Rapid Assessment: Prévention cardiovasculaire primaire dans la pratique du médecin généraliste en Belgique

KCE reports vol. 52B

Federaal Kenniscentrum voor de Gezondheidszorg
Centre fédéral d'expertise des soins de santé
2007

Le Centre fédéral d'expertise des soins de santé

Présentation : Le Centre fédéral d'expertise des soins de santé est un parastatal, créé le 24 décembre 2002 par la loi-programme (articles 262 à 266), sous tutelle du Ministre de la Santé publique et des Affaires sociales, qui est chargé de réaliser des études éclairant la décision politique dans le domaine des soins de santé et de l'assurance maladie.

Conseil d'administration

Membres effectifs : Gillet Pierre (Président), Cuypers Dirk (Vice-Président), Avontroodt Yolande, De Cock Jo (Vice-Président), De Meyere Frank, De Ridder Henri, Gillet Jean-Bernard, Godin Jean-Noël, Goyens Floris, Kesteloot Katrien, Maes Jef, Mertens Pascal, Mertens Raf, Moens Marc, Perl François Smiets, Pierre, Van Massenhove Frank, Vandermeeren Philippe, Verertbruggen Patrick, Vermeyen Karel.

Membres suppléants : Annemans Lieven, Boonen Carine, Collin Benoît, Cuypers Rita, Dercq Jean-Paul, Désir Daniel, Lemye Roland, Palsterman Paul, Ponce Annick, Pirlot Viviane, Praet Jean-Claude, Remacle Anne, Schoonjans Chris, Schrooten Renaat, Vanderstappen Anne.

Commissaire du gouvernement : Roger Yves

Direction

Directeur général : Dirk Ramaekers

Directeur général adjoint : Jean-Pierre Closon

Contact

Centre fédéral d'expertise des soins de santé (KCE).
Rue de la Loi 62
B-1040 Bruxelles
Belgium

Tel: +32 [0]2 287 33 88
Fax: +32 [0]2 287 33 85

Email : info@centredexpertise.fgov.be
Web : http://www.centredexpertise.fgov.be

Rapid Assessment: Prévention cardiovasculaire primaire dans la pratique du médecin généraliste en Belgique

KCE reports vol. 52B

CHRIS DE LAET, MATTIAS NEYT, HANS VAN BRABANDT, DIRK RAMAEKERS,
EN COLLABORATION AVEC DOMUS MEDICA, DEPARTEMENT DE RECHERCHE

Federaal Kenniscentrum voor de Gezondheidszorg
Centre fédéral d'expertise des soins de santé
2007

KCE reports vol. 52B

Titre :	Rapid Assessment: Prévention cardiovasculaire primaire dans la pratique du médecin généraliste en Belgique
Auteurs :	Chris De Laet, Mattias Neyt, Hans Van Brabandt, Dirk Ramaekers. En collaboration avec Domus Medica, département de recherche : Nicole Boffin, Ester Cornelis, Valérie Hubens, Jean Laperche, Bram Spinnewijn, Bert Vaes, Veerle Van der Stighelen, Edward Van Rossen.
Experts externes:	Guy De Backer (UZGent), Benoit Boland (UCL), Paul De Cort (KUL), Etienne Vermeire (UA), Michel Wensing (Radboud Universiteit Nijmegen, Nederland), William Wijns (OLV Aalst).
Validateurs :	Lieven Annemans (UGent), Luc Berghmans (Observatioire de la Santé du Hainaut), Oscar Franco (Unilever UK).
Conflicts of interest :	Oscar Franco est employé par Unilever UK. Lieven Annemans a collaboré à des publications, fait de la consultance pour ou a été financé pour la participation à des congrès par Bayer et AstraZeneca. Guy De Backer a reçu du financement pour des études scientifique et été financé pour la participation à des congres par MSD, Schering-Plough, Pfizer, AstraZeneca, et Sanofi-Aventis. Benoit Boland a été financé pour la participation à des congres de MSD, Schering-Plough, Pfizer et Unilever. Domus Medica supporte la campagne de Unilever 'Becel teste le coeur des Belges'.
Disclaimer :	Les experts externes et validateurs ont collaboré à la rédaction du rapport scientifique mais ne sont pas responsables des recommandations aux Autorités. Les recommandations aux Autorités ont été rédigées par le Centre d'expertise (KCE).
Mise en Page :	Ine Verhulst, Nadia Bonnouh, Patrice Chalon.

Bruxelles, 02 Avril2007

Etude nr 2005-02
Domaine : Good Clinical Practice (GCP)

MeSH : Cardiovascular Diseases ; Costs and Cost Analysis ; Guidelines ; Primary Prevention
NLM classification : WG 120

Language : français, anglais
Format : Adobe® PDF™ (A4)

Dépôt légal : D/2007/10.273/04

Comment citer ce rapport ?
De Laet C, Neyt M, Van Brabandt H, Ramaekers D. Rapid Assessment: Prévention cardiovasculaire primaire dans la pratique du médecin généraliste en Belgique. Good Clinical Practice (GCP). Bruxelles: Centre fédéral d'expertise des soins de santé (KCE); 2007. KCE reports 52 B (D/2007/10.273/04).

PRÉFACE

La prévention est un sujet porteur sur le plan politique. Les maladies du coeur et des vaisseaux constituent la première cause de mortalité et en conséquence, de nombreuses personnes seront tôt ou tard touchées. Différer cette échéance, tel est l'enjeu. Les personnes qui ont largement dépassé l'âge moyen d'espérance de vie ont déjà atteint cet objectif.

Pour les patients qui ont déjà souffert par exemple d'un infarctus, il est prouvé qu'un certain nombre d'interventions peut prévenir un second infarctus, ou du moins le retarder: ces interventions constituent la prévention secondaire. Or nous savons que ces interventions sont bien trop peu souvent utilisées.

La prévention primaire concerne les personnes « en bonne santé » : elle a pour objectif de prévenir une première manifestation de maladie cardiovasculaire. Il s'agit dans ce cas d'un groupe cible très large, plusieurs centaines de milliers de personnes dans notre pays. Commercialement parlant, elle représente un marché de rêve comme en témoignent les promotions pour les tests du cholestérol, la vaste gamme de compléments alimentaires et – le plus pertinent pour la sécurité sociale – une palette de médicaments. Tout ne baigne pas toujours dans l'huile : une illustration en est la douloureuse constatation, il y a quelques années, que la prescription de préparations hormonales pour les femmes ménopausées faisait plus de tort que de bien alors qu'elle était fortement recommandée lors des formations médicales sous un prétexte de prévention cardiovasculaire.

Brusquement, la majorité de la population a été atteinte d'une nouvelle affection dénommée hypercholestérolémie. Cependant, ce n'est ni plus ni moins un des nombreux facteurs de risque des maladies cardiovasculaires. Parmi ceux-ci, le tabac reste sans conteste le facteur numéro un.

Dans le domaine de la prévention cardiovasculaire, quelles interventions ont actuellement prouvé leur utilité et sont par ailleurs sûres tant chez les hommes que chez les femmes ? Lesquelles peuvent être considérées comme coût efficaces ou en d'autres mots valent la peine d'être financées par les fonds publics ? Et pourquoi ne réussissons-nous pas à traiter tous les patients qui peuvent tirer bénéfice de ces traitements ?

Vu l'énorme investissement budgétaire de l'assurance-maladie pour des interventions de prévention, vous vous attendez probablement à trouver une multitude d'études scientifiques qui répondent de façon catégorique aux questions ci-dessus. Dans ce rapport, nous avons tenté d'analyser les données actuelles et, en collaboration avec Domus Medica, de mettre en évidence les barrières à la mise en place d'interventions efficaces.

Probablement jetterons-nous un proverbial pavé dans la mare, dans le cas présent mare envahie par des conflits d'intérêt. Etayer des thèses sur base de données – ou mettre en évidence leur absence – telle est en effet la mission du KCE.

Jean-Pierre CLOSON
Directeur Général Adjoint

Dirk RAMAEKERS
Directeur Général

Résumé du rapport

Les maladies cardiovasculaires constituent la première cause de mortalité en Belgique et dans le monde occidental. Chaque année, près de 40 000 Belges décèdent de leurs conséquences, soit environ un tiers du total des décès. Les maladies cardiovasculaires touchent le cœur et les vaisseaux. Les manifestations les plus fréquentes sont les coronaropathies cardiaques. Elles sont causées par des rétrécissements des artères qui alimentent le muscle cardiaque (artères coronaires), suite à la constitution progressive de plaques d'athérome. Ces rétrécissements peuvent occasionner un infarctus du myocarde ou causer une angine de poitrine. D'autres formes de maladies cardiovasculaires sont les accidents vasculaires cérébraux, les accidents ischémiques transitoires et les affections des vaisseaux périphériques.

Les maladies cardiovasculaires ne sont pas seulement une cause importante de décès: elles représentent également un fardeau considérable en terme de morbidité. Telles sont les raisons pour lesquelles la prévention primaire et secondaire des maladies cardiovasculaires revêt une importance particulière. Dans ce 'rapid assessment', nous décrivons la situation belge relative à la prévention cardiovasculaire en médecine générale et nous formulons des recommandations stratégiques afin d'éviter que les personnes présentant un risque élevé soient insuffisamment traitées tandis que d'autres personnes présentant un faible risque sont traitées de manière excessive.

Comparaison entre recommandations

En 2003, une recommandation européenne a été rédigée par le "3rd Joint European Societies Task Force" (3rd ETF). Son adaptation pour la Belgique a été réalisée grâce à une traduction vers le français et le néerlandais et également par une adaptation des cartes d'évaluation des risques (SCORE) à l'épidémiologie des maladies cardiovasculaires en Belgique. Dans le courant de 2006, Domus Medica a en outre développé pour les médecins généralistes un projet de recommandation de bonne pratique "Gestion globale du risque cardio-vasculaire".

A première vue, de nombreuses divergences et contradictions existaient entre ces deux recommandations. Cette situation a généré des remous dans le monde cardiovasculaire belge. Une analyse plus détaillée a révélé des différences moins graves qui concernaient trois points importants. Il s'agit d'une application des mêmes idées de base: les deux recommandations s'appuient sur l'évaluation des risques SCORE. Les points essentiels de divergence sont 1) un algorithme complémentaire dans la recommandation en cours de développement de Domus Medica afin d'en faciliter l'utilisation par le médecin généraliste, 2) le seuil à partir duquel une personne est définie "à haut risque" d'un point de vue cardiovasculaire (la recommandation de la "European Task Force" définit ce seuil à 5%, soit un risque de 5% de décéder de maladie cardiovasculaire dans les 10 années; cette limite est fixée à 10% dans la recommandation en cours pour les médecins généralistes) 3) cette dernière recommandation utilise des cartes d'évaluation du risque basées sur le ratio cholestérol total sur HDL cholestérol plutôt que des cartes basées sur le cholestérol total.

La discussion relative à l'utilisation du cholestérol total versus le ratio cholestérol total/HDL est principalement basée sur la question relative aux mesures actuelles du HDL cholestérol en Belgique qui seraient systématiquement plus élevées que les valeurs antérieures sur lesquelles étaient basées les cartes SCORE. De l'avis des experts que nous avons consultés, ce problème existe mais son effet serait mineur pour avoir des répercussions significatives sur l'évaluation du risque. Les pays limitrophes qui utilisent également ce ratio n'éprouvent pas ce problème. Par ailleurs, les deux types de cartes SCORE sont disponibles pour la Belgique et peuvent être utilisées avec les deux recommandations.

La limite pour étiqueter une personne "à haut risque cardiovasculaire" avait été initialement définie par le "European Task Force" comme étant égale à 5%. Elle correspondait à peu près au risque défini précédemment par la Framingham study, soit un risque d'événement coronaire (fatal ou non) égal à 20%. De manière idéale, la définition de cette limite devrait être un sujet de discussion au niveau de la société

puisqu'une des conséquences est le nombre de personnes en bonne santé qui doivent être effectivement, sinon pharmacologiquement traitées dans le cadre d'une prévention primaire cardiovasculaire ?

Notre recherche montre qu'une simple transposition d'évaluation de risque pour les maladies coronaires (Framingham) en risque pour une maladie cardiovasculaire fatale (SCORE) n'est pas possible : la relation entre les deux est influencée par le sexe, le statut tabagique et principalement par l'âge. Vers 50 ans, le rapport entre les deux évaluations de risque équivaut environ à un facteur 9, vers 60 ans ce rapport diminue à peu près vers 5 et à l'âge de 70 ans il est égal à 2.4. Un score Framingham de 20% correspond donc à 50 ans à un risque d'événement fatal SCORE d'environ 3%; ce risque augmente à 4% à 60 ans et équivaut à 7% à 70 ans.

Par ailleurs, le choix d'une limite a des conséquences importantes pour la taille de la population-cible qui se trouve au-dessus de cette limite: entre 40 et 65 ans, à peu près 450 000 personnes (dont 340 000 hommes) sont au-dessus de la limite de 5%. Rehausser le seuil à 10% a pour effet de faire chuter la taille du groupe à 80 000 personnes à peu près (72 000 hommes).

Efficacité de la prévention primaire

Une distinction est classiquement effectuée entre prévention primaire et secondaire. La prévention secondaire concerne une population qui souffre de maladie cardiovasculaire : les mesures de prévention visent à limiter le risque de nouvelles manifestations cliniques. La prévention primaire concerne une population asymptomatique et vise à prévenir toute manifestation initiale de maladie cardiovasculaire. Quoique les interventions chez les personnes diabétiques puissent être *stricto sensu* considérées comme prévention primaire, nous les avons exclues ici vu le risque cardiovasculaire a priori élevé.

Différents facteurs de risque sont connus et utilisés lors d'une évaluation globale du risque cardiovasculaire. Les principaux sont l'âge, le sexe, la pression artérielle, la cholestérolémie, le tabagisme, l'anamnèse personnelle et familiale. L'intervention dépend en principe de l'évaluation du risque : plus celui-ci est élevé, plus l'intervention sera intensive. Toutes les recommandations de bonne pratique prônent des interventions en rapport avec le style de vie: principalement l'arrêt du tabac chez les fumeurs mais également la promotion d'une alimentation saine et la pratique d'une activité physique.

Dans le chapitre relatif à la prévention primaire cardiovasculaire nous étudions en particulier l'efficacité des interventions diététiques et des statines. Les mesures diététiques concernent principalement la limitation de l'utilisation des graisses saturées et/ou l'augmentation de l'apport/l'ajout d'aliments ou composants alimentaires tels que les poissons gras, les fruits, légumes, vitamines, acides gras oméga-3 et stérols d'origine végétale. Aucune donnée scientifique ne permet d'affirmer que ces interventions diététiques diminuent la mortalité totale. Seule la diminution des acides gras saturés a prouvé qu'elle peut réduire quelque peu les maladies cardiovasculaires, à condition que cette diminution soit maintenue, ce qui est loin d'être simple.

Parmi les nombreuses études cliniques avec des statines, seulement un nombre limité concerne des situations de prévention primaire pure. En conséquence, les données probantes sont rares, certainement pour certains sous-groupes. A titre d'exemple, les essais réalisés en prévention primaire ne peuvent fournir de données probantes formelles quant à l'influence des statines sur la diminution de mortalité totale. Toutefois, certaines études ont constaté une diminution de la mortalité due aux maladies coronaires. Une diminution de l'incidence des maladies coronaires a bien été observée, avec une réduction du risque absolu variant de 0.8% à 2.2% pour une période de cinq années de traitement. Cette diminution correspond à une diminution globale de risque relatif de 25% environ. Ces chiffres signifient également que plus le risque initial est bas, plus faible sera le gain de la prévention. Les essais de prévention primaire devaient traiter entre 50 et 130 individus durant trois à cinq années pour éviter un événement coronaire important (NNT, number needed to treat).

Pour des sous-groupes déterminés, il n'existe aucune donnée probante spécifique: l'effet présumé des statines en prévention primaire chez les femmes de tout âge et chez les hommes de plus de 70 ans est basé sur des extrapolations. Des preuves d'efficacité dans ces sous-groupes n'existent pas.

Evaluation économique

Nous avons entrepris une revue systématique des évaluations économiques de prévention cardiovasculaire primaire, en utilisant 19 évaluations économiques publiées depuis 2001.

De la littérature mise en évidence ressort à nouveau l'importance du risque cardiovasculaire de départ dans la population cible pour la prévention primaire, vu que toutes les études partent d'une réduction du risque relatif similaire chez tous les individus. De manière générale, les interventions sont donc d'autant plus coûts efficaces que le niveau de risque initial de la population à qui elles s'appliquent est plus élevé.

De toutes les interventions potentielles, celles pour l'arrêt du tabagisme sont de loin les plus coût efficaces et elles entraînent même des économies. C'est la raison pour laquelle lors de l'évaluation du risque, il est important chez les fumeurs d'examiner quel serait le risque après arrêt du tabagisme. Si le tabagisme place spécifiquement la personne dans un groupe à risque plus élevé, l'arrêt du tabagisme est la première intervention recommandée. Ce conseil s'applique aussi si le risque reste toujours élevé indépendamment du tabagisme mais dans ce cas, d'autres interventions complémentaires sont indiquées.

Pour les non-fumeurs avec un risque cardio-vasculaire élevé, une dose faible d'aspirine reste le traitement le plus indiqué d'un point de vue coût efficacité. Une aspirine à faible dose a des effets positifs importants pour un coût relativement bas tant sur le total des années de vies gagnées et que sur les années de vie gagnées sans maladies cardiovasculaires.

Les statines peuvent en principe apporter un bénéfice encore plus important en termes d'années de vie gagnées mais leur coût est trop élevé pour considérer ce traitement comme coût efficace lors d'un risque coronaire total inférieur à 30% (Framingham). Il n'y a pas de données probantes relatives à un risque coronaire supérieur à 30%. Même en prenant en considération la récente baisse substantielle du prix des statines, celui-ci reste généralement trop élevé pour envisager cette intervention comme coût efficace dans ces catégories de risque. En considérant le prix le plus bas sur le marché belge avec une dose faible (pravastatine 20 mg/jour), le coût est inférieur à 90€ par an. Dans cette situation uniquement le rapport coût efficacité est estimé aux environs de 30 000€ par année de vie gagnée pour les hommes à partir de 60 ans qui présentent un risque Framingham supérieur à 20%, ce qui correspond à cet âge à un SCORE d'environ 5%.

Implémentation des recommandations de bonne pratique en médecine générale

Une enquête auprès de 286 médecins généralistes belges montre que 4 sur 5 d'entre eux ont déjà utilisé un instrument pour évaluer le risque cardiovasculaire tandis qu'une minorité en font un usage régulier. De même, à peu près 4 médecins généralistes sur 5 avaient l'impression qu'ils étaient bien au courant des recommandations de bonne pratique actuelles. La plupart avaient suivi une formation relative au risque cardiovasculaire dans les deux années précédentes.

De nombreux médecins utilisent un système de dossiers médicaux informatisés (plus fréquemment les médecins généralistes néerlandophones). Cependant, les paramètres nécessaires pour l'évaluation du risque cardiovasculaire ne sont pas toujours facilement disponibles : le statut tabagique par exemple ne semble que partiellement connu.

Une étude de littérature a identifié 71 indicateurs de pratique relatifs à la prise en charge du risque cardiovasculaire et elle décrit 46 projets belges qui se sont déroulés

ces dernières années en relation avec la prévention cardiovasculaire. Vingt-six d'entre eux concernaient les soins du diabète mais dans sept projets le sujet concernait spécifiquement la prise en charge du risque cardiovasculaire global. De manière générale, les exemples belges et étrangers montrent que pour une implémentation réussie de recommandations dans la pratique, mieux vaut combiner des interventions qui doivent être régulièrement répétées, sans que l'on puisse déterminer quelles interventions doivent être privilégiées en Belgique.

Finalement, quelques groupes de médecins généralistes ont encore été interrogés afin d'examiner ce qu'ils considéraient comme facteurs facilitateurs ou comme freins à l'application des recommandations de bonne pratique relatives à la prise en charge du risque cardiovasculaire. La difficulté principale qui ressort est l'introduction d'un changement dans le style de vie des patients. Seule une collaboration entre toutes les parties peut donner un résultat: les patients doivent mieux ressentir un besoin de changement, les médecins généralistes doivent disposer de plus de temps et de moyens pour s'atteler à la prévention, les medias peuvent apporter de l'eau au moulin par des campagnes de sensibilisation tandis que les autorités peuvent contribuer à la mise en place de ces campagnes. La majorité des médecins généralistes dans ces groupes de discussion accordaient relativement peu d'importance à l'amélioration des connaissances, des aptitudes et attitudes du médecin lui-même et ils en concluaient qu'en pratique, les choses se passent relativement bien.

Conclusions et recommandations

- L'implémentation optimale d'interventions efficaces pour la prévention cardiovasculaire primaire chez les patients à haut risque laisse à désirer en Belgique, de même que dans beaucoup d'autres pays. Cette implémentation en pratique de médecine générale n'est pas favorisée par la fragmentation des initiatives et le caractère partiellement contradictoire de celles-ci. Une meilleure coordination et un accord proactif sont nécessaires entre les différentes instances qui développent les recommandations de bonne pratique, en partie financées sur des fonds publics.
- Parmi toutes les interventions potentielles, un arrêt du tabac couronné de succès est clairement la plus efficace et produit même des économies.
- Il existe des preuves qu'une alimentation pauvre en graisses saturées diminue l'apparition des maladies cardiovasculaires. De nombreuses autres interventions diététiques et suppléments alimentaires qui prolifèrent sur le marché n'ont pas prouvé qu'ils entraînent des conséquences similaires. Des suppléments alimentaires spécifiques tels que la vitamine E et le ß-carotène peuvent causer du tort. La confusion actuelle entre promotion de la santé d'une part et d'autre part les intérêts commerciaux des fabricants alimentaires a pour conséquence que la qualité de l'information au citoyen relative à l'efficacité des interventions préventives n'est pas garantie, ce qui peut éventuellement créer un faux sentiment de sécurité. Cette assertion n'est évidemment pas un plaidoyer en faveur d'un mode de vie inactif sans souci d'alimentation équilibrée. Il y a toutes sortes d'autres bonnes raisons de continuer à conseiller un mode de vie sain.
- La grande différence entre les seuils au-dessus desquels une personne en bonne santé cardiovasculaire devient une personne étiquetée "à haut risque" (5% de risque de décès dans les dix années, versus 10%) est plus fondamentale qu'une simple discussion sémantique. Tout d'abord, le choix de ce seuil détermine de manière fondamentale une médicalisation. Par ailleurs, des conséquences budgétaires majeures sont en jeu, vu le lien avec le remboursement actuel des statines. Le KCE ne prend pas position sur cette question : il est d'avis que, vu l'impact budgétaire, cette question devrait être soumise à une discussion sociétale relative au "*willingness to pay*", pour ce choix relatif à la prévention primaire.

- De manière idéale, une décision relative au remboursement est basée sur un équilibre entre d'une part l'impact sur la santé et d'autre part des considérations relatives à l'économie de la santé et à l'impact budgétaire. Les guides de pratique ne tiennent pas nécessairement compte de cet équilibre puisqu'ils se basent fréquemment sur un consensus médical de leaders d'opinion et par la force des choses ne s'appuient pas nécessairement sur des faits scientifiques établis.
- Dans la situation actuelle, l'impact d'interventions de prévention cardiovasculaire primaire sur la santé est limité tandis que l'impact budgétaire est important. Si une dose faible d'aspirine est envisagée sur base médicale et sans contre-indication, cette prise peut toujours être considérée comme coût efficace au-delà d'un risque cardio-vasculaire équivalent à 20% (selon Framingham). Au-delà d'un risque de 10% (selon Framingham) l'aspirine à faible dose est coût efficace à partir de 60 ans pour les fumeurs et à tous les ages pour les non-fumeurs. La Belgique ne dispose toutefois pas de critères clairs pour l'aspect coût efficacité d'un médicament.
- La diminution du cholestérol à l'aide de statines est à considérer comme *borderline* coût efficace (30 000 € par année de vie gagnée) comparé à l'aspirine pour les hommes à partir de 60 ans et présentant un risque Framingham supérieur à 20% (SCORE d'environ 5%). A la condition expresse que le prix annuel des statines soit inférieur à 90 €, ce qui implique que chacun reçoive une prescription de l'alternative la moins chère. Pour les femmes (de tous âges) et les hommes au-delà de 70 ans, aucune donnée claire n'est disponible au sujet de l'efficacité de la prévention primaire avec statines.
- Les données de la littérature révèlent que de nombreuses tentatives ont été entreprises afin d'améliorer l'implémentation des recommandations de bonne pratique relatives à la gestion du risque cardiovasculaire, par des interventions simples ou combinées. Il manque des preuves irréfutables et il est impossible de déterminer quelles interventions devraient avoir la préférence dans le paysage belge.

TABLE OF CONTENTS

1 INTRODUCTION

Cardiovascular disease (CVD) is a disease of the heart and the blood vessels. The most common manifestation of CVD is coronary heart disease (CHD). CHD is caused by the narrowing of the arteries that supply the heart due to a gradual build-up of fatty material (atheroma). The narrowing can cause myocardial infarction (MI) or angina. Other forms of CVD include stroke, transient ischemic attack (TIA) and peripheral artery disease (PAD). CVD is a common cause of death in Belgium and prevention is therefore considered very important.

The aim of this report is to describe the current situation of prevention of CVD in Belgian general practice and to recommend possible strategic changes. The current situation is indeed not ideal since individuals at high risk are often under treated while individuals at lower risk are often over treated. In the EUROASPIRE II survey from the European Society of Cardiology a high prevalence of unhealthy lifestyles, modifiable risk factors and inadequate use of prophylactic drug therapies was found in coronary patients across Europe.

Several interventions that aim to prevent CVD can be discussed ranging from lifestyle and dietary interventions to the daily and lifelong intake of drugs. The so-called 'polypill',[1] a theoretical combination of six existing drugs (low-dose aspirin, 3 low-dose antihypertensive drugs, folic acid and a statin) is not treated in this report since to date the concept is based on theoretical assumptions only and no firm clinical data on its clinical preventive effectiveness exist yet.

Preventive efforts are most efficient when they are directed at those at highest risk, and all guidelines stress the need of combining several preventive interventions and to act increasingly vigorously with increasing baseline CHD risk. The best described preventive interventions are:

- lifestyle interventions: physical activity and dietary interventions[2]
- smoking cessation[3-5]
- blood pressure lowering[6]
- anti-platelet aggregation therapy (low-dose Aspirin)[7, 8]
- pharmaceutical lipid management (statins)

This report starts with a comparison of the available guidelines: the current guideline emanating from the 3rd Joint European Societies' Taskforce that was published in 2003 and for which the SCORE risk charts were adapted for Belgium, and the draft guideline for GPs that is currently developed by Domus Medica.

The choice of who to treat and how, has important health economic implications: how many people qualify for each of the risk categories and what would be the cost-effectiveness of those treatments in each of these categories? Therefore, we additionally evaluate the recent evidence about lipid management through dietary interventions and through statin use. The focus was placed on lipid management and specifically on statins, since lifestyle changes have no direct health insurance budgetary impact. Other preventive pharmacological interventions such as aspirin are mentioned but aspirin is a low cost drug and available over the counter (OTC). The effectiveness of antihypertensive pharmacological treatment was beyond the scope of this report.

Next, we explore the health economic aspects of lipid management and how this compares to other preventive strategies, through a systematic literature review of economic evaluations of cardiovascular primary prevention published since 2001, and we discuss the relevance for Belgium.

In the last chapter, we look at current practice: what are the attitudes, beliefs and practices of Belgian GPs about global cardiovascular risk management, why do they or don't they apply guidelines, and what strategies can be considered to reduce the barriers for implementation or reinforce the facilitators?

2 GUIDELINES FOR CV PREVENTION IN BELGIUM: CURRENT CONTROVERSIES

2.1 SITUATION EARLY 2007

A guideline, produced by the 'Third Joint European Societies' Task Force on Cardiovascular Disease Prevention in Clinical Practice' (3rd ETF), which was constituted by representatives of eight scientific societies (Eur. Soc. Cardiology, WONCA Europe, Eur. Soc. Hypertension, Eur. Atherosclerosis Soc., EASD, IDF-Europe, Eur. Heart Network, Int. Soc. Behavioural Med.) and by invited experts, was published in 2003.[9, 10] This guideline has been promoted in Belgium by the 'National Task Force of Scientific Societies for the Prevention of Coronary Heart disease in Clinical Practice', formed by representatives of Belgian scientific societies. In both the European and in the national task force, general practitioners are represented through their respective scientific societies. This guideline, although based on the available evidence, is obviously also based on consensus. The executive summary was translated into Dutch and French, the tables to evaluate cardiovascular risk were calibrated and adapted for Belgium, and all this was widely distributed to Belgian clinicians through publication in scientific journals,[11-14] and by the 'Belgische Cardiologische Liga' and the 'Belgische Vereniging voor Cardiologie' in a pocket guide format with the help of a financial contribution from AstraZeneca.[15, 16] The risk assessment tables recommended in the guideline are based on the European SCORE charts (Systematic Coronary Risk Evaluation) system,[17] estimating the 10-year probability of a fatal CVD event. Those SCORE tables were intended to be adapted to local countries and were adapted for Belgium taking into account the epidemiological characteristics of CVD in the Belgian population.[13, 14] In the Belgian adaptation, the SCORE tables were additionally modified to estimate the risk not at a specific threshold (for instance at age 60), but to estimate the average risk for a group between given thresholds (for instance from age 58 to age 62)

In 2004, the Flemish Scientific Society for General Practice (WWVH) started the process of writing a guideline for GPs on the same topic. After reviewing the literature the author group decided to base its guideline largely on the same principles and risk factors as the guideline originating from the 3rd ETF, but also decided to recommend the diagnostic approach of using an additional algorithm developed by Boland et al,[18] prior to using the SCORE chart approach, with the idea that this would facilitate the usage in daily practice of the global cardiovascular risk assessment tools by GPs.[19] Domus Medica (heir of the former WVVH), circulated this draft guideline for comments to a group of experts during the summer of 2006, and it was first field tested on October 14th, 2006 at a guideline testing conference. It is intended to be submitted to CEBAM (the Belgian Centre for Evidence Based Medicine) in early 2007 for validation.

After the field testing, however, the draft version caught the attention of various stakeholders and started a controversy about perceived contradictions with the existing 3rd ETF guideline.

We compared both guidelines and highlight the similarities and discrepancies between them. Both guidelines embrace the concept that decisions regarding the intensity of preventive actions for apparently healthy individuals should be guided by a global CVD risk assessment and both guidelines are largely, but not entirely, based on the same risk factors. They also both stress that the highest priority in CVD management should be given to individuals with proven CVD and those at high risk for developing CVD. The **most substantial differences** between both are:

1. The draft Domus Medica guideline, is largely based on the same European SCORE risk assessment system (adapted for Belgium) but has, however, an additional implementation algorithm (the so-called 'Boland' algorithm), allowing that for a minority of patients (those who are clearly at high risk, and those at very low risk) the SCORE tables should not be used, implying that cholesterol levels in this minority of patients are considered irrelevant for risk classification. An advantage of this approach is the mnemotechnic system where each of the 6 risk factors considered corresponds to a letter from A to F.
2. The original 3rd ETF guideline provides two sets of SCORE tables: one based

on total cholesterol levels and another based the total/HDL cholesterol ratio. In the Belgian adaptation pocket guide only the tables for total cholesterol are used while the draft Domus Medica guideline specifically recommends using the charts with the total/HDL cholesterol ratio.

3. After risk classification, individuals are categorized by risk level. By definition, any risk threshold is arbitrary and based on judgement, but the importance of the definition lies in its consequences. In the 3rd ETF based guideline, the threshold for high risk is ≥5% ten-year risk for a fatal CVD event. In the draft Domus Medica guideline the threshold for high risk is a ten-year 10% risk for a fatal CVD event, while a risk from 5 to 9% is termed moderate CVD risk ('*matig risico*'). Although at first glance this might seem the largest difference, it might be the easiest to overcome since it is dependent on health care policy and judgement and also dependent on the stated diagnostic and therapeutic consequences.
4. The therapeutic guidance in the 3rd ETF guidelines appears to be less directive and more left to the appreciation of the treating physician, probably related to the consensus development process that forms the basis of this guideline, while the draft Domus Medica guideline is more directive in its statements for interventions, albeit at higher absolute risk thresholds.
5. Many other differences are noted on apparently less important issues, but the importance of those cannot be judged before a final version of the GP guideline is available. Many of those differences might indeed disappear during final editing.
6. The 3rd ETF guideline is largely based on available evidence, but also importantly on consensus development. It does not explicitly describe how literature was searched and selected, and no levels of evidence are given for the conclusions and recommendations. In the draft Domus Medica guideline formal levels of evidence for the recommendations are mentioned using a standard scoring system,[20] and for each of the topics the search strategy is described. It is unclear, however, how the literature was ultimately selected.

2.2 OVERVIEW OF THE EXISTING 3RD ETF GUIDELINE

The aim of this guideline is the primary and secondary prevention of Cardiovascular Disease (CVD), a combination of Coronary Heart Disease (CHD), ischemic stroke and peripheral arterial disease (http://www.escardio.org). The guideline is based on evidence and on consensus and was published in 2003. Neither formal levels of evidence, nor grades of recommendation are given. An update of this guideline by the 4th ETF is planned to be published at the end of summer 2007.

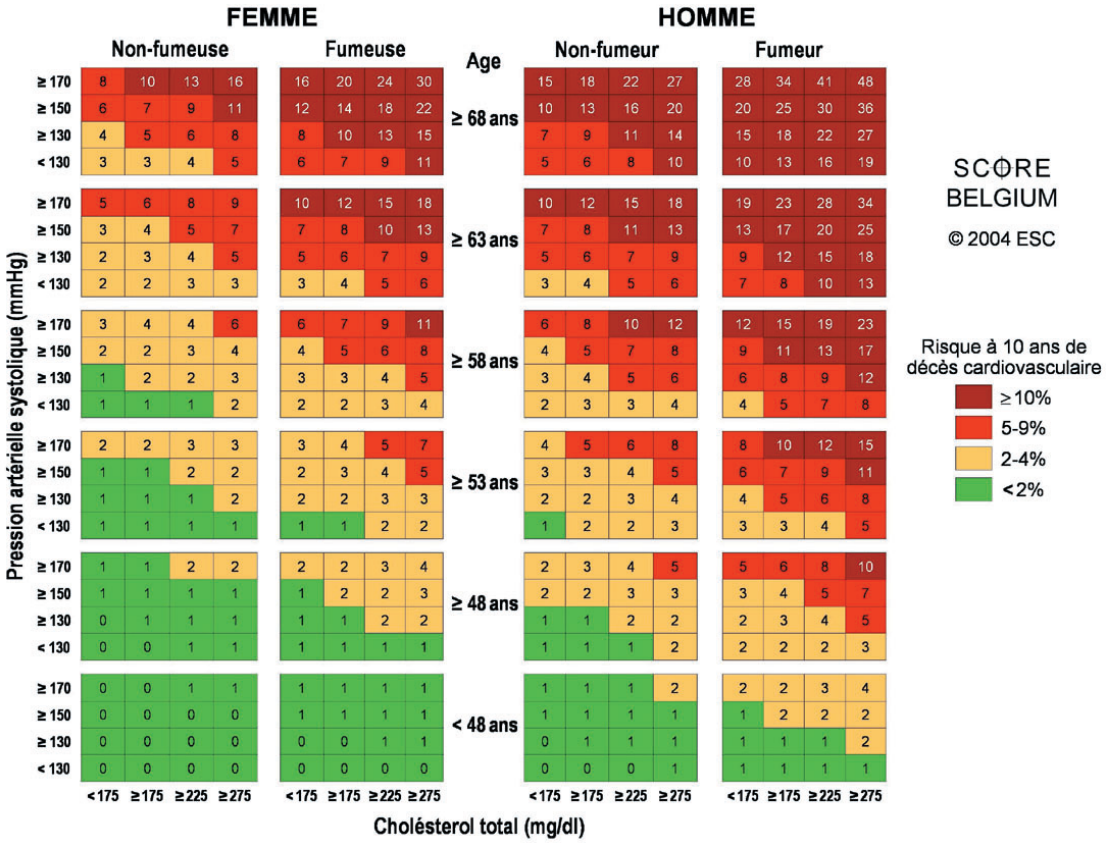
2.2.1 Risk assessment

Because of their similar aetiology and because intervention trials show effects on the different forms of CVD, a global estimate of the CVD risk can be used as a guidance for whether or not to start preventive action.[9] For CVD risk assessment, multifactorial risk models had been developed previously including those originating from the Framingham Heart Study,[21] or the modification by SIGN (ASSIGN score) adjusted for social deprivation.[22] The ESC Committee for Practice Guidelines (CPG) advocates using the SCORE model based on the large European SCORE database.[17] A core element of this CVD risk assessment using the SCORE system is that risk is defined as the absolute 10 year probability of developing a *fatal cardiovascular event*, contrary to the previously used risk for a *composite coronary endpoint*. This obviously implies that the absolute risk thresholds need to be adapted to the new definition.

The risk assessment tables are organised by gender and smoking status, and for each of those four groups the table indicates the 10-year risk estimate based on age, systolic blood pressure (SBP) and either the total cholesterol level or the total/HDL cholesterol ratio. Those risk assessment tables originally came in two versions; one for high risk European countries and another for low risk countries.[9] Originally, Belgium was considered to be in the low risk group of countries but these two versions gave only crude approximations for specific countries; for

Belgium for example the risk would have been underestimated.[14] Therefore, countries were encouraged to develop local versions based on local epidemiological evidence. For Belgium this was done in 2005,[13, 14] and those adapted tables were used in the translated pocket guide versions of the guideline for use in Belgium, while the content of the guidelines remained unchanged.[15, 16] Another important, and easily overlooked, difference is that the original SCORE tables give the risk estimate at a specific threshold, for example at age 60, a SBP of 160 mmHg and a cholesterol level of 200 mg/dl. The Belgian SCORE tables, on the contrary, give average risk estimates for a group, for example for those aged 58 to 62, with SBP of 150 to 170 mmHg and a cholesterol level between 175 and 224. This was a conscious decision by the Belgian national task force,[13, 14] but it slightly changes the interpretation of the charts, for example regarding the *'qualifier'* age. The guidelines, however, were adopted and translated without further modifications of the text (except for translation).

Figure 1: the SCORE chart 'adapted for Belgium' based on total cholesterol levels



The full guideline presents the option of either using the table based on total cholesterol or the table based on the total/HDL cholesterol ratio, but in the pocket guide version only the one based on total cholesterol is presented. The stated reason for this apparent preference for using total cholesterol in the Belgian version rather than the ratio is that although both tables perform equally well for risk estimation in a population, measurement of HDL cholesterol appears to be less reliable, and therefore more subject to errors in risk assessment in clinical practice.[14]

Additional to the risk estimate based on the risk factors described, several so called *'qualifiers'* are mentioned that can increase the risk as estimated by the charts:

- Approaching the next age category
- Obese and sedentary subjects
- Subjects with a strong family history of premature CVD
- Subjects with low HDL cholesterol levels, raised triglyceride levels, impaired glucose tolerance, raised levels of C-reactive protein, fibrinogen, homocysteine,

apolipoprotein B or Lp(a)

- Subjects with pre-clinical evidence of atherosclerosis based on technical assessments (CT, ultrasound, MRI, …)

The 3rd ETF guideline was intended to encourage the development of national guidelines on cardiovascular risk prevention as was done for Belgium with the 2005 adaptation.

2.2.2 Management of CVD risk in Clinical Practice

The 3rd ETF guideline emphasises the importance of prioritization, since preventive efforts are most efficient when they are directed at those at highest risk. Therefore, the priorities are explicitly stated in the following hierarchical order:[9]

1. Patients with established CVD (CHD, peripheral artery disease and cerebrovascular atherosclerotic disease)
2. Asymptomatic individuals at high risk of developing atherosclerotic cardiovascular disease
    - multiple risk factors according to SCORE charts
    - single risk factor with markedly increase level
    - diabetes type 2 or diabetes type 1 with microalbuminuria
3. Close relatives of
    - patients with early onset CVD
    - asymptomatic individuals at particularly high risk
4. Other individuals encountered in routine clinical practice

The guideline stresses the major objectives for CVD prevention in patient with existing CVD or with a high risk. These include not smoking, healthy food choices, increased physical activity, control of overweight and obesity, blood pressure and plasma lipids, and diabetes control. For each of these objectives specific targets are defined. Those targets and recommendation are as much as possible based on available evidence but often mainly based on consensus.

The SCORE charts allow the assessment of the current absolute 10-year risk but they also recommend the extrapolation of future risk at age 60, although the therapeutic consequences of this extrapolation are unclear: there is considerable vagueness in the guideline whether this projection into future age also implies a more vigorous diagnostic and therapeutic attitude at younger ages and, apparently, this will be a topic for discussion during the preparation of the 4th ETF guideline.

In the 3rd ETF guideline, individuals with established CVD are defined as being at high risk regardless of the risk factors in the charts. Also at high risk are those with diabetes type 2 or diabetes type 1 with microalbuminuria and those with markedly high levels (specific thresholds are given in the guideline) of single risk factors. For those individuals the SCORE charts are explicitly not to be used and, according to the guideline, they require the most intensive lifestyle intervention, and where appropriate drug therapies.

Further at high risk are asymptomatic individuals with multiple risk factors resulting in a 10-year risk of fatal CVD ≥ 5% now or extrapolated to age 60 (taking also into account the 'qualifiers'). Those with the highest total risk levels should be identified and targeted for intensive lifestyle interventions and when appropriate, drug therapies.[9]

Specifically for the management of blood pressure and lipids in asymptomatic subjects, the guideline also translates the risk score into specific guidance for appropriate lifestyle and drug therapy interventions. For both these domains, the 5% risk threshold is an important determinant for the further action suggested.

The guideline, however, leaves much room for interpretation and judgement to physicians and patients and in general, practitioners are encouraged not to take mechanistic decisions based on single risk factors or specific arbitrary thresholds. Instead they should use the continuous total CVD risk distribution and the guidelines emphasise the importance of a good mutual

understanding between patient and physician to enable them to take the most appropriate actions for lifestyle interventions and drug therapies. This is, of course, also the result of the consensus process that forms the basis of this guideline; this process leads to a multipurpose guideline searching for a common denominator that suits all parties involved.

2.3 OVERVIEW OF THE DRAFT DOMUS MEDICA GUIDELINE

As in the 3rd ETF guideline, the scope of the guideline is primary and secondary prevention of CVD. The stated objective of this specific guideline for General Practice is to provide a practical tool to allow GPs to quickly identify patients with high CVD risk. The underlying idea is that in CVD prevention GPs need to prioritize and that the largest health gains can be obtained in those high risk individuals. The authors make a clear argument for the important role of the GP in global cardiovascular risk management, but are less clear on the specific reasons for a separate guideline for General Practice. Levels of evidence are mentioned,[a] and are based on a standard scoring system.[20]

2.3.1 Risk assessment

The scope of the draft Domus Medica guideline is similar to the 3rd ETF guideline: the primary and secondary prevention of CVD. The major problem in analysing this draft guideline is effectively that it is at the moment of writing an unfinished draft and therefore subject to changes. We used the version provided by Domus Medica on 9 January 2007, and we will therefore concentrate this discussion on those elements that appear stable and that are markedly different from the 3rd ETF guideline.

2.3.1.1 The SCORE charts

The draft guideline is also based on SCORE (Belgian adaptation), but refers specifically to SCORE based on TC/HDL ratio and this is one of the reasons for the current discussion. No strong reasons for this preference are advanced for this, and in personal discussions one of the reasons appears to be an educative purpose because of a relation of HDL cholesterol with physical exercise, not-smoking and otherwise healthy living. The intended use of the 3rd ETF qualifiers while interpreting the SCORE chart is unclear: although many of the same risk factors are mentioned somewhere in the draft, much information is hidden in footnotes and not readily available in the overview charts. This might change during final layout.

2.3.1.2 The 'Boland' algorithm

The draft guideline proposes to evaluate the CVD risk in men and women between the ages of 40 and 75 years of age. To avoid having to use the table for a proportion of the patients the draft guideline promotes using the 'Boland' algorithm. This is based on earlier work from Boland et al.[18] and used in a variant form by French speaking GPs in Belgium and published with the support of the Communauté Française.

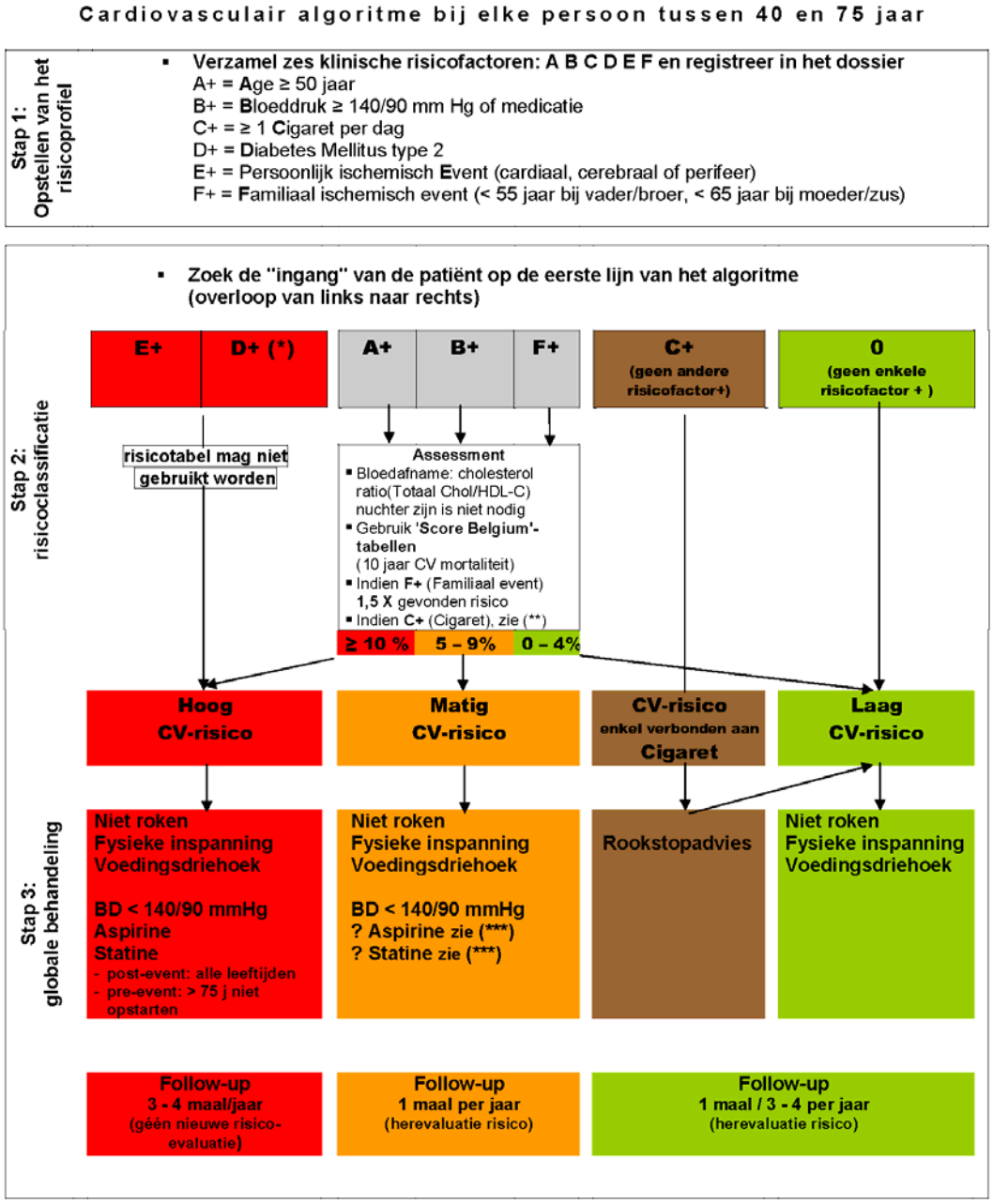
In the original implementation,[18] this algorithm is based on a mnemotechnic system to help the GP remember the risk factors (A=age, B=blood pressure, C= cigarettes, D=Dyslipidaemia, E= Event (CVD), F=Family history, G= Glucose). The algorithm is intended to make it easier for the GP 1) because of the mnemotechnic system and 2) because it would make it unnecessary to look at the SCORE charts for a proportion of patients. The draft Domus Medica guideline state that by using the algorithm, using the SCORE table is not needed in 40% of patients between the ages of 40 and 75, half of them (20%) being obviously at high risk, the other half being obviously at low risk. In the original manuscript that is used as the reference for this statement,[18] a different algorithm was tested, however, and only in men: 17% had a high risk (and would therefore also not be candidates for using the SCORE tables in the 3rd ETF guidelines neither), while only 14% had an obvious low risk and 6% had a smoking related risk.

Therefore, by using this algorithm about 20% of patients, at obvious low risk or with only smoking as a risk factor, should not be evaluated using the SCORE tables in this specific validation

[a] These levels of evidence were, however, not yet complete in the version we used for this assessment.

study in men. This seems to be a low yield for introducing an extra tool. Apart from the obvious advantage of the mnemotechnic aid, the algorithm seems to add little to the ease of use and could, on the contrary increase the complexity of going from patient profile to risk assessment by having to use two instruments rather than only one for the majority of patients. However, during the field test of the draft guideline this was not mentioned as a problem by the participating GPs (personal communication). In previous research using the original version of the algorithm in a randomised evaluation, this algorithm compared well to no training,[19] but its performance was not compared to using only the SCORE charts from the 3rd ETF guideline.

Figure 2: the 'Boland' algorithm in the draft Domus Medica guideline (from draft guideline version 2/3/07)



(*) In het uitzonderlijke geval dat uw diabetes type 2-patiënt jonger is dan 50 jaar en geen andere risicofactoren heeft (B, C, F negatief en ook geen microalbuminurie), zal hij ingedeeld worden in de oranje groep.

(**) Rookstopadvies bij rokers is in alle gevallen dé prioritaire maatregel. Het cardiovasculair risico verbonden aan roken is na 2 jaar rookstop verdwenen. Soms kan rookstop medicamenteuze behandeling overbodig maken of uitstellen.

(***) Overweeg het opstarten van medicamenteuze therapie. De beslissing hangt daarbij af van aan- of afwezigheid van bijkomende risicofactoren (zoals obesitas, sedentarisme), wens en motivatie van de patiënt, alsook comorbiditeit die impact heeft op de levensverwachting

The original algorithm was evaluated with a retrospective analysis in a population-based prospective cohort of 962 CHD free men aged 30-64 years. A main problem, however, is that the so-called 'Boland' algorithm in the draft Domus Medica guideline is very different, both from the original algorithm and from the one used in the 'Communauté Française' (see figure 2 for the

algorithm as proposed in the draft guideline). The main differences are:

- The original system included 7 risk factors, while the draft Domus Medica guideline implementation includes 6, since dyslipidaemia (defined as 'history or use of lipid-lowering medication') was taken out without further reference or obvious validation. On the other hand, the version used in the Communauté Française includes 8 risk factors,[23] because BMI was added to the original 7 risk factors. As a minor complication the meaning of the letters changed in all versions because of the changes in number of risk factors included and because of language differences.
- For the 6 risk factors that were included in the draft guideline, the thresholds have changed from the original version for age of individual and the age of the relative for family history
- In the validation of the original algorithm (in men only), the British CAD risk assessment chart was used,[24] instead of SCORE.

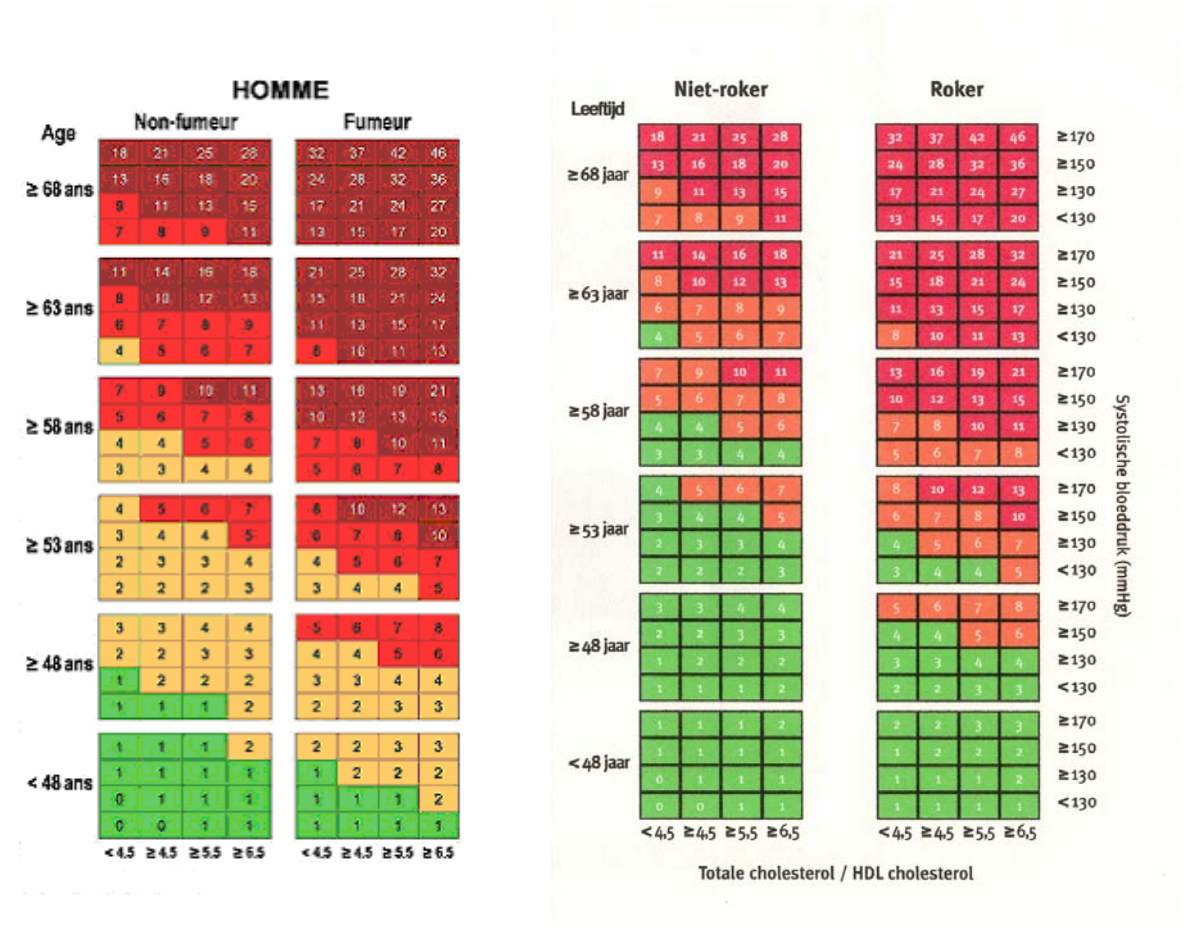
Because of this additional algorithm there is no a-priori need to check cholesterol levels in patients where no other risk factor is present. In practice this would cause only marginal differences in the ultimate interpretation. In the SCORE charts cholesterol levels have little influence on the ultimate risk assessment at ages below 50 and in the absence of increased blood pressure, especially in non-smokers and only in a few marginal situations this would have any influence on risk classification. However, the inclusion of what the 3rd ETF guideline calls the *'qualifiers'* could cause some different interpretations (see higher), but this is not yet clear from this draft version. Finally, it should also be emphasized that this draft was not intended to be a guideline on the case finding of hypercholesterolaemia; the guideline recommends that in those cases the patient should be referred to specialist care. A possible advantage of this algorithm is the strong emphasis on the potential impact of smoking cessation.

2.3.2 Management of CVD risk in Clinical Practice

2.3.2.1 The threshold for 'high risk'

In the draft Domus Medica guideline the threshold for high risk is set at 10% ten-year risk for a fatal CVD event, while in the 3rd ETF guideline it was set at 5%. The most obvious consequence of using another threshold value is that the SCORE card proposed, is much greener than the chart from the 3rd ETF, giving a very different visual impression (see figure 3) although showing exactly the same numbers.

Figure 3: the original SCORE chart (adapted for Belgium) from the 3rd ETF to the left and the chart proposed by Domus Medica for men on the right based on the total/HDL cholesterol ratio



Several arguments are proposed for this different threshold, but an important argument is psychological. While the therapeutic consequence in the draft Domus Medica guideline for individuals with a risk between 5 and 9% is that they will receive recommendations for lifestyle interventions and possibly (depending on other risk factors) pharmaceutical interventions, it is feared that a 'high risk' label would induce the patient to always expect pharmaceutical intervention. Therefore, the authors argue that this is more than a semantic discussion about classifications. The underlying discussion is obviously also an important health economic discussion: how many people qualify for each of these risk categories, and what would therefore be the budget-impact and the cost-effectiveness of treatment in each of those categories. We will return to this discussion later.

2.3.2.2 *Guidance for risk management*

Guidance on actions to take are much more directive and detailed than in the 3rd ETF guideline for those at an estimated risk of 10% and higher, while the 3rd ETF guideline is less directive and leaves those issues more to the decision of physicians and patients, probably due to the consensus process leading to this guideline. For the group with a risk below 10%, on the contrary the draft Domus Medica guideline is less rigid, proposing lifestyle interventions and to consider pharmaceutical intervention if other risk factors are present. However, the draft guideline in this stage was clearly unfinished in this respect and will probably become more balanced and consistent in further versions.

2.4 RECENT DEVELOPMENTS

2.4.1 Future 4th ETF guideline (Fourth European Task Force)

It is anticipated that in early September 2007 the guideline from the Fourth Task Force will be presented at the ESC conference. From personal communications it can be anticipated that this revision will confirm the main content of the current guideline but their might be some revisions on specific details:

- More attention for glucose metabolism disturbances and on BMI and obesity
- Less emphasis on the 5% threshold, and more attention to an increasingly aggressive response at increasing levels of the continuous CVD risk
- Less emphasis on the extrapolation to the age of 60 years old for treatment initiation at early ages
- The international GP organisation (WONCA) had reportedly expressed concern about the level of the 'high risk' threshold and it's endorsement of the guideline will depend on whether the expressed concerns are answered (personal communication Thierry Christiaens, 16 february 2007)

2.4.2 Recent guidelines in surrounding countries

In the Netherlands, both the NHG (Nederlands Huisartsengenootschap) and CBO released guidelines on cardiovascular risk management in 2006.[25, 26] Those guidelines are for the risk assessment based on the SCORE charts (calibrated for the Netherlands). They do not classify the levels of risks in low, intermediate or high, but they recommend lifestyle interventions for everybody and mostly no pharmaceutical intervention for risk levels below 5% ten-year fatal CVD risk. They further recommend that at risk levels between 5 and 10% pharmaceutical intervention should only be considered if additional risk factors are present, such as the '*qualifiers*' from the 3rd ETF. At risk levels of 10% and more, most often pharmaceutical intervention is indicated according to those guidelines.

In the UK, the Scottish SIGN released a guideline in February 2007,[22] while the Prodigy guideline was updated in October 2006.[27] The Joint British Societies' Guideline was updated in December 2005.[28] Those guidelines use a risk assessment based on the 10-year risk for any CVD event (fatal or not). Both use risk assessment charts (and calculators) that are based on the formulae from the Framingham study, but in the SIGN guideline, these formulae were adapted to included indicators on social deprivation (the ASSIGN score). Persons at high risk are in those guidelines defined as those having a CVD risk of 20% or higher.

Considering specifically the use of statins, NICE released a guidance on the primary and secondary prevention of CVD[29] based on a full report from the Sheffield ScHARR.[30] Statin therapy is recommended as part of the management strategy for the primary prevention of CVD for adults who have a 20% or greater 10-year risk of developing CVD. A clinical guideline on cardiovascular risk assessment is currently in development and is expected to be published in September 2007.

2.5 TOTAL CHOLESTEROL OR THE RATIO OF TOTAL/HDL CHOLESTEROL?

The 3rd ETF guidelines present SCORE charts for either total cholesterol or for the ratio total/HDL cholesterol. Both charts are described as performing equally well for the classification of the population at specific risk levels. So the choice would logically be a pragmatic one. Moreover, in most cases both total cholesterol and the ratio are readily available.

During the preparation of this report, concern was expressed by external experts that the technique for measuring HDL cholesterol has fundamentally changed since the second part of the nineties, when the SCORE algorithm was developed. The HDL measurement was reported to be rather imprecise when the older selective precipitation technique was used, with high coefficients of variation.[31] Recently the selective precipitation method has become less popular and the

technique of homogeneous assays was introduced in many Belgian laboratories, allowing for a further automation of the HDL measurement in the laboratory. Although this technique enhances the standardization of the measurement of lipoproteins, it is reported by some to give on average higher values than the previous test on which the SCORE charts were based. This would obviously call for a recalibration of those charts.

We checked this assertion in the literature and with several experts in clinical biology. The improved precision is indeed well reported in the literature,[32] and is also obvious from the quarterly external quality audits performed by the Belgian Institute of Public Health (WIV-ISP).[31] But, evidence about a systematic bias is incoherent. A direct comparison in diabetic and non-diabetic patients published in 2002 and 2004 reported a positive bias, especially at low HDL cholesterol levels, sufficiently great to affect cardiovascular risk assessment.[33, 34] In an early assessment in the Netherlands by Cobbaert et al. a positive bias was seen of around 6% at the level of 500 mg/L.[35] The performance of those tests is monitored by the Cholesterol Reference Method Laboratory Network (CRMLN) that uses reference methods and designated comparison methods (HDL-C reference method),[32] that are rigorously standardized to the CDC reference methods. One of the CRMLN labs is located at the Erasmus MC, Rotterdam, where the homogeneous HDL assay was introduced very early (1996). No major problems of bias were observed there, with a negative bias of maximal 1%. In the meantime, the lyophilised homogeneous assays have been replaced by newer generations of liquid homogeneous assays. Small biases were observed in both directions, but always below 5% (Robert De Jonge, Erasmus MC, personal communication). The importance of checking the CRMLN certification for specific reagents is also emphasized.[36] Other experts reported that biases mainly occur in samples with atypical lipoprotein characteristics and hypertriglyceridaemia and that monoclonal paraproteins are important interfering factors leading to a positive bias in the measurement.[36] In the Dutch CBO guideline, the ratio was used for the risk charts, and no questions were raised concerning this problem.[25] Also in the UK guidelines the risk assessment are based on the ratio.

2.6 THE 5 OR 10% RISK THRESHOLD: A SOCIETAL DISCUSSION

2.6.1 Equivalence of assessments

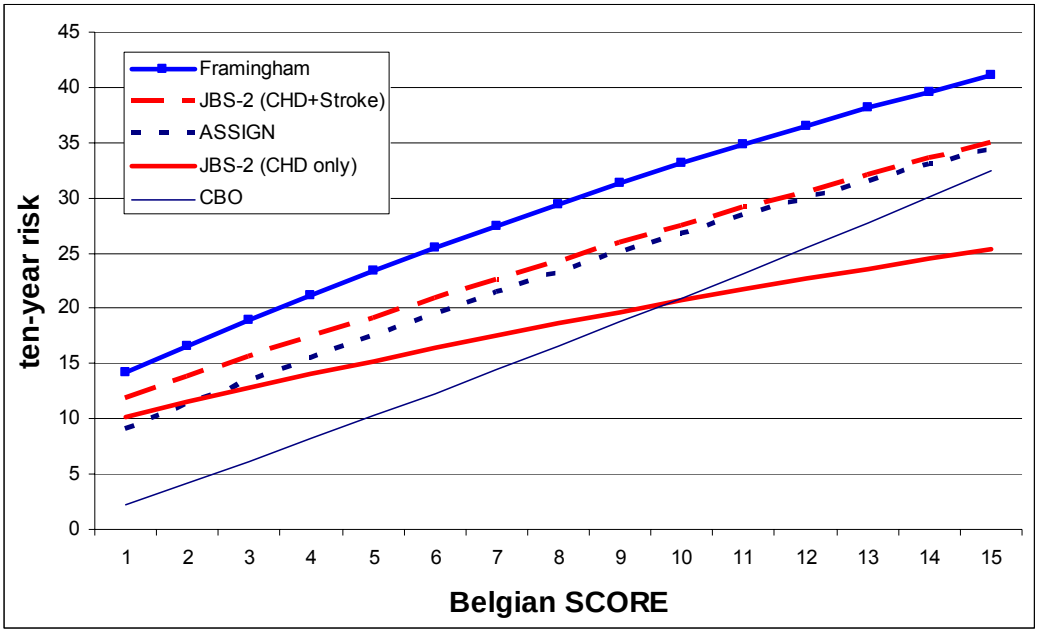
2.6.1.1 Different risk assessment schemes

An important part of the current discussion about thresholds is how the 20% risk for CHD from Framingham translates into the SCORE risk assessment for fatal CVD. In the Guideline from the 3rd ETF it was stated, without much evidence, that this 20% risk for a composite coronary endpoint was roughly equivalent to 5% risk for a fatal CVD. According to a report for the Belgian minister of health,[37] using the SCORE threshold of 5% would lead to substantially fewer patients at high risk than using the Framingham composite coronary risk threshold of 20%, under the condition that current risk was calculated, and not the risk extrapolated to the age of 60 years. This report, however, was based on the low risk SCORE and not yet on the recalibrated Belgian SCORE that gives a higher risk assessment. For its guideline on cardiovascular risk assessment the CBO assessed this question using a model and they published next to the original SCORE charts (adapted for the Netherlands) also the morbidity risk for MI and stroke. In these charts a 20% risk for MI or stroke corresponded to a 10% risk in SCORE,[25] and in general in this CBO document a conversion factor of approximately 2 was used for all ages and categories.

To further address this question we assessed the risk for 80 hypothetical patients (men/women, smoker/non smoker, 50/55/60/65/70 years of age, and systolic blood pressure of respectively 120, 140, 160 or 180 mmHg). Those patients were assessed using two risk calculators from the UK. We first used the Coronary Heart Disease Event and Stroke Risk calculator available from the British Hypertension Society (http://www.bhsoc.org/Cardiovascular_Risk_Charts_and_Calculators.stm), recommended in the JBS-2 guideline.[28] This calculator gives the risk for CHD and for stroke separately. We also used the Cardiovascular Risk Assessment Score from SHHEC ASSIGN,[22] available at http://assign-score.com/calculate.asp (with SIMD Scottish Index of Multiple Deprivation (SIMD) put at 20 as recommended when it is unknown). This calculator gives the CVD risk as estimated for Scotland, alongside the original Framingham score. We compared the 4 results of these 2 risk calculators with the equivalent Belgian SCORE risk assessment. Since the British calculators depend on the

Total/HDL cholesterol ratio, we used the SCORE chart for the ratio, with a ratio of 5 for all patients. We additionally included the CBO conversion as published in the CBO consensus document.[25]

Figure 4: comparison of Belgian SCORE with results from 2 risk calculators and the CBO conversion.



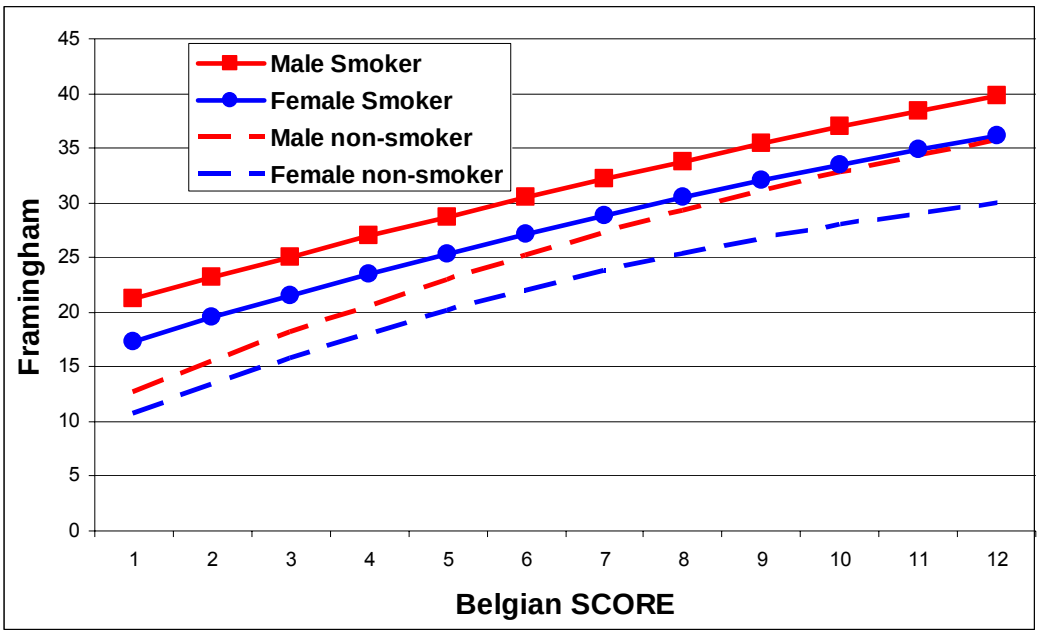
The Framingham and the JBS-2 (CHD only) refer to CHD risk. The other curves refer to CVD risk. Time horizon is 10-year risk for any event. For the Belgian SCORE the time horizon is also 10 years, but this refers to the risk for a fatal CHD event.

There is a striking difference between the different risk assessments by the various methods as can be seen in figure 4. In Framingham a 20% risk corresponds to a SCORE value of 3.5%. For the composite (CHD + stroke) from JBS-2, 20% corresponds to a SCORE of 5.5%. For the ASSIGN score the corresponding SCORE value is 6.3% while for the CHD only assessment it is 9.3%. For the CBO assessment, a 20% CVD risk corresponds to a SCORE of 9.6%. Therefore, any comparison clearly depends on the risk assessment technique used. This observation also concurs with the results from the Belgian simulation study that concluded that with a SCORE threshold of 5% fewer patients would be labelled high risk than with the previous Framingham assessment using a 20% threshold.[37]

2.6.1.2 Heterogeneity

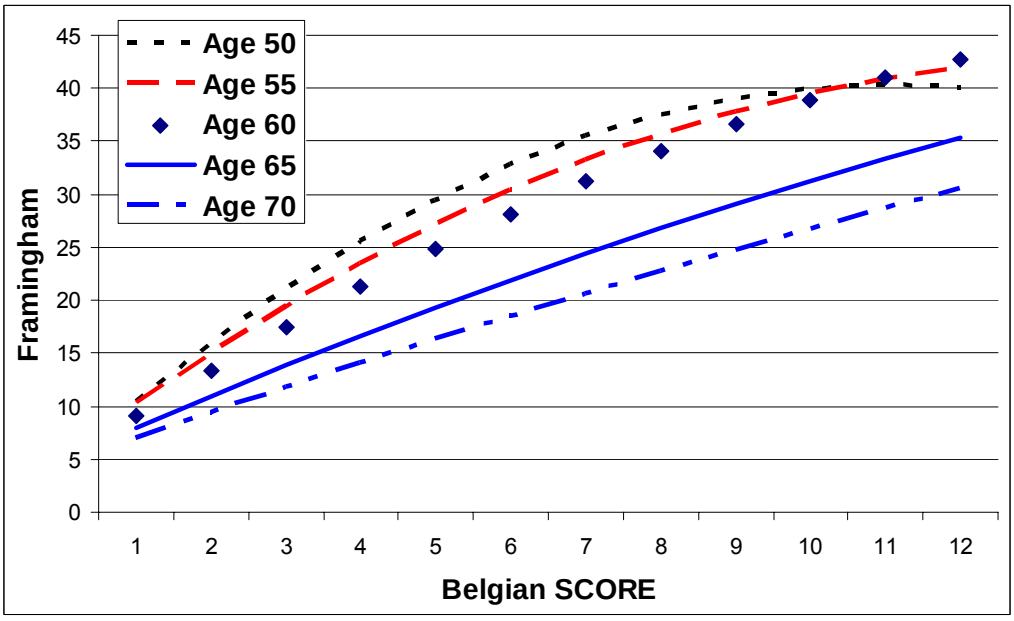
Another observation, apart from the important differences, is that most curves in figure 4 (except for the CBO curve) do not converge to the origin. Instead, at a SCORE level of 0, most curves are still at CHD risk levels of 7 to 12%. This is due to a considerable heterogeneity in those data. Figure 5 shows a stratified analysis by gender and smoking status comparing the Framingham risk assessment with the Belgian SCORE. This figure shows that both smoking status and male gender have a heavier weight within the Framingham assessment than in the Belgian SCORE. It also shows that a 20% Framingham risk corresponds with SCORE values going from 0.4% tot 5%.

Figure 5: Framingham risk assessment vs. Belgian SCORE, stratified by gender and smoking status.



Age is an even more important source of heterogeneity. Figure 6 shows the relation of the Framingham risk assessment with Belgian SCORE by age. At age 50, the average ratio Framingham/Belgian SCORE is close to 9, by age 60 this has decreased to 5 and at age 70 the average ratio is around 2.4. At age 50 a 20% ten-year risk calculated by the Framingham formula, corresponds to a SCORE (fatal event risk) of approximately 3%. At age 60 this is around 4% and at age 70 this has increased to a SCORE of 7%. But, also those approximations are still confounded by gender, smoking status and probably other confounders.

Figure 6: Framingham risk assessment vs. Belgian SCORE, stratified by age.



2.6.1.3 Conclusion

Unfortunately, there is no easy conversion rule between the original Framingham risk assessment (or other risk assessments of CVD) and the SCORE assessment. The reason is that the weights of the risk factors depend on the different assessments, and moreover, that SCORE measures a completely different outcome, i.e. fatal CVD. Most important to keep in mind, however, is the age effect: the ratio between the two measures decreases with ageing.

2.6.2 Thresholds, interventions and economic assessment

Choosing a given threshold of risk is by nature an arbitrary decision. In general the intervention build-up will be gradual: the higher the risk the more vigorous the intervention. But labelling a patient as being at 'high risk' also has important consequences by transforming an apparently healthy individual into a patient. It can, especially in general practice, also be a handicap since it might be difficult to argue that although a patient is labelled high risk, lifestyle changes are the first option and not medication.

All guidelines mention the importance of lifestyle interventions as a first step in CV risk management. Next to these, 4 interventions form the cornerstone of CVD risk management in primary prevention and in populations without diabetes: lipid management (cholesterol modification), blood pressure lowering, anti-platelet aggregation therapy, and of course smoking cessation. There is evidence that these interventions benefit almost all populations to some degree, and that the relative risk reductions are comparable in different populations independently of the levels of the risk factor or the pre-treatment absolute risk.[29, 38] Smoking cessation is obviously an exception as it can only be applied to smokers.

Therefore, anybody could in theory benefit from those interventions, but since the relative risk reduction is similar, the absolute benefit will be dependent of the pre-treatment absolute risk, and treating a large proportion of the population would also require large budgets. For Belgium it was estimated that, for individuals in the age range of 40 tot 65 and based on current risk around 210 000 men and 37 000 women would be in the high risk group as defined by the original low risk SCORE (not the Belgian SCORE) threshold of 5% or more.[37] When not the current risk, but the risk extrapolated to age 60 would be used this population would increase dramatically with 530 000 men and 46 000 women falling in this category. It is, however, understood that this extrapolation to 60 years of age was intended primarily as a tool to influence lifestyle, rather than for the initiation of a pharmaceutical intervention. A Norwegian study also estimated this proportion of the population that would be at high risk, using the high risk SCORE chart from the 3rd ETF guideline: at the age of 40 almost 86% of men would be catalogued high risk, but in this result the risk factors were all extrapolated to the age of 60 years.[39]

Based on the same sources,[37] on personal communication from Prof. De Bacquer and on our own calculations using population data from the year 2005, we estimated that the number of individuals between age 40 and 65 with a risk above the 5% threshold based on the Belgian SCORE would be around 450 000 (340 000 men). Using a 10% threshold would dramatically reduce this number to 80 000 (72 000 men). This would also result in a shift towards older ages.

Therefore, the choice of threshold values essentially depends on health economic arguments and societal choices. Chapter 4 gives an overview of the recently performed cost-effectiveness analyses and the implication for choices in Belgium.

Key points

- **The existing guideline from the 3rd ETF and the draft Domus Medica guideline are largely based on the same principles, risk factors and risk assessments.**
- **The main differences are: 1) the draft Domus Medica guideline used an additional implementation algorithm, 2) it recommends using the ratio of total cholesterol over HDL cholesterol, rather than total cholesterol and 3) the threshold to label an individual to be at high cardiovascular risk is set at 10% fatal ten-year CVD risk, compared to 5% in the 3rd ETF guideline.**
- **The measurement of HDL cholesterol in Belgian laboratories is more precise than previously, but there is concern that there might be an overestimate, especially at low levels of HDL, biasing the comparison with previous results. Evidence about a systematic bias is incoherent and test-specific. However, the possible bias is reported to be too small to cause any significant effect on risk classification.**
- **There is no easy conversion rule from risk assessments using any coronary, or any CVD risk to risk assessments using the risk for a fatal event, as these conversions depend on gender, smoking status and especially on age.**
- **The choice of a threshold has a very important impact on the number of people classified to be at high risk. In the age groups 40-65 years, a 5% SCORE threshold corresponds to approximately 450 000 individuals, a threshold of 10% corresponds to approximately 80 000 individuals.**

3 EFFECTIVENESS OF PRIMARY PREVENTION OF CV DISEASE

3.1 INTRODUCTION

The cause of cardiovascular atherosclerotic disease is only partially understood. Its occurrence is linked to certain patient characteristics that seem to influence the development of disease or that are associated with it. Several of these characteristics, called "risk factors", have been identified. Some of these are modifiable, such as raised LDL-cholesterol levels, arterial hypertension, cigarette smoking, diabetes mellitus, reduced HDL-cholesterol levels and sedentary lifestyle. Others are non-modifiable personal characteristics, such as age, male gender or family history of early onset cardiovascular disease (CVD). In addition to these 'classic' risk factors, several other variables have been proposed as predictors of CVD: left ventricular hypertrophy, infectious agents, markers of inflammation, oxidative stress, increased levels of fibrinogen, triglycerides, homocysteine, lipoprotein-a and many other. Socio-economic factors also play a role. Convincing evidence shows that the risk for myocardial infarction (MI) and stroke declines after smoking cessation, when blood pressure is lowered and, cholesterol levels are reduced.

Risk factor interventions traditionally have been divided in secondary and primary prevention targeting well-defined populations: either patients known with occlusive arterial disease or people without any overt or known cardiovascular problem in whom the aim is to prevent the occurrence of cardiovascular disease. The concept of primary prevention is important because in about 50% of cases, coronary heart disease (CHD) presents itself as acute MI or sudden cardiac death as its first manifestation.[40] Depending on the presence of one or more risk factors, asymptomatic patients can be classified according to their risk to develop CVD. The risk is greatest when a combination of several risk factors is present: several individual risks are not added to one another but they interact multiplicatively. This has lead to a changing paradigm of cardiovascular risk stratification in which not so much single risk factors are considered but where the entire risk profile of a patient is taken into consideration leading to the concept of a global cardiovascular risk.

Both arterial hypertension and serum cholesterol levels show a continuous relation with the risk of developing CHD. Some authors, recognising cardiovascular disease risk as a continuum, have challenged the traditional concept of primary and secondary prevention and only refer to the risk certain patients run to develop cardiovascular disease. The rationale for this position is not only that a first manifestation of cardiovascular disease can be an acute MI or sudden death, but also that most cardiovascular events occur in patients at an intermediate level of absolute risk; they have indeed a lower risk but there are many more of them. Also, the fact that cardiovascular disease will affect the majority of the (Western) population at some point in their lifetime implies that any adult is at risk and hence, is a potential target for cardiovascular preventive measures which poses substantial organisational, ethical and economic problems. Patients with a history of cardiovascular disease have a certainty to be at high risk (their cardiovascular risk = 100%) for developing cardiovascular disease and are therefore good candidates for (multiple) risk factor intervention, i.e. secondary prevention. Thus, the categorization of patients into primary and secondary prevention subgroups or rather on a continuous risk-spectrum renders the discussion rather semantic (see figure 7).

Patients with type 2 diabetes are at high risk of developing cardiovascular disease. Haffner et al.[41] showed that diabetic patients without previous MI have as high a risk of MI as non-diabetic patients with previous MI. This observation provides the rationale for treating cardiovascular risk factors in diabetic patients as aggressively as in non-diabetic patients with prior myocardial infarction.

Figure 7: schematic overview of the prevention of CVD

1	PRIMARY PREVENTION in NON-DIABETICS	PRIMARY PREVENTION in DIABETICS	SECONDARY PREVENTION

2	PRIMARY PREVENTION in NON-DIABETICS	HIGHEST RISK

3	LOW RISK	HIGH RISK	HIGHEST RISK

A further change in perspective that has been noted in recent years is that the focus of risk factor intervention has been extended from coronary heart disease to the whole spectrum of atherosclerotic vascular disease, encompassing acute coronary syndromes, stable angina, cerebrovascular disease and peripheral atherosclerotic disease. This enlargement of the target population is justified by the fact that scientific evidence has shown that any symptomatic manifestation of atherosclerosis in any vascular territory puts a person at high risk of dying from cardiovascular disease (CVD), mainly from coronary artery disease. One of the practical consequences of this policy was that guidelines on prevention of cardiovascular disease nowadays are mostly edited jointly by different specialist societies: e.g. the Joint British Societies' Guidelines on Prevention of Cardiovascular Disease were prepared jointly by the British Cardiac Society, the British Hypertension Society, Diabetes UK, Heart UK, the primary care Cardiovascular Society and The Stroke Association.[28]

The concept of what used to be denoted as secondary prevention, nowadays refers to treating patients who already developed any cardiovascular problem or who present themselves – even asymptomatically – with type 2 diabetes. In primary prevention people at lower cardiovascular risk are considered.

3.2 SCOPE

Although we fully endorse the concept of "total cardiovascular risk management", we will in this chapter concentrate on lipid management in primary prevention through either dietary interventions as recommended by all guidelines or through the use of statins. Throughout the LDL cholesterol range in Western populations, lower blood concentrations are associated with lower cardiovascular disease risk. Early trials of cholesterol-lowering were not convincing because the available interventions (drugs or diet) lowered cholesterol to only a modest degree, the interventions were not well-tolerated, or the studies lacked adequate statistical power. With the development of statins, large reductions in cholesterol concentrations were more easily and safely achievable.[42] This finding led to a series of trials that demonstrated, especially in populations at high cardiovascular risk, that reducing LDL cholesterol diminishes the development of vascular disease, largely irrespective of initial cholesterol concentrations. Because statins have become the most prescribed lipid lowering drugs, because of the inconsistent results of their effectiveness in primary prevention, and their potential impact on health care resources, we opted to limit our review to the clarification of the role of statins in primary prevention as defined higher and on dietary interventions.

3.3 METHODOLOGY

No full systematic review (SR) of the clinical literature has been performed for this rapid assessment. We started our search by studying the two most recently published guidelines (NHS in 2005/2006 and SIGN in 2007) on prevention of cardiovascular disease.[29, 22] Furthermore, a

limited literature search was performed through Medline (PubMed), Cochrane, SUMSearch and DARE for RCTs and SRs published in 2006 and 2007 and earlier if needed. Our interest for the clinical effectiveness of risk factor interventions focused on dietary interventions and on statins. The reference tables of the retrieved papers were examined for further relevant information. The search strategies including the subject headings used can be found in appendix.

3.4 DIETARY INTERVENTIONS IN PRIMARY PREVENTION

Several lifestyle modifications have been advocated to prevent cardiovascular disease, both in asymptomatic individuals and in patients with established CVD. In this part, we will briefly review current knowledge on the effectiveness of dietary interventions that are commonly recommended in primary prevention.

The first evidence of the impact of nutrition on CVD came from observational studies indicating a link between dietary patterns and subsequent cardiovascular events. Most intervention studies carried out later on, studied the effect of dietary modifications on risk factors for coronary heart disease. The resulting effects on these risk factors were then related to the cardiovascular disease impact obtained in other risk factor intervention trials, an extrapolation that may not be warranted. What matters is not how intermediary endpoints can be altered by dietary measures but rather to what extent myocardial infarction and stroke can be prevented.

3.4.1 Saturated fat

The most commonly advised dietary intervention for preventing cardiovascular disease is a low saturated fat diet which aims to modify serum lipid levels and is expected to affect cardiovascular morbidity and mortality. A Cochrane review, published in 2000 and updated in 2005, examined the effect of a change in dietary fats on these hard endpoints[43] Twenty seven studies were included (40 intervention arms, 30 901 person-years). There was no significant effect on total mortality (rate ratio 0.98, 95% CI 0.86-1.12), a trend towards protection from cardiovascular mortality (rate ratio 0.91, 95% CI 0.77-1.07), and significant protection from cardiovascular events (rate ratio 0.84, 95% CI 0.72-0.99). This effect was not statistically significant if studies with a high risk of bias were excluded in sensitivity analysis. Trials with at least two years follow-up showed significant reductions in the rate of cardiovascular events (rate ratio 0.76, 95% CI 0.65-0.90). The degree of protection from cardiovascular events appeared similar in high and low risk groups, but was statistically significant only in the high risk group. It should be noted that from the 27 trials included in this meta-analysis, seven included only people at high risk of CVD and all these high risk trials included men only. The authors conclude that a sustained (at least 2 years) reduction or modification of dietary fat intake leads to a small but potentially important reduction in cardiovascular risk.

The Women's Health Initiative Randomized Controlled Dietary Modification Trial (referred to hereafter as WHI-trial) tested the hypothesis that a dietary intervention, intended to be low in fat and high in vegetables, fruits, and grains would reduce the risk of breast cancer and colorectal cancer in postmenopausal women. It is the largest long-term RCT of dietary interventions ever conducted and included 48 835 women followed over a mean of 8.1 years. A secondary aim of the study was to test whether such a dietary intervention (which did not focus on the intake of specific fats) would also reduce the risk of CVD. The results of the latter analysis were published in 2006.[44] Most women included had no known CVD at baseline. By year 6, mean fat intake decreased by 8.2% of energy intake in the intervention vs. the comparison group, with small decreases in saturated, monounsaturated, and polyunsaturated fat. Increases occurred in intakes of vegetables/fruits (1.1 servings per day) and grains (0.5 serving per day). The diet had no significant effects on incidence of CHD (HR 0.97; 95% CI, 0.90-1.06), stroke (HR, 1.02; 95% CI, 0.90-1.15), or CVD (HR, 0.98; 95% CI, 0.92-1.05). These rather disappointing results were explained by the fact that the dietary intervention focused mainly on a lowering on total fat intake which led to only very small reductions in LDL-cholesterol. Unfortunately, the intervention did not test current dietary guidelines, which focus less on total fat intake and more on saturated fats and cholesterol intake.

It is important to consider how much cholesterol lowering can be obtained, solely by giving dietary advice to asymptomatic people. As discussed earlier, the Cochrane Review suggests that health promotion activities, aimed at sustained rather than temporary dietary changes in the

general population are needed. However, these have not been very successful.[43] This is illustrated in some way by the WHI-trial which shows that major efforts are needed to obtain a rather modest long-term effect on dietary habits, even in a clinical trial environment, incorporating motivated patients and personnel. This trial involved an intensive behavioural modification program with 18 group sessions in the first year and quarterly maintenance sessions thereafter, led by specially trained and certified nutritionists. Group activities were supplemented during the intervention period by individual interviews that used validated reflective listening techniques, targeted-message campaigns, and personalized feedback on fat intake. Individual contacts were completed by telephone or mail. In this way, at year 6, an 8.2% reduction in total fat intake and a mean daily increase of 1.1 servings of vegetables and fruits and 0.5 serving of grains were achieved.

In an older trial individual dietary advice was provided to different groups of patients by a dietician using a diet history, a practice nurse using a structured food frequency questionnaire, and a detailed diet leaflet sent by post. All three groups were advised to limit the energy provided by fat to 30% or less and to increase carbohydrate and dietary fibre. No significant differences were found at the end of the trial between groups in mean concentrations of lipids. After data were pooled from the three groups, the mean total cholesterol concentration fell by only 1.9%.[45]

In its latest guideline, SIGN is rather vague in its recommendations on how to give dietary advice: "Interventions to improve diet should be based on educational competencies: improved knowledge, relevance, individualisation feedback, reinforcement and facilitation".[22] How this is to be further implemented by health workers confronted with sometimes poorly motivated people is not further elucidated.

3.4.2 Fruit and vegetables

The evidence of the beneficial effect of eating more fruit and vegetables on the occurrence of MI and stroke results from observational studies. These suggest that a 14 to 23% relative risk reduction of CVD in people consuming high levels of fruit and vegetables (corresponding to approximately 8 servings per day of fruit and vegetables) compared to those consuming low levels.[46, 22] There are no RCTs on this subject which means that the size and nature of any real protective effect is uncertain. The observed associations could be the result of confounding as people who eat more fruit and vegetables often come from higher socioeconomic groups and have other healthy lifestyles.[47]

3.4.3 Antioxidants

A meta-analysis of RCTs of vitamin supplementation identified a lack of any statistically significant or clinically important effects of vitamin E on CVD.[48, 22] Very recently, the American Heart Association (AHA) issued new guidelines on the prevention of CVD in women.[49] They no longer recommend antioxidant vitamin supplements such as vitamins E, C and ß-carotene. Folic acid, which was recommended in the 2004 guidelines, is no longer judged useful in preventing CVD. Several RCTs suggested that vitamin E and ß-carotene may be harmful.[47] and a recent meta-analysis of several antioxidant supplements for primary and secondary prevention in general concludes that treatment with ß-carotene, vitamin A or vitamin E may increase mortality[50].

3.4.4 Omega-3 fatty acids

Consumption of long chain omega-3 fatty acids (eicosapentaenoic acid, docosapentaenoic acid, and docosahexaenoic acid) found in fatty fish and fish oils has been linked to the low incidence of coronary heart disease in the Inuit people of Greenland. α-linolenic acid, a shorter chain omega-3 found in some plant oils may also be protective. Otherwise, toxic compounds, such as fat soluble methylmercury and dioxins are also found in fatty fish and fish oils. These substances may increase the risk of cancer and myocardial infarction and cause neurological damage.

There is conflicting evidence on the benefits associated with increased consumption of omega-3-fats. Cohort studies suggested that omega-3-fats would reduce total mortality. This was not supported by a SR of studies on benefits and risks of omega-3 fats for mortality, CVD and cancer. Dietary supplements were given in 44 trials (either as capsules, as oil, or as a liquid emulsion and enriched margarine), advice on eating fatty fish in three, and advice on diet and food supplements in one. Hooper et al. concluded from their meta-analysis that omega-3 fats do not have a clear

effect on total mortality, combined cardiovascular events, or cancer.[51]

In a systematic review on the effect on mortality combining both primary and secondary prevention studies of different antilipidaemic agents and diets, Studer et al found a risk ratio for overall mortality of 0.97 (95% CI 0.91-1.04) for diet and 0.77 (95% CI 0.63-0.94) for omega-3 fatty acids. For cardiac mortality, the risk ratio indicated a benefit for omega-3-fatty acids compared with control groups: RR 0.68 (95% CI 0.52-0.90). This SR included only one small trial on omega-3 fats in primary prevention, which showed no benefit on overall mortality.[52]

In the 2007 guidelines on the prevention of CVD in women, issued by the American Heart Association very recently, women are recommended to consume a diet rich in fruits and vegetables and consume fish, especially oily fish, at least twice a week. The latter advice is supplemented however with the following warning: "Pregnant and lactating women should avoid eating fish potentially high in methylmercury (e.g. shark, swordfish, king mackerel, or tile fish) and should eat up to 12 oz/wk of a variety of fish and shellfish low in mercury and check the Environmental Protection Agency and the US Food and Drug Administration's Web sites for updates and local advisories about safety of local catch."[49]

In their most recent clinical guideline, SIGN laconically recommends the following relating to omega-3-fats: "In view of this uncertain effect and in order to avoid conflicting dietary advice, no change is recommended from the advice given in the current dietary guideline (two 140 g portions of fish, one of which should be fatty fish, per week".[22]

3.4.5 Plant sterols

Plant or phytosterols and stanols (saturated sterols) reduce absorption of cholesterol by interfering with the solubilisation of the cholesterol in the intestinal micelles. They also reduce the absorption of some fat soluble vitamins such as certain carotenes.

Regular and even daily ingestion of plant sterol or stanol supplements in margarines, milk products and other foods is currently being mass marketed.[53-55] In marketing campaigns – some of them endorsed by the patient association Cardiovascular Ligue, Domus Medica and the Professional Unions of Flemisch and Frenchspeaking Dieticians - a hypocholesterolaemic effect is claimed and a beneficial effect on cardiovascular disease is suggested.

Recent systematic and narrative reviews indeed provide evidence for the effect of plant sterols (1.5 to 2g/d) on the biochemical lipid profile of both healthy people and of subjets with familial hypercholesterolemia.[56-59] In general, a reduction of especially LDL-cholesterol of 10-15% is found in most RCTs.

The effect of phytosterols on the incidence of coronary heart disease is unknown. Furthermore, no clinical trials showing an effect on hard clinical outcomes such as cardiovascular events and mortality were retrieved. Well-designed studies with long-term relevant clinical outcome data are thus needed. A Cochrane review on the effectiveness of supplemental plant sterols and stanols for serum cholesterol and cardiovascular disease is planned.[60]

Published post-market monitoring program data from consumer complaints by a major food company showed no hazards related to the daily ingestion of phytosterols.[61] There has been some concern that high doses of phytosterol supplementation could inadvertently increase cardiovascular risk: in patients with phytosterolaemia, a rare genetic disease, phytosterols are overabsorbed and they develop atherosclerosis prematurely.[62] Further research on the long term safety (sustained intake for more than 5 years) is warranted. However, the power of both clinical trials and larger observational studies is often insufficient to find rare increases in common disorders due to food supplementation or replacements.

In some guidelines, the use of phytosterols as an adjunctive treatment for hypercholesterolemia is currently recommended. In the ETF consensus guideline, phytosterols are recommended under the heading dietary changes for treatment of dyslipidemia. In the draft Domus Medica guideline, phytosterols are not recommended under the title 'healthy diet'. The 2006 Diet and Lifestyle Recommendations of the AHA discusses phytosterols under the heading 'Dietary Factors With Unproven or Uncertain Effects on CVD Risk' and thus does not recommend the use of phytosterols explicitly.[63] The recent evidence-based SIGN guideline on the prevention of CHD, explicitly states that plant sterols and stanol esters are not recommended since more research is needed to find out if they can help prevent CVD.

The 2005 dietary recommendations for children and adolescents of the AHA[64] state that formal recommendation of the use of plant sterols for children awaits clinical trial data.

3.5 STATIN USE IN PRIMARY PREVENTION

3.5.1 Randomised controlled trials of statins in primary cardiovascular prevention

The above mentioned reviews lead us to six RCTs on statin use (primarily) in primary prevention, the characteristics of which are depicted in table 1. Two of these trials[65, 66] were strictly limited to primary prevention patients while in the others, part (up to 18%) of the patients were in fact treated in secondary prevention. In one study including both primary and secondary prevention patients, data on primary prevention were separately presented in a pre-specified subgroup of primary prevention.[67] As far as diabetic patients are concerned, WOSCOPS[65] and AFCAPS[68] contained only a few percent of them while in the other trials a considerable number (12.2 to 34.4%) of diabetic patients were included. We deliberately excluded studies on primary prevention that were strictly limited to diabetic patients, in order to concentrate on people at low or moderate risk of cardiovascular disease (see scope of the project).

Table 1: Characteristics of primary prevention trials.

TRIAL	year	% PP	% male	age, y	diabetes %	N	statin	Dose (mg/day)	follow-up, mean, y	annual CHD risk % (plcb)	Baseline chol (change%)
WOSCOPS	1995	84	100	55,3	1	6595	pravastatin	40	4,9	1,54	274(-20,0)
AFCAPS/TexCAPS	1998	100	85	58	3,8	6605	lovastatin	20-40	5,2	0,55	220(-19,3)
PROSPER (PP subgroup)	2002	100	42	75	12,2	3239	pravastatin	40	3,2	2,74	220
ALLHAT-LLT	2002	86	51	66,4	34,4	10355	pravastatin	20-40	4,8	1,69	227(-9,6)
ASCOT-LLA	2003	82	81,1	63,1	24,3	10305	atorvastatin	10	3,3	0,91	212(-18,2)
MEGA	2006	100	31,6	58,3	21	7832	pravastatin	10 à 20	5,3	0,5	242(-11,0)

PP: proportion of study patients treated in primary prevention. N: total number of patients in study.

We briefly describe the major inclusion criteria of these trials. Table 2 summarizes the outcome results on cholesterol levels, major coronary events and all-cause mortality. It should be noted that the primary outcome measure was not the same in all trials: in some it was all-cause mortality,[69] in others it was "major coronary events" defined as fatal CHD plus non-fatal MI.[65, 70] In another trial, the primary outcome was "major cardiovascular events", i.e. a combined endpoint of fatal CHD, non-fatal MI and fatal or non-fatal stroke.[67] In the MEGA-trial, the primary endpoint was a composite of the first occurrence of CHD, which included fatal and non-fatal MI, angina, cardiac and sudden death or any coronary revascularisation procedure.

In none of the studies, all-cause mortality was statistically significantly changed by treatment with a statin. As far as the prevention of CHD events is concerned, the trials provide somewhat inconsistent results: four of them have shown a significantly lower risk of coronary events in the intervention group while in two other, statistical significance was not reached.

Table 2: Main outcome results in primary prevention trials.

TRIAL	annual CHD risk %	Baseline chol (change%)	RR of major coronary events	RR of all-cause mortality
WOSCOPS	1,54	274(-20,0)	0,70 (0,58-0,85)	0,78 (0,61-1,01)
AFCAPS/TexCAPS	0,55	220(-19,3)	0,63 (0.50-0,79)	1,04 (0,76-1,42)
PROSPER (PP subgroup)	2,74	220	0,91 (0,71-1,15)	0,98 (0,79-1,21)
ALLHAT-LLT	1,69	227(-9,6)	0,91 (0,79-1,04)	0,99 (0,88-1,10)
ASCOT-LLA	0,91	212(-18,2)	0,65 (0,50-0,83)	0,87 (0,71-1,06)
MEGA	0,5	242(-11,0)	0,67 (0,49-0,91)*	0,72 (0,51-1,01)*

*Hazard ratios

Major coronary events: definitions of primary endpoints vary between studies

3.5.1.1 WOSCOPS

The West of Scotland Coronary Prevention Study (WOSCOPS),[65] was the first large scale primary prevention statin trial. Only men who had no history of MI, who were ranging in age from 45 to 64 years, and who had a high total serum cholesterol level of at least 252 mg/dl were included. During an average follow-up of 4.9 years, there were 248 definite coronary events (specified as nonfatal myocardial infarction or death from coronary heart disease) in the placebo group (n=3293), and 174 in the pravastatin group (n=3302) corresponding to an absolute risk of 7.5% vs. 5.3%, i.e. an absolute risk reduction of 2.2%. Treatment with pravastatin significantly reduced the incidence of nonfatal MI or death from cardiovascular causes without adversely affecting the risk of death from non-cardiovascular causes: RR 0.70 (0.58-0.85). There was an almost significant 22 % (0 – 40) reduction in the risk of death from any cause in the pravastatin group (P = 0.051).

3.5.1.2 AFCAPS/TexCAPS

The Air Force/Texas Coronary Atherosclerosis Study (AFCAPS/TexCAPS),[68] compared lovastatin with placebo for prevention of a first acute major coronary event in men and women without clinically evident atherosclerotic cardiovascular disease. They had average total cholesterol and below average HDL-cholesterol levels. The annual CHD risk in this population was very low: 0.55 % in the control group. Lovastatin significantly reduced the incidence of the combined endpoint, i.e. acute major coronary events defined as fatal or nonfatal myocardial infarction, unstable angina or sudden cardiac death: RR 0.63 (0.50-0.79). All cause mortality was not statistically affected.

3.5.1.3 PROSPER

The Prospective Study of Pravastatin in the Elderly at Risk trial (PROSPER),[67] studied the effect of pravastatin compared to placebo in an older populations of patients (men and women, 70 – 82 years). Patients with and without a cardiovascular history were included but data on primary prevention were separately presented in a pre-specified subgroup containing 56% of the total study population (i.e. the subgroup referred to in tables 1 and 2). Pravastatin significantly reduced the number of primary endpoints (coronary heart disease death, non-fatal infarction, fatal or non-fatal stroke) in the total study population: RR 0.85 (0.74-0.97) but not in the primary prevention subgroup.

3.5.1.4 ALLHAT-LTT

The Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial - Lipid Lowering Treatment (ALLHAT-LTT),[69] was designed to determine whether pravastatin compared with usual care reduces all-cause mortality in moderately hypercholesterolaemic, hypertensive participants with at least one additional CHD risk factor. The population was not purely primary prevention but contained 14% secondary prevention. In this trial Pravastatin did not statistically reduce either all-cause mortality or CHD significantly.

3.5.1.5 ASCOT-LLA

The Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm (ASCOT-LLA),[70] assessed the benefits of cholesterol lowering with atorvastatin in the primary prevention of CHD in hypertensive patients who are not conventionally deemed dyslipidaemic (baseline total cholesterol 212 mg/dl) and who had at least three other cardiovascular risk factors. Part of the total population had a cardiovascular disease history; 82% of it was treated in primary prevention. There was a significant reduction of major coronary and cerebrovascular events for which the trial was stopped early after a median follow-up of 3.3 year. All-cause mortality was not significantly reduced.

3.5.1.6 MEGA

The Management of Elevated cholesterol in the primary prevention Group of Adult Japanese study (MEGA),[66] was an exclusive Japanese study in which 3966 patients were randomly assigned to a diet and 3866 to a diet plus pravastatin, 10-20 mg daily. It was initiated to assess whether the

evidence for treatment with statins derived from western populations could be extrapolated to the Japanese population. Apart from the ethnic difference, this population differed from that in previous studies in that they had a higher mean HDL-cholesterol and included a much higher number of women (69%). These characteristics lead to a lower event rate in the placebo group as compared to other studies. The primary endpoint was the first occurrence of CHD. Over a mean follow-up of 5.3 years, 66 events occurred in the intervention group (1.71%) and 101 in the control group (2.55%), resulting in a 5.3 years absolute risk reduction of less than 1%. CHD was significantly lower in the diet plus pravastatin group than in the diet group alone (HR 0.67, 95% CI 0.49-0.91).

3.5.2 Systematic reviews of statins in primary prevention

We analysed two SRs that were published in 2006. One was limited to RCTs with at least 80% of the population without a cardiovascular disease history[71] and one considered separately both primary prevention and secondary prevention in diabetic and non-diabetic patients.[72]

3.5.2.1 Thavendiranathan et al.

Thavendiranathan et al.[71] additionally include in their meta-analysis two primary prevention (sub)studies that were strictly limited to diabetes patients, HPS[73] and CARDS.[74] The data from the Japanese MEGA-trial that was published in September 2006 were not yet included in this SR.

In this SR, overall, 90% of enrolled patients had no evidence of cardiovascular disease and received statins for primary prevention. During a mean follow-up of 4.3 years, statin therapy reduced the RR of major coronary events, major cerebrovascular events, and revascularizations by 29.2% (95% CI, 16.7%-39.8%), 14.4% (95% CI, 2.8%-24.6%), and 33.8% (95% CI, 19.6%-45.5%) respectively. Statin therapy produced a non significant 22.6 % (95% CI, 44%-8%) reduction in CHD mortality and no significant reduction in all-cause mortality. The absolute risk reduction for major coronary events in this population would be 1.7% over an average of 4.3 years (baseline average risk 5.7%). Therefore, 60 patients would need to be treated for an average of 4.3 years to prevent 1 major coronary event in this population.

3.5.2.2 Costa et al.

Costa et al.[72] considered all lipid lowering drug trials that reported outcomes in diabetic and non-diabetic patients separately, in primary and secondary prevention. Consequently, of 12 trials, two were not statin-related but used gemfibrozil instead. WOSCOPS was excluded because no data were separately reported for the included diabetic patients.

It was calculated that in primary prevention, the risk reduction for major coronary events was 21% (95% CI 11% to 30%) in diabetic patients and 23% (12% to 33%) in non-diabetic patients. Costa used a broader definition for "major coronary events" than Thavendiranathan and included percutaneous and surgical myocardial revascularization procedures as well. In the control group of primary prevention in non-diabetic patients treated with statins, the 4.5 years event rate for major coronary events was 8.0%. In the intervention group the event rate was 6.3%, indicating an absolute risk reduction of 1.7%. In secondary prevention, the absolute risk difference was three times higher. Coronary artery disease death was a secondary outcome measure in this review and was discussed in secondary prevention only.

3.5.3 Safety

The withdrawal of cerivastatin (Cholstat™, Lipobay™) in August 2001 because of excess fatal toxicity due to rhabdomyolysis alarmed the pharmaceutical industry, government regulatory agencies and the lay public alike.

In 2006, a SR on statin safety was published, combining the results of RCTs, cohort studies, case reports and notifications to regulatory authorities.[75] The resulting analysis confirmed an increased risk in muscle disease. Other side-effects that had been reported, such as liver and renal disease, peripheral neuropathy, hemorrhagic stroke and cognitive function disturbances seemed to occur very rarely, and it was even doubted whether they could be attributed to statins at all.

Myotoxicity of statins covers a broad spectrum of clinical symptoms, ranging from mild myalgias

over myopathy to the potentially fatal rhabdomyolysis. Myopathy is defined as diffuse muscle symptoms (pain, tenderness, weakness) with elevated creatine kinase (CK), sufficient to consult a physician or to stop taking prescribed tablets but insufficient to warrant hospital admission. In Law's SR, the incidence of myopathy was rare (11 per 100.000 person-years) and most muscle symptoms in patients taking a statin were not attributable to the drug.

Rhabdomyolysis is a potentially fatal adverse event, accompanied by profoundly elevated levels of CK which can lead to acute renal failure due to myoglobinuria. The incidence of it is especially high with cerivastatin, which has been withdrawn from the market after 31 deaths that where attributed to rhabdomyolysis were identified (among several million patients who had received the drug). Based on an analysis of pharmacy data in the US, the incidence of rhabdomyolysis due to cerivastatin was estimated at 53 per 100.000 person-years.[76] In an estimate supported by data from 20 RCTs in statins other than cerivastatin, Law obtained an incidence of 3.4 (1.6 to 6.5) per 100.000 person-years with a case fatality of 10%. The incidence was about ten times higher when gemfibrozil, a fibrate that causes rhabdomyolysis in monotherapy as well, was used in combination with statins.

The incidence of rhabdomyolysis is not only related to the combined use of a statin with fibrates (in most instances gemfibrozil), but also to the circulating concentration of the statin. Serum levels depend on the dose of the drug taken and on the concurrent co-administration of drugs that inhibit cytochrome P450 3A4 (CYP3A4), such as diltiazem, erythromycin or other macrolide-antibiotics and azole-antifungals. Drugs that inhibit CYP3A4 were taken by about 60% of persons using simvastatin, lovastatin or atrovastatin who developed rhabdomyolysis.

The Safety Task Force of the US National Lipid Association[76], following its extensive evaluation of available data on adverse events of statins, concluded that on the whole, statins have a very good safety profile. In the latest European guidelines on cardiovascular disease prevention in clinical practice,[10] statins are recommended as first-line drugs for lowering LDL-cholesterol because they have provided the most convincing evidence of effectiveness and "because of their good safety record".

Concern has been expressed over hazards from cholesterol reduction as such. Data from 58 trials of reducing cholesterol concentration by any means resulted in odds ratios (treated/placebo) for a 40 mg/dl decrease in serum cholesterol of 0.87 (0.73-1.03) for CVD other than CHD or stroke, 1.06 (0.96-1.16) for cancer, 0.94 (0.72-1.23) for injuries and suicides and 0.88 (0.78-1.01) for diseases other than CVD and cancer.[77]

3.5.4 Conclusion

From a clinical point of view, the following questions regarding statin therapy in primary prevention should be advanced:

1. What is the overall health impact (mortality/morbidity) of statins in primary prevention and which individuals are most likely to benefit from statins?
2. Lipid levels: do they matter? Should the dose of the statin be titrated to achieve target levels?
3. What are the potential harms of this treatment and how to prevent them?

3.5.4.1 Mortality

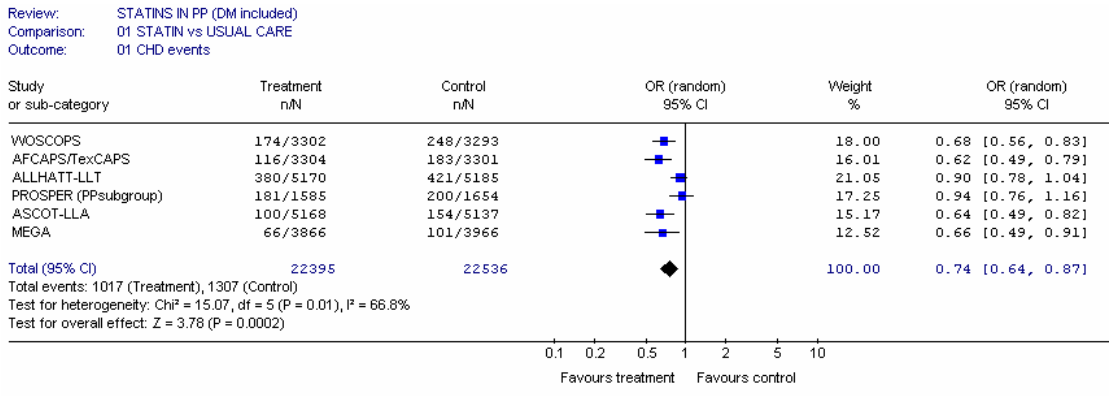
Thavendiranathan found no statistically significant reduction in coronary mortality (RR 0.77 (0.56-1.08)) or overall mortality (RR 0.92 (0.84-1.01)). WOSCOPS showed a significant reduction in coronary mortality (RRR 33%, ARR 0.6%) and a nearly statistically significant reduction in all-cause mortality. In AFCAPS/TexCAPS, the other pure primary prevention trial, the number of deaths in both placebo and intervention groups were so small that no conclusions could be drawn.

3.5.4.2 Morbidity

To assess the overall impact of any statin treatment on morbidity in primary prevention we added the results of the MEGA trial to the meta-analysis of Thavendiranathan and omitted from it two RCTs: CARDS[74] that was a statin trial on primary prevention in type 2 diabetes and HPS[73]

that contained only diabetics in its primary prevention group. Thus we present a meta-analysis[b] of data on six RCTs, reflecting a population of which 89% of patients are treated in primary prevention and 19% were diabetics (figure 8). CHD events are defined here as nonfatal MI and CHD death. As expected, we obtained a slightly lower risk reduction of a major coronary event: instead of a 29% relative risk reduction in Thavendiranathan, we obtained an odds ratio of 0.74 (0.64-0.87).

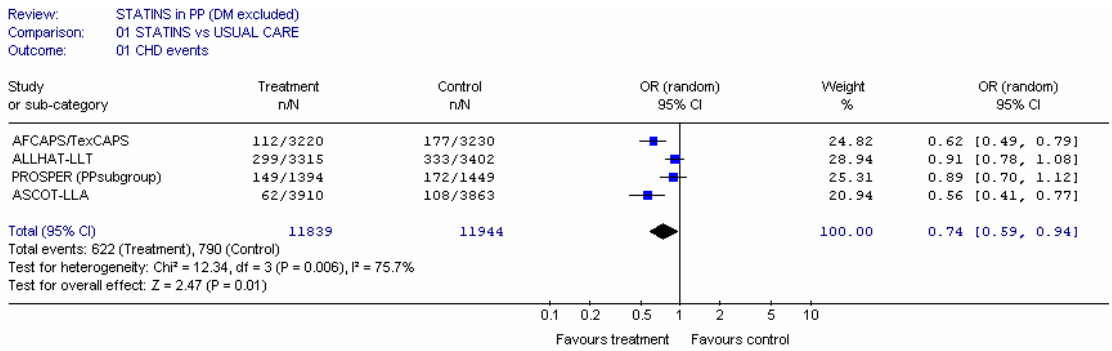
Figure 8 Odds ratios for major coronary events in primary prevention RCTs on statins – meta-analysis.



See text for abbreviations of different study acronyms.

As already mentioned, Costa's meta-analysis is of interest because it calculates the incidence of major coronary events for non-diabetics distinctly, resonating with the primary prevention in non-diabetics population which we were especially interested in. We re-run his meta-analysis (figure 9) but omitted the gemfibrozil studies and the secondary prevention trials. In this way, we obtained results from four trials from which all diabetes patients were excluded. This resulted in an odds ratio of 0.74 (0.59-0.94) for the development of a CHD event in statin treated (mostly) primary prevention patients vs. no lipid lowering drug.

Figure 9: Odds ratios for major coronary events in primary prevention RCTs on statins in non-diabetic patients – meta-analysis.



In order to better appreciate the real impact on health, we have to relate this 26% relative risk reduction to the absolute risk of developing a cardiovascular event incurred by apparently healthy people. Table 3 shows the NNT to prevent one major coronary event in the subgroups of the primary prevention patients without diabetes.

[b] The Cochrane Collaboration. RevMan 4.2. Random effects model.

Table 3: Major coronary events in primary prevention RCTs on statins in non-diabetic patients

	CHD risk % (3-5 y)	Ni	ni	Nc	nc	ARR (3-5 y)	RRR	NNT (3-5 y)
AFCAPS/TexCAPS	5,5	3220	112	3230	177	2,00	36,5	50
ALLHAT-LLT	9,8	3315	299	3402	333	0,77	7,9	130
PROSPER	11,9	1394	149	1449	172	1,18	10,0	85
ASCOT-LLA	2,8	3910	62	3863	108	1,21	43,3	83

See text for study acronyms. CHD risk = risk in control group during study period. Ni, total number of patients in intervention group, Nc, total number of patients in control group, ni, number of major coronary events in intervention group, nc, number of major coronary events in control group. Mean follow-up ranges between 3.2 and 5.2 years (see also table 1). ARR, absolute risk ratio. RRR, relative risk ratio. NNT, number needed to treat to prevent 1 major coronary event during the duration of the study. The definition of major coronary events is not the same in all studies.

It is clear that, depending on baseline risk, one has to treat between 50 and 130 apparently healthy subjects during 3 to 5 years to prevent one single coronary heart event. This benefit is not statistically significantly reflected in CHD mortality or all-cause mortality probably due to the design and size of the primary studies.

In a recent comment in the Lancet, Abramson and Wright[78] argue that statins should not be prescribed for true primary prevention in women of any age or for men older than 69 years, based on the fact that these subgroups of patients are not adequately represented in RCTs on primary prevention.[79] In PROSPER[67], the only statin trial in elderly people (75.4 ± 3.3 years), an overall significant reduction of coronary disease was obtained with pravastatin. However, in a post hoc analysis in primary prevention patients, no significant effect on any endpoint was obtained. In the Japanese MEGA trial,[66] a majority of patients were females (69%). Overall in this study, a significant reduction of CHD was obtained with pravastatin, but in a subgroup analysis, the hazard rate for CHD was not significantly different from 1.0 in women 0.71 (0.44-1.14). In men it was 0.63 (0.42-0.95).

From this we can conclude that the absolute health impact of statin therapy in primary prevention is at most modest. Because the greatest benefit occurs among patients at greatest risk, international guidelines recommend prescription of these drugs in high risk subjects. A meta-regression analysis of major primary and secondary prevention statin RCTs found that statin use itself could possibly be associated with an increase in mortality of 1% in 10 years.[80] This would, according to the author, be sufficiently large to negate statin's beneficial effect on CHD mortality in patients with a CHD event risk less than 13% over 10 years. It should be stressed, however, that this analysis was speculative and purely based on a mathematical model, and that no specific causes of increased mortality were suggested.

The guideline developed by the 3rd Joint European Societies' Task Force recommends pharmacological treatment in asymptomatic people with a cardiovascular mortality risk of at least 5% according to the SCORE-tables,[10] who present with a total cholesterol > 190 mg/dl on an adequate diet. Both SIGN and NICE recommend that all adults over the age of 40 years who are assessed as having a ten year risk of having a first cardiovascular event > 20% should be considered for treatment with a statin. These guidelines clearly do not take into consideration the fact that the evidence for treating women and elderly men (> 70 years) with statins is very limited.

3.5.4.3 Lipid levels, do they matter?

RCTs have shown that the absolute benefit from lowering cholesterol is related to an individual's baseline risk of cardiovascular events and to the degree of cholesterol lowering rather than to the individual's cholesterol concentration. In the secondary prevention HPS-trial, lowering of LDL cholesterol by approximately 40 mg/dl resulted in the same degree of benefit, irrespective of whether LDL cholesterol was 115, 155 or 195 mg/dl at the beginning of the study.[9] In a commentary on this study in ACP Journal Club[81] it is concluded that, since benefits conferred by statins are mainly determined by pre-morbid CHD risk rather than by the lipid level, identifying persons with "abnormal" lipid profiles and dosage titration to preset target lipid levels become questionable.

The JBS2 guideline states that there are no clinical trials which have evaluated the benefits of cholesterol lowering to different cholesterol targets in relation to clinical events.[28] Establishing a cholesterol target for therapy is therefore an extrapolation from the apparent benefits indicated by major trials of lipid lowering, while maintaining appropriate margins for safety.[22]

3.5.4.4 Harms

Statins are safe drugs, the most serious adverse effect being rhabdomyolysis. This remains however a very rare event that is related to concomitant intake of a fibrate or other drugs that interfere with statin metabolism such as diltiazem and certain antibiotics. Lowering the dose of the statin in these circumstances or suspending them, could prevent the occurrence of rhabdomyolysis.

Key points

- **Primary cardiovascular prevention implies an intervention in asymptomatic people who do not have cardiovascular disease or diabetes but are considered to be at increased risk to develop cardiovascular disease.**
- **This rapid assessment assesses the effectiveness of dietary interventions and statin use in the primary prevention of cardiovascular disease.**
- **Reduction and/or modification of dietary fats result in a small but potentially important reduction in cardiovascular risk when these dietary changes are sustained longer than two years. This is best substantiated in men.**
- **It is not clear how asymptomatic people can be motivated to a long-lasting change in dietary habits.**
- **There is no evidence of benefit from omega-3-fats in primary prevention.**
- **Antioxidant vitamin supplementation is not recommended for the prevention of CVD. RCTs suggest that vitamin E and ß-carotene may be harmful.**
- **Phytosterols can modestly reduce LDL-cholesterol. No evidence of benefits in primary prevention of CHD exists. The safety of long term daily intake (>5 years) is unknown.**
- **Primary prevention studies on statins include up to 18% secondary prevention-patients and up to 34 % diabetics making these studies vulnerable to potential bias.**
- **In patients without cardiovascular disease, statin therapy does not decrease overall mortality. Coronary mortality was reduced in some of the trials but not according to the meta-analysis.**
- **There is a modest effect on coronary events in primary prevention with an estimated absolute risk reduction in non-diabetics of 1 to 2% over 3 to 5 years (depending on baseline risk), indicating that one needs to treat 50 to 100 persons during 3 to 5 years to prevent one non-fatal coronary event. This corresponds to an overall relative risk reduction of 26%.**
- **The evidence for prescribing statins in primary prevention in women or in elderly men is limited. Subgroup analysis of RCTs suggest no benefit in women.**
- **Most muscle symptoms in patients taking a statin are not drug related, but rhabdomyolysis is a potentially fatal adverse effect of statin use that occurs very rarely (3.4 per 100.000 person-years). Rhabdomyolysis can at least partially be prevented by avoiding concomitant use of certain other drugs.**

4 ECONOMIC LITERATURE ON PRIMARY PREVENTION OF CV DISEASE: SYSTEMATIC REVIEW

We performed a systematic review of the published economic evaluations of interventions for the primary prevention of CVD. Interventions considered for primary prevention include in the first place lifestyle interventions such as smoking cessation, increased physical activity and healthy diet. Furthermore, drug treatments with aspirin, antihypertensives, and lipid-lowering drugs such as statins are considered.

The objective of this review is to identify which interventions are appropriate for particular subgroups of the population from an economic point of view. Search strategy and search results are detailed in appendix.

4.1 RESULTS FROM ECONOMIC EVALUATIONS

The retrieved economic evaluations are categorized according to the intervention that was considered. We first look at the results and conclusions from the authors. Next, we do a critical appraisal, discussing some important methodological aspects.

All articles have been summarized in tables provided in appendix (tables 7-24). The tables provide the following: column 1) authors, country, year of publication, conflict of interest, perspective, time window, discount rate; column 2) intervention, population and/or base risk and/or applied risk function, relative risk benefit; column 3) analytic technique, year of costs and currency, details of costs, utilities (if relevant); column 4) cost-effectiveness results; column 5) sensitivity analysis; and column 6) conclusions.

For practical reasons all costs will be presented in the original currency. To be able to compare results, exchange rates are provided in table 4, and three different threshold values are provided, i.e. €20 000, €30 000, and €40 000.

Table 4: Exchange rates on February 8th, 2007

Currency	Exchange rate	€20 000	€30 000	€40 000
1.00 USD (United States Dollars) ($)	€0.768190	26 035	39 053	52 070
1.00 GBP (United Kingdom Pounds) (£)	€1.50307	13 306	19 959	26 612
1.00 CAD (Canadian Dollars)	€0.647293	30 898	46 347	61 796
1.00 AUD (Australian Dollars)	€0.599696	33 350	50 025	66 700
1.00 SEK (Swedish Krona)	€0.110045	181 744	272 616	363 488
1.00 JPY (Japanese Yen) (¥)	€0.00633693	3 156 102	4 734 154	6 312 205

4.1.1 Statins versus no treatment

9 studies were found comparing statins with no treatment. First of all, we discuss a pooled analysis (table 7 in appendix) reviewing 24 studies published between 1991 and 2001 in seven different countries.[82] The ratios reported ranged over an enormous range, from cost savings to $489 000/YLS. A strong inverse relation between absolute risk at baseline and the cost-effectiveness ratios exists. The pooled estimates show values of $21 571/YLS for an annual CHD risk of 2% and $16 862/YLS for annual risk of 3% of CHD. Most studies agreed that statin treatment is cost effective for high risk patients (annual absolute risk >4%) but not cost effective for low risk patients (annual risk <1%). For medium risk patients (annual absolute risk 1 to 4%) the decision of whether treatment is cost effective depends on the choice of the study. The most probable explanation for these differences was methodological differences and the impact of funding sources, i.e. provided by the industry versus others (academic or governmental institutions or none). The differences were most striking at low levels of risk, representing large eligible populations. Potential conflict of interest were suggested as an explanation, however, the authors could not prove this.[82] In our summary tables, we mentioned the declared conflicts of

interest.

This pooled analysis also included studies evaluating statin treatment for secondary prevention. Compared with primary prevention, secondary prevention represents a decrease of 62% in the cost-effectiveness ratio.[82] Therefore, it is important to clearly separate the results of different categories of prevention. If the following studies included both primary and secondary prevention, only results for the former are provided and discussed.

A second study (table 8 in appendix) compared treatment according to the Australian Pharmaceutical Benefits Scheme (PBS) criteria against treatment criteria based on 15-year risk of CHD mortality cut-offs of ≥2.5% and ≥5%.[83] The main conclusion was that treatment according to the PBS criteria was not the most cost effective. With the ≥2.5% and ≥5% 15-year risk of CHD mortality, the cost per added year of life was respectively AUD31 000/YLS and AUD23 000/YLS for men compared to AUD110 000/YLS using the PBS criteria. Targeting of therapy for primary CHD prevention should be based on population-specific, multivariable risk.

The third study (table 9 in appendix) was a threshold analysis estimating at what coronary risk it is cost effective to initiate cholesterol lowering drug treatment in primary prevention for men and women of different ages in Sweden.[84] Depending on the threshold value, age, and sex, the 5-year risk of CHD to reach this threshold was calculated. A wide range of 5-year risks of CHD was found to make treatment cost effective, from 2% for women aged 35 years up to more than 10% for men aged 70 applying the $60 000/QALY threshold. The authors concluded that cholesterol lowering treatment was not cost-effective for all patients with elevated cholesterol levels. Age and sex have a big influence on the cost effectiveness of treatment.

A general criticism on the Canadian study of Spaans (table 10 in appendix) is its lack of transparency.[85] The perspective and time window were not explicitly mentioned, for cost details the authors refer to another study without providing general numbers, and no sensitivity analysis was performed. The risk of CHD was also not expressed as a percentage over a certain time period. Cost-effectiveness was expressed according to the number of risk factors present. Risk factors were age (men 45 years or older, women 55 years or older), diabetes, smoking, premature heart disease in a first-degree relative (i.e., coronary artery disease occurring at less than 55 years in men or less than 65 years in women), hypertension (systolic blood pressure of 140 mmHg or greater, or diastolic blood pressure of 90 mmHg or greater) or taking antihypertensive medication. In contrast to all other studies, this study found that lifetime statin therapy had acceptable cost effectiveness for all risk levels, even for the low risk level (≤1 risk factor).

The next Canadian study (table 11 in appendix), involving two authors from the previous study, focussed on the influence of taking into account indirect costs on the cost effectiveness of statin treatment.[86] If only direct medical care costs were considered, acceptable cost-effectiveness results were reached for both high and low risk men and women. If indirect costs representing the loss of employment income and the decreased value of housekeeping services after different manifestations of CVD were included, statin treatment even became cost saving (with the exception of low risk women aged 40 years).

A Japanese study (table 12 in appendix) defined eight distinctive subgroups on the basis of several risk factors.[87] Cost effectiveness of treating patients with pravastatin was separately calculated for these groups for men and women and for different age groups. Depending on the initial total cholesterol level, 20mg (initial level of 240 mg/dl) or 10mg (initial level of 220 mg/dl) pravastatin was taken daily. The combination of risk factors present, age, sex and initial total cholesterol level resulted in very different cost-effectiveness outcomes. However, the probabilistic sensitivity analysis revealed that about 90% of results showed that pravastatin therapy was more costly than 5 million Yen per QALY (about €32 000). The authors concluded that treating hyperlipidaemia with pravastatin is not cost-effective in persons at low cardiac risk in Japan.

The two following studies performed in the UK are discussed as one. The report published by Ward and colleagues in 2005[30] provides more data and disaggregated results than the report for the National Institute for Health and Clinical Excellence published in 2006[88]. Tables for both studies are provided (respectively table 13 and 14 in appendix), however, we will focus on the most extensive report (table 13). Three scenario analyses were conducted: the base case CHD analysis, a first scenario of CHD analysis with CVD outcomes and a second scenario of CVD analysis. Due to the large number of results presented in the original report, only base case

results are tabulated and discussed here. The ICERs for primary prevention of CHD with statin treatment varied widely according to risk level and age. The results suggest it is more cost effective to commence treating patients at younger ages than older ages. At aged 45 years the estimated discounted cost per QALYs range from £9 500 to £20 900 for males between 3% and 0.5% annual risk of a CHD event and £13 700 to £30 500 for females between the same risk levels. At aged 85 years the corresponding values are £36 800 to £105 200 for males and £47 400 to £110 600 for females. For diabetics the cost per QALYs in primary prevention were better ranging from £6 200 for males aged 45 years at 3% annual risk of a CHD event to £96 200 for females aged 85 years at 0.5% risk.[30] As such, applying a £20 000/QALY threshold value, statin treatment was not cost-effective for older patients (males and females >75 years), for males older than 65, 55 or 45 with an annual risk level of CHD ≤2%, ≤1%, and ≤0.5%, respectively, and for females older than 65, 55 or 45 with an annual risk level of CHD ≤2.5%, ≤1.5%, and ≤1%, respectively.

The Irish study (table 15 in appendix) comparing statin therapy versus no treatment calculated cost effectiveness of several types of statins: atorvastatin, rosuvastatin, fluvastatin, simvastatin, and pravastatin for asymptomatic male patients older than 55 years, with a 10-year risk of at least 15% for the development of CVD.[89] Depending on the statin administered and the payment scheme applied, cost-effectiveness varied between 17 900€/LYG and 48 500€/LYG. In their analysis, atorvastatin was the most cost effective statin.

Two other studies[90, 38] looking at the cost effectiveness of statin treatment are discussed in one of the following parts since they compare several treatment options.

In conclusion, based on the results of the different studies, the cost effectiveness of statin treatment varies tremendously. Next to methodological considerations, the main determinants for cost effectiveness are the level of CHD risk, gender and age. Treatment is cost effective only at high levels of risk and expensive for low levels. Most of the times, results are more favourable (i.e. lower ICERs) for men than for women. For age, with exception of one study,[86] results are more favourable for younger patients at the same thresholds of absolute risk.

4.1.2 Fibrates versus no treatment

We found one study in the US that determined the cost effectiveness of the fibrates gemfibrozil and fenofibrate in the primary prevention of CHD (table 16 in appendix).[91] The study calculated the cost per QALY according to age and gender for people with certain characteristics (details in table). ICERs for females were much less favourable compared to those for men. Gemfibrozil was much more cost effective in comparison with fenofibrate and cost effective for both men and women aged 45-70 years if a threshold of $30 000/QALY was considered. Furthermore, the study showed comparable cost-effectiveness results for gemfibrozil and for lovastatin therapy in the same study population.

4.1.3 Aspirin versus no treatment

The authors of four published studies consisted of the same core of authors (Annemans, Evers, Kubin and Lamotte) and some other authors. One study[92] was excluded since it provided the results specifically for Spain which were also published in one of the other studies. Two other studies[93, 94] are summarized in the same table (table 17 in appendix) since they use exactly the same input data and model. Only the base risk, results, sensitivity analysis, and conclusions differ slightly. These elements are provided separately in the right corner of the table.

In the first study, treatment with low-dose aspirin was evaluated in four countries, i.e. UK, Germany, Spain, and Italy.[93] Low-dose aspirin treatment becomes cost-saving at a relatively low 10-year risk of fatal CVD, i.e. 2-5% 10-year risks according to the SCORE equation. A Monte Carlo analysis showed that aspirin is dominant in more than 90% of patients at a 10-year risk of 4% and 5% in the four countries. This decreases to 89% and 86%, respectively, at 3% and 2% 10-year risk for the UK, Germany and Spain. In Italy, it decreases to 60% and 24%, respectively, at 3% and 2% risk. The lower degree of dominance in Italy is due to the high cost of gastrointestinal bleeding in that country. The second study based on the same model and with the same cost data, modelled cost effectiveness for an annual risk of CHD of 1.5%, which was assumed to correspond to a 10-year CHD risk of approximately 14%. As expected, the results were even more favourable. In their conclusion, the authors stated that low-dose aspirin therapy could be

recommended in the primary prevention of CVD in all individuals who have at least a 0.6% per year risk of CHD in the UK, Germany and Spain and a risk of 1% per year in Italy, and who do not have an increased risk of GI bleeding events.[94]

The last study performed with the same model was applied to Japanese patients with the same annual risk of CHD, i.e.1.5% annual (table 18 in appendix). Costs of cardiovascular disease were adjusted to Japanese costs. Benefits of aspirin treatment were, although represented in another way, exactly the same and not adjusted for the Japanese population. Consequently, it is not surprising that the authors come to a similar conclusion, i.e. aspirin therapy should be recommended in the primary prevention of CVD in all individuals who have at least a moderately increased risk of CHD (1.5% annual) and who do not have an increased risk of GI bleeding events.[95]

A last study comparing aspirin treatment to no treatment was performed in the US (table 19 in appendix).[96] This is the only study in our review performing a cost-utility analysis strictly for a female population. The analysis for a male population was published separately and will be discussed in the following part. The cohort consisted of moderate risk 65-year-old women with an estimated 10-year total CHD risk of 7.5%, applying the Framingham risk equation. In this population, aspirin use cost $13 300 per additional QALY gained. The probabilistic sensitivity analysis found a 27% chance that aspirin produces fewer QALYs than no treatment, a 35% chance that the cost-utility ratio was less than $50 000 per QALY gained, and a 37% probability that it was greater than $50 000 per QALY gained. In contrast to the previous studies, no cost savings were reported. The authors concluded that aspirin is indicated for women at higher risk for stroke but should not be prescribed for low-risk women, including most younger women.[96]

4.1.4 Aspirin vs no treatment and combination of aspirin and statin vs aspirin

Pignone and colleagues published a second study on the cost effectiveness of aspirin treatment in the US (table 20 in appendix).[90] This time, the study population consisted exclusively of men at six levels (2.5%, 5%, 7.5%, 10%, 15%, and 25%) of 10-year risk of CHD (Framingham risk equation). In their cost–utility analysis, the authors considered, next to aspirin treatment, the effects of statin therapy, a combination therapy with both drugs, and no pharmacotherapy for the primary prevention of CHD events in men.

For 45-year-old men who do not smoke, are not hypertensive, and have a 10-year risk for CHD of 7.5%, aspirin was more effective and less costly than no treatment. The addition of a statin to aspirin therapy produced more QALYs gained than aspirin alone but at a higher cost. The cost per additional QALY gained was approximately $56 200 for 10 years of combination therapy. The cost-effectiveness ratios for aspirin alone and in combination with statin therapy improved as risk for CHD increased. When the 10-year risk was 10% or 15%, the addition of a statin to aspirin therapy had a cost of $33 600 and $42 500, respectively.

However, the authors remark that the effectiveness of aspirin was dependent on how the risk for stroke was modelled. In their alternate scenario that modelled hemorrhagic stroke explicitly, aspirin appeared less effective and more costly than no therapy for men with a 10-year risk for CHD of 5% or less. Consequently, the authors believe that aspirin should not be routinely recommended for men at or below these risk levels.[90]

4.1.5 Antihypertensives versus no treatment

One study, which was performed in the UK, was found on the cost effectiveness of the ramipril treatment for primary prevention of cardiovascular disease (table 21 in appendix).[97] This study modelled cost effectiveness both in a high and low risk population. The low risk population with annual mortality rate of 1% at age 66 was considered as a primary prevention group similar to the WOSCOPS (West of Scotland Coronary Outcome Prevention Study) population. The high risk group was disregarded as being no population for primary prevention.

Treatment with ramipril in the low risk group had a cost effectiveness of £5 300 per life year gained for lifetime treatment (20 years). Based on this outcome, the authors concluded that even for patients at lower risk, cost effectiveness for lifelong ramipril treatment, being below a threshold of £25 000 per LYG, is acceptable. However, as mentioned by the authors, a possible limitation of the analysis is the projection of cost effectiveness to 10, 15, and 20 years of treatment based on the assumption that the benefits from ramipril would persist beyond five

years.[97] A more conservative approach altered conclusions. For the low risk population, cost effectiveness at present drug costs was poor at five years, i.e. £36 600/LYG.

A second study, performed in Sweden, investigated the cost-effectiveness of candesartan-based antihypertensive treatment (table 22 in appendix).[98] The population consisted of elderly patients (70-89 years) with mild or moderate hypertension (systolic blood pressure 160–179mmHg and/or diastolic blood pressure 90–99mmHg). Because of changes in treatment guidelines in the underlying study, additional open-label active antihypertensive treatment was recommended in both treatment groups for patients whose blood pressure remained high. The study therefore actually compared candesartan-based treatment with usual antihypertensive treatment not including candesartan. Patients were assumed to be treated with candesartan for a maximum of 4 years. Candesartan-based antihypertensive treatment was associated with a cost of €13 000 per QALY gained. Since this is within the range of society's willingness to pay for health gains, the authors concluded this treatment is acceptable for the prevention of nonfatal stroke.[98]

4.1.6 Dietary advice and/or exercise

We only found one study evaluating the cost effectiveness of dietary advice, exercise, and the combination of both (table 23 in appendix).[99] The population consisted of 60-year old men in the county of Stockholm (Sweden). The combination of dietary advice and exercise were dominated by dietary advice. The cost effectiveness of dietary advice compared to no intervention was SEK11 642/LYG (€1 280)) and 98 725/LYG (€10 900) from the payer's perspective assuming a remaining and declining effect of the intervention on risk factors, respectively. From the societal perspective, this was SEK141 555/LYG (€15 500) and SEK127 065/LYG (€14 000), respectively. The authors concluded that dietary advice appears to be a cost-effective strategy among 60-year-old men both from a societal and from a payer's perspective.

The authors of this study remark that it is surprising that the groups receiving dietary advice and exercise in combination performed poorly compared to the groups receiving dietary advice or exercise. A possible explanation is that it could be regarded as easier to focus on either diet or exercise when motivating oneself to changing habits. This view is also consistent with what was observed in the trial. Another possible explanation could be that this group contained outliers that had impact since the sample size was small.[99]

4.1.7 Smoking cessation, aspirin, antihypertensives and statins

The last study in this overview, performed in the Netherlands, evaluates the cost-effectiveness of four risk-lowering interventions for the primary prevention of cardiovascular disease: smoking cessation, antihypertensives, aspirin, and statins (table 24 in appendix).[38] Three smoking cessation therapies were regarded: with GP advice, nicotine substitutes or bupropion. The population was divided into three groups based on their 10-year risk level of CHD, based on the Anderson risk equation from Framingham: low risk (<10% risk, 2 396 participants), moderate risk (10-<20%, 714 participants), and high risk (≥20%, 222 participants). There were too few participants with very high risk (≥30 percent) to enable the calculations for this group. Results for the low risk group were not presented since only smoking cessation was considered as an appropriate intervention for this healthy population (personal communication, Chris De Laet, March 1 2007). For both the moderate and high risk group, results were calculated for two age groups, i.e. 50 and 60 years of age.

Compared to no treatment, smoking cessation therapy is the most cost-effective treatment, representing savings in all situations. Statin therapy is the least cost-effective treatment (ranging from €73 971 to €190 276 per YLS). Aspirin was the second most cost-effective intervention (ranging from €2 263 to €16 949 per YLS) followed by antihypertensive treatment (ranging from €28 187 to €79 843 per YLS). These rankings were maintained for all age group/risk group categories analyzed.[38]

The cost effectiveness of the interventions on the efficiency frontier is calculated by comparing the incremental effects and costs of an intervention with the previous most effective intervention. This analysis shows that smoking cessation with GP advice is dominated by smoking cessation with bupropion (bupropion has lower costs and greater effects). Compared with smoking cessation, aspirin is cost-effective for moderate risk populations in the 60 years age group and for high-risk populations irrespective of age. At a population level, antihypertensives are dominated

by aspirin treatment. Statins have very high ICERs compared to aspirin treatment. However, as they have higher effectiveness, they are never dominated by the other treatments.[38]

Based on these results, for cost-effective pharmacological population prevention of CHD, the first line of intervention should be smoking cessation therapy for smokers and aspirin for moderate and high levels of risk. Statin therapy is an expensive option and should not represent a first choice in the primary prevention of cardiovascular disease.[38]

4.2 CRITICAL APPRAISAL OF ECONOMIC EVALUATIONS

We provide some general remarks and critically appraised the study in this review using several general criteria, and we will comment on methodological differences, strengths and weaknesses. The purpose is to identify those studies and conclusions on which we can rely for general conclusions that might be most valid for Belgium.

4.2.1 Multiple risk factor and risk functions

Multiple risk factor

Particularly in primary prevention, the presence of multiple risk factors is an important marker for future CVD events and cost-effective therapy.[86] For example, in devising treatment recommendations for cholesterol lowering it is not sufficient to focus on the cholesterol levels alone, but the entire risk factor profile of the patient needs to be taken into account. This is because the absolute coronary risk reduction will depend on the absolute risk of the patient, which is a function of all the risk factors.[84]

The PBS (Pharmaceutical Benefit Scheme) criteria from Australia (table 8), according to which treatment was not cost effective, are a good example of this. In contrast to treatment based on the 15-year risk of CHD mortality of $\geq$2.5% or $\geq$5% based on the risk equations, the PBS criteria do not adequately take into account the strong contribution of age to CHD risk; they do not recognise the major contribution of smoking to CHD risk; and they do not acknowledge the presence of more than one additional risk factor.[83]

Risk function

We especially have to be careful while comparing results for subgroups that are defined according to different risk functions. Risk functions from the Framingham study,[99, 82, 91, 30, 90, 88, 38, 96] the SCORE equation,[93-95] MRFIT criteria,[83] and others were applied. For example, a 5% 10-year risk of fatal CVD calculated using SCORE is believed to equate to approximately 20–25% 10-year risk of any CHD event using the Framingham risk equation.[93]

Comparison of extrapolated Australian mortality risk with the unadjusted mortality risk derived from the MRFIT equations showed that MRFIT risk scores consistently overestimate 15-year risk of CHD mortality.[83] This highlights the problem of directly applying mortality risk derived from studies in a different time frame and context (e.g., MRFIT and Framingham).[100]

The difference between CHD and CVD also has to be taken into account. Ward and colleagues defined a CHD event as onset of stable angina, unstable angina, a non-fatal MI, or death from CHD related causes. A CVD event is defined as a CHD event plus a non-fatal stroke, transient ischemic attack (TIA), or death from stroke or TIA related causes.[30] It is considered that a 1.5% annual CHD risk, as reported in the report, was approximately equivalent to a 15% 10-year CHD risk and a 20% 10-year CVD risk.[88] The comparison of those multiple risk assessment equations is discussed in more detail in chapter 2.

4.2.2 Treatment effect and compliance

Treatment effect

Several studies have modelled treatment effects based on cholesterol lowering. In the study of Ward, a relative risk reduction is calculated from the relative difference between baseline CHD

risk and cholesterol altered CHD risk for males and females at each of the baseline risk levels.[30] Spaans assumed reductions in total cholesterol (TC) and LDL-C of 25% and 35%, respectively, and an increase in HDL-C of 8% with the use of statin therapy.[85] In the study of Grover, daily treatment with a 10-mg tablet of atorvastatin calcium among subjects free of CVD and diabetes at baseline was evaluated. Among such patients in the CURVES Study,[101] TC and LDL-C levels were reduced by 28% and 38%, respectively, whereas HDL-C level increased by 5.5%.[86] The Japanese study on statins assumed that daily 10 or 20 mg pravastatin reduced the TC from 220 mg/dl to 200 mg/dl (a 10% reduction) and from 240 mg/dl to 200 mg/dl (a 17% reduction), respectively.[87]

One study conducted a literature review to find previous studies investigating the link between cholesterol lowering and CHD risk.[30] The studies offered no conclusive evidence of a strong and consistent relationship between cholesterol lowering and CHD risk. The cost-effectiveness results based on such interim cholesterol lowering endpoint are therefore subject to significant uncertainty over and above that incorporated within the main economic analysis.

Furthermore, several analyses for primary prevention are extrapolating effectiveness results from relatively higher risk primary prevention populations to the treatment of populations at much lower risk. Evidence, however, does not currently exist to demonstrate whether the same level of relative risk reductions will be achieved in very low risk populations. The results therefore have to be treated with caution.[30]

Compliance

Effectiveness of statins in routine clinical practice could well be lower than suggested by the trials due to a number of issues, particularly compliance and continuance (or persistence).[30] Medication compliance is the extent to which a patient acts in accordance with the prescribed interval and dose of a dosing regime. The unit of measure for compliance is administered doses per defined period of time (in %). Medication persistence is the accumulation of time from initiation to discontinuation of therapy. This is measured by time metric.[102]

A few studies mention which compliance to treatment was assumed in their model. Two studies assumed compliance to be similar to that achieved in the clinical trial setting by using the relative risks results of intention-to-treat randomized controlled trials, which incorporate the trial compliance.[89, 38] Another study assumes full treatment compliance in terms of drug costs, but bases CHD risk reduction estimates on intent-to-treat results from clinical trials with less than perfect compliance.[91] This underestimates the cost-effectiveness ratios. Only one study took into account that compliance in the general community is less than that observed in clinical trials. Community studies on statin use suggest discontinuation rates of 30%-60%.[103, 104] Based on this evidence, Lim modelled an exponential decline in compliance which levelled off at 50% after three years.[83]

Compliance in primary prevention is subject to huge uncertainty. It is shown in a sensitivity analysis that the impact on cost effectiveness is relatively limited, particularly in cases where patients are not picking up their prescriptions and therefore not accruing treatment costs. Only in the case of patients who are long term poor compliers, failing to take the medication according to the prescription but continuing to pick up prescriptions will treatment costs be accrued without the corresponding benefit.[30]

4.2.3 Age and gender

Age

In the cost-effectiveness analysis, ICERs vary in the first place according to the baseline risk of CHD or CVD. However, it is also important to incorporate age. For primary CHD prevention, the estimated cost per QALY varied substantially according to risk level and age of treatment initiation, being lower at higher levels of risk and in younger age cohorts at similar levels of risk.[88] Preventing a coronary death will lead to a greater gain in life-years for a younger person than for an older person.[84] At younger ages there is also a greater period of time over which to accrue the benefits of treatment. At older age groups death rates from other causes are higher, reducing the potential of avoiding CHD events when on treatment.[30]

However, as mentioned by Ward, it should be noted that there is greater uncertainty in the ICERs at younger ages. This is particularly the case if the modelling is undertaken over the lifetime of the patients (see further). For younger patients the length of extrapolation required is significant as the modelling timeframe goes well beyond the duration of major outcome trials to date.[30] In addition there is greater uncertainty in the baseline data for younger and very old patients since datasets and trials have much smaller numbers of patients at those ages.

Gender

As for age, gender also may have an important influence on the ICERs. Women at the same age have on average a lower heart disease risk than men. Several studies did not differentiate results according to sex. Other studies explicitly reported results solely for men.[82, 89, 38] The studies on statins most of the times provided better results for men than for women.[83, 86, 91, 30] However, in the threshold analysis of Johannesson, lipid lowering treatment became cost-effective at lower 5-year risks of CHD for women (table 9 in appendix). According to the Japanese study, treatment could be more cost effective for men or women depending on the risk group specified (table 12).

The most important problem is that, similar to data for very young or very old patients, there are few trial data available for women. Pignone published two studies separately for men and for women comparing aspirin versus no treatment.[90, 96] Although the base case scenario started from an estimated 10-year total CHD risk of 7.5%, result were hard to compare directly due to the difference in age, i.e. 45 years in the male population versus 65 for females.

4.2.4 Time horizon and discounting

Most sensitivity analyses show that, next to the costs of treatment (for statins) and uncertainty associated with the treatment benefit, the time window has a large influence on the cost-effectiveness results. The discount rate also had a big influence on results if longer time horizons were applied.

The majority of trials on which the studies rely are under 5 years of duration. In theory, a lifetime time horizon for analysing cost effectiveness is appropriate for examining cost effectiveness since therapy has costs and benefits which extend over the lifetime of a patient. However, extrapolating treatment benefit towards the future should be done with caution. In all sensitivity analyses incorporating this uncertainty,[97, 86, 30, 94, 89] a shorter timeframe clearly increased the incremental cost per LYG or QALY.

It would be more conservative to apply a time horizon of in between 5 years and lifetime or to estimate results for several extrapolations. Using a shorter time horizon as opposed to life time has a greater impact on the results for a younger population. Younger patients are relatively less likely to benefit from treatment in the first years of treatment as the risk of subsequent and fatal events is lower in younger patients.[30] Therefore, results from analysis with a shorter time horizon will most probably suggest it is less cost-effective to treat younger than older patients.

4.2.5 Perspective and cost items included

The perspective of the study is directly related to which cost items are included and how they were valued. Especially for studies claiming to perform the analysis from the societal perspective, including indirect costs, different approaches exist about which costs are included and how they are valued. One study mentioned to perform the analysis from a societal perspective but used medical charges based on the reimbursement schedule as a substitute for medical costs and did not include indirect costs.[87] This rather reflects the health care payer's perspective.

Very different indirect costs are included when comparing the studies performing their analysis from the societal perspective: Johannesson includes indirect costs associated with lost productivity due to a coronary event and the difference between total consumption and production in added years of life (table 9 of appendix), Grover incorporates estimated annual employment income and value of housekeeping services lost due to CVD (table 11), Hay adds the time cost of visits as an indirect cost (table 16), Lundkvist includes costs for living arrangement (table 22), and Lindgren takes both the indirect costs related to loss of production due to the disease and cost in added years of life into account (table 23). It is normal that altering the in- or exclusion of certain cost items may have a very big influence on results.

4.2.6 Side-effects and disutility of taking medication

Side-effects

Most studies do not take into account the extra costs and loss in utility due to side-effects of treatment. The associated costs of managing adverse events are expected to be small and are therefore not modelled.[30] However, especially when talking about a large low-risk healthy population, small side-effects may counterweight the relatively small benefits.

Some very small side effects, such as the impact of aspirin on skin bruising and nasal bleeding, may be ignored without largely influencing results. However, correctly modelling more important side-effects may alter conclusions. For example, aspirin treatment increased the risk of major gastrointestinal bleeding (OR 1.7, 95% CI 1.4 - 2.1).[105] Increasing the excess risk for gastrointestinal bleeding with aspirin use above base-case values or modelling an excess risk for hemorrhagic stroke separately reduced the cost-effectiveness of aspirin. When Pignone modelled hemorrhagic stroke separately, aspirin was less effective and more costly than no therapy, instead of being dominant, for men with a 10-year CHD risk of 5% or less (table 20).[90]

Disutility of taking medication

None of the studies included the disutility of taking daily medication in their base case. As medication is prescribed for life, there may be a disutility associated with it. Most studies do not comment on this or assume this loss in utility is small in comparison to the benefits received and therefore is not modelled.[30] Only Pignone[90, 96] included this in a sensitivity analysis. In his two studies, results were sensitive to whether or not this was taken into account. If persons with a 10-year risk for CHD of 7.5% who take aspirin are assumed to have even small reductions in utility (<0.9975) from the burden of taking a pill each day, aspirin becomes less effective than no treatment.[90]

4.2.7 Comparator

In economic evaluations, it is important to choose the right comparator. Almost all studies evaluating the cost effectiveness/utility of statins compare treatment with no treatment. The cost-effectiveness of interventions should, however, be calculated according to the efficiency frontier. Aspirin, for example, which is cheaper but less effective than statins, is a more appropriate comparator for statins than placebo. From a health economic point of view, using placebo as the comparator will result in more favourable ICERs for statins.

Most studies mention that they use placebo as a comparator. Sometimes, however, this does not mean that no treatment is given at all. For example, in one of the Swedish studies, treatment guidelines in the underlying study recommended additional open-label active antihypertensive treatment in both treatment groups for patients whose blood pressure remained high.[98] The study therefore actually compared the intervention (candesartan-based treatment) with usual antihypertensive treatment (not including candesartan). Other studies do not explicitly comment on this. The underlying trials should be studied to have a clear view on the exact meaning of 'placebo'.

In one of the Japanese studies, lifestyle modification and dietary therapy was mentioned to be basic treatment in all categories. The authors therefore assumed that patients had already tried therapeutic lifestyle modifications for several months (e.g., reduced intake of saturated fat and cholesterol, increased physical activity, and weight control).[87] Some studies are critical towards the benefit of diet and exercise. Studies of dietary and other lifestyle modification strategies to reduce lipid and non-lipid risk factors for coronary artery disease (CAD) have failed to consistently show any long term health benefits in terms of significantly decreased mortality or CAD morbidity.[85] The benefits of these risk reduction strategies in terms of cholesterol reduction are typically small and of short duration, often due to poor adherence to dietary changes.[106, 107]

Pignone mentioned he did not examine other effective options for reducing risk for CHD, such as smoking cessation, hypertension treatment, and counselling to increase physical activity. Because these treatments have benefits that go beyond reducing the risk for CHD, they should

be considered independently of the decision to prescribe aspirin or statins for patients in whom they are applicable.[90]

Only two studies explicitly take a no placebo comparator into account: the first compares aspirin versus no therapy and the combination of aspirin and statins versus aspirin (table 20),[90] while the second evaluates the cost effectiveness of four risk-lowering interventions and calculated the ICER of these interventions on the efficiency frontier (table 24).[38] As results show, this approach has a large influence on the ICERs. Treatment with antihypertensives and smoking cessation with GP advice, which is cost saving if the comparator is no treatment, become subject to extended dominance. Treatment with statins is not cost effective when comparing with aspirin treatment in a population with a 10-year coronary heart disease risk below 30% according to the Anderson risk equation.[38]

4.2.8 Transferability

None of the studies included in this review have been conducted for Belgium according to the Belgian pharmacoeconomic guidelines.[108] Transferability of results to other settings and across countries may be limited. Taking into account methodological, cost and benefit differences, we looked for the studies that are most suitable to make general recommendations for the Belgian situation.

In the first place, we excluded the Japanese studies. Mortality from CHD in Western countries is considered to be about fourfold higher than that in Japan. It has been reported that validated age-standardized CHD mortality rate ratios in the United States were 4.1 times higher for men (95% CI: 3.1, 5.4) and 3.9 times higher for women (95% CI: 2.4, 6.3) than those in Japan.[109]

Next, the Belgian guidelines recommend to perform the analysis from the perspective of the health care payer. One third of the studies performed the analysis from the societal perspective taking into account different indirect costs which influence results.

From the remaining studies, our preference goes in the first place to the Dutch study.[38] It was the only study taking into account smoking cessation and antihypertensives, next to aspirin and statin treatment, and presenting the ICERs toward the other interventions instead of placebo. In contrast to several other studies, the time horizon applied was 10 years for both costs and benefits, which is a more conservative approach than assuming a lifetime benefit. In contrast to the Belgian guidelines, which recommend discounting costs and benefits at respectively 3% and 1.5%, the discount rate applied in the study was 4% for both costs and benefits. However, the sensitivity analysis confirmed that the order in the cost-effectiveness ratios was not sensitive to changing discount factors for either costs or effects.

The most important problem to transfer results of the Dutch study to Belgium may be the cost differences. Lundkvist remarks it may be reasonable to assume that the results of his cost-effectiveness analysis are valid for at least Northern and Western European countries,[98] since the first-year costs for stroke are similar in Sweden, Denmark, France, Germany and the Netherlands.[110] However, results are especially sensitive to the initial cost of treatment. At the moment of the Dutch study, the cheapest generic statin (medication cost: €157/year) could still not compete with smoking cessation or aspirin in terms of cost effectiveness, but ICERs were at about the level of antihypertensive treatment.[38] However, prices for statins have a tendency to decrease even further. Therefore, it will be important to compare the costs from this study with current and future prices in Belgium.

Estimates for Belgium

Table 5 describes the cost data applied in the original study of Franco et al.[38] and the current Belgian cost data for these interventions. Antihypertensives were not taken into account since this intervention was dominated by aspirin treatment. A scenario in favour of statins was worked out. Table 5 presents the costs of interventions both from the original study and current Belgian costs. Whereas the costs for smoking cessation and aspirin were conservative, the costs for statins were very low assuming the cheapest alternative. Taking into account current prices and a 20mg dose per day for pravastatin, these costs accounted for €87.08.

Table 5: costs (in euro) for interventions (data original model versus Belgian costs)

Intervention	Data original study	Belgian data
SC GP advice	**26.29**	**20.79**
GP fee	26.29	20.79[a]
SC Nicotine substitutes	**117.79**	**150.58**
medication costs	117.79	150.58[b]
SC bupropion	**188.64**	**184.91**
medication costs	135.85	140.11[c]
GP fee	26.29	41.58
Costs telephonic consultation	13.14	0.00[d]
costs for prescriptions and prescription renewals	13.36	3.22[e]
Aspirin	**54.26**	**48.77**
medication costs	27.97	27.98[f]
GP fee	26.29	20.79
Statins	**602.69**	**150.52**
medication costs	484.92	87.08[g]
GP fee	52.58	41.58[h]
Costs for blood sample taking	12.19	15.42[i]
costs for prescriptions and prescription renewals	53.00	6.44[j]

[a] Fee consultation accredited general practitioner (GP).
[b] Depending on the type of nicotine patch, the cost for the cheapest alternative varied between €142.59 and €158.56. The average of these two costs was taken into account.
[c] One box of 100 units (€97.91) completed with one box of 30 units (€42.2) is enough to fulfil this therapy.
[d] In Belgium there is no possibility to pay a fee for a telephonic consultation. Instead, the fee of a normal consultation was taken into account, i.e. two visits instead of one visit and one telephonic consultation.
[e] A fee for advice is taken into account. Prescriptions and prescription renewals fall into this category. This fee can not be added with a fee for consultation.
[f] The average cost of 75mg (€7.68/120 units) and 100mg (€2.68/30 units) aspirin per day for 365 days was taken into account.
[g] The cheapest statin on the market at the moment of the study, taking into account a normal dose, was Pravastatine Teva® 20mg (€23.38 for 98 units of 20mg).
[h] The fee for two consultations.
[i] This is the sum of the following three costs: €2.33 (dose total cholesterol), €4.36 (Dose HDL-cholesterol), and €8.73 (Dose LDL-cholesterol).
[j] The cost for two renewals (fee for advice: €3.22).

We obtained access to the original model by kind permission of Dr. Franco and used this to calculate the ICER's using the Belgian cost estimates for the interventions. The description of the population is the same as in the original study. Moderate risk is defined as 10-20% 10-year absolute risk of CHD (Framingham). For high risk patients this is 20-30%. Modelling outcomes above 30% risk was not possible in the original study due to a lack of data.

The results of the ICER when comparing interventions with placebo are shown in table 6. Table 7 presents the ICER of the interventions on the efficiency frontier. The efficiency frontier is constructed by ranking the interventions in terms of their effect, excluding strictly dominated and extended dominated options, and linking the remaining interventions. The ICER of interventions is not calculated versus placebo but towards the previous most effective and non-dominated intervention. Graphically, the slope of this frontier corresponds to the ICERs of the non-dominated interventions.

Table 6: ICERs (cost per year of life saved) of interventions versus placebo

Risk group	Moderate		High	
Age / Intervention	50	60	50	60
SC GP advice	Cost saving		Cost saving	
SC nicotine substitutes	Cost saving		Cost saving	
SC bupropion	Cost saving		Cost saving	
Aspirin	14 090	10 570	1 519	986
Statins[a]	40 987	28 253	15 593	12 992

SC: smoking cessation; GP: general practitioner.
[a]: a very optimistic price scenario is applied, i.e. the lowest price when administering a low dose (pravastatin Teva® 20mg).

Table 7: ICERs (cost per year of life saved) of interventions on the efficiency frontier

Risk group	Moderate		High	
Age / Intervention	50	60	50	60
SC GP advice	dominated by SC nicotine substitutes			
SC nicotine substitutes	Cost saving		Dominated by SC bupropion	
SC bupropion	2 792	2 287	Cost saving	
Aspirin	30 504	13 038	6 892	4 749
Statins[a]	87 259	50 649	49 810	29 350

SC: smoking cessation; GP: general practitioner.
[a]: a very optimistic price scenario is applied, i.e. the lowest price when administering a low dose (pravastatin Teva® 20mg).

The results show that smoking cessation is an intervention which should be encouraged both from a health impact and from an economic point of view. For smokers, low-dose aspirin treatment could be considered for a high-risk population (Framingham 20-30%) or for older people with moderate risk (Framingham 10-20%). For non-smokers, i.e. comparing low-dose aspirin treatment with placebo (table 6), aspirin treatment is cost effective in all subgroups. The results for statin treatment are not very cost-effective. Only for the high risk group aged 60, the intervention could be considered borderline cost-effectiveness (€29 350/YLS). This is under the assumptions that only the cheapest alternative (less than €90 per year) would be prescribed. In reality this is not the case. Therefore, we can conclude statin treatment not to be cost effective for primary prevention of CVD/CHD in the moderate or high risk population with current prescribing practices. For the very high risk population (Framingham >30%) no results are shown. In theory, due to the higher baseline risk on coronary events, an equal relative improvement would translate in a higher absolute risk reduction and improve the cost-effectiveness of this intervention. As such, cost-effectiveness could decrease under €30 000/YLS. This is still under the assumption that the cheapest alternative of less than €90 per year is administered which is not true if the dose would increase or if more expensive statins are prescribed. Further research is needed to be able to make clear conclusions on the very-high risk group.

Not only cost-effectiveness but also affordability (budget impact) should be considered. Increasing the Belgian SCORE threshold from 5% risk to 10% decreases the target population with about 370 000 individuals. The health benefits per patient are smaller for lower-risk populations. In contrast, a lower-risk population corresponds to a much larger population. Therefore, in these relatively healthy populations, the health gains are smaller but they have a much larger budget impact.

4.3 CONCLUSIONS

From this systematic review of economic literature of primary prevention of CVD, we conclude that it is necessary to incorporate not only baseline risk of CHD but also age and gender into the discussion, just as guidelines also take into account the combination of these factors and estimate the global cardiovascular risk.

Depending on which study is selected, more positive or negative conclusions for certain interventions can be presented. However, based on several arguments, we judge the results of one study, i.e. the recently published Dutch study,[38] most transferable to the Belgian context.

Smoking cessation therapies represent savings in all situations, but obviously, this therapy can only be offered to smokers. It is important to assess the CHD risk level of smokers after quitting smoking. If smoking is the factor that brings the person into the 'treatment zone' of risk, smoking cessation is the natural intervention. If this risk remains high also without smoking, further treatment may be necessary.

For non-smokers, low-dose aspirin treatment is the most cost-effective option, with important effects and relatively low cost for its benefits. Statins in contrast showed better results in the Dutch study in terms of YLS, YLS free of CHD, and number of deaths prevented. The cost of treatment, however, was still too high to offer this therapy to everybody who may benefit, even when statins off-patent were considered. Larger reductions in the price of statins are needed before they can be given to populations at levels of 10-year CHD risk below 30 percent.[38]

We have to remark that it can be misleading to recommend the prescription of a certain treatment based on simulations using the cheapest alternative, if in reality more expensive alternatives are prescribed to a large extent. When the decision has been made to prescribe a statin, it is recommended that therapy should usually be initiated with a drug with a low acquisition cost, taking into account required daily dose and product price per dose.[88]

It is also important to focus on the population. Low-cost lifestyle interventions are important for the majority of the population, but when pharmaceutical interventions are considered, more attention should be given to high-risk populations and less to those at lower risk. First of all, in absolute numbers, the benefits for low-risk populations are limited and may be questionable because expected effects come from extrapolations of effects from high-risk groups. In contrast, the disutility of treatment and possible side-effects apply to the whole population. Moreover, the budget impact should not be underestimated since we are talking about a large population.

Treatment benefits are also questionable for women, as is also discussed in chapter 3. A study performing an analysis exclusively for a female population found in a probabilistic sensitivity analysis that for 65-year-old women at moderate CVD risk (10-year total CHD risk of 7.5%) there was a 27% chance that aspirin produces fewer QALYs than no treatment, a 35% chance that the cost-utility ratio was less than $50 000/QALY, and a 37% probability that it was greater than $50 000/QALY.[96] The wide range of possible outcome reflects important uncertainty, showing that there is a real danger of doing more harm than good. For elderly man, no data were retrieved.

Most of the clinical trials did not include people at very low risk of a CHD event or a large proportion of women. Before recommendations can be made for these populations, additional empirical research is needed to have a clear view on benefits and side effects of treatment in these populations.

Key points

- **Smoking cessation is the most recommended intervention for smokers and is even cost-saving.**
- **In low risk individuals (Framingham < 10%), there are no arguments to initiate pharmaceutical treatment, since it is uncertain that benefits outweigh possible harms.**
- **Low-dose aspirin is a more cost-effective preventive intervention than statins and anti-hypertensives at all risk levels.**
- **Available simulations highly depend on the cost of treatment. Taken into consideration the recent lowering of statin prices, cost-effectiveness measures will be rendered more favourable.**
- **Statin therapy in primary prevention of CVD for men at levels of 10-year Framingham CHD risk above 20% and at ages above 60 years, becomes borderline cost-effective compared to low-dose aspirin (€ 30 000 per life-year gained) only if there is a widespread prescription of the cheapest alternative (< €90 per year).**
- **In women of all ages and in men above the age of 70 no solid evidence about clinical effectiveness of statin use in primary prevention is available. Economic evaluations for those populations were based on extrapolations of effectiveness in other subgroups. More research should be performed first to the benefits and harms of treatment in these populations.**

5 CV GUIDELINE IMPLEMENTATION IN GENERAL PRACTICE IN BELGIUM

This chapter is the summary of a study performed by Domus Medica (previously 'Wetenschappelijke Vereniging van Vlaamse Huisartsen') between October 2005 and February 2007, as part of the KCE project "2005-02 GCP - cardiovascular prevention". The full study (mainly in Dutch) can be found in the appendix.

The original research questions were:

- What is the current practice of preventive cardiovascular care in Belgian general practice, and what are the main factors that either hinder or facilitate correct implementation of the guidelines (barriers and facilitators), without focusing on any specific guideline or tool?
- Which interventions are most likely to promote the correct implementation of preventive cardiovascular care in general practice in terms of effectiveness, cost-effectiveness, applicability and acceptation by GPs?

This study consisted of a **telephone survey** in a random sample of Belgian GPs (Dutch or French speaking) to assess current practice. For the Dutch speaking GP population this was performed by Domus Medica (DM), and for the French speaking GPs they collaborated with 'Promotion Santé et Médecine Générale' a joint organisation formed by the 'Société Scientifique de Médecine Générale' (SSMG) and the 'Fédération des Maisons Médicales' (FMM). The **desk research** on previous implementation efforts was done by DM in collaboration with the DM guideline development author group for CV care (see also chapter 1 of this report). This desk research assessed previous implementation efforts in Belgium and on the international level. The initial intention was to validate these results and find out about additional facilitators and barriers in 4 **focus groups** with 8 to 12 participants. However, ambitions had to be revised due to the very low attendance, so it was decided to consider those sessions with in total 13 participants not as focus groups but rather as informative GP group discussions. Those discussion sessions were conducted by DM, and in collaboration with 'Promotion Santé et Médecine Générale' for the French speaking GP's

5.1 CURRENT PRACTICE: THE TELEPHONE SURVEY

The telephone survey (for full report see chapter 2 of the appendix to this chapter) was intended to describe knowledge, attitudes and practice about preventive CV care. The central questions of the survey were 3 quality criteria: use of an instrument to assess the CV risk, knowledge of the smoking status of the patient and the attitude towards delivering the 'short smoke stop advice'.

The surveyed populations were two random samples of 250 Dutch and 250 French language GPs who, in 2004, did at least a 1000 consultations per year.

The semi-structure questionnaire was developed based on previous questionnaires, on literature and on internal discussion. It should be noted that the French questionnaire differed slightly from the Dutch questionnaire. The interviews in Dutch were performed by 3 Flemish GPs participating in the study. The interviews in French were performed by a non-GP. Interviewers were briefed orally and on paper. If GPs were not available for interview by the third, or sometimes the fourth contact they were considered as non-responders.

The complete survey was effectively performed in 286 of the 448 GPs who were eligible for participation (63.8%). Response rates were higher in the Dutch speaking GPs (75% vs. 53% in French speaking). Over 4 in 5 Belgian GPs (82.9%) ever used an instrument for the evaluation of CV risk, but current use was 39.7% in Dutch speaking GPs and 12.9% in French speaking GPs. A similar number (85%) thought of themselves as 'up to date with current recommendations'. Most GPs (68%) received training about CV risk assessment in the preceding two years.

An electronic medical record system is used more by Dutch speaking than by French speaking GPs (73% vs. 49%). Smoking status is *'mostly'* available in the medical records of 62.5% of the respondents in general and in 59.8% of those using an electronic medical record system, more than could be expected from previous research on electronic medical records in Belgium.

The average proportion of medical records that actually contain smoking status is reported to be higher with French speaking (64.8%) than with Dutch speaking (38.3%) GPs. Most GPs (87%) report they tend to give a 'short smoke stop advice' and they estimate that on average 12% of smokers will quit smoking after this, a much higher proportion than apparent from evidence (2%). Those who actually do give this advice estimate the effect to be even higher.

This survey shows that most Belgian GPs are familiar with global CV risk management, and especially the usage of the tools. In daily practice, however, those tools are not frequently used, especially not by French speaking GPs. GPs overestimate their performance on the risk factor smoking.

5.2 PREVIOUS IMPLEMENTATION EFFORTS: THE DESK RESEARCH

The purpose of the desk research (for full report see chapter 1 of the appendix to this chapter) was to describe:

- the conceptual framework surrounding implementation strategies to reduce discrepancies between recommended and actual CV risk assessment practice
- the quality indicators from Belgian GP recommendations
- the available values for this indicators for Belgian GPs (mainly Flemish), in other words, data from practice
- the studies and projects where Belgian GPs (mainly Flemish) are involved

Literature is based on a literature search in both Medline and in the documentation resources from DM (including 'Huisarts Nu', and the abstracts from the yearly first line symposia: ELS). Additional literature was found through reference searching and grey literature was also found.

Quality criteria for CV preventive care were retrieved and from those potential indicators were defined, limiting this list to those indicators that at least 2 researchers found relatively useful, clear, acceptable and achievable.

For the overview of local projects and practice data the ELS abstracts were screened from 2003-2005 and the GP journal 'Huisarts Nu' starting in 2000.

Successful implementation strategies are essentially a combination of strengthening the facilitators and reducing the barriers, to achieve a change in attitude in the GP. Those factors are often categorized as:[111]

- Individual factors such as GPs' and patients knowledge, skills, and attitudes
- Social factors surrounding health care
- Organisation of health care
- Factors related to the texts and tools or instruments

Interventions that were described in Belgium target the GP mainly as a professional, while in the international intervention studies also more combined implementation strategies were tested. However, due to the different health care systems and the specific settings of these studies, we have to take great care while trying to extrapolate results to Belgian general practice or even while comparing the results between them. Factors from all 4 categories mentioned above are addressed in those studies.

Based on quality criteria in the existing Belgian recommendations, **71 indicators** were developed. The 'a priori' position was that the indicator values need to come from an electronic medical record system, and most of these are related to clinical care. Since the GP guideline on CV care was still under development, few indicators are related specifically to global CV risk management, and most indicators are related to single CV risk factors such as diabetes, hypertension and overweight. There are a similar number of indicators related to pharmaceutical intervention as related to life style intervention. From those 71 Belgian indicators, 38 were also used in international intervention studies.

Information from **46 Belgian GP projects** related to cardiovascular prevention are described,

and 4 larger projects are described in more detail. In 24 projects a small, prospective audit of the electronic medical records was performed in one or more practices, mostly within the framework of GP professional training. In 26 projects the focus was diabetes care, and in 7 projects (including 2 large-scale projects) the topic was global cardiovascular risk management.

From 27 of these projects indicator values could be extracted. For 25 of the 71 quality indicators in the Belgian recommendations no values could be found from research. The number of projects with indicator values on hypertension, diabetes and smoking is relatively important. Most indicator values were found for an indicator that was broadly interpreted as 'being able to produce a list of patients with a personal ischemic history or other specific problems'. Few indicator values on lifestyle advice and the follow-up on it were found.

5.3 CONCLUSIONS FROM TELEPHONE SURVEY AND DESK RESEARCH

To effectively implement current or future guidelines on CV risk management in general practice the authors suggest two priorities in the implementation strategy (for full conclusions see chapter 3 of the appendix to this chapter):

1. Electronic Medical Records Systems (EMRS) should be better equipped to collect risk factors and to allow GPs to perform a self-audit. GPs should receive appropriate training and support for using their EMRS for systematic registration.
2. Instruments should be developed to aid GPs to better communicate CV risk, and if necessary its management, to their patients.

In the literature there is consensus that a combined, multifaceted and repeated intervention is the best way to achieve effective change of practice. However, if interventions are implemented in a context other than the one in which they have proved to be successful, it is uncertain that they will be equally successful in this different context. As a consequence, it is impossible at this stage to present a list of interventions that are certain to be generally effective in implementing CV risk management in Belgian general practice. In Belgium, intervention studies were only conducted within groups of French speaking GPs, through studies to implement an algorithm for CV risk management. For Dutch speaking GPs the research was limited to the description of interventions that mainly had the GP as a professional as its target. About the effects of additional funding, incentives, (re-)organization of care and the promotion of patient involvement almost no data are available. About the effect of the global medical record (GMD), again, no data are presented since it has not been the target of primary research so far. In the current ResoPrim project the research question about the potential impact of the GMD has been asked, but validated data are missing at the moment.

Although this report is about Belgian general practice, the focus was on Dutch language projects, and therefore no systematic search was performed for information about projects and research with French speaking GPs, other than the information available through Medline, or through the documentation recourses from DM. The homologue of 'Huisarts Nu', the 'Revue de la Médecine Générale' for example was not searched. However, through contacts with their French speaking research partners, the authors believe that they have not missed important information about CV care by French speaking GPs in Belgium, including the educational projects conducted by the 'Observatoire de la Santé du Hainaut',[112] and the various feasibility studies in daily general practice concerning the 'Boland' algorithm.[18]

5.4 PERCEPTION: GP GROUP DISCUSSION SESSIONS

Originally 4 focus groups were planned with 8 to 12 participants (GPs) to validate the results of the telephone survey and the desk research. The focus groups also aimed to find out about additional facilitators and barriers to the implementation of CV risk management. However, ambitions had to be revised due to the very low attendance. Therefore we could not consider those sessions as focus groups but rather as informative discussion sessions.

The sessions took place during January and early February 2007. Three discussion sessions were held with in total 13 participants (7 Dutch and 6 French speaking participants).

There was a large consensus (see chapter 4 of the appendix for full report) between participants in terms of the factors they mentioned as facilitating or hindering for the implementation of global cardiovascular risk management in their daily practice, both within as between the groups.

The key factor perceived by GPs as hindering the implementation of global cardiovascular risk management in general practice was that it is very hard to change lifestyle behaviour in patients. Four important stakeholders were identified to facilitate this lifestyle behaviour change: patients themselves need to understand and feel the need for change, GPs need to have enough time available as well as tools to assess and communicate risk, the media can contribute through information campaigns targeted to educate and motivate patients and finally the authorities can contribute by launching such campaigns (for more details see appendix for this chapter).

Also noteworthy is the opinion of our participants that the most important barriers and facilitators were the same regardless of a patient's cardiovascular history. Both in patients with a previous cardiovascular event as in those without, the patient's motivation is rarely considered high enough in comparison to his/her respective risk level.

The majority of the GPs in our 3 group discussions attributed relatively little importance to improvement of the knowledge, skills, and attitudes of GPs themselves. Nevertheless our past research and experience showed that there is a need for GPs to further work on their own expertise and skills and to pay more attention to prevention. Several possible explanations are advanced why this seemed to be no important issue according to the GPs in our discussion groups.

6 APPENDIX

APPENDIX FOR CHAPTER 3

RAPID ASSESSMENT OF RECENT EVIDENCE FOR LIPID MANAGEMENT THROUGH DIETARY INTERVENTIONS AND STATIN USE.

No full systematic review (SR) of the clinical literature has been performed in this rapid assessment. We started our search by studying the two most recently published guidelines (NHS in 2005/2006 and SIGN in 2007) on prevention of cardiovascular disease.[29, 22] Furthermore, a limited literature search was performed through Medline (PubMed), Cochrane, SUMSearch and DARE for RCTs and SRs published in 2006 and 2007 and earlier if needed.

Our interest for the clinical effectiveness of risk factor interventions focused on dietary interventions and on statins. For Medline, the following MeSH terms were used: "primary prevention" and "cardiovascular disease". For phytosterols we additionally searched for MeSH terms: phytosterols, phytosterols AND hypercholesterolemia. The reference tables of the retrieved papers were examined for further relevant information. Specific searches were performed for systematic reviews and guidelines, subsequently followed by searches by study type, i.e. individual clinical trials.

After sifting the literature our main sources of evidence were:

1. SIGN: Risk estimation and the prevention of cardiovascular disease. February 2007.[22]
2. P. Thavendiranathan et al. Primary prevention of cardiovascular diseases with statin therapy. A meta-analysis of randomised controlled trials. Arch Intern Med 2006;166:2307-2313.[71]
3. Nakamura et al. Primary prevention of cardiovascular disease with pravastatin in Japan (MEGA Study): a prospective randomised controlled trial. Lancet 2006;368:1155-63.[66]
4. J. Costa et al. Efficacy of lipid lowering drug treatment for diabetic and non-diabetic patients: meta-analysis of randomised controlled trials. BMJ 2006;332;1115-1124 (3 April 2006).[72]
5. NHS: Statins for the prevention of cardiovascular events. January 2006. Technology appraisal 94, based on: Ward S, Lloyd Jones M, Pandor A et al. Statins for the prevention of coronary events, January 2005.[29]
6. L Hooper et al. Reduced or modified dietary fat for preventing cardiovascular disease. Cochrane Database of Systematic Reviews, most recent update: 19 august 2005.[43]
7. B Howard et al. Low-fat dietary pattern and risk of cardiovascular disease: the Women's Health Initiative Randomized Controlled Dietary Modification Trial. JAMA. 2006;295(6):655-66.[44]
8. L. Hooper et al. Risks and benefits of omega 3 fats for mortality, cardiovascular disease, and cancer: systematic review. BMJ. 2006;332(7544):752-60.[51]
9. Alice H. Lichtenstein, Lawrence J. Appel, Michael Brands, Mercedes Carnethon, Stephen Daniels, Harold A. Franch, Barry Franklin, Penny Kris-Etherton, William S. Harris, Barbara Howard, Njeri Karanja, Michael Lefevre, Lawrence Rudel, Frank Sacks, Linda Van Horn, Mary Winston, and Judith Wylie-Rosett. Diet and Lifestyle Recommendations Revision 2006: A Scientific Statement From the American Heart Association Nutrition Committee. Circulation 2006;114: 82-96.

APPENDIX FOR CHAPTER 4

SEARCH STRATEGY

We searched the databases Medline, Embase, and the three databases of the Centre for Reviews and Dissemination (CRD) (i.e. the National Health Service Economic Evaluation Database (NHS EED), Database of Abstracts of Reviews of Effectiveness (DARE), and the Health Technology Assessment database (HTA)).

We searched for papers published between 2001 and February 2007. One of the included studies provided a pooled analysis on the cost-effectiveness of statins in coronary heart disease.[82] This study searched for papers between 1990 and July 2002. The most recent published papers included in their analysis were published in 2001. Therefore, we preferred to take 2001 as our cut-off.

The following four tables provide an overview of our search strategy.

Table 1: Search strategy for Medline (performed on 12 February 2007)

1	Economics/	16	letter.pt.
2	exp "costs and cost analysis"/	17	editorial.pt.
3	"Value of Life"/ec [Economics]	18	historical article.pt.
4	Economics, Dental/	19	16 or 17 or 18
5	exp Economics, Hospital/	20	15 not 19
6	Economics, Medical/	21	Animals/
7	Economics, Nursing/	22	Humans/
8	Economics, Pharmaceutical/	23	21 not (21 and 22)
9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8	24	20 not 23
10	(econom$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).tw.	25	(metabolic adj cost).ab,hw,ti.
		26	((energy or oxygen) adj cost).ab,hw,ti.
		27	24 not (25 or 26)
11	(expenditure$ not energy).tw.	28	exp Cardiovascular Diseases/
12	(value adj1 money).tw.	29	exp Primary Prevention/
13	budget$.tw.	30	28 and 29
14	10 or 11 or 12 or 13	31	("2001" or "2002" or … or "2007").yr.
15	9 or 14	32	27 and 30 and 31

Table 2: Search strategy for Medline In-Process & Other Non-Indexed Citations (performed on 13 February 2007)

1	cost$.mp. [mp=title, original title, abstract, name of substance word]
2	economic$.mp. [mp=title, original title, abstract, name of substance word]
3	budget$.mp. [mp=title, original title, abstract, name of substance word]
4	expenditure$.mp. [mp=title, original title, abstract, name of substance word]
5	1 or 2 or 3 or 4
6	cardiovascular disease.mp. [mp=title, original title, abstract, name of substance word]
7	primary prevention.mp. [mp=title, original title, abstract, name of substance word]
8	6 and 7
9	5 and 8

Table 3: Search strategy for Embase (performed on 13 February 2007)

1	'socioeconomics'/exp	20	variable*:ti,ab,de,cl
2	'cost benefit analysis'/exp	21	unit:ti,ab,de,cl
3	'cost effectiveness analysis'/exp	22	'#19 *4 #18' or '#18 *4 #19'
4	'cost of illness'/exp	23	'#19 *4 #20' or '#20 *4 #19'
5	'cost control'/exp	24	'#19 *4 #21' or '#21 *4 #19'
6	'economic aspect'/exp	25	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #16 or #17 or #22 or #23 or #24
7	'financial management'/exp		
8	'health care cost'/exp		
9	'health care financing'/exp	26	'cardiovascular symptom'/exp
10	'health economics'/exp	27	'heart disease'/exp
11	'hospital cost'/exp	28	'hypertension'/exp
12	'finance'/exp	29	'vascular disease'/exp
13	'funding'/exp	30	#26 or #27 or #28 or #29
14	Fiscal	31	'primary prevention'/exp
15	Financial	32	#30 and #31
16	#12 or #13 or #14 or #15	33	#32 and ([article]/lim OR [review]/lim)
17	'cost minimization analysis'/exp	34	#33 and ([english]/lim or [dutch]/lim or [french]/lim)
18	estimate*:ti,ab,de,cl		
19	cost*:ti,ab,de,cl	35	#25 and #34 and [2001-2007]/py

Table 4: Search strategy for CRD: DARE, NHS EED and HTA (performed on 12 February 2007)

1	MeSH Cardiovascular Diseases
2	MeSH Heart Diseases
3	1 or 2
4	MeSH Primary Prevention
5	3 and 4
6	RESTRICT YR 2001 2007

RESULTS OF SEARCH STRATEGY

We found 447 references using the databases: 124 with Medline, 307 with Embase and 16 with the NHS EED, DARE, and HTA databases (table 5). After removing 28 duplicates, 419 articles were left.

Table 5: Result of our search strategy for cost-effectiveness studies.

Database	**Years**	**References identified**
Medline	2001 - week5 2007	119
Medline In-Process & Other Non-Indexed Citations	February 12, 2007	5
Embase	2001-2007	307
CRD	2001-2007	
DARE		5
NHS EED		9
HTA		2
Total references identified		447
Duplicates		28
Total		419

CRD: Centre for Reviews and Dissemination; DARE: Database of Abstracts of Reviews of Effects; NHS EED: NHS Economic Evaluation Database.

Inclusion and exclusion criteria

Full economic evaluations that compare two or more options and consider both costs and consequences were eligible. Cost-effectiveness and cost-utility analysis expressing results as costs per life-year gained (LYG) or costs per quality-adjusted life years (QALYs) gained were taken into account. Cost analysis or studies presenting results as cost per event avoided were not considered. The populations described had to fulfil criteria to be able to speak of primary prevention and the studies had to be conducted for people in developed countries. Only non-hypothetical interventions were taken into account. In case of doubt, the full text was retrieved. Articles in English, French or Dutch were considered.

From the 419 references, 377 articles were excluded based on title, abstract and keywords (figure 1). Most of them were no full economic evaluations. The remaining 42 studies were retrieved. 11 studies fulfilled our selection criteria. The reference lists of the original 42 articles were hand searched for further references. Eight additional articles matched our inclusion criteria.

Figure 1: Flow chart for the selection of relevant economic evaluations

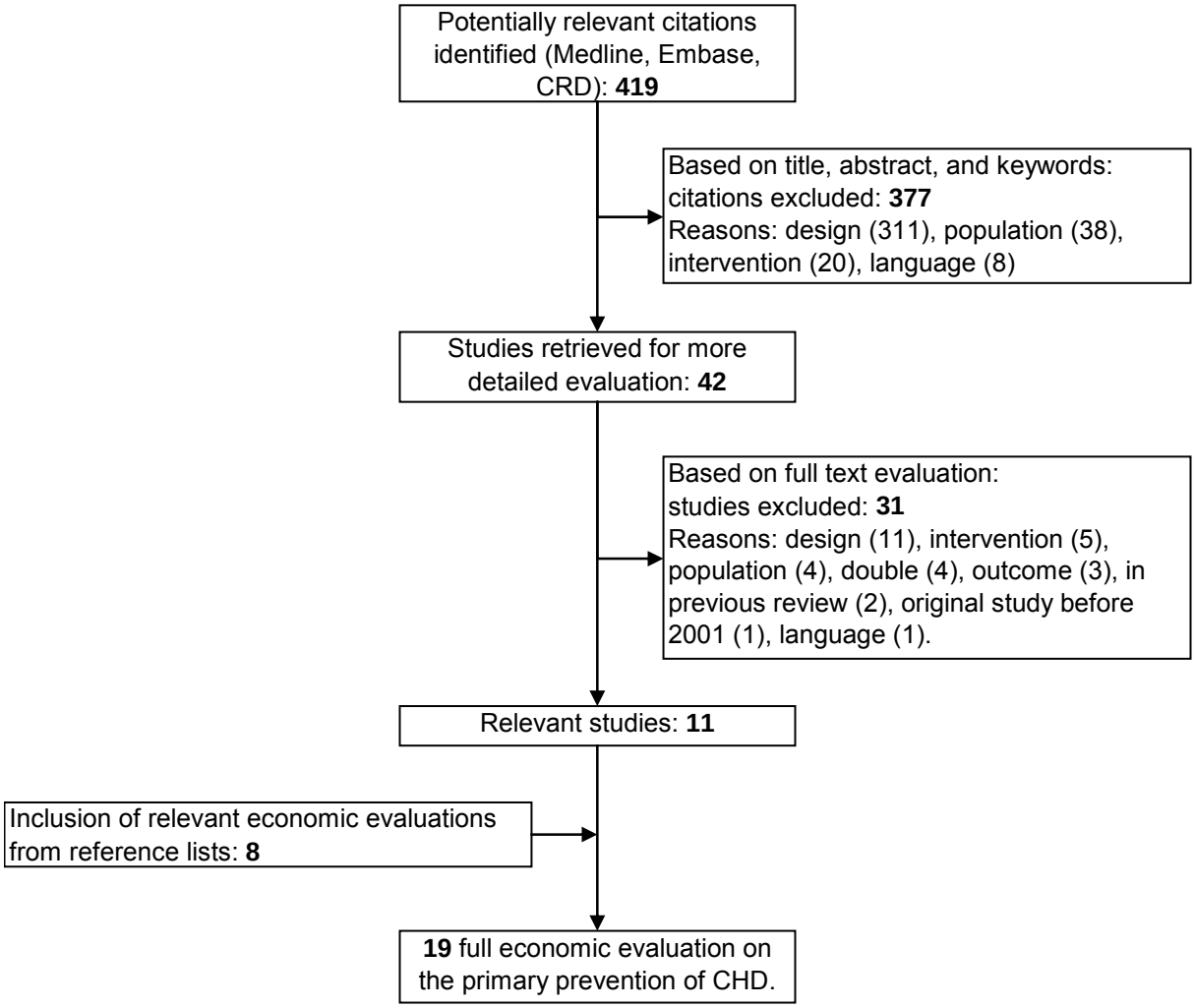


Table 6 presents the 19 studies satisfying all inclusion and exclusion criteria and form the basis of this review.

Table 6: 19 economic evaluations on the primary prevention of CHD/CVD.

Authors	Title
Statins versus no treatment	
Johannesson M.[84]	At what coronary risk level is it cost-effective to initiate cholesterol lowering drug treatment in primary prevention? Eur Heart J. 2001;22(11):919-25.
Lim SS, Vos T, Peeters A, Liew D, McNeil JJ.[83]	Cost-effectiveness of prescribing statins according to Pharmaceutical Benefits Scheme criteria. Medical Journal of Australia. 2001;175(9):459-64.
Grover SA, Ho V, Lavoie F, Coupal L, Zowall H, Pilote L.[86]	The importance of indirect costs in primary cardiovascular disease prevention: can we save lives and money with statins? Archives of Internal Medicine. 2003;163(3):333-9.
Spaans JN, Coyle D, Fodor G, Nair R, Vaillancourt R, Grover SA, Coupal L.[85]	Application of the 1998 Canadian cholesterol guidelines to a military population: health benefits and cost effectiveness of improved cholesterol management. Can J Cardiol. 2003;19(7):790-6.
Franco OH, Peeters A, Looman CWN, Bonneux L.[82]	Cost effectiveness of statins in coronary heart disease. J Epidemiol Community Health. 2005;59(11):927-33.
Nagata-Kobayashi S, Shimbo T, Matsui K, Fukui T.[87]	Cost-effectiveness of pravastatin for primary prevention of coronary artery disease in Japan. International Journal of Cardiology. 2005;104(2):213-23.
Ward S, Lloyd J, Pandor A, Holmes M, Ara R, Ryan A, Yeo W, Payne N.[30]	Statins for the Prevention of Coronary Events. Technology assessment report commissioned by the HTA Programme on behalf of the National Institute for Clinical Excellence. Sheffield: ScHARR The University of Sheffield; 2005 January 2005.
Scotland NHSQI.[88]	Statins for the prevention of cardiovascular events. 2006.
Walshe V, Nash A, Barry M.[89]	Cost effectiveness of statin therapy for the primary prevention of coronary heart disease. Irish Medical Journal. 2006;100(1):144-5.
Fibrates versus no treatment	
Hay JW, Sterling KL.[91]	Cost effectiveness of treating low HDL-cholesterol in the primary prevention of coronary heart disease. PharmacoEconomics. 2005;23(2):133-41.
Aspirin versus no treatment	
Annemans L, Lamotte M, Kubin M, Evers T, Verheugt FWA.[93]	Which patients should receive aspirin for primary prevention of cardiovascular disease? An economic evaluation. International Journal of Clinical Practice. 2006;60(9):1129-37.
Lamotte M, Annemans L, Evers T, Kubin M.[94]	A multi-country economic evaluation of low-dose aspirin in the primary prevention of cardiovascular disease. Pharmacoeconomics. 2006;24(2):155-69.
Pignone M, Earnshaw S, Pletcher MJ, Tice JA.[96]	Aspirin for the primary prevention of cardiovascular disease in women: a cost-utility analysis. Arch Intern Med. 2007;167(3):290-5.
Tsutani K, Igarashi A, Fujikawa K, Evers T, Kubin M, Lamotte M, Annemans L.[95]	A health economic evaluation of aspirin in the primary prevention of cardiovascular disease in Japan. Intern Med. 2007;46(4):157-62.
Aspirin versus no treatment and aspirin plus statin versus aspirin	
Pignone M, Earnshaw S, Tice JA, Pletcher MJ.[90]	Aspirin, statins, or both drugs for the primary prevention of coronary heart disease events in men: a cost-utility analysis. Annals of Internal Medicine. 2006;144(5):326-36.
Antihypertensives versus no treatment	
Malik IS, Bhatia VK, Kooner JS.[97]	Cost effectiveness of ramipril treatment for cardiovascular risk reduction. Heart. 2001;85(5):539-43.

Authors	Title
Lundkvist J, Ekman M, Kartman B, Carlsson J, Jonsson L, Lithell H.[98]	The cost-effectiveness of candesartan-based antihypertensive treatment for the prevention of nonfatal stroke: Results from the Study on COgnition and Prognosis in the Elderly. Journal of Human Hypertension. 2005;19(7):569-76.
Diet and/or exercise	
Lindgren P, Fahlstadius P, Hellenius M-L, Jonsson B, de Faire U.[99]	Cost-effectiveness of primary prevention of coronary heart disease through risk factor intervention in 60-year-old men from the county of Stockholm--a stochastic model of exercise and dietary advice. Preventive Medicine. 2003;36(4):403-9.
Smoking cessation, antihypertensives, aspirin and statins	
Franco OH, der Kinderen AJ, De Laet C, Peeters A, Bonneux L.[38]	Primary prevention of cardiovascular disease: Cost-effectiveness comparison. International Journal of Technology Assessment in Health Care. 2007;23(1):71-9.

SUMMARY TABLES OF ECONOMIC STUDIES ON THE PRIMARY PREVENTION OF CV DISEASE

STATINS VERSUS NO TREATMENT

Table 7: Franco et al.[82]

Authors **Country** **Year of publication** **Conflict of interest**	**Intervention** **Population and/or base risk and/or applied risk function** **relative risk benefit**	**Analytic technique** **Year of costs, currency** **Costs details** **Utilities**	**Cost-effectiveness**	**Sensitivity analysis**	**Conclusion**
Franco OH, Peeters A, Looman CWN, Bonneux L. 24 studies were included: US (6), UK (3), Canada (8), Sweden (3), Belgium (1), Germany (2), and the Netherlands (1). 2005. No conflict of interest declared. **Perspective** **Time window** **Discount rate** Perspective: depending on primary study. The time horizon of treatment was classified in three categories: five years, 10 years, or >10 years/lifetime. Four discount rate categories were used: 3%, 5%, 6%, or none.	Statins versus no treatment. Only studies reporting results for male populations were included. The categories of annual risk of CHD at the start of treatment were: <1%, 1%–<2%, 2%–<3%, 3%–4%, and >4%. For each CER the authors wanted absolute risk of CHD of the study population before treatment. If not stated in the paper, they estimated risk by the D'Agostino CHD function using these variables: levels of total cholesterol (or LDL), HDL cholesterol, smoking, blood pressure, diabetes history, and personal history of CHD. RR benefit: depending on primary study.	Results of CEA were included (216 cost effectiveness ratios), pooled estimate and multilevel linear regression. As the CERs were reported using different currencies and dates, the authors standardised by calendar year and currency. Firstly, to correct for inflation, they converted all currencies into the same date: 30 December 2001, using the correspondent consumer price index (CPI). Afterwards all currencies were converted into US dollars of the date 30 December 2001.	The ratios reported ranged over an enormous range: from savings to $489 000/YLS. distribution of CERs by category of absolute risk (number of ratios): $ per YLS. Centile 10 / Median / Centile 90 <1% (33): 24505 / 48559 / 255893 1%-<2% (33): 10205 / 26933 / 73124 2%-<3% (13): 12951 / 23060 / 46273 3%-<4% (42): 7987 / 15048 / 48701 >4% (95): 5449 / 10607 / 21545	The aim of the authors was to evaluate the degree to which explanatory variables account for the observed variability in CERs between the studies. In the univariate analysis only absolute risk and category of prevention (primary or secondary) are significant. The interaction effects between absolute risk and the other explanatory variables: for age, cost country, category of prevention, funding source, year of publication, and discount factor the effect of absolute risk in the CER differed significantly between categories.	In conclusion, this review confirms how the cost effectiveness of statins treatment in the prevention of CHD is related to the absolute risk of CHD, but shows that within risk strata there still exists large variability in cost effectiveness estimates. Nearly all studies agree that treatment at high levels of risk is cost effective and at low levels is expensive. But in practice, it is not difficult to find CERs that fit any decision for the population at large with intermediate annual risk of CHD (1% to 4%). The most probable explanation for these differences is different methodology in the CEA, and the impact of funding source suggests the potential for some estimates to be biased.

Table 8: Lim et al.[83]

Authors Country Year of publication Conflict of interest	Intervention Population and/or base risk and/or applied risk function relative risk benefit	Analytic technique Year of costs, currency Costs details Utilities	Cost-effectiveness	Sensitivity analysis	Conclusion
Lim SS, Vos T, Peeters A, Liew D, McNeil JJ. Australia. 2001. No conflict of interest declared. **Perspective** **Time window** **Discount rate** The health system perspective. 20 years. An overall annual discount rate of 3% was used for all future costs and YOLS.	Pravastatin (40 mg/day for 20 years) versus no treatment. Australian men and and women, aged 25-85 years, excluding those with diabetes and existing CHD. The cost-effectiveness of treatment according to Pharmaceutical Benefits Scheme (PBS) criteria was compared against treatment criteria based on 15 year risk of CHD mortality cut-offs of ≥2.5% and ≥5% (MRFIT equation). PBS criteria for lipid-lowering therapy: In presence of: initiate drug therapy if: Existing CHD: TC > 5.5 mmol/L Diabetes mellitus, familial hyper-cholesterolaemia, family history of CHD, hypertension, or peripheral vascular disease: TC > 6.5 mmol/L or TC 5.5 mmol/L and HDL cholesterol < 1 mmol/L Patients with HDL cholesterol <1 mmol/L: TC > 6.5 mmol/L Men 35-75 years and postmenopausal women up to 75 years: TC > 7.5 mmol/L or fasting triglycerides > 4 mmol/L Others: TC > 9 mmol/L or fasting triglycerides > 8 mmol/L An exponential decline in compliance was modelled, which levelled off at 50% after three years. The effect of fully compliant therapy, 40 mg/day pravastatin was assumed to reduce the risk of CHD death within each age and sex stratum by 38% (95%CI: 23%-50%).	CEA, the CHD Prevention Model was used (type not explicitly mentioned). 1999, in Australian dollars (AUD). Annual drug acquisition cost per person: AUD924.42. Additional treatment related costs: uniform distribution, AUD27 - AUD153.80 Mean treatment-related costs were AUD76.90 and estimated to vary between AUD54.00 (two GP consultations, no serum lipid or liver function tests) and AUD153.80 (four GP consultations, two serum lipid and two liver function tests). Mean potential cost savings per death prevented (ranging between AUD20234 and AUD85677 per death prevented depending on age and sex).	Cost (AUD) per year of life saved. PBS criteria: men 110000 (80% uncertainty range) (96000-150000); women 87000 (80% uncertainty range) (80000-130000) ≥2.5% 15-year risk of CHD mortality: men 31000 (27000-40000); women 39000 (33000-53000) ≥5% 15-year risk of CHD mortality: men 23000 (20000-29000); women 37000 (32000-51000)	Probabilistic sensitivity analysis: The results of the uncertainty analyses examining the influence of uncertainty on cost per YOLS varied depending on the age at start of treatment. In general, uncertainty associated with the efficacy of statin therapy had the greatest impact (correlation coefficient between 0.7 and 0.8) on the cost per YOLS.	While PBS criteria do target patients at risk of CHD, there is room for improvement in identifying those most at risk of CHD, and treatment according to PBS criteria is not likely to be the most cost-effective. For optimal cost-effectiveness, targeting of therapy for primary CHD prevention needs to be based on population-specific, multivariable risk.

Table 9: Johannesson[84]

Authors Country Year of publication Conflict of interest	Intervention Population and/or base risk and/or applied risk function relative risk benefit	Analytic technique Year of costs, currency Costs details Utilities	Cost-effectiveness	Sensitivity analysis	Conclusion
Johannesson M. Sweden. 2001. No conflict of interest declared. **Perspective** **Time window** **Discount rate** The societal perspective. Lifetime: the members of the cohort were followed from their current ages to the age of 110 years. Costs and QALYs were discounted using a 3% discount rate.	Cholesterol lowering drug treatment versus no treatment. (a treatment duration of 5 years was used) The estimations were carried out for men and women separately at eight different ages: 35, 40, 45, 50, 55, 60, 65 and 70 years. The average risk of coronary heart disease for men and women in Sweden who are initially free from CVD (based on Swedish incidence data): 5-year risk of a CHD event (%) age men women 35 0.23 0.06 40 0.61 0.18 45 1.29 0.42 50 2.36 0.81 55 3.83 1.39 60 5.41 2.22 65 6.99 3.34 70 8.12 4.64 Treatment was assumed to reduce the annual risk of coronary heart disease by 31% each year of treatment in all patient groups.	Threshold analysis (CUA), a Markov model. We estimated at what coronary risk it is cost-effective to initiate cholesterol lowering drug treatment in primary prevention for men and women of different ages in Sweden. Three different threshold values were used: $40 000, $60 000 and $100 000 per QALY gained. 1999 Swedish Crowns (SEK), converted to $ (June 1999: $1=SEK 8.50). The costs of the intervention were divided into the costs of the drug, the costs of laboratory tests and the costs of physician visits. The total annual intervention cost used was $894. Annual drug cost: $600 (40 mg of pravastatin daily). Annual cost of laboratory tests: $40. Annual cost of physician visits: $254 (the health care costs and the travelling and time costs for the patients). Morbidity-associated costs after a coronary event were divided into health care costs (direct costs) and lost productivity (indirect costs) due to the coronary event. Direct costs: first year subsequent years MI $5882 $824 unstable angina pectoris $10 000 $824 Indirect costs first year subsequent years age: 35–49 $12 941 $7647 age: 50–64 $10 588 $6471 age: >65 years none Difference between total consumption and production in added life-years. age: 35–49 -$9882 age: 50–64 -$4353 age: >65 years $18 706 Utilities The following quality weights were used in different age-groups: 0.93 (35–49 years), 0.91 (50–64 years), 0.81 (65–74 years), 0.65 (75–84 years), and 0.60 (85 years). The reduction in the quality weight due to coronary heart disease was assumed to be 0.10. The treatment as such was not assumed to affect the quality of life.	Lipid lowering treatment is cost-effective if the 5-year-risk of CHD exceeds the following per cent risk: (in function of the CE threshold, in %): $40 000 age men women 35 3.34 2.95 40 4.06 3.17 45 5.09 3.93 50 6.50 5.07 55 8.27 6.80 60 11.59 10.08 65 17.33 15.82 70 21.36 20.30 $60 000 age men women 35 2.45 1.99 40 3.00 2.28 45 3.71 2.80 50 4.61 3.51 55 5.63 4.53 60 7.19 6.11 65 9.13 7.55 70 10.37 9.10 $100 000 age men women 35 1.66 1.24 40 2.03 1.51 45 2.47 1.86 50 3.01 2.27 55 3.60 2.86 60 4.45 3.53 65 5.28 4.23 70 5.90 4.96	Various analyses of sensitivity were performed for a threshold value of $60 000/QALY. Reduction in risk: 17%, 43%, and 40% <55 years and 27% ≥55 years. Increase in mortality risk after CHD was varied between 30% and 90% of the increase in the risk of CHD. Annual intervention cost was varied between $600 and $1200. Annual morbidity-associated costs after a coronary event were raised and lowered by 50%. Analysis was carried out without future costs of decreased mortality. Analysis with both the future costs of decreased mortality and the indirect morbidity costs excluded. Reduction in quality of life after CHD was varied between 0 and 0.20. Rate of discounting costs and QALYs was varied between 0% and 5%, and in one analysis costs were discounted by 3% whereas QALYs were not discounted at all. The result was most sensitive towards the variations in the risk reduction, the intervention cost, and the rate of discounting costs and QALYs.	In primary prevention, cholesterol lowering treatment is unlikely to be cost-effective for all patients with elevated cholesterol levels, and so it is crucial to determine in which patient populations treatment should be initiated. The results can serve as a basis for treatment guidelines based on cost-effectiveness.

Table 10: Spaans et al.[85]

Authors **Country** **Year of publication** **Conflict of interest**	**Intervention** **Population and/or base risk and/or applied risk function** **relative risk benefit**	**Analytic technique** **Year of costs, currency** **Costs details** **Utilities**	**Cost-effectiveness**	**Sensitivity analysis**	**Conclusion**
Spaans JN, Coyle D, Fodor G, Nair R, Vaillancourt R, Grover SA, Coupal L. Canada. 2003. No conflict of interest declared. **Perspective** **Time window** **Discount rate** Perspective and time window not explicitly mentioned. All results generated by the model were discounted at a rate of 3%.	Statin therapy versus no treatment. In all estimates of life expectancy and cost effectiveness, model simulations conservatively assumed that while statin therapy would be lifelong, patients would not derive any benefit from the therapy after age 75 because the effect of statin therapy in the elderly is not well understood. Charts of 1424 Canadian military personnel (age 45 or older) were reviewed. Of the 1313 personnel not on lipid lowering medication, 172 were identified as drug therapy candidates. Baseline coronary artery disease risk factors for drug therapy candidates: risk factor — number / percentage Smoking 102 62.2 Hypertension 37 21.5 Diabetes 12 7 Coronary arterydisease 2 1.2 Family history 39 22.7 The model assumed reductions in TC and LDL-c of 25% and 35%, respectively, and an increase in HDL-c of 8% with the use of statin therapy.	CEA, based on a previously published Markov model. 1996, in Canadian dollars (CAD). The life expectancy model considers direct treatment, surgical and intervention costs. No cost details provided in the study. The authors refer to a previous study.	cost-effectiveness according to risk level. Risk factors were age (men 45 years or older, women 55 years or older), diabetes, smoking, premature heart disease in a first-degree relative (ie, CAD occurring at less than 55 years in men or less than 65 years in women), hypertension (systolic blood pressure of 140 mmHg or greater, or diastolic blood pressure of 90 mmHg or greater) or taking antihypertensive medication. risk level low: ≤1 risk factor; moderate: 2 risk factors; high: 3 risk factors; and very figh: ≥4 risk factors or coronary artery disease (CAD). ICER of lifetime statin therapy (in CAD per year of life saved): risk level — undiscounted — discounted low 9 500 11 800 moderate 7 700 9 200 high 7 400 8 400 very high 7 400 7 700 total 8 000 9 300	Not performed.	The health benefits of statin therapy in this population are substantial and the cost effectiveness is acceptable. Statin therapy warrants greater attention as a preventive strategy for coronary artery disease.

Table 11: Grover et al.[86]

Authors Country Year of publication Conflict of interest	Intervention Population and/or base risk and/or applied risk function relative risk benefit	Analytic technique Year of costs, currency Costs details Utilities	Cost-effectiveness	Sensitivity analysis	Conclusion
Grover SA, Ho V, Lavoie F, Coupal L, Zowall H, Pilote L. Canada 2003 Dr Grover has received honoraria as a consultant or speaker for the following companies: Pfizer Canada Inc, Kirkland; Merck Frosst Inc, Pointe-Claire/Dorval, Quebec; Bristol-Myers Squibb, Wallingford, Conn; and AstraZeneca Canada Inc, Mississauga, Ontario. Dr Grover also owns shares of Pfizer Inc, New York, NY, and Merck Inc, Whitehouse Station, NJ. Additional financial support was provided by an unrestricted grant from Pfizer Canada Inc, Kirkland, Quebec. **Perspective** **Time window** **Discount rate** The societal perspective. Lifetime Future costs and benefits were discounted 3% annually.	daily treatment with a 10-mg tablet of atorvastatin calcium subjects free of CVD and diabetes at baseline. Estimates were generated for low- and high-risk patients aged 40, 50, and 60 years. Low risk: Defined as nonsmokers with a blood pressure of 120/80 mm Hg. High risk: Defined as smokers with a blood pressure of 160/100 mm Hg. Benefits of atorvastatin calcium therapy The authors assumed that modifying blood lipid levels lowers cardiovascular risk (after a lag of 1 year) to that of untreated individuals with the same blood lipid levels. At baseline, CURVES Study participants had an average total cholesterol level of 300 mg/dL (7.76 mmol/L), average LDL-C level of 217 mg/dL (5.62 mmol/ L), and average HDL-C level of 49 mg/dL (1.28 mmol/L). Total cholesterol and LDL-C levels were reduced by 28% and 38%, respectively, whereas HDL-C level increased by 5.5%.	CEA, the Cardiovascular Life Expectancy Model (a Markov model) was applied. 2000, Canadian dollars (CAD). Direct and indirect costs were considered: The direct costs included all medical care costs associated with CVD. The annual cost of a daily 10-mg tablet of atorvastatin calcium (incl. dispensing fees) was CAD704. The indirect costs represented the loss of employment income and the decreased value of housekeeping services after different manifestations of CVD. Estimated annual employment income and value of housekeeping services lost due to CVD: (in Canadian $) Without CVD / Angina Pectoris / Coronary Insufficiency Men 40-49 y 49 788 / 9268 / 9185 50-59 y 43 759 / 6212 / 4473 60-69 y 25 739 / 2404 / 2549 70-79 y 9498 / 417 / 461 ≥80 y 6174 / 315 / 299 Women 40-49 y 34 399 / 7163 / 6638 50-59 y 28 203 / 4749 / 4989 60-69 y 19 525 / 1117 / 1134 70-79 y 9291 / 689 / 666 ≥80 y 7035 / 177 / 162 Men: Myocardial Infarction / Cong. Heart Failure / Stroke 40-49 y 5912 / 17 561 / 17 685 50-59 y 6378 / 7119 / 14 494 60-69 y 3463 / 2939 / 6259 70-79 y 382 / 522 / 1042 ≥80 y 219 / 312 / 457 Women 40-49 y 7143 / 7353 / 9189 50-59 y 5380 / 5628 / 6753 60-69 y 1304 / 1328 / 2090 70-79 y 694 / 667 / 632 ≥80 y 175 / 174 / 238	Cost-effectiveness of atorvastatin calcium therapy (according to risk level & age). When only direct medical care costs were considered age: 40 / 50 / 60 low risk level men 11 816 / 7885 / 5365 women 19 866 / 10 747 / 4275 high risk level men 5124 / 4161 / 3846 women 7580 / 4982 / 3756 When direct medical care costs and indirect costs were included. age: 40 / 50 / 60 low risk level men cost savings women 6625 / cost savings high risk level men cost savings women cost savings	A sensitivity analysis was performed under the assumption that the benefits of lipid therapy would cease at 75 years of age but that the costs of lipid therapy would continue until death. Under this hypothesis, the benefits of lipid therapy are substantially reduced across all ages and risk factors owing to increased numbers of fatal and nonfatal CVD events.	Lipid therapy with statins can reduce CVD morbidity and mortality as demonstrated in a number of clinical trials. Adding the indirect CVD costs associated with productivity losses at work and home can result in forecasted cost savings to society as a whole such that lipid therapy could potentially save lives and money.

Table 12: Nagata-Kobayashi et al.[87]

Authors Country Year of publication Conflict of interest	Intervention Population and/or base risk and/or applied risk function relative risk benefit	Analytic technique Year of costs, currency Costs details Utilities	Cost-effectiveness	Sensitivity analysis	Conclusion
Nagata-Kobayashi S, Shimbo T, Matsui K, Fukui T. Japan. 2005. No conflict of interest declared. **Perspective** **Time window** **Discount rate** The societal perspective. Lifetime. All future medical costs and health effectiveness were discounted 3% annually.	Lifetime pravastatin therapy (20 or 10 mg/day depending on initial TC (total cholesterol) level) versus no treatment. For the baseline analysis, we targeted Japanese men and women aged 60 years with hypercholesterolemia and no history of CHD. We assumed that their TC level before initiating pravastatin therapy (20 mg/day) was 240 mg/dl and that they had already tried therapeutic lifestyle modifications for several months (e.g., reduced intake of saturated fat and cholesterol, increased physical activity, and weight control). In terms of age and sex, our model targeted men aged 45 to 70 years and women aged 55 to 70 years. Eight distinctive groups were defined on the basis of these cardiac risk factors: (1) persons who meet the criteria for hypercholesterolemia and age; (2) smoking; (3) hypertension; (4) hyperglycemia; (5) smoking and hypertension; (6) smoking and hyperglycemia; (7) hypertension and hyperglycemia; and (8) smoking, hypertension, and hyperglycemia. Relative risk of MI: TC 200, 220 and 240 mg/dl: 1.0, 1.5 and 2.0 resp. Other RR of MI associated with cardiac risk factors (e.g., smoking, hypertension, hyperglycemia) were derived from the Japan Lipid Intervention Trial (J-LIT). The authors assumed the magnitude of the reduction in TC level as follows: (1) pravastatin 20 mg/day reduces the TC level from 240 mg/dl to 200 mg/dl (a 17% reduction); or (2) pravastatin 10 mg/day reduces the TC level from 220 mg/dl to 200 mg/dl (a 10% reduction).	CUA, a Markov model. 2002, in Yen (JPY). Medical costs (yen/year) Treatment cost in clinic for patients with hyperlipidemia (20 mg/day) 240 000 Treatment cost in clinic for patients with hyperlipidemia (10 mg/day) 180 000 Hospitalization cost for acute MI under invasive treatment 3 260 000 Hospitalization cost for acute MI under conservative treatment 1 430 000 Hospitalization cost for patients dying of acute MI 1 190 000 Treatment cost for chronic stage of MI with 20 mg/day of pravastatin 290 000 Treatment cost for chronic stage of MI with 10 mg/day of pravastatin 220 000 Utility: Healthy 1 Acute stage of MI 0.73 Chronic stage of MI 0.91 Recurrent MI 0.73 Dead 0	Cost-effectiveness in persons treated with pravastatin 20 mg/day (initial TC 240 mg/dl). (ICER in million yen/QALY) age: 45 50 55 60 65 70 group: 1) ♂ 76 56 53 44 64 120 ♀ 100 76 82 74 2) ♂ 63 47 44 36 53 91 ♀ 44 33 33 29 3) ♂ 31 22 20 16 22 31 ♀ 40 30 30 26 4) ♂ 48 35 32 27 38 61 ♀ 34 24 25 21 5) ♂ 26 18 17 13 17 24 ♀ 17 12 12 9.5 6) ♂ 40 29 27 22 30 47 ♀ 15 10 9.8 7.5 7) ♂ 19 14 12 9.3 12 15 ♀ 13 9.3 9 6.8 8) ♂ 16 11 10 7.5 9.4 11 ♀ 6.8 4.3 4 2.4 Cost-effectiveness in persons treated with pravastatin 10 mg/day (initial TC 220 mg/dl). age: 45 50 55 60 65 70 group: 1) ♂ 110 85 81 69 100 210 ♀ 150 120 120 110 2) ♂ 95 71 67 57 82 150 ♀ 68 50 51 46 3) ♂ 47 34 31 26 35 54 ♀ 62 46 46 42 4) ♂ 72 53 50 42 61 100 ♀ 51 37 38 34 5) ♂ 39 28 26 21 28 42 ♀ 27 19 19 16 6) ♂ 61 21 41 16 49 79 ♀ 22 16 16 13 7) ♂ 29 21 19 15 20 27 ♀ 21 15 14 12 8) ♂ 25 18 16 12 16 21 ♀ 10 6.7 6.4 4.4	One-way sensitivity analysis: Sensitivity analyses were performed to confirm the robustness of the model for the following variables: incidence of MI, proportion of patients with MI under invasive treatment, case-fatality rate of MI, recurrence rate of MI, RR of MI associated with cardiac risk factors, medical costs, utility, and discount rate. The sensitivity analysis was performed for baseline cases, i.e., persons aged 60 years with an initial TC level of 240 mg/dl and no cardiac risk factors except for hyperlipidemia and age. Probabilistic sensitivity analysis. 90.7% of results showed that pravastatin therapy was more costly at >5 000 000 yen/QALY.	The cost-effectiveness of pravastatin therapy for primary prevention of MI varies widely depending on the combination of cardiac risks. Treating hyperlipidemia with pravastatin is not cost-effective in persons at low cardiac risk in Japan.

Table 13: Ward et al.[30]

Authors
Country
Year of publication
Conflict of interest

Ward S, Lloyd J, Pandor A, Holmes M, Ara R, Ryan A, Yeo W, Payne N.

UK

2005

Dr Yeo has received speaker fees from Novartis, Pfizer, MSD and AstraZeneca for talks to GPs and prescribing advisors on the National Service Framework for CHD, which includes the use of statins. However, for the duration of his involvement with the preparation of this report, he has declined to comment on statins nor attend any advisory boards where statins may have been discussed. His department has received research funding for the Anglo-Scandinavian Cardiac Outcomes Trail, an investigator-led multi-centre study in high-risk hypertension patients of older versus more modern BP lowering drugs, with statin therapy in a factorial design. This study used atorvastatin and was part funded by Pfizer.

Intervention
Population and/or base risk and/or applied risk function
relative risk benefit

Statin treatment versus no treatment.

The model utilises a cohort of 1000 patients at a specified annual risk of a CHD event.

Patient data were grouped according to gender and baseline risk levels between 0.5% and 3% annual risk (in increments of 0.1%). The average CHD risk following cholesterol reduction was calculated at each level of baseline risk. A relative risk reduction is calculated from the proportionate difference between baseline CHD risk and cholesterol altered CHD risk for males and females at each of the baseline risk levels.

The model is run separately for each age group, sex and risk level.

The authors point at the difference between CHD and CVD risk:

	male		female	
	annual CHD risk	annual CVD risk	annual CHD risk	annual CVD risk
age				
35-54	3.00%	3.83%	3.00%	4.00%
	2.50%	3.21%	2.50%	3.36%
	2.00%	2.58%	2.00%	2.73%
	1.50%	1.96%	1.50%	2.09%
	1.00%	1.33%	1.00%	1.46%
	0.50%	0.71%	0.50%	0.82%
55+	3.00%	4.30%	3.00%	4.71%
	2.50%	3.67%	2.50%	3.99%
	2.00%	3.03%	2.00%	3.27%
	1.50%	2.40%	1.50%	2.55%
	1.00%	1.76%	1.00%	1.83%
	0.50%	1.13%	0.50%	1.11%

Perspective

The perspective of the health care payer.

Time window

Lifetime (until patients die or reach the age of 100 years).

Discount rate

Discount rates of 6% and 1.5% are applied to costs and health benefits.

Analytic technique
Year of costs, currency
Costs details
Utilities

CUA, a Markov model.

2004, in £.

Cost of health states (in £):

	1st year	Subsequent year	Fatal event
Stable angina	171	171	/
Unstable angina	440	171	/
Myocardial infarction	4448	171	1166
Transient isch. attack	1064	264	/
Stroke	8046	2163	7041

Statin cost (for 28 tabs):

Statin	10 mg	20 mg	40 mg	80 mg
simvastatin*	14.01	20.21	23.18	29.03
atorvastatin	18.03	29.69	29.69	29.69
fluvastatin		12.72	12.72	16
pravastatin	16.18	29.69	29.69	
rosuvastatin	18.03	29.69	29.69	

* Combined proprietory and generic cost based on 2004 prices and 2003 prescribing data.

Weighted cost of statins used in analysis:

Statin	
atorvastatin	243.1
fluvastatin	204
pravastatin	387.3
rosuvastatin	244.1
simvastatin*	296.9
Combined*	316.8

* rosuvastatin not included

Costs of monitoring

Monitoring costs are £124 for the first year and £33.42 for subsequent years.

Utility values by age:

age	utility	age	utility	age	utility
45	0.869	65	0.784	85	0.699
50	0.848	70	0.763	90	0.678
55	0.826	75	0.741	95	0.656
60	0.805	80	0.72	100	0.635

Utilities for health states (utility mean (se)):

Stable angina	0.808
Unstable Angina	0.770 (0.038)
MI	0.760 (0.018)
TIA	1
Stroke	0.629 (0.04)

Cost-effectiveness

Undiscounted cost per QALY (in £x1000):

Male

Annual CHD risk	Age				
	45	55	65	75	85
3.0%	15.7	18.5	22	30.9	39.9
2.5%	16.3	19.6	24.1	34.6	44.9
2.0%	17.3	21.5	27.3	40	52
1.5%	19.3	24.6	32.5	48.6	62.4
1.0%	23.1	30.4	41.8	63.8	79.3
0.5%	31.8	43.4	62.9	97.8	111.5

Female

Annual CHD risk	Age				
	45	55	65	75	85
3.0%	23.2	24.2	26.4	38.4	52.3
2.5%	23.4	25	28.6	42.6	57.7
2.0%	24.4	26.9	32.1	48.7	65
1.5%	26.8	30.5	38	58.6	75.5
1.0%	32.3	38	49.5	76.4	91.6
0.5%	47.7	58.1	78.6	117.4	119

Discounted cost per QALY (in £x1000):

Male

Annual CHD risk	Age				
	45	55	65	75	85
3.0%	9.5	12.6	16.8	26.2	36.8
2.5%	10	13.5	18.5	29.4	41.5
2.0%	10.8	14.9	21	34.1	48.1
1.5%	12.2	17.2	25.1	41.5	58
1.0%	14.9	21.5	32.5	54.7	74.1
0.5%	20.9	31.1	49.5	84.8	105.2

Female

Annual CHD risk	Age				
	45	55	65	75	85
3.0%	13.7	15.9	19.3	31.5	47.4
2.5%	14	16.6	21	35	52.4
2.0%	14.9	18	23.7	40.2	59.3
1.5%	16.6	20.6	28.2	48.5	69.1
1.0%	20.3	25.9	37	63.7	84.3
0.5%	30.5	40	59.3	98.9	110.6

Estimated ICER according to CHD risk:

3.0%	2.5%	2.0%	1.5%	1.0%	0.5%
Male					
20	18.8	21	21.9	23	27.5
Female					
21.3	21.7	26.6	28.1	40.5	56.8

Sensitivity analysis

Subgroup analysis for diabetici (discounted):

Male

Annual CHD risk	Age				
	45	55	65	75	85
3.0%	6.2	8.6	11.9	18.5	26.8
2.5%	6.6	9.3	13.2	20.9	30.5
2.0%	7.3	10.3	15.1	24.4	35.8
1.5%	8.4	12.1	18.2	29.9	43.8
1.0%	10.4	15.3	23.7	39.9	57.4
0.5%	14.9	22.5	36.5	63.1	85.4

Female

Annual CHD risk	Age				
	45	55	65	75	85
3.0%	8.6	10.4	13.8	23.1	36.7
2.5%	9	11	15.2	25.8	41
2.0%	9.8	12.2	17.3	29.9	47
1.5%	11.1	14.2	20.8	36.4	55.8
1.0%	14	18.3	27.6	48.5	69.9
0.5%	21.6	29	45	77.6	96.2

The univariate sensitivity analysis shows that results are most sensitive to assumptions on the cost of statins, discount rates and the timeframe of the model. The model is robust to changes in other parameters:

Shortening the time frame of the model to 10 years increases the costs per QALY from basecase levels, particularly at the lower risk levels (from £21 k to £170 k for males and £30 k to £296 k for females aged 45 years at 0.5% CHD risk and from £105 k to £237 k for males and £110 k to £367 k for females aged 85 years at 0.5% CHD risk). In addition the results are sensitive to the discount rates used, with ICERs increasing to £19 k for males and £30 k for females at aged 45 years at 3% CHD risk when using 3.5% discounting for both costs and benefits. At 1.5% CHD risk from aged 45 to aged 85 the ICERs risk increases from £26 k to £74 k for males and £38 k to £91 k for females. A fall in the price of statins of 40% reduces the ICERs for males and females at the age of 65 from around £60 to £70 k to around £35 k at 0.5%.

Results from a probabilistic analysis are close to the results from the basecase analysis.

Conclusion

In the basecase primary prevention analyses the ICERs vary according to risk level and age. The estimated average ICER by risk level increases from £20k to £28k from men between 3% and 0.5% CHD risk and between £21 k and £57 k for women. There is however significant variation within risk levels by age. At an annual CHD risk of 3%, the estimated cost per QALY ranges from £9.5 k to £36.8 k for males and from £13.7 k to £47.4 k for females between the ages of 45 and 85. At aged 85 the estimated cost per QALY rises from £36.8 k (£47.4 k) for males (females) at 3% CHD risk, to around £105.2 k (£110.6 k) for males (females) at 0.5% CHD risk.

Table 14: Scotland NHSQI[88]

Authors Country Year of publication Conflict of interest	Intervention Population and/or base risk and/or applied risk function relative risk benefit	Analytic technique Year of costs, currency Costs details Utilities	Cost-effectiveness	Sensitivity analysis	Conclusion
Scotland NHSQI (report for National Institute for Health and Clinical Excellence). UK. 2006. Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal. **Perspective** **Time window** **Discount rate** The health care payer perspective. Costs and benefits were estimated over a lifetime horizon. Costs and benefits were discounted at 6% and 1.5%, respectively.	The cost effectiveness of statin therapy compared with no treatment. People at different ages and levels of risk (at an annual risk of a CHD event ranging from 3% to 0.5%). The Committee acknowledged that its recommendations should be based on 10-year CVD risk. It considered that a 1.5% annual CHD risk, as reported in the Assessment Report, was approximately equivalent to a 15% 10-year CHD risk and a 20% 10-year CVD risk.	CEA, a Markov model. 2004, in £. The acquisition cost are mentioned for: atorvastatin, fluvastatin, pravastatin, rosuvastatin, and simvastatin. No further cost details provided in the document at our disposal.	At an annual risk of a CHD event ranging from 3% to 0.5%, the ranges of cost per QALY gained were: age 45 years £10 000 to £31 000 55 years £13 000 to £40 000 65 years £17 000 to £59 000 75 years £26 000 to £99 000 85 years £37 000 to £111 000 for people with diabetes, and, at an annual risk of CHD ranging from 3% to 0.5%. age 45 years £6000 to £22 000 85 years £27 000 to £96 000	The base case primary prevention results were most sensitive to a reduction in the cost of statins, the discount rates used and the timeframe of the model. A 40% reduction in the weighted statin cost: 45 years £6000 to £20 000 85 years £24 000 to £72 000 Applying 3.5% discount rates to costs and QALYs: 45 years £19 000 to £72 000 85 years £46 000 to £149 000 Using a shorter time horizon of 10 years 45 years £36 000 to £286 000 85 years £53 000 to £367 000 Probabilistic sensitivity analysis produced results that were consistent with the primary prevention base case results	Statin therapy is recommended as part of the management strategy for the primary prevention of CVD for adults who have a 20% or greater 10-year risk of developing CVD. This level of CVD risk should be estimated using an appropriate risk calculator, or by clinical assessment for people for whom an appropriate risk calculator is not available (for example, older people, people with diabetes or people in high-risk ethnic groups).

Table 15: Walshe et al.[89]

Authors Country Year of publication Conflict of interest	Intervention Population and/or base risk and/or applied risk function relative risk benefit	Analytic technique Year of costs, currency Costs details Utilities	Cost-effectiveness	Sensitivity analysis	Conclusion
Walshe V, Nash A, Barry M. Ireland. 2006 No conflict of interest declared. **Perspective** **Time window** **Discount rate** Perspective not explicitly mentioned (health care payer). A 15-year follow up period was applied. Both costs and outcomes were discounted at 3.5% per year.	Statin therapy versus no treatment. Asymptomatic male patients, 55 years and over, with a 10 year risk of at least 15% for the development of CVD. Transition probabilities were determined from the West of Scotland Coronary Prevention Study (WOSCOPS) for primary prevention.	CEA, a Markov model. Year of costs was not explicitly mentioned (2005), in €. The dose of each statin medication producing a 35% reduction in LDL cholesterol was used to determine drug acquisition cost. It was assumed that all patients would be reviewed by the general practitioner every six months and have laboratory investigations including lipid profile, liver function tests and creatine kinase performed. The annual cost of review and laboratory investigations was estimated at €200 per patient. Expenditure under the GMS scheme (abbreviation not specified) included the dispensing fee whilst the drugs payment scheme (DP) included the 50% mark up on drug acquisition cost in addition to the dispensing fee. No further cost details were provided.	Cost-effectiveness of statins under the GMS and DP schemes: (€/LYG) drug: GMS scheme DP scheme Atorvastatln 17 900 24 500 Rosuvastatin 18 500 25 500 Fluvastatin 18 700 25 800 Slmvastatin (generic) 20 910 29 999 Simvastatin 27 300 38 700 Pravastatin (generic) 26 752 38 999 Pravastatin 33 800 48 500	Sensitivity analysis analysed the impact of statin efficacy, patient age at the onset of therapy, the follow up period, and lowering drug cost. Results: A 10% reduction in statin efficacy resulted in an increase in the ICER for atorvastatin 10mg daily from €17 900/LYG to €29 000/LYG. Patient age at the onset of therapy had a significant influence as the cost/LYG ranged from €4 191/LYG for a 45 year old male patient to €57 498/LYG for a 65 year old patient. The follow up period also impacted on the cost effectiveness ranging from €79 429/LYG over a 5-year period to €8 502/LYG if the benefits accrue over 25 years in the case of atorvastatin 10mg daily. Lowering drug cost by 20% resulted in a similar percentage reduction in the ICER.	All the statins could be considered cost effective, i.e. threshold below €50 000/LYG. However, atorvastatin proved the most cost effective statin in this pharmacoeconomic study.

FIBRATES VERSUS NO TREATMENT

Table 16: Hay et al.[91]

Authors Country Year of publication Conflict of interest	Intervention Population and/or base risk and/or applied risk function relative risk benefit	Analytic technique Year of costs, currency Costs details Utilities	Cost-effectiveness	Sensitivity analysis	Conclusion
Hay JW, Sterling KL. US. 2005. No conflict of interest declared. **Perspective** **Time window** **Discount rate** The societal perspective. A lifetime incremental cost-effectiveness model was developed. A 3% per annum rate is used to discount future intervention costs and outcomes.	The fibrates gemfibrozil and fenofibrate (and lovastatin as comparison scenario) versus no treatment. The study population consisted of a hypothetical cohort of males and females in the US aged 45–74 years, with low levels of HDL-cholesterol and no prior history of CHD. Male and female patients were assumed to have a mean total cholesterol level of 175 mg/dL (4.53 mmol/L), mean HDL-cholesterol of 32 mg/dL (0.83 mmol/L), mean LDL-cholesterol of 112 mg/dL (2.90 mmol/L) and a mean systolic blood pressure of 132mm Hg, and no evidence of ECG-detectable left ventricular hypertrophy. It was assumed that 57% of patients would have a history of hypertension, 20% smoking and 25% diabetes mellitus. The Framingham study was used to establish absolute CHD risk levels in the target population. the model assumes an equivalent 22% CHD risk reduction for both gemfibrozil and fenofibrate and a 31% CHD risk reduction for lovastatin.	CUA, a previously developed model was applied (the type was not explicitly mentioned). 2004, in $. The total direct 5-year medication treatment and monitoring costs for gemfibrozil and fenofibrate were $US2102 and $US4956, resp. The total 5-year drug-related cost of lovastatin treatment was 2919$. Gemfibrozil (600mg): $0.22. Fenofibrate (200mg): $2.18. Lovastatin (20mg once daily): $1.11. Dispensing fee: $7.00/prescription (30 days). For both fibrates, four physician visits ($41.13/visit), four lipid panels ($118.50/panel) and four complete blood count (CBC) tests ($16.00/test) in the first year of treatment. In subsequent years, two physician visits, two lipid panels and two CBC tests. Fenofibrate: four liver function tests in the first year and two tests in the subsequent years ($52.30/test). 4.5% of gemfibrozil patients were provided with one ranitidine 150mg tablet per day ($0.12/tablet), in order to treat dyspepsia. Lovastatin: two physician visits, two lipid panels and two liver function tests in the first year and one physician visit, one lipid panel and one liver function test ($52.30/test for AST/ALT levels) in subsequent years and an adverse event rate of 4.5% for dyspepsia. Indirect costs: Each visit was estimated to last an hour and the average wage per hour was $22. The discounted lifetime cost of a CHD event ($32505) was calculated as the weighted average of: cost to treat MI ($40726), angina ($30106), & CHD death ($18626). Utilities The average CHD utility (0.77) was a weighted average of the MI (72.9, 95%CI: 62.8-83) and angina (78.6, 95%CI: 72.9-84.2) utilities from the Beaver Dam Health Outcomes study.	cost per QALY (according to age and sex) male |	gemfibrozil	fenofibrate	lovastatin
---	---	---	---
45	5 409	20 967	5 514
50	8 665	37 739	7 239
55	6 383	31 760	5 176
60	4 740	27 387	3 695
65	3 586	24 540	2 647
70	2 829	23 667	1 911 | female |	gemfibrozil	fenofibrate	lovastatin
---	---	---	---
45	26 870	84 479	23 984
50	22 347	73 158	19 848
55	20 110	67 253	17 825
60	19 761	65 999	17 541
65	21 314	69 774	18 996
70	25 782	81 882	23 092		Five parameter categories were the focus of the sensitivity analysis: baseline CHD risk factors, fibrate treatment risk reduction effectiveness, 5-year CHD treatment costs, 5-year medication costs and the health state utilities for MI and angina. A 25% increase and decrease in base-case parameter values were used for all of these parameters except for utilities. The sensitivity analysis for the utilities of MI and angina were based on the 95% CI values The model is highly sensitive to baseline CHD risk factors, fibrate treatment costs and treatment effectiveness.	This analysis suggests that fibrate therapy, particularly with generic gemfibrozil, is cost effective in the primary prevention of CHD in individuals with low HDL-cholesterol levels, with or without elevated triglyceride levels. Comparable cost-effectiveness results are also shown for lovastatin therapy in the target patient population.

ASPIRIN VERSUS NO TREATMENT

Table 17: Annemans et al.[93] and Lamotte et al.[94]

Authors Country Year of publication Conflict of interest	Intervention Population and/or base risk and/or applied risk function relative risk benefit	Analytic technique Year of costs, currency Costs details Utilities	Cost-effectiveness	Sensitivity analysis	Conclusion
Annemans L, Lamotte M, Kubin M, Evers T, Verheugt FWA. Four European countries (UK, Germany, Spain and Italy). 2006. This study was carried out under an unrestricted grant from Bayer Healthcare AG. **Perspective** **Time window** **Discount rate** The healthcare payer perspective. A total time horizon of 10 years was chosen. Country-specific annual discount rates were applied on costs and effects (3.5% in the UK, 5% in Germany, 3% in Spain and Italy).	Low-dose aspirin versus no aspirin. The model was applied to patients at different 10-year risks (2–5%) of fatal CVD according to the SCORE equation. 10-year risk of fatal CVD 2% 3% 4% 5% high-risk country gender ♂ ♀ ♀ ♂ age (years) 50 55 55 60 smoker No Yes Yes No systolic blood press. 132 135 145 130 total cholesterol 200 245 260 199 HDL-cholesterol 40 40 40 40 low-risk country gender ♂ ♀ ♂ ♂ age (years) 50 60 55 60 smoker Yes Yes Yes Yes systolic blood press. 132 130 130 130 total cholesterol 200 240 240 190 HDL-cholesterol 40 40 41 40 Data on the efficacy of aspirin in primary prevention were taken from the published primary prevention meta-analyses. Risks, assuming a 10-year risk of a fatal CVD event of 5% (in %): First year Tenth year Outcome No asp./aspirin No asp./aspirin CHD 0.93 / 0.68 2.33 / 1.69 Fatal CHD 0.24 / 0.21 0.60 / 0.52 Stroke 0.5 / 0.51 1.26 / 1.28 Fatal stroke 0.07 / 0.09 0.17 / 0.22 Alive 0.44 / 0.43 1.09 / 1.06 Haem. stroke 0.06 / 0.07 0.16 / 0.18 Isch. stroke 0.37 / 0.36 0.93 / 0.89 Gastrointestinal bleeding 0.18 / 0.31 0.18 / 0.31 Other death 0.53 1.26	CUA, a state-transition (Markov) model. 2003, in €. average cost data cost item (in €) UK Germ. aspirin (100mg) 0.01 (75mg) 0.025 MI 1593 3123 isch./haem. stroke 3385 3390 gastrointestinal bleed 1218 1534 fatal MI 1824 2880 fatal stroke 5309 1897 in-hosp. Follow-up (per year) non-fatal MI 1234 1907 non-fatal stroke 892 676 non-fatal MI plus non-fatal stroke 1628 1907 Spain Italy aspirin (100mg) 0.081 0.077 MI 5978 4209 isch./haem. stroke 9437 3927 gastrointestinal bleed 1987 3937 fatal MI 4954 3511 fatal stroke 7821 1897 in-hosp. Follow-up (per year) non-fatal MI 5149 3232 non-fatal stroke 7453 3852 non-fatal MI plus non-fatal stroke 9536 3852 Utilities post-MI 0.88 (95% CI 0.84–0.93) post-stroke 0.68 (95% CI 0.53–0.83) stroke and MI 0.68 (95% CI 0.53–0.83) acute event (MI or stroke) utility of 0 for 1 week Extracranial haemorrhage utility of 0.5 for 2 weeks	ICER (€/QALY gained) 2% 3% 4% 5% UK dominant Germ. dominant Italy 1030 dominant Spain dominant	The Monte Carlo analysis showed that aspirin is dominant (cost-saving and more effective) in more than 90% of patients at a 10-year risk of 4% and 5% in the four countries (Figure 2). This decreases to 89% and 86%, respectively, at 3% and 2% 10-year risk for the UK, Germany and Spain. In Italy, it decreases to 60% and 24%, respectively, at 3% and 2% risk.	Even at a fairly low risk of a fatal CVD event, this risk can be decreased further with low-dose aspirin. This is not only of benefit to the patient, but also results in cost-savings for the healthcare payer.
			Lamotte M, Annemans L, Evers T, Kubin M.	**Sensitivity analysis**	**Cost-effectiveness**
			Population and/or base risk and/or applied risk function **relative risk benefit** The base-case results are calculated based on an annual risk of CHD of 1.5% (10-year risk of approximately 14%). Annual transition probabilities, assuming a baseline annual CHD risk of 1.5% an 1%: baseline CHD risk: 1.5% 1.0% Outcome No asp./aspirin No asp./aspirin CHD 1.50 / 1.09 1.00 / 0.73 Fatal CHD 0.39 / 0.34 0.26 / 0.22 Stroke 0.81 / 0.82 0.54 / 0.55 Fatal stroke 0.11 / 0.14 0.07 / 0.09 Alive 0.70 / 0.68 0.47 / 0.46 Haem. stroke 0.10 / 0.11 0.07 / 0.08 Isch. stroke 0.60 / 0.57 0.40 / 0.38 Gastrointestinal bleeding 0.18 / 0.31 0.18 / 0.31 Other death 0.54 / 0.50 0.54 / 0.50	One-way sensitivity analysis was performed for: base line CHD risk, discount rates (0–6%), cost of complications (lower and upper estimates or decreased and increased by 50%), utilities (lower and upper estimates), time horizon (1, 3, 5, 15 and 20 years), risk of bleeding and risk of stroke. Sensitivity analyses on cost of complications, utility, discounting, stroke rate and gastrointestinal bleeding rate showed the robustness of the results. If longer time horizons (15 and 20 years) are studied, the benefits, both on costs and effects (LY and QALYS gained) increase. After 20 years, the savings are doubled and the LY and QALY gained are tripled compared with the base case for all four countries. threshold analysis From an annual risk of CHD of 0.236% for the UK, 0.324% for Germany, 0.244% for Spain and 0.560% for Italy, low-dose aspirin was cost saving compared with placebo. Monte Carlo simulation Based on an annual risk of CHD of 1.5%, 1.0% and 0.6%, aspirin treatment is dominant in 97.3%, 97.2% and 97.2% of cases in the UK; 97.7%, 98.7% and 97.1% of cases in Germany; 98.0%, 97.1.% and 97.8% of cases in Spain; and 98.0%, 96.2% and 59.7% of cases in Italy, resp.	For patients with an annual risk of CHD of 1.5%, the model resulted in 10-year savings with low-dose aspirin of on average €201 (95%CI: 81-331), €281 (95%CI: 141-422), €797 (95%CI: 301-1331) and €427 (95%CI: 122-731) per patient in the UK, Germany, Spain and Italy, respectively. **Conclusion** Administering low-dose aspirin to patients with an annual risk of CHD of ≥1% appears to be significantly cost saving from the healthcare payer's perspective in all countries analysed. Low-dose aspirin therapy could be recommended in the primary prevention of CVD in all individuals who have at least a 0.6% per year risk of CHD in the UK, Germany and Spain and a risk of 1% per year in Italy, and who do not have an increased risk of GI bleeding events.

Table 18: Tsutani et al.[95]

Authors Country Year of publication Conflict of interest	Intervention Population and/or base risk and/or applied risk function relative risk benefit	Analytic technique Year of costs, currency Costs details Utilities	Cost-effectiveness	Sensitivity analysis	Conclusion
Tsutani K, Igarashi A, Fujikawa K, Evers T, Kubin M, Lamotte M, Annemans L. Japan. 2007. No conflict of interest declared. **Perspective** **Time window** **Discount rate** The perspective of the health care payer. A 10-year time horizon was applied. A 3% discount rate was applied on effectiveness and costs.	Administering aspirin 100 mg per day versus no treatment. Patients with a moderately increased annual risk of CHD (1.5% annual, 10-year risk ±15%). Annual risk of events in primary prevention, assuming that the annual risk of CHD is 1.5%: outcome: — no aspirin — aspirin CHD 1.50% 1.09% Fatal CHD (25.8%) (31%) Non-fatal CHD (74.2%) (69%) Stroke 0.81% 0.82% Fatal stroke (13.4%) (17.2%) Non-fatal stroke (86.6%) (82.8%) Hemorrhagic stroke (14.3%) (16.7%) Ischemic (85.7%) (83.3%) Gastro-intestinal bleeding 0.18% 0.31% Other death 0.54% 0.50%	CEA, a Markov model. Year of costs was not explicitly mentioned, in Yen (JPY). Cost of cardiovascular disease in Japan (in JPY): Fatal MI 2 780 000 Non-fatal MI 2 784 000 Fatal stroke 1 000 000 Non-fatal stroke 1 000 000 Yearly follow-up cost after cardiovascular (stroke or MI) event 179 000 Hemorrhagic stroke or bleeding 2 020 000 Gastro-intestinal bleeding 345 000	For patients with a 1-year risk of CHD of 1.5% (10-year risk of ±15%), the model demonstrated 'dominance' of the 'aspirin' arm versus 'no aspirin' arm; the 10-year costs were JPY634 000 (€4 857) and JPY518 000 (€3 968) in the 'no aspirin' arm and 'aspirin' arm, respectively, while LYG was 8.33 and 8.36, respectively. Low-dose aspirin treatment saved on average JPY116 000 (€889) (95%CI: JPY57 077-175 151) per patient.	Threshold analysis to reach dominance: low-dose aspirin was dominant to 'no aspirin' arm from an annual risk of 0.20%. The results indicated that the 'aspirin' arm was dominant to 'no aspirin' arm, regardless of the cost of stroke treatment. Other results of sensitivity analysis on gastrointestinal (GI) bleeding rate, stroke rate, cost of each event and discounting showed the robustness of the results.	Administering low-dose aspirin to patients with a 1-year risk of CHD of 1.5% and more is significantly costsaving from the insurers' perspective in Japan.

Table 19: Pignone et al.[96]

Authors Country Year of publication Conflict of interest	Intervention Population and/or base risk and/or applied risk function relative risk benefit	Analytic technique Year of costs, currency Costs details Utilities	Cost-effectiveness	Sensitivity analysis	Conclusion
Pignone M, Earnshaw S, Pletcher MJ, Tice JA. US. 2007. Dr Pignone has received consulting fees and honoraria from Bayer Inc and has provided expert testimony. His institution has received licensing fees from Bayer for use of the Web-based cardiovascular risk calculator "Heart to Heart." The work was supported by a grant from Bayer Inc. **Perspective** **Time window** **Discount rate** Third-party payer perspective. Lifetime. All costs and outcomes were discounted at 3%.	Aspirin treatment versus no therapy. In the base case scenario, the authors examined the effectiveness of low-dose aspirin compared with no aspirin in cohorts of moderate risk 65-year-old women with an estimated 10-year total CHD risk of 7.5%. Baseline risks of initial cardiovascular events (ie, myocardial infarction, stroke, angina, and CHD death) were drawn from Framingham risk equations. The authors modeled hemorrhagic stroke and ischemic stroke as separate health states. Relative risk of primary prevention with aspirin: Myocardial infarction 1.01 (0.84-1.21) Stroke 0.76 (0.63-0.93) Angina 1.00 (0.80-1.20) Death from CHD 1.00 (0.80-1.20) Annual excess risk for adverse events with aspirin: Gastrointestinal bleeding (GI) 0.0007 (0.0004-0.0100) Death resulting from GI 0.00001 (0.000001-0.0001) Hemorrhagic stroke 20/100 000 (5/100 000 to 35/100 000)	CUA, a Markov model. 2005, in $. Annual cost data (in $): Drug cost Generic aspirin 5.75 Myocardial infarction Year 1 care 14629 Ongoing care 3109 Stroke Year 1 care 10263 Ongoing care 1589 Hemorrhagic stroke Year 1 care 21248 Ongoing care 7523 Angina Year 1 care 3778 Ongoing care 2897 Gastrointestinal bleeding Nonfatal 7538 Fatal 7538 Miscellaneous Physician visit 38.66 Day institutionalized 40.93 Utilities: Healthy 1 Death 0 Myocardial infarction and angina Year 1 0.88 (0.80–0.96) Subsequent years 0.90 (0.80–0.95) Stroke Nondisabling 0.75 (0.60–0.90) Disabling 0.5 (0.0–0.75) Gastrointestinal bleeding (year 1) 0.94 (0.88–1.0) Act of taking aspirin or statin 1.0 (0.99–1.0)	Aspirin produced 10.963 QALYs in the base case analysis of moderate-risk women, with mean costs of $3145. No treatment produced 10.957 QALYs and mean costs of $3069. The cost per additional QALY gained with aspirin was $13 300.	The authors examined the effect of changing several different parameters in one-way sensitivity analyses Results: Results were sensitive to age, cardiovascular disease risk, relative risk reductions with aspirin for ischemic strokes and myocardial infarction, excess risk of hemorrhagic stroke and gastrointestinal bleeding, and the disutility of taking medication. Probabilistic sensitivity analysis for 65-year-old women at moderate cardiovascular disease risk found a 27% chance that aspirin produces fewer QALYs than no treatment, a 35% chance that the cost-utility ratio was less than $50 000 per QALY gained, and a 37% probability that it was greater than $50 000 per QALY gained.	Aspirin use appears to have a favorable cost-utility ratio for older women with moderate cardiovascular risk, but firm conclusions about its effects are limited by the imprecision of available evidence, which comes mainly from 1 trial. Aspirin is indicated for women at higher risk for stroke but should not be prescribed for low-risk women, including most younger women.

ASPIRIN VS NO TREATMENT AND COMBINATION OF ASPIRIN AND STATIN VS ASPIRIN

Table 20: Pignone et al.[90]

Authors Country Year of publication Conflict of interest	Intervention Population and/or base risk and/or applied risk function relative risk benefit	Analytic technique Year of costs, currency Costs details Utilities	Cost-effectiveness	Sensitivity analysis	Conclusion
Pignone M, Earnshaw S, Tice JA, Pletcher MJ. US 2006 Potential Financial Conflicts of Interest: M. Pignone: consultancies (Bayer, Pfizer Inc.), honoraria (Bayer, Pfizer Inc.), expert testimony (Bayer), grants received (Bayer) and other. S. Earnshaw: grants received (Bayer). **Perspective** **Time window** **Discount rate** Third-party payer perspective. Lifetime. All costs and outcomes were discounted at 3%.	Interventions compared: low-dose aspirin, a statin, both drugs as combination therapy, or no therapy. Middle-aged men without a history of cardiovascular disease at 6 levels of 10-year risk for CHD (2.5%, 5%, 7.5%, 10%, 15%, and 25%). In the base-case scenario, the authors compared the effectiveness of 10 years of aspirin therapy, statin therapy, combination therapy with both drugs, and no therapy in 45-year old men with a 10-year risk for CHD of 7.5%. Baseline risks for initial cardiovascular events (myocardial infarction, stroke, angina, and death from CHD) were drawn from Framingham risk equations by using hypothetical scenarios of nonsmoking, nonhypertensive, nondiabetic men at different levels of risk for CHD. The effect of treatments on all-cause mortality was estimated from meta-analyses of secondary prevention trials: Relative risk of primary prevention, % Myocardial infarction Statin 0.70 (0.62–0.79) Aspirin 0.70 (0.62–0.79) Stroke Statin 0.85 (0.57–1.28) Aspirin 1.06 (0.91–1.24) Angina Statin 0.68 (0.49–0.95) Aspirin 1.00 (0.80–1.20) Death from coronary heart disease Statin 0.71 (0.56–0.91) Aspirin 0.87 (0.70–1.09)	CUA, a Markov model. 2003, in dollars. Annual cost data (in $): Drug cost Statin 713 Aspirin 16 Myocardial infarction Year 1 care 16085 Ongoing care 2576 Stroke Year 1 care 11161 Ongoing care 1664 Hemorrhagic stroke Year 1 care 27605 Ongoing care 8013 Angina Year 1 care 5662 Ongoing care 2460 Gastrointestinal bleeding Nonfatal 6928 Fatal 6928 Myopathy-related death 10000 Miscellaneous Physician visit 36.42 Serum lipid level testing 30.9 Hepatic function test 11.4 Day institutionalized 43.41 Utilities: Healthy 1 Death 0 Myocardial infarction and angina Year 1 0.88 (0.80–0.96) Subsequent years 0.90 (0.80–0.95) Stroke Nondisabling 0.75 (0.60–0.90) Disabling 0.5 (0.0–0.75) Gastrointestinal bleeding (year 1) 0.94 (0.88–1.0) Myopathy (year 1) 0.97 (0.94–1.0) Act of taking aspirin or statin 1.0 (0.99–1.0)	cost per QALY gained (in $): Base-Case Analysis: aspirin vs. no therapy men at low risk (2.5%) 9800 men at low to moderate risk (5%) dominant men at moderate risk (7.5%) dominant men at moderate to high risk (10%) dominant men at high risk (15%) dominant men at very high risk (25%) dominant aspirin + statin vs. aspirin men at low risk (2.5%) 164700 men at low to moderate risk (5%) 97900 95%CI: (46 700 - 288 800) men at moderate risk (7.5%) 56200 95%CI: (26 100 -246 276) men at moderate to high risk (10%) 42500 95%CI: (20 600 - 188 000) men at high risk (15%) 33600 men at very high risk (25%) 15300 95%CI: (7600 to - 71 000) In an alternate model, the authors used separate health states for hemorrhagic and ischemic strokes. aspirin vs. no therapy / aspirin + statin vs. aspirin 2.5% dominated / / 5% dominated / / 7.5% dominant 57100 10% dominant 43100 15% dominant 33900 25% dominant 15500	The authors examined the effect of changing several different parameters in one-way sensitivity analyses, including the effect of different levels of 10-year risk for CHD (2.5%, 5%, 10%, 15%, and 25%) and different starting ages (55, 65, and 75 years). The authors also examined the effect of varying individual values for all of our main efficacy, adverse event, cost, and utility estimates by using plausible ranges of values from the literature, 95% CIs, or estimates that varied by as much as 50% in each direction. Results: Excess risk for hemorrhagic stroke and gastrointestinal bleeding with aspirin, risk for CHD, the cost of statins, and the disutility of taking medication had important effects on the cost–utility ratios. Probabilistic sensitivity analyses : In the base case, 91% of the results fall within the cost-saving quadrant (aspirin is less costly and more effective).	Compared with no treatment, aspirin is less costly and more effective for preventing CHD events in middle-aged men whose 10-year risk for CHD is 7.5% or higher. The addition of a statin to aspirin therapy becomes more cost-effective when the patient's 10-year CHD risk before treatment is higher than 10%.

ANTIHYPERTENSIVES VERSUS NO TREATMENT

Table 21: Malik et al.[97]

Authors Country Year of publication Conflict of interest	Intervention Population and/or base risk and/or applied risk function relative risk benefit	Analytic technique Year of costs, currency Costs details Utilities	Cost-effectiveness	Sensitivity analysis	Conclusion
Malik IS, Bhatia VK, Kooner JS. UK. 2001. No conflict of interest declared. **Perspective** **Time window** **Discount rate** The health care provider. Five years up to lifetime (20 years). No discounting.	Five, 10, 15, and 20 year (lifetime) ramipril treatment assuming continued benefit from treatment versus no treatment. The authors modelled the cost effectiveness in a low risk population with annual mortality rate of 1% at age 66, a primary prevention group similar to the WOSCOPS (west of Scotland coronary outcome prevention study) population. The landmark HOPE (heart outcome prevention evaluation) showed that at five years' follow up ramipril treatment reduced cardiovascular events by 22% ($p < 0.001$) and total mortality by 16% ($p = 0.005$) compared with placebo in patients with proven atherosclerotic disease (coronary artery disease, cerebrovascular disease, or peripheral vascular disease) or diabetes mellitus plus one additional vascular risk factor.	CEA, the life table method was used. Year of costs not explicitly mentioned, in £. The majority of patients in the HOPE trial took ramipril 10 mg/day. The authors used the price quoted in the British National Formulary to calculate a cost of £170 per patient year. Costs CHD events and therapeutic procedures (in £): Procedure: Myocardial infarction 1900 PTCA 3500 CABG 5500 Average revascularisation (50% PTCA: 50% CABG) 4500 Other coronary disease related admissions (unstable angina/heart failure) 1500	In the low-risk group, cost effectiveness was £36 600 per life year gained at five years and £5300 per life year gained at 20 years (lifetime treatment).	The effect of discounting estimates of life years gained, costs, and savings at 6% per annum was assessed. To account for possible regional price differences, we assessed cost effectiveness at treatment prices varying between 50% and 200%. Estimates of cost savings were varied from 50–200% of initial values. Results: Apart from pre-treatment level of risk, the major determinant of the cost effectiveness of treatment was drug cost. Adjusting drug cost between 50% and 200% of initial values altered lifetime cost effectiveness from £2200 to £11 400 per life year gained (basecase: £5300).	Even for patients at lower risk, cost effectiveness for lifelong treatment is well below £25 000 per life year gained, a standard below which treatment is considered acceptable.

Table 22: Lundkvist et al.[98]

Authors Country Year of publication Conflict of interest	Intervention Population and/or base risk and/or applied risk function relative risk benefit	Analytic technique Year of costs, currency Costs details Utilities	Cost-effectiveness	Sensitivity analysis	Conclusion
Lundkvist J, Ekman M, Kartman B, Carlsson J, Jonsson L, Lithell H. Sweden. 2005. No conflict of interest declared. **Perspective** **Time window** **Discount rate** The societal perspective. Lifetime of the patients (limited to 110 years of age). Costs and outcomes were discounted at a real rate of 3%.	Candesartan-based antihypertensive treatment versus no treatment. However, because of changes in treatment guidelines and for ethical reasons, it was decided during the recruitment period to recommend additional open-label active antihypertensive treatment in both treatment groups for patients whose blood pressure remained high. The study therefore actually compared candesartan-based treatment with usual antihypertensive treatment not including candesartan. Patients in the candesartan group were therefore assumed to be treated with candesartan for a maximum of 4 years. Elderly patients (70–89 years) with mild or moderate hypertension (systolic blood pressure 160–179mmHg and/or diastolic blood pressure 90–99mmHg). A risk reduction of 27.8% (95%CI: 1.3–47.2, p=0.04) was observed in the SCOPE study.	CUA, a Markov model. 2001 price level, SEK converted into euros (9.25 SEK/EUR). Stroke-related costs in SCOPE (in €): Cost 1 year before stroke 5510 Cost 1 year after stroke 14717 Stroke-related cost (cost 1 year after - cost 1 year before) 9206 Cost year 2 and onwards after stroke 14680 Follow-up time year 2 and onwards after stroke (days) 544 Cost per year of follow-up 9850 Stroke-related cost (cost per year of follow-up - cost 1 year before) 4340 Since all patients were over 70 years of age, there were no indirect costs for productivity losses due to disease. Costs for concomitant medications (except those with less than 20 prescriptions), living arrangements, in-patient care, and unscheduled visits were included. Utilities: The average utility during 1 year before stroke was 0.77. During the first year after stroke, the weighted average utility was 0.70. The utility for the second year was used also for subsequent years, but the authors took account of the aging of the population by using the age-specific relative decline by age.	The cost per patient was €1 949 in the candesartan group and €1 578 in the control group. Candesartan-based antihypertensive treatment was associated with 0.0289 additional QALYs per patient and an incremental cost per QALY gained of approximately €13 000.	One-way sensitivity analysis: The sensitivity of the base-case results to changes in key parameter values in the model was analysed with regard to variation in annual antihypertensive treatment cost (upper and lower limit of the 95% CI for the difference between treatment groups), first-year stroke cost (upper and lower 95%CI limit), second-year stroke cost, stroke risk, first- and second-year utilities, mortality risks and discount rate (varied between 0 and 5%). Costs in added years of life in the general Swedish population were also included in the sensitivity analysis. The sensitivity analyses showed that the base-case results were fairly stable. Risk of stroke and stroke cost during the second year and onwards were the most important parameters for the cost-effectiveness ratio. As expected, the cost-effectiveness ratio increased when costs in added years of life were included.	The cost per QALY gained with candesartan-based antihypertensive treatment lies within the range of society's willingness to pay for health gains. The results indicate that candesartan-based antihypertensive treatment is cost-effective for the prevention of nonfatal stroke.

DIETARY ADVICE AND/OR EXERCISE

Table 23: Lindgren et al.[99]

Authors Country Year of publication Conflict of interest	Intervention Population and/or base risk and/or applied risk function relative risk benefit	Analytic technique Year of costs, currency Costs details Utilities	Cost-effectiveness	Sensitivity analysis	Conclusion
Lindgren P, Fahlstadius P, Hellenius M-L, Jonsson B, de Faire U. Sweden. 2003. No conflicts of interest with industry declared (The work was funded by a grant from Stockholm County Council and the Swedish Heart and Lung Foundation). **Perspective** **Time window** **Discount rate** The societal and payer perspective. Lifetime: the maximum age allowed in the model is 109 years. A discount rate of 3% has been applied to both costs and effects.	Comparing dietary advice (D), exercise (E), and the combination of both (DE) applied to an observed cohort of 60-year-old men in the county of Stockholm. The risk factor profile of these individuals: risk factor: DBP (mm Hg) 84.1 Total cholesterol (mmol/L) 6.1 Current smoker (%) 19.9 LVH (%) 2.7 Glucose intolerance (%) 7.1 The coefficients of the risk function are taken from the Framingham study. Effect of intervention on some cardiovascular risk factors based on the diet and exercise study (mean reduction (SD)). Patients were followed up at 6 and 18 months. Total cholesterol (mmol/L) Treatment group: 0–6 months 6–18 months Diet -0.19 (0.94) -0.32 (0.69) Exercise -0.12 (0.71) -0.22 (0.59) Diet + exercise -0.45 (0.99) -0.15 (0.77) Diastolic blood pressure (mm Hg) Treatment group: 0–6 months 6–18 months Diet -6.07 (6.78) -3.76 (7.95) Exercise -4.21 (7.23) -3.0 (7.19) Diet + exercise -1.23 (7.36) -2.87 (7.52)	CEA, a Markov model. 2000, in Swedish Kroner (SEK). Patient level direct and indirect costs related to cardiovascular disease were taken from a previous study by Zethraeus and colleagues (1999). The average direct costs for 1 year after the different events were SEK49 078 (recognized MI), SEK95 699 (unstable angina), and SEK47 634 (angina pectoris). The corresponding indirect costs were SEK107 315,SEK96 535, and SEK76 010. The authors also assumed that an unrecognized MI costs SEK3 500 yearly in direct costs and SEK27 500 in indirect costs and that the second and following year after all other events cost SEK7 000 in direct costs and SEK55 000 in indirect costs. Three types of costs were used in the model: Direct costs relating to direct health care expenditures as a result of the disease or intervention. Indirect costs related to loss of production due to disease. Costs in added years of life defined as the difference in production and consumption due to extra survival. All treatment groups: three visits to a physician (one at baseline and two follow-up visits) at a cost of SEK696. Patients in groups D and DE made one visit to a dietitian at a cost of SEK340 + follow-up by phone estimated to half that cost. Time and travel costs for making a visit: SEK336. Attend exercise groups (for groups DE (26% accepted) and E (54% accepted)): cost of running a group of 15 people is SEK7 500. 50% of members of both groups invested in new shoes, estimated to SEK700.	The model predicts lower costs and higher effectiveness for dietary advice compared to the alternatives. In fact, this alternative is a dominating strategy. Cost-effectiveness of dietary advice compared to no intervention: (SEK/LYG) Declining effect Societal perspective 127 065 Payer perspective 98 725 Remaining effect Societal perspective 141 555 Payer perspective 11 642	QALYs were not included in the main analysis. However, they were included in a sensitivity analysis: Cardiovascular event: QALY loss was assumed to be 0.10. QALY weights: 0.91 (60-64 years), 0.81 (65-74 years), 0.65 (75-84 years), and 0.60 (85+ years). Result: Dietary advice is still the better strategy, with an incremental effectiveness of 0.022 QALYs assuming declining effects of treatment and 0.086 QALYs if risk factors are kept constant after treatment. The corresponding cost-effectiveness ratios are SEK130 505 and SEK164 348/QALY gained (societal perspective) and SEK101 398 and SEK13 561/QALY gained (health care payer perspective).	Based on the model, dietary advice appears to be the most cost-effective of the studied interventions. The predicted cost-effectiveness ratios are well within the limits of what is considered cost-effective, regardless of perspective and assumptions about the lasting effects on risk factors.

SMOKING CESSATION, ASPIRIN, ANTIHYPERTENSIVES AND STATINS

Table 24: Franco et al.[38]

Authors Country Year of publication Conflict of interest	Intervention Population and/or base risk and/or applied risk function relative risk benefit	Analytic technique Year of costs, currency Costs details Utilities	Cost-effectiveness	Sensitivity analysis	Conclusion
Franco OH, der Kinderen AJ, De Laet C, Peeters A, Bonneux L. The Netherlands. 2007. No conflict of interest declared with pharmaceutical companies. **Perspective** **Time window** **Discount rate** The third party payer perspective. The time horizon used for costs and effects was 10 years. Future net costs and benefits were discounted at a nominal discount rate of 4 percent per year.	four risk-lowering interventions: smoking cessation (SC) antihypertensives aspirin statins Participants (men only) were classified by age group and by level of absolute risk of CHD estimated with the Anderson risk equation. Subjects were categorized into three groups based on their level of 10-year absolute risk of CHD: low risk, <10 percent (2 396 participants) moderate risk, 10 -<20 percent (714 part.) high risk, ≥20 percent (222 participants). Risk reduction effect of interventions (%): (only mentioned for primary prevention) primary CHD death / nonfatal CHD / stroke aspirin 13 / 28 / 20 antihypertensives 26 / 20 / 39 statins 29 / 34 / 29 smoking cessation (SC) reduction effect from published function for SC in CVD prevention.	CEA, multistate life tables (MSLTs) were built to model the cost-effectiveness. 2003, in €. Aspirin treatment: A visit to the general practitioner (GP) costs €26.29, a telephonic consultation €13.14, a blood sample test €12.19, a prescription renewal €13.14, and each pharmacist's fee €6.68 (2). Aspirin treatment includes per year, one GP visit plus the cost of aspirin 100 mg/day (€27.97) for a total of €54.26. Antihypertensives: Yearly treatment with antihypertensives includes two GP visits, two prescription renewals, four pharmacist's fees, one blood analysis, and the medication costs (€122.78), leading to a total annual cost of €240.55. Statins: Statin therapy includes two GP visits, two prescription renewals, four pharmacist's fees, one blood analysis, and medication costs (€484.92) for an annual total of €602.69. Three different strategies were considered for smoking cessation: GP's advice: one-time cost of €26.29. Nicotine substitutes: medication costs for 3 months of €117.79 Bupropion: total cost of €188.64 in the first year. Direct medical costs of events: nonfatal myocardial infarction (MI) €6972, fatal MI €1602, nonfatal stroke €11870, fatal stroke prevented €3851, major bleeding event $5300.	Cost-effectiveness moderate risk population (€/YLS) age 50 age 60 SC GP advice Cost saving SC nicotine substitutes Cost saving SC bupropion Cost saving Aspirin 16 949 12 862 Antihypertensives 79 843 51 217 Statins 190 276 133 083 Cost-effectiveness high risk population age 50 age 60 SC GP advice Cost saving SC nicotine substitutes Cost saving SC bupropion Cost saving Aspirin 2 716 2 263 Antihypertensives 36 399 28 187 Statins 85 715 73 971 ICER of interventions on the efficiency frontier moderate risk age 50 age 60 SC nicotine substitutes Cost saving SC bupropion 8 033 6 107 SC GP advice Dominated Aspirin 36 207 15 799 Antihypertensives Dominated Statins 488 460 287 608 ICER of interventions on the efficiency frontier high risk age 50 age 60 SC nicotine substitutes Cost saving SC bupropion 2 188 2 355 SC GP advice Dominated Aspirin 9 336 7 213 Antihypertensives Dominated Statins 287 496 171 670	sensitivity analysis on discount rates, annual relapse rates for the smoking cessation strategies, lower drug cost for statin therapy, adverse effects for aspirin treatment, different proportions of smokers, different proportions of populations with suboptimal blood pressure (BP), giving antihypertensives to all participants with moderate/high level of absolute CHD risk irrespective of BP level. Results: The order in the CERs was not sensitive to changing discount factors for either costs or effects. The order of results was not altered when different annual relapse rates (20% & 40%) were considered for the three SC strategies, or when costs of adverse events were taken into account for aspirin treatment. In an incremental cost-effectiveness analysis, the cheapest statins still cannot compete with smoking cessation or aspirin. Changing the proportion of smokers and participants with SBP ≥ 140 mm Hg or giving antihypertensives by level of absolute risk irrespective of level of SBP changed the CERs mildly, but not their order nor the order for the cost-efficiency frontier.	A cost-effective strategy should offer smoking cessation for smokers and aspirin for moderate and high levels of risk among men 45 years of age and older. Statin therapy is the most expensive option in primary prevention at levels of 10-year coronary heart disease risk below 30 percent and should not constitute the first choice of treatment in these populations.

APPENDIX FOR CHAPTER 5

The appendix for chapter 5 has been published as a separate document and is available in Dutch mainly.

Boffin N, Cornelis E, Hubens V, Laperche J, Spinnewijn B, Vaes B, et al. Rapid Assessment: Cardiovasculaire Primaire Preventie in de Belgische Huisartspraktijk - bijlage voor hoofdstuk 5. Good Clinical Practice (GCP). Brussel: Federaal Kenniscentrum voor de Gezondheidszorg (KCE); 2007. KCE reports 52 Suppl. (D/2007/10.273/05)

7 REFERENCES

1. Wald NJ, Law MR. A strategy to reduce cardiovascular disease by more than 80%. BMJ. 2003;326(7404):1419.
2. Paffenbarger RS, Jr., Blair SN, Lee IM. A history of physical activity, cardiovascular health and longevity: the scientific contributions of Jeremy N Morris, DSc, DPH, FRCP. Int J Epidemiol. 2001;30(5):1184-92.
3. Wilson K, Gibson N, Willan A, Cook D. Effect of smoking cessation on mortality after myocardial infarction: meta-analysis of cohort studies. Arch Intern Med. 2000;160(7):939-44.
4. Van den Bruel A, Cleemput I, Van Linden A, Schoefs D, Ramaekers D, Bonneux L. Effectiviteit en kosten-effectiviteit van behandelingen voor rookstop. Federaal Kenniscentrum voor de Gezondheidszorg (KCE); 2004.
5. Wu P, Wilson K, Dimoulas P, Mills EJ. Effectiveness of smoking cessation therapies: a systematic review and meta-analysis. BMC Public Health. 2006;6:300.
6. European Society of Hypertension-European Society of Cardiology Guidelines C. 2003 European Society of Hypertension-European Society of Cardiology guidelines for the management of arterial hypertension. J Hypertens. 2003;21(6):1011-53.
7. Antithrombotic Trialists C. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ. 2002;324(7329):71-86.
8. Berger JS, Roncaglioni MC, Avanzini F, Pangrazzi I, Tognoni G, Brown DL. Aspirin for the primary prevention of cardiovascular events in women and men: a sex-specific meta-analysis of randomized controlled trials. JAMA. 2006;295(3):306-13.
9. De Backer G, Ambrosioni E, Borch-Johnsen K, Brotons C, Cifkova R, Dallongeville J, et al. 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 (constituted by representatives of eight societies and by invited experts). Eur J Cardiovasc Prev Rehabil. 2003;10(Suppl 1):S1-S78.
10. De Backer G, Ambrosioni E, Borch-Johnsen K, Brotons C, Cifkova R, Dallongeville J, et al. 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. 2003;24(17):1601-10.
11. De Backer G, De Bacquer D, Brohet C, De Ceukelier S, Franck A, Krzentowsky G, et al. Recommendations for the prevention of cardiovascular diseases in clinical practice. Journal de Pharmacie de Belgique. 2005;60(2):41-50.
12. De Backer G, De Bacquer D, Brohet C, De Ceukelier S, Franck A, Krzentowsky G, et al. Recommendations for the prevention of cardiovascular diseases in clinical practice. Belgian Working Group on Prevention of Ccardiovascular Diseases. Revue Medicale de Bruxelles. 2005;26(2):77-87.
13. De Backer G, De Bacquer D, Brohet C, De Ceukelier S, Franck A, Krzentowsky G, et al. Recommandations relatives a la prevention des maladies cardio-vasculaires en pratique clinique. Revue Medicale de Liege. 2005;60(3):163-72.
14. De Backer G, De Bacquer D, Brohet C, De Ceukelier S, Franck A, Krzentowsky G, et al. Aanbevelingen voor de preventie van Cardiovasculaire aandoeningen in de klinische praktijk. Tijdschrift voor Geneeskunde. 2005;61(8):601-13.
15. Third Task Force of European and other Societies on Cardiovascular Disease Prevention in Clinical Practice. Europese Richtlijnen voor cardiovasculaire preventie (Adapted for Belgium). Sophia Antipolis (France): European Society of Cardiology; 2006.
16. Third Task Force of European and other Societies on Cardiovascular Disease Prevention in Clinical Practice. Recommandations européennes pour la prévention des maladies cardiovasculaires (Adapted for Belgium). Sophia Antipolis (France): European Society of Cardiology; 2006.

17. Conroy RM, Pyorala K, Fitzgerald AP, Sans S, Menotti A, De Backer G, et al. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. European Heart Journal. 2003;24(11):987-1003.

18. Boland B, De Muylder R, Goderis G, Degryse J, Gueuning Y, Paulus D, et al. Cardiovascular prevention in general practice: development and validation of an algorithm. Acta Cardiol. 2004;59(6):598-605.

19. De Muylder R, Tonglet R, Nackers F, Boland B. Randomised evaluation of a specific training of general practitioners in cardiovascular prevention. Acta Cardiol. 2005;60(2):199-205.

20. Van Royen P. Niveaus van bewijskracht. Levels of evidence. Huisarts Nu. 2002;31:54-7.

21. Anderson KM, Wilson PW, Odell PM, Kannel WB. An updated coronary risk profile. A statement for health professionals. Circulation. 1991;83(1):356-62.

22. Scottish Intercollegiate Guidelines Network (SIGN). Risk estimation and the prevention of Cardiovascular Disease. A national clinical guideline. Edinburgh: SIGN; 2007. (97) Available from: http://www.sign.ac.uk/pdf/sign97.pdf

23. http://www.ssmg.be/new/files/IMP_Cardio_PSMG_Plaquette.pdf. 2006.

24. Joint British recommendations on prevention of coronary heart disease in clinical practice. British Cardiac Society, British Hyperlipidaemia Association, British Hypertension Society, endorsed by the British Diabetic Association. Heart. 1998;80 Suppl 2:S1-29.

25. Kwaliteitsinstituut voor de Gezondheidszorg CBO. Multidisciplinaire richtlijn Cardiovasculair risicomanagement 2006. Utrecht: CBO; 2006. Available from: www.cbo.nl

26. Nederlands Huisartsen Genootschap. NHG-Standaard Cardiovasculair Risicomanagement. Utrecht: NHG; 2006. Available from: http://nhg.artsennet.nl/uri/?uri=AMGATE_6059_104_TICH_R1785801378709573

27. Prodigy. Cardiovascular risk - assessment and management. 2006. Available from: http://www.prodigy.nhs.uk/cardiovascular_risk/view_whole_guidance

28. Joint British Societies. Joint British Societies' Guidelines on Prevention of Cardiovascular Disease in Clinical Practice. Heart. 2005;91(Supp V):v1-v52.

29. National Institute for Health and Clinical Excellence. Statins for the prevention of cardiovascular events. London: NICE; 2006 January 2006. Technology Appraisal (TA94) Available from: http://www.nhshealthquality.org/nhsqis/files/TA094guidance.pdf

30. Ward S, Lloyd J, Pandor A, Holmes M, Ara R, Ryan A, et al. Statins for the Prevention of Coronary Events. Technology assessment report commissioned by the HTA Programme on behalf of the National Institute for Clinical Excellence. Sheffield: ScHARR The University of Sheffield; 2005 January 2005. Available from: http://www.nice.org.uk/pdf/statins_assessment_report.pdf

31. Wetenschappelijk Instituut Volksgezondheid. Brussels: WIV-ISP. Quarterly reports on External Quality Assessment for Clinical Biology Analyses Available from: http://www.iph.fgov.be/ClinBiol/bckb33/activities/external_quality/rapports/_nl/rapports_annee.htm

32. Warnick GR, Nauck M, Rifai N. Evolution of methods for measurement of HDL-cholesterol: from ultracentrifugation to homogeneous assays. Clin Chem. 2001;47(9):1579-96.

33. Saeed BO, Smart P, Keeka G, Handley GH, Weaver JU. Comparison of two direct methods for HDL cholesterol measurement with an indirect precipitation method in diabetic patients. Diabetes Nutr Metab. 2002;15(3):169-72.

34. Saeed BO, Keeka J, Smart P. Comparison of three homogeneous methods for measuring high-density lipoprotein cholesterol with a precipitation method in diabetic and non-diabetic subjects. Br J Biomed Sci. 2004;61(4):194-9.

35. Cobbaert C, Zwang L, Ceriotti F, Modenese A, Cremer P, Herrmann W, et al. Reference standardization and triglyceride interference of a new homogeneous HDL-cholesterol assay compared with a former chemical precipitation assay. Clin Chem. 1998;44(4):779-89.

36. Langlois MR, Blaton VH. Historical milestones in measurement of HDL-cholesterol: impact on clinical and laboratory practice. Clin Chim Acta. 2006;369(2):168-78.

37. De Bacquer D, De Backer G. Vergelijking van de Framingham en SCORE modellen voor het inschatten van het risico op de ontwikkeling van hart- en vaatziekten. Een simulatiestudie. Gent: 2004.

38. Franco OH, der Kinderen AJ, De Laet C, Peeters A, Bonneux L. Primary prevention of cardiovascular disease: Cost-effectiveness comparison. Int J Techn Assessment in Health Care. 2007;23(1):71-9.

39. Getz L, Sigurdsson JA, Hetlevik I, Kirkengen AL, Romundstad S, Holmen J. Estimating the high risk group for cardiovascular disease in the Norwegian HUNT 2 population according to the 2003 European guidelines: modelling study. BMJ. 2005;331(7516):551.

40. Hobbs FDR. Primary prevention of cardiovascular disease: managing hypertension and hyperlipidaemia. Heart. 2004;90 Suppl 4:iv22-5.

41. Haffner SM, Lehto S, Ronnemaa T, Pyorala K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. N Engl J Med. 1998;339(4):229-34.

42. Yusuf S. Two decades of progress in preventing vascular disease. Lancet. 2002;360(9326):2-3.

43. Hooper L, Summerbell CD, Higgins JPT, Thompson RL, Clements G, Capps N, et al. Reduced or modified dietary fat for preventing cardiovascular disease. Cochrane Database of Systematic Reviews. 2007;1:1.

44. Howard BV, Van Horn L, Hsia J, Manson JE, Stefanick ML, Wassertheil-Smoller S, et al. Low-fat dietary pattern and risk of cardiovascular disease: the Women's Health Initiative Randomized Controlled Dietary Modification Trial. JAMA. 2006;295(6):655-66.

45. Neil HA, Roe L, Godlee RJ, Moore JW, Clark GM, Brown J, et al. Randomised trial of lipid lowering dietary advice in general practice: the effects on serum lipids, lipoproteins, and antioxidants. BMJ. 1995;310(6979):569-73.

46. Law MR, Morris JK. By how much does fruit and vegetable consumption reduce the risk of ischaemic heart disease? Eur J Clin Nutr. 1998;52(8):549-56.

47. BMJ Publishing Group. Clinical Evidence. BMJ Publishing Group Ltd.; 2007.

48. Eidelman RS, Hollar D, Hebert PR, Lamas GA, Hennekens CH. Randomized trials of vitamin E in the treatment and prevention of cardiovascular disease. Arch Intern Med. 2004;164(14):1552-6.

49. AHA. Evidence-Based Guidelines for Cardiovascular Disease Prevention in Women: 2007 Update. Circulation. 2007.

50. Bjelakovic G, Nikolova D, Gluud LL, Simonetti RG, Gluud C. Mortality in randomized trials of antioxidant supplements for primary and secondary prevention: systematic review and meta-analysis. JAMA. 2007;297(8):842-57.

51. Hooper L, Thompson RL, Harrison RA, Summerbell CD, Ness AR, Moore HJ, et al. Risks and benefits of omega 3 fats for mortality, cardiovascular disease, and cancer: systematic review. BMJ. 2006;332(7544):752-60.

52. Studer M, Briel M, Leimenstoll B, Glass TR, Bucher HC. Effect of different antilipidemic agents and diets on mortality: a systematic review. Arch Intern Med. 2005;165(7):725-30.

53. Danone. http://www.danone.be/danacol.

54. Le Coeur des Belges. http://www.lecoeurdesbelges.be/testthenation/fr/fr_home.asp.

55. Nationaal Hart Onderzoek. http://www.nationaalhartonderzoek.be/testthenation/nl/nl_home.asp.

56. Law M. Plant sterol and stanol margarine and health. BMJ. 2000;320:861-4.

57. Katan MB, Grundy SM, Jones P, Law M, Miettinen T, Paoletti R, et al. Efficacy and safety of plant stanols and sterols in the management of blood cholesterol levels. Mayo Clin Proc. 2003;78(8):965-78.

58. Qullez J, Garcla-Lorda P, Salas-Salvado J. Potential uses and benefits of phytosterols in diet: present situation and future directions. Clin Nutr. 2003;22(4):343-51.

59. Moruisi KG, Oosthuizen W, Opperman AM. Phytosterols/stanols lower cholesterol concentrations in familial hypercholesterolemic subjects: a systematic review with meta-analysis. J Am Coll Nutr.

2006;25(1):41-8.

60. Potter D, Whittaker V, Burke M, Rigby P, Summerbell C, Hooper L. Supplemental plant sterols and stanols for serum cholesterol and cardiovascular disease. (Protocol). Cochrane Database of Systematic Reviews 2004. 2004(Issue 2. Art. No.: CD004814).

61. Lea LJ, Hepburn PA. Safety evaluation of phytosterol-esters. Part 9: Results of a European post-launch monitoring programme. Food Chem Toxicol. 2006;44(8):1213-22.

62. John S, Sorokin AV, Thompson PD. Phytosterols and vascular disease. Curr Opin Lipidol. 2007;18(1):35-40.

63. American Heart Association Nutrition C, Lichtenstein AH, Appel LJ, Brands M, Carnethon M, Daniels S, et al. Diet and lifestyle recommendations revision 2006: a scientific statement from the American Heart Association Nutrition Committee. Circulation. 2006;114(1):82-96.

64. Gidding SS, Dennison BA, Birch LL, Daniels SR, Gillman MW, Lichtenstein AH, et al. Dietary recommendations for children and adolescents: a guide for practitioners: consensus statement from the American Heart Association. Circulation. 2005;112(13):2061-75.

65. Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, MacFarlane PW, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. N Engl J Med. 1995;333(20):1301-7.

66. Nakamura H, Arakawa K, Itakura H, Kitabatake A, Goto Y, Toyota T, et al. Primary prevention of cardiovascular disease with pravastatin in Japan (MEGA Study): a prospective randomised controlled trial. Lancet. 2006;368(9542):1155-63.

67. Shepherd J, Blauw GJ, Murphy MB, Bollen ELEM, Buckley BM, Cobbe SM, et al. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. Lancet. 2002;360(9346):1623-30.

68. Downs JR, Clearfield M, Weis S, Whitney E, Shapiro DR, Beere PA, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. JAMA. 1998;279(20):1615-22.

69. Officers A, Coordinators for the ACRGTA, Lipid-Lowering Treatment to Prevent Heart Attack T. Major outcomes in moderately hypercholesterolemic, hypertensive patients randomized to pravastatin vs usual care: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT). JAMA. 2002;288(23):2998-3007.

70. Sever PS, Dahlof B, Poulter NR, Wedel H, Beevers G, Caulfield M, et al. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial--Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. Lancet. 2003;361(9364):1149-58.

71. Thavendiranathan P, Bagai A, Brookhart MA, Choudhry NK. Primary prevention of cardiovascular diseases with statin therapy: a meta-analysis of randomized controlled trials. Arch Intern Med. 2006;166(21):2307-13.

72. Costa J, Borges M, David C, Vaz Carneiro A. Efficacy of lipid lowering drug treatment for diabetic and non-diabetic patients: meta-analysis of randomised controlled trials. BMJ. 2006;332(7550):1115-24.

73. Collins R, Armitage J, Parish S, Sleigh P, Peto R, Heart Protection Study Collaborative G. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. Lancet. 2003;361(9374):2005-16.

74. Colhoun HM, Betteridge DJ, Durrington PN, Hitman GA, Neil HAW, Livingstone SJ, et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. Lancet. 2004;364(9435):685-96.

75. Law M, Rudnicka AR. Statin safety: a systematic review. Am J Cardiol. 2006;97(8A):52C-60C.

76. Gotto AM, Jr. Statins, cardiovascular disease, and drug safety. Am J Cardiol. 2006;97(8A):3C-5C.

77. Law MR, Wald NJ, Rudnicka AR. Quantifying effect of statins on low density lipoprotein cholesterol, ischaemic heart disease, and stroke: systematic review and meta-analysis. BMJ. 2003;326(7404):1423.

78. Abramson J, Wright JM. Are lipid-lowering guidelines evidence-based? Lancet. 2007;369(9557):168-9.

79. Jauca C, Wright J. Therapeutic letter: update on statin therapy. Int Soc Drug Bull Newsletter. 2003;17:7-9.

80. Jackson PR, Wallis EJ, Haq IU, Ramsay LE. Statins for primary prevention: at what coronary risk is safety assured? Br J Clin Pharmacol. 2001;52(4):439-46.

81. Kumana CR, Cheung BM, Lauder IJ. Simvastatin reduced mortality and vascular events in high-risk patients. ACP J Club. 2003;138(1):2-3.

82. Franco OH, Peeters A, Looman CWN, Bonneux L. Cost effectiveness of statins in coronary heart disease. J Epidemiol Community Health. 2005;59(11):927-33.

83. Lim SS, Vos T, Peeters A, Liew D, McNeil JJ. Cost-effectiveness of prescribing statins according to Pharmaceutical Benefits Scheme criteria. Medical Journal of Australia. 2001;175(9):459-64.

84. Johannesson M. At what coronary risk level is it cost-effective to initiate cholesterol lowering drug treatment in primary prevention? Eur Heart J. 2001;22(11):919-25.

85. Spaans JN, Coyle D, Fodor G, Nair R, Vaillancourt R, Grover SA, et al. Application of the 1998 Canadian cholesterol guidelines to a military population: health benefits and cost effectiveness of improved cholesterol management. Can J Cardiol. 2003;19(7):790-6.

86. Grover SA, Ho V, Lavoie F, Coupal L, Zowall H, Pilote L. The importance of indirect costs in primary cardiovascular disease prevention: can we save lives and money with statins? Archives of Internal Medicine. 2003;163(3):333-9.

87. Nagata-Kobayashi S, Shimbo T, Matsui K, Fukui T. Cost-effectiveness of pravastatin for primary prevention of coronary artery disease in Japan. International Journal of Cardiology. 2005;104(2):213-23.

88. Scotland NHSQI. Statins for the prevention of cardiovascular events. 2006.

89. Walshe V, Nash A, Barry M. Cost effectiveness of statin therapy for the primary prevention of coronary heart disease. Irish Medical Journal. 2006;100(1):144-5.

90. Pignone M, Earnshaw S, Tice JA, Pletcher MJ. Aspirin, statins, or both drugs for the primary prevention of coronary heart disease events in men: a cost-utility analysis. Annals of Internal Medicine. 2006;144(5):326-36.

91. Hay JW, Sterling KL. Cost effectiveness of treating low HDL-cholesterol in the primary prevention of coronary heart disease. PharmacoEconomics. 2005;23(2):133-41.

92. Lamotte M, Pinol C, Brotons C, Annemans L, Guardiola E, Evers T, et al. Health economic evaluation of low-dose acetylsalicylic acid in the primary prevention of cardiovascular disease. Rev Esp Cardiol. 2006;59(8):807-15.

93. Annemans L, Lamotte M, Kubin M, Evers T, Verheugt FWA. Which patients should receive aspirin for primary prevention of cardiovascular disease? An economic evaluation. International Journal of Clinical Practice. 2006;60(9):1129-37.

94. Lamotte M, Annemans L, Evers T, Kubin M. A multi-country economic evaluation of low-dose aspirin in the primary prevention of cardiovascular disease. Pharmacoeconomics. 2006;24(2):155-69.

95. Tsutani K, Igarashi A, Fujikawa K, Evers T, Kubin M, Lamotte M, et al. A health economic evaluation of aspirin in the primary prevention of cardiovascular disease in Japan. Intern Med. 2007;46(4):157-62.

96. Pignone M, Earnshaw S, Pletcher MJ, Tice JA. Aspirin for the primary prevention of cardiovascular disease in women: a cost-utility analysis. Arch Intern Med. 2007;167(3):290-5.

97. Malik IS, Bhatia VK, Kooner JS. Cost effectiveness of ramipril treatment for cardiovascular risk reduction. Heart. 2001;85(5):539-43.

98. Lundkvist J, Ekman M, Kartman B, Carlsson J, Jonsson L, Lithell H. The cost-effectiveness of candesartan-based antihypertensive treatment for the prevention of nonfatal stroke: Results from the Study on COgnition and Prognosis in the Elderly. Journal of Human Hypertension. 2005;19(7):569-76.

99. Lindgren P, Fahlstadius P, Hellenius M-L, Jonsson B, de Faire U. Cost-effectiveness of primary prevention of coronary heart disease through risk factor intervention in 60-year-old men from the

county of Stockholm--a stochastic model of exercise and dietary advice. Preventive Medicine. 2003;36(4):403-9.

100. Menotti A, Lanti M, Puddu PE, Kromhout D. Coronary heart disease incidence in northern and southern European populations: a reanalysis of the seven countries study for a European coronary risk chart. Heart. 2000;84(3):238-44.

101. Jones P, Kafonek S, Laurora I, Hunninghake D. Comparative dose efficacy study of atorvastatin versus simvastatin, pravastatin, lovastatin, and fluvastatin in patients with hypercholesterolemia (the CURVES study). Am J Cardiol. 1998;81(5):582-7.

102. ISPOR Medication Compliance and Persistence Special Interest Group. http://www.ispor.org/sigs/MCP_accomplishments.asp, accessed 13 March, 2007.

103. Simons LA, Levis G, Simons J. Apparent discontinuation rates in patients prescribed lipid-lowering drugs. Med J Aust. 1996;164(4):208-11.

104. Simons LA, Simons J, McManus P, Dudley J. Discontinuation rates for use of statins are high. BMJ. 2000;321(7268):1084.

105. Hayden M, Pignone M, Phillips C, Mulrow C. Aspirin for the primary prevention of cardiovascular events: a summary of the evidence for the U.S. Preventive Services Task Force. Ann Intern Med. 2002;136(2):161-72.

106. Ramsay LE, Yeo WW, Jackson PR. Dietary reduction of serum cholesterol concentration: time to think again. BMJ. 1991;303(6808):953-7.

107. Tang JL, Armitage JM, Lancaster T, Silagy CA, Fowler GH, Neil HA. Systematic review of dietary intervention trials to lower blood total cholesterol in free-living subjects. BMJ. 1998;316(7139):1213-20.

108. Cleemput I, Crott R, Vrijens F, Huybrechts M, Van Wilder P, Ramaekers D. Recommandations provisoires pour les évaluations pharmacoéconomiques en Belgique. Brussels : Belgian Health Care Knowledge Centre (KCE) ; May 2006. KCE Reports vol. 28B. Ref. D/2006/10.273/11. 2006.

109. Saito I, Folsom AR, Aono H, Ozawa H, Ikebe T, Yamashita T. Comparison of fatal coronary heart disease occurrence based on population surveys in Japan and the USA. Int J Epidemiol. 2000;29(5):837-44.

110. Ekman M. Economic evidence in stroke: a review. Eur J Health Econ. 2004;5 Suppl 1:S74-83.

111. Saillour-Glenisson F, Michel P. Individual and collective facilitators of and barriers to the use of clinical practice guidelines by physicians: a literature review. Rev.Epidemiol.Sante Publique. 2003;51(1 Pt 1):65-80.

112. Jates N, Massot C, Schoefs D, Tellier V. Rapport d'enquête téléphonique dans le cadre d'un programme de Formation des Médecins Généralistes à la Prévention Cardiovasculaire. 2004.

This page is left intentionally blank.

Dépôt légal : D/2007/10.273/04

KCE reports

1. Efficacité et rentabilité des thérapies de sevrage tabagique. D/2004/10.273/2.
2. Etude relative aux coûts potentiels liés à une éventuelle modification des règles du droit de la responsabilité médicale (Phase 1). D/2004/10.273/4.
3. Utilisation des antibiotiques en milieu hospitalier dans le cas de la pyélonéphrite aiguë. D/2004/10.273/6.
4. Leucoréduction. Une mesure envisageable dans le cadre de la politique nationale de sécurité des transfusions sanguines. D/2004/10.273/8.
5. Evaluation des risques préopératoires. D/2004/10.273/10.
6. Validation du rapport de la Commission d'examen du sous financement des hôpitaux. D/2004/10.273/12.
7. Recommandation nationale relative aux soins prénatals: Une base pour un itinéraire clinique de suivi de grossesses. D/2004/10.273/14.
8. Systèmes de financement des médicaments hospitaliers: étude descriptive de certains pays européens et du Canada. D/2004/10.273/16.
9. Feedback: évaluation de l'impact et des barrières à l'implémentation – Rapport de recherche: partie 1. D/2005/10.273/02.
10. Le coût des prothèses dentaires. D/2005/10.273/04.
11. Dépistage du cancer du sein. D/2005/10.273/06.
12. Etude d'une méthode de financement alternative pour le sang et les dérivés sanguins labiles dans les hôpitaux. D/2005/10.273/08.
13. Traitement endovasculaire de la sténose carotidienne. D/2005/10.273/10.
14. Variations des pratiques médicales hospitalières en cas d'infarctus aigu du myocarde en Belgique. D/2005/10.273/12
15. Evolution des dépenses de santé. D/2005/10.273/14.
16. Etude relative aux coûts potentiels liés à une éventuelle modification des règles du droit de la responsabilité médicale. Phase II : développement d'un modèle actuariel et premières estimations. D/2005/10.273/16.
17. Evaluation des montants de référence. D/2005/10.273/18.
18. Utilisation des itinéraires cliniques et guides de bonne pratique afin de déterminer de manière prospective les honoraires des médecins hospitaliers: plus facile à dire qu'à faire.. D/2005/10.273/20
19. Evaluation de l'impact d'une contribution personnelle forfaitaire sur le recours au service d'urgences. D/2005/10.273/22.
20. HTA Diagnostic Moléculaire en Belgique. D/2005/10.273/24, D/2005/10.273/26.
21. HTA Matériel de Stomie en Belgique. D/2005/10.273.28.
22. HTA Tomographie par Emission de Positrons en Belgique. D/2005/10.273/30.
23. HTA Le traitement électif endovasculaire de l'anévrysme de l'aorte abdominale (AAA). D/2005/10.273.33.
24. L'emploi des peptides natriurétiques dans l'approche diagnostique des patients présentant une suspicion de décompensation cardiaque. D/2005/10.273.35
25. Endoscopie par capsule. D2006/10.273.02.
26. Aspects médico-légaux des recommandations de bonne pratique médicale. D2006/10.273/06.
27. Qualité et organisation des soins du diabète de type 2. D2006/10.273/08.
28. Recommandations provisoires pour les évaluations pharmacoéconomiques en Belgique. D2006/10.273/11.
29. Recommandations nationales Collège d'oncologie : A. cadre général pour un manuel d'oncologie B. base scientifique pour itinéraires cliniques de diagnostic et traitement, cancer colorectal et cancer du testicule. D2006/10.273/13.
30. Inventaire des bases de données de soins de santé. D2006/10.273/15.
31. Health Technology Assessment : l'antigène prostatique spécifique (PSA) dans le dépistage du cancer de la prostate. D2006/10.273/18.
32. Feedback: évaluation de l'impact et des barrières à l'implémentation - Rapport de recherche: partie II. D2006/10.273/20.
33. Effets et coûts de la vaccination des enfants Belges au moyen du vaccin conjugué antipneumococcique. D2006/10.273/22.
34. Trastuzumab pour les stades précoces du cancer du sein. D2006/10.273/24.

35. Etude relative aux coûts potentiels liés à une éventuelle modification des règles du droit de la responsabilité médicale – Phase III : affinement des estimations. D2006/10.273/27.
36. Traitement pharmacologique et chirurgical de l'obésité. Prise en charge résidentielle des enfants sévèrement obèses en Belgique. D/2006/10.273/29.
37. Health Technology Assessment Imagerie par Résonance Magnétique. D/2006/10.273/33.
38. Dépistage du cancer du col de l'utérus et recherche du Papillomavirus humain (HPV). D/2006/10.273/36
39. Evaluation rapide de technologies émergentes s'appliquant à la colonne vertébrale : remplacement de disque intervertébral et vertébro/cyphoplastie par ballonnet. D/2006/10.273/39.
40. Etat fonctionnel du patient: un instrument potentiel pour le remboursement de la kinésithérapie en Belgique? D/2006/10.273/41.
41. Indicateurs de qualité cliniques. D/2006/10.273/44.
42. Etude des disparités de la chirurgie élective en Belgique. D/2006/10.273/46.
43. Mise à jour de recommandations de bonne pratique existantes. D/2006/10.273/49.
44. Procédure d'évaluation des dispositifs médicaux émergeants. D/2006/10.273/51.
45. HTA Dépistage du Cancer Colorectal : état des lieux scientifique et impact budgétaire pour la Belgique. D/2006/10.273/54.
46. Health Technology Assessment. Polysomnographie et monitoring à domicile des nourrissons en prévention de la mort subite. D/2006/10.273/60.
47. L'utilisation des médicaments dans les maisons de repos et les maisons de repos et de soins Belges. D/2006/10.273/62
48. Lombalgie chronique. D/2006/10.273/64.
49. Médicaments antiviraux en cas de grippe saisonnière et pandémique. Revue de littérature et recommandations de bonne pratique. D/2006/10.273/66.
50. Contributions personnelles en matière de soins de santé en Belgique. L'impact des suppléments. D/2006/10.273/69.
51. Besoin de soins chroniques des personnes âgées de 18 à 65 ans et atteintes de lésions cérébrales acquises. D/2007/10.273/02.
52. Rapid Assessment: Prévention cardiovasculaire primaire dans la pratique du médecin généraliste en Belgique. D/2007/10.273/04.