Pharmacoeconomics of cardiovascular disease prevention

Stevanovic, Jelena

Publication date:
2015

Citation for published version (APA):
Stevanovic, J. (2015). *Pharmacoeconomics of cardiovascular disease prevention*. [Thesis fully internal (DIV), University of Groningen]. University of Groningen.

Chapter 1

General introduction

CARDIOVASCULAR DISEASES – HEALTH AND ECONOMIC BURDEN IN DEVELOPED COUNTRIES

Cardiovascular diseases (CVD) comprise disorders that affect the heart, blood vessels or both. Some of the most common CVD disorders are coronary heart disease ((CHD) i.e. stable angina and acute coronary syndrome (ACS)), cerebrovascular disease (i.e. transient ischemic attack and stroke), peripheral arterial disease, rheumatic heart disease, congenital heart disease, heart failure (HF), venous thromboembolism (VTE) (1).

CVD had a leading position in contribution to global disease burden among the non-communicable diseases in the last couple of decades. In 2008, 17 million persons died from CVD worldwide. However, in some developed countries, a declining trend of CVD mortality rates is observed in recent years. In the Netherlands, CVD are now the second largest cause of death accounting for 29% of total deaths after cancer being the first with a toll of 33% of total deaths (1). This significant drop in CVD mortality, reaching almost 50% in both men and women in the Netherlands, might be explained by the advances in both treatment and CVD prevention strategies (2-4). Nevertheless, hospital admissions due to CVD do not seem to follow the mortality trend and remain high (5). Moreover, patients who experience non-fatal CVD events are severely affected with disability and impairment of health-related quality of life (HRQoL). For example HRQol of patients after a major stroke were on average half of perfect health (6). Given that this estimate is positioned approximately only in the middle of the scale, the burden of major stroke on patient's HRQoL is undisputable. Although there is significant variation on the level of HRQoL across CVD disorders and across severity levels it consistently indicates impairment.

CVD do not only account for a major share of overall morbidity and mortality worldwide, but also significantly contribute to global healthcare expenditures. Some of the major drivers of resources used within the healthcare system are the costs of hospitalizations, long-term management and rehabilitation care due to CVD. From a broader societal viewpoint, next to healthcare costs accounting for approximately two thirds of total economic burden due to CVD, one third of costs can be attributed to the productivity loss costs associated with the CVD patients being absent from work and the costs of informal care of these patients (7,8). In the Netherlands, economic burden of CVD led to healthcare expenditures of €5.5 billion annually, while in the whole European Union it mounted to €105 billion (7,8).

CARDIOVASCULAR DISEASES PREVENTION – RISK PREDICTION APPROACH

The most recent European guidelines on CVD prevention recommend the combination of two different approaches to achieve the highest level of prevention (9). One approach

focuses on promoting lifestyle and environmental changes in the population at large (i.e. the public health/population-based approach) while an alternative approach aims to modify risk factors only in individuals identified to be at a high risk (i.e. the high-risk approach). Although the large-size benefits may be reached by applying the population prevention approach, the benefits that can be achieved with individual risk assessment should not be disregarded. Furthermore, implementing individual risk assessment to identify high-risk individuals remains a recommended strategy in regular clinical practise (9).

Nowadays risk assessment tools are derived using data from decades-long studies designed to follow large cohorts for a sufficient length of time and for which both patient characteristics (i.e. risk factor characteristics) and outcomes are known over time. For example, studies based on the Framingham population were among the first ones to find the association between a number of, often correlated, modifiable and/or non-modifiable risk factors and the onset of CVD (10)(11). Elevated blood pressure (BP), cholesterol or glucose levels and smoking have been identified as some of the major modifiable risk factors, and age, gender and genetic predisposition are some of the non-modifiable risk factors, whose conjoint influence can lead to CVD.

The aforementioned types of observations have set the grounds for the development of various multivariable risk prediction models that attempt to translate this conjoint impact of various risk factors on the onset of CVD into a mathematical relation. Numerous differences exist between the various proposed CVD risk prediction models. These models often differ in the specific risk factors they comprise, the underlying study populations (different geographical regions, baseline CVD risks) as well as whether they reflect the risk of overall CVD or one of its specific CVD forms (e.g. myocardial infarction, stroke etc.). Moreover, they give predictions over different time horizons (e.g. 1-4 years (12), 10 years (13) or 30 years (14)), for different clinical endpoints (e.g. fatal (13) or overall CVD (12)) and for primary or secondary CVD events (12).

Because of the aforementioned differences across risk models, the choice and consequent utilization of a model for projecting CVD risk in a certain setting is not straightforward. The choice of a model might need to be made with respect to specific characteristics of the population of interest (e.g. middle-aged or elderly patients, or diabetics), or with respect to the need to estimate CVD risk over a specific time-horizon. An example of a model for CVD risk assessment in European populations is the SCORE model developed on data from 12 European cohorts (9,13). The high- and low-risk region-specific multivariable risk functions of the SCORE model estimate the 10-year risk of a fatal CVD by accounting for age, gender, level of SBP, level of cholesterol and prevalence of smoking. Thus, if the 10-year risk of a fatal CVD needs to be estimated in individuals from a certain European setting, the choice of the SCORE model risk function should be made carefully with respect to the general population's risk level. Notably, the robustness and validity of the risk

prediction in a specific setting needs to be assessed, and if needed, it can be enhanced by various adjustments and validation methods.

PHARMACOLOGICAL INTERVENTIONS TO PREVENT CARDIOVASCULAR DISEASES

When it comes to implementing prevention strategies to reduce the overall CVD risk by identifying individuals at risk with the use of a suitable CVD risk prediction model (9), various national and international guidelines give different recommendations on the CVD risk threshold above which pharmacotherapy should be introduced in addition to lifestyle changes (15).

In the Netherlands, cardiology guidelines recommend pharmacotherapy to prevent CVD for patients at a 10-year CVD mortality or morbidity risk of 20% or exceptionally at lower levels of risk if accompanied with other comorbidities (e.g. diabetes or rheumatoid arthritis) or previous CVD (16). Prevention strategies can include antihypertensive treatment and/or statins, if high CVD risk is accompanied with systolic blood pressure (SBP) greater than 140 mmHg and/or low-density lipoprotein (LDL) greater than 2.5mmol/l (16). In patients with a medical history of previous CVD events and elevated SBP and/or LDL levels, immediate pharmacotherapy is recommended due to the relatively high risk of recurrent CVD events (16).

Moreover, in the presence of certain individual risk factors, such as atrial fibrillation (AF) or diabetes, pharmacological interventions additional to the ones previously mentioned may be indicated. For example, atrial fibrillation (AF) is considered to be an independent risk factor leading to an even 5-fold increased risk of stroke (17). To prevent stroke in patients with AF and minimum one stroke risk factor (i.e. congestive HF or left ventricular dysfunction, Hypertension, Age≥75 (doubled risk), Diabetes, Stroke (doubled)-Vascular disease, Age 65–74, Sex category (female) [CHA_2DS_2-VASc] ≥ 1), antithrombotic preventive treatment is recommended (17). Yet, this preventive strategy does not apply to patients younger than 65 years with an AF diagnosis and being female as the only risk factor.

Furthermore, once the criteria are satisfied for a patient to receive pharmacotherapy for CVD prevention, a choice of the most suitable treatment option needs to be made. From the healthcare perspective, this choice should consider both treatment effectiveness in modifying the risk factors of interest and its safety profile. For example, to prevent stroke in patients with AF, guidelines generally recommend the use of vitamin K-anticoagulants (VKAs) or novel oral anticoagulants (NOACs)(17). However, these medicines differ in their effectiveness to protect against stroke and other thromboembolic events as well as in the safety profile reflected by the incidence of major bleeding events (18).

Finally, next to considering the health-related aspects of choosing a certain pharmacological treatment, the economic consequences of that decision should not be ignored due to limited healthcare resources. Together, the health and economic

consequences of applying pharmacological interventions to prevent CVD should be assessed in a formal way through pharmacoeconomic analyses.

CHALLENGES IN PHARMACOECONOMICS OF CARDIOVASCULAR DISEASES PREVENTION

A number of governmental institutions worldwide request sound pharmacoeconomic evidence to aid health policy and reimbursement decisions regarding newly introduced interventions (19). Commonly, country-specific guidelines are available to assist analysts in conducting coherent pharmacoeconomic analyses for reimbursement purposes. Yet, when such analyses on pharmacological interventions to prevent CVD are needed, numerous methodological challenges can be encountered whose solutions are not explicitly discussed in the aforementioned guidelines.

To compare different pharmacological interventions in CVD prevention, numerous health and economic evidence are needed. In ideal circumstances, evidence on long-term treatment effectiveness of specific interventions (i.e. hard clinical endpoints, such as CVD morbidity and mortality), HRQoL values collected alongside clinical trial and all the relevant up-to-date country-specific costs would be available for such an analysis (Figure 1A). However, pragmatic pharmacoeconomic analysis needs to consider the use of less perfect evidence, as often this evidence is not available at the time when the pharmacoeconomic analysis is done (Figure 1B). Firstly, if the pharmacoeconomic analysis investigates the use of a new pharmacological intervention that is directed to modifying a certain risk factor, such an analysis would commonly have access only to short-term (intermediate) treatment effectiveness evidence. This is particularly the case when collecting pharmacological efficacy data from a relatively healthy population (commonly indicated for primary CVD prevention) where conducting a clinical trial to provide hard-clinical endpoints evidence would be too lengthy and costly. For example, the evidence on effectiveness of different antihypertensive medicines would only indicate the change in systolic and/or diastolic BP (SBP and/or DBP) when examined in patients with mild hypertension and mild to moderate CVD risk. In case treatment evidence (short or long term) is available from more than one study, analysts might consider the evidence synthesis of all the relevant data (20). As long-term evidence is generally lacking, it is necessary to apply a CVD risk prediction model to translate short-term treatment effectiveness to long-term consequences. Notably, given the previously mentioned differences across CVD risk prediction models, model choice and its application in pharmacoeconomic analysis is not straightforward (21). Finally, in case health outcomes of analysis will be expressed in terms of quality-adjusted life-years (QALYs) gained, all the available HRQoL evidence reflecting preferences for living in a certain state of CVD might need to be considered. Commonly, pharmacoeconomists tend to select a HRQoL value in a

less rigorous approach even if a couple of values are available in the literature. Yet, this should not be a random process. One may consider a value that is close to analysis's setting, what seems reasonable, but still it is not robust. Therefore, further effort should be made to also synthesize evidence on HRQoL, where appropriate.
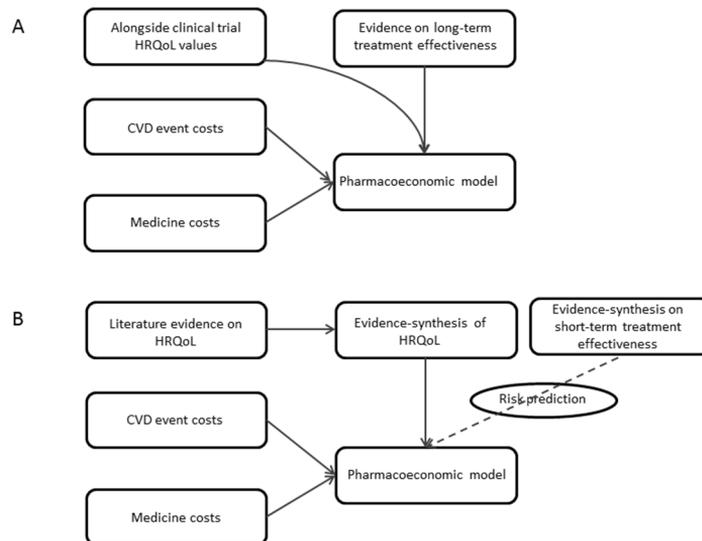
Figure 1 Evidence availability in ideal (A) and pragmatic (B) pharmacoeconomic analysis of pharmacological interventions in CVD prevention.
HRQoL, health-related quality of life; CVD, cardiovascular diseases.

Embedding and integrating the concepts of evidence synthesis and prediction/simulation in economic evaluation is one of the key challenges in providing reliable pharmacoeconomic evidence on interventions for CVD prevention. Moreover, the dynamic world of new pharmacological interventions for prevention and/or treatment of CVD, and changes in country-specific health-related economic factors urge for new pharmacoeconomic analysis accounting for those changes. Specifically, the introduction of NOACs to the Dutch market for the prevention of stroke in non-valvular AF, and treatment and prevention of VTE, requires sound pharmacoeconomic evidence to support reimbursement decisions. This evidence should account for all the specificities of the Dutch health system and indicate whether there is an additional value associated with the use of NOACs compared to the standard treatment with VKAs. Notably, such analyses should adequately consider core issues such as dealing with uncertainty and discounting in secondary prevention within the context of changing Dutch health-care with increasing roles for patient access schemes (such as price-volume arrangements), clinical guidelines-driven cost-effectiveness analyses and cost consciousness.

AIMS AND OUTLINE OF THIS THESIS

Part I of this thesis addresses some of the challenging issues on simulating and synthesizing health and economic evidence in primary CVD prevention. Here, one of the issues concerns the application of CVD risk prediction models in pharmacoeconomic analysis to project changes in CVD incidence based on changes in risk factor levels observed in short-term randomised clinical trials. In order to assess the adequacy of incorporating risk prediction models in available pharmacoeconomic analysis for primary CVD prevention interventions in high income countries, specify and propose methods for enhancing the robustness of such studies, a systematic literature review is described in *Chapter 2*. Based on the knowledge and caveats derived in this review, an attempt was made to design a simplified model of primary CVD prevention with antihypertensives using surrogate endpoints on lowering SBP projected to hard CVD endpoints. This modelling approach is described in *Chapter 3*. The aforementioned model was informed with various published Dutch cost estimates such as cost of HF, angina, stroke, etc. *Annex 1* provides an up-to-date estimate of hospital costs associated with HF in the Netherlands. Next, *Chapter 4* describes an evidence synthesis of instrument-specific preference-based HRQoL values in CHD and its underlying disease-forms (i.e. stable angina, ACS) while accounting for study-level characteristics (i.e. covariates) and relevant correlations between those values. This study aims to further enhance the robustness of HRQoL values used to inform cost-utility analyses on interventions in CHD prevention and/or treatment.

Part II of this thesis describes a number of pharmacoeconomic findings in secondary CVD prevention. In particular, this part of the thesis focuses on the health and economic findings associated with the use of VKAs and NOACs such as apixaban and dabigatran, for the prevention of CVDs in the Dutch setting. *Chapter 5* describes a budget impact analysis of increasing market-share scenarios of patient self-testing and patient self-management in patients on long-term indication for anticoagulation with VKAs. In *Chapter 6,* the cost-effectiveness of using apixaban compared to VKA was evaluated for the prevention of stroke in non-valvular AF in the Netherlands. Furthermore, *Chapter 7* focuses on the cost-effectiveness of another NOAC, dabigatran, for treatment and secondary prevention of VTE.

Finally, in *Chapter 8* the main findings of this thesis are summarized and discussed in the context of current knowledge and practice, and some recommendations for future research are given.

REFERENCES

(1) Cardiovascular diseases. Available at: http://www.who.int/topics/cardiovascular_diseases/en/. Accessed 01/01, 2015.

(2) Peeters A, Nusselder WJ, Stevenson C, Boyko EJ, Moon L, Tonkin A. Age-specific trends in cardiovascular mortality rates in the Netherlands between 1980 and 2009. Eur J Epidemiol 2011;26(5):369-373.

(3) Kelly BB, Fuster V. Promoting Cardiovascular Health in the Developing World:: A Critical Challenge to Achieve Global Health. : National Academies Press; 2010.

(4) Vaartjes I, O'Flaherty M, Grobbee DE, Bots ML, Capewell S. Coronary heart disease mortality trends in the Netherlands 1972-2007. Heart 2011 Apr;97(7):569-573.

(5) Reitsma JB, Dalstra JA, Bonsel GJ, van der Meulen JH, Koster RW, Gunning-Schepers LJ, Tijssen JG. Cardiovascular disease in the Netherlands, 1975 to 1995: decline in mortality, but increasing numbers of patients with chronic conditions. Heart 1999 Jul;82(1):52-56.

(6) Tengs TO, Lin TH. A meta-analysis of quality-of-life estimates for stroke. Pharmacoeconomics 2003;21(3):191-200.

(7) Leal J, Luengo-Fernandez R, Gray A, Petersen S, Rayner M. Economic burden of cardiovascular diseases in the enlarged European Union. Eur Heart J 2006 Jul;27(13):1610-1619.

(8) Poos M, Smit J, Groen J, Kommer G, Slobbe L. Kosten van ziekten in Nederland 2005. Bilthoven: Rijksinstituut voor Volksgezondheid en Milieu 2008.

(9) Perk J, De Backer G, Gohlke H, Graham I, Reiner Z, Verschuren M, Albus C, Benlian P, Boysen G, Cifkova R, Deaton C, Ebrahim S, Fisher M, Germano G, Hobbs R, Hoes A, Karadeniz S, Mezzani A, Prescott E, Ryden L, et al. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). Eur Heart J 2012 Jul;33(13):1635-1701.

(10) Kannel W, Gordon T. The probability of developing certain cardiovascular diseases in eight years at specified values of some characteristics. The Framingham Study: An epidemiological investigation of cardiovascular disease.Springfield, MA: US Department of Commerce National Technical Information Service 1987.

(11) Anderson KM, Odell PM, Wilson PWF, Kannel WB. Cardiovascular disease risk profiles. Am Heart J 1991;121(1):293-298.

(12) D'Agostino RB, Russell MW, Huse DM, Ellison RC, Silbershatz H, Wilson PWF, Hartz SC. Primary and subsequent coronary risk appraisal: new results from the Framingham study. Am Heart J 2000;139(2):272-281.

(13) Conroy R, Pyörälä K, Fitzgerald AP, Sans S, Menotti A, De Backer G, De Bacquer D, Ducimetiere P, Jousilahti P, Keil U. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. Eur Heart J 2003;24(11):987.

(14) Pencina MJ, D'Agostino RB, Larson MG, Massaro JM, Vasan RS. Predicting the 30-Year Risk of Cardiovascular Disease. Circulation 2009;119(24):3078-3084.

(15) Ferket BS, Colkesen EB, Visser JJ, Spronk S, Kraaijenhagen RA, Steyerberg EW, Hunink MM. Systematic review of guidelines on cardiovascular risk assessment: which recommendations should clinicians follow for a cardiovascular health check? Arch Intern Med 2010;170(1):27-40.

(16) Nederlands Huisartsen Genootschap. Multidisciplinaire richtlijn cardiovasculair risicomanagement, herziening 2011. Utrecht. Available at: https://www.nvvc.nl/media/richtlijn/106/2011_MDR_CVRM.pdf. Accessed 02/04, 2013.

(17) Goldstein LB, Bushnell CD, Adams RJ, Appel LJ, Braun LT, Chaturvedi S, Creager MA, Culebras A, Eckel RH, Hart RG, Hinchey JA, Howard VJ, Jauch EC, Levine SR, Meschia JF, Moore WS, Nixon JV, Pearson TA, American Heart Association Stroke Council, Council on Cardiovascular Nursing, et al. Guidelines for the primary prevention of stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2011 Feb;42(2):517-584.

(18) Lopes RD, Al-Khatib SM, Wallentin L, Yang H, Ansell J, Bahit MC, De Caterina R, Dorian P, Easton JD, Erol C. Efficacy and safety of apixaban compared with warfarin according to patient risk of stroke and of bleeding in atrial fibrillation: a secondary analysis of a randomised controlled trial. The Lancet 2012.

(19) Pharmacoeconomic Guidelines Around The World. Available at: http://www.ispor.org/peguidelines/index.asp. Accessed 02/04, 2015.

(20) Evans D. Hierarchy of evidence: a framework for ranking evidence evaluating healthcare interventions. J Clin Nurs 2003;12(1):77-84.

(21) Grieve R, Hutton J, Green C. Selecting methods for the prediction of future events in cost-effectiveness models: a decision-framework and example from the cardiovascular field. Health Policy 2003;64(3):311-324.

PART I

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