The use of lipid-lowering therapy for secondary prevention in patients undergoing percutaneous coronary intervention

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BACKGROUND: Recent literature suggests that lipid-lowering therapy may have an early beneficial effect among patients undergoing percutaneous coronary intervention (PCI) because the therapy decreases cardiac mortality, morbidity and possibly restenosis.

OBJECTIVE: The primary objective of the present study was to determine the proportion of PCI patients receiving lipid-lowering therapy at a large, tertiary-care referral centre.

METHODS: Patients undergoing a first PCI between August 2000 and August 2002 with corresponding inpatient medication information were included in the study. Patient demographics, procedural variables, and lipid-lowering and other evidence-based cardiac medication data were collected. A multiple logistical regression model was constructed to evaluate the factors associated with the use of lipid-lowering therapy.

RESULTS: Of the 3254 cases included in the analyses, 52% were elective, 44% were urgent or salvage, and 4% were emergent. The mean patient age was 63 years, and 73% of patients were male. Over 76% of patients were receiving lipid-lowering therapy at the time of PCI. Patient use of other medications was as follows: acetylsalicylic acid in 96%, beta-blocker in 80% and angiotensin-converting enzyme inhibitor in 59%. In the multiple regression analysis, variables significantly associated with lipid-lowering therapy use included hypercholesterolemia, beta-blocker use, angiotensin-converting enzyme inhibitor use, case urgency, prior coronary artery bypass graft surgery, age and sex.

CONCLUSION: Lipid-lowering therapy use rates exceeded those previously reported in the literature. Women and patients undergoing elective procedures appear to be treated less often with lipid-lowering therapy. There remains an opportunity to further optimize use in this high-risk cohort at time of PCI.

Key Words: Angioplasty; Cholesterol; Drugs; Hypercholesterolemia; Lipids

In large clinical trials, lipid-modifying agents have been shown to significantly reduce morbidity and mortality in patients with coronary artery disease (CAD), irrespective of baseline cholesterol levels (1-7). Lipid-lowering therapy is fundamental in the secondary prevention of patients with

Traitement hypolipédiant en prévention secondaire chez des patients devant subir une angioplastie coronarienne transluminale percutanée

HISTORIQUE : Une revue de la littérature récente indique que le traitement hypolipédiant pourrait exercer à court terme un effet bienfaisant chez les sujets qui subissent une angioplastie coronarienne transluminale percutanée (ACTP) puisqu'il réduit la mortalité, la morbidité et le risque de resténose.

OBJECTIF : Le principal objectif de la présente étude était de déterminer quelle proportion des patients devant subir une ACTP prenaient des hypolipédiants dans un grand centre de référence de soins tertiaires.

MÉTHODES : Les patients qui devaient subir une première ACTP entre août 2000 et août 2002 et qui répondaient aux critères pharmacologiques établis ont été inclus dans l'étude. Les caractéristiques démographiques des patients, les variables liées à l'intervention et les données sur leurs hypolipédiants ou autres médicaments cardiaques éprouvés ont été recueillies. Un modèle de régression logistique multiple a été élaboré pour évaluer les facteurs associés à l'utilisation des hypolipédiants.

RÉSULTATS : Parmi les 3 254 cas inclus dans les analyses, 52 % étaient électifs, 44 % étaient des interventions d'urgence ou de sauvetage et 4 % étaient émergents. L'âge moyen des patients était de 63 ans et 73 % étaient de sexe masculin. Plus de 76 % étaient sous hypolipédiants au moment de l'intervention. L'utilisation d'autres médicaments se répartissait comme suit : acide acétylsalicylique 96 %, bêta-bloquants 80 %, et inhibiteurs de l'enzyme de conversion de l'angiotensine (IECA) 59 %. Dans l'analyse de régression logistique, les variables significativement associées aux hypolipédiants ont été : l'hypercholestérolémie, le recours aux bêta-bloquants, aux IECA, l'urgence des cas, les antécédents de pontages coronariens, l'âge et le sexe.

CONCLUSION : Les taux d'utilisation des hypolipédiants sont supérieurs aux taux précédemment rapportés dans la littérature. Les femmes et les sujets soumis à des interventions non urgentes semblent moins souvent traités au moyen d'hypolipédiants. Il y a lieu d'améliorer encore leur utilisation dans cette cohorte à haut risque au moment de l'ACTP.

established CAD. Statins have been shown in vivo to exert anti-inflammatory and antiproliferative actions by inhibiting neointimal thickening in a cholesterol-independent manner, which helps to modulate vascular repair after injury (8). Plaque stability may also be increased by antithrombotic

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effects of statins, while plaque progression may be further reduced by inhibition of vascular smooth muscle cell proliferation (9). The favourable effects that statins have on platelet adhesion, thrombosis, endothelial function, inflammation and plaque stability have been shown to reduce cardiovascular morbidity and mortality, and possibly restenosis, after percutaneous coronary intervention (PCI) (10-14). In-hospital initiation of lipid-lowering therapy, when patients are focused on their cardiovascular risk and health care professionals are present to facilitate patient education, may in turn strengthen the perception that this therapy is essential for the prevention of recurrent events and may improve adherence to drug regimens (15,16). One study (17) demonstrated that after angiographic diagnosis of CAD, prescription of appropriate statin therapy at the time of hospital discharge improved long-term statin adherence and may significantly improve survival.

The current trend toward a more aggressive approach to lipid-lowering therapy coincides with a shift in the direction of early invasive strategies for CAD management. Contrary to past management, when PCI and medical therapy had been considered as alternate, competing strategies for symptomatic CAD (18,19), lipid-lowering therapy is now seen as providing early, complementary benefit in combination with coronary revascularization. However, in a recent survey, only 26.5% of 5052 patients undergoing PCI were receiving statin treatment at the time of the procedure (10).

Considering the potential, overall benefit of lipid-lowering therapy, high-risk cardiac patients, such as those undergoing PCI, should be specifically targeted to receive this therapy as secondary prophylaxis. The present study was conducted to determine the proportion of PCI patients receiving lipid-lowering therapy in the Interventional Cardiology Program of a large, tertiary-care, referral centre (University Health Network, Toronto, Ontario), and to evaluate the factors associated with its use in this population.

METHODS

All patients that had a first PCI between August 2000 and August 2002 at the University Health Network, a large, tertiary-care referral centre, with corresponding visit records in the in-patient medication use system were included in the study.

Patients were identified from the angioplasty database, which was established in 1994 as an ongoing initiative to monitor in-patient PCI-related outcomes. Data were prospectively collected by trained, qualified personnel in three main categories: patient demographics (age, sex, risk factors [smoking, hypertension, hypercholesterolemia, diabetes mellitus, family history of heart disease, prior myocardial infarction (MI), Canadian Cardiovascular Society class, prior PCI, prior coronary artery bypass graft (CABG) surgery, renal function and case urgency]); procedural variables (total number of vessels done, glycoprotein IIb/IIIa inhibitor use, ad hoc angioplasty and case success); and outcome variables (death, MI by enzymes, MI by electrocardiogram, acute reocclusion, CABG surgery, hematoma, pseudoaneurysm, true aneurysm, retroperitoneal bleed, fistula, intra-aortic balloon pump use, neurological events and nights in hospital).

Cases were defined in the angioplasty database as elective when the procedure was conducted according to a scheduled visit; urgent when the patient had a recent non-ST segment elevation acute coronary syndrome (ACS), was in the nonacute phase after ST elevation MI or was having salvage PCI (no surgical backup possible due to anatomical or comorbid factors); and emergent

when the patient had cardiogenic shock, primary or rescue PCI for ST segment elevation MI. Ad hoc angioplasty was defined as a coronary angioplasty case performed in conjunction with a diagnostic procedure. MI was defined as a rise in creatinine kinase of two times the upper limit of normal and/or the development of Q waves on electrocardiogram. Acute reocclusion was defined as occlusion occurring after removal of PCI hardware from the cannulation site. The presence of a hematoma was documented if it required treatment or prolongation of the length of hospital stay.

The hospital medication use system contains prospectively collected patient medication orders. After a physician has written a medication order in the patient's chart, a pharmacist reviews and enters the order into the medication use system. This information is interfaced with the nursing unit's drug distribution system, which is then accessed by a nurse to obtain the patient-specific medication that has been ordered. Patient-specific medication data were compiled: lipid-lowering therapy (atorvastatin, fluvastatin, lovastatin, pravastatin, simvastatin, bezafibrate, clofibrate, fenofibrate, gemfibrozil or niacin) and other evidence-based cardiac medications (such as angiotensin-converting enzyme [ACE] inhibitors, beta-blockers and acetylsalicylic acid [ASA]). The dose, schedule and start date were also recorded.

STATISTICAL ANALYSIS

Patient demographics, angiographic characteristics, medication use and in-hospital clinical outcomes were reported using descriptive statistics and measures of central tendency. Discrete variables were expressed as proportions and continuous variables as means $\pm$ SDs. For the logistical regression analysis, the dependent variable in the model was the use of lipid-lowering therapy. Univariate analysis was conducted with the following independent variables related to patient demographics and procedural characteristics: age, sex, case urgency, serum creatinine level, smoking status, hypertension, hypercholesterolemia, diabetes, family history of CAD, prior MI, prior PCI, prior CABG surgery, ACE inhibitor use, beta-blocker use, ASA use, glycoprotein IIb/IIIa inhibitor use and number of vessels done. Variables with a $P < 0.2$ by univariate analysis were subsequently retained and entered into a multiple logistical regression model using forward stepwise (likelihood ratio) technique. ORs with 95% CIs were estimated from the regression model. Two-sided P values were calculated for each variable, and $P < 0.05$ was considered statistically significant in the multiple logistical regression model. Regression diagnostics were accomplished using Cook's influence statistics, leverage values and standardized residuals. Classification plots and the Hosmer-Lemeshow goodness-of-fit test were used to assess how well the model fit the data. All statistical analyses were performed using SPSS version 11.5 (SPSS Inc, USA). The study was approved by the hospital's research ethics board.

RESULTS

In the two-year period, 4121 PCIs were performed, and there was corresponding medication information available for 3557 of these cases. Of the 564 cases without corresponding medication information, greater than 50% of the visits were from PCI-specific transfer patients who returned to their original hospital immediately after the procedure. There were 8.5% ($n=303$) repeat cases that were excluded from the analyses.

Of the 3254 cases included in the analyses, 73% were men and the mean age was 63 years. Baseline characteristics and procedural variables are shown in Table 1. Patients receiving

TABLE 1
Baseline demographics, clinical characteristics and procedural variables in patients undergoing percutaneous coronary intervention either on or not on lipid-lowering therapy (LLT)

Characteristics	On LLT (n=2478)	Not on LLT (n=776)	P
Age, years (mean $\pm$ SD)	62 $\pm$ 11.3	64.5 $\pm$ 11.3	<0.0001
Male sex, %	73.8	69.1	0.0104
Smoker, %	21.5	20.8	0.6698
Hypertension, %	57.2	55.6	0.4729
Hypercholesterolemia, %	79.0	44.8	<0.0001
Diabetes mellitus, %	26.3	23.6	0.1413
Family history of coronary artery disease, %	37.0	34.4	0.2196
Recent MI (within one year), %	40.1	31.3	<0.0001
Prior percutaneous coronary intervention, %	12.8	9.7	0.0250
Prior coronary artery bypass graft surgery, %	17.8	12.0	0.0002
Canadian Cardiovascular Society class, %			<0.0001*
Class I	3.6	4.8	
Class II	22.7	26.4	
Class III	29.2	36.7	
Class IV	38.6	25.7	
Baseline serum creatinine, μ mol/L (mean $\pm$ SD)	104 $\pm$ 76.4	114.97 $\pm$ 115.8	0.0273
Peak serum creatinine, μ mol/L (mean $\pm$ SD)	137 $\pm$ 117.7	170.4 $\pm$ 186.3	0.0131
Elective case, %	49.6	59.9	<0.0001*
Urgent case, %	46.6	37.1	
Emergent case, %	3.9	3.0	
Glycoprotein IIb/IIIa receptor inhibitor use, %	97.3	97.9	0.2957
Vessels, n (mean $\pm$ SD)	1.3 $\pm$ 0.6	1.3 $\pm$ 0.6	0.8572
Ad hoc angioplasty, %	14.5	11.1	0.0188

*Trend among groups. MI Myocardial infarction

lipid-lowering drug therapy were generally younger, or had hypercholesterolemia, a recent MI or prior CABG. Table 2 outlines the use of lipid-lowering drug therapy and other evidence-based cardiac medications. Over 76% of patients were receiving lipid-lowering therapy during their PCI visit. Only 73% of women and elective patients were receiving lipid-lowering therapy, compared with 77% of men and 80% of urgent patients. Mean daily doses of the most frequently prescribed statins were: atorvastatin 22 mg; simvastatin 26 mg; and pravastatin 26 mg. In-hospital clinical outcomes and adverse events are shown in Table 3. Adverse outcomes were uncommon, and there were no significant differences between the two groups.

Table 4 outlines those variables tested in the univariate analysis. Only those variables with a $P < 0.2$ (age [continuous], sex [male, female], case status [elective, urgent or emergent], baseline serum creatinine level, hypercholesterolemia, diabetes mellitus, prior MI, prior PCI, prior CABG, ACE inhibitor use, beta-blocker use and ASA use) were retained and entered in the multiple logistical regression model.

In the multiple logistical regression analysis, variables significantly associated with lipid-lowering therapy use in the model included hypercholesterolemia, beta-blocker use, ACE inhibitor use, case urgency, prior CABG surgery, age and sex (Table 5). Men were 25% more likely to be receiving lipid-lowering therapy than women. Patients undergoing PCI for an urgent or emergent indication had a 50% greater chance of receiving lipid-lowering therapy than those undergoing elective

TABLE 2
In-hospital lipid-lowering therapy and evidence-based cardiac medications

Medication	%
Any lipid-lowering drug	76.2
Any statin	72.6
Atorvastatin	44.0
Simvastatin	16.0
Pravastatin	11.0
Cerivastatin	1.2
Lovastatin	0.7
Fluvastatin	0.4
Any fibrate	5.8
Fenofibrate	4.7
Gemfibrozil	0.9
Bezafibrate	0.2
Acetylsalicylic acid	95.6
Angiotensin-converting enzyme inhibitor	58.8
Beta-blocker	80.2

TABLE 3
In-hospital clinical outcomes, bleeding events and other complications

Event	On LLT, % (n=2478)	Not on LLT, % (n=776)	P
Myocardial infarction by enzymes	2.1	1.6	0.4131
Myocardial infarction by ECG	0.7	0.3	0.2728
Intra-aortic balloon pump used	1.2	0.8	0.4122
Coronary artery bypass graft surgery	1.0	0.1	0.0355
Death	0.6	1.3	0.0694
Acute reocclusion	0.6	0.3	0.3201
Neurological event	0.2	0	0.5941

ECG Electrocardiogram; LLT Lipid-lowering therapy

PCI. Regression diagnostics did not detect any outliers or observations of influence, and both goodness-of-fit tests suggested that the model fit the data adequately.

DISCUSSION

Our study found utilization rates of lipid-lowering therapy at the time of PCI exceeding that previously reported for in-hospital use (20). This is encouraging in light of the growing evidence for early in-hospital initiation and the broader benefit of lipid-lowering therapy (6,7). More specifically, emerging data in the PCI population continues to substantiate the advantage of the pleiotropic properties of statin therapy in these patients (10-14).

Atorvastatin was the most frequently prescribed statin in our study. Although our study indicates a clear preference for the use of atorvastatin, current evidence has not clearly delineated a preferential use of one statin over another. At the time of our study, the strongest evidence for the statins was from the major landmark trials for simvastatin (1,7) and pravastatin (3,4), which have clearly demonstrated significant, long-term mortality and cardiovascular morbidity benefits, all with follow-up periods of longer than five years. However, these trials did not specifically investigate statin intervention early after acute events. At the time of the present study, the major evidence for atorvastatin was the Myocardial Ischemia Reduction with Acute Cholesterol Lowering (MIRACL) trial

TABLE 4
Univariate logistical regression analysis

Variable	OR	P
Age	0.983	<0.0001
Sex (female versus male)	0.791	0.009
Case urgency (urgent versus elective)	1.517	<0.0001
Case urgency (emergent versus elective)	1.581	0.055
Baseline serum creatinine	0.999	0.008
Smoker (current versus never)	1.062	0.588
Smoker (former versus never)	1.040	0.671
Hypertension	1.065	0.448
Hypercholesterolemia	4.619	<0.0001
Diabetes mellitus	1.157	0.129
Family history of coronary artery disease	1.116	0.204
Prior myocardial infarction	1.478	<0.0001
Prior percutaneous coronary intervention	1.365	0.022
Prior coronary artery bypass graft surgery	1.582	<0.0001
Angiotensin-converting enzyme inhibitor use	1.994	<0.0001
Beta-blocker use	2.732	<0.0001
Acetylsalicylic acid use	1.286	0.184
Glycoprotein IIb/IIIa receptor inhibitor use	0.746	0.297
Number of vessels done	1.013	0.857

Those variables with P<0.2 were entered in the multiple logistical regression model

(6), which investigated atorvastatin 80 mg/day started within 24 h to 96 h of ACS in 3086 patients. The MIRACL trial found a significant reduction in the primary end points of death and nonfatal ischemic events after 16-weeks of follow-up. Of note, however, is that those patients anticipated to undergo or those having recently undergone coronary revascularization were excluded from the MIRACL trial. Since the timeframe of the present study, newer evidence from clinical trials has shown the benefits of early and aggressive low density lipoprotein-lowering with atorvastatin (21-24). The comparative increased low density lipoprotein lowering potential of atorvastatin may have contributed to its preferential use (25). Marketing initiatives may also explain the high use of atorvastatin, as it holds the largest market share among all the statins in Canada (26).

Our analyses revealed lower daily statin doses than the target doses achieved in the major landmark trials. The mean daily doses of atorvastatin, simvastatin, and pravastatin were 22 mg, 26 mg and 26 mg, respectively. In comparison, doses of 80 mg for atorvastatin (6), 20 mg to 40 mg for simvastatin (1,7) and 40 mg for pravastatin (3,4) were the target doses used in major clinical trials at the time of our study. With limited evidence to ascertain whether the same cardiovascular morbidity and mortality benefits can be achieved with lower doses of statins, increasing to target statin doses as tolerated may be indicated. Recent evidence emphasizes the importance of achieving target doses of statins to achieve the desired clinical outcomes (21,24).

We found that women and patients undergoing elective PCI procedures were treated less often with lipid-lowering therapy. Sex bias is a well-known phenomenon in the use of cardiovascular medications, with women being less likely to receive evidence-based medications than men (27). Other studies assessing statin use post-PCI have either found no sex difference or a higher likelihood for women to use statins (20). No study has previously investigated the impact of elective

TABLE 5
Multiple logistical regression model*

Variable	OR (95% CI)	P
Age	0.985 (0.976 to 0.994)	0.001
Sex (female versus male)	0.781 (0.629 to 0.970)	0.026
Case urgency (urgent versus elective)	1.637 (1.323 to 2.026)	<0.0001
Case urgency (emergent versus elective)	1.859 (1.014 to 3.408)	0.045
Hypercholesterolemia	5.437 (4.445 to 6.649)	<0.0001
Prior coronary artery bypass grafting	1.378 (1.038 to 1.829)	0.026
Angiotensin-converting enzyme inhibitor use	1.919 (1.573 to 2.340)	<0.0001
Beta-blocker use	2.675 (2.145 to 3.335)	<0.0001

**Primary end point of utilization rates of lipid-lowering therapy*

versus urgent PCI on use of statins in hospital. A higher rate of statin use may have been observed in ACS patients due to a greater perceived opportunity for revision of the medication regimen at the time of an acute event.

The cardiovascular specialist should ensure that appropriate therapy is initiated and maintained (28). Using education and process changes in the hospital to target women and patients undergoing elective procedures may increase appropriate lipid-lowering use even further in these particular patients. Because use of lipid-lowering therapy in-hospital is associated with increased long-term adherence, it is necessary to ensure that as many patients as possible are receiving this beneficial therapy during their admission for PCI (29).

Despite the underuse of lipid-lowering therapy, PCI patients are still more likely to receive secondary preventative drugs than patients receiving medical treatment alone (30,31). We found that those patients receiving ACE inhibitors or beta-blockers were more likely to be receiving a lipid-lowering therapy. This represents possible synergy between the use of multiple, evidence-based therapies in PCI patients.

STUDY LIMITATIONS

With the use of a clinical angioplasty database, completeness and accuracy of data collection is related to the information available to the database coordinator from the procedure notes and the patient's paper or electronic medical record. While data collection is performed concurrently during the patient's hospitalization, it is possible that not all data were readily available. For example, data on the patient's risk factors, such as smoking or history of dyslipidemia, may be more difficult to obtain from written records. Factors such as lipoprotein levels or the presence of elevated liver function tests that may have influenced prescription of statin therapy were not assessed in the study. The medication use system does accurately reflect the in-hospital use of medications; however, we cannot be certain that these medications were continued after discharge from hospital. Because we used observational data, we can only detect association with the factors determining lipid-lowering use. Our study included data between 2000 and 2002. Because further landmark lipid-lowering trials were published after 2002, it is possible that the practice patterns of statin use at the institution may differ after our period of study. The study design allowed for assessment of in-hospital factors rather than long-term outcomes. However, because we assessed data with a large number of PCI cases occurring during a two-year period, our study reflects real-life experiences in the PCI setting of a large, tertiary-care hospital.

CONCLUSION

We found that lipid-lowering drug therapy use rates exceeding those previously reported in the literature. Women and patients undergoing elective procedures were treated less often with lipid-lowering therapy. There continues to be a window of opportunity to further optimize use of this proven, effective therapy in a high-risk PCI cohort. Furthermore, monitoring of cholesterol levels, aggressive titration of lipid-lowering therapy to achieve target levels and attention to medication adherence

by patients is necessary for patients already receiving lipid-lowering therapy (32).

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