Statin wars following coronary revascularization – Evidence-based clinical practice?

James M Brophy MD PhD^{1,2}, Vania Costa MSc²

JM Brophy, V Costa. Statin wars following coronary revascularization – Evidence-based clinical practice? *Can J Cardiol* 2006;22(1):54-58.

BACKGROUND: Randomized clinical trials (RCTs) have shown that statins provide substantial health benefits. Pharmaceutical companies spend enormous amounts of money on both clinical trials and marketing. The relative influence of information from clinical trials on physician prescription patterns for statins is unknown.

OBJECTIVE: To examine the correlation between statin prescription patterns and the quality of evidence from RCTs.

METHODS: Using the computerized administrative databases of the Quebec Health Insurance Board, the choice of statin for elderly patients (older than 65 years of age) following a coronary revascularization procedure (percutaneous coronary intervention or coronary artery bypass graft surgery) performed between January 1, 1994, and June 30, 2003, was examined. Prescriptions for each statin were compared with their evidence base obtained from a cumulative systematic literature review of RCTs that recorded mortality as an outcome and were published before December 31, 2002.

RESULTS: The study cohort comprised 27,979 elderly revascularized patients who received at least one statin prescription. In 1996, the year atorvastatin was introduced, simvastatin and pravastatin had 38.3% and 37.1% of the market share, respectively. By 2003, atorvastatin had 44% of the market share, compared with 29.9% and 24.1% for simvastatin and pravastatin, respectively. In contrast, RCTs published up to the end of 2002 had culminated in 133,341 and 140,565 patient-years of follow-up for simvastatin and pravastatin, respectively, and only 1459 patient-years for atorvastatin.

CONCLUSIONS: Prescription patterns regarding the choice of statin do not appear to be determined uniquely from high-quality RCTs. Further research into the other possible determinants of physician prescription patterns is necessary.

Key Words: Cholesterol; Prescription patterns; Secondary prevention; Statins

Cholesterol-lowering medications, particularly 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors – popularly known as statins – provide meaningful health benefits for patients (1). However, the importance of advertising as a means of advancing statin sales has become a cause célèbre, and a 2003 editorial in *The Lancet* (2) criticized AstraZeneca (United Kingdom) for its aggressive promotional plans for rosuvastatin. To evaluate whether this is a legitimate concern, we investigated the correlation between physicians'

La guerre des statines après une revascularisation coronarienne : pratique clinique fondée sur les preuves?

CONTEXTE : Les essais cliniques avec hasardisation (ECH) ont montré que les statines avaient un effet salutaire important. Les sociétés pharmaceutiques dépensent des sommes considérables pour les essais cliniques et pour la commercialisation. Toutefois, on ne sait pas dans quelle mesure l'information provenant des essais cliniques influence les médecins dans leurs habitudes de prescription des statines.

BUT : Étudier la corrélation entre les prescriptions de statines et la qualité des données provenant des ECH.

MÉTHODE : Nous avons examiné, à partir de la base de données administratives de la Régie de l'assurance maladie du Québec, le type de statines prescrit à des patients âgés (plus de 65 ans), après une revascularisation coronarienne (intervention coronarienne percutanée ou pontage coronarien) pratiquée entre le 1^{er} janvier 1994 et le 30 juin 2003. Les prescriptions pour chacune des statines ont été comparées aux données obtenues par un examen systématique de l'ensemble de la documentation sur les ECH qui avaient pour critère la mortalité et qui avaient été publiés avant le 31 décembre 2002.

RÉSULTATS : La cohorte à l'étude comptait 27 979 patients âgés qui avaient subi une revascularisation et qui avaient reçu au moins une ordonnance de statines. En 1996, année de l'arrivée de l'atorvastatine sur le marché, les parts de marché de la simvastatine et de la pravastatine étaient de 38,3 % et de 37,1 % respectivement. En 2003, la part de marché de l'atorvastatine était de 44 % par rapport à 29,9 % et à 24,1 % pour la simvastatine et la pravastatine respectivement. Par contre, la documentation publiée sur les ECH jusqu'à la fin de 2002 comptait 133 341 et 140 565 années-patient cumulées de suivi pour la simvastatine et la pravastatine respectivement contre seulement 1459 années-patient pour l'atorvastatine.

CONCLUSION : Les habitudes de prescription des médecins quant au choix des statines ne semblent pas uniquement déterminées par la bonne qualité des ECH. Aussi faudrait-il pousser plus loin la recherche sur les autres déterminants possibles des habitudes de prescription des médecins.

prescription patterns for a statin following coronary revascularization and the available published evidence base.

METHODS

The present study was conducted by using the computerized administrative databases of the Régie de l'assurance maladie du Québec, which were developed in the context of the universal insurance program provided to the residents of Quebec. These databases capture all data on physician visits, procedures, hospitalizations,

¹Division of Cardiology; ²Division of Clinical Epidemiology, Royal Victoria Hospital/McGill University Health Centre, Montreal, Quebec

Correspondence: Dr James M Brophy, Divisions of Cardiology and Clinical Epidemiology, Ross Pavilion Room 4.12, Royal Victoria

Hospital/McGill University Health Centre, 687 Pine Avenue West, Montreal, Quebec H3A 1A1. Telephone 514-934-1934 ext 36771,

fax 514-843-1493, e-mail james.brophy@mcgill.ca

Received for publication May 25, 2005. Accepted July 21, 2005

TABLE 1
Characteristics of the study cohort*

Age, years (mean $\pm$ SD)	72.3 $\pm$ 5.2
Male sex, n (%)	32,027 (63.9)
Length of follow-up, days (mean $\pm$ SD)	179.6 $\pm$ 6.7
Length of hospital stay, days (mean $\pm$ SD)	18.8 $\pm$ 20.6
Diabetes, n (%)	13,254 (26.4)
Hypertension, n (%)	24,704 (49.3)
Congestive heart failure, n (%)	8,016 (16.0)
Myocardial infarction, n (%)	17,762 (35.4)
Unstable angina, n (%)	20,854 (41.6)
Prior use of statins, n (%)	16,824 (33.6)
Time from discharge to prescription, days (mean $\pm$ SD)	24.4 $\pm$ 40.2

*The study cohort (n=50,120) comprised patients older than 65 years of age who filled a statin prescription in the 180 days following a revascularization procedure performed between January 1, 1994, to June 30, 2003

outpatient prescription drugs dispensed and vital status. Outpatient prescription data include information on the nature, quantity, strength, dose and dispensing date of all drugs. The hospital database contains information on all hospital procedures, patient demographics, admission and discharge dates, and up to 15 discharge diagnoses coded by using the *International Classification of Diseases, Ninth Revision* (3). In-hospital prescription drug use is, unfortunately, not captured.

All databases were linked through the use of a unique and anonymous identifier, thereby creating a longitudinal history of each patient's clinical outcome and pattern of drug use following their revascularization procedure. The outpatient prescription drug database is complete only for those 65 years of age or older. Cohort entry was defined by the first revascularization procedure occurring between January 1, 1994, and June 30, 2003, followed by at least one statin prescription within 180 days of hospital discharge. Patients may have had previous revascularization procedures and statin exposure. The only patients excluded from the cohort were those younger than 65 years of age at the time of their revascularization procedure, those dying during their initial hospitalization, and non-Quebec residents. The reliability of these hospital administrative databases for cardiac procedures and medications has been previously validated (4-6).

A systematic electronic search of the medical literature of original research from January 1, 1990, to December 31, 2002, was performed on MEDLINE using the key words 'statins' or 'cholesterol-lowering' or 'HMG CoA inhibitor' and 'clinical trials' and 'mortality'. Only blinded, randomized clinical trials that had a minimum of 12-weeks follow-up and that reported mortality were retained. If more than one article was published for a particular study, then only the first publication that included mortality results was retained. The references of meta-analyses of studies with statins were also searched to verify whether additional studies could be included. The total number of patient-years of follow-up for each study was calculated based on the average follow-up time reported for patients on both active treatment and placebo. All statistical analyses were performed using SAS statistical software (version 8.0, SAS Institute, USA). The Cochran-Armitage test was used to assess time trends in drug prescribing.

RESULTS

During the period of January 1, 1994, to June 30, 2003, 109,503 patients underwent a coronary revascularization

Figure 1 First statin prescribed after revascularization (percentage of each statin). Letters in the graph represent the publication of studies with more than 4000 patients and, as follows, are defined by the type of statin examined, the year of study publication, the name of the study and the number of patients examined: study A (simvastatin, 1994, Scandinavian Simvastatin Survival Study [4S], 4444 patients [7]); study B (simvastatin, 2002, Medical Research Council/British Heart Foundation Heart Protection Study, 20,536 patients [13]); study C (pravastatin, 1995, West of Scotland Coronary Prevention Study [WOSCOPS], 6595 patients [22]); study D (pravastatin, 1996, Cholesterol And Recurrent Events [CARE] study, 4159 patients [41]); study E (pravastatin, 1998, Long-Term Intervention with Pravastatin in Ischaemic Disease [LIPID] study, 9014 patients [28]); study F (pravastatin, 2000, Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico [GISSI], 4271 patients [29]); study G (pravastatin, 2002, Prospective Study of Pravastatin in the Elderly at Risk [PROSPER], 5804 patients [31]); study H (lovastatin, 1998, Air Force/Texas Coronary Atherosclerosis Prevention Study [AFCAPS/TexCAPS], 6605 patients [19])

procedure (64,765 underwent angioplasty and 44,738 underwent coronary artery bypass graft surgery), of whom 50,120 were older than 65 years of age and survived to hospital discharge (Table 1). Of these, 27,979 patients received at least one statin prescription in the 180 days following their revascularization procedure and formed the study cohort.

In 1995, the distribution of statins was evenly split among three statins: lovastatin, pravastatin and simvastatin (Figure 1). However, in 1996, the year atorvastatin was introduced, simvastatin, pravastatin and lovastatin had 38.3%, 37.1% and 20% of the market share, respectively. Over the study period, the rate of prescriptions for these three statins progressively declined, whereas the use of atorvastatin increased progressively to 50% of the total Quebec market by 2001. In 2003, atorvastatin still had 44% of the market share, compared with 29.9% and 24.1% for simvastatin and pravastatin, respectively.

Randomized clinical trials of statins reporting mortality were first published in 1994 and, by December 31, 2002, 30 studies (7-36) were identified that met the inclusion criteria (Table 2). Figure 2 shows the evidence base for each of the statins expressed as the number of patient-years of follow-up from these randomized, double-blinded trials. In summary, all of the statins, with the exception of atorvastatin and fluvastatin, had published large mortality trials before December 31, 2002; atorvastatin and fluvastatin both published large mortality trials after 2002 (37,38). The lateness of these publications is unlikely to have had an influence on prescribing patterns in the years of the present study.

The comparison between pravastatin and atorvastatin is most striking. Although there were over 100,000 patient-years of published experience with pravastatin from 1998 onward,

TABLE 2
Randomized clinical trials of statins reporting mortality results

Study (reference)	Year published	n	Mean follow-up (years)	Patient-years	Cumulative patient-years
Simvastatin					
4S (7)	1994	4444	5.4	23,998	23,998
Keech et al (8)	1994	621	3.4	2111	26,109
MAAS (9)	1994	404	4.0	1616	27,725
CIS (10)	1997	254	2.3	584	28,309
SCAT (11)	2000	460	4.0	1840	30,149
Brown et al (12)	2001	160	3.2	512	30,661
MRC/BHF Heart Protection Study (13)	2002	20,536	5.0	102,680	133,341
Lovastatin					
MARS (14)	1993	270	2.2	594	594
ACAPS (15)	1994	919	2.8	2611	3205
CRISP (16)	1994	431	1.0	431	3636
LRT (17)	1994	404	0.5	202	3838
Post-CABG (18)	1997	1351	4.3	5809	9647
AFCAPS/TexCAPS (19)	1998	6605	5.2	34,346	43,993
Pravastatin					
PMSG (20)	1993	1062	0.5	531	531
PLAC I and II (21)	1995	559	3.0	1677	2208
WOSCOPS (22)	1999	6595	4.9	32,315	34,523
REGRESS (23)	1995	885	2.0	1770	36,293
KAPS (24)	1995	424	3.0	1272	37,565
CARE (25)	1999	4159	5.0	20,795	58,360
Bertrand et al (26)	1997	695	0.5	350	58,710
CARS (27)	1997	80	2.0	160	58,870
LIPID (28)	1998	9014	6.1	54,985	113,855
GISSI-P (29)	2000	4271	1.9	8115	121,970
Den Hartog et al (30)	2001	99	0.2	22	121,992
PROSPER (31)	2002	5804	3.2	18,573	140,565
Fluvastatin					
LCAS (32)	1996	429	2.5	1073	1073
FLARE (33)	1999	1054	0.8	843	1946
Riegger et al (34)	1999	365	1.0	365	2311
Atorvastatin					
AVERT (35)	1999	341	1.5	512	512
MIRACL (36)	2001	3086	0.3	947	1459

4S Scandinavian Simvastatin Survival Study; ACAPS Asymptomatic Carotid Artery Progression Study; AFCAPS/TexCAPS Air Force/Texas Coronary Atherosclerosis Prevention Study; AVERT Atorvastatin Versus Revascularization Treatment study; CABG Coronary artery bypass graft; CARE Cholesterol And Recurrent Events study; CARS Coronary Artery Regression Study; CIS Coronary Intervention Study; CRISP Cholesterol Reduction in Seniors Program; FLARE Fluvastatin Angiographic Restenosis study; GISSI-P Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico - Prevenzione; KAPS Kuopio Atherosclerosis Prevention Study; LCAS Lipoprotein and Coronary Atherosclerosis Study; LIPID Long-Term Intervention with Pravastatin in Ischaemic Disease study; LRT Lovastatin Restenosis Trial; MAAS Multicentre Anti-Atheroma Study; MARS Monitored Atherosclerosis Regression Study; MIRACL Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering study; MRC/BHF Medical Research Council/British Heart Foundation; PLAC Pravastatin Limitation of Atherosclerosis in the Coronary Arteries study; PMSG Pravastatin Multinational Study Group; PROSPER Prospective Study of Pravastatin in the Elderly at Risk; REGRESS Regression Growth Evaluation Statin Study; SCAT Simvastatin/Enalapril Coronary Atherosclerosis Trial; WOSCOPS West of Scotland Coronary Prevention Study

with a cumulative total of over 140,000 patient-years in 2002, use of this medication continued to fall, while atorvastatin use increased despite an evidence base of less than 1500 patient-years of clinical outcomes by the end of 2002.

Figure 2) Evidence base for each of the statins expressed as the number of patient-years of follow-up from double-blind, randomized controlled trials (RCTs). Data from references listed in Table 2

Family physicians were responsible for the initial statin prescription following revascularization for 12,498 (44.7%) patients, and atorvastatin was prescribed in 41.2% of cases. Medical specialists initiated the first prescription in the remaining patients and chose atorvastatin in 33.5% of cases (a difference of 7.7% [95% CI 6.6 to 8.8, $P < 0.0002$]).

DISCUSSION

The present study of statin prescription trends following coronary revascularization performed between 1994 and 2003 shows a dramatic increase in the use of atorvastatin, with a corresponding decrease in the earlier marketed statins, namely, lovastatin, pravastatin and simvastatin. This change in prescribing patterns occurred during a time when an abundance of evidence showed the salutary clinical benefits of lovastatin, pravastatin and simvastatin. Conversely, atorvastatin studies generally involved the surrogate end point of cholesterol lowering with very little evidence for benefits on clinical outcomes (39). Both general practitioners and specialists initiated a substantial number of new prescriptions with atorvastatin, although general practitioners did favour atorvastatin slightly more.

In an evaluation of prescriptions of statins in Canada until April 1999, Mamdani and Tu (40) noted that statin prescription trends for pravastatin and simvastatin increased following publication of their major (positive) clinical trials. They also noted the advancing sales of atorvastatin without the same evidence base. Our study extends their observations by including not only major clinical trials but by systematically including all clinical studies and by quantifying the evidence in patient-years, as well as extending the time of observation until 2003. A recent study from Britain (41) has also noted a large increase in atorvastatin prescriptions in Britain from 1998 to 2002, suggesting that this phenomenon is not restricted to Canadian prescribing patterns.

Although the observed trends may suggest that prescribing patterns are influenced by variables other than clinical research, it also possible that clinicians were simply prescient about the added advantages of aggressive cholesterol lowering. For example, in 1993, the National Cholesterol Education Program guidelines (42) recommended that target low density lipoprotein cholesterol levels should be less than 2.6 mmol/L in patients with coronary artery disease, but little evidence was provided as to what additional clinical benefit could be expected with that

degree of cholesterol lowering. Because laboratory studies (39,43-45) have shown that atorvastatin is associated with more intense cholesterol lowering than with other statins, it is perhaps not surprising that atorvastatin prescriptions increased dramatically. However, some may find it both troubling and perplexing that a drug with so little information concerning clinical outcomes, including mortality, could capture such a large amount of the market share, especially when existing, high-quality clinical information had already shown the benefits of other statins. It was only in 2003 that the first mortality trial showing the efficacy of atorvastatin was published (37) and in 2004 that the first comparative trial of the different statins was completed (46).

Although the Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT) trial (46), which randomly assigned acute coronary syndrome patients to either atorvastatin or pravastatin, suggests that atorvastatin is associated with improved clinical outcomes, the practice of assuming drug equivalency without the necessary clinical research (especially when proven alternatives exist) is potentially dangerous. Is the gamble of theoretical but unknown benefits worth the risk of taking an understudied drug? There is no clear answer to this question, and different people may react differently to this decision. It is unknown whether patients were given the complete facts surrounding the strength of the evidence regarding the different statins. A reasonable and informed patient may elect to take a proven medication with over 100,000 patient-years of clinical benefit over another medication with a theoretical advantage but only 1% of the clinical evidence.

Although randomized trials are not powered to detect rare side effects, and postmarketing pharmacovigilance is a necessary component of all drug regulation, many patients may find the 140,000 patient-years of detailed follow-up with pravastatin to be more reassuring toward the quantification of any adverse events than the 1500 patient-years for atorvastatin. In this context, the example of cerivastatin, another very potent statin that markedly lowers cholesterol levels (47), is worth recalling. In postmarketing studies, cerivastatin was found to be associated with an increased risk of rhabdomyolysis (48), which led to its withdrawal from the market and the initiation of extensive litigation (49).

Statins provide a major source of revenue for the pharmaceutical industry and have been estimated to have an annual market of US\$22 billion worldwide (50), with atorvastatin

having the largest share at US\$8 to US\$11 billion (2,51). The breakdown between research and development and marketing costs is not specifically available for atorvastatin or the other statins. However, it has been reported that expenses attributed to 'marketing and administration' constitute more than 33% of sales and have twice the cost of research and development (52).

Although pharmaceutical companies are renowned for their marketing largesse, they should not be seen as the only culprits in shifting prescription patterns. Many leading academics, including authors of guidelines, have advanced the need to attain the lowest possible cholesterol levels without, at least for the initial time period of the present study, any concrete proof that more potent statins are superior or, indeed, even equivalent to other statins. These data suggest that some combination of surrogate laboratory studies, early endorsement by leading clinicians and professional societies, and extensive marketing strategies carry more influence over the prescribing patterns of malleable clinicians than high-quality, published clinical research of randomized trials.

Does the recent publication of the head-to-head trial showing improved outcomes with the more potent atorvastatin provide a happy conclusion to the statin wars saga? Not necessarily. The large financial rewards that the manufacturers of atorvastatin attained with little investment in clinical research risks the encouragement of other pharmaceutical companies to follow the same strategy. Where is the incentive for companies to perform clinically relevant research if they are not adequately rewarded by responsible prescribing habits? In the absence of demonstrated, incremental, clinically worthwhile health benefits, the continuous adoption of newer 'me-too' drugs cannot be justified because these drugs also come with extended patent protection and higher purchase costs, further accentuating already overwhelming drug costs. The development of more me-too drugs implies less effort and spending on innovative research and the development of new drugs.

The present study suggests that concern over the marketing tactics of pharmaceutical companies in the statin wars (2) is justified. Sensitizing physicians to the importance of basing prescribing patterns on evidence-based medicine may serve to mitigate its rapacious impact.

ACKNOWLEDGEMENTS: Dr Brophy receives financial support from le Fonds de la Recherche en Santé du Québec.

REFERENCES

- Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *JAMA* 2001;285:2486-97.
- The statin wars: Why AstraZeneca must retreat. *Lancet* 2003;362:1341.
- International Classification of Diseases, Ninth Revision. Geneva: World Health Organization, 1979.
- Conseil d'évaluation des technologies de la santé. Revascularization techniques used in the treatment of stable angina pectoris. Montréal: Conseil d'évaluation des technologies de la santé, 1996.
- Levy AR, Tamblyn RM, Fitchett D, McLeod PJ, Hanley JA. Coding accuracy of hospital discharge data for elderly survivors of myocardial infarction. *Can J Cardiol* 1999;15:1277-82.
- Tamblyn R, Lavoie G, Petrella L, Monette J. The use of prescription claims databases in pharmacoepidemiological research: The accuracy and comprehensiveness of the prescription claims database in Quebec. *J Clin Epidemiol* 1995;48:999-1009.
- Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: The Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994;344:1383-9.
- Keech A, Collins R, MacMahon S, et al. Three-year follow-up of the Oxford Cholesterol Study: Assessment of the efficacy and safety of simvastatin in preparation for a large mortality study. *Eur Heart J* 1994;15:255-69.
- Effect of simvastatin on coronary atheroma: The Multicentre Anti-Atheroma Study (MAAS). *Lancet* 1994;344:633-8.
- Bestehorn HP, Rensing UF, Roskamm H, et al. The effect of simvastatin on progression of coronary artery disease. The Multicenter coronary Intervention Study (CIS). *Eur Heart J* 1997;18:226-34.
- Teo KK, Burton JR, Buller CE, et al. Long-term effects of cholesterol lowering and angiotensin-converting enzyme inhibition on coronary atherosclerosis: The Simvastatin/Enalapril Coronary Atherosclerosis Trial (SCAT). *Circulation* 2000;102:1748-54.
- Brown BG, Zhao XQ, Chait A, et al. Simvastatin and niacin, antioxidant vitamins, or the combination for the prevention of coronary disease. *N Engl J Med* 2001;345:1583-92.
- Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in

- 20,536 high-risk individuals: A randomised placebo-controlled trial. *Lancet* 2002;360:7-22.
14. Blankenhorn DH, Azen SP, Krams DM, et al; MARS Research Group. Coronary angiographic changes with lovastatin therapy. The Monitored Atherosclerosis Regression Study (MARS). *Ann Intern Med* 1993;119:969-76.
15. Furberg CD, Adams HP Jr, Applegate WB, et al. Effect of lovastatin on early carotid atherosclerosis and cardiovascular events. Asymptomatic Carotid Artery Progression Study (ACAPS) Research Group. *Circulation* 1994;90:1679-87.
16. LaRosa JC, Applegate W, Crouse JR III, et al. Cholesterol lowering in the elderly. Results of the Cholesterol Reduction in Seniors Program (CRISP) pilot study. *Arch Intern Med* 1994;154:529-39.
17. Weintraub WS, Bocuzzi SJ, Klein JL, et al. Lack of effect of lovastatin on restenosis after coronary angioplasty. Lovastatin Restenosis Trial Study Group. *N Engl J Med* 1994;331:1331-7.
18. The effect of aggressive lowering of low-density lipoprotein cholesterol levels and low-dose anticoagulation on obstructive changes in saphenous-vein coronary-artery bypass grafts. The Post Coronary Artery Bypass Graft Trial Investigators. *N Engl J Med* 1997;336:153-62. (Erratum in 1997;337:1859).
19. Downs JR, Clearfield M, Weis S, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: Results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. *JAMA* 1998;279:1615-22.
20. The Pravastatin Multinational Study Group for Cardiac Risk Patients. Effects of pravastatin in patients with serum total cholesterol levels from 5.2 to 7.8 mmol/liter (200 to 300 mg/dl) plus two additional atherosclerotic risk factors. *Am J Cardiol* 1993;72:1031-7.
21. Furberg CD, Pitt B, Byington RP, Park JS, McGovern ME. Reduction in coronary events during treatment with pravastatin. PLAC I and PLAC II Investigators. Pravastatin Limitation of Atherosclerosis in the Coronary Arteries. *Am J Cardiol* 1995;76:60C-63C.
22. Caro J, Klittich W, McGuire A, et al. International economic analysis of primary prevention of cardiovascular disease with pravastatin in WOSCOPS. West of Scotland Coronary Prevention Study. *Eur Heart J* 1999;20:263-8.
23. Jukema JW, Bruschke AV, van Boven AJ, et al. Effects of lipid lowering by pravastatin on progression and regression of coronary artery disease in symptomatic men with normal to moderately elevated serum cholesterol levels. The Regression Growth Evaluation Statin Study (REGRESS). *Circulation* 1995;91:2528-40.
24. Salonen R, Nyyssönen K, Porkkala E, et al. Kuopio Atherosclerosis Prevention Study (KAPS). A population-based primary preventive trial of the effect of LDL lowering on atherosclerotic progression in carotid and femoral arteries. *Circulation* 1995;92:1758-64.
25. Flaker GC, Warnica JW, Sacks FM, et al. Pravastatin prevents clinical events in revascularized patients with average cholesterol concentrations. Cholesterol and Recurrent Events CARE Investigators. *J Am Coll Cardiol* 1999;34:106-12.
26. Bertrand ME, McFadden EP, Fruchart JC, et al. Effect of pravastatin on angiographic restenosis after coronary balloon angioplasty. The PREDICT Trial Investigators. Prevention of Restenosis by Elisor after Transluminal Coronary Angioplasty. *J Am Coll Cardiol* 1997;30:863-9.
27. Tamura A, Mikuriya Y, Nasu M. Effect of pravastatin (10 mg/day) on progression of coronary atherosclerosis in patients with serum total cholesterol levels from 160 to 220 mg/dl and angiographically documented coronary artery disease. Coronary Artery Regression Study (CARS) Group. *Am J Cardiol* 1997;79:893-6.
28. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N Engl J Med* 1998;339:1349-57.
29. GISSI Prevenzione Investigators (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico). Results of the low-dose (20 mg) pravastatin GISSI Prevenzione trial in 4271 patients with recent myocardial infarction: Do stopped trials contribute to overall knowledge? *Ital Heart J* 2000;1:810-20.
30. Den Hartog FR, Van Kalmthout PM, Van Loenhout TT, Schaafsma HJ, Rila H, Verheugt FW. Pravastatin in acute ischaemic syndromes: Results of a randomised placebo-controlled trial. *Int J Clin Pract* 2001;55:300-4.
31. Shepherd J, Blauw GJ, Murphy MB, et al; PROSPER study group. PROspective Study of Pravastatin in the Elderly at Risk. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): A randomised controlled trial. *Lancet* 2002;360:1623-30.
32. West MS, Herd JA, Ballantyne CM, et al. The Lipoprotein and Coronary Atherosclerosis Study (LCAS): Design, methods, and baseline data of a trial of fluvastatin in patients without severe hypercholesterolemia. *Controlled Clinical Trials* 1996;17:550-83.
33. Serruys PW, Foley DF, Jackson G, et al. A randomized placebo-controlled trial of fluvastatin for prevention of restenosis after successful coronary balloon angioplasty; final results of the fluvastatin angiographic restenosis (FLARE) trial. *Eur Heart J* 1999;20:58-69.
34. Riegger G, Abletshauser C, Ludwig M, et al. The effect of fluvastatin on cardiac events in patients with symptomatic coronary artery disease during one year of treatment. *Atherosclerosis* 1999;144:263-70.
35. Pitt B, Waters D, Brown WV, et al. Aggressive lipid-lowering therapy compared with angioplasty in stable coronary artery disease. Atorvastatin versus Revascularization Treatment Investigators. *N Engl J Med* 1999;341:70-6.
36. Schwartz GG, Olsson AG, Ezekowitz MD, et al; Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) Study Investigators. Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes: the MIRACL study: A randomized controlled trial. *JAMA* 2001;285:1711-8.
37. Sever PS, Dahlof B, Poulter NR, et al; ASCOT Investigators. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial – Lipid Lowering Arm (ASCOT-LLA): A multicentre randomised controlled trial. *Lancet* 2003;361:1149-58.
38. Holdaas H, Fellstrom B, Jardine AG, et al; Assessment of LEscol in Renal Transplantation (ALERT) Study Investigators. Effect of fluvastatin on cardiac outcomes in renal transplant recipients: A multicentre, randomised, placebo-controlled trial. *Lancet* 2003;361:2024-31.
39. Lea AP, McTavish D. Atorvastatin. A review of its pharmacology and therapeutic potential in the management of hyperlipidaemias. *Drugs* 1997;53:828-47.
40. Mamdani MM, Tu JV. Did the major clinical trials of statins affect prescribing behaviour? *CMAJ* 2001;164:1695-6.
41. Teeling M, Bennett K, Feely J. The influence of guidelines on the use of statins: Analysis of prescribing trends 1998-2002. *Br J Clin Pharmacol* 2005;59:227-32.
42. National Cholesterol Education Program. Second Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II). *Circulation* 1994;89:1333-445.
43. Dallongeville J, Fruchart JC, Maigret P, et al. Double-blind comparison of apolipoprotein and lipoprotein particle lowering effects of atorvastatin and pravastatin monotherapy in patients with primary hypercholesterolemia. *J Cardiovasc Pharmacol Ther* 1998;3:103-10.
44. Dart A, Jerums G, Nicholson G, et al. A multicenter, double-blind, one-year study comparing safety and efficacy of atorvastatin versus simvastatin in patients with hypercholesterolemia. *Am J Cardiol* 1997;80:39-44.
45. Davidson M, McKenney J, Stein E, et al. Comparison of one-year efficacy and safety of atorvastatin versus lovastatin in primary hypercholesterolemia. Atorvastatin Study Group I. *Am J Cardiol* 1997;79:1475-81.
46. Cannon CP, Braunwald E, McCabe CH, et al; Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 Investigators. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med* 2004;350:1495-504.
47. Davignon J, Hanefeld M, Nakaya N, Hunninghake DB, Insull W Jr, Ose L. Clinical efficacy and safety of cerivastatin: Summary of pivotal phase IIb/III studies. *Am J Cardiol* 1998;82(Suppl 4B):32J-39J.
48. Farmer JA. Learning from the cerivastatin experience. *Lancet* 2001;358:1383-5.
49. How a statin might destroy a drug company. *Lancet* 2003;361:793.
50. Gilpin KN. What Cholesterol Studies Mean For Stocks. *The New York Times*, March 14, 2004.
51. Berenson A. Mixed Reviews for 2 of Pfizer's Top Drugs. *The New York Times*, March 9, 2005.
52. Angell M. The Truth About the Drug Companies. <<http://www.nybooks.com/articles/17244>> (Version current at December 7, 2005).