Cholesterol Management and Risk Reduction

Cardiovascular Disease Risk Management in Diabetes – The Implications of the REALITY Asia Study

a report by
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As a result of increasing urbanisation and economic development, the prevalence of type 2 diabetes worldwide is rapidly increasing to epidemic proportions. The global burden of diabetes was estimated at 124 million people in 1997, with a projected increase to 221 million people by 2010.\(^1\) The projected increase is greatest in Asia, where there is a predicted rise of 57% from 2000 to 2010. Data showing increases in type 2 diabetes in Singapore, China and Taiwan provide indicators of the potential scale of the problem in Asia.\(^2\)

The World Health Organization (WHO) projects that by 2030 more than half of diabetes sufferers in the world will live in Asia, and diabetes is set to become the 21st century’s biggest health crisis.\(^3\) Reasons for this explosive increase include heightened genetic susceptibility and environmental and lifestyle factors. Changes in work patterns from heavy labour to sedentary occupations and an increase in computerisation and mechanisation have resulted in more sedentary lifestyles.\(^4\) Nutrition and obesity are also important contributory factors.

Diabetes has both economic and health implications: it can lead to loss of vision, kidney failure, amputations and cardiovascular disease (CVD), including coronary heart disease (CHD) and stroke. This will result in a rise in the cost of public healthcare, putting strain on the financial and medical resources of many Asian governments. The implications for CVD are the most serious: people with diabetes have twice the risk of myocardial infarction (MI) and stroke as the general population. Furthermore, many patients with diabetes do not survive their first event, and if they do survive, their mortality rate over the subsequent months to years is higher than that of the general population. This applies to both type 1 (insulin-dependent) and type 2 (non-insulin-dependent) diabetes, but because type 2 diabetes accounts for over 90% of all cases of diabetes, the majority of clinical manifestations of CVD and other atherosclerotic diseases in people with diabetes occur in patients with type 2 diabetes. As many as 80% of patients with type 2 diabetes will develop and possibly die of macrovascular disease.\(^5\) Diabetes patients have a similar risk of CV events over 10 years to patients without diabetes but with prior myocardial infarction.\(^6\)

There is extensive evidence to suggest that lowering blood cholesterol, specifically low-density lipoprotein cholesterol (LDL-C), lowers the risk of CVD. Several landmark clinical trials have demonstrated the secondary prevention of CV events by lipid-lowering therapies (the majority of which are statins) following cardiac events.\(^7-10\) In addition, lipid-lowering therapies have been proved to reduce the incidence of primary cardiac events in stable coronary artery disease.\(^11-13\) Clinical trial data also support the use of statins in primary prevention of CVD in patients with diabetes and no known CVD.\(^14\)

The Adult Treatment Panel III (ATP III) of the National Cholesterol Education Program (NCEP) issued an evidence-based set of guidelines on cholesterol management in 2001, which were revised in 2004 following further clinical trial data.\(^15\) These guidelines are followed in many Asian countries. Targets for levels of LDL-C are summarised in Table 1.

There are limited data on cholesterol goal achievement in Asia, and very little among Asians with diabetes.\(^16\) The Return on Expenditure Achieved for Lipid Therapy (REALITY) study was the first Asian study to assess cholesterol goal attainment and therapeutic patterns using the same methodologies across countries.\(^17\) It also recognised the significant risk of diabetes. This article will discuss the results of the study in the context of reducing CVD risk in patients with diabetes.

The REALITY Asia Study

Objectives

The REALITY study had the following objectives:

- to evaluate lipid-lowering therapy prescribing patterns and cholesterol goal attainment in patients with and without CHD and other risk factors in the ‘real world’ setting in six major Asian countries: China, Singapore, Malaysia, Korea, Thailand and Taiwan;
- to estimate the proportion of patients with diabetes on statin monotherapy to achieve the NCEP-ATP III goal of <70mg/dl; and
- to assess the impact of certain patient and treatment factors on goal attainment in these countries.

Study Design

The study was a retrospective cohort analysis of patient medical records. Patients recently initiated on statin monotherapy were recruited from randomly selected endocrinology, internal medicine, general practice and cardiology centres. These were divided into three subgroups:

- those with diagnosed CHD and/or diabetes (66% of the cohort);
- those with no CHD but two or more Framingham risk factors (24%); and
- the remainder, with no CHD and fewer than two risk factors (10%).

Table 1
Cardiovascular Disease Risk Management in Diabetes – The Implications of the REALITY Asia Study

**Summary of Results**

Data from 2,622 patients were analyzed. Of the patients studied, 41% had diabetes, and of these 29% had CHD. Within the diabetes subgroup, mean age was 58 years, 48% were male and 43% were post-menopausal female. Furthermore, 11% had a family history of CHD, 65% had hypertension, 28% exhibited low high-density lipoprotein cholesterol (HDL-C) levels and 13% were smokers. The mean LDL-C level was 149mg/dl, although there was considerable variation between countries (from 125mg/dl in China to 161mg/dl in Malaysia and Korea). The mean HDL-C level was 48mg/dl and the mean triglyceride level was 199mg/dl. Cholesterol goal achievement was inversely related to cardiovascular risk, with the diabetes/CHD subgroup the least likely to reach LDL-C targets: only 38% goal attainment was seen in this subgroup compared with 48% overall. The NCEP-ATP III-recommended cholesterol goal of 70mg/dl for those with diabetes and CVD was achieved in only 12% of patients.

Despite considerable baseline CV risk, statin monotherapy in the majority of patients was at low doses: 89% of the patients were taking low- or moderate-potency statins. The type of statin used varied according to country, but the majority of Asians (77%) were taking simvastatin or atorvastatin. Other statins used are summarised in Table 3.

**Table 1: Targets for Low-density Lipoprotein Cholesterol Levels**

<table>
<thead>
<tr>
<th>Guidelines</th>
<th>LDL-C Goal (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes without CVD (Optional/Reasonable Goal)</td>
<td>Diabetes with CVD</td>
</tr>
<tr>
<td>ESC 4th Joint Task Force 2007*</td>
<td>&lt;70</td>
</tr>
<tr>
<td>AHA/ADA/ACC 2003*</td>
<td>&lt;70</td>
</tr>
<tr>
<td>JBS 2 2005</td>
<td>&lt;70</td>
</tr>
<tr>
<td>NCEB ATP III 2004</td>
<td>&lt;70</td>
</tr>
</tbody>
</table>

*Or low-density lipoprotein cholesterol (LDL-C) reduction of 30% from baseline.

ACC = American College of Cardiology; AHA = American Heart Association; ESC = European Society of Cardiology; JBS = Second Joint British Societies.

**Table 2: Categories of Statin Therapy**

<table>
<thead>
<tr>
<th>Statin Type Overall % Use</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin – 35</td>
<td>Statin Type Overall % Use</td>
</tr>
<tr>
<td>Fluvastatin – 4</td>
<td>Statin Type Overall % Use</td>
</tr>
<tr>
<td>Lovastatin – 9</td>
<td>Statin Type Overall % Use</td>
</tr>
<tr>
<td>Pravastatin – 8</td>
<td>Statin Type Overall % Use</td>
</tr>
<tr>
<td>Rosuvastatin – 5</td>
<td>Statin Type Overall % Use</td>
</tr>
<tr>
<td>Simvastatin – 42</td>
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</tr>
</tbody>
</table>

To be eligible for the study, a patient required at least one cholesterol measurement at first prescription of statin (baseline) and at least one further cholesterol measurement within the 12-month follow-up period. Other inclusion criteria were an age range of 18–75 years at baseline and the presence of one or more of the following: diabetes, hypertension, ischaemic heart disease and a history of MI and/or stroke. Medical records were reviewed for up to six months before the baseline and for at least 12 months afterwards.

The lipid-lowering therapies were categorised according to efficacy of the statin and dose, as follows: very low, low, medium, high or very high (see Table 2). Cholesterol treatment goals were based on NCEP-ATP III guidelines and goal attainment was assessed at months three, six, nine and 12. Multiple logistic regression models were used to assess factors associated with cholesterol goal attainment.

Factors associated with a significantly reduced likelihood of goal attainment included having a higher baseline LDL-C (odds ratio [OR] 0.990, 95% confidence interval [CI] 0.987–0.993; p<0.0001 per 1mg/dl increment), having CHD/diabetes or having one or more risk factors at baseline. Factors associated with a significantly increased likelihood of goal attainment included advancing age (OR 1.015, 95% CI 1.015–1.206; p=0.038 per one-year increment), country of residence (ranging from 16% in the diabetes subgroup in Taiwan to 56% in China) and treatment with high-potency statins (OR 2.2253, 95% CI 1.364–3.722; p=0.0015). Of the differing treatment centres used, the greatest success rate (40%) was achieved in cardiology centres, with 19–22% elsewhere.

**Table 3: Summary of Statin Use in REALITY Asia Study**

<table>
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<tr>
<td>Simvastatin</td>
<td>42</td>
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</table>

There was very little change in therapeutic approach over the 12-month study period: in 80% of cases the statin doses were not uptitrated or switched to a different drug despite targets not being met. Dose titration occurred most frequently in China and least frequently in Korea. However, of the small group of patients (n=228) whose dose was uptitrated, only 54% of patients attained their cholesterol goal, i.e. <100mg/dl LDL-C after 12 months of therapy. When the target of <70mg/dl was considered, only 28% of patients met this target.

Among those who had not reached their cholesterol goal after one year, approximately 44% with CHD/diabetes required 6% incremental LDL-C lowering, 8% required 6–12% LDL-C lowering, 7% required 12–18% LDL-C lowering and 29% required >18% LDL-C lowering. It was found that the greatest rate of cholesterol goal attainment was in the first three months. After this time there was a plateau in which little further improvement was observed.
Cholesterol Management and Risk Reduction

Implications of the REALITY Asia Study

Diabetes Subgroup Analysis

This study has clearly demonstrated that Asian therapeutic approaches are not achieving the recommended targets for cholesterol goal achievement. The greatest paradox in these results is that the patient group with the highest risk – i.e., those with diabetes/CHD – are the most under-treated group. Their rate of goal attainment was only 38% compared with 62 and 81% in the other primary prevention groups; therefore, the first aim for Asian healthcare professionals should be to improve treatment of this group.

A striking observation was that the initial statin dose was in the low to moderate potency range. The average LDL-C level of the sample cohort was 149mg/dl; therefore, a 35% reduction was needed to achieve the cholesterol goal of <100mg/dl. Data obtained from the STELLAR trial, which compared rosuvastatin with other statins across dose ranges for reduction of LDL-C, suggest that such a reduction cannot be achieved in high-risk groups at the statin potencies used. High doses are required, i.e., 40mg simvastatin, 20mg atorvastatin or 10mg rosuvastatin. In terms of data obtained in this study, in order for those in the diabetes/CHD subgroup to achieve a target of 70mg/dl, a greater than 50% reduction in LDL-C was needed. Even the highest dose of simvastatin and pravastatin could not achieve this; atorvastatin falls slightly short of this target. However, such a reduction could be achieved with rosuvastatin at 20mg.

Other drugs in combination with statins have the potential to lower LDL-C more than statins alone. Ezetimibe (Zetia) was licensed as a cholesterol-lowering drug by the US Food and Drug Administration (FDA) in 2002 and is frequently used in combination with statins, e.g., with simvastatin as Vytorin. Vytorin at a dose of 10/20mg has the potential to achieve the 50% reduction of LDL-C required in this study. The ENHANCE study demonstrated that simvastatin and ezetimibe in combination reduced LDL-C considerably more than the statin alone; however, this reduction was not accompanied by a reduction in intima-media thickness of the carotid artery. The value of up titration of statins was also analysed. Studies have shown that doubling the dose achieves only a 6% reduction in LDL-C. Since more than 40% of patients in this study required more than 18% reduction, even an up titration of 3x would not achieve cholesterol targets. Logistic regression analysis confirmed that up titration was not associated with goal achievement, whereas high initial statin potency was an important factor.

A further important finding was the rate of improvement across the study period. A clear pattern emerged of improvement over the first three-month period, followed by a plateau, providing further evidence that high initial statin potency was an important factor.

A sub-optimal level of cholesterol goal attainment has been observed outside Asia. The EUROASPIRE I and II studies found that 41% of the participants and 49% of those on lipid-lowering therapy attained the more conservative goal of total cholesterol <5mmol/l and LDL-C <3mmol/l (116mg/dl). Among two-thirds of the diabetes subgroup taking lipid-lowering drugs, 52% attained <3.0mmol/l and 32.4% achieved <2.5mmol/l (<97mg/dl). The findings of the Europe REALITY study were similar: 90% of patients were initially on medium- or lower-potency statin doses, despite many requiring a 50% reduction in LDL-C to attain the NCEP-ATP III-recommended level. Cholesterol goals were achieved overall in 41% of participants, with a significantly lower figure in the diabetes/CHD subgroups. Overall, these data confirm the need to develop and use more effective and well-tolerated initial lipid-lowering therapies in order to help Asian patients with diabetes to achieve cholesterol goals.

Limitations of the Study

A study across six countries in different clinical settings can lead to some misleading results. For example, the high rate of goal attainment in China could be attributable to lower baseline levels of LDL-C. The distinct clinical setting of the Chinese patients may also have been a factor: most were hospitalised due to the onset of CHD, and of these patients 50% had undergone percutaneous coronary intervention (PCI). As a result, these patients may have been more intensively treated and/or more compliant with the therapy. The goal attainment in Korea may have been low because the study period was earlier than that of other countries (2002–2004 versus 2004 for others). When the study was repeated in 2007, goal attainment significantly improved. Practice patterns across treatment centres are highly variable. Furthermore, the effects of lifestyle changes on cholesterol goal attainment were not assessed.

Conclusion

More than half of the participants in the REALITY Asia study did not achieve the LDL-C levels recommended by NCEP-ATP III, particularly those with CVD/diabetes. Although goal attainment was no worse than that observed in European studies, the rapid growth of diabetes in this continent makes these findings highly significant. The high risk status of patients with diabetes should lead to a more aggressive approach in their preventative care. The results have clearly demonstrated the importance of commencing treatment using the correct drug (either a statin or combination therapy) and dose in the shortest possible time, so as to achieve a sufficient reduction in LDL-C to attain the required cholesterol goal target. This clearly requires a change in mindset in the treatment of patients with diabetes.

Rather than increasing the dose, highly effective starting doses of statins or combination therapies are required at the onset. High-potency statins such as rosuvastatin should also be considered, as should the use of combination therapies containing ezetimibe. More effective patient monitoring, more effective treatments – and adherence to these treatments – and therapeutic lifestyle counselling may facilitate goal attainment.

Cardiovascular Disease Risk Management in Diabetes – The Implications of the REALITY Asia Study


**Associated Articles**

**Simvastatin with or without Ezetimibe in Familial Hypercholesterolemia**

Kastelein JJ, et al.


Ezetimibe, a cholesterol-absorption inhibitor, reduces levels of low-density lipoprotein (LDL) cholesterol when added to statin treatment. However, the effect of ezetimibe on the progression of atherosclerosis remains unknown. The authors conducted a double-blind, randomised, 24-month trial comparing the effects of daily therapy with 80mg simvastatin either with placebo or with 10mg ezetimibe in 720 patients with familial hypercholesterolaemia.

Patients underwent B-mode ultrasonography to assess the intima-media thickness of the walls of the carotid and femoral arteries. The primary outcome measure was the change in the mean carotid-artery intima-media thickness, which was defined as the average of the means of the far-wall intima-media thickness of the right and left common carotid arteries, carotid bulbs and internal carotid arteries. The primary outcome, the mean (±SE) change in the carotid-artery intima-media thickness, was 0.0058±0.0037mm in the simvastatin-only group and 0.0111±0.0038mm in the simvastatin-plus-ezetimibe (combined-therapy) group (p=0.29). Secondary outcomes (consisting of other variables regarding the intima-media thickness of the carotid and femoral arteries) did not differ significantly between the two groups.

At the end of the study, the mean (±SD) LDL cholesterol level was 192.7±60.3mg/dl (4.98±1.56mmol/l) in the simvastatin group and 141.3±52.6mg/dl (3.65±1.36mmol/l) in the combined-therapy group (a between-group difference of 16.5%; p<0.01). The differences between the two groups in reductions in levels of triglycerides and C-reactive protein were 6.6 and 25.7%, respectively, with greater reductions in the combined-therapy group (p<0.01 for both comparisons). Side-effect and safety profiles were similar in the two groups. In patients with familial hypercholesterolaemia, combined therapy with ezetimibe and simvastatin did not result in a significant difference in changes in intima-media thickness compared with simvastatin alone, despite decreases in levels of LDL cholesterol and C-reactive protein.

**Lipid-modifying Therapy and Attainment of Cholesterol Goals in Europe: the Return on Expenditure Achieved for Lipid Therapy (REALITY) Study**

Van Gans E, et al.


The study’s objective was to determine lipid-modifying therapy practices and their effects on low-density lipoprotein cholesterol (LDL-C) and/or total cholesterol (TC) goal attainment in Europeans based on prevailing guidelines at the time of therapy in each country. The study applied retrospective cohort analysis involving 58,223 patients initiated on lipid-modifying therapies in 10 European countries, with a median patient follow-up on lipid-modifying therapy of 15.3 months. Data on prescriptions of lipid-modifying therapies, laboratory data including LDL-C and TC, achievement of cholesterol goals for LDL-C and/or TC and hospitalisations were obtained from healthcare administrative databases and/or patient chart reviews. Results showed that across Europe, statin monotherapy was the initial lipid-modifying treatment in 51,786 of 58,009 patients (89.3%) with available data. In addition, 38,853 of 43,410 patients (89.5%) with available follow-up statin potency data were initiated on statin regimens of medium or lower equipotency. Low-equipotency regimens include atorvastatin 5mg, simvastatin 10mg and pravastatin 20mg, whereas medium-equipotency regimens include atorvastatin 10mg, simvastatin 20mg and pravastatin 40mg. Regimens were adjusted to higher equipotency via either up-titration or switches to combination regimens in 16.2% of patients. On average, 40.5% of patients across Europe who were not initially at guideline recommended cholesterol goals (either LDL-C or TC) and had follow-up data attained recommended cholesterol levels, including <30% of patients in Spain, Italy and Hungary. In many countries, the likelihood of goal attainment was inversely associated with baseline cardiovascular risk and/or LDL-C levels. The study concluded that lipid management strategies in Europe during the study period were dominated by statin monotherapy. Even after prolonged follow-up on lipid-modifying therapy, approximately 60% of Europeans studied did not achieve guideline-recommended cholesterol goals. Future emphasis must be placed on subsequent lipid panel monitoring, as well as the use of more efficacious, well-tolerated lipid-modifying therapies such as dual cholesterol inhibitors, to enable more European patients to attain their recommended cholesterol goals.