University of Groningen

Costs and health effects of adding functional foods containing phytosterols/-stanols to statin therapy in the prevention of cardiovascular disease

Eussen, Simone R B M; Feenstra, Talitha L; Toxopeus, Ido B; Hoekstra, Jeljer; Klungel, Olaf H; Verhagen, Hans; van Kranen, Henk J; Rompelberg, Cathy J M

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Link to publication in University of Groningen/UMCG research database

Review

Costs and health effects of adding functional foods containing phytosterols/-stanols to statin therapy in the prevention of cardiovascular disease

Simone R.B.M. Eussen [a,b,*], Talitha L. Feenstra [a,c], Ido B. Toxopeus [a], Jeljer Hoekstra [a], Olaf H. Klungel [b], Hans Verhagen [a], Henk J. van Kranen [a], Cathy J.M. Rompelberg [a,1]

[a] National Institute for Public Health and the Environment (RIVM), P.O. Box 1, 3720 BA Bilthoven, The Netherlands
[b] Utrecht Institute for Pharmaceutical Sciences, P.O. Box 80082, 3508 TB Utrecht, The Netherlands
[c] Department of Epidemiology, University Medical Centre Groningen, P.O. Box 30001, 9700 RB Groningen, The Netherlands

ARTICLE INFO

ABSTRACT

The present modelling study aimed to evaluate if and by how much functional foods containing phytosterols/-stanols add to the benefits of statins in the prevention of cardiovascular disease in terms of cost-effectiveness. Long-term health effects, measured as quality-adjusted life-years gained, and costs for scenarios with additional phytosterol/-stanol use were compared to scenarios without extra use. Phytosterols/-stanols were given only to persons who were eligible for use according to their 10-year absolute risk of fatal cardiovascular disease (SCORE-risk). Intake levels and discontinuation rates as observed in daily practice were included in the model. Two situations were compared: 1) A real-life situation in which persons at high SCORE-risk were identified through clinical case-finding and, 2) A theoretical maximum situation where universal screening was implemented resulting in known SCORE-risks for the whole Dutch population aged 35–75 years (8.4 million people). Sensitivity analyses were performed for variations in the cholesterol-lowering effect and intake level of phytosterols/-stanols, indirect health care costs, time horizon and discount rates. At the model's start year, a total of 1.0 (real-life situation) to 3.3 (maximum situation) million persons qualified for phytosterol/-stanol use based on their SCORE-risk (both statin users and statin non-users). Over the model's time horizon, this resulted in a gain of 2700 to 16,300 quality-adjusted life-years, and yielded cost-effectiveness ratios that ranged between €92,000 and €203,000 per quality-adjusted life-year. This simulation study showed that the cost-effectiveness of phytosterols/-stanols as monotherapy and as add-on to statins is above thresholds for cost-effectiveness, generally ranging between €20,000 and €50,000, and is thus a non-cost-effective strategy to reduce cardiovascular disease.

© 2011 Elsevier B.V. All rights reserved.

Contents

* Corresponding author at: P.O. Box 80082, 3508 TB Utrecht, The Netherlands. Tel.: +31 30 253 7324; fax: +31 30 253 9166.
  E-mail addresses: S.Eussen@uu.nl (S.R.B.M. Eussen), Cathy.Rompelberg@rivm.nl (C.J.M. Rompelberg).
[1] P.O. Box 1, 3720 BA Bilthoven, The Netherlands. Tel.: +31 30 274 2387; fax: +31 30 274 4466.

1. Introduction

Despite the steady decline in death rates from cardiovascular disease during the last decades, cardiovascular disease continues to be one of the biggest health care problems in terms of burden of disease and health care costs (http://www.who.int/en/). The beneficial effects of statins in the primary and secondary prevention of cardiovascular disease are well established (Baigent et al., 2005; Heart Protection Study Collaborative Group, 2002). These benefits are primarily attributed to the lipid-lowering properties of statins: it has been estimated that statins reduce low-density-lipoprotein (LDL)-cholesterol levels by 18–55% (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, 2002; Jones et al., 2003; Law et al., 2003). In addition to this cholesterol-lowering activity, statins possess multiple pleiotropic effects (Ray and Cannon, 2005; Ray and Cannon, 2007). In Europe, current recommendations for cardiovascular risk management are based on the Systematic COronary Risk Evaluation (SCORE)-risk charts (Conroy et al., 2003; De Backer et al., 2003). In 2006, for The Netherlands an adapted SCORE-risk chart has been developed using national data (Dutch Institute for Healthcare Improvement and Dutch College of General Practitioners, 2006). From the charts, the 10-year absolute risk of fatal cardiovascular disease can be derived, taking into account several risk factors (gender, age, smoking, systolic blood pressure, and serum total cholesterol or total/HDL-cholesterol ratio). According to the Dutch guidelines, treatment with a statin in the primary prevention of cardiovascular disease is recommended for all persons with a 10-year SCORE-risk of fatal cardiovascular disease ≥10%, unless LDL-cholesterol is less than 2.5 mmol/l. For subjects with type 2 diabetes mellitus or established cardiovascular disease, treatment is recommended for all persons with LDL-cholesterol ≥2.5 mmol/l.

The use of functional foods enriched with phytosterols and phytostanols is an alternative strategy to lower elevated total and LDL-cholesterol levels. Phytostanol- and phytosterol-enriched mar-garines were launched on the Dutch market in 1999 and 2000, respectively and its use has increased in the past years in both users and non-users of statins (Eussen et al., unpublished data). In a recent meta-analysis, Demonty et al. (2009) found that a daily dose of 2.15 g phytosterols/-stanols reduces LDL-cholesterol by 8.8%. Furthermore, phytosterols and -stanols seem to be equally effective in both statin users and statin non-users (Eussen et al., 2010a). It is generally assumed that phytosterols/-stanols will decrease coronary heart disease by lowering cholesterol levels, although there are no studies yet to confirm this (Katan et al., 2003). The guidelines for cardiovascular risk management recommend that all persons with a 10-year SCORE-risk ≥5% should be given lifestyle recommendations, including the encouragement of the use of phytosterols/-stanols as part of a healthy diet (Dutch Institute for Healthcare Improvement and Dutch College of General Practitioners, 2006; Law, 2000).

There is currently no universal screening for risk factors of cardiovascular disease in The Netherlands, nor in any other EU country. Consequently, the detection of high cholesterol values and other cardiovascular disease risk factors occurs primarily through clinical case-finding. As a result many people are unaware that they are at high risk for cardiovascular disease and could benefit from statin and/or phytosterol/-stanol use (Mantel-Teeuwisse et al., 2003).

The aging of the population together with the rising health care costs requires considering the cost-effectiveness and budgetary impact of different intervention strategies. In cost-effectiveness analyses the costs and health effects of an intervention are compared to determine whether the intervention provides value-for-money (Morris et al., 2007). Statins have been assessed for cost-effectiveness in a range of publications (for review see Franco et al. (2005) and Gumbs et al. (2007)), and were found to be cost-effective for high risk patients (Franco et al., 2005; Ward et al., 2007). In contrast, to date only two studies evaluated the cost-effectiveness of phytosterols or -stanols (Gerber et al., 2006; Martikainen et al., 2007). In both studies it was concluded that phytosterols and -stanols are (potentially) cost-effective

Table 1
Overview of scenarios in the real-life and theoretical maximum situation.

Situation	Scenario		Phytosterol/-stanol use	Statin use
Real-life (RL)				
	RL reference	Real-life	(No change in phytosterol/-stanol use)	(No change in statin use)
	RL plus PS (min)	Minimum real-life plus PS	By all current real-life statin users	(No change in statin use)
	RL plus PS (max)	Maximum real-life plus PS	By all current real-life statin users and all subjects with a 10-year SCORE-risk ≥5%, <10%	(No change in statin use)
Theoretical maximum (TM)				
	TM reference	Maximum statin use	(No change in phytosterol/-stanol use)	By all subjects with a 10-year SCORE-risk ≥10%
	TM plus PS	Maximum statin and PS use	By all current real-life statin users and all subjects with a 10-year SCORE-risk ≥5%	By all subjects with a 10-year SCORE-risk ≥10%

PS, Phytosterols/-stanols.

under optimal conditions of use, i.e. taking the daily recommended amount of 2 g phytosterols/-stanols (without discontinuation). However, neither study included an economic evaluation in which real-life consumption patterns of phytosterols/-stanols were taken into account, nor were all health benefits and costs considered. Moreover, the incremental costs and health effects of phytosterols/-stanols in addition to statins have not been evaluated.

Therefore, the present study aimed to evaluate the health benefits, i.e. the prevention of cardiovascular disease, and health care costs of functional foods enriched with phytosterols/-stanols in addition to statin therapy, taking into account the intake levels and discontinuation rates as observed in daily practice.

2. Methods

The cost-effectiveness of the use of functional foods with phytosterols/-stanols as monotherapy and as add-on to statin therapy was estimated both in a real-life situation, i.e. passive clinical case-finding to identify subjects eligible for treatment with statins, and in a theoretical maximum situation, i.e. assuming that free population-based screening is implemented resulting in known 10-year SCORE-risks for the whole Dutch population between 35 and 75 years of age and all subjects with a SCORE-risk ≥10% are treated with statins. This theoretical situation gives information about the maximum health benefits that can be achieved with phytosterols/-stanols in addition to optimal statin therapy.

In both the real-life and theoretical maximum situation, long-term disease prevalence and mortality rates, as well as health care resource use, were simulated and compared for two scenarios using the RIVM Chronic Disease Model (Section 2.2). The first scenario is the current situation in which functional foods enriched with phytosterols/-stanols are used as customary in the Dutch population. A large part of the population does not use phytosterols/-stanols, whereas others use them on their own initiative or on general practitioner's advice. In the second scenario an increase in phytosterol/-stanol use is considered, both as a monotherapy for subjects with a modestly elevated risk (SCORE-risk ≥5%, <10%), and as add-on to statin therapy for subjects with a highly elevated risk (SCORE-risk ≥10%) (Table 1).

2.1. Scenarios

2.1.1. Real-life (RL) situation

In a clinical case-finding or real-life situation the SCORE-risk is only known for subjects who have their cholesterol level and blood pressure assessed, presumably the ones that are susceptible to a high risk of cardiovascular events and/or health-conscious people.

2.1.1.1. RL reference: real-life situation with customary phytosterol/-stanol use. The *RL reference* scenario assumed no additional phytosterol/-stanol use in a real-life situation. It reflects the real-life consumption patterns of phytosterols/-stanols, including actual daily intake levels and discontinuation rates (Sections 2.3.2 and 2.3.3). In this scenario population numbers, morbidity rates and health care costs of the Dutch population that was between 35 and 75 years of age in 2007 were simulated over a time horizon of 50 years. Data from the population-based Doetinchem Cohort Study were used to estimate subjects' 10-year SCORE-risk and current phytosterol/-stanol use in the Dutch population (Verschuren et al., 2008). In this ongoing cohort study, participants are examined in consecutive 5-year intervals. The most recent data were used for the current study, collected during the years 2003–2007, which included about 4500 persons. Current statin and combined users of both statins and phytosterols/-stanols were identified by linking the data of each participant of the Doetinchem Cohort Study to their pharmacy-dispensing records using the Pharmacomorbidity-Record Linkage System (http://www.pharmo.nl/) (Eussen et al., 2010b).

2.1.1.2. RL plus PS: real-life situation with additional phytosterol/-stanol use. In the *RL plus PS* scenario subjects who have a known SCORE-risk ≥5% were assumed to start phytosterol/-stanol use. We assumed that in the Dutch population all current statin users had their SCORE-risk assessed at the beginning of their therapy and their SCORE-risk was ≥10%, conforming to the guidelines. These subjects start using phytosterols/-stanols. In addition, we assumed that subjects with a known modestly elevated risk (SCORE-risk ≥5, <10%) start using phytosterols/-stanols. However, in a real-life setting it is difficult to identify which fraction of the Dutch population has their SCORE-risks assessed and no general practitioners' data were available on which to make a reliable estimate. Therefore, we defined a minimum and maximum scenario for phytosterol/-stanol use. In the *minimum* real-life plus phytosterols/-stanols scenario (*RL plus PS* (*min*)), only current statin users start using phytosterols/-stanols, which results in a minimum number of additional phytosterol/-stanol users. In the *maximum* real-life plus phytosterols/-stanols scenario (*RL plus PS* (*max*)), both current statin users and all subjects with a SCORE-risk ≥5, <10% start using phytosterols/-stanols, resulting in a maximum number of additional phytosterol/-stanol users (Table 1). The true number of additional phytosterol/-stanol users in the general population lies somewhere between these two extremes.

The cost-effectiveness of additional phytosterol/-stanol use in a real-life situation was obtained by subtracting the results of the real-life scenario (*RL reference*) from the scenarios with added phytosterols/-stanols (*RL plus PS* (*min*) and *RL plus PS* (*max*)).

2.1.2. Theoretical maximum (TM) situation

In the theoretical maximum situation it is assumed that the SCORE-risk for the whole Dutch population aged between 35 and 75 years is known. In this situation, all subjects with a 10-year SCORE-risk ≥10% start using statins in both scenarios. Subjects already using statins before the start of the scenario were assumed to continue taking their current medication.

2.1.2.1. TM reference: maximum situation with customary phytosterol/-stanol use. The *TM reference* scenario assumed customary use of phytosterols/-stanols in a situation with maximum statin use. It reflects the real-life consumption patterns of phytosterols/-stanols, including actual daily intake levels and discontinuation rates (Sections 2.3.2 and 2.3.3).

2.1.2.2. TM plus PS: maximum situation with additional phytosterol/-stanol use. In this scenario, we assumed phytosterol/-stanol use in all subjects with a 10-year SCORE-risk ≥5% and combined use of phytosterols/-stanols and statins in all subjects with a 10-year SCORE-risk ≥10%. Because all current statin users supposedly have or had a SCORE-risk ≥10%, they were also assumed to start using phytosterols/-stanols (Table 1).

The cost-effectiveness of additional phytosterol/-stanol use in the maximum situation was obtained by subtracting the results of the scenario without added phytosterols/-stanols (*TM reference*) from the scenario with added phytosterols/-stanols (*TM plus PS*).

2.2. The Chronic Disease Model

The RIVM Chronic Disease Model is a Markov-type, dynamic population-based model developed at the National Institute for Public Health and the Environment (RIVM) with the purpose to evaluate effects of public health policy on the incidence and prevalence of chronic diseases in the Dutch population (Hoogenveen et al., 2008; Hoogenveen et al., 2010; van Baal et al., 2005). The model links lifestyle and lifestyle related risk factors to morbidity and mortality using relative risks for disease incidence. It contains data on smoking, alcohol, cholesterol levels, blood pressure and food intake, as well as data on 13 chronic diseases (van Baal et al., 2005). For the current

application, the modelling of cholesterol in relation to cardiovascular disease is especially important. The Chronic Disease Model includes different relative risk estimates for acute myocardial infarction, stroke, and chronic heart failure, and accounts for interactions between these diseases, with for instance myocardial infarction increasing the risk of chronic heart failure (Fig. 1). For an example of a recent application of the model in the evaluation of nutritional effects on the risk of cardiovascular disease see Engelfriet et al. (2010).

The Chronic Disease Model simulates effects on health and costs over the model's time horizon for a model population, accounting for a background rate of new phytosterol/-stanol and statin users and background changes in cholesterol level (e.g., due to aging) over time. The model population was stratified into four classes based on total cholesterol level, with cut-off values of 5.0, 6.5 and 8.0 mmol/l. Each class was further subdivided into two groups based on the use of statins (yes/no), resulting in eight different classes of cardiovascular risk. The incidence of cardiovascular disease is increased for higher classes of total cholesterol and absence of statin use (due to the pleiotropic effects of statins), and also, e.g., with higher age and male gender. Transitions between the classes are possible, reflecting starting or stopping the use of statins, and changes in total cholesterol level, e.g. due to increased phytosterol/-stanol use in our scenarios (Fig. 1).

2.3. Model input data

2.3.1. General demographic data and data on risk factors and diseases

General demographic data on total mortality, birth rates and population size were obtained from Statistics Netherlands (http://statline.cbs.nl/statweb/). Age- and sex-specific initial prevalences of risk factors, including cholesterol levels, and transitions between risk factor classes were obtained from large representative Dutch Health monitoring studies (Hofman et al., 1995; Houterman et al., 2001; Verschuren et al., 2008; Westert et al., 2005). Finally, data on disease specific prevalence, incidence, remission and mortality were obtained from four general practitioners' registrations (Donker, 2010; Engelfriet et al., 2011; Verheij et al., 2009; Verheij et al., 2010; Westert et al., 2005).

2.3.2. Intake and effect of phytosterols/-stanols and statins

The average per person daily intake of phytosterols/-stanols in the scenarios with additional phytosterol/-stanol use was derived from the averages assessed in the Doetinchem Cohort Study by a food frequency questionnaire. The questionnaire contained an open question on the brand name of bread spread used (e.g. phytosterol/-stanol-enriched bread spreads) and photographs of 4 differently sized portions. The average intake level was 1.05 g phytosterols/-stanols per day. This intake level would cause a reduction in total cholesterol of 4.7% (95% CI: −7.2 to −3.2) based on the dose–response relation in the meta-analysis by Demonty et al. (2009) (Appendix A).

The use of different types and dosages of statins in The Netherlands in 2009 was derived from the GIP-databank, a drug information system of the Dutch Health Care Insurance Board (http://www.gipdatabank.nl/), containing reimbursement data on almost the whole Dutch population. The average hypocholesterolemic effect of these different statins was estimated to be 24.6% (Illingworth and Tobert, 1994; Maron et al., 2000; Penning-van Beest et al., 2007) (Appendix A).

It was assumed that statins and phytosterols/-stanols had additive cholesterol-lowering effects, i.e. 29.3%, when used in combination (Eussen et al., 2010a; Neil et al., 2001; Simons, 2002).

2.3.3. Discontinuation of phytosterols/-stanols and statins

In daily life, many subjects discontinue the use of phytosterols/-stanols and/or statins (Luoto et al., 2004; Mantel-Teeuwisse et al., 2004). Suffering from side effects such as myalgia, for example, is
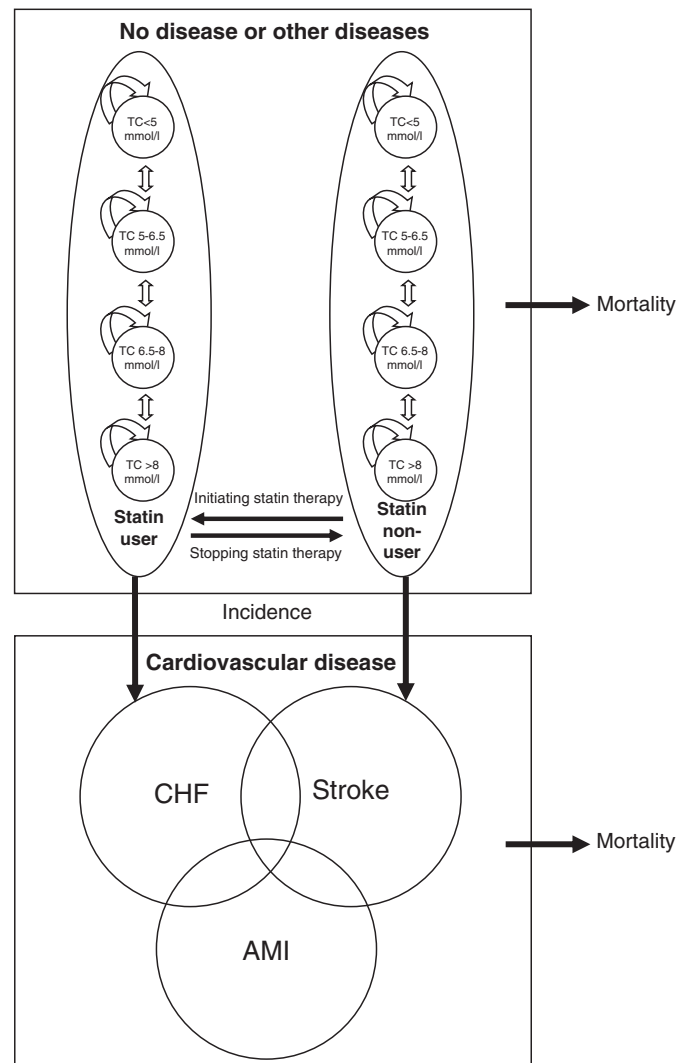

Fig. 1. The modelling of cholesterol in relation to cardiovascular disease in the Chronic Disease Model. In the Chronic Disease Model the model population is stratified into eight classes of cardiovascular risk, based on total cholesterol levels (TC) and the use of statins (upper part of figure). After a change in cholesterol level, subjects may either transit to another cholesterol class (⇕) or remain in the same cholesterol class (↺). After initiating statin therapy, subjects transit from one of the right four classes ('Statin non-user') to one of the left four classes ('Statin user'). Subjects in all classes are at risk of cardiovascular disease, with different classes having different risks of developing cardiovascular disease (lower part of figure). The model includes different relative risk estimates for chronic heart failure (CHF), stroke and acute myocardial infarction (AMI), and accounts for interactions between these diseases. Subjects are always of risk of death from cardiovascular disease-related and other-cause mortality. This risk depends on the class the subject belongs to.

considered a reason for stopping statin therapy (Bates et al., 2009). To adapt our scenarios to this daily life experience, we have included discontinuation rates for new users of phytosterol/-stanol and new statin users. For phytosterols/-stanols these were estimated from the percentage of subjects who stopped the use of phytosterols/-stanols between subsequent rounds in the Doetinchem Cohort Study. We assumed that subjects who discontinued phytosterols/-stanols, stopped in the first and second year with discontinuation rates of 33% after one year and 44% after two years. Subjects who adhere to the use of phytosterols/-stanols for at least two years, were assumed to continue use during the rest of their lives. In subjects who discontinued the use of phytosterols/-stanols, the total cholesterol level was assumed to return to the same level as before the start of the scenario.

Discontinuation rates for statins were 38.5% after one year and 53.5% after two years (Mantel-Teeuwisse et al., 2004). As for

phytosterols/-stanols, we assumed total cholesterol levels to increase to the same level as before the start of the scenario in subjects who discontinued statin therapy. New combined users of statins and phytosterols/-stanols were assumed to stop both with a probability as if they were statin only users.

2.3.4. Health effects

Health effects were computed in terms of quality-adjusted life-years, a measure of the life expectancy of a person (in years) adjusted for the quality of life (Gold et al., 2002), by using data from the Global and Dutch Burden of Disease studies (Lopez and Murray, 1998; Melse et al., 2000; Stouthard et al., 2000; van Baal et al., 2005; van Baal et al., 2006). Total quality-adjusted life-years lived by the model population in each year of the simulation were found by tracking population sizes and disease prevalence. Net present values of quality-adjusted life-years were calculated by adding annual quality-adjusted life-years over the model's time horizon of 50 years, discounting future quality-adjusted life-years at 1.5% according to Dutch guidelines for pharmacoeconomic research (College voor Zorgverzekeringen, 2006). Similarly, net present values of life-years saved were obtained.

2.3.5. Intervention costs and health care costs

We have calculated all intervention costs as well as both directly and indirectly related health care costs. Costs are expressed in Euros and are based on Dutch unit prices of 2010. Future costs were discounted at 4% annually according to the Dutch guidelines (College voor Zorgverzekeringen, 2006).

Intervention costs included all costs related to the intervention, i.e. costs related to phytosterols/-stanols and, additionally for the theoretical maximum situation, all costs related to statin use. With respect to intervention costs for phytosterols/-stanols, we assumed that phytosterols/-stanols were incorporated into a bread spread. The additional costs of using the phytosterol/-stanol-enriched margarine instead of regular bread spread without phytosterols/-stanols was estimated at €6.20/kg (€9.68/kg for enriched margarine minus €3.48/kg for regular margarine) which amounts to €31.68/yr for current phytosterol/-stanol intake levels (1.05 g phytosterols/-stanols per day equals 5.1 kg margarine per year). In addition, we assumed that all phytosterol/-stanol users had one doctor visit (€24,80) (Nederlandse Zorgautoriteit, 2009) and one lipid test (€24,98) (Nederlandse Zorgautoriteit, 2010) every 5 years costing in total €10,-/yr. Annual statin drug costs were estimated at €150/yr, based on the distribution of the different types and dosages of statin use in The Netherlands and the

corresponding costs (http://www.gipdatabank.nl/). Statin users were assumed to have one doctor visit, one lipid test (Dutch Institute for Healthcare Improvement and Dutch College of General Practitioners, 2006) and three repeat prescriptions every year (€12.40 each) (Nederlandse Zorgautoriteit, 2009), summing up to a total of €237,-/yr.

Health care costs included future savings related to diseases averted by using phytosterols/-stanols and/or statins and those resulting from surviving longer (indirect health care costs) (van Baal et al., 2007). Lifetime health care costs were calculated in the Chronic Disease Model based on disease prevalence combined with age and gender specific data from the Dutch Cost of Illness Study (http://www.kostenvanziekten.nl/) (Poos et al., 2005; van Baal et al., 2005; van Baal et al., 2008).

2.4. Calculation of cost-effectiveness

Cost-effectiveness ratios were calculated by dividing incremental costs (Euros) by health benefits (quality-adjusted life-years) gained due to the additional use of phytosterols/-stanols. First, intervention costs per quality-adjusted life-year gained were computed and second, total costs per quality-adjusted life-year gained, i.e. intervention costs plus all differences in health care costs. These cost-effectiveness ratios represent the value-for-money provided by adding treatment with phytosterols/-stanols to current statin use (real-life situation) as well as to maximal statin use resulting from screening (maximum situation).

2.5. Uncertainty and sensitivity analysis

Probabilistic uncertainty analysis was used to evaluate the combined effect of uncertainty regarding the effectiveness of phytosterols/-stanols and the use of the Doetinchem Cohort data to estimate the cholesterol levels in the Dutch population. For this uncertainty analysis, Monte Carlo simulation was used, with 100 independent simulations drawing for each simulation new parameter-values for the dose–response curve from their 95% confidence interval (CI). Each simulation used a new distribution over the eight cholesterol classes, assuming Dirichlet distributions for the conversion of the cholesterol distribution of the Doetichem Cohort to the Dutch population.

A series of univariate sensitivity analyses were performed to evaluate the impact of other important model assumptions and parameters on the results. The daily phytosterol/-stanol intake amount was set at the recommended level of 2 g/day. We assumed this was obtained by an increased concentration in bread spread at

Table 2
The number of phytosterol/-stanol (PS) users and the effect of additional phytosterol/-stanol use on health effects, costs, and the cost-effectiveness ratios in the real-life (RL) and theoretical maximum (TM) situation, cumulative over the 50-year period of the simulation (as compared to the reference scenario for each situation, *RL reference* and *TM reference*). Costs were discounted at 4%, and life-years and quality-adjusted life-years at 1.5%. Data for the Dutch population aged 35–75 years (8.4 million people).

	Real-life (RL)			Theoretical maximum (TM)	
		Effect of additional PS use			Effect of additional PS use
	RL reference	RL plus PS (min)	RL plus PS (max)	TM reference	TM plus PS
No. of subjects[a] (×1000)	8407	+0	+0	8,407	+0
No. of PS users[a] (×1000)	615	+1048	+2571	615	+3333
No. of statin users[a] (×1000)	1193	+0	+0	1514	+0
Health effects (×1000)					
Life-years	199,100	+3.6	+15.5	199,100	+19.5
QALYs	132,400	+2.7	+12.4	132,400	+16.3
Costs (mln €)					
Intervention	0	+473	+993	0	+1,255
Health care (direct and indirect)[b]	895,800	+29	+118	896,500	+133
Total	895,800	+502	+1111	896,500	+1388
Cost-effectiveness (€ per QALY gained)					
Intervention costs		192,200	86,900		83,900
Total costs		203,000	96,400		92,200

PS, Phytosterols/-stanols; QALY, Quality-adjusted life-years.
[a] At onset of scenario.
[b] Direct costs include all future savings related to diseases averted by using PS and/or statins; indirect costs include all costs resulting from surviving longer.
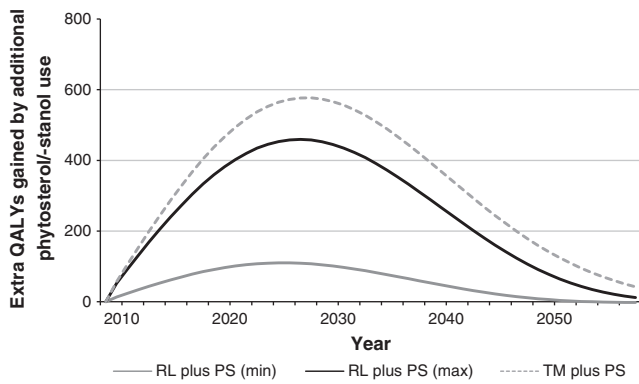
Fig. 2. Effect of additional phytosterol/-stanol (PS) use on discounted (1.5%) quality-adjusted life-years (QALYs) gained per year in the real-life (RL) and theoretical maximum (TM) situation. Data are expressed as extra QALYs gained compared to the reference scenario for each situation (*RL reference* and *TM reference*).

equal costs. Discontinuation rates for phytosterols/-stanols and statins were set to zero and indirectly related health care costs were disregarded. Furthermore, discount rates on costs and effects of 0%, 3% and 5% were used, and a discount rate of 4% for costs combined with 0% for effects. Finally, time horizons of 10, 20 and 30 years were evaluated.

3. Results

3.1. Number of phytosterol/-stanol and statin users

At the start of the simulation (year 2007), about 615,000 members (7%) of the Dutch population aged between 35 and 75 years used functional foods enriched with phytosterols/-stanols in the reference

Fig. 3. Effect of additional phytosterol/-stanol (PS) use on discounted (4%) annual intervention costs (A) and health care costs (B) in the real-life (RL) and theoretical maximum (TM) situation. Data are expressed as extra costs compared to the reference scenario for each situation (*RL reference* and *TM reference*).

scenarios (*RL reference* and *TM reference*) (Table 2). Statins were used by approximately 1.2 million (14%) and 1.5 million (18%) persons in the real-life and theoretical maximum situation, respectively.

Due to the implementation of the scenarios the number of phytosterol/-stanol users increased. The number of extra phytosterol/-stanol users in a real-life situation ranged between 1.0 million (*RL plus PS* (*min*)) and 2.6 million (*RL plus PS* (*max*)). In the theoretical maximum situation, a total of 3.3 million subjects started phytosterol/-stanol use (*TM plus PS*).

3.2. Health effects

For both the real-life and theoretical maximum situation, the discounted total health effects at the end of the simulation (after 50 years), expressed as life-years and quality-adjusted life-years gained, in the scenarios with additional phytosterol/-stanol use as compared to the reference scenarios (*RL reference* and *TM reference*) are shown in Table 2. In the real-life situation, a total of 3600 life-years or 2700 quality-adjusted life-years (on average 0.0034 life-year or 0.0026 quality-adjusted life-year per extra phytosterol/-stanol user) were gained if all current statin users would start the use of phytosterols/-stanols (*RL plus PS* (*min*)). A total of 15,500 life-years or 12,400 quality-adjusted life-years (on average 0.0060 life-year or 0.0048 quality-adjusted life-year per extra phytosterol/-stanol user) were gained when additionally also all subjects with a modestly elevated risk ($\geq$5, <10%) would start using phytosterols/-stanols (*RL plus PS* (*max*)). Additional phytosterol/-stanol use in the theoretical maximum situation resulted in a total of 16,300 quality-adjusted life-years (19,500 life-years) gained, or 0.0049 quality-adjusted life-year (0.0059 life-year) per extra phytosterol/-stanol user (*TM plus PS*). Fig. 2 shows the discounted extra quality-adjusted life-years gained per year by additional phytosterol/-stanol use compared to the reference scenario for each situation (*RL reference* or *TM reference*). In both situations, the quality-adjusted life-years gained by extra phytosterol/-stanol use reached a maximum after some 20 years when most people in the cohort are old but still alive, and some cardiovascular events can be delayed or prevented by the use of phytosterols/-stanols. Further in time, more and more people die and fewer events can be prevented.

3.3. Intervention costs and health care costs

The effect of additional phytosterol/-stanol use on cumulative discounted intervention and health care costs over the 50-year period
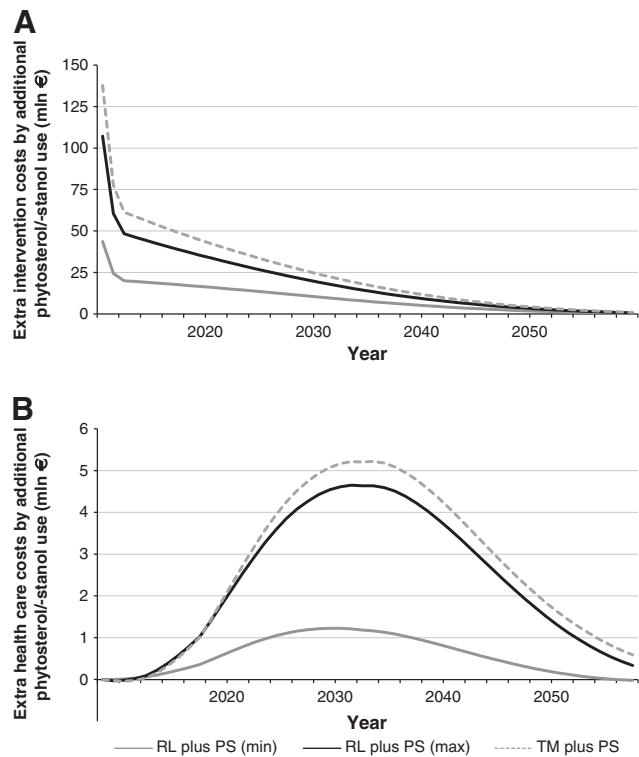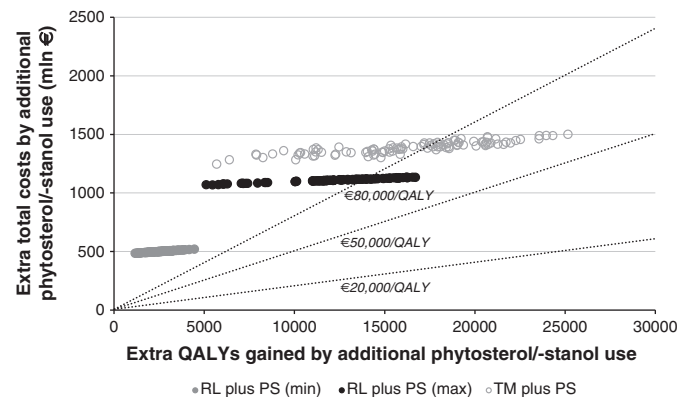

Fig. 4. Cost-effectiveness of additional phytosterol/-stanol (PS) use in the real-life (RL) and theoretical maximum (TM) situation. Costs and quality-adjusted life-years (QALYs) are expressed as extra total costs and extra QALYs gained, cumulative for the years 2007–2057 (as compared to the reference scenario for each situation, *RL reference* and *TM reference*). The symbols are the cost-effectiveness ratio of each model run in the uncertainty analysis (100 runs in total). The lines represent cost-effectiveness ratios of €20,000, €50,000 and €80,000.

Table 3
Results for cost-effectiveness ratio of the uncertainty and sensitivity analyses. The influence of changes in effectiveness and intake level of phytosterols/-stanols, discontinuation, discount rates and time horizon on the cost-effectiveness ratio (total extra costs per quality-adjusted life-year gained) of additional phytosterol/-stanol use in the real-life (RL) and theoretical maximum (TM) situation (as compared to the reference scenarios). Data are cumulative over the 50-year period of the simulation.

Variable	Values	Real-life (RL)		Theoretical maximum (TM)
		RL plus PS (min)	RL plus PS (max)	TM plus PS
		Cost-effectiveness ratio (€ per QALY gained)[a]		
	Reference	203,000	96,400	92,200
Effectiveness of PS on reducing TC[b]	Lower bound of 95% CI (−3.2%)	349,300	171,700	151,800
	Upper bound of 95% CI (−7.2%)	134,400	69,700	63,200
PS intake[c] (g/day)	2	168,600	78,800	86,400
Discontinuation[d] (%)	0	193,600	101,100	121,500
Indirect health care costs	0	210,500	96,700	88,100
Discount rates[e] (%)	0, 0	334,000	155,300	122,300
	3, 3	348,300	174,000	145,500
	5, 5	368,300	191,400	165,300
	4, 0	177,100	83,400	65,600
Time horizon (years)	10	589,900	330,500	374,000
	20	335,200	155,500	167,100
	30	238,200	123,000	123,400

PS, Phytosterols/-stanols; QALY, Quality-adjusted life-years. TC, total cholesterol.

[a] Cost-effectiveness ratio is expressed as extra costs per extra quality-adjusted life-year gained compared to costs and quality-adjusted life-years of the reference scenario for each situation (*RL reference* and *TM reference*).

[b] Combined effect of uncertainty regarding the effectiveness of PS (Appendix A) and the use of the Doetinchem Cohort data to estimate the cholesterol levels in the Dutch population.

[c] Intake of PS was increased without additional costs.

[d] Discontinuation rates for both PS and statins.

[e] Discount rates for costs and effects, respectively.

in both situations are presented in Table 2. Discounted intervention costs were about a factor 10 higher than health care costs, and ranged between €0.47 billion for added phytosterols/-stanols in the *minimum* real-life situation (*RL plus PS (min)*) to €1.26 billion for added phytosterols/-stanols in the theoretical maximum situation (*TM plus PS*). Intervention costs were the highest at the beginning of the simulation, declined steadily during the first two years due to discontinuation of phytosterol/-stanol and statin use, and gradually reached zero near the end of the simulation when most of the cohort has died (Fig. 3a). Fig. 3b shows the difference in discounted health care costs per year in the scenarios with additional phytosterol/-stanol use compared to the reference scenarios (*RL reference* or *TM reference*). Apart from minor savings in health care costs during the first three years, health care costs were higher with additional phytosterol/-stanol use than without the additional use. This can be explained by the fact that subjects with a healthier cholesterol level live longer. During their longer lifetime they develop more diseases, with associated costs (van Baal et al., 2007). The costs of these indirectly related health effects turn out to be higher than the prevented costs of cardiovascular events. Consequently, the more people that start using phytosterols/-stanols, the higher the health care costs.

3.4. Cost-effectiveness

Mean incremental total costs per quality-adjusted life-year for additional phytosterol/-stanol use varied between €96,000 and €203,000 in the real-life situation, and were about €92,000 in the theoretical maximum situation (Table 2). When only the costs of the intervention itself were considered, mean costs were approximately €10,000 lower per quality-adjusted life-year, resulting in mean costs per quality-adjusted life-year between €84,000 and €192,000. Fig. 4 shows the cost-effectiveness of additional phytosterol/-stanol use for the different scenarios. The cost-effectiveness ratios were compared to threshold values of €20,000, €50,000 and €80,000 per additional quality-adjusted life-year (Boersma et al., 2010; van Gils et al., 2010). In the *maximum* real-life situation (*RL plus PS (max)*) and the maximum situation (*TM plus PS*), the addition of phytosterols/-stanols had a probability between 30% and 44% of being cost-effective at a threshold value of €80,000. When a threshold for cost-effectiveness of €20,000 or

€50,000 was considered, the addition of phytosterols/-stanols was not cost-effective in any of the 100 uncertainty simulation runs, neither in the real-life situation, nor in the theoretical maximum situation.

3.5. Uncertainty and sensitivity analyses

Results of the uncertainty and sensitivity analyses are shown in Table 3. As expected, an increase in effectiveness of phytosterols/-stanols (total cholesterol reduction increased from 4.7% to 7.2%, the upper bound of the 95% CI) and an increased intake of phytosterols/-stanols (from 1.05 g/day to the recommended levels of 2 g/day) resulted in more favourable cost-effectiveness ratios. Assuming no discontinuation of phytosterols/-stanols or statins did only marginally affect the cost-effectiveness ratio. Apparently, lifetime health benefits of the phytosterols/-stanols seem to be counterbalanced by the lifetime payment for phytosterols/-stanols. Disregarding indirect health care costs did not change the results, due to the fact that health care costs (both direct and indirect) were only 10% of the total costs. Considering a greater difference in discount rates for costs and effects, i.e. a higher discount rate for costs and a lower rate for effects, resulted in a more favourable cost-effectiveness ratio, explained by the fact that the costs of the intervention are largely made in the first years, whereas a longer time-span is required to achieve effects of the intervention. Shorter time horizons led to a less cost-effective intervention, because much intervention costs are made at the start, whereas most of the health gains appear later.

4. Discussion

The present study suggests that the use of functional foods enriched with phytosterols/-stanols as monotherapy and as add-on to statin therapy is a non-cost-effective strategy to reduce cardiovascular disease. In a situation in which persons eligible for use were identified through passive clinical case-finding, the cost-effectiveness of phytosterols/-stanols ranged from about €96,000 to €203,000 per quality-adjusted life-year. A slightly lower (more favourable) cost-effectiveness ratio of €92,000 was obtained when subjects qualifying for phytosterols/-stanols were found through a (hypothetical) universal screening program for cardiovascular disease (costs of the universal screening program were not included in the analyses). In

both situations, cost-effectiveness ratios are well above established threshold values for cost-per-quality-adjusted life-year, which generally range between €20,000 and €50,000 (Boersma et al., 2010; van Gils et al., 2010). These threshold values for cost-effectiveness ratios were also not reached in sensitivity analyses in which treatment effect or intake level of phytosterols/-stanols was increased, or future health care costs were not taken into account.

This is the first study evaluating whether functional foods enriched with phytosterols/-stanols are a cost-effective strategy in addition to the beneficial effects of statins in the prevention of cardiovascular disease. Two studies have been performed to assess the cost-effectiveness of phytosterols/-stanols alone (Gerber et al., 2006; Martikainen et al., 2007). Gerber et al. (Gerber et al., 2006) found that €52 per person could be saved when phytosterol/-stanol-enriched margarine was consumed by the entire German population between 30 and 79 years of age. In contrast to our study Gerber et al. disregarded intervention costs, i.e. costs of the functional foods enriched with phytosterols/-stanols and costs for doctor visits and lipid tests. Martikainen et al. (Martikainen et al., 2007) found cost-effectiveness ratios between €7436 and €112,151, conditional on age and gender, and concluded that phytosterol/-stanol-enriched functional foods were a cost-effective option for high-risk persons (adult men and women aged 60 years or older). One of the reasons for the difference between the results of these two studies and the present one is that, although phytosterols/-stanols are recommended for subjects with elevated cholesterol levels (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, 2002; Clifton, 2009) or elevated SCORE-risks (Dutch Institute for Healthcare Improvement and Dutch College of General Practitioners, 2006; Law, 2000), all persons in a certain age group were treated with phytosterols/-stanols in the previous studies, regardless of a person's cholesterol level or SCORE-risk (Gerber et al., 2006; Martikainen et al., 2007). Moreover, both previous studies assumed perfect adherence to phytosterols/-stanols, i.e. the continuous use of the recommended daily amount of 2 g phytosterols or -stanols. Actual adherence is, however, known to be less than optimal (Luoto et al., 2004; Wolfs et al., 2006). People do stop the use of phytosterols/-stanols and consume less than the recommended intake amount. Finally, neither previous study considered costs caused by diseases other than cardiovascular disease, acquired later in the life-years saved. Yet, it is more and more recommended that these indirectly related health care costs should be included in economic evaluations (van Baal et al., 2007; Feenstra et al., 2008; Nyman, 2004; Meltzer, 2008). Nevertheless, with respect to the latter two aspects, sensitivity analyses which disregarded discontinuation of phytosterols/-stanols or indirect health care costs did not substantially alter the results.

We assumed that phytosterols/-stanols were incorporated into a bread spread. Although enriched bread spreads are the most commonly used source for phytosterols/-stanols today, the market is expanding to include other dairy products, like yoghurt (drinks) and milk. Nevertheless, costs (in Euros 2010) for recommended daily intake levels of enriched yoghurt drinks and milk are €0.60 and €1.05, respectively, which is notably higher than costs for recommended intake levels of the bread spread (€0.25). Consequently, this would result in even more unfavourable cost-effectiveness ratios.

In the present study, the cost-effectiveness of phytosterols/-stanols was evaluated both in a real-life situation and in a theoretical maximum situation. In the maximum situation, persons eligible for statin treatment or lifestyle modifications (phytosterols/-stanols) were selected following the Dutch guidelines for cardiovascular risk management. However, it is known that not all general practitioners follow these guidelines and use the SCORE risk calculation charts that accompany the guidelines (Hobbs and Erhardt, 2002; Scheltens et al., 2009). Besides general practitioner-related factors, also patient-related factors may have contributed to the fact that in the present study, one fifth ($n = 321,000$) of the subjects eligible for statin use were not using them. Patients may refrain from starting statin therapy, or may discontinue the medication because of side effects or lack of effect (Finn et al., 2009). In addition, a few deviations between the guidelines and the implementation of the guidelines in our scenarios should be mentioned. Firstly, the guidelines offer separate recommendations for subjects with and subjects without type 2 diabetes mellitus or established cardiovascular disease. In the current analysis, all patients suffering from type 2 diabetes or cardiovascular disease were considered to have the same probability of receiving phytosterols/-stanols and statins as the general population. Thus, we underestimated the chance of being treated for these patients. Furthermore, the guidelines consider subjects with a 10-year SCORE-risk of fatal cardiovascular disease ≥10% eligible for statin treatment, unless their LDL-cholesterol level is <2.5 mmol/l. We were not able to include this limitation as in the Doetinchem Cohort Study, which was assumed to represent the Dutch population, only subjects' total and HDL-cholesterol level was assessed. However, under the assumption that 80% of the circulating cholesterol in the human body is bound to LDL (Crowley, 2009), less than 1% of the Dutch population with a SCORE-risk ≥10% has a LDL-cholesterol level below 2.5 mmol/l. This would not have affected the estimated cost-effectiveness of phytosterols/-stanols.

We have used the Chronic Disease Model to project future effects on health and health care costs. Some limitations of the use of this model need to be addressed. Most importantly, continuous risk factors, such as total cholesterol level, in the Chronic Disease Model are categorized into four classes (Fig. 1). As a consequence, subjects already in the lowest cholesterol risk factor class before the start of the simulation cannot gain benefits from the phytosterols/-stanols. This may result in an underestimation of the effects of phytosterols/-stanols. Nonetheless, there is currently no evidence that lowering total cholesterol levels below the established target values of 5 mmol/l is associated with lower mortality (Jacobson, 2000; Warren, 2008). Moreover, estimates of relative risks of cardiovascular disease in the Chronic Disease Model are based on studies from different countries. Although this results in the best approximation of the available data, it is unknown whether this approach gives the best values for the Dutch relative risk estimate. Finally, in using the Chronic Disease Model, some assumptions had to be made. Firstly, it was assumed that the association between cholesterol-lowering effects of phytosterols/-stanols and reduction in cardiovascular disease was similar to the associations seen for other cholesterol-lowering strategies and cardiovascular disease risk reduction. Secondly, we assumed that subjects entering the model were similar to those enrolled in the Doetinchem Cohort Study with respect to SCORE-risk and phytosterol/-stanol and statin use. However, the Doetinchem Cohort is not entirely representative for the Dutch population. Smokers and the lower educated appear to be underrepresented in the cohort (Verschuren et al., 2008). Since smoking is associated with increased total cholesterol levels (Craig et al., 1989) and phytosterol/-stanol-enriched margarines are less often used by the lower educated (Eussen et al., 2011), SCORE-risks and the percentage of phytosterol/-stanol- and statin-users in the Dutch population are likely to be slightly different than those estimated from the Doetinchem Cohort Study.

In conclusion, this simulation study shows that the intake of functional foods enriched with phytosterols/-stanols for those with elevated cardiovascular disease risk, as encouraged in the guidelines for cardiovascular risk management, is above Dutch and international thresholds for cost-effectiveness, and is thus a non-cost-effective strategy to reduce cardiovascular disease. This study demonstrates the importance of incorporating cost-effectiveness assessments in health care resource allocation decision-making. Comparing the cost-effectiveness of phytosterol/-stanol-enriched functional foods to other (functional) foods and drugs is suggested to be a critical step in assessing their broader applicability.

Disclosure statement

Appendix A

Calculation of total cholesterol-lowering effect of phytosterols/-stanols

Predicted LDL-cholesterol change (%) $= -a \cdot \left(1 - \exp\left(-\frac{dose}{b / \ln(2)}\right)\right)$ (Demonty et al., 2009), where a is −12.68% (95% CI: −15.38 to −9.99) and b is 1.12 g/day (95% CI: 0.62 to 1.63).

The average daily intake level of phytosterols/-stanols, estimated from the food frequency questionnaire used in the Doetinchem Cohort Study, was 1.05 g phytosterols/-stanols per user. From the distributions in a and b 10,000 random drawings were taken, resulting in a predicted LDL-cholesterol change of −5.85% (95% CI: −8.94 to −4.03). Under the assumptions that the cholesterol-lowering effect of phytosterols/-stanols only affects LDL-cholesterol and that 80% of the circulating cholesterol in bound to LDL (Crowley, 2009), this results in a predicted total cholesterol reduction of 4.7% (95% CI: −7.2 to −3.2).

Calculation of total cholesterol-lowering effect of statins

Estimated reductions in total cholesterol resulting from the defined daily dose (DDD), i.e. the average maintenance dose per day for a drug in adults (World Health Organization (WHO) Collaborating Centre for Drug Statistics Methodology, 2010), were taken from Penning-van Beest et al. (Penning-van Beest et al., 2007) (Supplemental Table 1). Information about the number of users of various types of statins and the DDD consumed in The Netherlands was taken from the GIP databank (http://www.gipdatabank.nl/). Subsequently, the reduction in total cholesterol resulting from the average consumed dose was calculated per type of statin (Supplemental Table 2).

The average reduction in total cholesterol of all different types and doses of statins that were consumed was calculated by multiplying the percentages of the various statins used by the reduction in total cholesterol at the consumed dose, and was found to be 24.6%.

References

Baigent, C., Keech, A., Kearney, P.M., Blackwell, L., Buck, G., Pollicino, C., Kirby, A., Sourjina, T., Peto, R., Collins, R., Simes, R., 2005. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet 366, 1267–1278.

Bates, T.R., Connaughton, V.M., Watts, G.F., 2009. Non-adherence to statin therapy: a major challenge for preventive cardiology. Expert Opin. Pharmacother. 10, 2973–2985.

Boersma, C., Broere, A., Postma, M.J., 2010. Quantification of the potential impact of cost-effectiveness thresholds on dutch drug expenditures using retrospective analysis. Value Health. 13, 853–856. doi:10.1111/j.1524-4733.2010.00736.x; 10.1111/j.1524-4733.2010.00736.x.

Clifton, P., 2009. Lowering cholesterol – a review on the role of plant sterols. Aust. Fam. Physician 38, 218–221.

College voor Zorgverzekeringen, 2006. Richtlijnen voor farmaco-economisch onderzoek: evaluatie en actualisatie [in Dutch]. Available from: http://www.cvz.nl/binaries/live/cvzinternet/hst_content/nl/documenten/rapporten/2005/rpt0510+richtlijnen+fe-onderzoek.pdf Accessed 10 March 2011.

Conroy, R.M., Pyorala, K., Fitzgerald, A.P., Sans, S., Menotti, A., De Backer, G., De Bacquer, D., Ducimetiere, P., Jousilahti, P., Keil, U., Njolstad, I., Oganov, R.G., Thomsen, T., Tunstall-Pedoe, H., Tverdal, A., Wedel, H., Whincup, P., Wilhelmsen, L., Graham, I.M., SCORE project group, 2003. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. Eur. Heart J. 24, 987–1003.

Craig, W.Y., Palomaki, G.E., Haddow, J.E., 1989. Cigarette smoking and serum lipid and lipoprotein concentrations: an analysis of published data. BMJ 298, 784–788.

Crowley, L.V., 2009. An introduction to human disease. Pathology and pathophysiology correlations, 8th ed. Jones and Bartlett Publishers, Sudbury.

De Backer, G., Ambrosioni, E., Borch-Johnsen, K., Brotons, C., Cifkova, R., Dallongeville, J., Ebrahim, S., Faergeman, O., Graham, I., Mancia, G., Manger Cats, V., Orth-Gomer, K., Perk, J., Pyorala, K., Rodicio, J.L., Sans, S., Sansoy, V., Sechtem, U., Silber, S., Thomsen, T., Wood, D., Third Joint Task Force of European and Other Societies on Cardiovascular Disease Prevention in Clinical Practice, 2003. European guidelines on cardiovascular disease prevention in clinical practice. Third Joint Task Force of European and Other Societies on Cardiovascular Disease Prevention in Clinical Practice. Eur. Heart J. 24, 1601–1610.

Demonty, I., Ras, R.T., van der Knaap, H.C., Duchateau, G.S., Meijer, L., Zock, P.L., Geleijnse, J.M., Trautwein, E.A., 2009. Continuous dose–response relationship of the LDL-cholesterol-lowering effect of phytosterol intake. J Nutr 139, 271–284.

Donker, G.A., 2010. Continue Morbiditeits Registratie Peilstations Nederland 2009. Available from: http://www.nivel.nl/pdf/Rapport-Nederlands-jaarverslag-CMR-2009.pdf Accessed 18 March 2011.

Dutch Institute for Healthcare Improvement and Dutch College of General Practitioners, 2006. Dutch Guideline Cardiovascular Risk Management 2006. Available from: http://www.cbo.nl/Downloads/211/guide_cvrm_07.pdf Accessed 18 March 2011.

Engelfriet, P., Hoekstra, J., Hoogenveen, R., Bchner, F., van Rossum, C., Verschuren, M., 2010. Food and vessels: the importance of a healthy diet to prevent cardiovascular disease. Eur. J. Cardiovasc. Prev. Rehabil. 17, 50–55.

Engelfriet, P., Hoogenveen, R., Boshuizen, H., van Baal, P.H.M., 2011. To die with or from heart failure: a difference that counts: why official vital statistics are unsuitable for studying mortality in heart failure patients. Eur. J. Heart Fail. doi:10.1093/eurjhf/hfq223.

Eussen, S., Klungel, O., Garssen, J., Verhagen, H., van Kranen, H., van Loveren, H., Rompelberg, C., 2010a. Support of drug therapy using functional foods and dietary supplements: focus on statin therapy. Br. J. Nutr. 103, 1260–1277. doi:10.1017/S0007114509993230.

Eussen, S.R., de Jong, N., Rompelberg, C.J., Garssen, J., Verschuren, W.M., Klungel, O.H., 2010b. Effects of the use of phytosterol/-stanol-enriched margarines on adherence to statin therapy. Pharmacoepidemiol. Drug Saf. 19, 1225–1232. doi:10.1002/pds.2042.

Eussen, S., de Jong, N., Rompelberg, C., Garssen, J., Verschuren, W., Klungel, O., 2011. Dose-dependent cholesterol-lowering effects of phytosterol/phytostanol-enriched margarine in statin users and statin non-users under free-living conditions. Public Health Nutr. doi:10.1017/S1368980011000164.

Expert Panel on Detection Evaluation and Treatment of High Blood Cholesterol in Adults, 2002. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation 106, 3143–3421.

Feenstra, T., van Baal, P.H.M., Gandjour, A., Brouwer, W.B.F., 2008. Future costs in economic evaluation. A comment on Lee. J. Health Econ. 27, 1645–1649.

Finn, A., Kramer, M.C.A., Vorpahl, M., Kolodgie, F., Virmani, R., 2009. Pharmacotherapy of coronary atherosclerosis. Expert Opin. Pharmacother. 10, 1587–1603.

Franco, O., Peeters, A., Looman, C.W.N., Bonneux, L., 2005. Cost effectiveness of statins in coronary heart disease. J. Epidemiol. Community Health 59, 927–933.

Gerber, A., Evers, T., Haverkamp, H., Lauterbach, K.W., 2006. Cost-benefit analysis of a plant sterol containing low-fat margarine for cholesterol reduction. Eur. J. Health. Econ. 7, 247–254. doi:10.1007/s10198-006-0363-0.

Gold, M., Stevenson, D., Fryback, D., 2002. HALYS and QALYS and DALYS, Oh My: similarities and differences in summary measures of population Health. Annu. Rev. Public Health 23, 115–134.

Gumbs, P.D., Verschuren, M.W., Mantel-Teeuwisse, A.K., de Wit, A.G., de Boer, A., Klungel, O.H., 2007. Economic evaluations of cholesterol-lowering drugs: a critical and systematic review. Pharmacoeconomics 25, 187–199.

Heart Protection Study Collaborative Group, 2002. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. Lancet 360, 7–22. doi:10.1016/S0140-6736(02)09327-3.

Hobbs, F.D.R., Erhardt, L., 2002. Acceptance of guideline recommendations and perceived implementation of coronary heart disease prevention among primary care physicians in five European countries: the Reassessing European Attitudes about Cardiovascular Treatment (REACT) survey. Fam. Pract. 19, 596–604.

Hofman, A., Boerlage, P.A., Bots, M.L., den Breeijen, J.H., de Bruijn, A.M., Grobbee, D.E., Hoes, A.W., de Jong, P.T., Koenders, M.J., Odding, E., 1995. Prevalence of chronic diseases in the elderly; the ERGO study (Erasmus Rotterdam Health and the Elderly). Ned. Tijdschr. Geneeskd. 139, 1975–1978.

Hoogenveen, R.T., van Baal, P.H., Boshuizen, H.C., Feenstra, T.L., 2008. Dynamic effects of smoking cessation on disease incidence, mortality and quality of life: the role of time since cessation. Cost. Eff. Resour. Alloc 6, 1. doi:10.1186/1478-7547-6-1.

Hoogenveen, R., van Baal, P.H.M., Boshuizen, H., 2010. Chronic disease projections in heterogeneous ageing populations: approximating multi-state models of joint distributions by modelling marginal distributions. Mathematical medicine and biology 27, 1–19.

Houterman, S., Verschuren, W.M., Oomen, C.M., Boersma-Cobbaert, C.M., Kromhout, D., 2001. Trends in total and high density lipoprotein cholesterol and their determinants in The Netherlands between 1993 and 1997. Int J Epidemiol 30, 1063–1070.

Illingworth, D.R., Tobert, J.A., 1994. A review of clinical trials comparing HMG-CoA reductase inhibitors. Clinical therapeutics 16, 366–385 discussion 365.

Jacobson, T.A., 2000. "The lower the better" in hypercholesterolemia therapy: a reliable clinical guideline? Ann. Intern. Med. 133, 549–554.

Jones, P.H., Davidson, M.H., Stein, E.A., Bays, H.E., McKenney, J.M., Miller, E., Cain, V.A., Blasetto, J.W., 2003. Comparison of the efficacy and safety of rosuvastatin versus atorvastatin, simvastatin, and pravastatin across doses (STELLAR* Trial). Am. J. Cardiol. 92, 152–160.

Katan, M.B., Grundy, S.M., Jones, P., Law, M., Miettinen, T., Paoletti, R., 2003. Efficacy and safety of plant stanols and sterols in the management of blood cholesterol levels. Mayo Clin Proc 78, 965–978.

Law, M.R., 2000. Plant sterol and stanol margarines and health. West J Med 173, 43–47.

Law, M.R., Wald, N.J., Rudnicka, A.R., 2003. Quantifying effect of statins on low density lipoprotein cholesterol, ischaemic heart disease, and stroke: systematic review and meta-analysis. BMJ 326, 1423.

Lopez, A.D., Murray, C.C., 1998. The global burden of disease, 1990–2020. Nat. Med. 4, 1241–1243.

Luoto, R., Simojoki, M., Uutela, A., BJ Jr., D., McLaughlin, J.K., Puska, P., 2004. Consistency of use of plant stanol ester margarine in Finland. Public Health Nutr 7, 63–68.

Mantel-Teeuwisse, A.K., Verschuren, W.M.M., Klungel, O.H., Kromhout, D., Lindemans, A.D., Avorn, J., Porsius, A.J., de Boer, A., 2003. Undertreatment of hypercholesterolaemia: a population-based study. Br. J. Clin. Pharmacol. 55, 389–397.

Mantel-Teeuwisse, A.K., Goettsch, W.G., Klungel, O.H., de Boer, A., Herings, R.M., 2004. Long term persistence with statin treatment in daily medical practice. Heart 90, 1065–1066.

Maron, D.J., Fazio, S., Linton, M.F., 2000. Current perspectives on statins. Circulation 101, 207–213.

Martikainen, J.A., Ottelin, A.M., Kiviniemi, V., Gylling, H., 2007. Plant stanol esters are potentially cost-effective in the prevention of coronary heart disease in men: Bayesian modelling approach. Eur. J. Cardiovasc. Prev. Rehabil. 14, 265–272. doi:10.1097/01.hjr.0000216550.74258.12.

Melse, J.M., Essink-Bot, M.L., Kramers, P.G., Hoeymans, N., 2000. A national burden of disease calculation: Dutch disability-adjusted life-years. Dutch Burden of Disease Group. Am. J. Public Health 90, 1241–1247.

Meltzer, D., 2008. Response to "Future costs and the future of cost-effectiveness analysis". J. Health Econ. 27, 822–825.

Morris, S., Devlin, N., Parkin, D., 2007. Principles of Economic Evaluation in Health careIn: Economic Analysis in health care. John Wiley & Sons, Ltd, England, pp. 241–246.

Nederlandse Zorgautoriteit, . Maximumtarieven voor huisartsenzorg (5000-1900-09-3) [in Dutch]. Available from: http://www.nza.nl/regelgeving/tarieven/ Accessed 5 November 2010.

Nederlandse Zorgautoriteit, 2010. (CI-1136-b1) [in Dutch]. Available from: http://www.nza.nl/regelgeving/tarieven/ Accessed 5 November 2010.

Neil, H.A., Meijer, G.W., Roe, L.S., 2001. Randomised controlled trial of use by hypercholesterolaemic patients of a vegetable oil sterol-enriched fat spread. Atherosclerosis 156, 329–337.

Nyman, J., 2004. Should the consumption of survivors be included as a cost in cost-utility analysis? Health Econ. 13, 417–427.

Penning-van Beest, F.J., Termorshuizen, F., Goettsch, W.G., Klungel, O.H., Kastelein, J.J., Herings, R.M., 2007. Adherence to evidence-based statin guidelines reduces the risk of hospitalizations for acute myocardial infarction by 40%: a cohort study. Eur Heart J 28, 154–159. doi:10.1093/eurheartj/ehl391.

Poos, M.J.J.C., Smit, J.M., Groen, J., Kommer, G.J., Slobbe, L.C.J., 2005. Kosten van Ziekten in Nederland 2005. Available from: www.costofillness.eu Accessed 18 March 2011.

Ray, K.K., Cannon, C.P., 2005. The potential relevance of the multiple lipid-independent (pleiotropic) effects of statins in the management of acute coronary syndromes. J. Am. Coll. Cardiol. 46, 1425–1433. doi:10.1016/j.jacc.2005.05.086.

Ray, K.K., Cannon, C.P., 2007. Lipid-independent pleiotropic effects of statins in the management of acute coronary syndromes. Curr. Treat. Options Cardiovasc. Med. 9, 46–51.

Scheltens, T., Grobbee, D.E., Kok, L., Verschuren, W.M.M., Bots, M.L., Numans, M.E., Hoes, A.W., 2009. Prevention of cardiovascular diseases in primary care: proven principles and persistent practice. From guideline 'Cholesterol' to guideline 'Cardiovascular risk management': so what? Available from: http://igitur-archive.library.uu.nl/dissertations/2009-1104-200144/UUindex.html Accessed 18 March 2011.

Simons, L.A., 2002. Additive effect of plant sterol-ester margarine and cerivastatin in lowering low-density lipoprotein cholesterol in primary hypercholesterolemia. Am J Cardiol 90, 737–740.

Stouthard, M.E.A., Essink-Bot, M., BONSEL, G.J., 2000. Disability weights for diseases. A modified protocol and results for a Western European region. Eur J Public Health 10, 24–30.

van Baal, P.H.M., Feenstra, T.L., Hoogenveen, R.T., de Wit, G.A., 2005. Cost Effectiveness Analysis with the RIVM Chronic Disease Model. Report No. 260706002.

van Baal, P.H.M., Hoeymans, N., Hoogenveen, R., de Wit, G.A., Westert, G., 2006. Disability weights for comorbidity and their influence on health-adjusted life expectancy. Population Health Metrics 4, 1.

van Baal, P.H.M., Feenstra, T., Hoogenveen, R., de Wit, G.A., Brouwer, W.B.F., 2007. Unrelated medical care in life years gained and the cost utility of primary prevention: in search of a 'perfect' cost-utility ratio. Health Econ. 16, 421–433.

van Baal, P.H.M., Polder, J., de Wit, G.A., Hoogenveen, R., Feenstra, T., Boshuizen, H., Engelfriet, P., Brouwer, W.B.F., 2008. Lifetime medical costs of obesity: prevention no cure for increasing health expenditure. PLoS medicine 5, e29.

van Gils, P., Tariq, L., Verschuuren, M., van den Berg, M., 2010. Cost-effectiveness research on preventive interventions: a survey of the publications in 2008. Eur. J. Public Health 21, 260–264. doi:10.1093/eurpub/ckq069.

Verheij, R.A., Van Dijk, C.E., Abrahamse, H., Davids, R., Van den Hoogen, H., Braspenning, J., Van Althuis, T., 2009. Landelijk Informatie Netwerk Huisartsenzorg. Feiten en Cijfers over huisartsenzorg in Nederland. Available from: http://www.nivel.nl/linh/ 2009Accessed 18 March 2011.

Verheij, R.A., van Dijk, C.E., Abrahamse, H., Davids, R.L., Wennekes, L., van den Hoogen, H., Visscher, S., Braspenning, J., van Althuis, T., 2010. Landelijk Informatie Netwerk Huisartsenzorg (LINH) Kerncijfers 2008. Available from: http://www.nivel.nl/pdf/Rapport-kerncijfers-LINH-2008.pdf Accessed 18 March 2011.

Verschuren, W.M., Blokstra, A., Picavet, H.S., Smit, H.A., 2008. Cohort profile: the Doetinchem Cohort Study. Int J Epidemiol 37, 1236–1241.

Ward, S., Jones, M.L., Pandor, A., Holmes, M., Ara, R., Ryan, A., Yeo, W., Payne, N., 2007. A systematic review and economic evaluation of statins for the prevention of coronary events. Health Technol. Assess. 11, 1–160 iii.

Warren, J.B., 2008. Cholesterol–when is lower better? Clin. Pharmacol. Ther. 83, 777–780.

Westert, G.P., Schellevis, F.G., de Bakker, D.H., Groenewegen, P.P., Bensing, J.M., van der Zee, J., 2005. Monitoring health inequalities through general practice: the Second Dutch National Survey of General Practice. Eur. J. Public Health 15, 59–65. doi:10.1093/eurpub/cki116.

Wolfs, M., de Jong, N., Ocke, M.C., Verhagen, H., Monique Verschuren, W.M., 2006. Effectiveness of customary use of phytosterol/-stanol enriched margarines on blood cholesterol lowering. Food Chem Toxicol 44, 1682–1688.

World Health Organization (WHO) Collaborating Centre for Drug Statistics Methodology, 2010. Guidelines for ATC classification and DDD assignment. http://www.whocc.no/filearchive/publications/2010guidelines.pdf Accessed 18 March 2011.