Lipid Lowering Therapy Use and Achievement of Cholesterol Targets in an Australian Diabetes Clinic

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Brief abstract:

We documented temporal changes in the use of lipid lowering medications and achievement of cholesterol targets in an Australian diabetes clinic. The number of patients using lipid lowering therapy for primary or secondary cardiovascular prevention increased from 6% to 69% between 1993-1995 and 2014-2016 which corresponded to a decrease in LDL-C levels from 3.7 to 2.4mmol/L ($p<0.01$).

Patients with diabetes are at high risk for the development of cardiovascular (CV) disease. Statins have been shown to reduce CV events in direct relationship to their LDL-cholesterol (LDL-C) lowering effect(2). However, there have been no long-term studies documenting the achievement of LDL-C targets and the uptake of lipid lowering medications in patients attending diabetes clinics in Australia. Our objective was to document temporal changes in LDL-C levels and the use of lipid lowering medications in patients attending diabetes clinics at an Australian university teaching hospital.

We studied patients attending diabetes clinics at St Vincent's Hospital Melbourne, Australia With ethical approval for this quality assurance project being obtained from St Vincent's Research and Governance Department Melbourne. Information was extracted from a clinic database from 1993 to 2016. The patient population had a mean age of 62.8 years (62.8 ± 19.11), of which, 75.9% had type 2 diabetes and 18.2% had a history of CV disease. We determined the percentage of patients on lipid-lowering therapy and LDL-C levels and grouped the data by number of patients results in order to ensure a minimum overall sample size was greater than 30 patients per 3 year observation period and then represented the results as a line of best fit using lowess smoothing(5). All analysis was done using STATA 14.1.

Figure 1: Uptake of Lipid Lowering Therapy and Mean LDL-C Results over Time.

Figure 1 shows that the use of anti-lipid therapy increased from 6% to 69% of patients between the time periods 1993-1995 and 2014-2016 ($p < 0.01$, students t-test). This corresponded to a decrease in LDL-C levels from 3.7 mmol/L to 2.4 mmol/L ($p < 0.01$). There was a strong negative correlation between anti-lipid therapy use and LDL-C levels ($r = -0.88$, $p < 0.01$). The publication dates of three major 'statin-trials', arbitrarily selected for illustrative purposes only, in subjects with and without diabetes are also shown on the diagram, i.e. The Scandinavian Simvastatin Survival Study (4S)(1), Primary prevention for cardiovascular disease with atorvastatin in type 2 diabetes (CARDS)(3) and the Cardiovascular benefits and diabetes risks of statin therapy in primary prevention (JUPITER)(4). In patients with and without a history of CV disease, the use of anti-lipid therapy and LDL-C levels achieved at 8 different observation periods during the study period is shown in table 1. Patients with or without a history of CV disease had a decrease in mean LDL-C from 1993-1995 to 2014-2016 of 3.55 to 2.29 ($p < 0.01$) and 3.67 to 2.52 mmol/L ($p < 0.01$), respectively. There was a similar decrease in non-HDL-C levels from 4.66 to 3.22 mmol/L ($p < 0.01$) between 1993-1995 to 2014-2016, respectively. Generally the percentage of patients who have achieved lipid treatment targets that were current at the time the data was collected was found to have increased. For 1992-1995, 35.8% were meeting the 1992 American Diabetes Association (ADA) target of < 3.36 mmol/L, in 2004-2006 this rose to 46.3%, reaching the target of < 2.60 mmol/L set in 2003 by the ADA. In 2013 targets were introduced by the ADA with specific reference to CVD history with 66.5% of our patients without a history of CVD meeting a target of 2.60 mmol/L during 2013-2015. However, only 29.4% with a history of CVD met the target of < 1.80 mmol/L(6-8). Similar results have been reported for the community based Australian, Fremantle Diabetes Study 1 and 2 which ran during 1993-1996 and 2009-2011 and saw a reduction in LDL-C from 3.3 to 2.3mmol/L. These studies were also able to show a similar uptake of lipid lowering therapy from 11% to 68%(9). In the years

2010-2016 the breakdown of lipid-lowering medication was 79% for statins, 14% for fibrates, 5% for ezetemibe and 2% for other agents. During the years 2010-2016, the majority of patients (44%) taking a statin were on a dosage greater than 40mg a day, 23% were taking a dose between 20-40mg a day and 33% took a dosage less than 20mg a day. Information regarding the type of lipid lowering therapy prescribed for patients attending our clinic was not available prior to 2010

Table 1: LDL-C measurements and cardiovascular disease history

The results of our audit suggest that there has been a substantial increase in the use of lipid lowering therapies by patients with diabetes over the last 20 years, which has resulted in a significant improvement in LDL-cholesterol levels. It should be noted that our clinic population includes patients with type 1 and type 2 diabetes. There are known limitations in the use of the Friedewald equation for the calculation of LDL-C in patients with elevated triglyceride levels(10). For this reason patients with a triglyceride level $>4.5\text{mmol/L}$ were not included in our audit. Although statin therapy is recommended for the vast majority of patients with diabetes the use of statins in very young patients with type 1 diabetes may not be warranted. The above trends appear to be influenced by the publication of the results from major statin trials. A preliminary analysis of the HbA1c and blood pressure data over time from our clinic found a lack of improvement compared to the significant reduction in LDL-C. In the STENO-2 study, patients in the conventional arm only experienced minor reductions in HbA1c ($0.2\pm0.3\%$), systolic blood pressure ($-3\pm3\text{ mm Hg}$) and diastolic blood pressure ($-8\pm2\text{ mm Hg}$) over 8 years. The STENO-2 study showed a reduction of $0.72\pm0.33\text{ mmol/L}$ in LDL-C in the conventional therapy arm (11).

The risks and benefits associated with statin use has been a recent topic for discussion both in the medical and broader community(12). A recent review has suggested that for every 10,000 patients treated with an effective statin regime for 5 years, there are 5 cases of myopathy, 50-100 of new

onset diabetes and 5-10 of haemorrhagic strokes (13). It is estimated that for every year an individual takes a statin, the risk of a major vascular event or the need for coronary revascularisation decreases by 25% for each mmol/L reduction in LDL-C, with absolute benefits being dependant on an individual's background CV risk profile(13). Although these rates may be lower than seen in clinical practice our clinic does not routinely systematically collect information on statin myopathy incidence.

There are a range of varied recommendations for the commencement for lipid lowering therapy and targets for LDL-C levels. These range from assessments based on an individual's risk factors to group based risk level assessment as advocated by The Canadian Cardiovascular Society(14). The Canadian Cardiovascular Society recommends the use of statins in any patients with diabetes over the age of 40, diabetes patients with microvascular disease or type 1 patients over the age of 30 who have had had diabetes for more than 15 years(14). These guidelines recommend targeting a LDL-C level of below 2.0 mmol/L. The US Preventative Services Task Force released an updated version of their 2008 recommendations regarding statin use in November 2016. They recommend the use of low to moderate dose statins in adults aged 40-75 years without a history of CV disease but with 1 or more risk factors, including diabetes, and a 10% or greater risk of experiencing a CV event during the next 10 years. The guidelines suggest using the Pooled Cohort Equations to calculate 10 year risk of CVD as developed by the American College of Cardiology and American Heart Association(15). The Australian College of General Practitioners bases their recommendation for the use of statins in patients with type 2 diabetes on an assessment of each individual's absolute CV risk and also recommend a LDL-C target of <2 mmol/L(16). The National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand recommend a general primary prevention target of <2.0 mmol/L and a secondary prevention target of <1.8 mmol/L(17, 18). Our results suggest that there has been a substantial decrease in LDL-C in patients with diabetes who do not have a clinical

history of CV disease. This must likely reflects the appreciation of the increase CV disease risk that a diagnosis of diabetes conveys, and the proven benefits of statins for the primary prevention of CV disease in diabetes(19).

The release of generic statins, and regulatory interventions aimed at reducing the cost of many medications should improve access to statin therapy for many patients with diabetes, who currently do not fulfil the Pharmaceutical Benefit Scheme indications for subsidised prescriptions. The impact of these changes on the actual uptake of statins and an expected corresponding drop in LDL-C levels await to be documented by future audits. The use of newer lipid lowering therapies, such as the PCSK9 inhibitors, although not currently used in patients with diabetes shows promise, with some early studies showing a greater mean reduction in LDL-C when treated with a PCSK9 inhibitor compared to standard treatment with statins in patients with type 2 diabetes(20,).

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Legend for tables and graphs:

Figure 1: Uptake of Lipid Lowering Therapy and Mean LDL-C Results over Time.

The publication dates of major trials in subjects with and without diabetes are also shown.

4S Study - The Scandinavian Simvastatin Survival Study (4S). The Lancet. 1994 (1)

CARDS Study - Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes. The Lancet. 2004(3)

JUPITER Study - Cardiovascular benefits and diabetes risks of statin therapy in primary prevention. The Lancet. 2012(4)

Table 1: LDL-C measurements and cardiovascular disease history

¹ Patients were classified as having a history of CV disease if they had one of the following: AMI, stroke, CABG, Angioplasty or carotid artery disease.

Note: Only the first LDL-C level available for an individual patient per time period was included in this analysis.

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Year	History of CV disease [†]	No History of CV disease	Total
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	Mean LDL-C	N	Mean LDL-C	N	
1993-1995	3.55 (1.7, 6.3)	37	3.67 (1.40, 8.90)	118	155
1996-1998	2.85 (2.46, 3.24)	64	3.18 (1.17, 4.44)	40	104
1999-2001	2.30 (2.36, 3.64)	212	3.19 (2.20, 4.12)	105	317
2002-2004	2.50 (1.17, 3.71)	378	2.38 (1.32, 4.23)	174	552
2005-2007	2.48 (0.97, 3.38)	301	2.64 (1.32, 3.82)	100	401
2008-2010	2.14 (0.98, 4.4)	478	2.43 (0.99, 4.13)	237	715
2011-2013	2.09 (0.27, 5.55)	427	2.27 (0.23, 5.54)	477	904
2014-2016	2.29 (0.03, 6.72)	831	2.52 (0.14, 6.09)	192	1023

[†] Patients were classified as having a history of CV disease if they had one of the following: AMI, stroke, CABG, Angioplasty or carotid artery disease.

Note: Only the first LDL-C level available for an individual patient per time period was included in this analysis.

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