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Viewpoint

A Reappraisal of the Safety and Cost-Effectiveness of Statin Therapy in Primary Prevention

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ABSTRACT

Statins are among the most investigated drugs of all time. There is now a wealth of evidence supporting their use in the primary and secondary prevention arenas. The reduction in event recurrence has since been demonstrated across all levels of risk and in elderly patients. As a result, it is now accepted practice for statins to be prescribed universally in secondary prevention unless contraindicated. The extension of this policy into the primary prevention setting is more problematic, with moral and financial issues arising from the long-term treatment of many young apparently healthy individuals. For these reasons it is necessary to prove not only the financial sustainability of such a strategy but also the long-term safety of statins and the degree of benefit that might be expected.

RÉSUMÉ

Les statines sont parmi les médicaments les plus étudiés de tous les temps. Il existe maintenant une quantité de données probantes appuyant leur utilisation dans la sphère de la prévention primaire et secondaire. La réduction de la récurrence des événements a été depuis démontrée à tous les niveaux de risque et chez les patients âgés. Par conséquent, la pratique admet maintenant universellement de prescrire les statines en prévention secondaire, à moins de contre-indication. L'élargissement de cette pratique à la prévention primaire est plus problématique, du fait des questions morales et financières découlant du traitement à long terme de plusieurs jeunes individus apparemment en santé. Pour ces raisons, il est nécessaire de non seulement prouver la viabilité financière d'une telle stratégie, mais de prouver également l'innocuité à long terme des statines et les avantages auxquels on pourrait s'attendre.

The care of patients with cardiovascular disease has been revolutionized with the use of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins), and as a commercial entity, statins have been unprecedented.

After the development of the first statin in the 1970s, mevastatin, the class has enjoyed exponential market growth with one particular product, atorvastatin, becoming the most profitable pharmaceutical in history and dominating world best-selling lists for almost a decade. To sustain this level of marketability, the pharmaceutical industry has continued to search for new potential avenues to exploit the effects of statins on cardiovascular risk. If the drugs were ever to be recommended for the primary prevention of cardiovascular events in a low-risk population, it would represent a major coup for industry and as such, considerable pressure exists for this strategy to be adopted. It is therefore essential that a compelling level of independent evidence supports the long-term use and safety of these drugs before any significant change to existing guidelines is implemented.

Statin Trials

It is now accepted practice for statins to be prescribed universally in secondary prevention unless contraindicated. The extension of this policy into the primary prevention setting is more problematic, with moral and financial issues arising from the long-term treatment of many young apparently healthy individuals. Some of the major primary prevention trials of the past 2 decades are summarized herein (Table 1), but it is necessary to prove not only the financial sustainability of such a strategy but also the long-term safety of statins.

Cost-Effectiveness

The financial outlook for long-term statin use is not unfavourable. After the loss of simvastatin's patent protection in 2006 and the subsequent advent of generically available statins, market competition has driven down the cost of this preparation making it a more attractive long-term prescription[13]

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Table 1. Data for subjects without clinically manifest coronary heart disease

Trial	Subjects	Mean age, years	% Male	Intervention	% Diabetic	Mean follow-up, years	Event rates per 1000 person-years (statin arm)	Event rates per 1000 person-years (placebo arm)	Number needed to treat
JUPITER (2008)[2]	17,802	66	62	Rosuvastatin 20 mg daily	0	2.2	10	12.5	95
MEGA (2006)[3]	7832	58	32	Pravastatin 40 mg daily	21	4.6	2.4	3.6	119
ASPEN (2006)[4]	1905	61	62	Atorvastatin 10 mg daily	100	4.3	10.8	10.2	-
HYRIM (2005)[5]	65,229	62	65	Fluvastatin 40 mg daily	19	3.7	10.7	11.4	-
PREVEND IT (2004)[6]	864	51	65	Pravastatin 40 mg daily	2.5	3.8	7.7	7.2	55
CARDS (2004)[7]	2838	62	68	Atorvastatin 10 mg daily	100	4	10.7	14.5	32
ASCOT (2003)[8]	8715	63	81	Atorvastatin 10 mg daily	25	3.3	10.9	12.4	32
ALLHAT (2002)[9]	8880	66	51	Pravastatin 40 mg daily	35	4.8	24.3	24.3	91
PROSPER (2002)[10]	3239	75	42	Pravastatin 40 mg daily	12	3.2	27.2	26	21
AFCAPS/TexCAPS IT (1998)[11]	6605	58	85	Lovastatin 20-40 mg daily	6	5.2	4.6	4.4	24
WOSCOPS (1995)[12]	5981	55	100	Pravastatin 40 mg daily	1	4.9	6.4	8.2	44

AFCAPS/TexCAPS, **A**ir **F**orce/**Tex**as **C**oronary **A**therosclerosis **P**revention **S**tudy; ALLHAT, **A**ntihypertensive and **L**ipid-**L**owering Treatment to Prevent **H**eart **A**ttack **T**rial; ASCOT, **A**nglo-**S**candinavian **C**ardiac **O**utcomes **T**rial; ASPEN, **A**torvastatin **S**tudy for **P**revention of Coronary Heart Disease **E**ndpoints in **N**on-Insulin-Dependent Diabetes Mellitus; CARDS, **C**ollaborative **Ator**vastatin **D**iabetes **S**tudy; HYRIM, **H**ypertension High **R**isk **M**anagement; JUPITER, **J**ustification for the **U**se of Statins in **P**revention: An **I**ntervention **T**rial **E**valuating **R**osuvastatin; MEGA, **M**anagement of **E**levated Cholesterol in the Primary Prevention **G**roup of **A**dult Japanese; PREVEND IT, **P**revention of **R**enal and **V**ascular **End**stage Disease **I**ntervention Trial; PROSPER, **Pro**spective **S**tudy of **P**ravastatin in the **E**lderly at **R**isk; WOSCOPS, **W**est **o**f **S**cotland **Co**ronary **P**revention **S**tudy.

(USD$4 per month vs CAD$10 per month). A recent American analysis found that the treatment of all persons older than the age of 34 years with low-density lipoprotein levels > 130 mg/dL would be cost-effective if the cost of statins was no greater than 10 cents per pill.[14] Data from the Heart Protection Study on the cost-effectiveness of prescribing simvastatin 40 mg daily for a range of risk profiles confirmed the cost saving of lifetime statin use.[15] In those aged 40-49 years with a 42% and 12% 5-year risk of a cardiovascular event, 2.49 and 1.67 life-years were gained from treatment, respectively. Moreover, the cost of treatment was found to be economical in subjects aged 35-85 years, costing < $4500 per life-year gained.[15]

A recent European meta-analysis examined data for 45- to 75-year-old individuals without antecedent cardiovascular disease in trials of low-dose statin therapy vs no treatment.[16] Cost per quality-adjusted life-year ranged from €5000-125,000 for men aged 55 years with an estimated risk of a cardiovascular event of 2.5%-5%, with an incremental cost-effective ratio with increasing risk. The conclusion was that statin therapy is not yet cost-effective in a low-risk primary prevention population, highlighting the need for more accurate identification of subgroups within the low-risk population in whom it would be cost-effective to initiate early statin therapy.

Safety

There is also the issue of exposing an apparently healthy cohort to lifelong medical therapy with uncertainties regarding long-term safety profiles. Could it be that significant numbers of initially healthy individuals could develop a statin-induced health problem after years of treatment? At this moment such a scenario seems unlikely because the intense postmarketing attention received by this group to date has failed to identify a common serious side effect.

Statins as a group have an excellent safety profile, the most widely identified adverse effect is liver dysfunction, however, recent data with respect to this are encouraging. Statins increase levels of the liver enzyme alanine transferase in 10% of cases and results in an increase greater than 3 times the upper limit of normal in approximately 1%.[17] Subsequently values return to normal even if the same statin is continued.[17] In a post hoc analysis of the **G**reek **A**torvastatin and Coronary Heart Disease **E**valuation (GREACE) trial, Athyros et al.[18] examined the efficacy and safety of statins in those with increased liver enzyme levels less than 3 times the upper limit of normal. No adverse effect of therapy was found and interestingly, the group with abnormal baseline enzyme levels had the greatest benefit from statin therapy. This is of great concern because it is common practice for individuals with baseline mild liver dysfunction to be denied treatment. Data from the Heart Protection Study on usage of simvastatin 40 mg daily in > 20,000 patients found no significant difference between control and treatment groups in the incidence of serious liver damage and an undetectable rate of hepatitis.[19] In a large prospective cohort study of over 2 million primary care patients aged 30-84 years, the number needed to harm over 5 years for severe liver dysfunction was 136.[20] This study also examined the evidence of nonliver side effects from statin usage and reported numbers needed to harm as 434 for acute renal failure, 33 for cataract, and 259 for severe myopathy in women and 91 in men. The risk of these effects all returned to normal within 1-3 years of statin treatment cessation.[20] In addition, the study examined number needed to treat and found that based on the 20% threshold for 10-year cardiovascular risk for women, the number needed to treat with any statin to prevent 1 case of cardiovascular disease over 5 years was 37 and for men 33. Overall the evidence argues against there being any significant link between statin use and liver dysfunction beyond that seen in the general population.[17] In addition to this another much publicized adverse effect, the serious muscle disorder rhabdomyolysis has been reported extremely rarely at a rate of 3-4 per 100,000 person-years of treatment.[21]

One recent meta-analysis has also highlighted the potential increase in diabetes risk, with use of a statin over 4 years associated with a 1 in 255 excess risk of developing