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Long-Term Risk Stratification for Survivors of Acute Coronary Syndromes

Results From the Long-Term Intervention With Pravastatin in Ischemic Disease (LIPID) Study

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OBJECTIVES We developed a prognostic strategy for quantifying the long-term risk of coronary heart disease (CHD) events in survivors of acute coronary syndromes (ACS).

BACKGROUND Strategies for quantifying long-term risk of CHD events have generally been confined to primary prevention settings. The Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) study, which demonstrated that pravastatin reduces CHD events in ACS survivors with a broad range of cholesterol levels, enabled assessment of long-term prognosis in a secondary prevention setting.

METHODS Based on outcomes in 8,557 patients in the LIPID study, a multivariate risk factor model was developed for prediction of CHD death or nonfatal myocardial infarction. Prognostic indexes were developed based on the model, and low-, medium-, high- and very high-risk groups were defined by categorizing the prognostic indexes.

RESULTS In addition to pravastatin treatment, the independently significant risk factors included: total and high density lipoprotein cholesterol, age, gender, smoking status, qualifying ACS, prior coronary revascularization, diabetes mellitus, hypertension and prior stroke. Pravastatin reduced coronary event rates in each risk level, and the relative risk reduction did not vary significantly between risk levels. The predicted five-year coronary event rates ranged from 5% to 19% for those assigned pravastatin and from 6.4% to 23.6% for those assigned placebo.

CONCLUSIONS Long-term prognosis of ACS survivors varied substantially according to conventional risk factor profile. Pravastatin reduced coronary risk within all risk levels; however, absolute risk remained high in treated patients with unfavorable profiles. Our risk stratification strategy enables identification of ACS survivors who remain at very high risk despite statin therapy.
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Assessment of prognosis is a critical step in evaluating the need for treatment and lifestyle modifications to manage the risk of future coronary events. Prognostic instruments for quantifying coronary risk should be applicable to patients seen in clinical practice and should, therefore, be based on large databases representative of contemporary clinical experience. Although uncertainty regarding treatment decisions may be greater in primary prevention settings, prognostic assessment for patients with established coronary heart disease (CHD) is still an important aid to decisions about the aggressiveness of secondary prevention interventions.

A number of prior studies have quantified long-term coronary risk levels based on data from primary prevention settings (1–4). Although there are published guidelines for treatment of patients with established CHD (5–7), explicit quantification of long-term risk levels for patients with CHD, based on traditional risk factors, is less common than in primary prevention settings. When patients have recovered from an acute coronary syndrome (ACS), the risk of myocardial infarction (MI) or unstable angina has been largely assessed based on left ventricular function, the extent and severity of CHD based on angiography and the presence of ongoing ischemia (8). Although traditional risk factors such as age, diabetes mellitus, dyslipidemia, hypertension and gender are known to have continuing importance, a convenient method for quantifying long-term coronary risk in patients surviving an ACS has not been developed. As noted in primary prevention risk factor studies, predicted risk levels based on data from patients with no prior CHD cannot simply be applied to patients with established CHD (4,9). Thus, there is a need for risk stratification instruments directly applicable to patients with a history of CHD.

The Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) study (10) was a very large long-term secondary prevention trial of the lipid-lowering drug pravastatin conducted in a typical population of CHD patients.

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Abbreviations and Acronyms

ACE = angiotensin-converting enzyme
ACS = acute coronary syndrome
CHD = coronary heart disease
HDL = high-density lipoprotein
LDL = low-density lipoprotein
LIPID = Long-term Intervention with Pravastatin in Ischemic Disease study
MI = myocardial infarction
TIA = transient ischemic attack

We present an analysis of the LIPID database, which was used to develop a multivariate risk factor model for patients with established CHD, together with an accompanying risk stratification strategy that can be routinely used for long-term prognostic assessment based on a patient's risk factor profile.

METHODS

Study design. The LIPID study enrolled 9,014 patients with an acute MI or hospitalization for unstable angina between 3 and 36 months before study entry. Participants were aged between 31 and 75 years and were recruited from 87 centers in Australia and New Zealand. Patients were eligible for the study if they had a total cholesterol level between 4 and 7 mmol/l (155 mg/dl and 271 mg/dl) and fasting triglyceride level <5 mmol/l (445 mg/dl). Exclusion criteria included a clinically significant medical or surgical event in the three months before study entry and current cardiac failure, renal or hepatic disease or use of lipid-lowering therapy. Eligible patients were randomized to either 40 mg pravastatin or matching placebo daily and were followed up every six months to collect data on outcomes. The prespecified chosen outcome for this risk factor study was a major CHD event, defined as CHD death or nonfatal MI. More detailed information about patient characteristics, study design and outcomes assessment is reported elsewhere (10,11).

Baseline risk factors. Baseline lipid levels were measured by a core laboratory using fasting blood samples taken before commencement of study treatment and included total cholesterol, high-density lipoprotein cholesterol (HDL), triglycerides, apolipoprotein A1 and apolipoprotein B. Low-density lipoprotein cholesterol (LDL) was estimated indirectly, using the formula of Friedwald et al. (12).

Due to the large number of risk factors, baseline risk factors were divided into two classes, and the final model was developed in a two-stage process described in the Statistical Methods section. The first class included the following core risk factors: total cholesterol, HDL cholesterol, triglycerides, age, gender, smoking status, qualifying event, prior occurrence of reinfarction, revascularization (never, since qualifying event or before qualifying event), diabetes mellitus, history of hypertension, history of stroke, history of transient ischemic attacks (TIA), history of claudication and history of dyspnea. Low-density lipoprotein cholesterol was not included in multivariate analyses because it was derived from the other three lipid parameters and had a greater level of missing data due to the Friedwald formula only applying when triglyceride levels do not exceed 5 mmol/l (443 mg/dl). There were 457 patients with missing baseline information who were excluded, leaving a total of 8,557 patients available for the risk factor analyses (4,271 in the placebo group, 4,286 in the pravastatin group).

In addition to the core risk factors, three groups of auxiliary risk factors were considered. The first group included refinements of core risk factors and additional characteristics: height, weight, body mass index, nationality, diastolic and systolic blood pressure, heart rate, site of MI, time since qualifying event, years since stopped smoking (≤5 years, >5 years or never smoked), duration of angina (≤5 years, >5 years or never had angina), angina grade (I, II, ≥III, using Canadian Cardiovascular Society definition [13]), dyspnea grade (I, II, ≥III, using New York Heart Association definition [14]). The second group included baseline medications: aspirin, beta-adrenergic blocking agents, angiotensin-converting enzyme (ACE) inhibitors, nitrates, calcium channel blockers, insulin, diuretics and oral hypoglycemic agents. Finally, the third group of auxiliary risk factors included additional lipid parameters: apolipoprotein A1 and apolipoprotein B.

Based on the final risk factor model, a simpler risk score was developed using only ten risk factors: total cholesterol, HDL cholesterol, age, gender, smoking status, nature of qualifying ACS, revascularization since qualifying event, diabetes mellitus, history of stroke and history of hypertension. These risk factors were chosen for routine prognostic assessment based on the following considerations: their significance in the full risk factor model, their traditional importance in assessing coronary risk and their lack of grading or retrospective assessment of duration.

Statistical methods. A Cox proportional hazards model was used for intent-to-treat analysis of the prespecified composite outcome of time from randomization to CHD death or nonfatal MI (15). Initially, backwards stepwise regression analyses (16) were used to select the best model based on the core risk factors previously described. Subsequently, the final model was obtained based on backwards stepwise analyses conducted on the auxiliary risk factors after adjusting for the significant core risk factors identified in the first stage. For continuous risk factors, the final model was expressed using prespecified categorical classifications after verification that the significance of the other risk factors was not sensitive to whether continuous or categorical specifications were used. The categorical specifications were favored due to their more convenient use in a routine prognostic tool.

A prognostic index (16) was defined as the product of the adjusted hazard ratios associated with each of the risk factors, and, hence, a formula was obtained for calculating the risk (or probability) of coronary event within any given

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time frame. For more routine prognostic assessment, a simple risk score was derived based on the model refitted with a reduced collection of risk factors described in the preceding text. To calculate this risk score, the adjusted log-hazard ratio of each risk factor was divided by the smallest significant adjusted log-hazard ratio, and this was rounded to the nearest integer to provide the risk points associated with each risk factor. The overall risk score was then defined as the sum of the risk points corresponding to any given risk factor profile. Categories of low, medium, high and very high risk were defined by categorizing the prognostic index and simplified risk score into quartiles based on the study sample. Using the derived risk formula, the risk of coronary event for each of the risk groups was calculated based on the average value of the prognostic index within each risk group.

RESULTS

Patient characteristics. The median age at study entry was 62 years. Most patients were male (83%) nonsmokers (90%) who qualified for the study with an MI (64%). A minority of patients had a history of stroke (4%), diabetes mellitus (9%), claudication (10%) and hypertension (42%). Median lipid levels at study entry were 5.6 mmol/l (218 mg/dl) for total cholesterol, 3.9 mmol/l (150 mg/dl) for LDL cholesterol, 0.93 mmol/l (36 mg/dl) for HDL cholesterol and 1.6 mmol/l (140 mg/dl) for triglycerides. Median follow-up for the study was 6 years. Further information about patient characteristics for the LIPID study is provided elsewhere (10).

Univariate analyses. The rate of major coronary events (CHD death or nonfatal MI) was 13.9% overall (1,190 events in 8,557 patients). With the exception of total cholesterol ($p = 0.083$), all of the other core lipid risk factors were significantly predictive of coronary event in continuous univariate analyses ($p < 0.033$ in each case). All core nonlipid risk factors were significantly predictive of coronary events in univariate analyses. The strongest predictors of coronary event ($p < 0.001$ in each case) were presence of diabetes mellitus, history of stroke, prior multiple infarctions, age ≥70 years (hazard increases of 68%, 70%, 107% and 109%, respectively) and coronary revascularization between the qualifying event and randomization (hazard reduction of 41%).

Since total cholesterol was found to be important in multivariate analyses (see Multivariate Analyses section), the lack of strong predictive ability in the univariate analyses was investigated further. It was found that total cholesterol and HDL cholesterol were significantly associated ($p < 0.001$). This positive association had the effect of weakening the predictive ability of total cholesterol in the unadjusted analysis because the negative effect of high total cholesterol was dampened by its association with the protective effect of high HDL cholesterol level. This was confirmed in an analysis of total cholesterol adjusting for HDL cholesterol alone, in which total cholesterol was found to be a statistically significant predictor ($p = 0.037$).

Multivariate analyses. In multivariate analyses of the core risk factors, three risk factors were found not to be statistically significant predictors of coronary events: fasting triglyceride level, history of TIA and history of claudication ($p > 0.20$ in each case). All statistically significant core risk factors were associated with a clinically important level of risk, involving at least a 15% increase in hazard rate. Table 1 lists the multivariate results for the significant core risk factors including the additional auxiliary risk factor analyses described in the following text. As in the univariate analyses, the risk factors associated with the greatest increase in risk were prior occurrence of multiple infarctions and age ≥70 years (71% and 89% increase, respectively).

In multivariate analyses of the auxiliary risk factors, adjusting for the core risk factors, an additional four risk factors were found to be statistically significant and were added to the model, while one of the core risk factors (history of dyspnea) was modified in definition. In summary, dyspnea grade ≥III was found to be associated with significantly increased risk ($p = 0.007$), while there was no statistically significant difference between grades I and II; thus, the final risk factor model included history of dyspnea as either <III or ≥III. In addition, angina duration of >5 years was predictive of increased coronary event rate ($p = 0.024$), as was angina grade ≥III ($p = 0.014$) and New Zealand nationality ($p = 0.004$). Patients taking aspirin medication at baseline had a significantly reduced risk of coronary event ($p = 0.007$). The complete results for the final risk factor model are listed in Table 1.

A number of auxiliary risk factors were statistically significant in multivariate analyses but were not included in the final risk factor model for reasons described in the following text. Among the baseline medications, in addition to aspirin, there were three other drug classes whose use was predictive of outcomes: ACE inhibitors, diuretics and nitrates. However, each of these medications was associated with an increase in the risk of coronary event, suggesting that these drug effects were a proxy for other risk factors, rather than reflecting the biological effects of the treatments themselves. After inclusion of these baseline medications in the risk factor model, history of hypertension and duration of angina were no longer statistically significant, which is consistent with these medications being treatments of hypertension and angina. The inclusion of these proxy variables in a prognostic tool would be confusing and counterintuitive for users, so it was decided that the final model should retain history of hypertension and duration of angina as risk factors, in preference to including the baseline medications ACE inhibitors, diuretics and nitrates. A similar decision was made with respect to apolipoprotein A1. When apolipoprotein A1 was added to the multivariate model, it was independently predictive and caused HDL cholesterol to become insignificant. This was consistent with the strong positive relationship observed between these

Table 1. Multivariate Risk Factor Analysis for CHD Death or Nonfatal MI

Risk Factor	Event Rate (%)	Hazard Ratio*	95% CI	p Value	Risk Points†
Total cholesterol:				0.003	
<5.5 mmol/l‡	12.9	1.00			0
≥5.5 mmol/l‡	14.7	1.20	1.06–1.35		1
HDL cholesterol:				<0.001	
>1.0 mmol/l‡	11.8	1.00			0
≤1.0 mmol/l‡	15.2	1.30	1.14–1.47		2
Age:				<0.001	
<60 yr	11.2	1.00			0
60–64 yr	12.8	1.16	0.98–1.37		1
65–69 yr	15.9	1.48	1.27–1.73		2
≥70 yr	19.6	1.89	1.60–2.23		3
Gender:				0.006	
Female	12.0	1.00			0
Male	14.3	1.27	1.07–1.50		2
Smoking status:				<0.001	
Nonsmoker	13.5	1.00			0
Current smoker	17.5	1.43	1.19–1.71		3
Nature of prior ACS:				<0.001	
Unstable angina	11.3	1.00			0
Single MI	13.3	1.30	1.12–1.50		1
Multiple MIs	25.1	2.28	1.93–2.70		6
Revascularization:				<0.001	
Never	12.3	1.00			0
Before ACS	17.5	1.24	1.05–1.45		—
Since ACS	9.2	0.65	0.55–0.76		subtract 4
History of stroke:				0.032	
No	13.6	1.00			0
Yes	21.8	1.36	1.02–1.64		3
Diabetes mellitus:				<0.001	
No	13.3	1.00			0
Yes	20.9	1.48	1.24–1.75		3
History of hypertension:				0.035	
No	12.9	1.00			0
Yes	15.3	1.14	1.01–1.28		1
Dyspnea grade:				0.007	
NYHA <III	13.2	1.00			—
NYHA ≥III	21.1	1.28	1.07–1.53		—
Angina grade:				0.014	
CCVS <III	13.2	1.00			—
CCVS ≥III	21.1	1.27	1.05–1.53		—
Angina duration:				0.028	
≤5 years	13.2	1.00			—
>5 years	18.6	1.20	1.02–1.40		—
Region:				0.004	
Australia	13.0	1.00			—
New Zealand	15.7	1.19	1.06–1.34		—
Aspirin usage:				0.007	
No	17.7	1.00			—
Yes	13.4	0.82	0.71–0.95		—

*The prognostic index is the product of the hazard ratios associated with the patient's risk factor profile; †the risk score is the sum of the risk points associated with the patient's risk factor profile. Risk factors without risk points were not considered for the simplified risk score; ‡to convert values to mg/dl, multiply by 38.67.

ACS = acute coronary syndrome; CCVS = Canadian Cardiovascular Society; CHD = coronary heart disease; CI = confidence interval; HDL = high-density lipoprotein; MI = myocardial infarction; NYHA = New York Heart Association.

two parameters ($p < 0.001$). Since apolipoprotein A1 provided similar information to HDL cholesterol, but is less available for routine usage in a prognostic tool, HDL cholesterol was retained in the final model.

The multivariate risk factor results in Table 1 are adjusted for the influence of treatment group. In this analysis, randomization to the pravastatin group was independently predictive of a reduced coronary event rate ($p < 0.001$, hazard ratio = 0.78). With the exception of history of hypertension, there was no evidence of heterogeneity of risk factor effects between the two treatment groups (interaction $p > 0.10$ in all cases). For history of hypertension, the

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Table 2. Predicted Rates of CHD Death or Nonfatal MI Within 5 Years and Corresponding NNT

		5-Year Risk		
Risk Level	**Range***	**Pravastatin**	**No Pravastatin**	**NNT**
Prognostic index:				
Low	≤1.8	5.0%	6.4%	71
Medium	1.8–2.6	7.8%	9.9%	48
High	2.6–3.7	10.7%	13.5%	36
Very high	>3.7	19.0%	23.6%	22
Risk score:				
Low	≤4	4.6%	5.8%	83
Medium	5–6	8.1%	10.3%	45
High	7–9	10.7%	13.5%	36
Very high	≥10	16.1%	20.2%	24

*Range of the prognostic index or risk score that defines the corresponding risk level. Event rates are broken down by risk level using both the detailed (prognostic index) and simplified (risk score) methods and are based on the multivariate model with common relative risk reduction for all risk levels.

CHD = coronary heart disease; MI = myocardial infarction; NNT = number needed to treat.

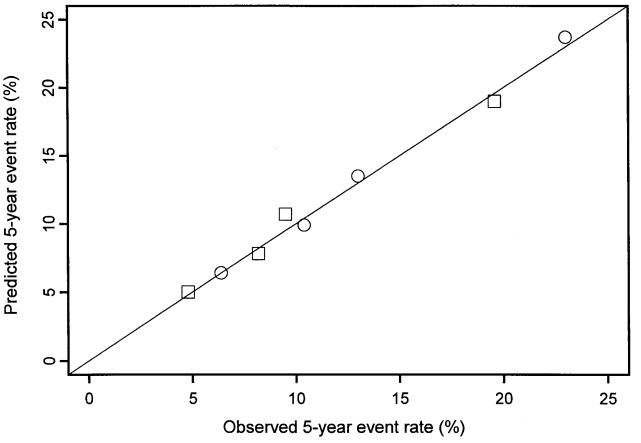

Figure 1. Five-year rates of coronary heart disease death and nonfatal myocardial infarction as predicted by the risk factor model versus the observed rates. Separate event rates are plotted for each of the four risk levels as determined by the prognostic index within each of the two treatment groups. **Open squares** = pravastatin; **open circles** = placebo.

interaction with treatment group was statistically significant (interaction p = 0.018), with the hazard ratio being 1.02 in the placebo group and 1.34 in the pravastatin group. In view of the large number of interaction tests carried out (multiple comparisons) and the lack of any prior reason why history of hypertension might be more predictive in the pravastatin group, it was decided that the increased risk of a coronary event associated with history of hypertension should be expressed as the combined effect across the two treatment groups (Table 1).

Detailed risk assessment. Based on the final risk factor model, the following formula was derived for calculating a patient's risk of CHD death or nonfatal MI within any given time frame:

$$\text{Risk of coronary event within the next Y years} = 1 - C(Y)^{I \times T}$$

where I indicates the prognostic index calculated by multiplying the hazard ratios associated with the patient's risk factor profile (Table 1); T is equal to 1 if the patient chooses not to initiate pravastatin therapy and is equal to 0.78 if the patient chooses to initiate pravastatin therapy and C(1) = 0.9896, C(2) = 0.9805, C(3) = 0.9724, C(4) = 0.9632, C(5) = 0.9536 and C(6) = 0.9434. For example, if a patient's risk factor profile is such that the prognostic index is equal to 5 and the patient chooses not to initiate pravastatin therapy, then the risk of a coronary event within the next five years is $1 - 0.9536^5 = 21.1\%$. Alternatively, if the same patient chooses to initiate pravastatin therapy, then the risk of a coronary event within the next five years is $1 - 0.9536^{5 \times 0.78} = 16.9\%$.

Categories of risk level according to the value of the prognostic index are provided in Table 2, together with the corresponding five-year risks of a subsequent coronary event, based on the prognostic model. The five-year risk of coronary event varied considerably between the different risk levels. For patients not assigned pravastatin therapy, the five-year risk ranged from 6.4% in the low-risk group (prognostic index ≤1.8) to 23.6% in the very high-risk group (prognostic index >3.7). These coronary risks were lower for patients assigned pravastatin therapy, ranging from 5% to 19%. For each risk level within each treatment group, the model-based five-year risks that assume a common relative risk reduction for all risk levels (Table 2) were in close agreement with the observed five-year risks (Fig. 1) (R^2 = 0.99). There was also good discrimination with respect to coronary mortality, which had an observed five-year risk that varied considerably between risk levels, ranging from 2% to 12.8% for patients assigned placebo and 1.7% to 11.7% for patients assigned pravastatin.

The relative reduction in coronary event rate associated with pravastatin treatment was statistically significant within three of the risk levels and approaching significance in the fourth (p = 0.057), while the magnitude of the relative reduction did not differ significantly between the four risk levels (interaction p = 0.31). These results are reflected in Figure 2, where the observed absolute reductions in five-year coronary event rates were larger for the higher risk levels (Fig. 2A), while the observed relative reduction in five-year coronary event rates were relatively consistent across risk levels (Fig. 2B). The corresponding observed numbers needed to treat to avoid one coronary event decreased substantially as risk level increased, consistent with the constant relative reduction (Fig. 2B).

Routine risk assessment. For routine calculation of a simplified risk score as described in the Methods section, Table 1 provides risk points for a smaller collection of basic risk factors. These risk points can be added to produce a simple aggregate risk score corresponding to a patient's risk factor profile. Thus, for example, a male smoker aged 73

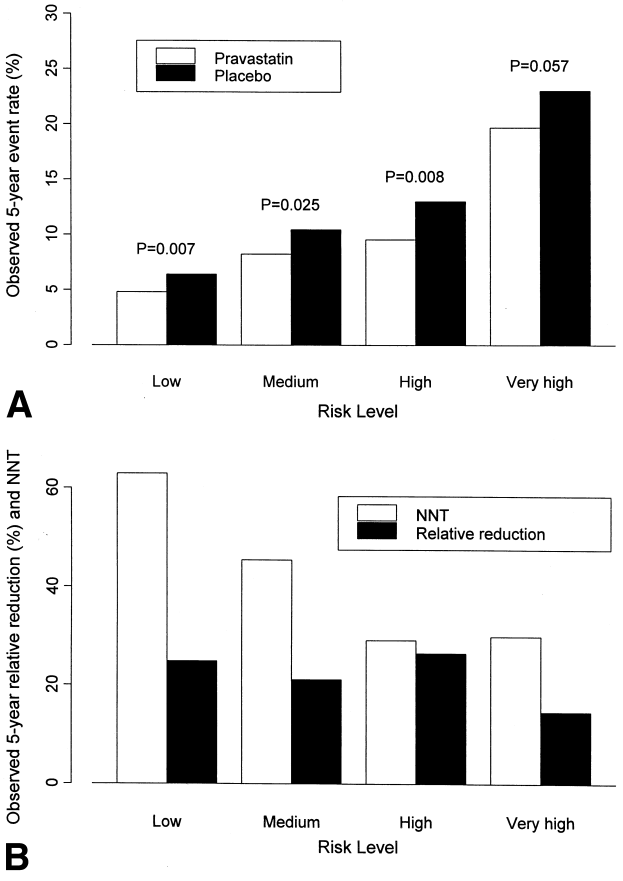

Figure 2. Observed five-year rates of coronary event (coronary heart disease death or nonfatal myocardial infarction) by risk level as determined by the prognostic index. **(A)** Observed rates broken down by treatment group. **(B)** Observed relative reduction in pravastatin group compared with placebo group and observed numbers needed to treat to prevent one coronary event (NNT).

years with total cholesterol 6 mmol/l (232 mg/dl), HDL cholesterol 0.8 mmol/l (31 mg/dl), a history of hypertension and a coronary revascularization since his ACS would have an aggregate risk score of 2 + 3 + 5 + 1 + 2 + 1 − 4 = 10 points.

Table 2 provides categories of coronary risk according to the simplified aggregate risk score and predicted five-year coronary event risks. The variation in risk between risk levels defined by the simplified risk score is consistent with that provided by the more detailed prognostic index. The detailed prognostic index provides marginally better discrimination between the groups with respect to coronary event risk, consistent with the fact that it uses a greater amount of information. For example, based on the simplified risk score classification, the five-year risk ranges from 5% to 16% for patients initiating pravastatin therapy compared with 5% to 19% based on the prognostic index. Consistent with Figure 2, the numbers needed to treat based on the two models in Table 2 decreased as risk level increased.

DISCUSSION

Population and risk factors. This analysis provides a method of long-term risk stratification for patients with established CHD based on patient-specific risk factor profiles. The method was developed based on patients who had survived at least three months after being admitted to the hospital for an ACS and will, therefore, be relevant to patients with stable manifest CHD. It provides a complement to previous long-term risk quantification strategies designed specifically for primary prevention (1–4) as well as adding important information to standard prognostic assessment of ACS survivors based on clinical findings and tests of cardiac function. Our approach is not designed to assess short-term risk in patients presenting with an ACS, and alternative risk stratification strategies have been developed for that purpose (17).

The central risk factors identified here for use in secondary prevention include demographics (age and gender), predisposing conditions and behaviors (diabetes mellitus, hypertension and smoking), prior cardiovascular events (stroke and MI, with or without reinfarction) and lipid levels (total and HDL cholesterol). The inclusion of both total and HDL cholesterol in this secondary prevention risk stratification strategy is consistent with results from primary prevention settings where the combination of these two parameters (in the form of a ratio) has been found to convey greater predictive ability than either parameter alone (18).

Uses of the method. Our approach to quantifying coronary risk can be implemented at various levels of detail. At the greatest level of detail, a large collection of patient-specific risk factors can be used to calculate a prognostic index from which the risk formula can be used to calculate the patient-specific risk of coronary event within any given time frame (up to six years). Alternatively, calculations based on the risk formula can be avoided by categorizing the patient into a risk level (low, medium, high or very high) according to the range in which the prognostic index falls. This risk level can then be used to assess the level-specific five-year coronary risk, as provided in Table 2. Finally, at the greatest level of simplicity, the categorization into risk level can be based on a simplified risk score that involves only the adding of risk points associated with a more basic risk factor profile. This approach has the advantage of simplicity of application while still retaining a reasonable level of discrimination between high- and low-risk patients. The more detailed approach, however, has the advantage of providing assessment of patient-specific risk across a range of time frames.

Risk stratification subsequent to the occurrence of a coronary event can provide important information about the aggressiveness of subsequent therapeutic interventions and lifestyle modifications. Our method may also be useful for identifying patients who, despite the existence of CHD, are at very low risk of subsequent major coronary events and

may not be candidates for immediate aggressive intervention. For example, recent guidelines for intervention in both primary and secondary prevention issued by the joint European Societies define high risk as a 10-year coronary event risk exceeding 20% (19). This is consistent with our classification scheme in which the low- and medium-risk groups are below the high-risk threshold specified by the European Societies. A further use of our prognostic strategy, aside from its uses in patient management, is in the design of secondary prevention studies where high-risk populations need to be identified and future event rates predicted.

For any given patient, our analysis allows determination of two levels of risk according to whether the patient intends to commence pravastatin therapy or not. In view of the intention-to-treat approach taken in the development of the risk factor model, the 22% risk reduction associated with pravastatin reflects the reduction associated with an intention-to-initiate treatment. Greater benefit may be achieved in patients who initiate and comply with therapy, while less benefit may be achieved in patients who initiate but later withdraw from therapy. Aside from the well known methodological advantages of intention-to-treat analyses, the approach is advantageous from an interpretive point of view in the context of prognostic models. In particular, it means that the magnitude of improvement in prognosis due to treatment takes realistic account of the future potential for patients not to comply with current therapy decisions.

Validation. Prognostic risk stratification strategies can be validated based on either internal "cross-validation" procedures or comparisons of predicted and observed event rates in external data. In this study, an internal validation procedure was conducted that supported the usefulness of our strategy for discriminating between low- and high-risk ACS survivors. After randomly dividing the data into 10 subgroups, we repeated the multivariate analysis 10 times, each time leaving out one of the 10 subgroups of data. We then assigned each patient to a cross-validation risk level determined by the model to which that patient did not contribute. Internal support for the validity of our strategy was provided by the fact that five-year coronary event rates varied substantially between the cross-validation risk levels, from 7% to 24% on placebo and 5% to 21% on pravastatin. External validation will require the use of our strategy to predict coronary event rates in other secondary prevention settings. Such an analysis is planned as part of a broader pooled analysis of pravastatin trials using data from the Prospective Pravastatin Pooling project (20).

Implications. Pravastatin was associated with a reduction in coronary event rates across the whole range of baseline risk profiles, and the corresponding relative risk reduction did not differ significantly between patients having different levels of coronary risk. An implication of this finding is that the greatest absolute reduction in coronary event rates is achieved in patients with high baseline risk. In particular, based on our more detailed risk factor analysis, we estimate that only 22 very high-risk patients need to be treated with pravastatin to avoid one coronary event within the next five years compared with 71 patients among those having low baseline risk (Table 2). Despite the benefits of pravastatin therapy in all risk groups, the absolute five-year risk of coronary event is still high (of the order of 15% to 20%) in treated patients with unfavorable risk factor profiles. Many of these patients may not have been identified as high-risk based on clinical and functional measurements alone. These results highlight the need for broad risk factor assessment subsequent to MI or hospitalization for unstable angina. While lipid-lowering therapy is an important step towards improving the long-term prognosis of patients with CHD, use of the prognostic strategy described here can provide important additional information to help identify patients who remain at high risk and who could potentially benefit from additional interventions.

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REFERENCES

1. Grundy SM, Pasternak R, Greenland P, et al. Assessment of cardiovascular risk by use of multiple risk factor assessment equations. J Am Coll Cardiol 1999;34:1348–59.
2. Wilson PWF, D'Agostino RB, Levy D, et al. Prediction of coronary heart disease using risk factor categories. Circulation 1998;97:1937–47.
3. The WOSCOPS Group. Baseline risk factors and their association with outcome in the West of Scotland Coronary Prevention study. Am J Cardiol 1997;79:756–62.
4. Ramsay LE, Haq IU, Jackson PR, et al. Targeting lipid-lowering drug therapy for primary prevention of coronary disease: an updated Sheffield table. Lancet 1996;348:387–8.
5. Pearson T, Rapaport E, Criqui M, et al. Optimal risk factor management in the patient after coronary revascularization. Circulation 1994;90:3125–33.
6. Smith SC, Blair SN, Criqui MH, et al. Preventing heart attack and death in patients with coronary heart disease. Circulation 1995;92:2–4.
7. Dyslipidaemia Advisory Group on behalf of the Scientific Committee of the National Heart Foundation of New Zealand. 1996 National Heart Foundation clinical guidelines for the assessment and management of dyslipidaemia. NZ Med J 1996;109:224–32.
8. Kulick DL, Shahbudin HR. Risk stratification in survivors of acute myocardial infarction: routine cardiac catheterization and angiography is a reasonable approach in most patients. Am Heart J 1991;121:641–56.
9. Grundy SM, Balady GJ, Criqui MH, et al. Primary prevention of coronary heart disease: guidance from Framingham. Circulation 1998;97:1876–87.
10. The 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.
11. The LIPID Study Group. Design features and baseline characteristics of the LIPID (Long-Term Intervention with Pravastatin in Ischaemic Disease) study: a randomized trial in patients with previous acute myocardial infarction and/or unstable angina pectoris. Am J Cardiol 1995;76:474–9.
12. Friedwald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without the use of the preparative ultracentrifuge. Clin Chem 1972;18:499–502.
13. Campeau L. Grading of angina pectoris. Circulation 1976;54:522.

14. American Heart Association Medical/Scientific Statement 1994. Revisions to classification of functional capacity and objective assessment of patients with diseases of the heart. Circulation 1994;90:644–5.
15. Collett D. Modelling Survival Data in Medical Research. London, UK: Chapman & Hall, 1994.
16. Parmar MKB, Machin D. Survival Analysis: A Practical Approach. Chichester, England: Wiley & Sons Ltd., 1995:178–92.
17. Morrow DA, Antman EM, Charlesworth A, et al. TIMI risk score for ST-elevation myocardial infarction: a convenient, bedside, clinical score for risk assessment at presentation: an intravenous nPA for treatment of infarcting myocardium early II trial substudy. Circulation 2000;102:2031–7.
18. Kinosian B, Glick H, Garland, G. Cholesterol and coronary heart disease: predicting risks by levels and ratios. Ann Intern Med 1994; 121:641–7.
19. Wood D, De Backer G, Faergemann O, et al. Prevention of coronary heart disease in clinical practice: recommendations of the Second Joint Task Force of European and Other Societies on Coronary Prevention. Eur Heart J 1998;19:1434–503.
20. The PPP Project Investigators. Design, rationale and baseline characteristics of the Prospective Pravastatin Pooling (PPP) project: a combined analysis of three large-scale randomized trials: Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID), Cholesterol And Recurrent Events (CARE) and West Of Scotland Coronary Prevention Study (WOSCOPS). Am J Cardiol 1995;76: 899–905.