome (post-ACS)) in developed countries. The study explicitly accounted for study-level characteristics and relevant correlations between those values. Using a systematic literature search, 40 studies were identified. In post-ACS, HRQoL estimates ranged from 0.64 (Quality-of-Well-Being) to 0.92 (EQ-5D European "tariff"); in stable angina, HRQoL ranged from 0.64 (SF-6D) to 0.89 (standard gamble) while in overall CHD the range of values was comparable to the aforementioned (i.e. from 0.60 (HALex) to 0.89 (standard gamble)). Chapter 4 indicated inequality in HRQoL values, both within and between the instrument-specific values, potentially explained by both observed and unobserved methodological differences across instruments and underlying study-level characteristics. Current economic models in CHD generally ignore the between-study study heterogeneity in HRQoL. Therefore, Chapter 4 suggests that multivariate meta-analysis should be applied for quantifying this uncertainty to improve estimates used in cost-utility analyses.

Part II: Pharmacoeconomic findings in secondary cardiovascular disease prevention; Focus on oral anticoagulation

Part II of this thesis described a number of pharmacoeconomic findings in secondary CVD prevention. Specifically, the health and economic findings associated with the use of oral anticoagulants - VKAs and NOACs such as apixaban and dabigatran - for the prevention of CVD in the Dutch setting were presented.

In Dutch clinical practice, VKAs are still the most commonly applied anticoagulants in indications such as atrial fibrillation (AF), arterial diseases or venous thromboembolism

(VTE)(5). Yet, their use comes with a narrow therapeutic range of international normalised ratio (INR) limits of 2.0 and 3.0, calling for regular monitoring. In the Netherlands, INR-monitoring is mostly performed at specialised anticoagulation testing centres. An alternative is patient self-testing and patient self-management (PST and/or PSM) that was internationally shown to lead to better coagulation care compared to monitoring in specialized anticoagulation centres (6,7). **Chapter 5** explored the budget impact of increasing market-share scenarios of PST and/or PSM in patients on long-term anticoagulation with VKAs. The occurrence of thromboembolic and haemorrhagic complications in the aforementioned patient population was assessed in a Markov model that incorporated Dutch specific costs and effectiveness data derived from a meta-analysis on self-monitoring of oral anticoagulation. Chapter 5 indicated that increasing PST and/or PSM in anticoagulation monitoring from the current 15.4% to 50%, 75% and 100%, would lead to significant savings in one to five year time horizons. This is driven mainly by considerably lowered complications-related costs associated with PST and/or PSM compared to conventional monitoring centres. Due to a lack of RCTs to compare the VKAs managed with PST and/or PSM with NOACs, the use of NOACs was not accounted for in this study. Further research should account for the potential increasing market share of NOACs as well as provide a formal cost-effectiveness analysis comparing the two VKA monitoring strategies.

Chapter 6 presents the cost-effectiveness analysis of using apixaban compared to VKAs for the prevention of stroke in non-valvular AF in the Netherlands. Using a previously developed Markov model (8,9), updated with the most recent Dutch costs and epidemiological data, the incremental cost-effectiveness ratio (ICER) of using apixaban compared to VKAs was €10,576 per quality adjusted life year (QALY). These results from the healthcare provider's perspective require confirmation from the studies on "real life" long-term benefits of the use of apixaban, primarily regarding the patients' adherence, and extension to aspects relevant within broader societal perspective inclusive production losses (10).

For the VTE indication, NOACs are not yet included in the Dutch reimbursement system. To support any further future decision-making on reimbursement, a formal pharmacoeconomic comparison of NOACs and standard treatment (i.e. VKAs) was needed. Thus, **Chapter 7** explored the cost-effectiveness of dabigatran, another NOAC, for treatment and secondary prevention of VTE. In contrast to Chapters 3, 5 and 6, in which the economic analyses were performed from a healthcare provider's perspective, the base-case analysis in this study considered the societal perspective. This perspective is preferred by the Dutch authorities. The base-case findings indicated that patients on dabigatran would gain an additional 0.585 discounted QALYs over a lifetime time horizon and savings of €1,996 per patient. Chapter 7 explored various scenarios comparing dabigatran to VKAs, for treatment as well as for secondary prevention in high-risk

patients. All scenarios consistently showed dabigatran to be a cost-saving alternative to VKAs. Finally, scenarios comparing the use of dabigatran and VKAs from the healthcare provider perspective and comparing dabigatran to placebo for the prevention of recurrent VTE in patients who are at equipoise for anticoagulation treatment, indicated the ICERs for dabigatran compared to VKAs of €1,005 and €33,305 per QALY gained, respectively.

PROVIDING ROBUST PHARMACOECONOMIC EVIDENCE IN CARDIOVASCULAR DISEASES (PRIMARY) PREVENTION

Healthcare decision making bodies recognize and/or require pharmacoeconomic evidence to guide or assist in allocating healthcare resources in many developed countries (11). In particular, decisions to reimburse pharmacological innovations for prevention of CVD often need to be firmly grounded on both the evidence of added therapeutic value in comparison to standard or usual intervention, and pharmacoeconomic evidence. Moreover, if local health and economic parameters change, pharmacoeconomic evidence is needed to guide changes in policy or reimbursement. Therefore, due to the health and economic implications of health policy and reimbursement decisions, the most robust evidence is needed nowadays. In that respect health technology assessment (HTA) has rapidly evolved in the recent decades.

Various country-specific and international guidelines for conducting pharmacoeconomic analyses assist analysts in providing sound and valid evidence. Some of the matters addressed by guidelines concern: the quality of health and economic inputs, modelling, sensitivity analyses, discounting future health effects and costs, etc. In assessing pharmacoeconomic evidence on interventions in CVD prevention, analysts can apply general methodological standards and criteria addressed in aforementioned guidelines. Yet, in Chapter 1 of this thesis, it was suggested that the standards or solutions to some potential challenges in analyses on interventions in (primary) CVD prevention are still to be faced.

One challenge relates to the common preference of the healthcare decision making bodies to assess the effectiveness of interventions with respect to their impact on life expectancy and quality of life rather than intermediate (surrogate) outcomes. Specifically, this can be a major issue in analyses on interventions in primary CVD prevention. Here, preventive interventions are indicated in patients with no medical history of hard clinical CVD events. Commonly, only short-term treatment effectiveness evidence (e.g. modification of CVD risk factor levels) is measured in clinical trials on pharmacological interventions for primary CVD prevention. For short-term effectiveness evidence to be incorporated into a pharmacoeconomic analysis, surrogates need to be projected to long-term hard clinical endpoints (e.g. fatal or non-fatal CVD events). In various studies, the use of CVD risk prediction models has already been established to provide the aforementioned projection adequately and validly (12,13). However, our review on pharmacoeconomic

analyses incorporating CVD risk prediction models (Chapter 2) indicated a lack of standardisation and quality consideration as well as failure to exactly report the implications of incorporating these models with their specific methodologies. To provide robust pharmacoeconomic evidence in analyses incorporating CVD risk prediction models, it may be beneficial to specify and expand methodological criteria and considerations (12). For example, a risk model can actually only be applied after the compatibility of the risk model and the study populations has been thoroughly investigated and assessed. Furthermore, to enhance the transparency of methods applied, the study should report the method used for the translation of cumulative risks to short-term probabilities and should clearly describe the method behind extrapolating this risk to longer time horizons, if applicable. Finally, the uncertainty surrounding risk predictions should be incorporated in a transparent way in the estimation of the overall uncertainty of the pharmacoeconomic model. Thus, by examining current practices and identifying areas for improvement in selecting and utilizing CVD risk prediction models in pharmacoeconomic analyses, we specified and proposed methods for enhancing the robustness of such studies. Moreover, we used these caveats and recommendations when conducting and interpreting the findings of the pharmacoeconomic analysis in Chapter 3. In this analysis, we used the modified SCORE CVD risk model to project surrogate endpoints on lowering SBP to hard CVD endpoints. This model was selected due to the similarity between the risk model's and study's populations characteristics, and its established validity in the Dutch population. Furthermore, the methods used for translating cumulative 10-year risk to short-term probabilities and extrapolating those risks to a lifetime horizon were explicitly reported. Finally, the uncertainty surrounding risk predictions was provided in such a form that could be incorporated in the overall probabilistic analysis.

Another challenging issue in conducting pharmacoeconomic analyses, in particular cost-utility analyses, on interventions in CVD prevention and/or treatment relates to the robustness of evidence on the HRQoL values used. When multiple HRQoL values are available in literature, analysts often select a value assessed in a setting and using a patient population that is comparable to their study/country. This seems highly reasonable, but still may not be fully robust. Solid methods for evidence-synthesis can be considered here as a potential tool for optimizing strategies confronting this challenge (14-16). Importantly, not only may evidence-synthesis provide summary data that is considered as the evidence of highest level in the hierarchy of evidence, but it can also indicate the level of heterogeneity in the HRQoL values assessed across the studies (17). In fact, the main finding of our evidence synthesis of HRQoL values in stable angina, post-ACS and, in general CHD (Chapter 4) was the indication of large heterogeneity within and between the instrument-specific values and inherent uncertainty if applied within cost-utility analysis. This finding was despite the fact that this evidence-synthesis was conducted on the instrument-specific level, accounting for underlying CHD disorder,

correlation between the instrument-specific values and a number of study-level covariates. Heterogeneity detected between the instrument-specific values may be partly explained by underlying methodological differences across the HRQoL instruments used. Still, the unobserved patients' characteristics (e.g. socio-economic, ethnical, religious characteristics, etc.) are potentially of even greater concern as crucially contributing to the overall heterogeneity. Thus, evidence-synthesis may be considered as a relevant tool to, where appropriate, synthesize HRQoL values in specific CVD disorders as well as to indicate the level of heterogeneity and possibly its sources across the studies. In this manner, robustness of HRQoL values used to inform cost-utility analyses on interventions in CVD prevention and/or treatment can be further enhanced.

In general, we conclude that conducting pharmacoeconomic analyses on interventions in CVD prevention can be confronted with challenges, with solutions not yet specified in pharmacoeconomic guidelines. Addressing these challenges could benefit from further standardization ideally with a consensus on methodological requirements and recommendations across pharmacoeconomic guidelines (18). In this thesis, we tackled some of the challenging issues and provided recommendations that could assist in providing more robust pharmacoeconomic evidence on interventions in CVD prevention. In fact, the expected benefit of standardizing methodological requirements and recommendations for conducting and reporting pharmacoeconomic analyses including the ones proposed in this thesis is to enhance the quality and validity of pharmacoeconomic analyses as well as reduce possible bias (19).

DIRECT IMPLICATIONS FOR CURRENT PRACTICE: VITAMIN K ANTAGONISTS OR NOVEL ORAL ANTICOAGULANTS IN THE DUTCH SETTING?

The work in the thesis may have some direct societal relevance and impact. During the last 60 years, VKAs have been established as highly effective anticoagulant treatment, shown to reduce the risks of thromboembolic events in a number of clinical situations (20). Yet, their position has recently been challenged when the European Medicines Agency granted market authorizations to NOACs (e.g. dabigatran, rivaroxaban, apixaban) for prevention of stroke in AF, and treatment of VTE. Notably, for NOACs to compete for the market share of VKAs, reimbursement approval is essential. In the Netherlands, health authorities require pharmacoeconomic evidence in reimbursement submissions. This evidence should indicate whether there is an economic rationale next to added value of innovative treatment (i.e. NOACs) compared to standard treatment (i.e. VKAs). Moreover, the health and economic consequences associated with possible improvements in the quality of standard care should be assessed.

In the Dutch healthcare system, the quality of anticoagulation care performed by specialised anticoagulation testing centres is measured with the percentage of patients on treatment with VKAs which INR measurements are within the limits of 2.0 and 3.5.

Notably, the estimate of approximately 80% for quality of anticoagulation care in the Dutch setting may be considered high (5). This suggests that further investments into optimizing the standard anticoagulant care with VKAs may be considered as an alternative to switching to NOACs. INR monitoring with PST and/or PSM may be considered as an alternative approach to optimizing the standard anticoagulant care with VKAs. This monitoring alternative was shown to be associated with lower occurrence of thromboembolic and haemorrhagic complications in patients on long-term indication for anticoagulation with VKAs, when compared to monitoring in specialized anticoagulation centres (21-24). Although PST and/or PSM is more costly than monitoring in Dutch specialized anticoagulation centres, Chapter 5 showed that increasing its market share would lead to overall cost-savings due to lower total direct medical costs driven by lower complication-related costs. However, using point-of-care devices solely for PST resulted in greater expenditures compared to testing in anticoagulation centres. Additionally, this study indicated less favourable findings of using PST and/or PSM in patients with atrial fibrillation.

Furthermore, anticoagulant treatment with NOACs was proven to be superior or at least non-inferior to VKAs for thromboprophylaxis, but also free from the need for regular INR-monitoring (25,26)(27,28). Yet, some concerns of clinicians and decision makers regarding the use of NOACs are still unresolved. These reflect the scarcity of antidotes for treatment with NOACs (29), real-world adherence to NOACs and finally the economic consequences in different treatment indications. In this thesis, to tackle some of the concerning issues regarding the use of NOACs, we examined the health and economic consequences associated with the use of apixaban for the prevention of stroke in non-valvular AF (Chapter 6) and the use of dabigatran for treatment and prevention of VTE in the Dutch setting (Chapter 7). Both apixaban and dabigatran were found to be favourable alternatives to treatment with VKAs. Both studies importantly contributed to discussions on reimbursement of NOACs in the Netherlands. Notably, the one on dabigatran was part of the formal submission to the Dutch authorities by the manufacturer. Importantly, given that these findings were based on RCTs evidence where drug adherence is usually up to 100%, further analyses are needed to examine the pharmaco-economic findings that reflect real-world adherence. Moreover, future research should also allow for comparison between the VKAs managed with PST and/or PSM and NOACs. This was currently hampered due to the lack of RCTs comparing VKAs managed with PST and/or PSM and NOACs.

We can conclude that in the Dutch setting, NOACs may present a valuable alternative to VKAs for thromboprophylaxis, supported by various other studies (30-32)(33). Still, fine-tuning of recommendations for the most optimal anticoagulant treatments in the Netherlands will require continuous confirmation and adaptation based on real-world data as well as full consideration of all treatment alternatives.

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