Les statines en Belgique: évolutions de l'utilisation et impact des politiques de remboursement

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Centre fédéral d'expertise des soins de santé
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AVANT-PROPOS

Les maladies cardiovasculaires constituent un déterminant majeur de mort prématurée et de morbidité dans notre société, et leur prévention est une priorité de santé publique. Cette prévention repose avant tout sur des changements du mode de vie : renoncement à la cigarette, exercice physique et régime alimentaire équilibré. Toutefois, si ceci ne suffit pas, il peut être indiqué de recourir à des médicaments, et notamment aux statines, qui abaissent le taux de cholestérol sanguin. Au cours des dix dernières années, cette classe de médicaments a pris une place prédominante dans ce type de prévention cardio-vasculaire, tant par le nombre d'utilisateurs que par son poids dans le budget de l'assurance maladie.

Outre la question de leur utilité médicale, l'usage de plus en plus répandu de ces molécules entraîne des interrogations fondamentales sur notre mode de vie actuel. Les statines sont-elles en train d'acquérir le statut de complément alimentaire utile à la santé comme l'iode dans le sel et le fluor dans le dentifrice ? On n'en est pas là, certes, mais dès qu'on préconise un médicament en prévention primaire, il y a d'énormes précautions qui s'imposent, non seulement sur le plan de la sécurité, mais aussi sur le plan budgétaire et en matière d'équité.

Compte tenu de ces éléments, il nous apparaissait important d'analyser les évolutions récentes dans l'utilisation des statines et le profil de leurs utilisateurs. Les mesures prises au fil des années quant aux modalités d'accès à certaines de ces molécules ont-elles eu un impact ? Dans quelles circonstances cliniques les différentes statines sont-elles utilisées en Belgique ? Et quelles sont les nouvelles tendances qui se dessinent ? Trouver une réponse à ces questions, tel est l'objectif du présent rapport. Il ne fait pour sûr pas le tour de ce sujet vaste et important mais nous osons espérer qu'il contribuera à mener plus avant une politique rationnelle en la matière.

Tout au long de ce projet, nous avons pu faire appel aux connaissances et à l'esprit critique d'experts issus du monde clinique, académique, des organismes assureurs, des autorités et de l'industrie. Leur apport dans un esprit franc et constructif a contribué de manière significative à la réalisation de l'étude, et nous les en remercions sincèrement.

Jean Pierre CLOSON
Directeur général adjoint

Raf MERTENS
Directeur général

Résumé

INTRODUCTION

Les maladies cardiovasculaires (MCV), et plus particulièrement la maladie coronarienne (MC), constituent la principale cause de mortalité et de morbidité dans notre société. Le taux de cholestérol, notamment de cholestérol associé aux lipoprotéines de faible densité (C-LDL), qu'on appelle souvent 'mauvais' cholestérol, représente un facteur de risque important de MCV. En plus des aménagements apportés au mode de vie, notamment l'abandon du tabac et l'exercice physique, on peut réduire le risque de MCV grâce à des médicaments hypocholestérolémiants dont les statines sont actuellement les molécules phares. C'est la classe de médicaments la plus utilisée en Belgique, et 7% des dépenses totales en médicaments ambulatoires lui sont alloués. La prévention primaire est définie comme le recours aux statines chez les personnes n'ayant pas d'antécédents connus de MCV mais qui présentent un facteur de risque pour cette affection. La prévention secondaire est le recours aux statines dans le but de prévenir de nouveaux accidents cardiovasculaires chez les sujets ayant des antécédents de MCV. Il est bien établi que les statines peuvent réduire le risque d'épisodes de MCV aussi bien en prévention primaire que secondaire. Ceci dit, la réduction de ce risque, en termes absolus, sera d'autant plus grande que le risque individuel de souffrir de MCV est élevé et que la diminution du C-LDL obtenue est grande. La diminution de C-LDL dépend de la dose de statines utilisée et de la molécule prescrite (par exemple 40 mg de simvastatine produisent le même effet sur le C-LDL que 10 mg d'atorvastatine). Les effets secondaires, essentiellement une myopathie et une élévation des enzymes hépatiques, dépendent aussi de la dose. Le risque de diabète est aussi modérément augmenté. Les effets secondaires sévères sont rares.

Contexte belge

Cinq statines bénéficient actuellement d'une autorisation de mise sur le marché en Belgique, avec des différences de prix importantes d'une molécule à l'autre (Tableau). La simvastatine et la pravastatine sont à la fois les molécules les moins onéreuses et celles dont le profil risque/bénéfice a été évalué depuis le plus longtemps. Le recours préférentiel à la simvastatine/pravastatine a été encouragé par diverses mesures en Belgique.

Tableau: Utilisation et coût des statines en Belgique en 2009

Molécule	Noms	Utilisateurs* (N)	DDD (mg)	Coût moyen global (en €) par: DDD	Comp	Utilisateur (par an)	Total
Simvastatine	Zocor®, génériques	647 529	30	0.28	0.26	70.4	45 601 398
Pravastatine	Prareduct®, Pravasine®, génériques	121 274	30	0.47	0.54	146.7	17 787 628
Fluvastatine	Lescol®	17 457	60	0.66	0.80	231.8	4 046 880
Atorvastatine	Lipitor®	293 325	20	1.26	1.47	416.3	122 107 090
Rosuvastatine	Crestor®	239 289	10	0.81	1.01	276.1	66 064 862
TOTAL		**1 318 874**					**255 607 858**

* ≅ 5% des utilisateurs achètent plus d'un type de molécules de statine pendant l'année; DDD: Defined Daily Dose (dose thérapeutique quotidienne) ; comp. : comprimé

Tout d'abord, depuis août 2004, la simvastatine/pravastatine est remboursable sans contrôle pour toutes les indications reprises dans la notice scientifique. Le remboursement des autres statines ne peut se faire que dans les conditions fixées par la Commission pour le remboursement des médicaments (CRM) de l'Institut National d'assurance maladie-invalidité (INAMI), c.à.d. un C-LDL ≥100 mg/dl en prévention secondaire et chez les patients diabétiques. En prévention primaire, il faut un C-LDL ≥115 mg/dl associé à un risque de mortalité à 10 ans pour cause de MCV ≥ 5% selon la méthode SCORE[a].

Ensuite, en 2008, un système d'appel d'offres a été mis en place pour les statines, entraînant une nouvelle diminution de prix pour la simvastatine. Enfin, en 2009, était inscrite dans l'accord Médico-Mutualiste la recommandation d'utiliser la simvastatine/pravastatine dans au moins 80% des nouveaux traitements. En 2010, la CRM a recommandé que ces deux molécules soient utilisées dans 100% des nouveaux traitements en prévention primaire et dans la majorité des nouveaux traitements en prévention secondaire et chez les patients diabétiques. Le passage à une autre statine ne peut être envisagé que si les objectifs thérapeutiques ne sont pas atteints après 3 mois de traitement. L'INAMI veillera à l'application effective de ces recommandations via un contrôle à posteriori des prescriptions.

Objectifs du rapport

Compte tenu de l'importance clinique de la MCV et du nombre énorme de bénéficiaires concernés, avec des retombées budgétaires importantes pour les finances publiques, les évolutions dans l'utilisation de ces médicaments doivent être documentées en temps utile pour orienter les politiques de santé. Dans le présent rapport, nous avons voulu analyser les changements dans l'utilisation des statines au cours du temps (1997-2009), et notamment l'influence des modifications des règles de remboursement introduites en 2004. En outre, des questions spécifiques intéressant les cliniciens et les politiques ont été abordées :

- Y-a-t-il une différence en termes d'utilisation des statines entre les patients en prévention primaire ou secondaire ?
- Quels sont les facteurs favorisant l'instauration d'une prévention secondaire après un épisode cardiovasculaire ?
- Qui sont les patients qui respectent le traitement prescrit et pendant combien de temps prennent-ils des statines ?
- Quels sont les déterminants du recours aux molécules les moins onéreuses ?
- Quelles sont les preuves de l'équivalence en termes d'efficacité et de sécurité cliniques des différentes molécules de statines ?
- Quel serait l'impact budgétaire d'une augmentation de la proportion des patients utilisant les molécules les moins onéreuses ?

[a] La méthode SCORE permet d'établir le risque individuel de mortalité par MCV dans les 10 ans sur base de la tension artérielle, de la consommation de tabac, de l'âge, du sexe et de la concentration sanguine en C-LDL

MÉTHODES

Évaluation des évolutions en termes d'utilisation et des profils d'utilisateur

Après obtention de l'autorisation de la Commission pour la protection de la vie privée, nous avons effectué une analyse de bases de données suivantes:

- Les données agrégées au niveau national de Pharmanet (médicaments délivrés en officine publique), mis à disposition par l'INAMI (de 1997 à 2009)
- Les données détaillées de remboursement des statines liées aux caractéristiques individuelles des patients dans un échantillon de la population générale (Echantillon Permanent - Permanente Steekproef, EPS), mis à disposition par l'Agence Intermutualiste (de 2002 à 2006)
- Les données cliniques d'hospitalisation (RCM) aux fins d'identification des épisodes cardiovasculaires, mises à disposition par le Service public fédéral de santé publique (de 2002 à 2006; 2006 étant la dernière année pour laquelle les données RCM étaient disponibles). Ces données ont été couplées aux données EPS.

Pour évaluer l'observance thérapeutique, nous avons chiffré le « *medication possession ratio* » personnel (MPR), en posant l'hypothèse que chaque utilisateur absorbe quotidiennement un des comprimés qui lui a été spécifiquement prescrit. Dans le droit fil d'autres études, les patients étaient considérés comme compliants (ou utilisateurs réguliers) s'ils avaient un MPR ≥ 80% pendant toute la période d'utilisation.

Un nouvel utilisateur a été défini comme un sujet achetant au moins un conditionnement de statines sans antécédents d'utilisation d'une statine au cours des 12 mois précédents. Chez les nouveaux utilisateurs sans épisode de MCV enregistré au cours des 12 mois qui précèdent le démarrage de la statine, on parle de prévention primaire. La prévention secondaire a été définie comme l'instauration chez un nouvel utilisateur d'une statine (quelle qu'elle soit) dans les 12 mois suivant une hospitalisation pour un épisode de MCV[b].

Dans le but de permettre un suivi suffisamment long pour calculer la durée jusqu'à l'arrêt du traitement, celle-ci n'a été analysée que chez les patients ayant débuté la prise d'une statine en 2003.

Toutes les analyses statistiques (régression logistique ou modèle de Cox) ont été ajustées afin de tenir compte de l'effet de l'âge, du sexe, de la coexistence d'un diabète (établi sur la base du recours à des médicaments antidiabétiques), du type de prévention (primaire/secondaire), de la molécule de statine, de l'initiateur du traitement (médecin généraliste/spécialiste), du droit à un remboursement majoré et de la présence d'un statut d'invalidité ou d'un handicap.

Comparaison de l'efficacité et de la sécurité d'emploi des différentes statines

Nous avons procédé à une revue systématique de la littérature. Les bases de données électroniques Medline, Embase, Database of Abstracts of Reviews of Effects (DARE) ainsi que le Cochrane Central Registry of Controlled Trials ont été utilisées. Pour comparer l'efficacité et la sécurité d'emploi des statines les moins onéreuses par rapport aux plus chères, des essais de type 'head-to-head' (face à face) comparant la simvastatine ou la pravastatine à la fluvastatine, l'atorvastatine ou la rosuvastatine ont fait l'objet d'une méta-analyse.

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b Un épisode de MCV a été défini sur la base des codes de la CIM 9 et comprenait : l'infarctus du myocarde aigu, d'autres formes de cardiopathie ischémique aiguë et subaiguë, l'angine de poitrine, d'autres formes de cardiopathie ischémique chronique, un accident vasculo-cérébral ischémique, et une ischémie cérébrale temporaire.

Impact budgétaire

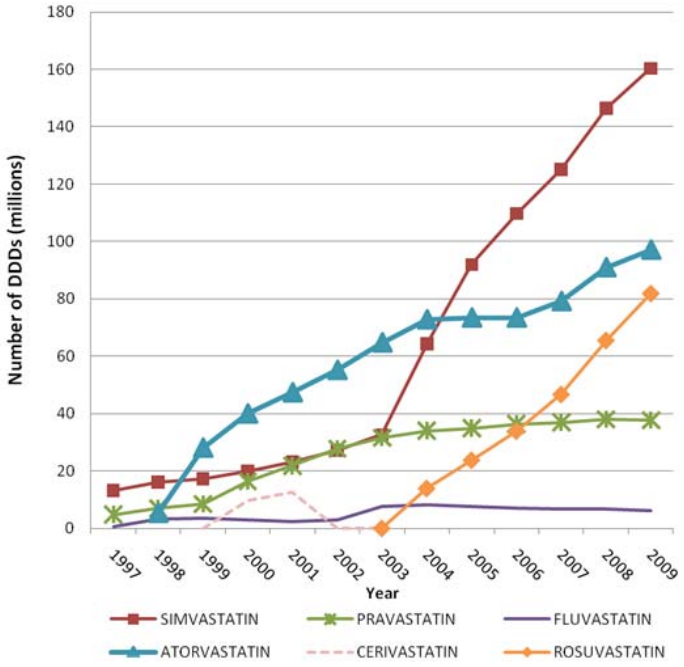
Dans la foulée des expériences de la Norvège et de la Finlande, nous avons utilisé les données cumulatives de l'INAMI afin de simuler l'impact budgétaire pour la période 2006-2009 d'une augmentation de la proportion des patients prenant de la simvastatine/pravastatine. À cette fin, nous avons calculé les 'dépenses moyennes' par patient pour chaque type de statine, en partant de l'hypothèse qu'il n'y avait pas de contre-indication au transfert des patients d'une statine à l'autre.

RÉSULTATS

Tendances en matière d'utilisation

Le nombre d'utilisateurs de statines a connu une croissance très importante au cours des dernières années. Ainsi, en 2009 plus de 1 300 000 personnes ont acheté au moins un conditionnement de statines. Comme le montre le graphique, le nombre de DDDs[c] remboursées dans le contexte ambulatoire a été multiplié par 20 entre 1997 et 2009 (pour passer de 18.6 millions à plus de 380 millions de doses). L'augmentation la plus forte a été observée pour la simvastatine et la rosuvastatine. Bien que n'étant sur le marché que depuis 2003, cette dernière représentait 21% des DDDs en 2009. Il convient de souligner que la proportion des utilisateurs de simvastatine/pravastatine est restée constante, autour de 60%, ces dernières années.

Figure: Tendance en termes de l'utilisation des statines de 1997 à 2009



Impact du changement de réglementation de 2004

Le changement de réglementation de mi-2004 a induit une forte augmentation du nombre de nouveaux utilisateurs de statines par rapport à l'année précédente (+83%). La part de nouveaux utilisateurs achetant de la simvastatine/pravastatine est passée de 58% durant l'année qui a précédé le changement de réglementation à 72% l'année qui l'a suivi. Toutefois, cette augmentation n'a eu qu'un impact modéré sur l'utilisation des autres statines chez les utilisateurs déjà sous statines : à peine 9% d'utilisateurs d'atorvastatine et 6% d'utilisateurs de rosuvastatine sont passés à la simvastatine/pravastatine.

[c] DDD : Defined Daily Dose (Dose thérapeutique quotidienne)

Profil d'utilisation des nouveaux utilisateurs de statines (période de 2003 à 2006)

La grande majorité des nouveaux utilisateurs (92% au cours de la période) se trouvaient en prévention primaire. Dans l'analyse multivariée, la simvastatine/pravastatine s'avère nettement moins choisie en prévention primaire (65.4% des nouveaux traitements) qu'en prévention secondaire (78.4%), et moins fréquemment par les MG (65.4%) que par les spécialistes (72.0%).

Le pourcentage d'utilisateurs réguliers (c'est-à-dire avec un MPR ≥ 80%) n'était que de 59%. Les utilisateurs 'occasionnels' de statines étaient soit des patients qui n'avaient reçu qu'une seule prescription de statine (18%) ou des utilisateurs dont le MPR était inférieur à 80% (23% des patients). Les facteurs le plus fortement associés à une prise régulière étaient les suivants : âge de plus de 50 ans, diabète (adjusted odds ratio (OR)=1.43 (1.34 - 1.53)) et utilisation d'une statine en prévention secondaire (OR=2.06 (1.86 - 2.27)). La probabilité pour les utilisateurs réguliers de toujours être sous statine un an après l'instauration du traitement était de 75% et tombait à 50% après 4 ans.

Prévention secondaire après un épisode cardiovasculaire (2006)

Après une hospitalisation pour un épisode de MCV (N=85.500) chez des patients qui ne prenaient pas de statine avant ledit épisode (N=51.300) et ont quitté l'hôpital en vie, un traitement par statine a été entamé dans seulement 52.4% des cas (données 2006). Cette proportion variait selon le diagnostic principal d'hospitalisation et l'âge des patients, les patients âgés de plus de 70 ans étant nettement moins susceptibles de recevoir une statine, quelle qu'elle soit. Les chiffres les plus élevés étaient observés en cas d'infarctus du myocarde aigu dans le groupe des 50-59 ans, où une prévention secondaire a été instaurée dans 95.8% des cas en 2006, alors que cette proportion était de 58% pour les cas d'AVC dans le même groupe d'âge.

Évaluation comparative des statines les plus onéreuses et les moins onéreuses

Cinq essais comparatifs ont été inclus dans l'évaluation. La plupart des essais incluaient des patients souffrant d'une MC et la majorité des participants étaient de sexe masculin. Dans chaque étude, on a utilisé l'atorvastatine 80 mg et on l'a comparée à la pravastatine 40 mg (3 essais), à la simvastatine 20 mg (1 essai) et à la lovastatine 5 mg (1 essai), la rosuvastatine n'étant utilisée dans aucun des essais. Sur l'ensemble des études, l'atorvastatine 80 mg réduisait le risque d' infarctus du myocarde de 16% (RR: 0.84 (0.73, 0.96)), tandis que le risque d'AVC et de mortalité toutes causes confondues (RR=0.92 (0.81, 1.04)) ne différait pas de manière significative entre l'atorvastatine et les comparateurs. Notons toutefois que les comparateurs ont été utilisés à des doses thérapeutiques inférieures à celle de l'atorvastatine (80mg=4 DDDs).

Pour ce qui concerne la sécurité, il n'y avait pas de différence manifeste entre les statines, mais nous ne disposions pas de données comparatives sur la molécule la plus récente, à savoir la rosuvastatine.

Considérations budgétaires

En 2009, les dépenses totales pour les statines représentaient € 255.6 millions. Entre 2004 et 2009, le prix par DDD pour la simvastatine et la pravastatine a baissé de plus de 60%, tandis que les prix sont restés relativement constants pour les autres molécules. L'appel d'offres public de 2008 ne s'est finalement appliqué qu'à la simvastatine, ramenant son prix par DDD à € 0.29. Grâce à ces réductions de prix, la simvastatine/pravastatine représentait en 2009 23% des dépenses totales pour les statines tout en fournissant plus de 50% des DDDs. Une augmentation du pourcentage d'utilisateurs des molécules les moins onéreuses d'environ 60% à 80% aurait réduit les dépenses totales en 2006, 2007, 2008 et 2009 de respectivement € 40.5 millions, € 45.7 millions, € 56.9 millions et € 64.4 millions.

DISCUSSION ET CONCLUSION

Des chiffres en hausse

En 2009, quelque 20% des Belges adultes ≥ 35 ans prenaient une statine, l'atorvastatine et la rosuvastatine occupant respectivement la première et la quatrième position dans la liste des dépenses publiques par médicament. Un constat qui illustre la nécessité d'utiliser rationnellement les statines.

L'essentiel de la hausse dans l'utilisation des statines était lié à la prévention primaire, et ce pour diverses raisons. La simplification administrative mi-2004 et la nouvelle diminution du prix de la simvastatine/pravastatine ont certainement joué un rôle, mais cela n'explique pas l'augmentation concomitante des utilisateurs de rosuvastatine et d'atorvastatine. Le mode de vie (grosso modo 83% des Belges de 35 à 74 ans ont un taux de cholestérol supérieur au plafond recommandé), le vieillissement séculaire de la population, de même qu'une tendance générale à la médicalisation de la prévention forment aussi une combinaison qui favorise l'évolution observée. Il convient de souligner le fait que des changements du mode de vie peuvent également se révéler efficaces pour réduire la morbidité et la mortalité cardiovasculaire et que mettre en œuvre des stratégies globales qui permettraient de tels changements est aussi crucial dans la lutte contre les MCV. Enfin, le seuil actuel à partir duquel un remboursement des statines dans la prévention primaire en Belgique est possible (risque de mortalité MCV à 10 ans ≥ 5%) est peut-être trop souvent interprété comme une indication pour l'utilisation de statines, alors qu'il ne constitue qu'un indicateur clinique pour adapter la prise en charge aux besoins du patient. Ainsi, 88.0 % des sujets belges de sexe masculin âgés de ≥ 63 ans présentent à la fois une hypercholestérolémie et un SCORE ≥ 5%. À lui seul, ce groupe représente 761.000 utilisateurs potentiels et prouve à quel point une approche uniquement basée sur une gestion médicamenteuse du risque serait responsable d'un lourd fardeau sociétal. La prévention avec une statine peut présenter d'importants avantages pour les patients à haut risque mais le gain clinique absolu sera moindre chez les patients avec des risques de MCV plus faibles, alors que les risques d'effets secondaires demeurent constants. C'est un élément important à discuter avec le patient avant de se lancer dans une thérapie pendant de nombreuses années.

Prévention secondaire

La couverture des patients ayant quitté l'hôpital avec un diagnostic de MCV, notamment un AVC, est perfectible, une observation qui s'inscrit dans le droit fil des constats posés dans d'autres pays européens. Cependant, nos analyses se sont limitées à l'année 2006 et la couverture de tels patients à haut risque peut s'être améliorée depuis cette date. En tout état de cause, cet aspect important de la prise en charge mérite une analyse de situation et des actions correctrices si nécessaires de la part des hôpitaux.

Comparaison de l'efficacité et de la sécurité d'emploi des statines

Nous n'avons trouvé aucune donnée probante d'un différentiel en matière de bénéfice clinique pertinent entre les statines commercialisées en Belgique lorsqu'elles sont administrées à une dose thérapeutique équivalente. En effet, les essais comparant les statines entre elles étaient à l'origine conçus dans le but d'évaluer les avantages d'une thérapie intensive par rapport à un dosage usuel. Toutefois, deux autres méta-analyses basées sur des comparaisons indirectes de l'efficacité théorique des statines sont parvenues à la même conclusion que la nôtre. Globalement, le profil de sécurité des statines a été rapporté comme étant satisfaisant à ce jour, à part le retrait de la cérivastatine en 2001 pour des raisons de sécurité. La molécule la plus récente, la rosuvastatine, disponible depuis 2003, semble présenter un profil de sécurité similaire aux autres molécules. Cependant, nous disposons pour évaluer son bilan risques/bénéfices cliniques de beaucoup moins de données que pour les autres statines. En conséquence, la recommandation de la CRM qui préconise de recourir en première intention à la simvastatine/pravastatine chez la majorité des patients en prévention primaire et secondaire repose sur des fondements scientifiques et son application doit être encouragée.

Aspects économiques

La mesure de 2004 a essentiellement entraîné une forte augmentation du nombre d'utilisateurs de la simvastatine, avec un impact minime sur les tendances de consommation des autres statines. L'importante réduction du prix par DDD de la simvastatine/pravastatine a quelque peu soulagé la forte élévation des dépenses globales observée au cours de ces dix dernières années (+133%). La part des patients prenant de la simvastatine/pravastatine est néanmoins restée stable au fil des années et toute augmentation de ce nombre résulterait en des économies financières considérables.

Il est cependant trop tôt pour évaluer la manière dont la nouvelle recommandation de la CRM sur l'utilisation des molécules les moins onéreuses en première intention se traduira en réalité au niveau des prescriptions. D'autres pays, tels que la Norvège en 2005 et la Finlande en 2006, ont mis en œuvre une politique plus systématique en rendant la simvastatine obligatoire pour tous les utilisateurs de statines, et non pas uniquement pour les nouveaux utilisateurs. Toutefois, compte tenu de la durée relativement courte du traitement en Belgique (50% des patients réguliers arrêtent leur traitement dans les quatre ans), il est probable que la politique belge actuelle donnera des résultats similaires à moyen terme.

Par ailleurs, le brevet de l'atorvastatine arrive à échéance en novembre 2011 et la possible réduction de prix de cette molécule qui suivra pour aura également un impact important sur les dépenses globales pour les statines.

RECOMMANDATIONS[d]

Au niveau opérationnel :

- **Les statines ne représentent qu'une composante de la gestion globale du risque de MCV : adapter le mode de vie devrait être prioritaire. Ceci dépasse le cadre de la consultation clinique et suppose des aménagements structurels et des campagnes d'information à destination du grand public.**
- **Les informations destinées aux prescripteurs devraient également insister sur le fait que les critères de remboursement actuels pour les statines en prévention primaire ne doivent pas être interprétés comme une indication absolue pour l'utilisation des statines.**
- **Si le recours à une statine s'avère nécessaire, la recommandation de la CRM visant à recourir en première intention à la simvastatine/pravastatine doit être appliquée de manière optimale. Par la même occasion, il y a lieu d'insister sur le fait que l'on dispose pour évaluer le bilan risques/bénéfices cliniques de moins de recul pour la rosuvastatine que pour les autres molécules.**
- **Le bilan risques/bénéfices d'une prévention avec statines et le nombre de patients à traiter pour prévenir un épisode de MCV sont plus favorables chez les patients à haut risque de MCV. Dès lors, avant d'instaurer une prévention avec une statine, le bénéfice clinique absolu escompté dans chaque cas particulier devrait être dûment débattu avec le patient.**

En matière de recherche :

- **Nous devons mieux comprendre les mécanismes sous-jacents de la faible observance thérapeutique et des niveaux bas de prévention secondaire pour certains types d'événements cardiovasculaires, afin de pouvoir améliorer ces aspects. Une étude spécifique, comprenant des entretiens approfondis avec les patients et des audits hospitaliers, représenterait une source d'informations cruciale.**
- **Les récentes recommandations de l'INAMI mais également l'émergence de copies et de génériques de l'atorvastatine dans la foulée de l'expiration de son brevet en novembre 2011 vont également modifier considérablement le rapport coût-efficacité de la prévention de la MCV basée sur les statines. Le rapport coût-efficacité des statines devrait être réévalué pour la Belgique en 2013.**

d Le KCE est le seul responsable des recommandations fournies aux pouvoirs publics.

Scientific Summary

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1 INTRODUCTION

1.1 BACKGROUND

Cardiovascular disease[a] (CVD), and particularly coronary heart disease (CHD), is the leading cause of mortality worldwide. An estimated 17.1 million people died from CVD in 2004, representing 29% of all deaths. Of these deaths, an estimated 7.2 million were due to CHD and 5.7 million were due to stroke. In Belgium, the age-standardized death rates of ischemic heart disease and cerebrovascular disease were 75.1 and 42.7 per 100 000, respectively, in 2004 (for a global rate of 508.9 per 100 000). The age-standardized rate of DALYs lost for both conditions were 596 and 350 per 100 000, respectively (for a global rate of 10 750 per 100 000)[b]. Tobacco use, an unhealthy diet, physical inactivity and harmful use of alcohol increase the risk of heart attacks and strokes. Among these risk factors, cholesterol level, particularly low-density lipoprotein (LDL-C), often labelled as "bad" cholesterol, play an important role. WHO estimates that 60% of CHD and 40% of strokes are due to elevated cholesterol levels. Thus besides changes in lifestyle, such as smoking cessation and exercise, CVD risk can be reduced by cholesterol-lowering diets and/or drugs, along with non-cholesterol drug treatments, including aspirin and antihypertensives.

Among cholesterol-lowering drugs, statins, a group that act by inhibiting the enzyme 3-hydroxy 3-methylglutaryl coenzyme A (HMG CoA) reductase involved in cholesterol biosynthesis, occupy a prominent place[1]. They reduce the concentration of downstream metabolic by-products including mevalonate, which in turn leads to increased expression of LDL-C receptors on hepatocytes, and to increased uptake of LDL-C from the circulation. Statins also tend to reduce the production of apolipoprotein B, leading to reduced VLDL (Very Low Density Lipoprotein) secretion from the liver. The main mechanism of the protective effect on CVD is believed to be the lowering of LDL-C concentrations [2]. The 5-year incidence of major coronary events, coronary revascularisation, and stroke can be reduced by about one fifth per mmol/L (39 mg/dL) in LDL-C, largely irrespective of initial lipid profile or other presenting characteristics[3,4]. Statins also exert pleiotropic effects[c], which could also contribute to the significant reduction in cardiovascular morbidity and mortality, although these mechanisms are still poorly understood today[5, 6].

Primary prevention is defined as the utilization of statins in individuals with no known history of but with risk factors for CVD. Secondary prevention is the use of statins to prevent further vascular events in patients with a history of CVD. The ability of statins to reduce the risks of CVD events and CVD-related deaths has been demonstrated in primary [3, 4, 7-12] and secondary [2-4, 9, 13] prevention trials.

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[a] The three major manifestations of CVD are: coronary heart disease (CHD), including myocardial infarction (MI, heart attack) and angina; cerebrovascular disease (transient ischaemic attack and stroke); and peripheral arterial disease.

[b] http://apps.who.int/ghodata/?vid=60150

[c] including reduction of inflammation, improvement of endothelial function, anti-oxidant properties and increased stability of atherosclerotic plaques

Five statins are currently licensed for use in Belgium: atorvastatin (Lipitor®), fluvastatin (Lescol®), pravastatin (Prareduct®, Pravasine®, generics), rosuvastatin (Crestor®), and simvastatin (Zocor®, generics). Statins represent a drug class which is widely used in our country: in 2009, more than 1.300.000 citizens purchased at least one packaging of statins (see Figure 2 p13), i.e. around 20% of Belgian adults ≥ 35 years[d]. Simvastatin and Pravastatin are the molecules with the most ascertained risk/benefit profile and with the lowest retail price (see Table 10, p17). The preferential utilization of simvastatin/pravastatin has been encouraged by various measures (details are provided in section section 2.1, p7). First, since August 2004, simvastatin/pravastatin have been reimbursable without control for all indications mentioned on the scientific information leaflet. The reimbursement of the other statins can only occur within specific official conditions. Second, in 2008, a system of public tender was implemented for statins, leading to a further price reduction of simvastatin. Finally, in late 2009, the National Institute of Insurance for Disease and Invalidity (INAMI/RIZIV) has recommended that simvastatin/pravastatin be used in 80% of new treatments, a recommendation extended to 100% since mid-2010. Switching patients to another statin can only be considered if therapeutic goals are not achieved after 3 months of treatment.

1.2 OBJECTIVES

Because of the clinical significance of CVD and the huge numbers of beneficiaries involved, with an important budgetary impact on public finances, the utilization trends of such drugs need to be documented in due time for policy-making purpose. In this report, we aimed at analysing changes in statin use over time (1997-2009), particularly as regards the change of reimbursement rules that occurred in mid-2004. Our objective was to yield a comprehensive description of statin utilization and statin users in Belgium between 1997 and 2009.

In addition, specific questions relevant for clinicians and policy-makers will be addressed:

- Is there a difference in statin use between patients on primary or secondary prevention?
- Who are the compliant patients and how long do they use statins?

  Managing the individual risk of CVD is a long-term process, and poor adherence to treatment might be an impediment to optimal CVD prevention [14, 15].
- What are the predictors of beginning a secondary prevention after a cardiovascular event?
- What are the determinants of using simvastatin or pravastatin versus the others statins?
- What do we know about the efficacy and safety equivalence of the various statins?
- What would be the budgetary impact of current recommendations for statin use?

[d] For the age distribution in Belgium, see: http://statbel.fgov.be/fr/statistiques/chiffres/population/structure/agesexe/pyramide/index.jsp

2 BELGIAN SITUATION

2.1 INDICATIONS AND REGULATIONS

The indications and regulations of statin use have evolved a great deal in the last few years. Initially, statins were reimbursed within the chapter IV, i.e. only after control and approval by advisors of sickness funds, and the level of blood cholesterol was the only criterion for reimbursement[e].

In December 2003, the indications for reimbursement were extended by taking into account the global cardiovascular risk[f]. By that time, the utilization of statins was recommended in patients with a primary hypercholesterolemia defined as a total cholesterol ≥190 mg/dl or a LDL-C ≥115 mg/dl, measured while fasting at least twice (with an interval of 1 to 8 weeks between the 2 measurements, in patients following appropriate dietary advices) AND at least one of the 2 following conditions:

- a 10-year CVD risk >20%, based on the Framingham risk score[g]
- a history of a coronary event (myocardial infarction, angina, acute coronary syndrome, coronary by-pass) AND/OR a cerebrovascular event (thrombotic stroke, documented transient ischemic attack) AND/OR a documented intermittent claudication

The reimbursement of statins was regulated through Chapter IV, also called the "a priori control". The reimbursement was possible only after obtaining the authorization from the medical advisor of a sickness fund.

In August 2004 the Belgian reimbursement criteria for statins changed drastically. The reimbursement of simvastatin and pravastatin, for which generic drugs were on the market and of which the drug companies agreed with a drastic price reduction was facilitated. In 2003, the price per Defined Daily Dose (DDD) was 1.40 AND 1.30 euros for simvastatin and pravastin, respectively. By 2005, theses prices went down to 0.68 and 0.85 euros, respectively. As of then, these statins are reimbursed (in category B[h]) according to Chapter I of the regulation which means that all indications that are mentioned on the scientific information leaflet are reimbursed without control[ij]. For the other statins marketed in Belgium – fluvastatin, atorvastatin and rosuvastatin - the Commission for Reimbursement of Pharmaceuticals (CTG-CRM) maintained the stricter reimbursement conditions of Chapter II of the regulation, also called the "a posteriori control". This implicates that only indications issued by the CTG-CRM are eligible for reimbursement (also in category B), and that the fulfilment of these conditions can be controlled by inspectors of the sickness funds[k].

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e http://www.inami.fgov.be/drug/nl/statistics-scientific-information/consensus/2002-05-28/pdf/lv.pdf

f http://www.riziv.fgov.be/drug/all/drugs/reglementation/legal-texts/list_ar_kb_am_mb/pdf/20031218edition1.pdf

g http://hp2010.nhlbihin.net/atpiii/calculator.asp?usertype=prof on the basis of the European Task Force which accounted for age, sex, serum cholesterol, systolic blood pressure and diabetes.

h socially and medically useful pharmaceuticals, 75% reimbursement (outside the BIM status)

i These indications for the use of simvastatin and pravastatin include: 1.treatment associated to dietary recommendations for a primary hypercholesterolemia or a mixed dyslipidemia; 2. treatment of a family homozygous hypercholesterolemia; 3. Treatment associated to dietary recommendations of an isolated hypertriglyceridemia in patients intolerant to nicotinic acid or fibrates; 4. primary and secondary prevention of cardio-vascular events.

j For pravastatine, the branded molecule remained in chapter II, while the generics are in chapter I. For simvastatin, all molecules have been moved to chapter I, but generics are not indicated for prevention, except a few generic molecules which are indicated for secondary prevention only.

k "a posteriori control" of the prescriptions is organized by the Department for Medical Evaluation and Control of the National Institute for Sickness and Disability Insurance (RIZIV-INAMI) in collaboration with the medical advisors from the sickness funds. This control consists of a retrospective analysis of prescriptions of individual physicians and determination of outliers.

These indications were defined[I] in 2006 as follows:

- a primary hypercholesterolemia defined as a total cholesterol ≥190 mg/dl or a LDL-C ≥115 mg/dl, measured at least twice (with an interval of 1 to 8 weeks between the 2 measurements, in patients following appropriate dietary advices and fasting on the day of the measurement) AND a risk of lethal CVD ≥ 5% for a 10 years period as measured with SCORE. SCORE is a risk chart for 10-years cardiovascular mortality based on age, sex, LDL-C concentration, smoking and hypertension. A risk chart adapted to the Belgian epidemiology is available [16](a copy of the SCORE Belgium is presented in annex).
- a primary hypercholesterolemia defined as a total cholesterol ≥175 mg/dl or a LDC≥100 mg/dl, measured while fasting at least twice (with an interval of 1 to 8 weeks between the 2 measurements, in patients following appropriate dietary advices) AND a history of at least one of the following conditions:
  - a coronary event: myocardial infarction, angina, acute coronary syndrome, coronary by-pass
  - a cerebrovascular event: thrombotic stroke or a documented transient ischemic attack
  - a documented intermittent claudication
  - a diabetes type II in patients ≥ 40 years
  - a diabetes type I with a microalbuminuria

Three additional conditions apply for the reimbursement.

- The physician prescribes a dose which is not higher than the maximum daily dose recommended in the scientific notice.
- The physician checks the treatment impact by achieving yearly a lipid profile of his/her patient and by reporting the results in the medical file of the patient
- The physician does not prescribe simultaneously another lipid-lowering drug (such as fibrates), except if the specific association of the 2 drugs can be officially reimbursed.

Statins prescribed for severe hypercholesterolemia (serum cholesterol ≥300 mg/dl), mostly from hereditary origin, can be 100% reimbursed (category A, i.e. pharmaceuticals for serious and long-term illnesses), but only after authorization (Chapter IV).

For a complete overview of the complex reimbursement conditions, please see the article by Chevalier P. [17].

In January 2008, the government launched a system of tender with acknowledged similarities with the so-called Kiwi model practiced in New-Zeeland. The law proposed to increase the reimbursement of the molecule with the lowest price within the therapeutic class of statins, with the aim of making the cheapest molecule the most attractive for patients. However, this eventually turn out to be a so-called "Kiwi light" as the tender did apply only to molecules off-patent and as the reference reimbursement price resulting from the tender did also apply only to off-patent molecules, i.e. other molecules are still reimbursed proportionally to their retail price. Only MSD, the manufacturer of Zocor®, participated to the tender. As a result, the price of simvastatin was reduced by 46%.

I Ministerial decree of April 2006: http://www.inami.fgov.be/drug/fr/drugs/groups/hypolipidemiants/pdf/arkb2006051001.pdf. The cut-offs for total cholesterol and LDL-C are also the ones recommended by the European guidelines of the 4th Joint Task force: http://www.escardio.org/guidelines-surveys/esc-guidelines/GuidelinesDocuments/guidelines-CVD-prevention-ES-FT.pdf

In the 2009-2010 agreement of the National Convention between Physicians and Sickness Funds (NCPS; "Commission nationale médico-mutualiste (CNMM)/Nationale commissie geneesheren-ziekenfondsen (NCGZ)), agreed physicians commit to prescribe "the least expensive" molecule in 80% of new statin users, provided that there are no contra-indications and that therapeutic targets are achieved. The "least costly" medication is identified by the INAMI/RIZIV based on the cost for the INAMI/RIZIV per Defined Daily Dose (DDD) (for the total consumption in 2008). Moreover, it is recommended to prescribe a branded or a generic molecule for which no financial supplement is requested to the patient, i.e. molecule sold at the reference reimbursement price. In practice, simvastatin (generic and copies; Zocor MSD) and pravastatin (generics and copies; Pravastatine Sandoz; Pravasine) are recommended[m]. The convention was signed by 82.8% of physicians.

The first evaluation of this measure was discussed on February 8, 2010 by the NCPS and representatives of the pharmaceutical sector, and was also made available on the website of the INAMI/RIZIV[n]. The objective to initiate therapy with either simvastatin or pravastatin in at least 8 of 10 patients was not reached. In June 2010, the CTG/CRM issued a new recommendation to use simvastatin or pravastatin to begin 100% new treatments in primary prevention, and most of new treatments in secondary prevention and in patients with diabetes[o]. In secondary prevention and in diabetic patients, atorvastatin or rosuvastatin can be considered in first intention for a new treatment only if the total cholesterol concentration is >290 mg/dl or the LDL-C is > 165 mg/dl. A new treatment is defined as the use of at least one packaging of statins without a history of statin intake in the 12 preceding months. Switching patients to atorvastatin, rosuvastatin, fluvastatin, or to a statin therapy complemented by other drugs can only be considered if therapeutic goals are not achieved after 3 months of treatment (total cholesterol<175 mg/dl or LDL-C<100 mg/dl in secondary prevention; total cholesterol<190 mg/dl or LDL-C<115 mg/dl in primary prevention). The official text of the recommendations is included in Annex. Doctors not complying with recommendations for statin utilization will be monitored during 6 months. If necessary, the physician monitored will be requested by the Medical Evaluation and Control Services of RIZIV/INAMI to justify his prescribing behaviour. The procedure could further lead to directly survey the prescription register of the incriminated MD and to administrative fines[p].

2.2 DATA ANALYSIS

Three databases have been used:

- a sample of claim data collected by sickness funds, for identification and description of statin users (the permanent sample/échantillon permanent/permanente steekproef – EPS, from the IMA-AIM databaseq),
- a sample of the hospital clinical data (RCM-MKG) to identify cardiovascular events,
- aggregates of national Pharmanet data to study trends of statin use over time.

These databases and the selection filters applied are described briefly in Table 1, and in extenso in the appendices. There is an unavoidable time delay to access administrative databases containing individual patient data. When this project started, the most recent data were available until 2006 for the hospital data and until the year 2007 for the EPS. The delay to receive aggregates of Pharmanet data is in general much shorter, and we received data up to November 2009.

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m The point 6 of the agreement is detailed at: http://www.inami.fgov.be/care/fr/doctors/general-information/agreements/2009-2010/pdf/20100501.pdf

n http://www.inami.fgov.be/care/fr/doctors/general-information/agreements/2009-2010/pdf/point6.pdf

o http://www.inami.fgov.be/drug/fr/drugs/recommendation/pdf/recommandations_statines.pdf

p http://www.inami.fgov.be/drug/fr/drugs/recommendation/pdf/brochure.pdf

q The permanent sample is an anonymous, representative sample of the IMA-AIM database. It consists of 1/40 sample of the Belgian assured <65 years old and a 1/20 sample of people ≥65 years old. This oversampling of people ≥65 years was taken into account in all analyses, and absolute numbers were extrapolated to the national population (unless specified otherwise).

Table 1: Summary of Data Sources

Sources	Population	Selection filters	Period of data collection
IMA-AIM (Pharmanet, health care and population data)	Random sample of assured persons (permanent sample)	Adult patients (≥ 18 years) with delivery of at least 1 packaging of statin in ambulatory care (ATC level 4 = C10AA)	2002 - 2007
Hospital Clinical Data (RCM-MKG)	Sample of patients	Hospitalisations with a cardio-vascular event (CVE) as main diagnosis	2002 - 2006
INAMI/RIZIV (Pharmanet aggregated)	All patients	Statin utilization per year (Number of DDDs, tablets and costs)	1997 – 2009
		Statin utilization per year (number of patients)	2004 – 2009

The IMA-AIM and RCM-MKG databases were coupled at the level of the patient. This linkage has been approved by the privacy commission[r].

This study is specific for the class of statin (ATC[s] level 4 = C10AA), and does not includes the new tablet which combines ezetimibe and simvastatin (ATC level 5 = C10BA02), and which is available on the Belgian market since 2007. Number of patients under this therapy is rather low (≅12 000 patients in 2008) compared to overall statin users.

A pre-assessment showed that the use of statin in hospital setting represents less than 1.5% of the total volume of statin (see detailed analysis in appendix). Nevertheless, patients taking statin in hospital setting could be identified and were flagged in order to be considered in the analyses but their detailed consumption was not analyzed as such.

The following definitions were used throughout all analyses (Table 2).

Table 2: Definitions used in all analyses

Term	Definition
User	Purchase of at least 1 packaging of statin in ambulatory care during the period under consideration
New user	Purchase of at least 1 packaging of statin in ambulatory care during the period under consideration with no statin delivery in the previous 365 days. Because data were available from 2002, new users are only defined from year 2003 onwards. Noteworthy, a same person can be counted several times as a new user provided that at least one year elapses during 2 purchases.
Medication Possession Ratio (MPR)	The Medication Possession Ratio is defined as the ratio of the number of tablets purchased divided by the number of days during the period of use ((date last delivery-date first delivery)+ number of medication days covered by the last delivery)
Regular user	New user with a Medication Possession Ratio (MPR) ≥80%.
Occasional user	New user who is not a regular user. This includes patients with a MPR < 80% and patients with only 1 statin packaging recorded.
Defaulter	Regular user stopping statin use during at least 3 months after the period theoretically covered by the last refill recorded.
Switcher	Consumer of different statin molecules within a defined period of time.
Major statin	If an individual received more than one type of statin, the statin mostly used (in tablet numbers) during the period considered was selected as the major

[r] Délibération n°09/024 du 21 avril 2009 relative à la communication de données à caractère personnel au centre fédéral d'expertise des soins de santé dans le cadre de l'étude n°2008-16. (https://www.ehealth.fgov.be/fr/page_a_t/website/home/ehealth.html)

[s] The Anatomical Therapeutic Chemical (ATC) classification system is a classification where drugs are classified in groups at five different levels (http://www.whocc.no/atc/structure_and_principles/)

Term	Definition
	statin used.
Cardiovascular Event	A cardiovascular event (CVE) is defined as a hospitalization with a principal diagnosis within the following list: • 410 Acute myocardial infarction (AMI) • 411 Other acute and subacute forms of ischemic heart disease • 413 Angina pectoris • 414 Other forms of chronic ischemic heart disease • 433 Occlusion and stenosis of precerebral arteries • 434 Occlusion of cerebral arteries • 435 Transient cerebral ischemia
Secondary prevention	Statin in new users within the year following a hospitalization CVE and without statin use in the year prior the hospitalisation.
Primary prevention	Statin in new users with no hospitalisation for CVE recorded in the year preceding the start of the statin use.
Diabetic	Consumer of at least one packaging of drugs used to treat diabetes, i.e. within the ATC level 2 = A10, in the year preceding the CVE or the start of statin therapy (depending on the analyses) • A10A – Insulins and analogues • A10B – Blood Glucose Lowering Drugs, excl. insulins • A10X – Other drugs used in diabetes

All analyses were performed using SAS 9.1 or Excel 2007.

2.2.1 Utilization trends (1997- 2009)

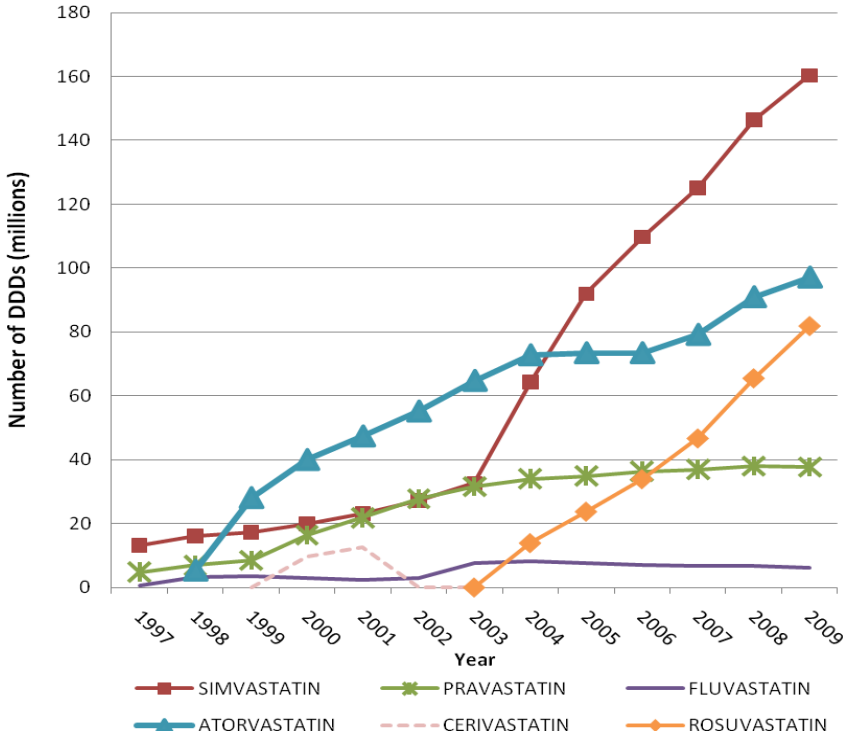
This section describes the statins delivered in the ambulatory sector, in terms of volume measures (DDDs, patients, tablets) and expenditures in Belgium between 1997 and 2009. Data from Pharmanet were aggregated per year by INAMI/RIZIV and plotted in Excel by KCE. As a unique patient identifier was available only from 2004 onwards, the number of patients was extrapolated from the EPS dataset for the years 2002 and 2003. The EPS was also used to study the variation in tablets strengths over the years.

2.2.1.1 Volume measures (DDDs, patients, tablets)

Figure 1 and Table 3 show the evolution over time of DDDs prescribed per statin molecule (volume in terms of tablets or by semester are presented in appendix). The total statin volume prescribed was multiplied by 20 from 1997 to 2009 (18.6 millions DDDs in 1997 to 383.1 millions DDDs in 2009), and almost doubled between 2004 and 2005. With the exception of cerivastatin, withdrawn in 2002 for safety reasons, and fluvastatin which utilization remained quite constant in the recent years (between 6 and 7 millions DDDs per year), all statins displayed a notable increase during the period. From 2002 to 2009 simvastatin DDDs increased by 492% and atorvastatin DDDs by 76.1%. Rosuvastatin volumes sharply increased by 488% from 2004 to 2009.

In 2009, simvastatin represented 41.9% of the statin volume, followed by atorvastatin (25.3%) and rosuvastatin (21.4%), the latter showing a steady growth since its marketing in 2003 (see synthesis in Table 9). Pravastatin volumes increased to a lesser extent, representing 9.8% in 2009. Fluvastatin remained the less prescribed statin (1.6% in 2009).

Figure 1: Total number of DDDs per year and statin type (in millions DDDs)



Source: INAMI/RIZIV 1997 - 2009

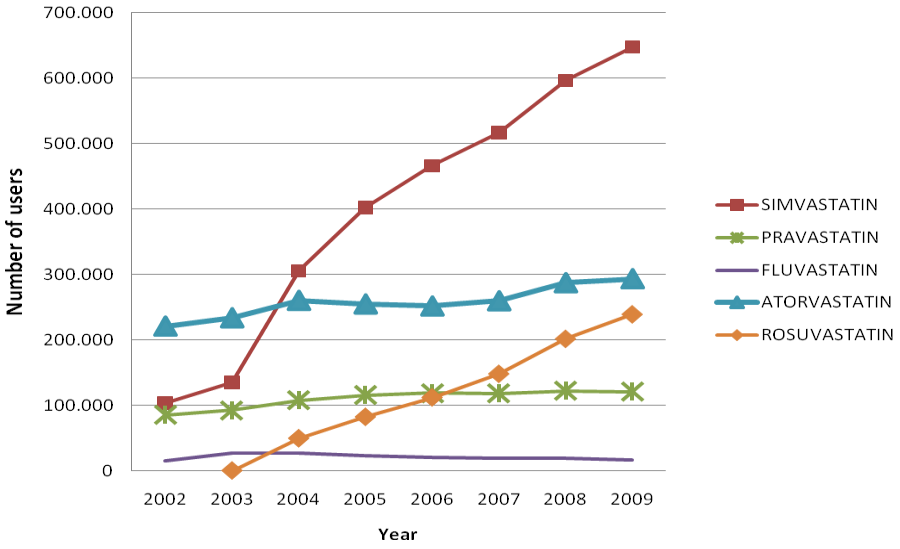
Table 3: Total number of DDDs per year and statin type (in millions DDDs)

	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
simvastatin	13.2	16.1	17.2	19.8	23.2	27.1	32.6	64.3	91.9	109.7	125.1	146.4	160.4
pravastatin	4.8	7.0	8.5	16.4	21.9	27.8	31.6	34.0	34.9	36.3	36.9	38.0	37.7
fluvastatin	0.7	3.2	3.5	3.0	2.3	2.9	7.6	8.2	7.6	6.9	6.7	6.7	6.1
atorvastatin		5.3	28.0	39.9	47.3	55.1	64.7	72.7	73.4	73.4	79.1	90.9	97.1
cerisvastatin			0.0	9.8	12.5	0.0007	0.0001						
rosuvastatin							0.03	13.9	23.8	33.9	46.7	65.5	81.9
TOTAL	**18.6**	**31.6**	**57.2**	**88.9**	**107.2**	**112.9**	**136.6**	**193.2**	**231.6**	**260.2**	**294.5**	**347.5**	**383.1**

Source: INAMI/RIZIV 1997 - 2009

Figure 2 and Table 4 present the evolution of the number of users per year. The sharpest increase was seen for simvastatin (528% from 2002 to 2009), compared to an increase of 33% for atorvastatin. Rosuvastatin users increased by 383% from 2004 to 2008.

Figure 2: Number of statin users per year and statin type



Source: EPS 2002, 2003, INAMI/RIZIV 2004-2009.

Table 4: Number of patients using statins per year and statin type

	2002	2003	2004	2005	2006	2007	2008	2009
SIMVASTATIN	103520	135120	305775	402691	466220	516779	596554	647529
PRAVASTATIN	85520	92520	107888	115810	118843	118598	122707	121274
FLUVASTATIN	15940	27220	26762	23384	20751	20101	19350	17457
ATORVASTATIN	221340	233980	260380	254952	251820	259787	287248	293325
ROSUVASTATIN		280	49556	82437	112163	148279	201761	239289
Total*	426320	489120	750361	879274	969797	1063544	1227620	1318874
*Total may be overestimated by ≅5% because of users taking more than 1 statin molecule per year								

Source: EPS 2002, 2003, INAMI/RIZIV 2004-2009.

2.2.1.2 *Expenditures (third party payer, co-payment, total and expenditure per DDD)*

Expenditures for third party payer amounted to € 216.8 millions in 2009 (Figure 3 and

Table 5). Atorvastatin expenditures increased from 1998 to 2004, followed by a slight decrease between 2004 and 2006 and a new increase in 2007. In 2009 the amount reimbursed by the INAMI/RIZIV for atorvastatin amounted to € 107.8millions which represents 49.7% of all reimbursements for statin for 25.3 % (97.1 millions DDDs) of all statins purchased. Conversely simvastatin represented 41.9% of the total volume (160.4 millions DDDs) for 16.3 % of the INAMI/RIZIV expenditures (35.4 millions €). In 2009, rosuvastatin reimbursements totalized 56.3 millions € or 26% of the third party payer expenditures for 21.4% of the DDD volume.

Figure 3: Cost per year and statin type – Third party payer (in millions €)

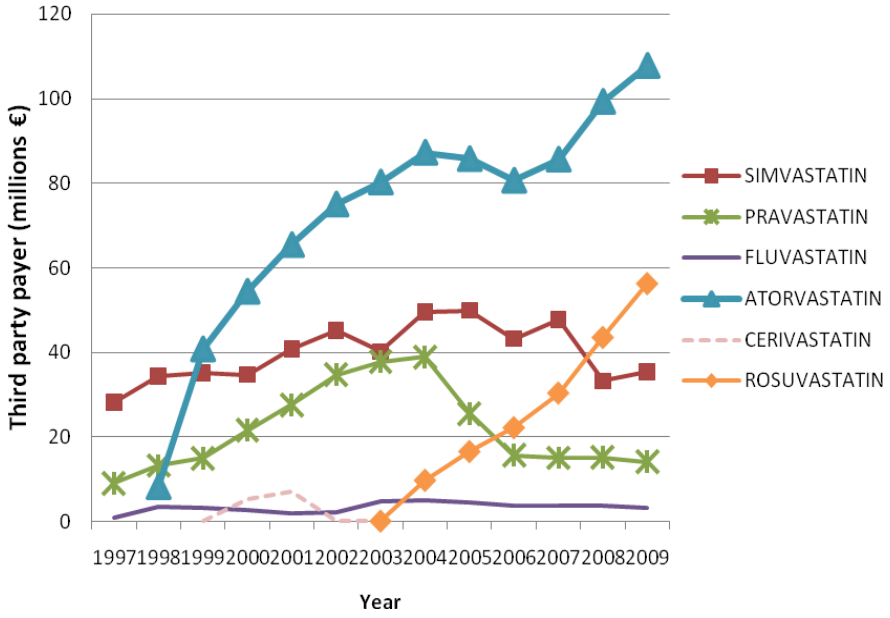


Table 5: Cost per year and statin type – Third party payer (in millions €)

	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
simvastatin	28.2	34.4	35.1	34.7	40.8	45.2	40.2	49.6	49.9	43.2	47.7	33.2	35.4
pravastatin	9.1	13.2	15.0	21.5	27.6	34.6	37.8	38.9	25.5	15.7	15.0	15.1	14.0
fluvastatin	0.8	3.6	3.3	2.6	2.0	2.3	4.8	5.0	4.5	3.8	3.8	3.8	3.3
atorvastatin		8.1	40.7	54.4	65.4	75.0	80.2	87.2	85.7	80.6	85.6	99.3	107.8
cerisvastatin			0.004	5.1	7.2	0.0004	0.0001						
rosuvastatin							0.02	9.7	16.5	22.2	30.4	43.5	56.3
Total	**38.1**	**59.3**	**94.0**	**118.3**	**142.9**	**157.1**	**163.0**	**190.4**	**182.2**	**165.5**	**182.4**	**194.9**	**216.8**

Source: INAMI/RIZIV 1997 - 2009

The picture is a bit different for the co-payment supported by the patient across the years (Figure 4 and Table 6). The shape of the curves for simvastatin, atorvastatin and pravastatin differ with those in Figure 3 and Figure 4. The co-payments went on rising after 2004 for simvastatin and atorvastatin.

In 2009, atorvastatin totalized 14.3 millions € (36.9% of statins co-payment) followed by rosuvastatin and simvastatin (respectively 9.8 millions € (25.3%) and 10.2 millions € (26.3%)). Pravastatin co-payments were stabilized from 2004 around 4 millions €, reaching 3.7 millions € in 2009 and representing less than 10% of the patient total statins co-payments.

Figure 4: Cost per year and statin type – Co-payments (in millions €)

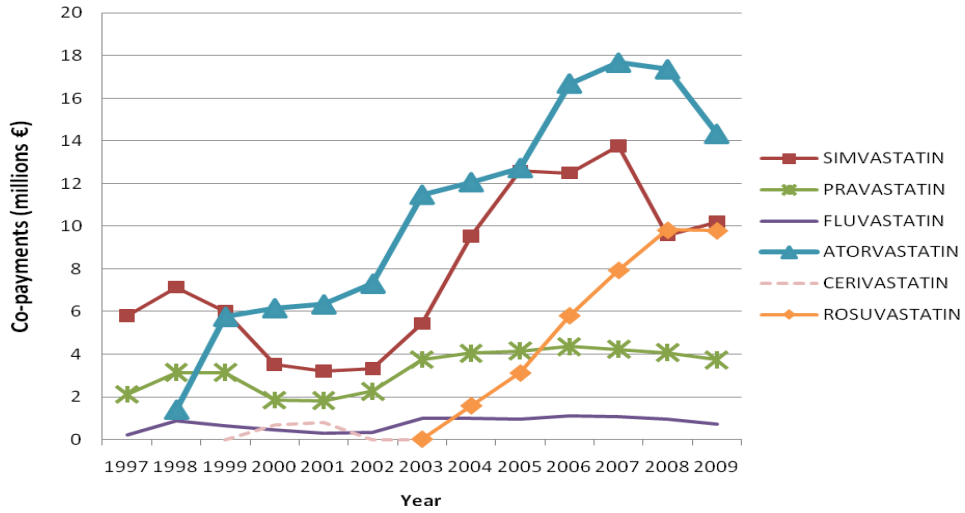


Table 6: Cost per year and statin type – Co- payments(in millions €)

	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
simvastatin	5.8	7.1	6.0	3.5	3.2	3.3	5.4	9.5	12.6	12.5	13.8	9.6	10.2
pravastatin	2.1	3.1	3.1	1.8	1.8	2.3	3.7	4.1	4.2	4.4	4.2	4.1	3.7
fluvastatin	0.2	0.9	0.6	0.4	0.3	0.4	1.0	1.0	1.0	1.1	1.1	1.0	0.7
atorvastatin		1.4	5.8	6.2	6.3	7.3	11.5	12.1	12.7	16.7	17.7	17.4	14.3
cerisvastatin			0.001	0.7	0.8	<0.001	<0.001						
rosuvastatin							0.004	1.6	3.1	5.8	7.9	9.8	9.8
Total	**8.1**	**12.5**	**15.5**	**12.6**	**12.5**	**13.2**	**21.6**	**28.2**	**33.5**	**40.5**	**44.7**	**41.8**	**38.8**

Source: INAMI/RIZIV 1997 - 2009

Total expenditure (the sum of third-party payer (approximately 85%) and co-payment) are pictured in Figure 5 and Table 7. Globally in 2009, atorvastatin accounted for 47.8% of the total expeditures of statin compared to 25.3% of the volume in DDDs of statin. On the other hand, simvastatin represented 17.8% of total expenditures for 41.9% of the DDD volume.

Figure 5: Cost per year and statin type – Total expenditures (in millions €)

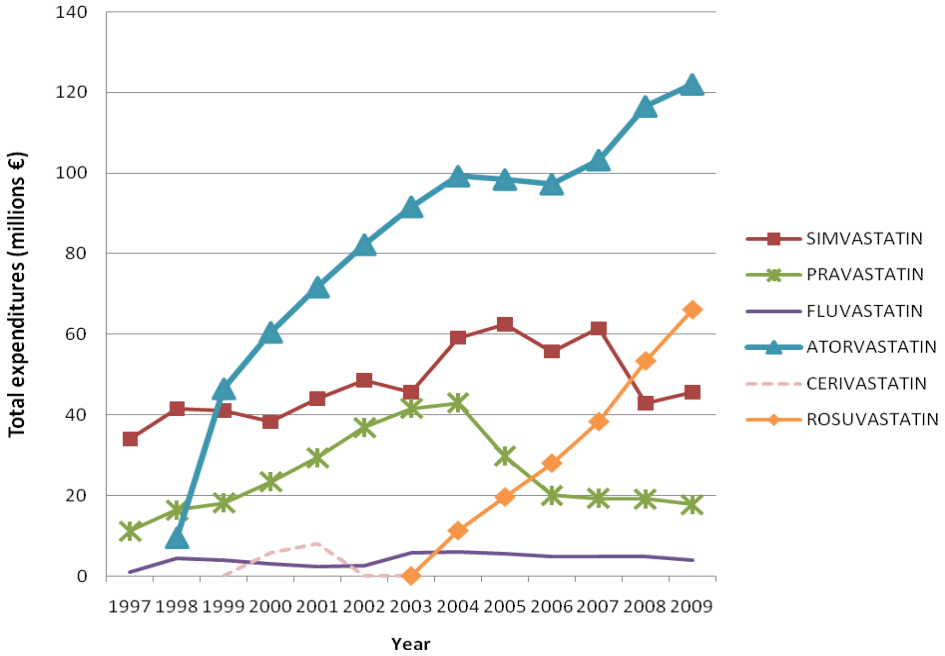


Table 7: Cost per year and statin type – Total expenditures (in millions €)

	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
simvastatin	34.0	41.5	41.1	38.2	44.0	48.5	45.6	59.1	62.5	55.7	61.4	42.8	45.6
pravastatin	11.2	16.4	18.1	23.4	29.4	36.9	41.6	43.0	29.7	20.0	19.3	19.2	17.8
fluvastatin	1.0	4.4	3.9	3.0	2.3	2.6	5.8	6.0	5.5	5.0	4.8	4.8	4.0
atorvastatin		9.5	46.5	60.5	71.7	82.3	91.7	99.3	98.5	97.3	103.3	116.6	122.1
cerisvastatin			0.005	5.8	8.0	0.0005	0.0001						
rosuvastatin							0.03	11.3	19.6	28.0	38.3	53.4	66.1
Total	46.26	71.80	109.53	130.95	155.38	170.35	184.65	218.61	215.74	206.00	227.11	236.75	**255.6**

Source: INAMI/RIZIV 1997 - 2009

Figure 6 gives the average expenditure paid by DDD (third party payer + co-payment). Rosuvastatin is the only statin which price per DDD never changed, staying around 0.8 €/DDD. The expenditure per DDD for other statins decreased over time. In the case of simvastatin, it culminated around 2.6€/DDD in 1997 but was divided by more than 8 times over ten years to 0.3€/DDD. Simvastatin shifted thus from the most expensive position to the cheapest one since 2005. Pravastatin expenditure per DDD was divided by almost five to 0.5€/DDD over the same period and atorvastatin decreased from 1.8 to 1.3 €/DDD, hence becoming the statin with the highest expenditure per DDD since 2005.

Figure 6: Mean (total) expenditures per DDD in € (Total expenditure / total DDD)

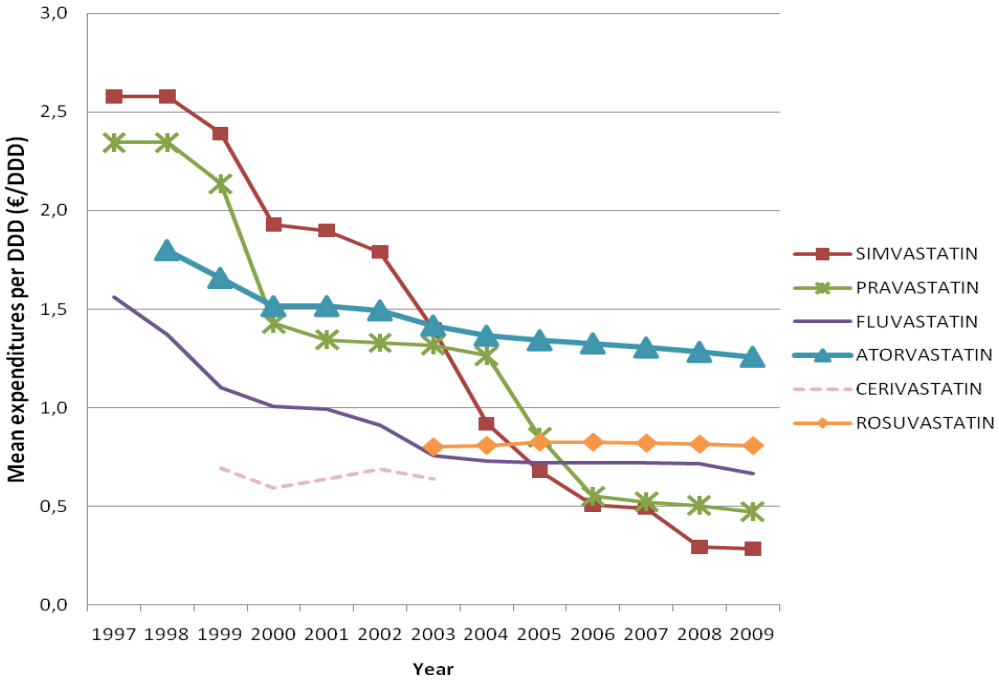


Table 8: Mean (total) expenditures per DDD in € (Total expenditure / total DDD)

	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
SIMVASTATIN	2.58	2.58	2.39	1.93	1.90	1.79	1.40	0.92	0.68	0.51	0.49	0.29	0.28
PRAVASTATIN	2.35	2.34	2.14	1.43	1.34	1.33	1.32	1.26	0.85	0.55	0.52	0.50	0.47
FLUVASTATIN	1.56	1.37	1.10	1.01	0.99	0.91	0.76	0.73	0.72	0.72	0.72	0.72	0.66
ATORVASTATIN		1.80	1.66	1.51	1.52	1.49	1.42	1.37	1.34	1.33	1.31	1.28	1.26
CERISVASTATIN			0.69	0.59	0.64	0.69	0.64						
ROSUVASTATIN							0.80	0.81	0.83	0.82	0.82	0.81	0.81
Total	**2.48**	**2.27**	**1.91**	**1.47**	**1.45**	**1.51**	**1.35**	**1.13**	**0.93**	**0.79**	**0.77**	**0.68**	**0.67**

Source: INAMI/RIZIV 1997 - 2009

In summary for 2009, as shows in Table 9 here below, simvastatin and pravastatin represented around 52% of the DDDs of statins for 25% of the total expenditures. Table 10 presents a comparison per statin molecule of the main characteristics.

Table 9: Summary data for the year 2009 (percentage of DDDs, tablets and percentage of expenditures) by statin type

	DDD	tablets	Third party payer	Co-payment	Total expenditures
simvastatin	41.9%	48.2%	16.3%	26.3%	17.8%
pravastatin	9.8%	9.2%	6.5%	9.6%	7.0%
Simvastatin or pravastatin	51.7%	57.3%	22.8%	35.9%	24.8%
Fluvastatin	1.6%	1.4%	1.5%	1.9%	1.6%
Atorvastatin	25.3%	23.1%	49.7%	36.9%	47.7%
Rosuvastatin	21.4%	18.1%	25.9%	25.3%	25.9%
Atorvastatin or Rosuvastatin or Fluvastatin	48.3%	42.6%	77.2%	64.1%	75.2%
Total	100.0%	100.0%	100.0%	100.0%	100.0%

Source: INAMI/RIZIV-2009

Table 10: Statin use and cost in Belgium in 2009

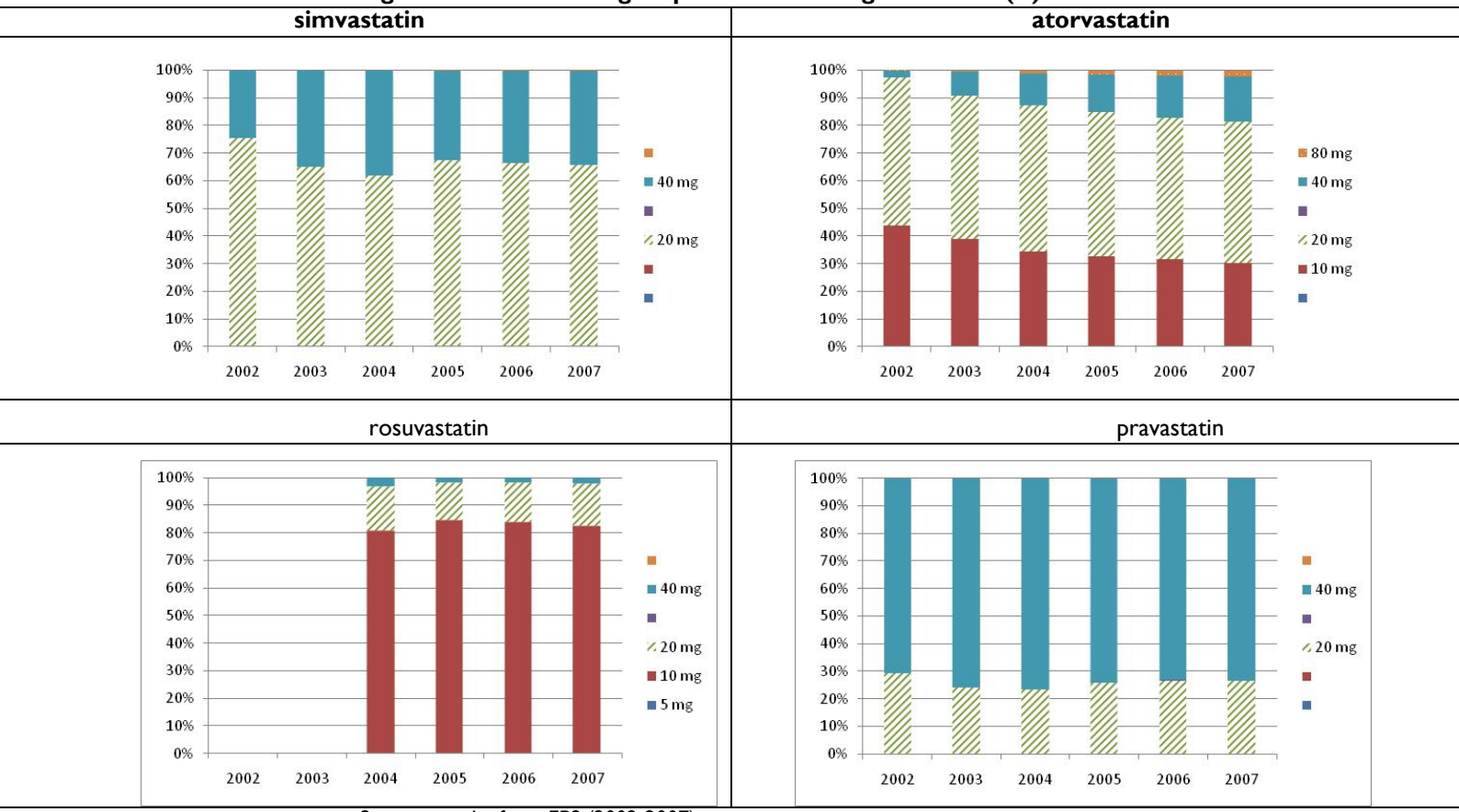
Molecule	Brand name	Users*	DDD	Cost (in €) per:			
			(mg)	DDD	Tablet	User (yearly)	Overall
Simvastatin	Zocor®, generics	647 529	30	0.28	0.26	70.4	45 601 398
Pravastatin	Prareduct®, Pravasine®, generics	121 274	30	0.47	0.54	146.7	17 787 628
Fluvastatin	Lescol®	17 457	60	0.66	0.80	231.8	4 046 880
Atorvastatin	Lipitor®	293 325	20	1.26	1.47	416.3	122 107 090
Rosuvastatin	Crestor®	239 289	10	0.81	1.01	276.1	66 064 862
TOTAL		1 318 874					255 607 858

*: individuals purchasing more than 1 statin molecule over the year ≅ 5% DDD: Defined Daily Dose

2.2.1.3 Trends in tablet strengths

Tablets strengths by statin type and year are presented in Figure 7. For simvastatin, around 60%-70% of packagings were for simvastatin 20mg (and the trend was stable over the years, except the increase in 2004 of simvastatin 40 mg). For atorvastatin, an increasing trend towards more strengthful tablets was observed: atorvastatin 40 mg or 80 mg represented less than 3% of prescriptions in 2002, but 18% in 2007. For rosuvastatin, 80% of prescriptions are for 10mg. For pravastatin, more than 70% of prescriptions are for the 40 mg tablet.

Figure 7: Tablets strengths prescribed during 2002-2007 (%)



Source: results from EPS (2002-2007)

2.2.1.4 Discussion

The number of statin users has sharply increased over the recent years, and in 2009 more than 1.300.000 persons purchased at least one packaging of statins. This evolution was uneven among statins. While the utilization of fluvastatin, pravastatin and atorvastatin remained fairly constant during the period, the utilization of simvastatin dramatically increased from 2004 onwards, a likely reflection of the change in reimbursement rules which occurred that year. Noteworthy, the newest molecule, rosuvastatin, also presented a tremendous increase since its marketing in 2003, and already constituted 21% of DDDs purchased in 2009. We will analyse in the further sections of the report if that increase in rosuvastatin utilization can be explained by specific clinical profiles.

The total number of atorvastatin DDDs increased more rapidly than the number of users. This could be due to a better adherence to treatment and/or the utilization of higher dose of statins. Our analysis showed that the latter was true, with a trend towards a more intensive therapy.

The price per simvastatin DDD has also decreased greatly between 1997 and 2009, resulting in a quite stabile volume of expenses for that molecule despite the rising number of users. The main explanation of this price evolution has been the availability of generic molecules and the negotiations between manufacturers and the ministry of public health. However, the additional step downward observed in 2008 is most likely related to the "Kiwi light" initiative. The price of atorvastatin also decreased but to a lesser extent, while the retail price of rosuvastatin remained constant. As a result, in 2009, these 2 last molecules represented together 73.6% of the total expenditure for less than half of the total statin DDDs purchased.

Atorvastatin and rosuvastatin occupied respectively the 1st and 4th position in the top list of highest public expenditures per drug. As the single most used drug class, statins accounted for 7% of overall ambulatory drug expenditure in Belgium in 2009. Noteworthy, atorvastatin will get off-patent in November 2011, which will result very likely in the emergence of generics and copies and in decreased cost per DDD.

Key points

Market evolution over time

- **For the period 1997 to 2009, the total statin DDDs delivered was multiplied by 20 (from 18.6 millions DDDs to 383.6 millions DDDs) and the mean expenditure per DDD dropped from 2.7€ to 0.67€.**
- **In 2009, 1 318 874 individuals purchased at least one packaging of statins. From 2002 to 2009, the number of patients increased by 528% for simvastatin and by 33% for atorvastatin. For rosuvastatin, the increase was 383% from 2004 to 2009.**
- **In the recent years, the proportion of users of simvastatin/pravastatin has remained around 60%.**
- **In 2009, total expenditure for statins amounted to 255 607 858 euros (7% of overall expenditure for ambulatory drug in Belgium). Simvastatin and pravastatin represented 52% of the DDDs but 25% of the global statin expenditure.**

2.2.2 Impact of the 2004 Regulation change

Expectedly, the regulation change that occurred in August 2004 (see Section 2.1) might have led to modified prescription behaviours, i.e. patients could have been preferentially prescribed simvastatin or pravastatin. The aim of this part was thus to describe the switch between statins when the new regulation was implemented.

All statin users recorded in the EPS were included in this analysis and results presented in this section are extrapolated to the Belgian population (taken into account oversampling of people ≥65 years old). In chapter 2.2.1, only data aggregated at the population level were used, with no possibilities to look at switches of users from 1 statin to another or to look specifically to new users. As the change in regulation occurred in August 2004, we aimed at comparing prescription behaviours before and after that measure, and thus we divided the overall observation period as follows:

- Period 1: 1st August 2002 to 31st July 2003
- Period 2: 1st August 2003 to 31st July 2004
- Period 3: 1st August 2004 to 31st July 2005
- Period 4: 1st August 2005 to 31st July 2006
- Period 5: 1st August 2006 to 31st July 2007

For each of these one-year period, we assessed the number of users and of statin switchers, in absolute and relative terms, per major statin type (as defined in Table 2). Noteworthy, preliminary analyses showed that the proportion of patients using more than one statin within a period was less than 5% (see appendix) and therefore using major statin type was unlikely to distort the results. To assess how the new 2004 regulation might have resulted in statin switches, we focused on the change in statins, if any, between the period preceding and following the new regulation, i.e. between Aug2003-Aug2004 and Aug2004-Aug2005. The analysis included patients with at least one statin packaging delivery in each of the periods, i.e. new users in the period Aug2004-Aug2005 were excluded from the analyses as the occurrence of a statin switch made no sense in such case.

2.2.2.1 Statin switches around August 2004

Overall, there were around 89% of patients who haven't changed of statin type between Aug2003-Aug2004 and Aug2004-Aug2005 (Table 11). The percentage of patients switching to another statin than the one they used before August 2004 was higher for the group of patients using fluvastatin (25%) or pravastatin (17%). Only 9% and 6% of atorvastatin and rosuvastatin users, respectively, switched to simvastatin or pravastatin (Table 12). Conversely, 36% (11 960/32 900) of rosuvastatin users in the period August 2004-August 2005 used another statins prior to Aug2004; this percentage amounted to 16% (27 400/166 360) for simvastatin (Table 12).

Table 11: Number and Percentage of Patients by Major Statin Type: switch patterns around August 2004

Statin type	Aug2004-Aug2005					
Aug2003-Aug2004 Weighted Frequency Row percent	**Any change**	**Atorvastatin N = 183780 (39%)**	**Fluvastatin N = 16100 (3%)**	**Pravastatin N = 69080 (15%)**	**Rosuvastatin N = 32900 (7%)**	**Simvastatin N = 166360 (36%)**
Atorvastatin N = 201 280 (43%)	22920	178360	320	2180	4200	16220
	11%	89%	0%	1%	2%	8%
Fluvastatin N = 20 240 (4%)	5080	520	15160	500	1440	2620
	25%	3%	75%	2%	7%	13%
Pravastatin N = 77 800 (17%)	13280	2160	220	64520	3440	7460
	17%	3%	0%	83%	4%	10%
Rosuvastatin N = 22 900 (5%)	1960	500	60	300	20940	1100
	9%	2%	0%	1%	91%	5%
Simvastatin N = 146 000 (31%)	7040	2240	340	1580	2880	138960
	5%	2%	0%	1%	2%	95%

Source: Extrapolated from EPS

Table 12: Frequency and Percentage of Patients by major statin type used during Aug2004-Aug2005 by previous period

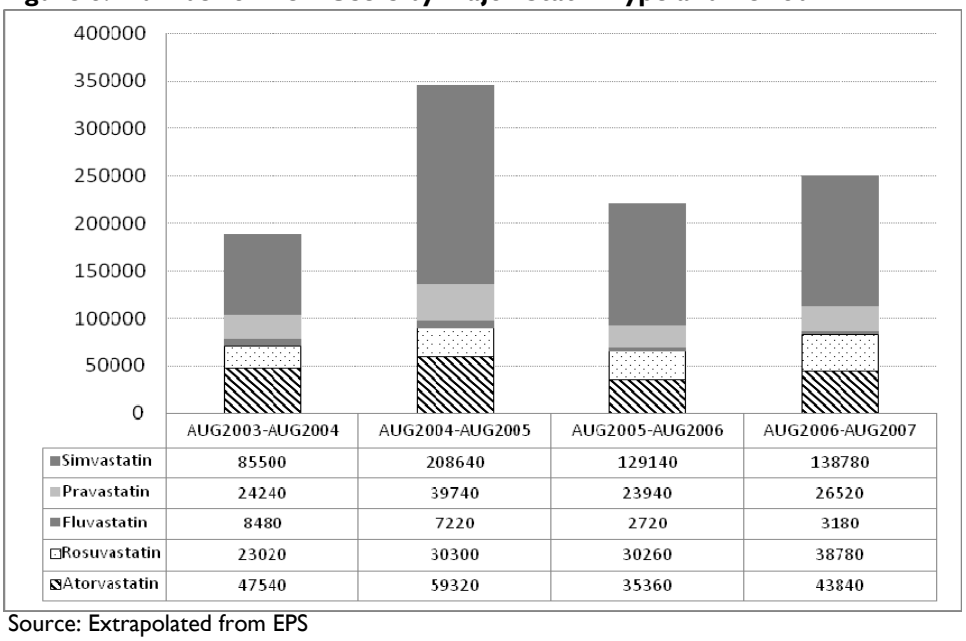
Aug2004-Aug2005	Previous period treatment	
	Same statin used in Aug2003-Aug2004	Different statin type used in Aug2003-Aug2004
Atorvastatin N=183780	178360	5420
	97%	3%
Rosuvastatin N=32900	20940	11960
	64%	36%
Fluvastatin N=16100	15160	940
	94%	6%
Pravastatin N=69080	64520	4560
	93%	7%
Simvastatin N=166360	138960	27400
	84%	16%

Source: Extrapolated from EPS

2.2.2.2 *New users around August 2004*

Figure 8 and Figure 9 show the estimated number and percentage, respectively, of new users by major statin type and by period. The numbers of new users of simvastatin and pravastatin greatly increased in the period Aug2004-Aug2005. The new simvastatin users were 45% and 60% of overall new users, in Aug2003-Aug2004 and Aug2004-Aug2005, respectively. For the other statins, the absolute number of new users remained stable, with a slow down for atorvastatin (from 59 320 new users in Aug2004-Aug2005 to 35 360 new users in Aug2005-Aug2006, and a relative change from 25% to 17%).

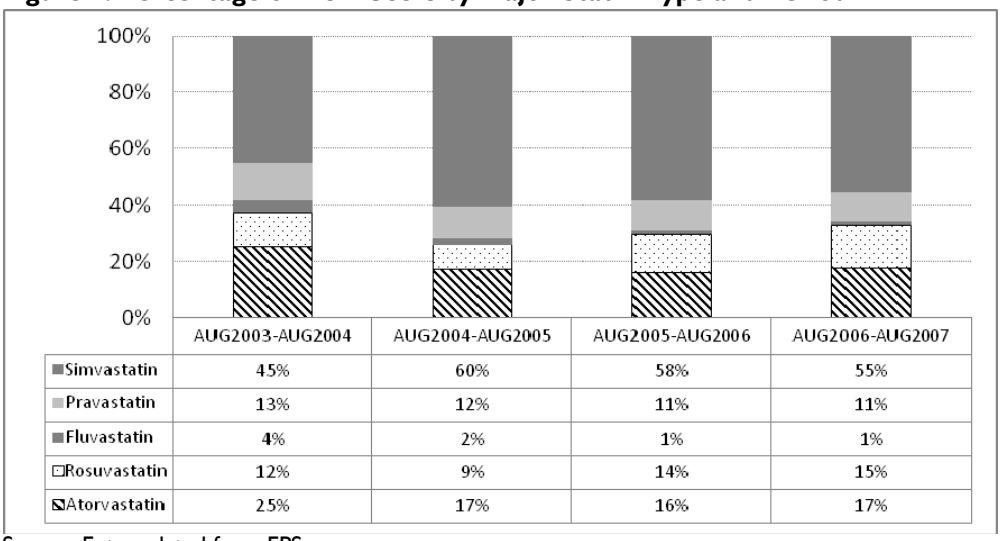
Figure 8: Number of New Users by Major Statin Type and Period



	AUG2003-AUG2004	AUG2004-AUG2005	AUG2005-AUG2006	AUG2006-AUG2007
Simvastatin	85500	208640	129140	138780
Pravastatin	24240	39740	23940	26520
Fluvastatin	8480	7220	2720	3180
Rosuvastatin	23020	30300	30260	38780
Atorvastatin	47540	59320	35360	43840

Source: Extrapolated from EPS

Figure 9: Percentage of New Users by Major Statin Type and Period



	AUG2003-AUG2004	AUG2004-AUG2005	AUG2005-AUG2006	AUG2006-AUG2007
Simvastatin	45%	60%	58%	55%
Pravastatin	13%	12%	11%	11%
Fluvastatin	4%	2%	1%	1%
Rosuvastatin	12%	9%	14%	15%
Atorvastatin	25%	17%	16%	17%

Source: Extrapolated from EPS

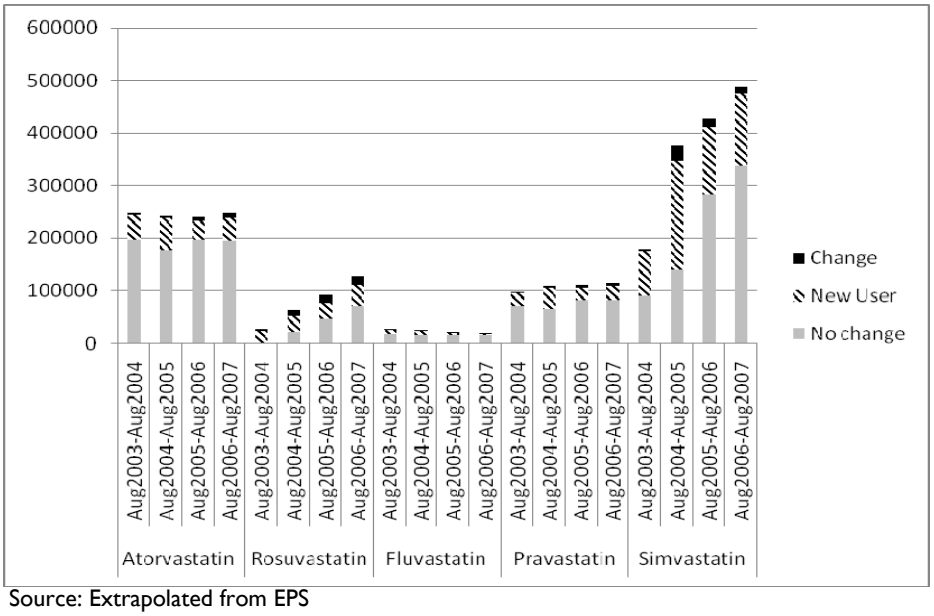
The limited number of switches observed directly after the regulation change might be due to a time lag between policy change and clinical practice, i.e. the switches might have occurred later on. To check that hypothesis, we present in Figure 10 the number of yearly switchers per statin up to August 2007 (data displayed in appendix) Clearly, the number of switchers remained quite stable over the years. For simvastatin, the numbers of new users peaked in Aug 2004-Aug 2005, and then slowed down, although keeping the most important share of new users year after year.

2.2.2.3 Discussion

Changing reimbursement rule in August 2004 generated a drastic increase in the number of new users of simavastatin and, to a lesser extent, of pravastatin, the 2 statins which had been transferred into the Chapter I of regulations and could be thus prescribed without control by the INAMI/RIZIV and/or the sickness funds. Whether this important inflow of users is the reflection of previously unmet needs in CVD prevention or whether it expresses an adaptation of prescription behaviours to a new regulatory environment is a question that cannot be solved in the frame of this report, given the fact that individual clinical data (e.g. concentration of LDL-C and presence of risk factors of CVD) were not available for analysis.

In opposition, the new regulation had a moderate effect on switching patients from one molecule to another. Eighty-nine percents and 91% of users of atorvastatin and rosuvastatin, respectively, kept on using the same molecule in spite of the low price and facilitated access of simvastatin/pravastatin. Even more strikingly, a proportion of users switched towards rosuvastatin at the same time: 36% of rosuvastatin users in the period Aug 2004-Aug 2005 used another molecule in the previous year (in absolute numbers this represents 11960 switchers; in comparison, 27400 users switched towards simvastatin). This is a counter-intuitive finding as rosuvastatin was a new molecule which clinical efficacy had been much less studied (the first assessment on clinical outcomes was published in 2008) and which was more expensive than other statins. This may reflect the shift of rosuvastatin from chapter IV to chapter II, which also resulted in easier access (from control a priori to control a posteriori). This may also reflect the successful marketing of a new pharmacologic brand.

Figure 10: Absolute Number of Patients by Major Statin Type, Status and Period



Source: Extrapolated from EPS

Key points

Impact of the 2004 regulation change

- **Less than 1 patient out of 10 switched from atorvastatin to simvastatin or pravastatin in the 12 months period after implementation of the new regulation change (aug 2004-aug 2005).**
- **36% (11 960/32 900) of rosuvastatin users in the period Aug 2004-Aug 2005 were using another molecule in the previous year.**
- **The total number of new statins users increased by 83% compared to the year period before the regulation change. The largest increase was observed for simvastatin (+144%) and pravastatin (+64%). For atorvastatin and rosuvastatin, increases were of 25% and 32%, respectively.**
- **Among the new users of statins, the proportion of simvastatin or pravastatin was 58% before the regulation change and 72% in the year after, mainly influenced by simvastatin results.**

2.2.3 Characteristics of new statin users (2003-2006)

This section describes the characteristics of new statin users in the 2003-2006 period: number of patients, reason for starting treatment (for primary or secondary prevention), specialty of treatment initiator, type of treatment and compliance, duration of statin use, factors associated with the discontinuation of treatment, and factors associated with the use of simvastatin or pravastatin (see section 2.1).

The analyses presented in this section are entirely based on new users in ambulatory care during the 2003-2006 period. However, for defining the specialty of the first prescriber, we took into account the fact that some patients started secondary prevention already in hospital. In that case, the treatment was considered to be started by a specialist, even if the first prescription in ambulatory care (after discharge) was made by a GP. The 2002 data were used as a selection filter to identify new users in 2003 (by excluding patients on statin therapy in the 365 previous days). All analyses are based on claims data from Pharmanet (in the EPS), linked to RCM-MKG data to identify hospitalizations for CVE leading to secondary prevention. All results are extrapolated (taking into account the oversampling of ≥65 years old) to the Belgian population except for the survival analyses (see below).

For assessing patient compliance, we made the assumption that every patient would utilize daily1 tablet of the strength specifically prescribed to him/her. This choice was made because exploratory analyses showed that the number of DDDs was not a good measure to assess compliance (results presented in appendix). Logistic regression was used to assess which factors predict good compliance (defined as at least 80% of medication possession ratio (MPR), see Table 2 for the definition of the MPR).

Factors influencing the probability of receiving simvastatin or pravastatin were also analyzed with a logistic regression model.

The duration of statin use was analyzed for the new regular users of year 2003 only (to allow for a 4 years observation period for all users) but excluding the deaths occurring between the estimated end date of statin therapy (last purchase date + number of days covered by the last refill) and an additional 3-months period. The treatment was considered stopped if no other statin delivery was registered within at least a 3-months period after the estimated end date. The duration was assessed as the time between the first delivery of statin in 2003 and the last estimated end date of treatment. As the number of rosuvastatin users in 2003 was marginal, those users were discarded from the analyses of the new regular users 2003. Data were censored in December 2007 as the data were not available afterwards. It has to be noted here that the deaths occurring before the estimated end date of the treatment and an additional 3-months period were not taken into account into the analyses. The Kaplan-Meier curve was used for graphical representation of the duration of statin use. Curves were split by type of statin used at the beginning of the prevention. A Cox proportional hazard regression model was used to analyze the influence of some characteristics on the duration of statin use. The test of proportionality of the hazard was tested and none of the time dependent variables were significant at the 10% level meaning that the proportional hazard assumption was valid. These specific analyses were based on a smaller sample than previous analyses (ie not taking into account the oversampling of the EPS) as analytical techniques for oversampled survival data are not (yet) available in SAS 9.1.

In all analyses, statins are considered as a group, therefore, switches between statins were considered as continuing therapy.

In all regression models mentioned above, the following characteristics were taken into account:

- Age category (<50, 50-59, 60-69, 70-79, 80 and +)
- Sex
- Patient is diabetic (use of anti-diabetic drugs in the year preceding the use of statin)
- Type of prevention (primary, secondary)

- Statin molecule (the first one prescribed)
- Specialty of first prescriber (GP or specialist)
- Patient entitled to increased reimbursement (yes, no)
- Invalidity or handicap status (yes, no)

2.2.3.1 Number of patients included in analyses, and extrapolations to Belgium

A total of 34 281 new statin users were identified in the EPS during the period 2003-2006. Extrapolated to the Belgian population, this corresponds to a total of 906 320 new users. All the following analyses are based on this extrapolation.

Table 13: Number of new statin users during period 2003-2006 (in sample and extrapolated to Belgium)

	Year of first use				All
	2003	2004	2005	2006	
N new users in sample	4394	10420	10915	8552	34281
N new users (extrapolated to Belgium)	116460	272480	288520	228860	906320

2.2.3.2 Start of statin treatment

The large majority of new users start statin treatment for primary prevention (91.7% over the 2003-2006 period). In 2006, nearly 70% of new users received simvastatin/pravastatin as a first treatment option, a proportion quite constant since 2004. Four out of 5 treatments were initiated by GPs.

Table 14: Start of Statin Treatment- New Statin Users

		Year of first use				All
		2003	2004	2005	2006	
N new users (extrapolated to Belgium)		116460	272480	288520	228860	906320
Type of cardio prevention:						
Primary	%	89.32	91.51	92.62	91.94	91.69
Secondary	%	10.68	8.49	7.38	8.06	8.31
Start Treatment with						
C10AA01 Simvastatin	%	38.43	55.32	56.08	58.64	54.23
C10AA03 Pravastatin	%	18.12	11.20	12.20	10.77	12.30
C10AA04 Fluvastatin	%	9.70	2.68	1.93	1.05	2.93
C10AA05 Atorvastatin	%	33.56	19.25	19.19	15.83	20.20
C10AA07 Rosuvastatin	%	0.19	11.55	10.61	13.72	10.34
Prescriber Specialty (1st prescription)						
GP	%	84.10	84.16	83.21	80.81	83.00
Specialists*	%	15.90	15.84	16.79	19.19	17.00
*Also include treatments initiated during hospitalisation for a cardiovascular event						

Source: Extrapolated from EPS

2.2.3.3 Compliance of patients and factors influencing compliance

Table 15 presents measures on statin compliance, based on the medication possession ratio (MPR). Overall, the percentage of regular statin users was 58.8%. The occasional users (see definition in Table 2) were either patients who received only one statin prescription (overall 18.3%) or patients who had a MPR below 80% (22.8%). The mean MPR was 94% among users when those purchasing only one packaging were discarded.

Table 15: Measures of statin compliance based on the Medication possession ratio

		Start Treatment with					
		Simva.	**Prava.**	**Fluva.**	**Atorva.**	**Rosuva**	**All**
N new users (extrapolated to Belgium)		491500	111460	26560	183100	93700	906320
Categorisation of patients based on the MPR							
MPR is not defined (only 1 prescription)	%	18.66	19.85	19.20	16.10	19.06	18.34
MPR is below 80%	%	23.08	21.23	21.61	24.12	21.37	22.84
Regular user, MPR >= 80%	%	58.26	58.93	59.19	59.78	59.57	58.81
Medication possession ratio *	Mean	0.93	0.93	0.93	0.92	0.93	0.93
	Std	0.26	0.25	0.24	0.24	0.23	0.25
	Median	0.94	0.94	0.95	0.93	0.94	0.94
*Only computed for patients with more than 1 prescription							

Source:extrapolated results from EPS.

Table 16 presents results from logistic regression to assess factors associated with a regular statin treatment (defined as MPR above 80%). The factors most strongly associated to a regular use are: being older than 50 years, being diabetic, using statin for secondary prevention, and receiving first prescription by a specialist.

Table 16: Factors predicting regular use of statin treatment (results from multivariate logistic regression)

Variable	**Level**	**N Total patients extrapolated**	**% regular users**	**OR***	**(95% CI)**	**p-value**
Age category	< 50 years	118640	47.0	1.00		<=0.001
	50-59 years	205960	58.3	1.56	(1.42-1.71)	
	60-69 years	276800	62.3	1.85	(1.70-2.01)	
	70-79 years	229420	60.7	1.68	(1.54-1.82)	
	80 years +	75500	59.9	1.63	(1.47-1.80)	
Gender	Male	446260	60.0	1.00		<=0.001
	Female	460060	57.6	0.92	(0.87-0.96)	
Use of anti-diabetic drugs in the previous year	No	754340	57.2	1.00		<=0.001
	Yes	151980	66.7	1.43	(1.34-1.53)	
Type of prevention	Primary	831000	57.3	1.00		<=0.001
	Secondary	75320	75.1	2.06	(1.86-2.27)	
Yeart start	2003	116460	61.2	1.00		<=0.001
	2004	272480	63.3	1.09	(1.01-1.18)	
	2005	288520	57.1	0.86	(0.79-0.93)	
	2006	228860	54.5	0.76	(0.70-0.83)	
First prescriber specialty	1- GP	752280	57.4	1.00		<=0.001
	2-Specialists	154040	65.6	1.15	(1.07-1.23)	
First molecule	Simvastatin	491500	58.3	1.00		0.002
	Pravastatin	111460	58.9	1.08	(1.01-1.16)	
	Fluvastatin	26560	59.2	1.06	(0.92-1.22)	
	Atorvastatin	183100	59.8	1.07	(1.01-1.14)	
	Rosuvastatin	93700	59.6	1.16	(1.07-1.26)	
Entitled to increased reimbursement	No	692040	58.2	1.00		0.19
	Yes	214280	60.9	1.04	(0.98-1.10)	
Invalidity or handicap	No	844880	58.8	1.00		0.692
	Yes	61440	58.8	1.02	(0.92-1.14)	
Odds ratio (OR) from multivariate model						

2.2.3.4 Primary and secondary prevention

We analysed the characteristics on new statin users, based on the fact that they started statin therapy for primary prevention (91.7% of the patients during the period 2003-2006) or secondary prevention (8.3% of patients) (Table 17).

Patients starting statin therapy for secondary prevention were 3 years older on average than those starting therapy for primary prevention (66 years old versus 63 years old). They were also treated differently: they received more DDDs (median DDDs during one year: 397 vs 296), and were more compliant with treatment (75% regular users vs 57%). Treatment for secondary prevention was started in ambulatory care by a GP in 34.5% of the cases, versus 87% for primary prevention. Simvastatin/pravastatin represented 78.5% of new treatments in secondary prevention, but only 65.4% of new treatments in primary prevention.

Table 17: Characteristics of new statin users, by type of prevention and year of start of treatment

		Type of cardio prevention								Type of cardio prevention		
		Primary				Secondary						
		Year of first use				Year of first use						
		2003	2004	2005	2006	2003	2004	2005	2006	Primary	Secondary	All
N new users (extrapolated to Belgium)		104020	249340	267220	210420	12440	23140	21300	18440	831000	75320	906320
Age	**Mean**	62.47	63.85	63.45	62.78	64.81	65.94	66.34	67.12	63.28	66.16	63.52
	Std	11.69	12.00	11.98	12.33	11.27	11.28	12.05	12.36	12.05	11.79	12.05
	Median	65.00	65.00	65.00	64.00	66.00	67.00	68.00	69.00	65.00	67.00	65.00
Use of anti-diabetic drugs												
No	%	86.16	81.81	84.43	82.34	83.44	81.16	82.82	81.67	83.33	82.13	83.23
yes	%	13.84	18.19	15.57	17.66	16.56	18.84	17.18	18.33	16.67	17.87	16.77
Start Treatment with												
Simvastatin	%	33.97	53.71	54.96	57.44	75.72	72.69	70.14	72.34	52.58	72.38	54.23
Pravastatin	%	19.53	11.62	12.53	11.44	6.27	6.66	8.08	3.04	12.86	6.11	12.30
Fluvastatin	%	10.36	2.82	2.02	1.14	4.18	1.21	0.75	.	3.08	1.27	2.93
Atorvastatin	%	35.92	19.69	19.40	15.76	13.83	14.43	16.53	16.59	20.63	15.45	20.20
Rosuvastatin	%	0.21	12.16	11.09	14.22	.	5.01	4.51	8.03	10.84	4.78	10.34
Prescriber Speciality												
GP	%	88.06	88.35	87.36	85.99	50.96	38.98	31.17	21.69	87.40	34.52	83.00
Specialist	%	11.94	11.65	12.64	14.01	49.04	61.02	68.83	78.31	12.60	65.48	17.00
Total statin DDD (within the year)	**Mean**	332.39	318.13	281.49	269.81	384.91	418.16	380.07	398.16	295.90	397.00	304.30
	Std	206.60	203.68	191.64	188.40	214.79	244.42	247.95	285.49	197.84	252.10	204.82
	Median	280.00	280.00	261.33	245.33	336.00	392.00	336.00	336.00	261.33	354.67	266.00
Compliance based on MPR tablets:												
MPR not defined*	%	17.46	14.90	20.34	23.58	10.13	8.38	9.58	9.33	19.17	9.24	18.34
MPR below 80%	%	22.59	22.98	24.05	23.84	18.01	15.99	14.74	14.75	23.49	15.67	22.84
Regular user**	%	59.95	62.12	55.61	52.58	71.86	75.63	75.68	75.92	57.34	75.09	58.81

*first prescription, ambulatory or hospital

** because only 1 delivery date

Source:extrapolated from EPS 2003-2006

2.2.3.5 *Duration of statin therapy*

As shown in Table 18 and in Table 19, the estimated probability of still being under a statin treatment within the first year is of 74.8%, 62.3% after 2 years, 55.1% after 3 years and 49.5% after 48 months (4 years).

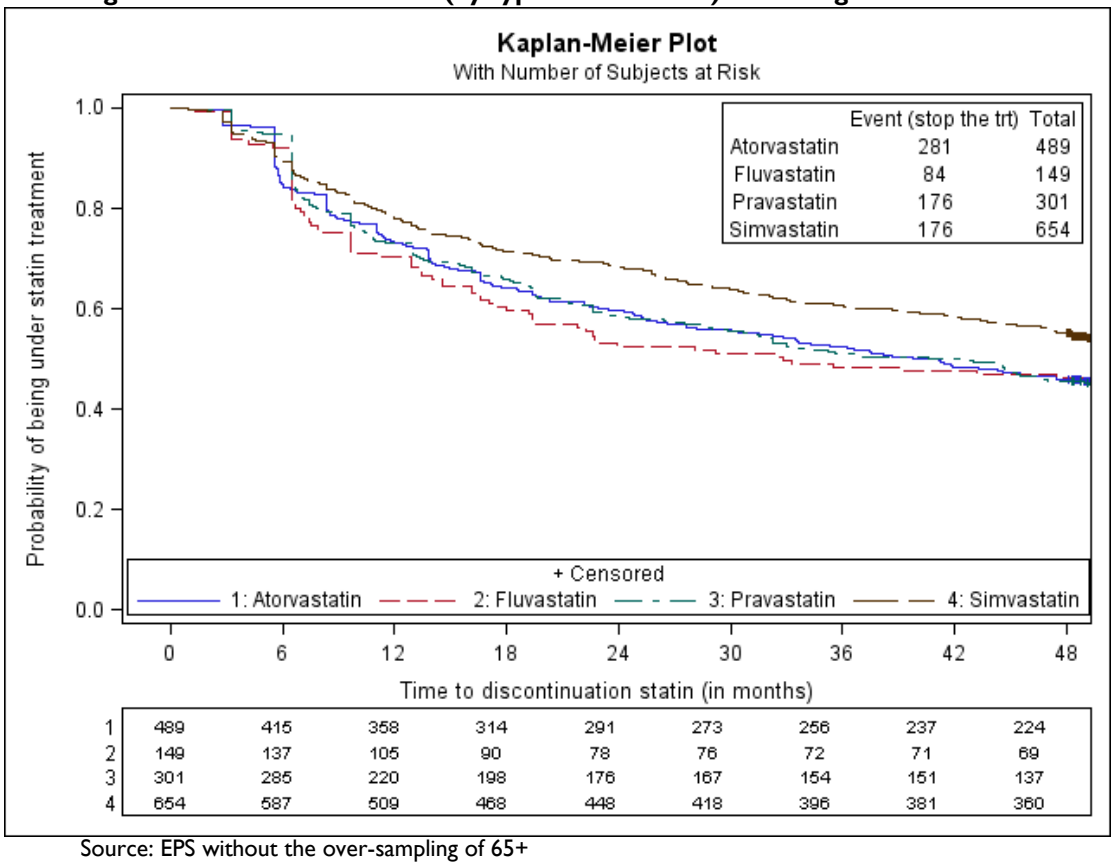
Table 18: Probability of continuing statin therapy over time

	Years since treatment initiation			
Statin*	**1 y**	**2 y**	**3 y**	**4 y**
Atorvastatin	73.0%	59.3%	52.1%	45.6%
Fluvastatin	68.5%	51.7%	47.6%	45.6%
Pravastatin	71.4%	58.1%	50.8%	45.1%
Simvastatin	77.7%	68.3%	60.4%	54.7%
All	**74.8%**	**62.3%**	**55.1%**	**49.5%**

Includes only new users of year 2003; Source: EPS without the over-sampling
* Statin used to initiate the therapy

Figure 11 and Table 19 present the time under statin for regular new users 2003 by statin used at the treatment start. The event, in this case, is the discontinuation of treatment during a period of more than 3 months. The median duration times are displayed in Table 19 only for comparison purpose. Because of the limited observation time, these values are not representative of an actual duration time.

Figure 11: Time under statin (by type of first statin)– New regular user 2003



Source: EPS without the over-sampling of 65+

Table 19: Summary table for the duration of statin use – New regular users 2003

Statin type	Total	Stop statin	Censored	%Censored	Median time	95% CI	
						[Lower	Upper)
Atorvastatin	489	281	208	42.5	40.4	32.3	49.6
Fluvastatin	149	84	65	43.62	32.8	19.4	undefined
Pravastatin	301	176	125	41.5	42.8	29.9	50.6
Simvastatin	654	313	341	52.1	54.3	49.9	undefined
Total	1593	854	739	46.4			

Source: EPS without the over-sampling

Table 20: Factors predicting stop of statin use (Cox regression)[t]

Analysis of Maximum Likelihood Estimates					
Parameter		Hazard Ratio	95% Hazard Ratio Confidence Limits		p-value
Statin type (p-value*=0.2939)	Atorvastatin vs Simvastatin	1.159	0.979	1.372	0.0863
	Fluvastatin vs Simvastatin	1.146	0.893	1.471	0.2857
	Pravastatin vs Simvastatin	1.158	0.955	1.404	0.1368
Type of prevention	Secondary vs Primary	0.801	0.640	1.003	0.0536
Prescriber	Specialist vs GP	1.197	0.945	1.518	0.1362
Use of anti-diabetic drugs	Use vs no use	0.975	0.802	1.184	0.7966
Age (category) (p-value* = 0.2884)	50-59 years vs < 50 years	0.820	0.652	1.031	0.0893
	60-69 years vs < 50 years	0.778	0.621	0.974	0.0288
	70-79 years vs < 50 years	0.833	0.656	1.058	0.1352
	80 years + vs < 50 years	0.867	0.598	1.257	0.4512
Gender	Male vs Female	0.728	0.631	0.839	<.0001
Entitled to increased reimbursement	Entitled vs not entitled	0.945	0.797	1.122	0.5207
Invalidity status	Invalidity status vs No	0.917	0.676	1.244	0.5773

*Result of the global test for the factor

Source: EPS without the over-sampling

Table 20 shows the global test for the covariates and the hazard ratios and their 95% confidence limits for the different variables taken into account in the model adjusting for the other ones. Globally, there was some evidence that the two significant factors influencing the time to stop the statin in new regular users 2003 were the type of prevention and gender. Patients in secondary prevention stayed longer under statin therapy than those in primary prevention. The rate of treatment stop is 19.9% higher in primary prevention than in secondary prevention. Men stayed longer under statin therapy than women. The rate to stop the use of statin therapy was 27.2% higher in women than in men.

2.2.3.6 Determinants of simvastatin/ pravastatin use

From the multivariate logistic model, it turned out that 2 factors were important determinants of receiving simvastatin/pravastatin for a new treatment: secondary prevention and receiving the prescription from a specialist increased the odds of receiving simvastatin or pravastatin. Moreover, being aged ≥70 years and being a female were also predisposing factors of such prescription.

[t] For interpretation purpose:
HR > 1 means that the rate of stopping the use of statin is increased by (HR-1)% in increasing the variable under consideration by 1 → lower duration of statin use when increasing the variable under consideration.
HR < 1 means that the rate of stopping the use of statin is decreased by (1-HR)% in increasing the variable under consideration by 1 → longer duration of statin use when increasing the variable under consideration.

Table 21: Determinants of simvastatin/pravastatin use in new users (logistic regression)

Variable	Level	N	% patients on SIMVA or PRAVA	Odds Ratio from Multivariate Model	(95% CI)	p-value
Age category	< 50 years	118640	64.1	1.00		<=0.001
	50-59 years	205960	65.5	1.06	(0.96-1.17)	
	60-69 years	276800	64.9	1.06	(0.97-1.16)	
	70-79 years	229420	68.8	1.21	(1.11-1.32)	
	80 years +	75500	72.1	1.36	(1.22-1.51)	
Gender	Male	446260	65.5	1.00		<=0.001
	Female	460060	67.5	1.09	(1.04-1.15)	
Use of anti-diabetic drugs	No	754340	66.6	1.00		0.056
	Yes	151980	66.2	0.94	(0.88-1.00)	
Type of prevention	Primary	831000	65.4	1.00		<=0.001
	Secondary	75320	78.5	1.84	(1.66-2.05)	
Start statin (year/Trimester)	2003 T 1	27960	43.6	1.00		<=0.001
	2003 T 2	25860	45.2	1.05	(0.87-1.26)	
	2003 T 3	27600	65.1	2.19	(1.82-2.64)	
	2003 T 4	35040	68.5	2.63	(2.20-3.16)	
	2004 T 1	55580	56.2	1.58	(1.35-1.85)	
	2004 T 2	59980	53.5	1.42	(1.21-1.66)	
	2004 T 3	76620	74.3	3.60	(3.07-4.21)	
	2004 T 4	80300	76.0	4.00	(3.41-4.69)	
	2005 T 1	108220	68.5	2.73	(2.35-3.16)	
	2005 T 2	76520	68.8	2.75	(2.36-3.21)	
	2005 T 3	47720	68.2	2.64	(2.23-3.12)	
	2005 T 4	56060	67.4	2.59	(2.20-3.05)	
	2006 T 1	58680	70.5	3.01	(2.56-3.54)	
	2006 T 2	57180	71.0	3.04	(2.58-3.59)	
	2006 T 3	50280	69.7	2.84	(2.41-3.36)	
	2006 T 4	62720	66.7	2.50	(2.13-2.94)	
First prescriber specialty	1- GP	752280	65.4	1.00		<=0.001
	2-Specialists	154040	72.0	1.14	(1.06-1.22)	
Entitled to increased reimbursement	No	692040	66.1	1.00		0.542
	Yes	214280	68.0	1.02	(0.96-1.08)	
Invalidity or handicap	No	844880	66.5	1.00		0.576
	Yes	61440	66.5	1.03	(0.92-1.16)	

Source:extrapolated from EPS 2003-2006

Key points

Characteristics of statin users (2003-2006)

- **The large majority of new users start statin treatment for primary prevention (91.7% over the 2003-2006 period). In 2006, nearly 70% of new patients received simvastatin or pravastatin as first treatment option. Four over 5 treatments were initiated by GPs.**
- **Overall, the percentage of regular statin users was 58.8%, without significant difference among molecules. The occasional users were either patients who received only one statin prescription (18.3%) either patients who had a medication possession ratio(MPR) below 80% (22.8%). The mean MPR was 94% when purchasers of only 1 packaging were discarded.**
- **The factors most strongly associated to a regular use were: being older than 50 years, being diabetic (66.7% vs. 57.2%), using statin for secondary prevention (75.1% vs. 57.3%), and receiving the first statin prescription by a specialist (65.6% vs. 57.4%).**
- **Simvastatin/pravastatin represented 78.5% of new treatments in secondary prevention, while they represented only 65.4% of new treatments in primary prevention. They were also more often prescribed by specialists than by GPs.**
- **After 4 years, around 50% of the regular users who started statin in 2003 were still under statin treatment. Statin therapy was significantly longer in males and in patients in secondary prevention.**
- **Socio-economic factors (entitlement to increased reimbursement, invalidity or handicap status) appear to have no influence neither on the compliance, the duration of treatment, nor the initial choice of statin.**

2.2.4 Cardiovascular events and secondary prevention

The following section aimed at estimating the rates of statin-based secondary prevention after a hospitalisation for a cardiovascular event (CVE), and at identifying patients characteristics influencing this prevention.

The RCM-MKG (hospital clinical data, RCM/MKG) have been used to identify patients hospitalized for a CVE (see list of ICD-9 codes in Table 2)[u]. These data have been linked to the individual claim data from the EPS. Beneficiaries of secondary prevention were patients having received any new statin treatment in ambulatory care in the year following the CVE[v].

Contrary to the previous sections, the unit of analysis was hospitalisation, and not patient, as some patients were hospitalized more than once for a CVE in the 2003-2006 period (19% of the patients were admitted twice and 5.2% thrice for a CVE). Probability of a secondary prevention were presented per year of discharge (from 2003 to 2006), per principal diagnoses and per APR-DRG.

The time to start a secondary prevention in ambulatory care was also analyzed, using Kaplan Meier curves. A Cox proportional hazard regression model was used to analyze the influence of some characteristics on the time to start a secondary prevention. The test of proportionality of the hazard was tested and in case of non-proportionality, individual plots of the hazard by factors were graphically displayed to investigate the reason of non-proportionality and the amplitude of the difference. These specific analyses (Cox regression model) were based on a smaller sample than previous analyses (i.e. not taking into account the over sampling of the EPS) as analytical techniques for oversampled survival data are not (yet) available in SAS 9.1.

2.2.4.1 Hospitalisations for a Cardiovascular event

There were 344 180 hospitalizations for a cardiovascular event during the 2003-2006 period (extrapolated from the EPS). The number of CVE hospitalization has remained fairly constant over the years, but the percentage of hospitalisations preceded by statin use has continually increased, from 19.1% in 2003 to 40.0% in 2006 (Table 22).

Table 22: Percentage of the hospitalizations for a cardiovascular event preceded by statin use the year before (12 months)

	Year of discharge				
Extrapolated N	2003	2004	2005	2006	**Total**
Not on statin therapy before CVE (potential candidate for secondary prevention)	71100 (80.89)	66740 (74.12)	52660 (65.22)	51300 (60.00)	241800 (70.25)
On statin therapy before CVE (excluded from following analyses)	16800 (19.11)	23300 (25.88)	28080 (34.78)	34200 (40.00)	102380 (29.75)
Total	87900	90040	80740	85500	344180

Source: Extrapolated from the EPS and coupled with the RCM-MKG

2.2.4.2 Rates of secondary prevention over time

Among the 241 800 hospitalizations with no documented previous statin use, 9% were followed by a patient death (0.02% at the hospital and 8.89% in the 3 months after discharge). A total of 220 260 stays was therefore included in further analyses. The proportions of patients getting a secondary prevention after a CVE are presented per category in Table 23

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[u] Hospitalizations for artherosclerosis (code 440) were not included in the list of CVE (code not specific enough). Nevertheless, statin use after those hospitalizations are presented in appendix for information.

[v] As the exact date of discharge from hospital was unavailable in the MCD, statins delivered during the month of discharge were also considered as secondary prevention. Thus the time span was 13 months (the month of discharge + 12 months).

Table 23: Rates of secondary prevention after a a CVE hospitalization for (2003-2006)

	secondary prevention	N	
	No	Yes	
N stays	120080	100180	220260
Gender			
Male	51.77%	48.23%	140780
Female	59.39%	40.61%	79480
Age category			
<50 years	46.12%	53.88%	19080
50-59 years	44.44%	55.56%	20800
60-69 years	45.96%	54.04%	27140
70-79 years	55.07%	44.93%	30120
80 years +	74.53%	25.47%	11840
Low income			
Yes	63.39%	36.61%	9560
No	54.11%	45.89%	210700
Invalidity or Handicap (40 missing)			
Yes	52.86%	47.14%	14000
No	54.62%	45.38%	206220
Entitlement to increased reimbursement (40 missing)			
Yes	60.35%	39.65%	70720
No	51.75%	48.25%	149500
Diabetes			
Yes	51.66%	48.34%	35620
No	55.07%	44.93%	184640

Source: Extrapolated from EPS 2003-2006

As shown in Table 24, the percentage of statin treatment after a hospitalization for a CVE increased from 34.3% in 2003 to 52.4% in 2006.

Table 24: Rates of secondary prevention after a hospitalization for a CVE

Statin the year after	**Year of discharge**				
Extrapolated N (%)	2003 N=65080	2004 N=60780	2005 N=48120	2006 N=46280	**Total N=220260**
Statin for Secondary prevention	22320 (34.30)	30200 (49.69)	23420 (48.67)	24240 (52.38)	100180 (45.48)

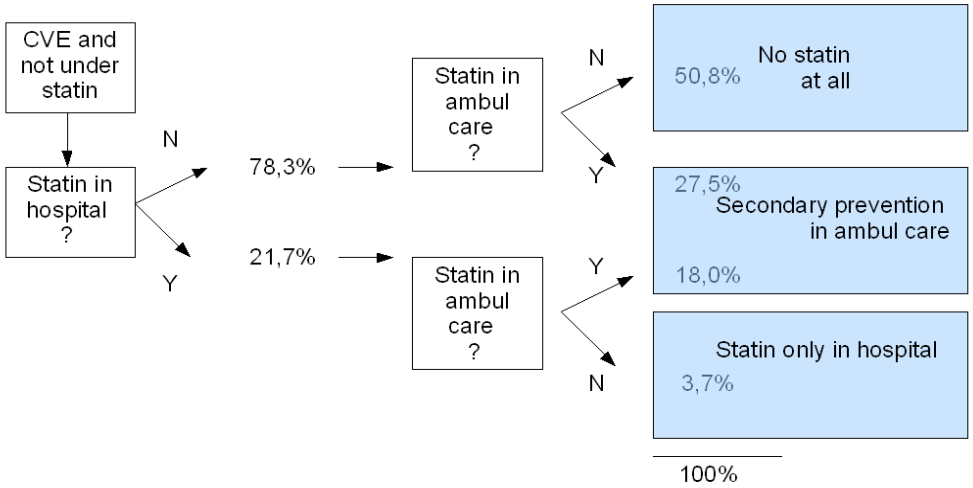
Source: Extrapolated from the EPS and coupled with the RCM-MKG

In 21.7% of the cases, statin was started during the hospitalization (Figure 12; detailed numbers are presented in appendix).

The 45.5 % of hospitalizations for CVE followed by a statin treatment in ambulatory care in the year after the discharge (see Table 24) were shared as follows:

- 18% already started statin during hospitalization
- 27.5% started after hospitalization discharge

Figure 12: Setting of start of statin (hospital or ambulatory)



2.2.4.3 *Rates of secondary prevention by principal diagnosis and APR-DRG (2006)*

The percentage of stays leading to a statin-based secondary prevention depended upon the principal diagnosis as presented in Table 25 (for 2006 only, results for all years are presented in appendix). This percentage ranged from 77% after an acute myocardial infarction (AMI) to 24% after a transient cerebral ischemia[w].

Table 25: Secondary prevention by principal diagnosis of hospitalization (year 2006)

Principal diagnosis in 3 digits	**Statin the year after**		
N extrapolated (%)	**No**	**Yes**	**Total**
410 Acute myocardial infarction (AMI)	1980 (23.19)	6560 (76.81)	8540
411 Other acute and sub-acute forms of ischemic heart disease	740 (36.27)	1300 (63.73)	2040
413 Angina pectoris	1940 (71.32)	780 (28.68)	2720
414 Other forms of chronic ischemic heart disease	7160 (38.96)	11220 (61.04)	18380
4140 Coronary atherosclerosis	6440 (37.31)	10820 (62.69)	17260
4141 Aneurysm and dissection of heart	20 (100.00)	0 (0.00)	20
4148 Other specified forms of chronic ischemic heart disease	620 (63.27)	360 (36.73)	980
4149 Chronic ischemic heart disease, unspecified	80 (66.67)	40 (33.33)	120
433 Occlusion and stenosis of precerebral arteries	1680 (64.62)	920 (35.38)	2600
434 Occlusion of cerebral arteries	4960 (68.13)	2320 (31.87)	7280
435 Transient cerebral ischemia	3580 (75.85)	1140 (24.15)	4720
Total	22040 (47.62)	24240 (52.38)	46280

Source: Extrapolated from the EPS and coupled with the RCM-MKG

[w] In the pre-assessment phase of this study, a larger selection of stays was done (including hospitalization for a cardiovascular *reason*, but not necessarily leading to an event). The results on this broader selection are presented in appendix.

The proportion of secondary prevention was not homogeneous across the different age strata.

Table 26 presents the percentage of secondary prevention by age stratum for the hospitalizations with two specific principal diagnosis: AMI (410) or one of the (pre)-cerebral occlusion diagnosis (ICD-9: 433, 434 or 435). In both cases, the percentage dropped when the age increased beyond 50 years.

Table 26: Secondary prevention for 2 principal diagnosis (2006)

	Acute myocardial infarction (AMI)			(Pre)-cerebral occlusion & transient ischemia		
Age range	**Secondary prevention N extrapolated (%)**			**Secondary prevention N extrapolated (%)**		
N extrapolated (%)	**No**	**Yes**	**Total**	**No**	**Yes**	**Total**
before 50 years	360 (31.03)	800 (68.97)	1160	800 (74.07)	280 (25.93)	1080
50-59 years	80 (4.17)	1840 (95.83)	1920	640 (42.11)	880 (57.89)	1520
60-69 years	340 (19.32)	1420 (80.68)	1760	1440 (62.07)	880 (37.93)	2320
70-79 years	540 (26.47)	1500 (73.53)	2040	2780 (66.83)	1380 (33.17)	4160
80 and more-	660 (39.76)	1000 (60.24)	1660	4560 (82.61)	960 (17.39)	5520
Total	1980 (23.19)	6560 (76.81)	8540	10220 (70.00)	4380 (30.00)	14600

Table 27 presents the split of hospitalization per APR-DRG. The pathology groups including acute myocardial infarctions, cardiovascular procedures (percutaneous or valves) or coronary by-passes showed the highest percentage of secondary prevention.

Table 27: Secondary prevention by APR-DRG of hospitalization (2006)

APR-DRG version 15/ MDC – p or m (surgery or medical)	**Statin the year after**		
N EXTRAPOLATED (%)	NO	YES	**Total**
004-Tracheostomy except for face, mouth & neck diagnoses / p3 - p	40 (40.00)	60 (60.00)	100
024-Extracranial vascular procedures / 1 - p	1120 (71.79)	440 (28.21)	1560
025-Nervous system proc. for peripheral nerve disorders / 1 - p	0 (0.00)	20 (100.00)	20
026-Nervous system proc for cranial nerves & other nervous system disorder / 1 - p	120 (85.71)	20 (14.29)	140
045-Cerebrovascular accident with infarction / 1 - m	4900 (65.33)	2600 (34.67)	7500
046-Nonspecific cerebrovascular accident & precerebral occlusion w/o infarct / 1 - m	460 (74.19)	160 (25.81)	620
047-Transient ischemia / 1 - M	3460 (75.88)	1100 (24.12)	4560
161-Cardiac defibrillator implant / 5 - P	0 (0.00)	20 (100.00)	20
162-Cardiac valve procedures with cardiac catheterization / 5 - p	40 (25.00)	120 (75.00)	160
163-Cardiac valve procedures w/o cardiac catheterization / 5 - p	40 (33.33)	80 (66.67)	120
165-Coronary bypass w/o malfunctioning coronary bypass with cardiac catheterization / 5 - p	400 (29.85)	940 (70.15)	1340
166-Coronary bypass w/o malfunctioning coronary bypass w/o cardiac	620	760	1380

APR-DRG version 15/ MDC – p or m (surgery or medical)	Statin the year after		
N EXTRAPOLATED (%)	NO	YES	**Total**
catheterization / 5 - p	(44.93)	(55.07)	
168-Major thoracic vascular procedures / 5 - P	0 (0.00)	100 (100.00)	100
170-Permanent cardiac pacemaker implant with AMI, heart failure or shock / 5 - p	20 (100.00)	0 (0.00)	20
173-Other vascular procedures / 5 - p	20 (6.25)	300 (93.75)	320
174-Percutaneous cardiovascular procedures w AMI / 5 - p	520 (15.95)	2740 (84.05)	3260
175-Percutaneous cardiovascular procedures w/o AMI / 5 - p	2060 (28.77)	5100 (71.23)	7160
177-Cardiac pacemaker & defibrillator revision except device replacement / 5 - p	0 (0.00)	20 (100.00)	20
190-Circulatory disorders with AMI / 5 - m	1020 (26.84)	2780 (73.16)	3800
191-Cardiac catheterization with circulatory disorder excl. ischemic heart disease / 5 - m	80 (40.00)	120 (60.00)	200
192-Cardiac catheterization for ischemic heart disease / 5 - m	4460 (52.35)	4060 (47.65)	8520
198-Atherosclerosis / 5 - m	840 (42.00)	1160 (58.00)	2000
202-Angina pectoris / 5 - m	1460 (54.48)	1220 (45.52)	2680
207-Other circulatory system diagnoses / 5 - m	180 (39.13)	280 (60.87)	460
950-Extensive procedure unrelated to principal diagnosis / 0 - p	140 (77.78)	40 (22.22)	180
951-Prostatic procedure unrelated to principal diagnosis / 0 - p	20 (100.00)	0 (0.00)	20
952-Nonextensive procedure unrelated to principal diagnosis / 0 - p	20 (100.00)	0 (0.00)	20
TOTAL	22040 (47.62)	24240 (52.38)	46280

Source: Extrapolated from the EPS and coupled with the RCM-MKG

For the percutaneous cardiovascular procedures (with and without AMI), the percentage of secondary prevention is presented in Table 28. In the case of an absence of AMI, the percentage was the highest in the oldest stratum (80 years and more).

Table 28: Secondary prevention after percutaneous cardiovascular procedures, per age range (2006)

174-PERCUTANEOUS CARDIOVASCULAR PROCEDURES with AMI			
Age	**Statin the year after discharge**		
N extrapolated (%)	**No**	**Yes**	**Total**
before 50 years	200 (31.25)	440 (68.75)	640
50-59 years	80 (10.53)	680 (89.47)	760
60-69 years	100 (11.90)	740 (88.10)	840
70-79 years	120 (18.75)	520 (81.25)	640
80 and more-	20 (5.26)	360 (94.74)	380
Total	520 (15.95)	2740 (84.05)	3260
175-PERCUTANEOUS CARDIOVASCULAR PROCEDURES without AMI			
before 50 years	120 (16.67)	600 (83.33)	720
50-59 years	360 (27.27)	960 (72.73)	1320
60-69 years	540 (25.96)	1540 (74.04)	2080
70-79 years	400 (22.73)	1360 (77.27)	1760
80 and more-	640 (50.00)	640 (50.00)	1280
Total	2060 (28.77)	5100 (71.23)	7160

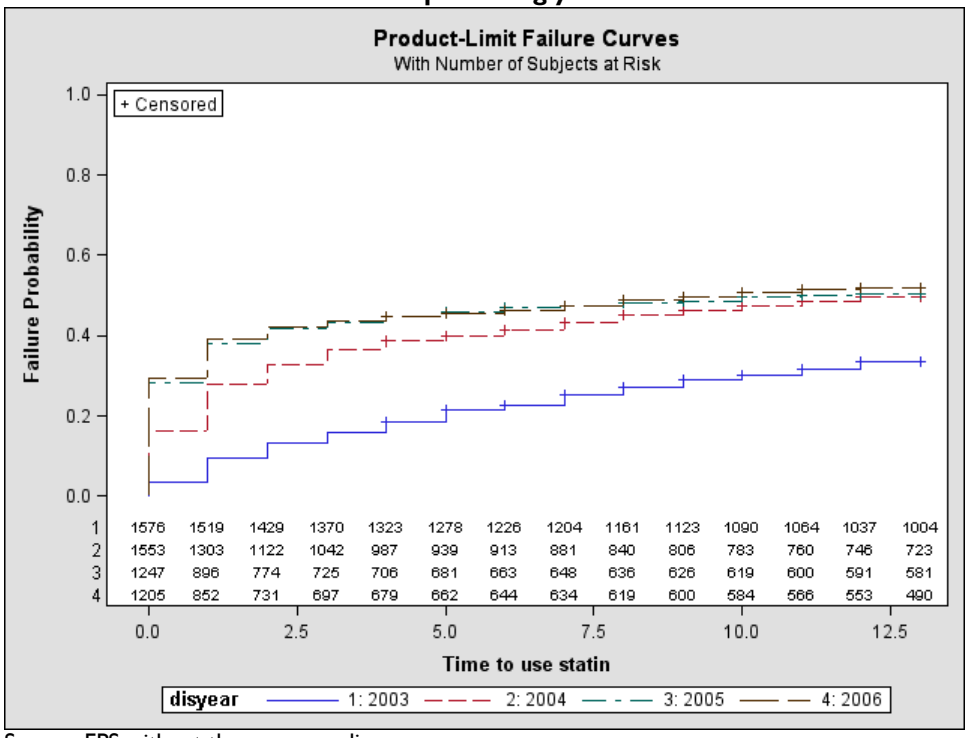
AMI: Acute Myocardial Infarction

2.2.4.4 Time to start secondary prevention

Figure 13 shows the survival function of the number of months between discharge and first statin use in ambulatory care, by year of discharge. It clearly shows that the time before receiving a statin decreased with the year of discharge.

In 17.3% of the hospitalizations, the statin treatment began during the month of discharge. In a third of the cases, the treatment began in the 3 months after the month of discharge.

Figure 13: Time to statin use as secondary prevention – Patients hospitalized for CVE and without statin in the preceding year



Source: EPS without the over-sampling

2.2.4.5 *Factors influencing the start of a secondary prevention*

Results from multivariate Cox model (Table 29) show that the following factors positively influenced the chance to receive statin therapy after a CVE hospitalization: year of discharge (in 2006 more than in 2003), being a female, being in the age range 50-69 years, diabetes.

The rate of starting a statin therapy after a CVE hospitalization was 84% higher in 2004 compared to 2003, and 127% higher in 2006 compared to 2003.

Table 29: Factors associated to a secondary prevention by statin after an hospitalization for CVE (Hazard ratio and 95% Confidence limits)

Parameter		Hazard Ratio	95% Hazard Ratio Confidence Limits		p-value
Year of discharge of hospital (p-value = <.0001)*	2004 vs 2003	1.844	1.650	2.062	<.0001
	2005 vs 2003	2.119	1.886	2.381	<.0001
	2006 vs 2003	2.267	2.017	2.548	<.0001
Diabetes treated in the year before	(Yes vs No)	1.111	1.000	1.234	0.0491
Age category (p-value = <.0001)*	50-59 years vs <50years	1.021	0.879	1.186	0.7839
	60-69 years vs <50years	0.992	0.858	1.147	0.9168
	70-79 years vs <50years	0.754	0.653	0.872	0.0001
	80 years + vs <50years	0.374	0.315	0.444	<.0001
Gender	Male vs Female	0.903	0.829	0.983	0.0182
Entitled to increased reimbursement:	Yes vs No	0.980	0.894	1.074	0.6668
Invalidity or Handicap:	Yes vs No	0.814	0.687	0.965	0.0175

*Results from the global test.

Source: EPS without the over-sampling

2.2.4.6 Discussion

In 2006, grossly half of the hospitalizations for CVE triggered the start of a secondary prevention with statins. Although this represents an improvement in comparison to 2003, the numbers remained strikingly low. However, looking at the main diagnosis which triggered the hospitalization provided a more accurate picture of the current practice. Secondary prevention is much higher in the case of an acute myocardial infarction. Still, nearly 25% of hospitalizations for an AMI and 70% of hospitalizations for a cerebrovascular event were not followed by a statin-based secondary prevention. One important determinant of not getting secondary prevention was age. In the age range 50-59 years, the rate of secondary prevention after an hospitalization for AMI was 95.8%, and 57.9% for a cerebrovascular event in 2006.

This analysis is based on data limited to 2006, and it might be that the clinical practice has evolved since then. Unfortunately, the clinical data up to 2009 are not available because of the time lag between routine data collection and archiving.

Key points

Secondary prevention after a CVE hospitalization (2003-2006)

- **The percentage of patients receiving a statin therapy before the hospitalization increased from 19% (2003) to 40% (2006). On the same period, overall secondary prevention rates (defined as statin use in ambulatory care within 1 year after CVE) increased from 34% to 52%.**
- **The rate of secondary prevention was specific to the type of CVE. In 2006, it was 76.8% for acute myocardial infarction, but much lower for ischemic cerebrovascular events. It was also related to patient age, with a significant decrease after 69 year.**

3 COMPARATIVE APPRAISAL OF STATINS

3.1 COMPARISON OF CLINICAL EFFICACY

As the number of patients in need for statin therapy continues to increase and as the retail prices of different molecules vary greatly, assessing the relative clinical efficacy and safety of the various statin molecules is important to inform decision makers.

In this chapter, we aimed at reviewing head-to-head trials comparing the clinical outcomes of less costly statins (ie. simvastatin or pravastatin) to more costly molecules (i.e. atorvastatin or rosuvastatin)[x]. For the purpose of evidence retrieval we included in the group of less costly statins fluvastatin and lovastatin, although the price per DDD is in-between for the former and the latter is not available in Belgium.

3.1.1 Methods

A systematic literature review was carried out. The electronic databases Medline, Embase, Database of Abstracts of Reviews of Effects (DARE) and the Cochrane Central Registery of Controlled Trials were searched with the following strategy:

1. simvastatin OR pravastatin OR fluvastatin OR lovastatin[y]

2. atorvastatin OR rosuvastatin

3. 1 AND 2

4. randomized controlled trial[ptyp]

5. 3 AND 4

The search was conducted in January 2010. Inclusion and exclusion criteria were defined a priori (Table 30). Data were extracted and imported in RevMan 5.0 for meta-analysis and forest-plots. Statistical heterogeneity among studies was assessed with the Q statistics. In case of significant heterogeneity, a random effect model was applied. Potential publication bias was explored visually with a funnel plot. To limit heterogeneity, we restricted the meta-analysis to clinical indicators reported in all the included studies and which definition was unambiguous, i.e. all causes mortality, myocardial infarction and stroke.

Table 30: Inclusion and exclusion criteria

Inclusion criteria	-Direct comparison of efficacy/safety of simvastatin and/or pravastatin and/or lovastatin with atorvastatin and/or rosuvastatin; -Reporting on specific/general mortality, on occurrence of cardiovascular events (myocardial infarction, stroke) or on occurrence of serious adverse events; -During a follow-up of at least 6 months; -Published in English, French, Dutch, or Spanish;
Exclusion criteria	- Reporting on outcomes[z] other than cardiovascular ones: atrial/ventricular fibrillation [18]; dementia [19]; sepsis [20]; - Reporting only on serum lipid changes or other surrogates; - Reporting on genetic variants modifying statin effects.

x In 2009, 1 DDD of rosuvastatin, atorvastatin, fluvastatin and pravastatin costed 286%, 441%, 239% the price of 1 DDD of simvastatin.

y Lovastatin is not available in Belgium. However, simvastatin and pravastatin are chemical modifications of lovastatin and as a result do not differ much in structure from lovastatin.

z to date the potential effect of statins on these pathologies mainly originate from observational studies

3.1.2 Results

Our search identified 240 citations (239 references from electronic databases + 1 reference retrieved by scrutinizing bibliography of previous reviews). The review of titles and abstracts showed that a significant proportion of these citations referred to other topics than the prevention of cardio-vascular events and survival improvement, or focused on measuring surrogates such as LDL-C concentration, CRP level or carotid intima thickness (Figure 14). Sixteen potentially relevant papers were retrieved in full. It appeared that 11 of those publications were sub-studies derived from primary RCTs. Therefore, 5 RCTs were eventually included in the review.

Table 1 summarizes the main characteristics of the 5 trials included. Most of the trials included participants with chronic coronary syndrome, with the exception of the PROVE IT-TIMI 22 [21], and the majority of participants were male patients. The mean age of patients ranged from 56 years in the REVERSAL study [22] to 72 years in the SAGE study [23]. Atorvastatin 80 mg was used in each study, and compared to pravastatin 40 mg in 3 trials. The follow-up duration was quite short (less than 2 years), except in the IDEAL study [24].

All-cause mortality was not significantly different between the atorvastatin group and the comparator groups (RR=0.92; 95%CI:0.81,1.04; p=0.18). However, there was quite heterogeneity among studies, with an important reduction of all-cause mortality in the SAGE study, and a marginally non-significant mortality reduction in the PROVE IT-TIMI 22, while atorvastatin 80mg was not more effective than simvastatin 20mg in the IDEAL study, the study with the highest weight in the meta-analysis. The risk of myocardial infarction was overall decreased by 16% (RR: 0.84; 95%CI: 0.73, 0.96; p=0.01), while the risk of stroke did not significantly differ between atorvastatin and comparators (Figure 16 & Figure 17). The funnel plot (Figure 18) showed no evidence of publication bias, but evidenced once again the ectopy of the SAGE study.

Figure 14: Flow chart of trials through the selection process

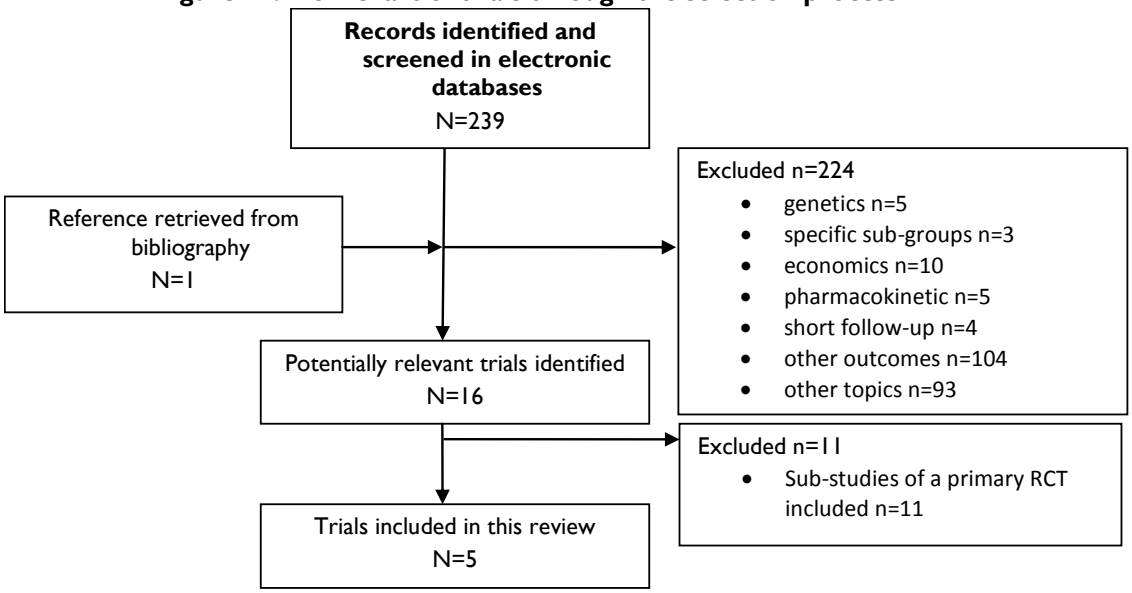


Table 31: Characteristics of included trials

	REVERSAL1[22]	PROVE IT-TIMI 22 [21]	IDEAL[24]	Vascular basis[25]	SAGE [23]
N	6542	4,1623	8,888	300	8934
Mean age (yr)	56	58	62	NR	72
Male (%)	72	78	81	86	69
Disease	Chronic coronary artery disease	Post acute coronary syndromes	Chronic coronary artery disease	Chronic coronary artery disease	Chronic coronary artery disease
Statins (daily dose)	Pravastatin (40 mg) vs. atorvastatin (80 mg)	Pravastatin (40 mg) vs. atorvastatin (80 mg)	Simvastatin (20 mg) vs. atorvastatin (80 mg)	Lovastatin5 (5 mg) vs. atorvastatin (80 mg)	Pravastatin (40 mg) vs. atorvastatin (80 mg)
Follow-up duration (yr)	1.5	2 (mean) (1.5, 3)	4.8	1	1
Inclusion criteria	30 to 75 years, at least 1 obstruction with angiographic luminal diameter narrowing of 20% or more, with an LDL-C level between 125 mg/dL (3.24 mmol/L) and 210 mg/dL (5.44 mmol/L) after a 4- to 10- week washout period.	>18 years, hospitalized for an acute coronary syndrome (acute myocardial infarction or unstable angina) in the preceding 10 days, being in stable condition, total cholesterol level of ≤240 mg per deciliter	≤80 years, a history of a definite myocardial infarction, who qualified for statin therapy according to national guidelines at the time of recruitment	age <85 years, fasting total cholesterol of 180 to 250 mg/dL, objective evidence of coronary disease, exercise-induced STsegment depression ≥1.0 mm, and ≥1 episode of reversible ST depression of ≥1.0 mm during 48-hour AECG monitoring of routine activities	65 to 85 years of age, a documented history of CAD, baseline LDL-C levels between 100 mg/dL (2.6 mmol/L) and 250 mg/dL (6.5 mmol/L), and ≥1 episode of myocardial ischemia with a total duration of ≥3 minutes during 48-hour ambulatory ECG monitoring at the screening visit
Exclusion criteria		A coexisting condition with survival time<2 years; already receiving 80 mg/d statin or lipid-lowering therapy with fibric acid derivatives or niacin that could not be discontinued before randomization, had received drugs that are strong inhibitors of cytochrome P-4503A4 within the month before randomization or were likely to require such treatment during	Any known contraindications to statin therapy, previous intolerance to statins in low or high doses, liver enzyme levels ≥2 times the upper limit of normal, pregnancy or breastfeeding, nephrotic syndrome, uncontrolled diabetes mellitus, uncontrolled hypothyroidism, plasma triglyceride levels higher than	acute coronary syndrome within 1 month of study entry, coronary revascularization procedure within 6 months of study entry, congestive heart failure greater than NYHA class III, significant valvular heart disease, cigarette smoking within 2 months of study entry, and a resting 12-lead ECG that was not	NR

		the study period, had undergone percutaneous coronary intervention within the previous 6 months or coronary-artery bypass surgery within the previous 2 months; were scheduled to undergo bypass surgery in response to the index event; had factors that might prolong the QT interval; had obstructive hepatobiliary disease or other serious hepatic disease; had an unexplained elevation in the creatine kinase level ≥times the upper limit of normal and that was not related to myocardial infarction, or a creatinine level ≥2.0 mg per deciliter	600 mg/dL (6.8 mmol/L), congestive heart failure, valvular heart disease, gastrointestinal conditions affecting absorption of drugs, treatment with other drugs that seriously affect the pharmacokinetics of statins, and treatment with other lipidlowering drugs, patients previously treated with statins qualified if they had not already had titration to a dose higher than the equivalent of 20 mg/d of simvastatin.	interpretable	
Quality appraisal					
Randomization process	Yes	Yes	Yes	NR	NR
Imbalances at baseline	No	No6	No	No	Yes7
Allocation concealment	Yes	Unclear	Open-label, blinded end point	Unclear	Unclear
Adherence	NR	NR	95% with simvastatin, 89% for atorvastatin	>95%	NR
% without endpoint	23%	Unclear (seems high in figure1)	<1%	9%	15%
Differential LFU	No	NR	No	Unknown	No
Intention-to-treat	Yes	Unclear	Yes	Unknown	Yes

Appropriate statistics	Yes	Yes	Yes	Management of repeated measurements unclear	Differences at baseline not inserted in models; multicenter design not accounted for; adjustment/interaction with preexistent CAD not reported
General comment		Number of events not reported but derived from a secondary paper [26]; no flow chart	Could have modeled the adherence No interaction with age [27]	Very low CE rate?	

1. The study was not designed to primarily look at cardiovascular events
2. In 34 centers
3: At 349 sites in 8 countries
4: in 192 sites worldwide in 16 countries
5: Patients in the control group were proposed diet modification + low-dose lovastatin, if necessary (eventually it was in 91%), to achieve an LDL of <130 mg/dL. There were 2 intervention groups: intensive atorvastatin titrated to achieve an LDL of<80 mg/dL or a maximum dose of 80 mg/d; intensive atorvastatin + vitamins C (1000 mg/d) + vitamin E (800 mg/d). For the meta-analysis, the 2 intervention groups have been merged.
6: except a history of peripheral arterial disease more common in the pravastatin group
7: Patients in the atorvastatin group had a higher body mass index (P=0.017) and weight (P=0.006) and higher levels of apolipoprotein B 100 (P=0.017) at baseline than did patients randomized to pravastatin. Medical history was similar in both treatment groups, although significantly more patients in the pravastatin group had a history of stroke than did those in the atorvastatin group (27 patients and 10 patients, respectively; P=0.004)

Table 32: Outcome in the 5 selected studies

	REVERSAL[22]	PROVE IT-TIMI 22 [21]	IDEAL[24]	Vascular basis[25]	SAGE [23]
All death	1/327 vs. 1/327	69/2063 vs. 50/2099	374/4449 vs. 366/4439	0/103 vs.1/197	18/445 vs. 6/446
Cardiovascular death		36/2063 vs. 27/2099	178/4449 vs. 175/4439		10/445 vs. 4/446
Any MACE		554/2063 vs. 496/2099	608/4449 vs. 533/4439	5/103 vs. 15/197	90/445 vs. 61/446
Myocardial infarction	7/327 vs. 4/327	136/2063 vs. 120/2099	321/4449 vs. 267/4439	1/103 vs. 4/197	17/445 vs. 18/446
Ischemic episodes (over 48 hours AECG)				2.0 vs. 2.5	
Unstable angina			235/4449 vs. 196/4439	2/103 vs. 2/197	29/445 vs. 15/446
Stroke	1/327 vs. 1/327	17/2063 vs. 20/2099	174/4449 vs. 151/4439	1/103 vs. 1/197	3/445 vs. 1/446
Coronary revascularization			743/4449 vs. 579/4439	1/103 vs. 4/197	33/445 vs. 22/446
Safety					
Serious adverse events (other than MACE)			2108/4449 vs. 2064/4439	NR	53/445 vs. 54/446
Adverse events (at least 1)			4202/4449 vs. 4204/4439	NR	287/445 vs. 273/446
Myalgia	12/327 vs. 9/327	56 vs. 69	51 vs 97		12 vs 14
Myopathya	NR	NR	11 vs 6		NR
Aminotransferase level elevations	5/327 vs. 7/327	23 vs 69	5 vs 43		1 vs 19
Adverse events leading to drug discontinuation	22/327 vs. 21/327	33.0% vs. 30.4%	186/4449 vs. 426/4439	NR	46/445 vs. 48/446

a: myalgia with creatine kinase elevation

Figure 15: All-cause mortality in 5 studies of statin comparison

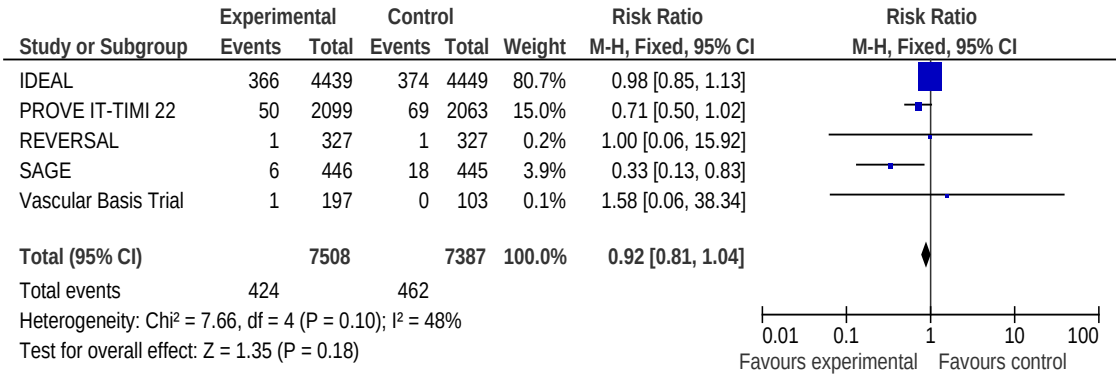


Figure 16: Risk of myocardial infarction in 5 studies of statin comparison

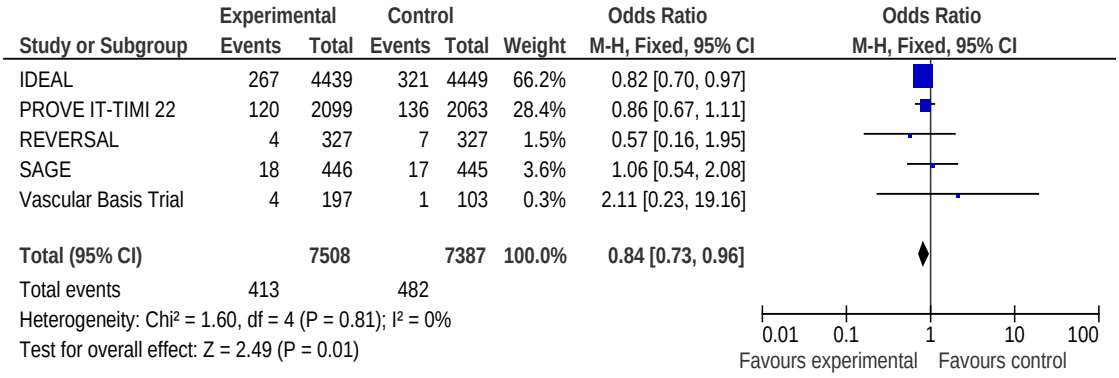


Figure 17: Risk of stroke in 5 studies of statin comparison

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
IDEAL	151	4439	174	4449	88.3%	0.87 [0.69, 1.08]
PROVE IT-TIMI 22	20	2099	17	2063	8.9%	1.16 [0.60, 2.22]
REVERSAL	1	327	1	327	0.5%	1.00 [0.06, 16.06]
SAGE	1	446	3	445	1.6%	0.33 [0.03, 3.20]
Vascular Basis Trial	1	197	1	103	0.7%	0.52 [0.03, 8.41]
Total (95% CI)		**7508**		**7387**	**100.0%**	**0.88 [0.72, 1.08]**
Total events	174		196			

Heterogeneity: Chi² = 1.57, df = 4 (P = 0.81); I² = 0%

Test for overall effect: Z = 1.19 (P = 0.23)

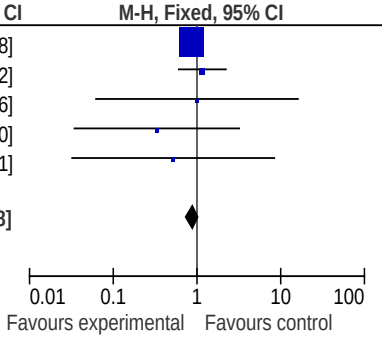
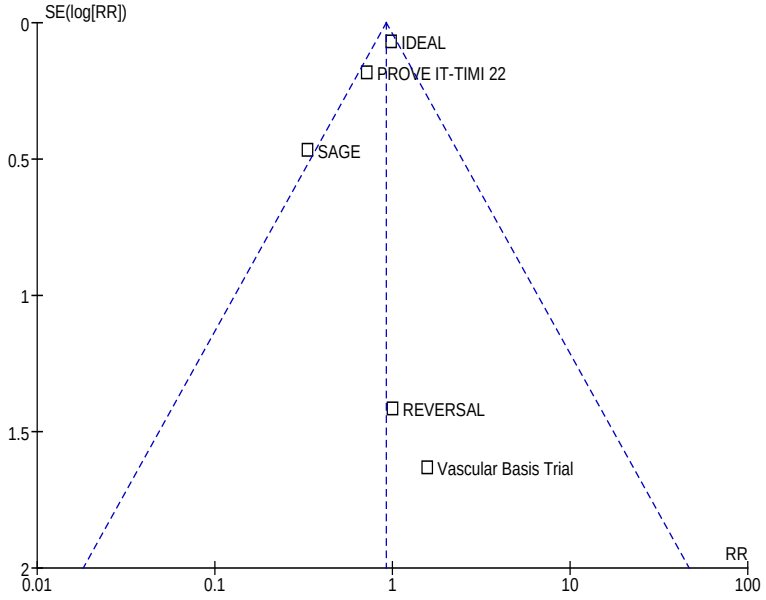


Figure 18: Funnel plot of the 5 trials included (all-cause mortality)



3.1.3 Discussion

Using atorvastatin 80mg in patients with mainly chronic coronary disease reduced the risk of myocardial infarction by 16% on average in comparison to pravastatin 40mg, simvastatin 20 mg or lovastatin 5 mg, but did not affect the risk of stroke nor the all-cause mortality risk. The absence of effect on the all-cause mortality risk in spite of the improvement observed on myocardial infarction could be due to the high standards of acute care in the trials but also to a lack of power given the small number of studies.

The comparison of the clinical efficacy of different statins encounters many limitations. First the number of head-to-head trials was very limited. We retrieved only 5 trials, and none of those included rosuvastatin. Second, head-to-head trials were primarily set to assess the benefits of an intensive therapy versus a usual statin dose. The intervention drug (atorvastatin) was given in much higher doses than the comparators: atorvastatin 80mg corresponds to 4 times the DDD, while pravastatin 40 mg is only 125% DDD and simvastatin 20 mg is even less than 1 DDD[aa].

The extent of risk reduction provided by statins appears to be directly proportional to the degree to which the LDL-C was lowered. On the basis of 58 trials, it was estimated that a LDL-C reduction of 0.5 mmol/L[bb], 1.0 mmol/L or 1.6 mmol/L resulted in 20%, 31% or 51 % reduction of ischaemic heart disease, respectively, after 2 years of treatment [2]. These findings were confirmed by more recent meta-analysis [3, 4, 28].

aa The DDDs for every drugs can be found at http://www.whocc.no/

bb 1mmol/L=39mg/dL

The latter reported that for every 0.65 mmol/L reduction in LDL-C, the risk of vascular mortality was reduced by 11% (95%CI: 8%-13%), that of major vascular events by 14% (95%CI: 12%-16%), that of major coronary events by 16% (14%-18%), and that of stroke by 8% (95%CI: 6%-10%) [28].

Although statins have qualitatively similar effects on lipid levels, their efficacy in lowering LDL-C varies. In their meta-analysis, Law. et al. have estimated that rosuvastatin 5 mg/day, atorvastatin 10 mg/day, lovastatin and simvastatin 40 mg/day reduced LDL cholesterol concentration by about 35% (1.8 mmol/l), but fluvastatin and pravastatin produced smaller reductions even at the highest doses tested (80 mg/day). Rosuvastatin 10 mg/day, atorvastatin 20 mg/day, lovastatin and simvastatin 80 mg/day reduced LDL-C concentration by about 45% (2.1 mmol/l) and rosuvastatin 80 mg/day by about 60% (2.8 mmol/l) [2]. In that meta-analysis, the absolute reductions (mmol/l) observed were greater in people with higher pre-treatment LDL-C concentrations, while the percentage reductions were independent of pre-treatment LDL-C concentrations.

Thus, an important limitation of the present meta-analysis was the difference in therapeutic doses between the intervention and comparator statins. It is plausible that at equivalent therapeutic doses, the clinical benefit would be similar. Another recent meta-analysis synthesizing the evidence from 75 head-to-head RCTs of statins reported that at comparable doses statins were therapeutically equivalent, i.e. yielded a similar LDL-C reduction, with a statistically significant but clinically minor difference (<7%) between statins [29]. The results of Zhou et al. also go in that direction [30]. The authors performed an adjusted indirect comparison of pravastatin, simvastatin and atorvastatin including 8 trials and reported no statistically significant difference in their effect on the long-term cardiovascular prevention [30]. This is also consistent with the results of a network meta-analysis (20 trials) reporting no benefit of atorvastatin over simvastatin, pravastatin or lovastatin on the risk of cardiovascular disease mortality in primary prevention [8].

Thus we found no good quality evidence that atorvastatin provides an added value on clinical outcomes in comparison to simvastatin, pravastatin, fluvastatin or lovastatin when given at equivalent therapeutic doses. It has even been suggested that atorvastatin could be inferior to other statins in patients with diabetes and the metabolic syndrome as atorvastatin has little or no ability to increase HDL-cholesterol [31]. Evidence on the efficacy of rosuvastatin to reduce the risk of CVD events is still limited to date. Such efficacy has been tested in 4 trials with specific patient populations (e.g. subjects with heart failure or on regular hemodialysis), and was found significant in only one, the JUPITER trial where rosuvastatin was given in primary prevention to individuals with a normal cholesterol concentration but an elevated level of C-reactive protein (CRP) [32]. Moreover, the JUPITER trial has fuelled a lot of methodological controversy since its publication [33].

Worth mentioning, we didn't review observational studies on the comparative effectiveness of various statins [34, 35] because of the difficulty to control for bias in such studies. Only well-designed head-to-head RCTs could provide a definite answer to the important question of the relative efficacy/safety of different statins. Such RCTs should include not only patients with cardio-vascular diseases, but also patients with risk factors of CVD, as no comparison trial of different statins in primary prevention has been yet reported. In the absence of such evidence, there is no scientific ground today to recommend one specific statin instead of another. Statins more potent in terms of LDL-C reduction could be preferred in patients who have trouble reaching LDL-C goal. However there is no data yet to support that once an LDL-C goal is reached, that one statin would be preferred over another one. Thus for cost-effectiveness, one may consider treating with less costly statin as first line choice if appropriate LDL-C target can be attained [36].

3.2 COMPARISON OF SAFETY

The publicity surrounding the removal of cerivastatin from the market in 2001 due to the increased risk of rhabdomyolysis has likely contributed to an increase in awareness of potential safety issues with statins. Although statins are generally well tolerated, there are well-described adverse events (AE), sometimes serious, associated with their use. The risk of a statin-associated adverse event (mild myalgia, myopathy, elevated hepatic transaminase and creatine kinase [CK] levels) has been reported to be increased by 40% relative to placebo [37]. The most common adverse effect, nonserious symptoms of myalgia[cc], has been reported by some 2% to 11% of patients [38]. Although this typically reversible effect is troublesome for patients, it may go unreported in many patients because of its self-limiting nature [39]. Although symptoms may subside after drug discontinuation, symptoms frequently return on rechallenge (95% of patients have a return of symptoms when restarting therapy at the same dose, 55% when restarting at a lower dose) [40]. Statin-induced myositis can progress to clinically important myositis (CK≥10 times the upper limit of normal) and to rhabdomyolysis, which is the most serious[dd] AE associated with statins [42, 43] and results in 1 statin-related death per 6.66 million statin prescriptions in the United States [39]. Elevated hepatic transaminases occur less frequently (0.5%-2.0% of patients) and there is no convincing evidence of an associated increase risk of serious hepatitis. Hepatic failure is also extremely rare [44, 45ee].

Recently, a slight increased risk of development of diabetes has been reported [46]. Among 13 statin trials including 91 140 participants, statin therapy was associated with a 9% increased risk for incident diabetes (OR=1.09; 95% CI: 1.02-1.17). Concerns regarding long term complication of statin therapy on cancer incidence have not been confirmed so far[47, 48]. A potential association of statin use with amyotrophic lateral sclerosis has not been confirmed to date [49]. Other potential unintended effects of statins, such as a protective effect on risk of Parkinson's disease, venous thromboembolism, rheumatoid arthritis, osteoporotic fracture, and dementia have also not been confirmed to date [50].

In this section, we aimed at reviewing head-to-head trials comparing the incidence of adverse events of less costly statins (ie. simvastatin or pravastatin) to more costly molecules (i.e. atorvastatin or rosuvastatin).

3.2.1 Methods

See section 3.1.1

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cc Myopathy is defined as any muscle symptom—pain, tenderness, or weakness—accompanied by a creatine kinase concentration greater than ten times the upper limit of normal for the particular laboratory40 (also called myositis). Rhabdomyolysis is severe myopathy involving muscle breakdown and myoglobin release into the circulation, which can cause a brown discolouration of urine and risk of renal failure. Rhabdomyolysis is usually diagnosed when creatine kinase concentration is greater than 40 times the upper limit of normal, or there is evidence of end organ damage (eg, acute renal failure or worsened renal function), or both, but differences in definition make comparisons between studies difficult. Myalgia refers to muscle pain with no rise in creatine kinase concentration to greater than ten times the upper limit of normal.

dd Severe myopathy leads to the release of muscle components such as creatine kinase into the bloodstream, which can accumulate in the kidney and lead to renal failure, sometimes resulting in death [41].

ee The question is whether the effect on transaminases indicates hepatotoxicity or rather some sort of hepatic reaction to reduction of lipid levels. Other cholesterol-lowering agents, including fibrates, resins (which are not systemically absorbed), niacin, and ezetimibe, all increase liver enzymes, which suggests these changes could be a hepatic response to lipid lowering rather than hepatotoxicity [1].

3.2.2 Results

The information on safety issues in the trials included was scarce. There was no obvious difference between statins, except in the IDEAL study where a doubling of the risk of myalgia leading to treatment discontinuation was observed (Table 32).

3.2.3 Discussion

We encountered for direct comparison of safety among different statins the same limitations as for efficacy (see 3.1.3), notably that published head-to-head trials compared high doses of atorvastatin to usual doses of other statins. However, although the risk of adverse events is dose-related [39], globally no excess adverse events was noted in the atorvastatin intervention group. The increase of side effects in the IDEAL study might be partially due to its open-label design. Noteworthy, none of these trials was not designed to assess such adverse events, and the corresponding outcomes were rarely reported.

Rosuvastatin was the first statin to be marketed after the withdrawal of cerivastatin, and there is thus considerable concern regarding its safety profile. The data presented in 2003 to the FDA included 20 controlled trials with placebo or comparator statins (these trials were not included in our meta-analysis as no clinical outcomes were reported). The safety profile of rosuvastatin appeared similar to those of the comparator statins investigated [51]. This was confirmed in a further review of head-to-head trials comparing rosuvastatin with atorvastatin [52]. An in-vitro study also showed that the cytotoxicity of rosuvastatin and pravastatin, 2 hydrophilic statins, was even lower than for lipophilic statins [53].

Notwithstanding, the appraisal of comparative safety can also be achieved by other means: indirect comparisons of RCTs and pharmacoepidemiology studies.

Indirect comparisons

Two previous meta-analyses achieved an indirect general comparison of statins [8, 30], but only one reported on AEs [8]. However, the latter did not apply a mixed-treatment comparison on the aspect of AEs.

Specific AEs were assessed in other meta-analyses. Two recent studies looked at induced diabetes. The first one suggested that the risk of incident diabetes with rosuvastatin (OR=1.18, 95% CI: 1.04-1.33) might be higher than with other statins, although the overall test for heterogeneity among statins was not statistically significant [46]. The second one found that statins as a drug class had no significant impact on insulin sensitivity (IS) as compared with placebo [54]. However, there were variations by statin molecules: pravastatin was found to significantly improved IS while simvastatin significantly worsened it.

Another meta-analysis reported that atorvastatin was associated with the greatest risk of adverse events (myalgia, elevated liver function tests, creatine phosphokinase) and fluvastatin with the least risk [37]. However, the global risk of serious adverse events was low (Number Need to Harm (NNH)=7428 for rhabdomyolisis).

Pharmacoepidemiology

The manufacturer of rosuvastatin (Astra Zeneca) set up an ambitious pharmacoepidemiological programme comparing rosuvastatin with other marketed statins [55]. This programme was designed and run by an independent third party. In this large sample (≅200 000 person-years), no significant difference in the risk of myopathy, rhabdomyolysis, acute liver injury or acute renal failure was seen between rosuvastatin and other statins [41, 56, 57]. This programme also allowed indirectly to have rates of AEs for the other statins. The incidence rates for myopathy, rhabdomyolysis, acute renal failure and acute liver injury were 0.42, 0.14, 4.36 and 1.13 per 10 000 person-years, respectively, for statins other than rosuvastatin [41].

A study carried out in primary care setting over a 6 year period and including 2 004 692 patients aged 30-84 years of whom 225 992 (10.7%) were new users of statins reported an apparent decreased risk of colon cancer in men prescribed pravastatin and an increased risk in men prescribed rosuvastatin [50]. It was unclear if such findings represented a genuine association or were due to chance, given the large number of outcomes under consideration in this study. In the same study, other potential adverse events associated to statins were investigated [50]. Adverse effects tended to be similar across the types of statins for most outcomes except for liver dysfunction, where the highest risks were associated with fluvastatin.

In conclusion, there is to date few, and sometimes contradictory, evidence of a safety difference in the utilization of various statins. The risk profile of statins is overall good. However, the potentially raised diabetes risk, particularly with rosuvastatin, should be taken into account when statin therapy is begun for primary prevention in patients with low cardiovascular risk [46].

3.2.4 Conclusion

We found no clear cut evidence of a differential toxicity among the various statin molecules. Such variations in drug toxicity were plausible given molecular specificities. First, some molecules are hydrophilic (rosuvastatin, pravastatin) and the others are more lipophilic. The more lipophilic statins tend to achieve higher levels of exposure in non-hepatic tissues, while the hydrophilic statins tend to be more hepatoselective. High hepatoselectivity is thought to translate into reduced risk of adverse effects [58]. Second, some statins are predominantly metabolized by the cytochrom 3A4 (an isoenzyme of cytochrom P450), such as simvastatin and atorvastatin. Subsequently, drugs inhibiting that isoenzyme will increase the concentration and toxicity of statins. Pravastatin and fluvastatin are not metabolized by any isoenzyme, and rosuvastatin is metabolized by another one (CYP2C9). A table of inducers and inhibitors of those isoenzymes is presented in Annex [59]. For instance, the risk of rhabdomyolysis increases with the concomitant use of ciclosporin or fibrates. Third, some categories of patients might be more at risk of AEs. Patients with renal impairment, hypothyroidism, serious debility, or those who are older than 80 years are more susceptible than others to myopathy.

The mechanisms by which statins cause myopathy and rhabdomyolysis is not precisely known, but this effect is dose-dependent and molecule-specific [1, 53]. However, the occurrence of AEs is not related to the cholesterol-lowering effect of a particular statin, as the case of cerivastatin showed it.

3.3 BUDGETARY CONSIDERATIONS

In view of the results in sections 3.1.3 and 3.2.3, recommending that patients use primarily simvastatin and pravastatin appears to be a reasonable strategy which respects the right of patients to access the best possible care.

In this section, simulations to have a better overview of how changes in prescription patterns impact on total statin expenditure are presented. Two different analysis reflecting two different policies are presented hereafter. Firstly, using INAMI/RIZIV aggregated data we simulated changes on use of different molecules for all users of statins for the period between 2006and 2009. This scenario is set based on the Norwegian experience, in which all users from the most expensive statin were switched to the least expensive alternatives. Secondly, we consider the impact of starting *new treatments* with the least expensive statins in at least 8 out of 10 patients (following recommendations included in the NCPS 2009 agreement). As recent data on new users is not available for 2009, we used the most recent data where we can identify this information. Thus an overview of the possible impact of the NCPS recommendations was done using data from the EPS for year 2006 (see details on data on section 2.2.3). For both analyses, the least expensive statins are those defined in the NCPS 2009 agreement: simvastatin and pravastatin.

3.3.1 Scenarios hypothesis

The following cost simulations are based on the "average expenditures" made by patients for each statin type. The general idea behind this hypothesis is to consider that patients on each molecule are correctly treated, thus that the cost per patient and per statin can be maintained as they are switched from the less to the more expensive molecules. Hereafter we describe in detail the different steps used for our simulations.

3.3.1.1 Simulations using aggregated INAMI/RIZIV data

The departure point for all scenarios is the proportion of patients using the least expensive molecules for each year. In 2006, 2007 and 2008 approximately 60% of all users used either simvastatine or pravastatine (see more details in section 2.2.1). As the NCPS 2009 agreement advises to prescribe either simvastatin or pravastatatin, the average cost of treatment for the less expensive statins is calculated as the sum of expenditures on simvastatin *(s)* and pravastatin*(p)* divided by the number of users (AC_y^{LC})'..

(1) $$AC_y^{LC} = \frac{E_y^p + E_y^s}{N_y^p + N_y^s}$$

E corresponds to total expenditures and *N* the number of users per year *(y)* and per molecule *(*simvastatin *(s)* and pravastatin*(p))*. For all other molecules, *(m)* average cost of treatment was calculated separately.

We then calculated the number of patients switched to the least expensive alternatives. Our departure point is the actual proportion of patients using the least costly alternative *(S)*.

(2) $$S = \frac{N^S + N^P}{\sum_{A,F,R} N^m}$$

From this point, we increased the percentage of patients using the least expensive alternative by Cs (consequently, decreasing in the same percentage the number of patients using the more expensive alternatives). The new total expenditure from switching patients to the least costly expensive was calculated per year as follows:

(3) $$TE = S*(1-C_s)*\sum_{A,F,R} AC^m * N^m + S*(1+C_S)*AC^{LC}*\sum_{A,F,R} N^m + \sum_{S,P} E^m$$	Estimated Expenditure for patients on more expensive molecule + Estimated Expenditure for patients switching to least expensive molecules + Expenditure of least costly molecules (baseline)

3.3.1.2 Simulations using extrapolated EPS data: for new and old user for year 2006

As for the previous scenario, the departure point is the baseline prescription of each type of statins for each year. However, in this case we used data from the EPS as it allows us to separate prescriptions for the new users of statins. This allows simulating new level of expenditures when new users of statins are prescribed simvastatin or pravastatin. The first step in our analysis was to set, according to each user type[ff] the average cost of treatment for the different molecules. This was calculated based on patient consumption as follows:

$$AC_t^m = \frac{\sum_m p_{ij_t}^m * q_{ij_t}^m}{N_t^m} \quad (4)$$

Where the subscript *m* designates the molecules and *t* whether the person is a new or an old statin user

p_{ij} = average price per dosage i and box size j

q_{ij} = number of prescription per dosage i and box size j

N^m = number of patients using the molecule

The average cost of treatment for the least expensive alternative was also calculated as in the previous section (including the sum of expenditures of simvastatin and pravastatin divided by the total number of users of both molecules).

The new total expenditures from switching patients to the least costly alternatives was thus calculated using equation (4).

3.3.2 Results

3.3.2.1 Simulations using aggregated INAMI/RIZIV data

In 2006, the average cost of a treatment varied from 120 euros for simvastine to 386 euros for atorvastatin. Following the 2008 law modification (so called the "Kiwi light"), the average cost of treatment with simvastatin dropped to 72 euros per year. For all other molecules, average cost of treatment was stable.

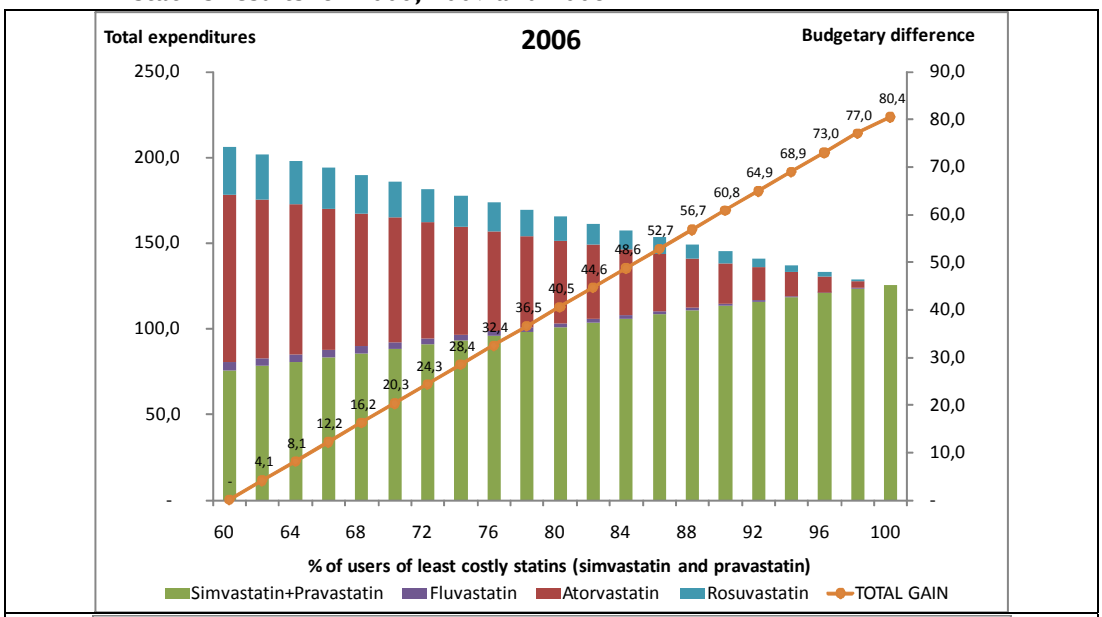
Table 33: Average cost of a yearly treatment per molecule (in euros; based on aggregated data)

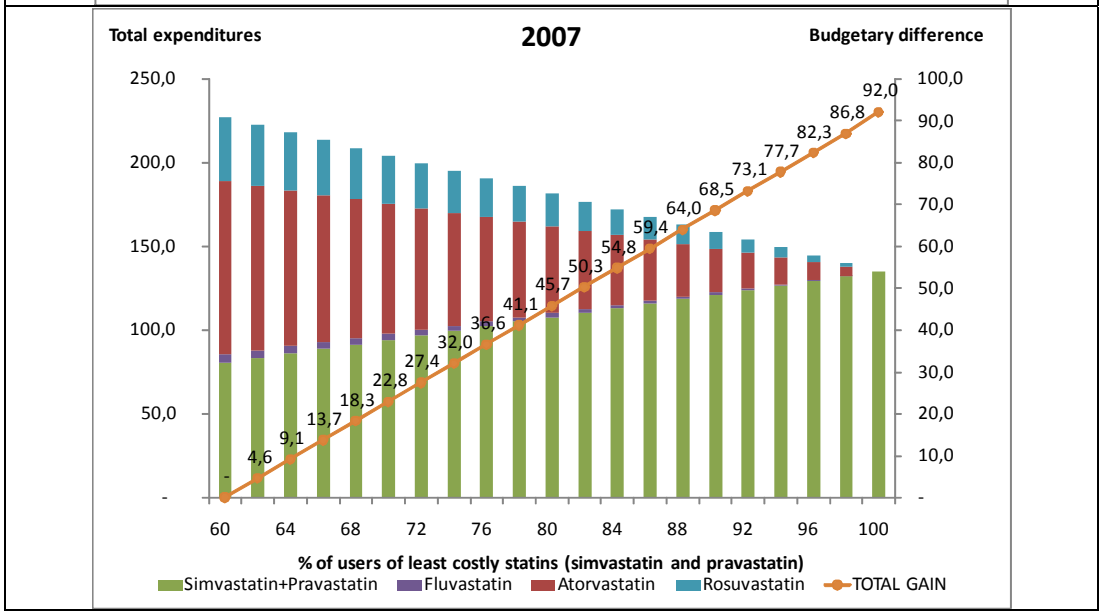
In Euros	**2006**	**2007**	**2008**	**2009**
SIMVASTATIN	120	119	72	70
PRAVASTATIN	169	163	156	147
Least expensive average	***130***	***127***	***86***	***82***
FLUVASTATIN	239	240	247	232
ATORVASTATIN	386	397	406	416
ROSUVASTATIN	249	258	264	276

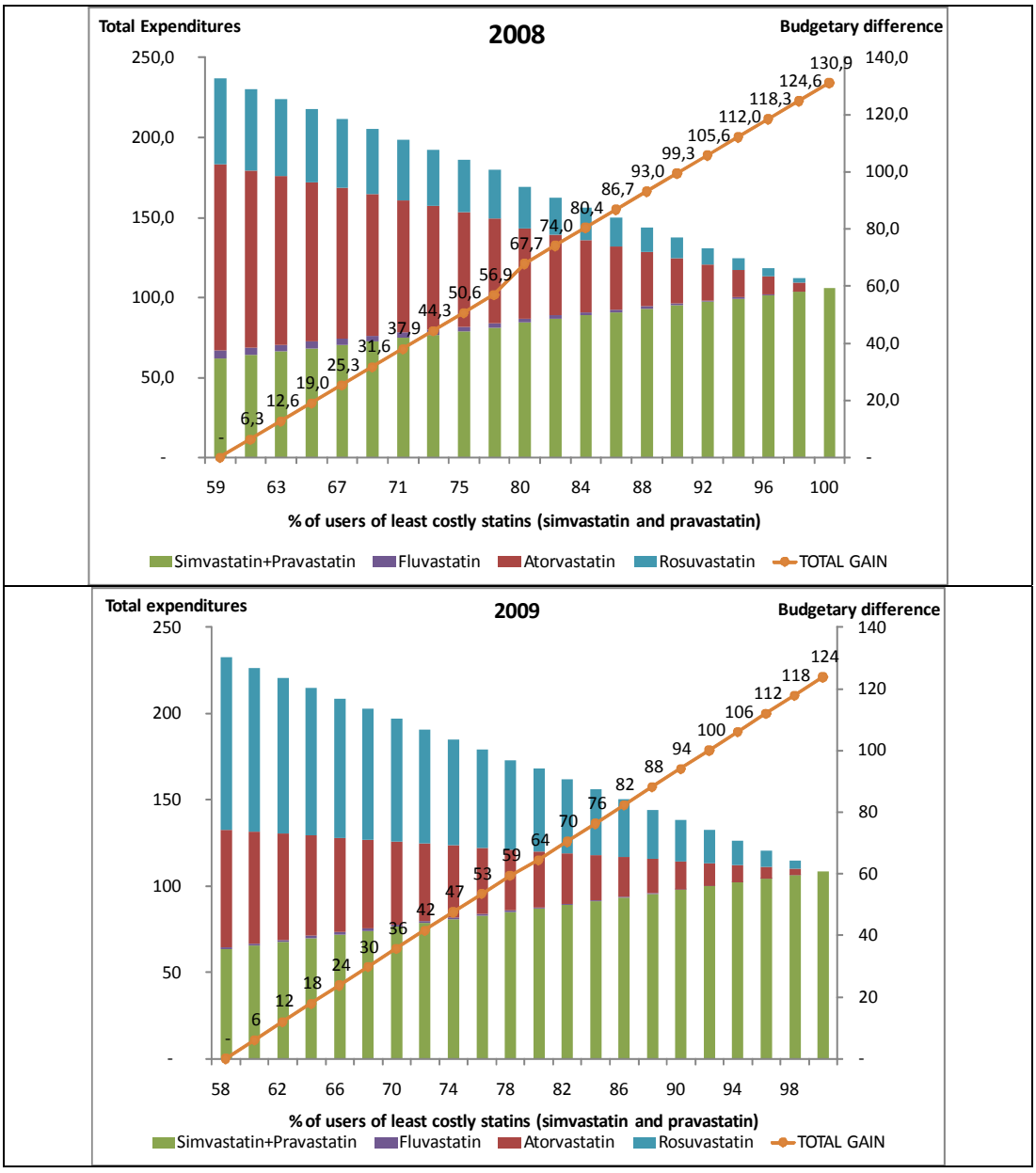
[ff] New users were previously defined as those purchasing at least 1 packaging of statin with no statin delivery in the previous year. Old users include all other users of statins whom received a prescription in the previous year (all users except new users).

In 2006, increasing the percentage of users of least expensive molecules from 60% to 70% and 80% would have reduced total expenditures by 20,3 and 40,5 millions euros respectively (see Figure 19). For 2007, increasing the percentage of users of simvastatine and pravastatine to 70% and 80% would have reduced total expenditures by 28,8 and 45,7 millions euros respectively. Simulations for 2008 and 2009 showed an even more spectacular reduction in expenditures (up to 56,9 millions euros and 64,4 millions euros respectively) when the percentage of users of less expensive statins is increased to 80%. This is due to the fact that in 2008 the price for simvastatine and pravastatine was furthered reduced.

Figure 19: Budgetary differences from switching patients to least expensive statins results for 2006, 2007 and 2008







3.3.2.2 *Simulations using extrapolated EPS data: for new and old user for 2006*

Using data from the EPS, the following simulations intend to provide estimates for new users and users of statins. Validation of our estimates was carried out by comparing the total expenditures for 2006 provided by the INAMI/RIZIV with the results obtained for our sample (see the appendix for detailed data)

3.3.2.3 *Simulations using extrapolated EPS data: for new and old user for 2006*

Average expenditures per patient and per molecule and per users type are presented in the following table.

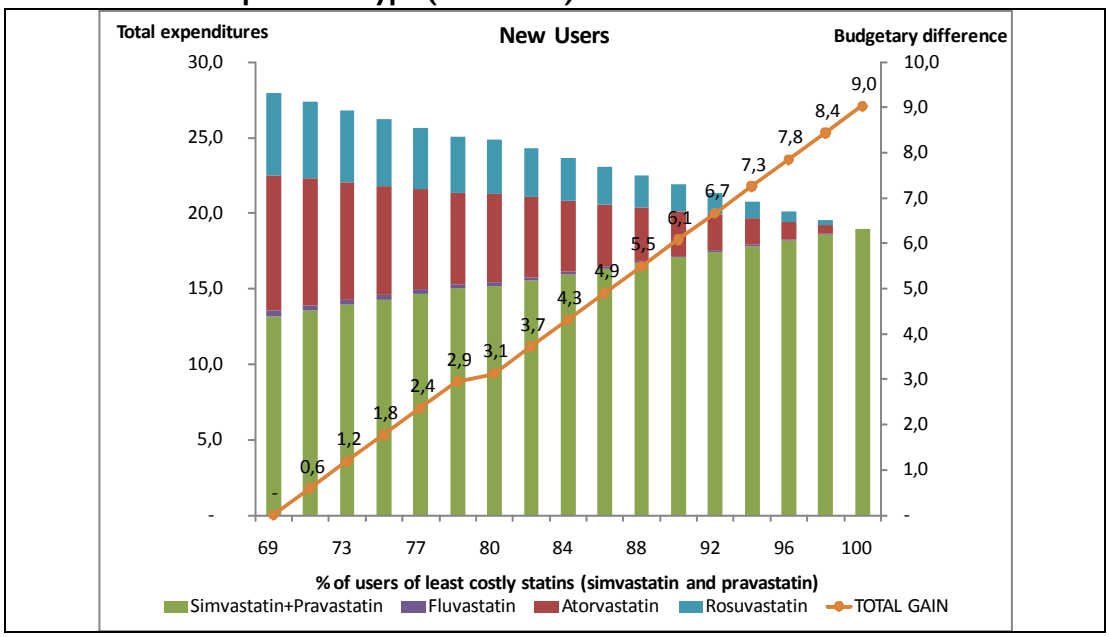
Table 34: Average cost per molecule and users type in 2006

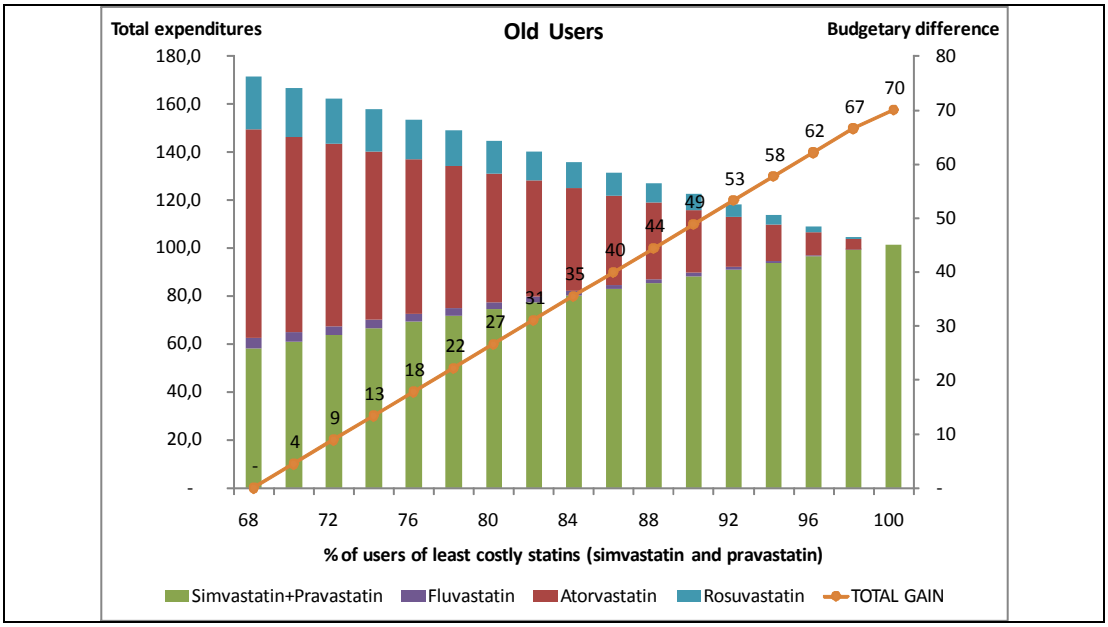
	2006		
	New	Old	All*
SIMVASTATIN	81	132	118
PRAVASTATIN	92	153	140
Least costly molecules	**83**	**137**	**122**
FLUVASTATIN	153	237	228
ATORVASTATIN	248	403	380
ROSUVASTATIN	174	271	244

* No differences between users type are calculated

In 2006, the percentage of new users in primary and secondary prevention receiving simvastatin or pravastatin was respectively of 69.8% and 79.8%. Figure 20 presents the simulations of total statin expenditures by users' type. Simulations for new statin users include both those receiving treatment in primary and secondary prevention. Increasing the percentage of new users receiving simvastatin (or pravastatine) from 69 to 80% (as required by the NCPS 2009 agreement) could have reduced expenditures on statins by 3,1 millions euro (see Figure 20).

Figure 20: Statins expenditures when increasing use of least costly molecules for 2006 per users type (in millions)





This saving seems rather small when comparing the possible savings of switching also other statin users to the less expensive alternatives. Indeed, increasing prescription of simvastatin among old users from 68% to 80% could have provided additional savings of 31 millions euros for that year.

3.3.2.4 *Discussion*

The present economic environment has increased pressure to improve prescription patterns that can reduce cost for both patients and the third-party payer while maintaining the same health benefits. This section presented analysis from a *cost perspective* for changes in prescription of statins. Statins are the most often use group of drugs in Belgium in terms of number of patients. Between 2006 and 2008, atorvastatin was ranked first in the ranking of total expenditures for the INAMI/RIZIV (on active ingredients in ambulatory care). During this period, other statins were also included in this ranking, with simvastatin occupying the 4th , 3rd and 13th place in 2006, 2007 and 2008 respectively. Moreover, with the increasing use of rosuvastatin, it passed from being ranked in the 19th place in 2006 to the 8th place in 2008 and 4th position in 2009.

The simulations provided in this section highlight the large savings in drug cost from increasing the percentage of users receiving the less expensive statins. However, these results should be interpreted in a larger context in order to insure to respect the often delicate balance between economic gains and changes in the health status of patients. Moreover, these results concern only savings in drug cost, thus we do not consider other cost relating to treatment such as physicians' visits, patients' follows-up or changes in hospitalization costs. However, an important issue when considering effectiveness and cost-effectiveness of different statin molecules is the lack of RCT as well as of appropriate cost-effectiveness studies [60]. It is also noteworthy that the general context is also evolving rapidly making any cost simulation rapidly out-dated. Noteworthy, atorvastatin will be off-patent in November 2011 and by that time the recommendation of prioritizing simvastatin/pravastatin will also need to be adapted.

Key points

Comparative effectiveness of statins

- **There is currently no clear-cut evidence of a differential risk/benefit balance between atorvastatin and simvastatin/pravastatin when used at equivalent therapeutic doses. Evidence is too scarce to date for ascertaining the risk/benefit profile of rosuvastatin.**
- **Ensuring that statin users primarily use simvastatin/pravastatin would allow important savings of public money**

4 GENERAL DISCUSSION

4.1 INCREASING NUMBERS

Because CVD is common and statins are widely dispensed, statins are among the most frequently prescribed drugs. In 2009, around 20% of Belgian adults ≥ 35 years utilized some statin, and atorvastatin and rosuvastatin occupied respectively the 1st and 4th position in the top list of highest public expenditures per drug. This emphasizes the need for a rational statin utilization.

Most of the utilization rise related to primary prevention, for various reasons. The administrative simplification occurred in mid-2004 and the further price reduction of simvastatin/pravastatin certainly played a role, but this doesn't explain the concurrent rise of rosuvastatin and atorvastatin users. Lifestyle (roughly 83% of the Belgians have a total cholesterol level higher than the recommended limits[61]), secular population ageing, and a general tendency towards medicalization of prevention also form a triggering combination. It should be emphasized that lifestyle interventions can also be effective in reducing CVD morbidity and mortality, and that there is an urgent need of implementing comprehensive strategies that would allow such changes. Finally, the current cut-off for reimbursing statins in Belgium in primary prevention (SCORE 10-years CVD mortality risk≥5%) might be interpreted too narrowly as a threshold for statin use when it is in reality a clinical indicator to adapt the CVD management to individual needs. For instance, 88.0 % of males ≥63 years have a high cholesterol concentration [61]. The SCORE is ≥5% for virtually all this sub-population. Thus 88% of males ≥63 years would be eligible for statin prevention. This only group represents 761 000 beneficiaries. Thirty-six percents of the adult population ≥35 years suffer from both hypertension and hypercholesteremia. Among those, 19.6% have a SCORE ≥5% [61]. As a result, more than 7% of adults ≥35 years could receive statins. This amounts to 21% of people 55-64 years, and to 63% of people 65-74 years. These figures clearly show that a management of CVD risk based essentially on drug use would result in a high societal burden. The cost-effectiveness of such strategy in our country has been evaluated pretty high in comparison to other strategies such as low-dose aspirin or smoking cessation [60]. Even when using the less costly molecule on the market at the time, the authors found that the incremental cost per life-year gained was 29 173 euros 87 022 euros in a male high-risk group aged 60 and a male moderate-risk aged 50, respectively. Very large beneficiary groups and high cost-effectiveness will result in an ever increasing proportion of health expenditures being dedicated to statin prescriptions.

It is also important to recall that the individual absolute clinical benefit of a statin prevention is related to an individual's absolute risk of CVD events. The decision whether to initiate statin therapy should be made after an informed discussion between the responsible clinician and the individual about the risks and benefits of statin treatment, and taking into account additional factors such as comorbidities and life expectancy. Also, the way of presenting to the patient the expected risk reduction (i.e. absolute or relative measures) influences his/her decision-making of beginning or not the statin [62]. Presenting the benefits of taking statins as a relative risk reduction increases the likelihood of people accepting treatment compared to presenting absolute summary statistics, independent of the relative importance they attach to the consequences. Natural frequencies may be the most suitable summary statistic for presenting treatment effects, based on self-reported preference, understanding of and satisfaction with the information, and confidence in the decision [62].

4.2 SECONDARY PREVENTION

At the same time, a statin therapy was initialized in only 52.4% of patients hospitalized for a CVD in 2006 (45.5% for 2003-2006). This proportion was very much dependent of the age group and the specific pathology considered. In 96 % of adults aged 50-59 hospitalized for an acute myocardial infarction in 2006 a statin therapy was started, while this proportion was 58% for an ischemic cerebrovascular event in the same age group. Such sub-optimal coverage of high-risk patients, particularly after a stroke, is consistent with what is observed in other European countries [63].

It is important to define innovative strategies to improve the coverage of such patients. Noteworthy, the utilization of statin-based secondary therapy after a CVD event has increased greatly between 2003 and 2006, and the coverage rate for all such events is plausibly better nowadays.

4.3 COMPARATIVE EFFICACY OF STATINS

Although the efficacy in lowering LDL-C varies by statin molecules, we found no clear-cut evidence of a differential risk/benefit balance between atorvastatin and simvastatin/pravastatin when used at equivalent therapeutic doses. Direct evidence was scarce because head-to-head trials were primarily designed to assess the benefits of an intensive therapy versus usual doses of statin, but other meta-analyses based on indirect methods reached the same conclusion as ours. The absolute benefit relates mainly to an individual's absolute risk of CVD events and to the absolute reduction in LDL-C achieved. Thus, what matters is the therapeutic target in terms of LDL-C concentration whatever the specific molecule used. There are indeed indications that simvastatin/pravastatin at higher doses could yield the same clinical benefit as atorvastatin/rosuvastatin. For instance, Nicholls et al. have reported that doubling the dose of each statin was accompanied by a 4% to 7% greater degree of lowering of all atherogenic lipids [64]. There was also no evidence of a different safety profile among statines [54]. However, the occurrence of adverse events is also dose-dependent. Worth mentioning, evidence for ascertaining the risk/benefit profile of rosuvastatin was scarce to date. Therefore the current recommendations by INAMI/RIZI to use primarily simvastatin or pravastatin in the majority of patients in primary and secondary prevention are scientifically sound.

4.4 COST CONTAINMENT

A number of measures were taken to curve the rising public expenses on statins while maintaining an equal access.

The facilitation of reimbursement conditions for simvastatin and pravastatin in 2004 resulted in an increase of users but had a moderate effect on the numbers of patients using other statins. The number of rosuvastatin users has also greatly increased since its marketing in 2003. In spite of the lower price and facilitated access to simvastatin and pravastatin, these 2 molecules represented still only 51.6% of DDD intake in 2009 (66.5% of users in 2003-2006). Surprisingly, the utilization of these 2 least-expensive molecules was more important in secondary prevention. For instance, in 2003-2006, 78.4% of patients in secondary prevention used simvastatin/pravastatin while this proportion was only 65.4% in primary prevention. This was a counterintuitive finding, as one would have expected that more potent molecules be utilized more often in patients with an history of CVD.

In 2008, a system of public tender was set up. It resulted in the price reduction of simvastatin, with no obvious effect however on the utilization of more expensive molecules.

In 2009, the INAMI/RIZIV recommended that simvastatin/pravastatin be used in 80% of new treatments, and extended its recommendation in 2010 to all patients beginning primary prevention, including diabetic patients, and to the majority of patients beginning a secondary prevention. Given the time lag in collection and analysis of routine data, it is too early to evaluate the impact of such strategy on prescription patterns.

4.5 STATIN SWITCH

Noteworthy, a more important budgetary impact would be obtained if all statin users, i.e. not only new users, were shifted towards simvastatin/pravastatin. This seems a reasonable scenario provided that the level of CVD protection is maintained constant for each patient and if switching back is possible. Such global shift has been implemented in Norway in 2005 [65] and Finland in 2006 [66], but also in Austria, Denmark and Sweden. Between 40% and 60% of patients using atorvastatin or rosuvastatin switched to a less expensive statins in Norway and Finland. However, the policy line was quite strict (expensive statins can be reimbursed only when less expensive ones are proved to be ineffective or not tolerated) and unlikely to be adapted to our national context. Moreover, given the relatively short treatment duration in Belgium (50% patients stop their treatment within a 4 year period), the proportion of patients who begun a statin regimen before the 2009 and 2010 recommendations will be washed out in the mid-term.

4.6 ADHERENCE

Among new users in 2003-2006 only 59% were regular users, and this proportion was similar for all statins. We identified a number of factors related to a low treatment adherence such as being younger than 50 years, being a male, following a primary prevention or being prescribed by a GP. A history of cardiovascular disease predicted a better adherence to statins. Similarly, a diagnosis of diabetes was associated with better adherence. This is very consistent with international results [67]. However, even in patients in secondary prevention, the proportion of adherents did not go over 75%, a finding also in line with other European countries [63]. This is a matter of concerns as non-adherence is associated with a marked increase in CVD and hospitalization rates [14, 15]. Higher adherence rates could dramatically improve patient outcomes while reducing overall health care spending [68,69]. Innovative ways to improve adherence are crucially needed.

4.7 SAFETY

Although statin therapy were reportedly well tolerated and relatively safe in trials, adverse events might be more common in clinical practice for several reasons. First, trial participants are generally younger and healthier and they are more closely followed than patients in usual clinical practice. In addition, these trials excluded over half of all screened patients because of co-morbidities (e.g., advanced age, renal failure, alcohol abuse, hepatic failure) or use of concomitant medications (e.g., other lipid lowering drugs, inhibitors of the cytochrome P450 system[gg]), which may increase the risk of adverse events [71]. Second, some of these trials only enrolled patients after they had successfully completed a run-in period without complication. Third, because of a relatively short time frame, these randomized trials may fail to detect retarded adverse event as follow-up duration is relatively short. For instance, no excess risk of cancer due to statin utilization has been detected. However, on average the follow-up of participants has not been longer than 4.1 (1.9-5.3) years [7], quite a short period to assess cancer incidence. Longer follow-up would be helpful to determine whether new cancer events occur with time. This also underscores the importance of postmarketing surveillance studies to track complication rates and drug-discontinuation rates in usual clinical practice.

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gg Statins that are metabolized predominantly by the cytochrome P-450 system can interact with other drugs, some of which involve commonly prescribed drugs [1]. Serum concentration of atorvastatin and simvastatin increases if used concomitantly with blockers of cytochrome P-3A4, while fluvastatine concentration increase with inhibitors of CYP2C9. Statins also vary in their propensity to cause drug interactions through other mechanisms (eg, by blocking organic anion transporter peptides) [70]. The genetic polymorphisms within these systems also affect drug disposition and the likelihood of interactions.

4.8 UNRESOLVED ISSUES

Theoretically, the lower the LDL-C concentration, the lower the risk of CVD would be. However, the association between lowering LDL-C and reduction of CVD risk has been tested for lowering LDL-C by up to 1.89 mmol/l (73.1 mg/dL). Thus, the clinical benefit of lowering LDL-C more than that amount is unknown, the vast majority of the studies reporting on a LDL-C reduction in the range 0.51-1.42 mmol/l (20-55 mg/dL) [28].

Another important consideration relates to treatment duration as the effect size increases dramatically after the 1st year of treatment [2 3]. Noteworthy, most of the systematic review excluded trials with a follow-up ≤1 year[2, 3, 7, 8] (exclusion ≤2 years for [3]). For instance, in the 24 trials where a mean reduction of 1 mmol/L of LDL-C was observed, the reduction (%) in risk of ischaemic heart disease events[hh] was 19%, 31% and 30% after 1-2 years, 3-5 years and ≥ 6 years in trial at time of the event, respectively [2]. The efficacy of therapy ≤1 year is unknown, but likely to be lower than the pooled estimates usually presented. The persistence of the protective effect once the treatment is stopped is also an aspect which is today not documented although plausible.

Effect modification by factors such as age, diabetes or sex has not been demonstrated [7]. It is thus not possible to define today one group of people who would benefit most from long term statin use. However, identification of such target groups is important as statin intervention can present large benefits when targeting high risk individuals [72]. Identification of target groups might be done by revising the criteria for starting a statin treatment or by the identification in the future of new biological/genetic/behavioural risk factors.

Changes in lifestyle and diet may also be a cost-effective alternative to prevent CVD. There is an urgent need of testing rigorously comprehensive strategies that would allow such changes in our society. There is also a crucial need to redirect some of the public money towards health promotion.

hh Ischaemic Heart Disease death and non fatal myocardial infarction

5 APPENDICES

5.1 DATA SOURCES AND DEFINITIONS

IMA-AIM DATA (PHARMANET, HEALTH CARE DATA, POPULATION DATA)

IMA-AIM (Intermutualistisch Agentschap (IMA) – Agence Intermutualiste (AIM)) is a non-profit institution with all Belgian sickness funds as its members.

Sickness funds have individual patient data on patient characteristics, reimbursed services and pharmaceuticals delivered by pharmacists, at the detailed level of the service or the prescription. This information can be found in three databases:

- "Pharmanet" is the database specific to pharmaceutical products delivered in community pharmacies (not in hospital).
- The database "Health Care" contains all other reimbursed acts and pharmaceutical products.
- The "Population" database contains information on the demographic and socioeconomic profile of each of the sickness funds members.

These data are collected and made available by the IMA-AIM (Intermutualistic Agency).

HOSPITAL CLINICAL DATA (HCD)

The registration of Hospital Clinical Data (HCD, MKG = 'Minimale Klinische Gegevens / RCM = Résumé Clinique Minimum) is mandatory for every hospital in Belgium since 1991. This means that for each hospitalized patient, information such as date of birth, sex, postal code of domicile and other information such as length of hospital stay, hospital ward and bed type occupation etc., has to be recorded, along with ICD-9-CM (International classification of diseases, version 9, clinical modification (WHO)) encoding of relevant diagnoses as well as diagnostic and therapeutic procedures performed. Diagnosis and procedure codes are collected per attended hospital department, each coding for one primary and several secondary diagnoses. After stripping of direct patient-identifying information, records have to be sent biannually to the federal Ministry of Health (MoH - Federale Overheidsdienst Volksgezondheid, Veiligheid van de Voedselketen en Leefmilieu / Service Public Fédéral Santé publique, Sécurité de la Chaîne alimentaire et Environnement). Here all department registrations are concatenated with assignment of the principal diagnosis of the whole stay, determinant for the APrDRG-grouper software (All Patient refined Diagnostic Groups, version 15.0).

Since 1995 the HCD records are afterwards linked to the Hospital Billing Data (HBD - MFG = 'Minimale Financiële Gegevens / RFM = Résumé Financier Minimum'), yearly transmitted by the national health insurance companies to the NIHDI and assembling all NIHDI remunerations for each hospital stay. HCD-HBD linkage is performed by a legally instituted 'Technical Cell' and requires separately sent matching tables containing for each identifiable hospital stay an unique patient pseudonym created by two separately executed hashings: the first one by the hospital or national health insurance companies respectively and the second one by an appointed security advisor of the MOH. Linkage process takes about 2 years to completion and full validation. Linkage percentages increased over the years and exceed nowadays 95% overall (Expressed as the fraction of the number of stays in HBD data as denominator; staycounts in HBD are always less than staycounts in HCD data since the latter cover all hospital stays, whether or not they were at the expense of the NIHDI.). This means that the relationship between treated pathology and the costs to the health care system can be studied for 'in patient' hospital admissions.

The advantage of the coupled HCD-HBD data is that registration is obligatory for all hospitals (HCD) and all national health insurance companies (HBD).

5.2 USE OF FIBRATES AND EZETIMIB WITH SIMVASTATIN

Co-treatment by fibrates and etizimibe were not analyzed because the delivery volume was relatively modest (4.4 %).

Table 35: Percentage of patients with statines who also had fibrates (ambulatory sector) (EPS)

Fibrate use	Year						
Frequency Col Pct	2002	2003	2004	2005	2006	2007	Total
No	15505 96.44	18079 97.04	23226 91.01	31548 96.54	34452 96.47	38418 95.99	161228 95.60
Yes	572 3.56	552 2.96	2293 8.99	1130 3.46	1262 3.53	1604 4.01	7413 4.40
Total	16077	18631	25519	32678	35714	40022	168641

Table 36: Total number of patients per year and fibrate type (ambulatory sector) (Pharmanet)

	2004	2005	2006	2007	2008
C10AB02 BEZAFIBRATE	4749	2 104	2 098	1 896	1 728
C10AB05 FENOFIBRATE	111260	71 458	90 345	94 902	109 669
C10AB08 CIPROFIBRATE	43052	17 848	16 399	14 968	14 105
C10AC01 COLESTYRAMINE	2703	2 444	2 520	2 552	2 888
C10AC02 COLESTIPOL	219	135	113	96	105
C10AD06 ACIPIMOX	341	227	208	204	212
C10AX09 EZETIMIB	5131	13 872	19 992	26 410	29 637
C10BA02 SIMVASTATINE with EZETIMIB				2 384	12 301

Table 37: Total number of DDDs per year and fibrate type (ambulatory sector)

	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008
CLOFIBRATE	26.0	19.8	14.5	7.4	0.0							
BEZAFIBRATE	3440.1	3172.3	2512.9	1993.8	1659.6	1391.7	1184.6	637.5	298.2	328.9	293.1	268.6
FENOFIBRATE	42508.7	42843.2	40181.1	37812.3	39528.0	49669.3	50853.9	34375.0	22194.3	28563.4	29470.8	30438.5
CIPROFIBRATE	28424.3	27706.2	24805.4	21994.8	19878.6	17839.8	15855.9	9053.8	4425.7	4234.1	3928.6	3722.9
COLESTYRAMINE	454.9	397.2	326.1	294.2	285.5	272.0	272.8	234.8	204.5	206.0	205.7	228.6
COLESTIPOL	72.7	57.3	43.2	38.0	33.9	32.8	29.5	20.4	12.9	10.4	9.4	10.1
ACIPIMOX	383.7	268.7	181.8	150.0	136.4	120.8	114.6	76.4	57.5	54.6	51.6	52.1
EZETIMIB								797.2	3513.8	5341.6	7334.8	8622.8
SIMVASTATINE with EZETIMIB											263.0	2985.5
TOTAL	75310.4	74464.7	68064.9	62290.7	61521.9	69326.4	68311.4	45195.2	30707.0	38739.0	41556.9	46329.1

5.3 USE OF STATIN BY SETTING (AMBULATORY VS HOSPITAL)

Table 38: Percentage of hospital volume in total volume (DDDs) per year and statin type

Only the ambulatory sector is considered because of the non-consistency of the hospital dispensation records in the IMA database (EPS source) and the relative volume of statins prescribed in hospital setting was negligible (< 2% of the delivery, source INAMI).

HOSPITAL	2000	2001	2002	2003	2004	2005	2006	2007	2008
C10AA01 Simvastatin	206444	133246	158709	275290	574521	941821	1236951	1443935	1695285
C10AA03 Pravastatin	95343	72036	111826	143597	172945	221103	281373	239880	258279
C10AA04 Fluvastatin	19651	13670	15169	34409	45143	42068	37886	35327	34363
C10AA05 Atorvastatin	270194	208885	258852	316419	419174	573356	641274	782586	948516
C10AA06 Cerivastatin	39130	28785						2	
C10AA07 Rosuvastatin				215	51410	109631	331090	261926	348347
TOTAL	632762	458623	546557	771932	1265196	1889984	2530580	2765662	3286798

AMBULATORY	2000	2001	2002	2003	2004	2005	2006	2007	2008
SIMVASTATIN	38 237 569	43 968 425	48 514 519	45 617 430	59 116 238	62 496 238	55 728 675	61 447 282	42 830 116
PRAVASTATIN	23 365 648	29 431 013	36 900 543	41 570 504	42 966 885	29 704 193	20 039 031	19 277 314	19 156 734
FLUVASTATIN	3 029 652	2 303 869	2 634 917	5 765 116	5 978 913	5 478 352	4 952 177	4 827 641	4 783 840
ATORVASTATIN	60 504 246	71 717 702	82 298 002	91 672 371	99 293 273	98 450 947	97 307 404	103 261 560	116 623 700
CERISVASTATIN	5 814 532	7 959 214	464	90					
ROSUVASTATIN				27 411	11 250 045	19 606 994	27 969 601	38 292 381	53 350 819
TOTAL	130 951 648	155 380 223	170 348 446	184 652 923	218 605 354	215 736 725	205 996 887	227 106 179	236 745 208

% Hospital in total volume	2000	2001	2002	2003	2004	2005	2006	2007	2008
SIMVASTATIN	0.54%	0.30%	0.33%	0.60%	0.96%	1.48%	2.17%	2.30%	3.81%
PRAVASTATIN	0.41%	0.24%	0.30%	0.34%	0.40%	0.74%	1.38%	1.23%	1.33%
FLUVASTATIN	0.64%	0.59%	0.57%	0.59%	0.75%	0.76%	0.76%	0.73%	0.71%
ATORVASTATIN	0.44%	0.29%	0.31%	0.34%	0.42%	0.58%	0.65%	0.75%	0.81%
CERISVASTATIN	0.67%	0.36%	0.00%	0.00%					
ROSUVASTATIN				0.78%	0.45%	0.56%	1.17%	0.68%	0.65%
TOTAL	0.48%	0.29%	0.32%	0.42%	0.58%	0.87%	1.21%	1.20%	1.37%

5.4 MARKET EVOLUTION OVER TIME

NUMBER OF TABLETS PER YEAR

The volume is expressed in number of tablets in Figure 21 and Table 39.

Figure 21 : Total number of tablets per year and statin (ambulatory sector)

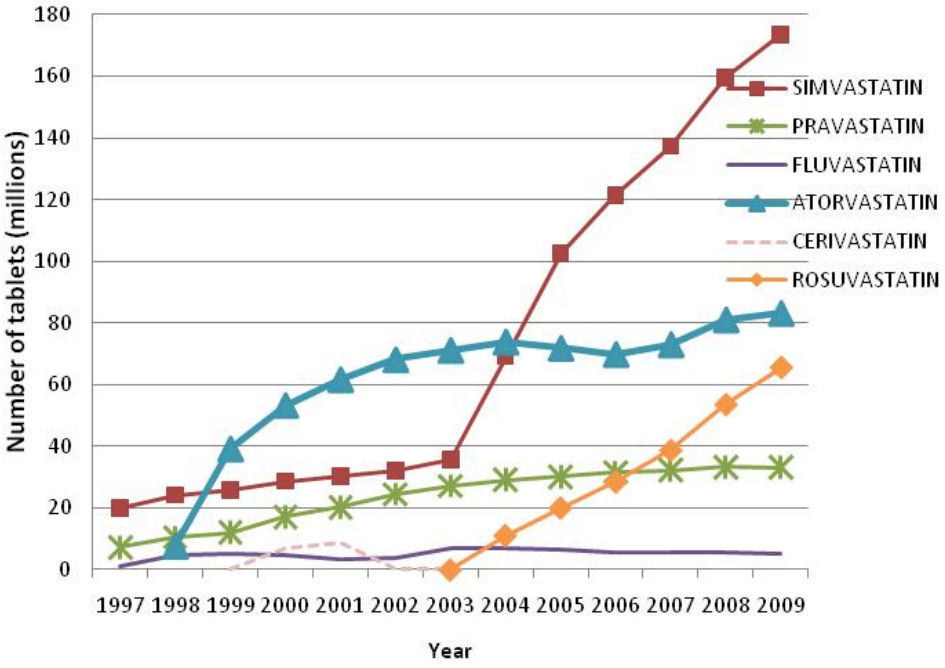


Table 39: Total number of tablets per year and statin type in millions tablets (ambulatory sector)

	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
simvastatin	19.8	24.1	25.8	28.7	30.1	32.0	35.8	69.1	102.6	121.4	137.3	159.5	173.5
pravastatin	7.2	10.5	12.0	17.1	20.2	24.5	27.1	29.0	30.2	31.7	32.2	33.3	33.1
fluvastatin	1.0	4.9	5.3	4.5	3.5	3.7	7.0	7.1	6.4	5.8	5.6	5.5	5.0
atorvastatin		7.6	39.2	53.4	61.7	68.2	71.3	74.0	71.9	69.9	73.1	81.2	83.3
cerisvastatin			0.0	6.9	8.7	0.0	0.0						
rosuvastatin							0.0	11.1	20.0	28.4	38.6	53.4	65.4
Total	**28.0**	**47.1**	**82.3**	**110.5**	**124.3**	**128.4**	**141.1**	**190.2**	**231.1**	**257.2**	**286.9**	**333.0**	**360.4**

VOLUME MEASURES PER SEMESTER

Figure 22 : Total number of DDDs per semester and statin type (ambulatory sector) – 1997 to 2009

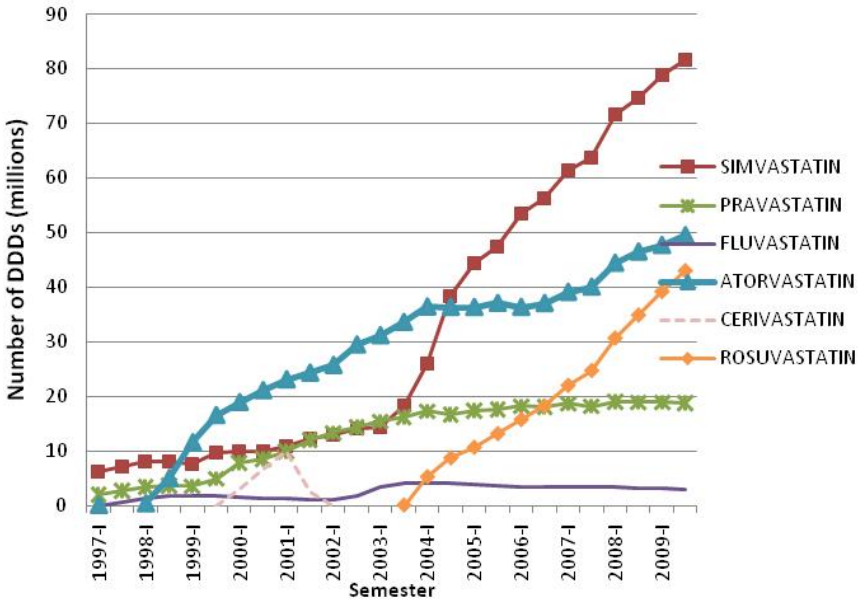


Table 40: Total number of DDDs per semester and statin type in millions DDDs (ambulatory sector) – 1997 to 2009

	1997-I	1997-II	1998-I	1998-II	1999-I	1999-II	2000-I	2000-II	2001-I	2001-II	2002-I	2002-II	2003-I	2003-II	2004-I	2004-II	2005-I	2005-II	2006-I	2006-II	2007-I	2007-II	2008-I	2008-II	2009-I	2009-II
SIMVASTATIN	6.1	7.1	8.0	8.1	7.6	9.6	10.0	9.8	11.0	12.2	13.1	14.0	14.4	18.3	26.0	38.3	44.4	47.5	53.5	56.2	61.5	63.6	71.7	74.7	78.8	81.7
PRAVASTATIN	2.1	2.7	3.4	3.6	3.6	4.9	7.8	8.5	9.9	12.0	13.3	14.4	15.4	16.1	17.3	16.7	17.3	17.6	18.2	18.1	18.7	18.2	19.1	18.9	18.9	18.8
FLUVASTATIN	0.0	0.6	1.4	1.8	1.8	1.8	1.6	1.4	1.2	1.1	1.0	1.9	3.5	4.2	4.2	4.0	3.9	3.7	3.5	3.4	3.4	3.3	3.4	3.3	3.1	3.0
ATORVASTATIN			0.3	5.0	11.5	16.5	18.9	21.1	23.1	24.3	25.7	29.4	31.1	33.6	36.4	36.3	36.3	37.1	36.3	37.0	39.1	40.0	44.4	46.5	47.7	49.5
CERIVASTATIN						0.0	3.0	6.7	9.9	2.5	0.0			0.0												
ROSUVASTATIN														0.0	5.2	8.7	10.6	13.1	15.7	18.2	22.0	24.7	30.6	34.9	39.2	43.0
Total	8.2	10.4	13.1	18.5	24.4	32.8	41.4	47.6	55.1	52.0	53.1	59.8	64.4	72.2	89.1	104.1	112.5	119.0	127.3	133.0	144.6	149.9	169.2	178.3	187.7	196.0

Figure 23 : Total number of DDDs per semester and statin type (ambulatory sector) – Focus on 2003 to 2006

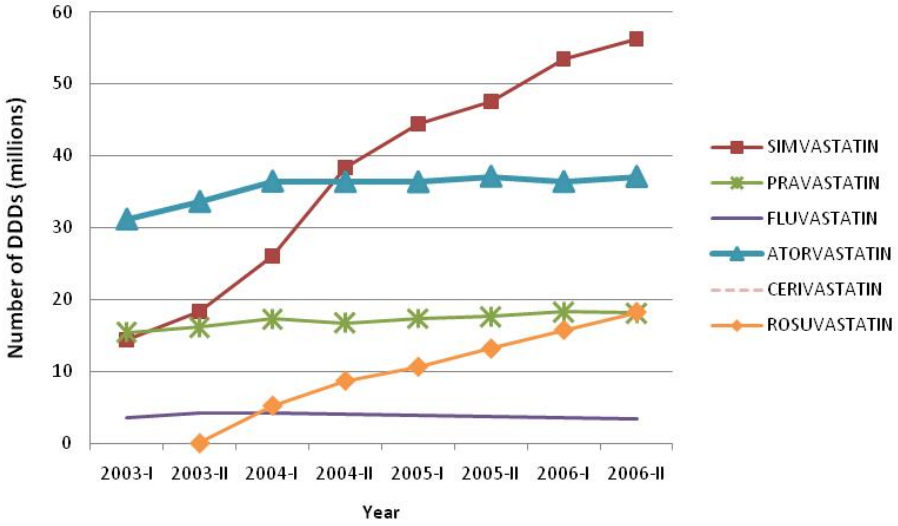
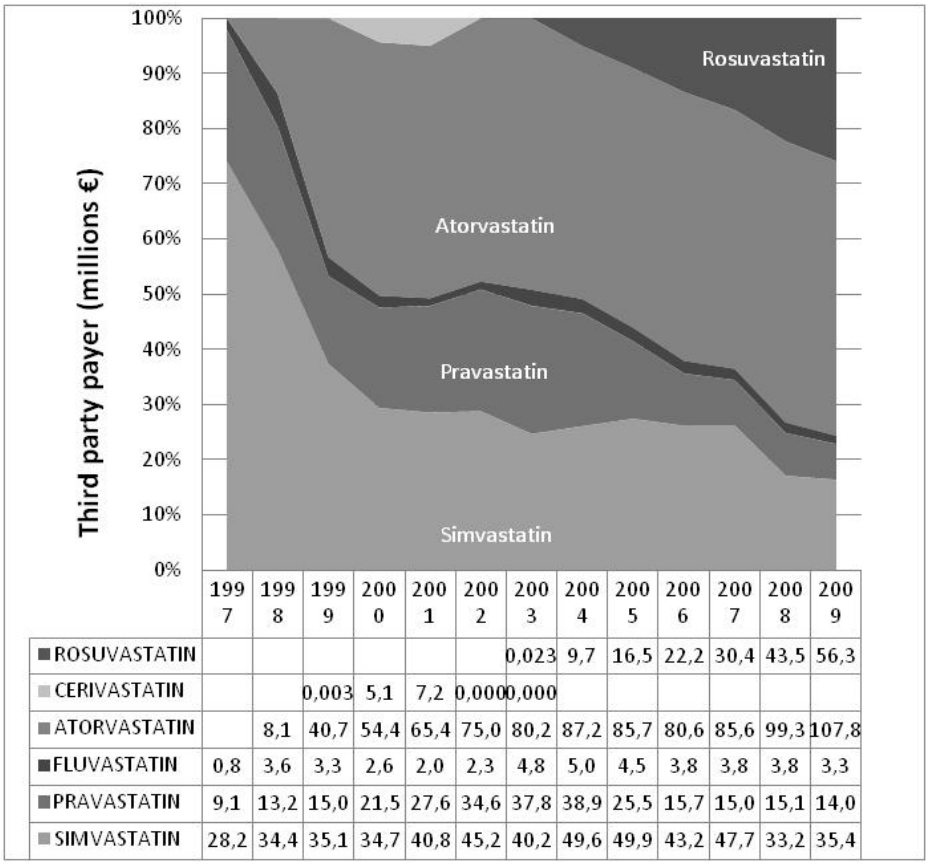


Table 41: Total number of DDDs per semester and statin type in millions DDDs (ambulatory sector) – Focus on 2003 to 2006

	2003-I	2003-II	2004-I	2004-II	2005-I	2005-II	2006-I	2006-II
SIMVASTATIN	14.4	18.3	26.0	38.3	44.4	47.5	53.5	56.2
PRAVASTATIN	15.4	16.1	17.3	16.7	17.3	17.6	18.2	18.1
FLUVASTATIN	3.5	4.2	4.2	4.0	3.9	3.7	3.5	3.4
ATORVASTATIN	31.1	33.6	36.4	36.3	36.3	37.1	36.3	37.0
CERISVASTATIN		0.0001						
ROSUVASTATIN		0.03	5.2	8.7	10.6	13.1	15.7	18.2
TOTAL	**64.4**	**72.2**	**89.1**	**104.1**	**112.5**	**119.0**	**127.3**	**133.0**

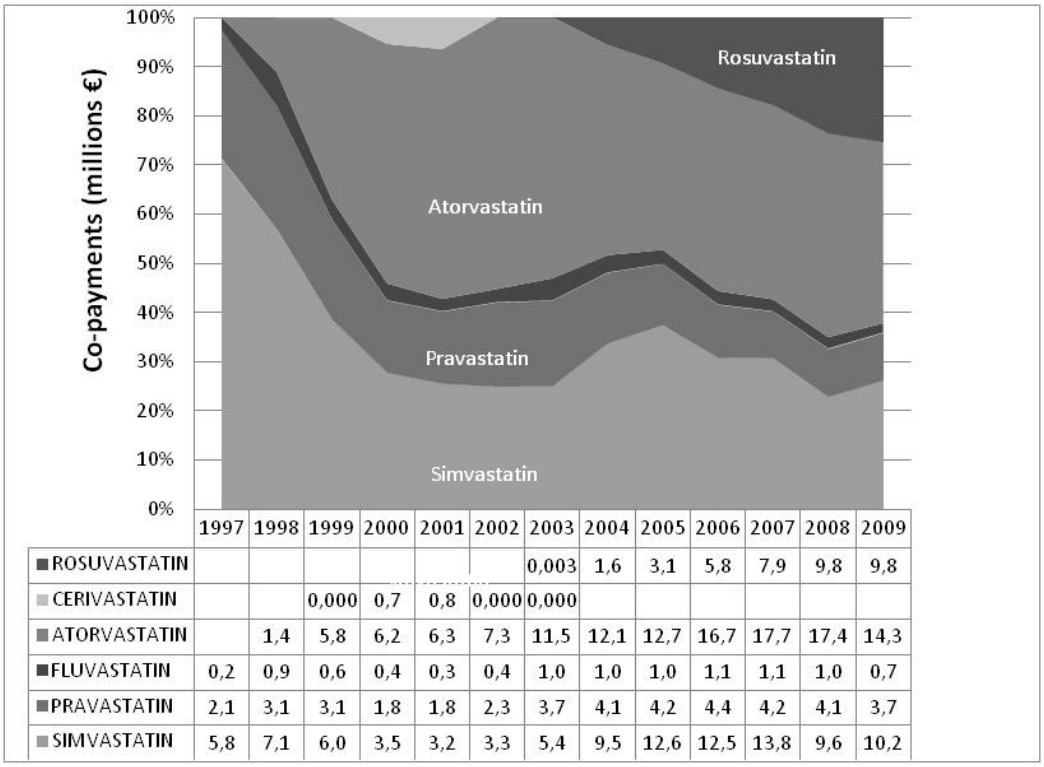
EXPENDITURES

Figure 24 : Cost per year and statin type – Third party payer intervention (ambulatory sector – in millions €)



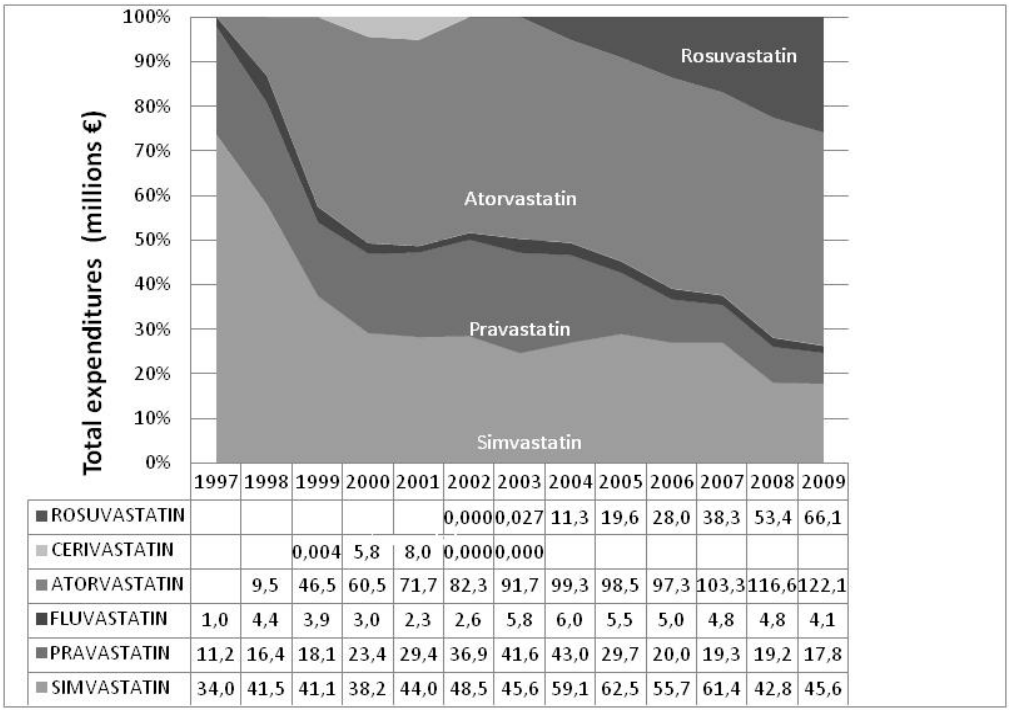
	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
ROSUVASTATIN							0,023	9,7	16,5	22,2	30,4	43,5	56,3
CERIVASTATIN			0,003	5,1	7,2	0,000	0,000						
ATORVASTATIN		8,1	40,7	54,4	65,4	75,0	80,2	87,2	85,7	80,6	85,6	99,3	107,8
FLUVASTATIN	0,8	3,6	3,3	2,6	2,0	2,3	4,8	5,0	4,5	3,8	3,8	3,8	3,3
PRAVASTATIN	9,1	13,2	15,0	21,5	27,6	34,6	37,8	38,9	25,5	15,7	15,0	15,1	14,0
SIMVASTATIN	28,2	34,4	35,1	34,7	40,8	45,2	40,2	49,6	49,9	43,2	47,7	33,2	35,4

Figure 25: Cost per year and statin type – Out-of-pocket payments (ambulatory sector – in millions €)



	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
ROSUVASTATIN							0,003	1,6	3,1	5,8	7,9	9,8	9,8
CERIVASTATIN			0,000	0,7	0,8	0,000	0,000						
ATORVASTATIN		1,4	5,8	6,2	6,3	7,3	11,5	12,1	12,7	16,7	17,7	17,4	14,3
FLUVASTATIN	0,2	0,9	0,6	0,4	0,3	0,4	1,0	1,0	1,0	1,1	1,1	1,0	0,7
PRAVASTATIN	2,1	3,1	3,1	1,8	1,8	2,3	3,7	4,1	4,2	4,4	4,2	4,1	3,7
SIMVASTATIN	5,8	7,1	6,0	3,5	3,2	3,3	5,4	9,5	12,6	12,5	13,8	9,6	10,2

Figure 26: Cost per year and statin type – Total expenditures (ambulatory sector – in millions €)



	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
ROSUVASTATIN						0,000	0,027	11,3	19,6	28,0	38,3	53,4	66,1
CERIVASTATIN			0,004	5,8	8,0	0,000	0,000						
ATORVASTATIN		9,5	46,5	60,5	71,7	82,3	91,7	99,3	98,5	97,3	103,3	116,6	122,1
FLUVASTATIN	1,0	4,4	3,9	3,0	2,3	2,6	5,8	6,0	5,5	5,0	4,8	4,8	4,1
PRAVASTATIN	11,2	16,4	18,1	23,4	29,4	36,9	41,6	43,0	29,7	20,0	19,3	19,2	17,8
SIMVASTATIN	34,0	41,5	41,1	38,2	44,0	48,5	45,6	59,1	62,5	55,7	61,4	42,8	45,6

5.5 IMPACT OF 2004 REGULATION CHANGE

Table 8 presents the number and percentage of patients by number of different statin type used during the period. As shown in this table, in each period, most of the patients (> 95%) had purchased only one type of statin during the period. Therefore, the rule for determining the major statin type was applied in less than 5% of the patients taking statin.

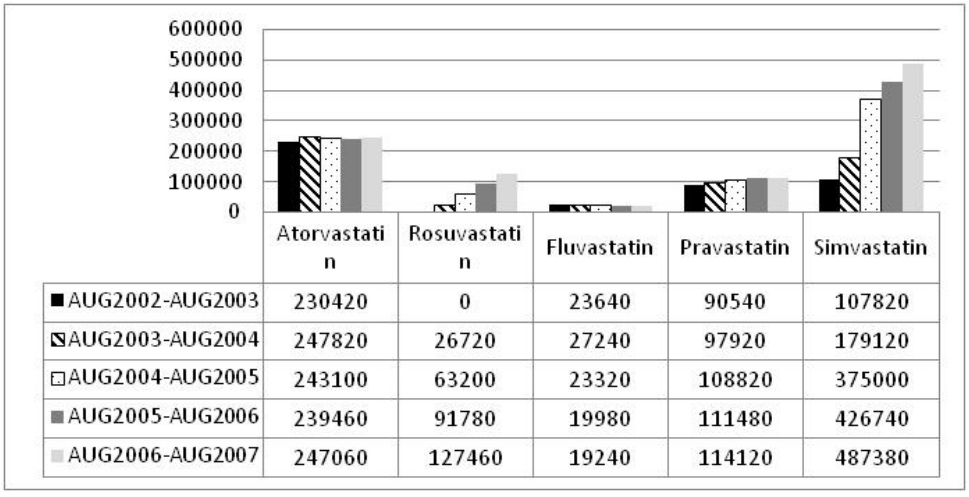
Table 42: Estimated Number and Estimated Percent of Patients by Number of Different Statin type used by Period – Patients taking Statin (extrapolated from EPS)

Number of Different type of Statin used	Aug2002 - Aug2003 N = 452 420 n (%)	Aug 2003 - Aug 2004 N = 578 820 n (%)	Aug 2004 – Aug 2005 N = 813 440 n (%)	Aug 2005 – Aug 2006 N = 889 440 n (%)	Aug 2006 – Aug 2007 N = 995 260 n (%)
1 Statin type	442 400 (98%)	559 740 (97%)	771 700 (95%)	845 820 (95%)	952 040 (96%)
2 Statin type	9 920 (2%)	18 760 (3%)	40 800 (5%)	42 680 (5%)	41 980 (4%)
3 Statin type	100 (0%)	320 (0%)	900 (0%)	940 (0%)	1 240 (0%)
4 Statin type	0	0	40 (0%)	0	0

Figure 7 and Figure 8 show the estimated absolute number and estimated percentage, respectively, of patients taking the statin by major statin type and by period. From Figure 27 it can be seen that there was an important increase in number of patients taking simvastatin from an estimation of 179 120 in the period Aug2003 to Aug2004 to an estimation of 375 000 patients during the period Aug2004 to Aug2005 while for the other statin type, the number of inidviduals between those 2 specific periods were quite stable. This is also supported by the results in Figure 28, the proportion of patients taking simvastatin increased over the periods with a higher difference prior and after Aug2004 (from 31% prior Aug2004 to 46% after Aug 2004). In the other hand, there were a decrease in proportion of patients taking the other statin type except for Rosuvastatin which increased over the periods.

Table 9 presents the estimated number of users of statin by status compared to the previous period (i.e. new user, no change in the statin type with previous period statin type, change in the statin type from the previous statin type).

Figure 27: Estimated Absolute Number of Patients by Major Statin Type and Period



	Atorvastatin	Rosuvastatin	Fluvastatin	Pravastatin	Simvastatin
AUG2002-AUG2003	230420	0	23640	90540	107820
AUG2003-AUG2004	247820	26720	27240	97920	179120
AUG2004-AUG2005	243100	63200	23320	108820	375000
AUG2005-AUG2006	239460	91780	19980	111480	426740
AUG2006-AUG2007	247060	127460	19240	114120	487380

Figure 28: Estimated Percent of Patients by Major Statin Type and Period

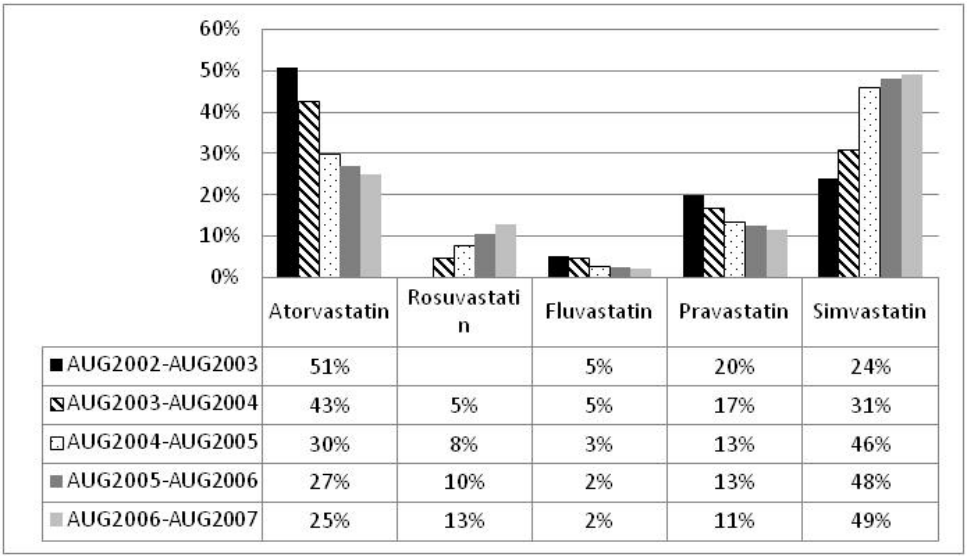


Table 43: Estimated number of patients by statin type, period and change status from previous period

Statin Type	Period	No change	New User	Change	Total
Atorvastatin	Aug2003-Aug2004	195820	47540	4460	247820
	Aug2004-Aug2005	178360	59320	5420	243100
	Aug2005-Aug2006	196940	35360	7160	239460
	Aug2006-Aug2007	195280	43840	7940	247060
Rosuvastatin	Aug2003-Aug2004	0	23020	3700	26720
	Aug2004-Aug2005	20940	30300	11960	63200
	Aug2005-Aug2006	47000	30260	14520	91780
	Aug2006-Aug2007	71780	38780	16900	127460
Fluvastatin	Aug2003-Aug2004	17000	8480	1760	27240
	Aug2004-Aug2005	15160	7220	940	23320
	Aug2005-Aug2006	16500	2720	760	19980
	Aug2006-Aug2007	15080	3180	980	19240
Pravastatin	Aug2003-Aug2004	71440	24240	2240	97920
	Aug2004-Aug2005	64520	39740	4560	108820
	Aug2005-Aug2006	81540	23940	6000	111480
	Aug2006-Aug2007	82960	26520	4640	114120
Simvastatin	Aug2003-Aug2004	90120	85500	3500	179120
	Aug2004-Aug2005	138960	208640	27400	375000
	Aug2005-Aug2006	282680	129140	14920	426740
	Aug2006-Aug2007	336400	138780	12200	487380

5.6 COMPLIANCE OF PATIENTS

There are different ways to assess compliance (or adherence with) medication during a specific period of time: the medication possession ratio (MPR) is usually defined when only claims data are available.

The MPR is defined as follows:

MPR = sum of the day's supply of medication divided by the number of days between first fill and the last refill plus the days' supply of the last refill.

If there are no gaps between the different refills, the MPR is thus 1. If there are lapses in prescription refilling, the MPR is below 1. Early refilling leads to a MPR higher than 1. When patient have no refill (only one fill during the study period, the MPR is not defined).

[Refs papers statin adherence Sikka 2005; Shalev 2009; Scheenweiss 2007; Helin-Salmivaara 2008; Gibson 2006;

The "number of day's supply medication" that a patient receives at each refill obviously depends of his/her treatment schedule (the dosage needed) and on the strength of the tablets he/she received. A patient receiving 28 tablets of simvastatin 20 mg has either 28 days day's supply medication if his treatment dosage is 20 mg (in that case MPR = 1), but only 14 days if his/her treatment dosage is 40 mg (in that case MPR = 2). The same patient, when receiving 28 tablets of simvastatin 40 mg, would have 56 days of supply (if he/she takes then half a tablet per day, and in that case MPR = 0.5).

The necessary assumption behinds the interpretation of the MPR in terms of compliance is that patients take the tablet strength corresponding to their treatment schedule (so that hey take 1 tablet a day). With this assumption, non regular users are defined as those having a MPR below 0.80 (meaning that less than 80% of days are covered with medication). Patients having only one statin prescription during the study period are also considered as non regular user.

Another approach is to base the definition of the MPR on DDD. The assumption behind this approach is that all patients need at least 1 DDD per day (and maybe more). The difficulty with this approach is when the dosage of the tablets available on the market do not correspond to the DDD: this is the case of simvastatin: DDD 30 mg but tablets of 5, 20, 40 or 80 mg available, and fluvastatin: DDD 60 mg but tablets of 40 or 80 mg available.

Table 10 shows measures of statin adherence based on the number of DDD received. Using this measure, the 5 statin molecules seem to have very different percentage of regular user. For simvastatin and atorvastatin, the two molecules for which a high number of patients receive tablets which strength is below the DDD, percentage of regular users drops to 34.4% and 44.4% respectively. This lead to the adoption of the MPR tablet as a better measure than the MPR DDD for measuring patient compliance with statin.

Table 44: Measures of statin compliance based on MPR DDD

		Start Treatment with					All
		C10AA01 Simvastatin	C10AA03 Pravastatin	C10AA04 Fluvastatin	C10AA05 Atorvastatin	C10AA07 Rosuvastatin	
N new users (extrapolated to Belgium)		491500	111460	26560	183100	93700	906320
Adherence based on MPR DDD							
MPR not defined (only 1 delivery date)	%	18.61	19.29	19.20	16.08	19.06	18.25
MPR below 80%	%	46.85	19.34	17.17	39.66	19.15	38.28
Regular user, MPR >= 80%	%	34.54	61.37	63.63	44.26	61.79	43.47
MPR (based on DDD)	Mean	0.84	1.08	1.09	0.90	1.01	0.91
	Std	0.35	0.34	0.33	0.46	0.38	0.39
	Median	0.74	1.11	1.10	0.83	0.97	0.83

5.7 SECONDARY PREVENTION

DEFINITION OF HOSPITALIZATION FOR CARDIOVASCULAR REASON

Cardiovascular disease (CVD) is disease of the heart and blood vessels, which can lead to cardiovascular events such as heart attack (myocardial infarction) and stroke. The most common form of CVD is coronary heart disease (CHD), which can result in angina and heart attack. Other forms of CVD are stroke, transient ischaemic attack and peripheral arterial disease.

Every hospitalisation discharged between 2002 and 2006 for a ***cardiovascular reason*** was initially selected. A cardiovascular reason was defined when the first three digits of the principal diagnosis equal to one of the following codes:

a cardiovascular "event" was defined as an hospitalisation. We considered

- 410 Acute myocardial infarction (AMI)
- 411 Other acute and subacute forms of ischemic heart disease
- 412 Old myocardial infarction
- 413 Angina pectoris
- 414 Other forms of chronic ischemic heart disease
- 430 Subarachnoid hemorrhage
- 431 Intracerebral hemorrhage
- 432 Other and unspecified intracranial hemorrhage
- 433 Occlusion and stenosis of precerebral arteries
- 434 Occlusion of cerebral arteries
- 435 Transient cerebral ischemia
- 436 Acute, but ill-defined, cerebrovascular disease
- 437 Other and ill-defined cerebrovascular disease
- 438 Late effects of cerebrovascular disease
- 440 Atherosclerosis
- 441 Aortic aneurysm and dissection

The discharge date was conventionally chosen as the cardiovascular event date. For privacy reasons, the exact discharge date is not recorded in the HCD; but the year, the month and the day of the week (e.g. monday) are available.

Table 45: Reason of hospitalization for Cardiovascular Reason (principal diagnosis) (2002-2006): N extrapolated

Principal diagnosis in 3 digits	Frequency N extrapolated	Percent	Cumulative Frequency	Cumulative Percent
414 Other forms of chronic ischemic heart disease	189580	34.06	189580	34.06
410 Acute myocardial infarction (AMI)	74620	13.41	264200	47.46
440 Atherosclerosis	59100	10.62	323300	58.08
434 Occlusion of cerebral arteries	48520	8.72	371820	66.80
435 Transient cerebral ischemia	34460	6.19	406280	72.99
433 Occlusion and stenosis of precerebral arteries	32540	5.85	438820	78.83
411 Other acute and subacute forms of ischemic heart disease	25100	4.51	463920	83.34
413 Angina pectoris	24220	4.35	488140	87.69
436 Acute, but ill-defined, cerebrovascular disease	17380	3.12	505520	90.82
431 Intracerebral hemorrhage	13580	2.44	519100	93.26
441 Aortic aneurysm and dissection	13240	2.38	532340	95.63
437 Other and ill-defined cerebrovascular disease	11520	2.07	543860	97.70
438 Late effects of cerebrovascular disease	5820	1.05	549680	98.75
430 Subarachnoid hemorrhage	3480	0.63	553160	99.37
432 Other and unspecified intracranial hemorrhage	3240	0.58	556400	99.96
412 Old myocardial infarction	240	0.04	556640	100.00

The most frequent principal diagnosis is 414 Other forms of chronic ischemic heart disease. This non specific group consists of four subgroups:

414.0 Coronary atherosclerosis (n=177 060 extrapolated stays)

414.1 Aneurysm and dissection of heart (n=140 extrapolated stays)

414.8 Other specified forms of chronic ischemic heart disease (chronic coronary insufficiency, chronic myocardial ischemia) (n=9540 extrapolated stays)

414.9 Chronic ischemic heart disease, unspecified (n=2840 extrapolated stays).

Table 46: APR-DRGs of hospitalizations for cardiovascular reason (2002-2006)

	Frequency N extrapolated	Percent	Cumulative Frequency	Cumulative Percent
192-cardiac catheterization for ischemic heart disease	88580	15.91	88580	15.91
175-percutaneous cardiovascular procedures w/o ami	68860	12.37	157440	28.28
045-cardiovascular disease w infarction	49240	8.85	206680	37.13
190-circulatory disorders w ami	43900	7.89	250580	45.02
173-other vascular procedures	38680	6.95	289260	51.97
047-transient ischemia	35900	6.45	325160	58.41
046-nonspecific cardiovascular disease & precerebral occlusion w/o infarct	28620	5.14	353780	63.56
202-angina pectoris	25460	4.57	379240	68.13
198-atherosclerosis	22220	3.99	401460	72.12
174-percutaneous cardiovascular procedures w ami	20760	3.73	422220	75.85
166-coronary bypass w/o malfunctioning coronary bypass w/o cardiac cath	18880	3.39	441100	79.24
024-extracranial vascular procedures	18100	3.25	459200	82.49
197-peripheral & other vascular disorders	15520	2.79	474720	85.28
044-intracranial hemorrhage	14880	2.67	489600	87.96
165-coronary bypass w/o malfunctioning coronary bypass w/ cardiac cath	10760	1.93	500360	89.89
058-other disorders of nervous system	10320	1.85	510680	91.74
168-major thoracic vascular procedures	9580	1.72	520260	93.46
021-craniotomy except for trauma	5920	1.06	526180	94.53
207-other circulatory system diagnoses	4880	0.88	531060	95.40
169-major abdominal vascular procedures	2700	0.49	533760	95.89
052-nontraumatic stupor & coma	2160	0.39	535920	96.28
191-cardiac catheterization w circulatory disorders excluding ischemic heart disease	2160	0.39	538080	96.67
950-extensive procedure unrelated to principal diagnosis	2080	0.37	540160	97.04
172-amputation for circulatory system disorder except upper limb & toe	2040	0.37	542200	97.41
447-other kidney & urinary tract procedures	1900	0.34	544100	97.75
004-tracheostomy except for face, mouth & neck diagnoses	1860	0.33	545960	98.08
163-cardiac valve procedures w/o cardiac catheterization	1580	0.28	547540	98.37
026-nervous system proc for cranial nervous & other nervous sys disorder	1560	0.28	549100	98.65
180-other circulatory system procedures	1420	0.26	550520	98.90
178-upper limb & toe amputation for circulatory system disorders	1000	0.18	551520	99.08
162-cardiac valve procedures w cardiac catheterization	960	0.17	552480	99.25
952-nonextensive procedure unrelated to principal diagnosis	960	0.17	553440	99.43
161-cardiac defibrillator implant	480	0.09	553920	99.51
171-perm cardiac pacemaker implant w/o ami, heart failure or shock	460	0.08	554380	99.59
167-other cardiothoracic procedures	340	0.06	554720	99.66
022-ventricular shunt procedures	320	0.06	555040	99.71

	Frequency N extrapolated	Percent	Cumulative Frequency	Cumulative Percent
170-permanent cardiac pacemaker implant w ami, heart failure or shock	300	0.05	555340	99.77
468-other kidney & urinary tract diagnoses / 11 - m	300	0.05	555640	99.82
951-prostatic procedure unrelated to principal diagnosis / 0 - p	200	0.04	555840	99.86
023-spinal procedures	160	0.03	556000	99.89
179-vein ligation & stripping	160	0.03	556160	99.91
176-cardiac pacemaker & defibrillator device replacement	120	0.02	556280	99.94
892-hiv w major hiv related diagnosis w/o mult major or signif hiv related diagnosis	120	0.02	556400	99.96
002-heart &/or lung transplant	40	0.01	556440	99.96
003-bone marrow transplant	40	0.01	556480	99.97
053-seizure	40	0.01	556520	99.98
177-cardiac pacemaker & defibrillator revision except device replacement	40	0.01	556560	99.99
201-cardiac arrhythmia & conduction disorders	40	0.01	556600	99.99
025-nervous system procedures for peripheral nervous disorders	20	0.00	556620	100.00
203-chest pain	20	0.00	556640	100.00

HOSPITAL MORTALITY

Table 47: Hospital mortality amongst hospitalizations for cardiovascular reason (2002-2006)

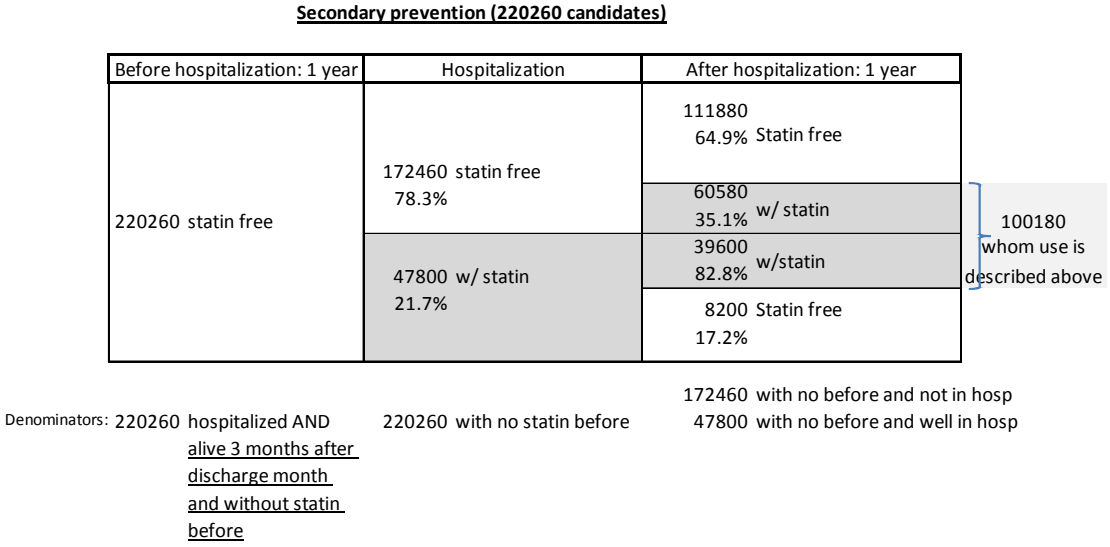
	Year of discharge					
Frequency: N extrapolated Col Pct	2002	2003	2004	2005	2006	Total
Discharged alive	108060 93.51	106860 93.49	108180 93.92	97940 94.23	101620 94.39	522660 93.90
Dead during hospitalization	7500 6.49	7440 6.51	7000 6.08	6000 5.77	6040 5.61	33980 6.10
Total	115560	114300	115180	103940	107660	556640

Table 48: Hospital mortality amongst hospitalizations for cardiovascular event (2002-2006)

	Year of discharge					
Frequency : N extrapolated Col Pct	2002	2003	2004	2005	2006	Total
Discharged alive	81300 95.58	83880 95.43	86220 95.76	76940 95.29	81480 95.30	409820 95.48
Dead during hospitalization	3760 4.42	4020 4.57	3820 4.24	3800 4.71	4020 4.70	19420 4.52
Total	85060	87900	90040	80740	85500	429240

SECONDARY PREVENTION DURING HOSPITALISATION

Figure 29: Statin users – Secondary prevention



The drugs delivered at hospital and recorded in the Hospital Billing Data were investigated to determine if statins were given during hospitalization and, in this case, which statin types were given. Figure 29 includes cardiac events of patients hospitalized, discharged alive and who survived 3 months, according to our definition of secondary prevention. This figure shows that, in 22% of the cases, a statin was delivered during hospitalization..

In general, the treatment administered during the hospitalization consisted in 1 statin type only (98.2 %, n=46960 extrapolated stays), the remaining treatments (1.8% n=840 extrapolated stays) combining two statin types. The first statin given are described in Table 49. Simvastatin stays clearly the first treatment choice as hospital initial statin in 80% of the hospitalizations (with statin). Nevertheless, this percentage drops between 2003 and 2006 in favour of atorvastatin and, to a lesser extent, rosuvastatin. Statin hospital use was not further analyzed.

When no statin was given at hospital but only after discharge, the first statin prescriber qualification was a general practitioner in 36 740 extrapolated cases. This means that the secondary prevention was administered by a GP in 36.7% of the extrapolated cases (36 740 out of 100 180 extrapolated stays).

Table 49: Statin use in hospitalization (new user)

First statin (start)	Year of discharge				
Frequency: N extrapolated Col Pct	2003	2004	2005	2006	Total
C10AA01 Simvastatin	4680 81.53	11620 81.83	10760 79.82	11180 77.75	38240 80.00
C10AA03 Pravastatin	140 2.44	520 3.66	480 3.56	300 2.09	1440 3.01
C10AA04 Fluvastatin	100 1.74	60 0.42	20 0.15	0 0.00	180 0.38
C10AA05 Atorvastatin	820 14.29	1780 12.54	1840 13.65	2460 17.11	6900 14.44
C10AA07 Rosuvastatin	0 0.00	220 1.55	380 2.82	440 3.06	1040 2.18
Total	5740	14200	13480	14380	47800

SECONDARY PREVENTION BY PRINCIPAL DIAGNOSIS

Table 50: Percentage of secondary prevention after hospitalization for cardiovascular reason per patient principal diagnosis (2006 only)

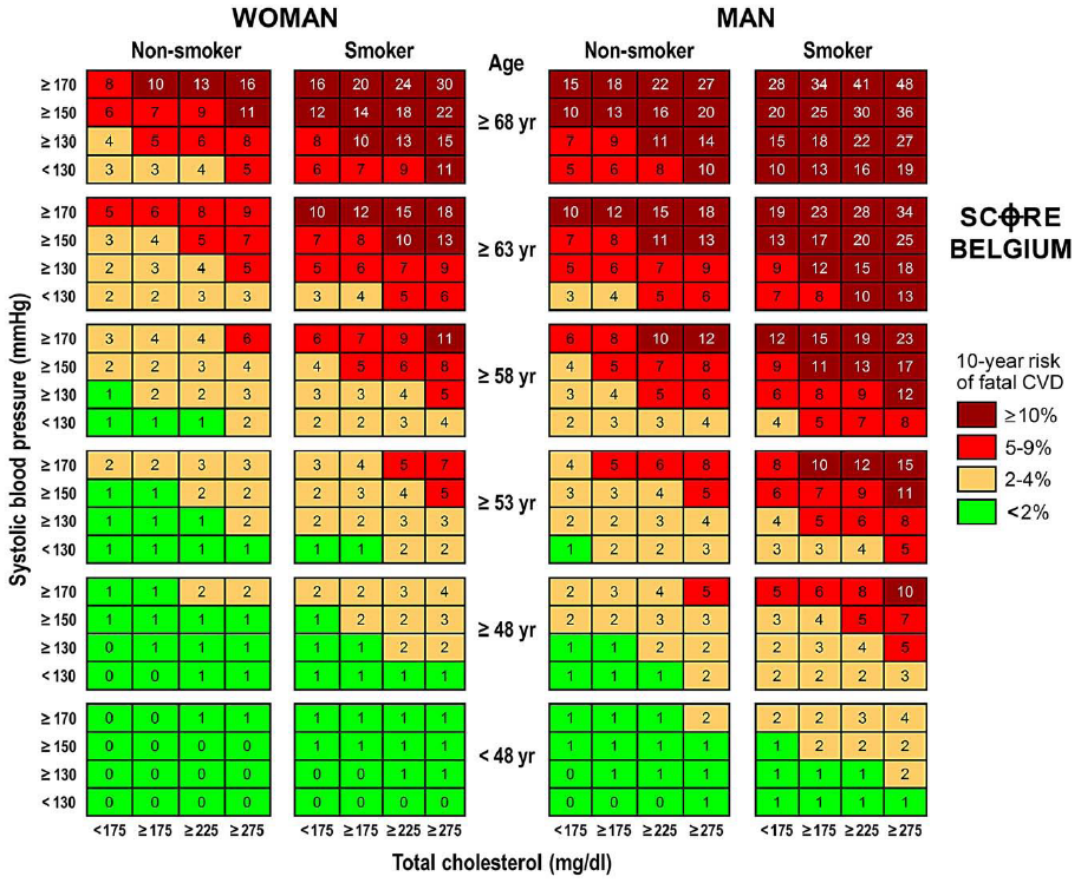
Principal diagnosis in 3 digits	**Statin the year after**		
Frequency: N extrapolated Row Pct	No	Yes	**Total**
410 Acute myocardial infarction (AMI)	1980 23.19	6560 76.81	8540
411 Other acute and subacute forms of ischemic heart disease	740 36.27	1300 63.73	2040
413 Angina pectoris	1940 71.32	780 28.68	2720
414 Other forms of chronic ischemic heart disease	7160 38.96	11220 61.04	18380
430 Subarachnoid hemorrhage	300 88.24	40 11.76	340
431 Intracerebral hemorrhage	700 76.09	220 23.91	920
432 Other and unspecified intracranial hemorrhage	480 96.00	20 4.00	500
433 Occlusion and stenosis of precerebral arteries	1680 64.62	920 35.38	2600
434 Occlusion of cerebral arteries	4960 68.13	2320 31.87	7280
435 Transient cerebral ischemia	3580 75.85	1140 24.15	4720
436 Acute, but ill-defined, cerebrovascular disease	320 59.26	220 40.74	540
437 Other and ill-defined cerebrovascular disease	1340 83.75	260 16.25	1600
438 Late effects of cerebrovascular disease	660 94.29	40 5.71	700
440 Atherosclerosis	5440 77.71	1560 22.29	7000
441 Aortic aneurysm and dissection	700 70.00	300 30.00	1000
Total	31980	26900	58880

Table 51: Percentage of secondary prevention for patients hospitalized for Atherosclerosis (Principal diagnosis code ICD9-CM = 440) (2006 only)

Principal Diagnosis	**Statin the year after**		
Frequency: N extrapolated Row Pct	No	Yes	Total
4400 Atherosclerosis of aorta	20 33.33	40 66.67	60
4401 Atherosclerosis of renal artery	180 64.29	100 35.71	280
44020 Atherosclerosis of the extremities, unspecified	340 73.91	120 26.09	460
44021 Atherosclerosis of the extremities with intermittent claudication	2280 77.55	660 22.45	2940
44022 Atherosclerosis of the extremities with rest pain	680 82.93	140 17.07	820
44023 Atherosclerosis of the extremities with ulceration	680 79.07	180 20.93	860
44024 Atherosclerosis of the extremities with gangrene	700 87.50	100 12.50	800
44029 Atherosclerosis of native arteries of the extremities, other	100 71.43	40 28.57	140
44030 Atherosclerosis of unspecified graft	80 66.67	40 33.33	120
44031 Atherosclerosis of autologous vein bypass graft	60 100.00	0 0.00	60
44032 Atherosclerosis of nonautologous vein bypass graft	0 0.00	20 100.00	20
4408 Atherosclerosis of other specified arteries	300 71.43	120 28.57	420
4409 Generalized and unspecified atherosclerosis	20 100.00	0 0.00	20
Total	5440	1560	7000

5.8 SCORE CHART

Figure 30: the SCORE Belgium risk chart for 10-year cardiovascular mortality [16]



5.9 DRUG INTERACTIONS

Table 52: Inducers and inhibitors of major cytochrom isoenzymes [59]

Enzyme; substrate	Enzyme inducers	Enzyme inhibitors
CYP1A2		
TCAs	Omeprazole, lansoprazole	Fluvoxamine (other SSRIs weak)
Haloperidol, olanzapine	Phenobarbital, phenytoin, carbamazepine	Ciprofloxacin (other quinolones weak)
Propranolol, local anesthetics	Erythromycin, clarithromycin, rifampin	Cimetidine
Theophylline, caffeine	Cigarette smoke	Isoniazid
Diazepam, chlordiazepoxide	Ritonavir	Oral contraceptives
Estrogens, tamoxifen	Insulin	Ticlopidine
CYP2C9		
ASA and most NSAIDs	Rifampin	Fluvoxamine (other SSRIs weak)
Phenobarbital, phenytoin	Phenobarbital, phenytoin, carbamazepine	Amiodarone
S-Warfarin, dicumarol		Omeprazole
Losartan (activation)		Ritonavir
Tolbutamide, sulfonamides, dapsone		HMG-CoA reductase inhibitors
Zidovudine		Tolbutamide
Diazepam, temazepam		Cimetidine (weak)
Fluoxetine, meclobemide		Azole antifungals (weak)
CYP2C19		
TCAs	Rifampin	Fluoxetine, fluvoxamine, paroxetine
Diazepam, temazepam	Phenobarbital, phenytoin, carbamazepine	Omeprazole, lansoprazole
Omeprazole, lansoprazole	Prednisone	Ritonavir
Propranolol	Norethindrone	Azole antifungals (weak)
Phenytoin, barbiturates, valproic acid		Cimetidine (weak)
Zidovudine		Ticlopidine
CYP2D6		
TCAs, SSRIs, venlafaxine		Quinidine
Phenothiazines, haloperidol		Fluoxetine, paroxetine, sertraline
Several β-blockers		TCAs, venlafaxine
Codeine, oxycodone, hydrocodone		Phenothiazines, haloperidol, nefazodone
Dextromethorphan		Ketoconazole
Omeprazole		Cimetidine
Halothane		Ritonavir
MDMA (ecstasy)		HMG-CoA reductase inhibitors
Encainide, flecainide, propafenone		Amiodarone, encainide
Selegiline		Chlorpheniramine
CYP2E1		
Acetaminophen	Ethanol	Disulfiram
Ethanol and other alcohols	Isoniazid	Ethanol
Inhalational anesthetics	Clofibrate	Cimetidine
Sulfonamides, dapsone		Isoniazid
CYP3A4		
Halothane	Phenytoin, barbiturates	Ketoconazole, itraconazole, fluconazole
Fentanyl, alfentanil, sufentanil	Rifampin	Erythromycin, clarithromycin
TCAs, SSRIs	Erythromycin	TCAs, nefazodone, venlafaxine
Erythromycin, clarithromycin	Omeprazole, lansoprazole	Fluvoxamine, fluoxetine, sertraline
HIV protease inhibitors	Dexamethasone, sex steroids	Cyclosporine, tacrolimus
Calcium-channel blockers (not diltiazem)	Cyclophosphamide	Omeprazole, lansoprazole
Lovastatin, simvastatin, atorvastatin		Calcium-channel blockers (esp. diltiazem)
Cyclosporine		Midazolam
Terfenadine, astemizole, loratadine		Corticosteroids
Midazolam, alprazolam, triazolam		Grapefruit juice
Cisapride		Tamoxifen

Note: TCA = tricyclic antidepressant, SSRI = selective serotonin reuptake inhibitor, HMG–CoA = hydroxymethylglutaryl – coenzyme A.

5.10 NEW BELGIAN RECOMMENDATIONS FOR THE USE OF STATINES

From:http://www.inami.fgov.be/drug/fr/drugs/recommendation/pdf/recommandations_statines.pdf

SERVICE PUBLIC FEDERAL SECURITE SOCIALE

Recommandations concernant l'usage et la prescription des statines:

Les médicaments suivants sont concernés:

- Simvastatine : 20 à 40 mg p.j., éventuellement augmenter jusqu'à 80 mg p.j. en 1 prise.
- Pravastatine : 10 à 20 mg p.j., éventuellement augmenter jusqu'à 40 mg p.j. en 1 prise.
- Atorvastatine : 10 mg p.j., éventuellement augmenter jusqu'à 80 mg p.j. en 1 prise.
- Rosuvastatine : 5 à 10 mg p.j., éventuellement augmenter jusqu'à 20 mg p.j. en 1 prise.
- Fluvastatine : 40 mg p.j., éventuellement augmenter jusqu'à 80 mg p.j. en 2 prises (ou en 1 prise pour la libération prolongée).

1. **La prévention primaire** concerne les sujets n'ayant pas présenté d'événement cardiovasculaire. Chez ces sujets, l'instauration d'un traitement par statine doit être guidé par la présence d'une hypercholestérolémie primaire avec un taux de cholestérol sérique total > ou = à 190 mg/dl ou d'un cholestérol LDL > ou = à 115 mg/dl, mesurés à jeun, à au moins deux reprises avec 1 à 8 semaines d'intervalle, en état stable, sous régime approprié et par la présence d'un risque cardiovasculaire dont le niveau est égal ou supérieur à 5 % à 10 ans. Ce risque est calculé sur base du modèle SCORE adapté à la situation belge en tenant compte de l'âge, du sexe, du taux de cholestérol sérique, de la pression artérielle systolique et du tabagisme.

   Pour débuter le traitement, il est recommandé de prescrire soit la simvastatine, soit la pravastatine. En cas de non-atteinte des objectifs thérapeutiques (taux de cholestérol sérique total < à 190 mg/dl ou cholestérol LDL < à 115 mg/dl) au terme d'une période de traitement d'au moins 3 mois avec une dose optimale, la prescription d'une autre statine ou d'une association médicamenteuse peut être prise en considération.

2. **La prévention secondaire** concerne les patients avec une maladie cardiovasculaire avérée. Chez ces patients, il est recommandé d'instaurer un traitement par statine sur base d'une hypercholestérolémie primaire avec un taux de cholestérol sérique total > ou = à 175 mg/dl ou d'un cholestérol LDL > ou = à 100 mg/dl, mesurés à jeun, à au moins deux reprises avec 1 à 8 semaines d'intervalle, en état stable, sous régime approprié et de la présence d'au moins une atteinte artérielle:

   2.1. soit coronaire : infarctus, angor, syndrome coronarien aigu, pontage aorto-coronaire, angioplastie coronaire ;

   2.2. soit cérébrale : accident vasculaire cérébral thrombotique, accident ischémique transitoire ;

   2.3. soit périphérique : claudication intermittente.

   Pour débuter le traitement, il est recommandé de prescrire soit la simvastatine, soit la pravastatine. En cas de non-atteinte des objectifs thérapeutiques (taux de cholestérol sérique total < à 175 mg/dl ou cholestérol LDL < à 100 mg/dl) au terme d'une période de traitement d'au moins 3 mois avec une dose optimale, la prescription d'une autre statine ou d'une association médicamenteuse peut être prise en considération. Chez les patients dont le taux de cholestérol total est > 290 mg/dl ou dont le cholestérol LDL est > 165 mg/dl, l'atorvastatine ou la rosuvastatine peut, si nécessaire, être utilisée pour débuter le traitement.

3. **Le diabète**: chez les patients en prévention cardiovasculaire primaire (absence d'événement cardiovasculaire) mais présentant soit un diabète type 2 si le patient est âgé de plus de 40 ans, soit un diabète type 1 avec micro-albuminurie, l'instauration d'un traitement par statine est recommandé en présence d'une hypercholestérolémie avec un taux de cholestérol sérique total > ou = à 175 mg/dl ou d'un cholestérol LDL > ou = à 100 mg/dl, mesurés à jeun, à au moins deux reprises avec 1 à 8 semaines d'intervalle, en état stable, sous régime approprié.

   Pour débuter le traitement, il est recommandé de prescrire soit la simvastatine, soit la pravastatine. En cas de non-atteinte des objectifs thérapeutiques (taux de cholestérol sérique total < à 175 mg/dl ou cholestérol LDL < à 100 mg/dl) au terme d'une période de traitement d'au moins 3 mois avec une dose optimale, la prescription d'une autre statine ou d'une association médicamenteuse peut être prise en considération. Chez les patients dont le taux de cholestérol total est > 290 mg/dl ou dont le cholestérol LDL est > 165 mg/dl, l'atorvastatine ou la rosuvastatine peut, si nécessaire, être utilisée pour débuter le traitement.

	Critères figurant dans les recommandations :	Eléments à conserver dans le dossier :
1.	**Hypercholestérolémie primaire**	
1.1.	Présence d'un cholestérol sérique total > ou = à 190 mg/dl, ou d'un LDL-cholestérol > ou = à 115 mg/dl, mesurés à jeun, à au moins deux reprises avec 1 à 8 semaines d'intervalle, en état stable, sous régime approprié.	Protocoles (datés) des deux biologies, émanant de laboratoires de biologie clinique.
1.2.	Présence d'un cholestérol sérique total > ou = à 175 mg/dl, ou d'un LDL-cholestérol > ou = à 100 mg/dl, mesurés à jeun, à au moins deux reprises avec 1 à 8 semaines d'intervalle, en état stable, sous régime approprié.	Protocoles (datés) des deux biologies, émanant de laboratoires de biologie clinique.
2.	**Calcul du risque cardiovasculaire absolu individuel**	
2.1.	> ou = à 5 % à 10 ans ((Rev Med Liege 2005 ; 60 : 3 : 163-172)) en tenant compte de l'âge, du sexe,	Mention du résultat du calcul et des différents éléments qui ont été pris en compte pour son établissement, ainsi que mention de la date, ou de la période, à laquelle se rapporte ce calcul.
2.2.	Du taux de cholestérol sérique,	S'il s'agit d'une biologie autre que celles figurant au point 1.1. : Protocole (daté) émanant d'un laboratoire de biologie clinique.
2.3.	De la pression artérielle systolique,	Mention de la valeur (datée) effectivement mesurée et du traitement anti-hypertensif éventuel.
2.4.	Du tabagisme.	Mention : fumeur, non fumeur, ancien fumeur.
3.	**Diabète sucré**	Mention du type de diabète et de son ancienneté, avec confirmation du diagnostic par une ou des biologies démonstratives, et/ou par un ou des protocoles médicaux. Mention de la présence de microalbuminurie pour le diabète de type 1.
4.	**Antécédent d'au moins une atteinte artérielle dûment documentée par un examen technique complémentaire**	
4.1.	Soit coronaire :	
4.1.1.	Infarctus, angor, syndrome coronarien aigu,	Mention de l'événement et de la date de sa survenue, avec confirmation du diagnostic par un ou des protocoles médicaux.
4.1.2.	Pontage aorto-coronaire, angioplastie coronaire.	Mention de l'intervention et de la date de sa réalisation, avec confirmation de l'intervention par un ou des protocoles médicaux.
4.2.	Soit cérébrale :	
4.2.1.	Accident vasculaire cérébral thrombotique,	Mention et description clinique de l'accident et de ses séquelles éventuelles, ainsi que de la date de sa survenue.
4.2.2.	Accident ischémique transitoire.	Mention et description clinique de l'accident et de la date de sa survenue.
4.3.	Soit périphérique :	
4.3.1.	Claudication intermittente.	Mention de la ou des localisation(s) de l'artériopathie des membres inférieurs, du ou des gradients bras/cuisse, avec confirmation du diagnostic par le protocole d'une imagerie médicale démonstrative ou d'un examen Doppler.

From:http://www.inami.fgov.be/drug/nl/drugs/recommendation/pdf/recommandations_statines.pdf

Aanbevelingen over het gebruik en het voorschrijven van statines:

De betrokken statines zijn:

- Simvastatine : 20 à 40 mg p.d., indien nodig opdrijven tot 80 mg p.d in 1 gift.
- Pravastatine : 10 à 20 mg p.d., indien nodig opdrijven tot 40 mg p.d in 1 gift.
- Atorvastatine : 10 mg p.d., indien nodig opdrijven tot 80 mg p.d in 1 gift.
- Rosuvastatine : 5 à 10 mg p;d., indien nodig opdrijven tot 20 mg p.d in 1 gift.
- Fluvastatine : 40 mg p.d., indien nodig opdrijven tot 80 mg p.d in 2 giften (of in 1 gift voor vertraagde vrijstelling).

1. **De primaire preventie** betreft patiënten die nog geen cardiovasculair event hebben doorgemaakt. Bij hen dient de start van een statinebehandeling gebaseerd te zijn op de aanwezigheid van een primaire hypercholesterolemie met een totaal cholesterol > of = 190 mg/dl of een LDL-cholesterol > of = 115 mg/dl, nuchter gemeten tijdens minstens twee afnames met 1 tot 8 weken tussentijd, in een stabiele toestand, onder een aangepast dieet en op een cardiovasculair risico hoger dan 5 % op 10 jaar. Dit risico wordt berekend op basis van het SCORE model aangepast aan de Belgische situatie rekening houdend met de leeftijd, het geslacht, het totale cholesterolniveau, de systolische arteriële druk, tabagisme.

   Er wordt aanbevolen de behandeling te starten met simvastatine of pravastatine. Indien de streefwaarde (totaal cholesterol < 190 mg/dl of LDL-cholesterol < 115 mg/dl) niet wordt bereikt na tenminste 3 maanden met de optimale dosering, kan een andere statine of een combinatie van verschillende geneesmiddelen worden voorgeschreven.

2. **De secundaire preventie** betreft patiënten met een bewezen cardiovasculaire aandoening. Bij hen dient de start van een statinebehandeling gebaseerd te zijn op de aanwezigheid van een primaire hypercholesterolemie met een totaal cholesterol > of = 175 mg/dl of een LDL-cholesterol > of = 100 mg/dl, nuchter gemeten tijdens minstens twee afnames met 1 tot 8 weken tussentijd, in een stabiele toestand, onder een aangepast dieet en op de aanwezigheid van minstens een arteriële aandoening:

   2.1. ofwel coronair : infarct, angor, acuut coronair syndroom, aorto-coronaire bypass, coronaire angioplastie;

   2.2. ofwel cerebraal : cerebrovasculair trombotisch accident, transitoir ischemisch accident;

   2.3. ofwel perifeer: claudicatio intermittens.

   Er wordt aanbevolen de behandeling te starten met simvastatine of pravastatine. Indien de streefwaarde (totaal cholesterol < 175 mg/dl of LDL-cholesterol < 100 mg/dl) niet wordt bereikt na tenminste 3 maanden met de optimale dosering, kan een andere statine of een combinatie van verschillende geneesmiddelen worden voorgeschreven. Bij patiënten met een totaal cholesterol > 290 mg/dl of een LDL cholesterol > 165 mg/dl kan, indien nodig, overwogen worden om de behandeling op te starten met atorvastatine of rosuvastatine.

3. **Diabetes**: bij patiënten in primaire cardiovasculaire preventie (afwezigheid van een cardiovasculair event) maar die ofwel een type 2 diabetes hebben aan een leeftijd van meer dan 40 jaar ofwel een type 1 diabetes met microalbuminurie dient de start van een statinebehandeling gebaseerd te zijn op de aanwezigheid van een hypercholesterolemie met een totaal cholesterol > of = 175 mg/dl of een LDL-cholesterol > of = 100 mg/dl, nuchter gemeten tijdens minstens twee afnames met 1 tot 8 weken tussentijd, in een stabiele toestand, onder een aangepast dieet.

   Er wordt aanbevolen de behandeling te starten met simvastatine of pravastatine. Indien de streefwaarde (totaal cholesterol < 175 mg/dl of LDL-cholesterol < 100 mg/dl) niet wordt bereikt na tenminste 3 maanden met de optimale dosering, kan een andere statine of een combinatie van verschillende geneesmiddelen worden voorgeschreven. Bij patiënten met een totaal cholesterol > 290 mg/dl of een LDL cholesterol > 165 mg/dl kan, indien nodig, overwogen worden om de behandeling op te starten met atorvastatine of rosuvastatine.

	Criterium dat voorkomt in de aanbevelingen:	**Elementen die in het dossier moeten worden bewaard:**
1.	**Primaire hypercholesterolemie**	
1.1.	Aanwezigheid van een totaal serumcholesterol > of = 190 mg/dl, of van een LDL-cholesterol > of = 115 mg/dl, in een nuchtere toestand en ten minste tweemaal gemeten, met een tussentijd van 1 tot 8 weken, in een stabiele toestand en met een aangepast dieet.	(Gedateerde) protocollen van de twee biologische testen door laboratoria voor klinische biologie.
1.2.	Aanwezigheid van een totaal serumcholesterol > of = 175 mg/dl, of van een LDL-cholesterol > of = 100 mg/dl, in een nuchtere toestand en ten minste tweemaal gemeten, met een tussentijd van 1 tot 8 weken, in een stabiele toestand en met een aangepast dieet.	(Gedateerde) protocollen van de twee biologische testen door laboratoria voor klinische biologie.
2.	**Berekening van het individueel absoluut cardiovasculair risico**	
2.1.	> of = 5 % op 10 jaar (Rev Med Liege 2005 ; 60 : 3: 163-172)) rekening houdende met de leeftijd, het geslacht,	Vermelding van het berekeningsresultaat en van de verschillende elementen die voor de vaststelling ervan in aanmerking zijn genomen, alsook vermelding van de datum of het tijdvak waarop die berekening betrekking heeft.
2.2.	Het serumcholesterol-gehalte,	Als het om een andere biologische test gaat dan die vermeld in punt 1.1.: (Gedateerd) protocol van een laboratorium voor klinische biologie.
2.3.	De arteriële systolische druk,	Vermelding van de (gedateerde) effectief gemeten waarde en van de eventuele behandeling met antihypertensiva.
2.4.	Tabaksgebruik.	Vermelding : roker, niet roker, ex-roker.
3.	**Diabetes mellitus**	Vermelding van het type diabetes, het aantal jaren dat men aan diabetes lijdt, met bevestiging van de diagnose door een of meer afdoende biologische testen en/of een of meer medische protocollen. Vermelding van de aanwezigheid van microalbuminurie indien type 1 diabetes.
4.	**Antecedent van ten minste één arteriële aandoening, behoorlijk gedocumenteerd door een bijkomend technisch onderzoek**	
4.1.	Ofwel coronair :	
4.1.1.	Infarct, angor, acuut coronair syndroom,	Vermelding van het voorval en datum van het voorval, met bevestiging van de diagnose door een of meer medische protocollen.
4.1.2.	Overbrugging tussen de aorta en de kransslagaders, coronaire angioplastiek.	Vermelding van de ingreep en datum van de uitvoering ervan, met bevestiging van de ingreep door een of meer medische protocollen.
4.2.	Ofwel cerebraal:	
4.2.1.	Cerebrovasculair trombotisch accident,	Vermelding en klinische beschrijving van het accident en van de eventuele gevolgen ervan, alsook de datum van het accident.
4.2.2.	Transitoir ischemisch accident.	Vermelding en klinische beschrijving van het accident en datum van het accident.
4.3.	Ofwel perifeer:	
4.3.1.	Claudicatio intermittens.	Vermelding van de lokalisatie(s) van de arteriopathie van de onderste ledematen, van de gradiënt(en) arm/dij, met bevestiging van de diagnose door het protocol van een afdoende medische beeldvorming of een doppleronderzoek.

6 BIBLIOGRAPHY

1. Armitage J. The safety of statins in clinical practice. Lancet. 2007;370(9601):1781-90.
2. 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.
3. Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C, et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet. 2005;366(9493):1267-78.
4. Gould AL, Davies GM, Alemao E, Yin DD, Cook JR. Cholesterol reduction yields clinical benefits: meta-analysis including recent trials. Clin Ther. 2007;29(5):778-94.
5. Bellosta S, Ferri N, Arnaboldi L, Bernini F, Paoletti R, Corsini A. Pleiotropic effects of statins in atherosclerosis and diabetes. Diabetes Care. 2000;23 Suppl 2:B72-8.
6. Robinson JG, Smith B, Maheshwari N, Schrott H. Pleiotropic effects of statins: benefit beyond cholesterol reduction? A meta-regression analysis. J Am Coll Cardiol. 2005;46(10):1855-62.
7. Brugts JJ, Yetgin T, Hoeks SE, Gotto AM, Shepherd J, Westendorp RGJ, et al. The benefits of statins in people without established cardiovascular disease but with cardiovascular risk factors: meta-analysis of randomised controlled trials. BMJ. 2009;338:b2376.
8. Mills EJ, Rachlis B, Wu P, Devereaux PJ, Arora P, Perri D. Primary prevention of cardiovascular mortality and events with statin treatments: a network meta-analysis involving more than 65,000 patients. J Am Coll Cardiol. 2008;52(22):1769-81.
9. Ward S, Lloyd Jones M, Pandor A, Holmes M, Ara R, Ryan A, et al. A systematic review and economic evaluation of statins for the prevention of coronary events. Health Technol Assess. 2007;11(14):1-160, iii-iv.
10. O'Regan C, Wu P, Arora P, Perri D, Mills EJ. Statin therapy in stroke prevention: a meta-analysis involving 121,000 patients. Am J Med. 2008;121(1):24-33.
11. 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.
12. Ray KK, Seshasai SRK, Erqou S, Sever P, Jukema JW, Ford I, et al. Statins and all-cause mortality in high-risk primary prevention: a meta-analysis of 11 randomized controlled trials involving 65,229 participants. Arch Intern Med. 2010;170(12):1024-31.
13. Manktelow BN, Potter JF. Interventions in the management of serum lipids for preventing stroke recurrence. Cochrane Database Syst Rev. 2009(3):CD002091.
14. Dragomir A, Cote R, White M, Lalonde L, Blais L, Berard A, et al. Relationship between adherence level to statins, clinical issues and health-care costs in real-life clinical setting. Value Health. 2010;13(1):87-94.
15. Tuppin P, Neumann A, Danchin N, de Peretti C, Weill A, Ricordeau P, et al. Evidence-based pharmacotherapy after myocardial infarction in France: adherence-associated factors and relationship with 30-month mortality and rehospitalization. Arch Cardiovasc Dis. 2010;103(6-7):363-75.
16. De Bacquer D, De Backer G. Predictive ability of the SCORE Belgium risk chart for cardiovascular mortality. Int J Cardiol. 2010;143(3):385-90.
17. Chevalier P. Les lipides enfin limpides. Revue de la Médecine Générale. 2007;239:30-5.
18. Abuissa H, O'Keefe JH, Bybee KA. Statins as antiarrhythmics: a systematic review part I: effects on risk of atrial fibrillation. Clin Cardiol. 2009;32(10):544-8.
19. McGuinness B, Craig D, Bullock R, Passmore P. Statins for the prevention of dementia. Cochrane Database Syst Rev. 2009(2):CD003160.
20. Kopterides P, Falagas ME. Statins for sepsis: a critical and updated review. Clin Microbiol Infect. 2009;15(4):325-34.
21. Cannon CP, Braunwald E, McCabe CH, Rader DJ, Rouleau JL, Belder R, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. N Engl J Med. 2004;350(15):1495-504.

22. Nissen SE, Tuzcu EM, Schoenhagen P, Brown BG, Ganz P, Vogel RA, et al. Effect of intensive compared with moderate lipid-lowering therapy on progression of coronary atherosclerosis: a randomized controlled trial. JAMA. 2004;291(9):1071-80.
23. Deedwania P, Stone PH, Bairey Merz CN, Cosin-Aguilar J, Koylan N, Luo D, et al. Effects of intensive versus moderate lipid-lowering therapy on myocardial ischemia in older patients with coronary heart disease: results of the Study Assessing Goals in the Elderly (SAGE). Circulation. 2007;115(6):700-7.
24. Pedersen TR, Faergeman O, Kastelein JJ, Olsson AG, Tikkanen MJ, Holme I, et al. High-dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction: the IDEAL study: a randomized controlled trial. JAMA. 2005;294(19):2437-45.
25. Stone PH, Lloyd-Jones DM, Kinlay S, Frei B, Carlson W, Rubenstein J, et al. Effect of intensive lipid lowering, with or without antioxidant vitamins, compared with moderate lipid lowering on myocardial ischemia in patients with stable coronary artery disease: the Vascular Basis for the Treatment of Myocardial Ischemia Study. Circulation. 2005;111(14):1747-55.
26. Cannon CP, Steinberg BA, Murphy SA, Mega JL, Braunwald E. Meta-analysis of cardiovascular outcomes trials comparing intensive versus moderate statin therapy. J Am Coll Cardiol. 2006;48(3):438-45.
27. Tikkanen MJ, Holme I, Cater NB, Szarek M, Faergeman O, Kastelein JJ, et al. Comparison of efficacy and safety of atorvastatin (80 mg) to simvastatin (20 to 40 mg) in patients aged <65 versus >or=65 years with coronary heart disease (from the Incremental DEcrease through Aggressive Lipid Lowering IDEAL study). Am J Cardiol. 2009;103(5):577-82.
28. Delahoy PJ, Magliano DJ, Webb K, Grobler M, Liew D. The relationship between reduction in low-density lipoprotein cholesterol by statins and reduction in risk of cardiovascular outcomes: an updated meta-analysis. Clin Ther. 2009;31(2):236-44.
29. Weng TC, Yang YHK, Lin SJ, Tai SH. A systematic review and meta-analysis on the therapeutic equivalence of statins. J Clin Pharm Ther. 2010;35(2):139-51.
30. Zhou Z, Rahme E, Pilote L. Are statins created equal? Evidence from randomized trials of pravastatin, simvastatin, and atorvastatin for cardiovascular disease prevention. Am Heart J. 2006;151(2):273-81.
31. Doggrell SA. Is atorvastatin superior to other statins? Analysis of the clinical trials with atorvastatin having cardiovascular endpoints. Rev Recent Clin Trials. 2006;1(2):143-53.
32. Ridker PM, Danielson E, Fonseca FAH, Genest J, Gotto AM, Jr., Kastelein JJP, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med. 2008;359(21):2195-207.
33. de Lorgeril M, Salen P, Abramson J, Dodin S, Hamazaki T, Kostucki W, et al. Cholesterol lowering, cardiovascular diseases, and the rosuvastatin-JUPITER controversy: a critical reappraisal. Arch Intern Med. 2010;170(12):1032-6.
34. Dieleman JP, van Wyk JT, van Wijk MA, van Herpen G, Straus SM, Dunselman H, et al. Differences between statins on clinical endpoints: a population-based cohort study. Curr Med Res Opin. 2005;21(9):1461-8.
35. Motsko SP, Russmann S, Ming EE, Singh VP, Vendiola RM, Jones JK. Effectiveness of rosuvastatin compared to other statins for the prevention of cardiovascular events-a cohort study in 395 039 patients from clinical practice. Pharmacoepidemiol Drug Saf. 2009;18(12):1214-22.
36. Narla V, Blaha MJ, Blumenthal RS, Michos ED. The JUPITER and AURORA clinical trials for rosuvastatin in special primary prevention populations: perspectives, outcomes, and consequences. Vasc Health Risk Manag. 2009;5:1033-42.
37. Silva MA, Swanson AC, Gandhi PJ, Tataronis GR. Statin-related adverse events: a meta-analysis. Clin Ther. 2006;28(1):26-35.
38. Thompson PD, Clarkson P, Karas RH. Statin-associated myopathy. JAMA. 2003;289(13):1681-90.
39. Silva M, Matthews ML, Jarvis C, Nolan NM, Belliveau P, Malloy M, et al. Meta-analysis of drug-induced adverse events associated with intensive-dose statin therapy. Clin Ther. 2007;29(2):253-60.
40. Golomb BA, Evans MA. Statin adverse effects : a review of the literature and evidence for a mitochondrial mechanism. Am J Cardiovasc Drugs. 2008;8(6):373-418.

41. Rodriguez L, Herings R, Johansson S. Use of multiple international healthcare databases for the detection of rare drug-associated outcomes: a pharmacoepidemiological programme comparing rosuvastatin with other marketed statins. Pharmacoepidemiol Drug Saf. 2010.

42. Grundy SM. The issue of statin safety: where do we stand? Circulation. 2005;111(23):3016-9.

43. Graham DJ, Staffa JA, Shatin D, Andrade SE, Schech SD, La Grenade L, et al. Incidence of hospitalized rhabdomyolysis in patients treated with lipid-lowering drugs. JAMA. 2004;292(21):2585-90.

44. Chalasani N. Statins and hepatotoxicity: focus on patients with fatty liver. Hepatology. 2005;41(4):690-5.

45. Chalasani N, Aljadhey H, Kesterson J, Murray MD, Hall SD. Patients with elevated liver enzymes are not at higher risk for statin hepatotoxicity. Gastroenterology. 2004;126(5):1287-92.

46. Sattar N, Preiss D, Murray HM, Welsh P, Buckley BM, de Craen AJM, et al. Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. Lancet. 2010;375(9716):735-42.

47. Dale KM, Coleman CI, Henyan NN, Kluger J, White CM. Statins and cancer risk: a meta-analysis. JAMA. 2006;295(1):74-80.

48. Kuoppala J, Lamminpaa A, Pukkala E. Statins and cancer: A systematic review and meta-analysis. Eur J Cancer. 2008;44(15):2122-32.

49. Sorensen HT, Lash TL. Statins and amyotrophic lateral sclerosis--the level of evidence for an association. J Intern Med. 2009;266(6):520-6.

50. Hippisley-Cox J, Coupland C. Unintended effects of statins in men and women in England and Wales: population based cohort study using the QResearch database. BMJ. 2010;340:c2197.

51. Shepherd J, Hunninghake DB, Stein EA, Kastelein JJP, Harris S, Pears J, et al. Safety of rosuvastatin. Am J Cardiol. 2004;94(7):882-8.

52. Wlodarczyk J, Sullivan D, Smith M. Comparison of benefits and risks of rosuvastatin versus atorvastatin from a meta-analysis of head-to-head randomized controlled trials. Am J Cardiol. 2008;102(12):1654-62.

53. Kobayashi M, Chisaki I, Narumi K, Hidaka K, Kagawa T, Itagaki S, et al. Association between risk of myopathy and cholesterol-lowering effect: a comparison of all statins. Life Sci. 2008;82(17-18):969-75.

54. Baker WL, Talati R, White CM, Coleman CI. Differing effect of statins on insulin sensitivity in non-diabetics: a systematic review and meta-analysis. Diabetes Res Clin Pract. 2010;87(1):98-107.

55. Johansson S, Ming EE, Wallander M-A, Rodriguez LAG, Herings RMC, Goettsch WG, et al. Rosuvastatin safety: a comprehensive, international pharmacoepidemiology programme. Pharmacoepidemiol Drug Saf. 2006;15(7):454-61.

56. Garcia-Rodriguez LA, Gonzalez-Perez A, Stang MR, Wallander M-A, Johansson S. The safety of rosuvastatin in comparison with other statins in over 25,000 statin users in the Saskatchewan Health Databases. Pharmacoepidemiol Drug Saf. 2008;17(10):953-61.

57. Garcia-Rodriguez LA, Masso-Gonzalez EL, Wallander M-A, Johansson S. The safety of rosuvastatin in comparison with other statins in over 100,000 statin users in UK primary care. Pharmacoepidemiol Drug Saf. 2008;17(10):943-52.

58. Hamelin BA, Turgeon J. Hydrophilicity/lipophilicity: relevance for the pharmacology and clinical effects of HMG-CoA reductase inhibitors. Trends Pharmacol Sci. 1998;19(1):26-37.

59. Herman RJ. Drug interactions and the statins. CMAJ. 1999;161(10):1281-6.

60. Neyt M, De Laet C, Van Brabandt H, Franco O, Ramaekers D. Cost-effectiveness of statins in the primary prevention of cardiovascular disease: a systematic review and economic analysis for Belgium. Acta Cardiol. 2009;64(1):1-10.

61. De Bacquer D, De Backer G. The prevalence of concomitant hypertension and hypercholesterolaemia in the general population. Int J Cardiol. 2006;110(2):217-23.

62. Carling CLL, Kristoffersen DT, Montori VM, Herrin J, Schunemann HJ, Treweek S, et al. The effect of alternative summary statistics for communicating risk reduction on decisions about taking statins: a randomized trial. PLoS Med. 2009;6(8):e1000134.

63. Kotseva K, Wood D, De Backer G, De Bacquer D, Pyorala K, Keil U, et al. Cardiovascular prevention guidelines in daily practice: a comparison of EUROASPIRE I, II, and III surveys in eight European countries. Lancet. 2009;373(9667):929-40.

64. Nicholls SJ, Brandrup-Wognsen G, Palmer M, Barter PJ. Meta-analysis of comparative efficacy of increasing dose of Atorvastatin versus Rosuvastatin versus Simvastatin on lowering levels of atherogenic lipids (from VOYAGER). Am J Cardiol. 2010;105(1):69-76.

65. Sakshaug S, Furu K, Karlstad O, Ronning M, Skurtveit S. Switching statins in Norway after new reimbursement policy: a nationwide prescription study. Br J Clin Pharmacol. 2007;64(4):476-81.

66. Martikainen JE, Saastamoinen LK, Korhonen MJ, Enlund H, Helin-Salmivaara A. Impact of restricted reimbursement on the use of statins in Finland: a register-based study. Med Care. 2010;48(9):761-6.

67. Mann DM, Woodward M, Muntner P, Falzon L, Kronish I. Predictors of nonadherence to statins: a systematic review and meta-analysis. Ann Pharmacother. 2010;44(9):1410-21.

68. Mitka M. Improving medication adherence promises great payback, but poses tough challenge. JAMA. 2010;303(9):825.

69. Bates TR, Connaughton VM, Watts GF. Non-adherence to statin therapy: a major challenge for preventive cardiology. Expert Opin Pharmacother. 2009;10(18):2973-85.

70. Shitara Y, Sugiyama Y. Pharmacokinetic and pharmacodynamic alterations of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors: drug-drug interactions and interindividual differences in transporter and metabolic enzyme functions. Pharmacol Ther. 2006;112(1):71-105.

71. Josan K, Majumdar SR, McAlister FA. The efficacy and safety of intensive statin therapy: a meta-analysis of randomized trials. CMAJ. 2008;178(5):576-84.

72. Manuel DG, Kwong K, Tanuseputro P, Lim J, Mustard CA, Anderson GM, et al. Effectiveness and efficiency of different guidelines on statin treatment for preventing deaths from coronary heart disease: modelling study. BMJ. 2006;332(7555):1419.

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