Dr Edmund Lee MBBS (WA) FRACP
CARDIOLOGIST
St John of God Murdoch Medical Clinic
Suite 34/100 Murdoch Drive
Murdoch WA 6150
Tel: (08) 9366 1916
Fax: (08) 9311 4147

LDL TARGETS – The Controversy

With the introduction of the 2013 American College of Cardiology (ACC)/American Heart Association (AHA) Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults came a radical departure from existing guidelines. Targets for low-density lipoprotein cholesterol (LDL-C), or indeed any lipid measure, were eliminated. This brought about wide debate.
Many experts believe that targets are important and valuable—for both the provider and the patient. Existing guidelines in Australia, Europe, Canada, and by the International Atherosclerosis Society and recommendations by the National Lipid Association (NLA) include LDL-C targets based on risk scores, as did the previous National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III).

Where do lipid targets come from? In general, cut-offs for cholesterol levels are drawn from population (epidemiologic) studies showing a log-linear relationship between serum cholesterol levels and coronary artery disease (CAD) events. The ACC/AHA Guideline writers based their recommendations on randomized clinical trials (RCTs) only. They concluded that there were no direct data from RCTs to support the use of LDL-C or any lipid target. Thus, the panel could not make any recommendation regarding targets to guide therapy because the evidence for these comes from population studies that were not considered.

The recent IMPROVE-IT trial provided evidence that "lower is better" for LDL-C. This study of more than 18,000 post-acute coronary syndrome patients on simvastatin therapy randomly assigned to have ezetimibe or placebo added showed an additional 0.4mmol/L reduction in LDL-C at 1 year with ezetimibe. Baseline LDL-C was 2.6mmol/L in both groups and was reduced to 1.8mmol/L at 1 year in the statin-only group vs 1.4mmol/L with ezetimibe. There was a significant reduction in cardiovascular (CV) events, including a 10% reduction in CV death, myocardial infarction, and stroke in the group that received ezetimibe. Although this study was for secondary prevention, many feel that benefits would extend to those who do not have manifest disease.

Studies such as TNT, IDEAL, and PROVE IT-TIMI 22 also show a direct association between a greater reduction in LDL-C (equating to a lower LDL-C level) and a greater reduction in events.

So the question remains, should we be utilising targets and how low should the future target LDL be?
I believe that targets are useful for patients to encourage compliance, by engaging them in the treatment process. I also believe that in patients who are at high risk for future CVS events (ie secondary prevention), we should be trying to get the LDL-C as low as possibly tolerated. That means prescribing high intensity statins (ie rosuvastating 20-40mg or atorvastatin 40-80mg) and possibly adding in a non-statin such as ezetrol when residual LDL-C is still >1.8 or when high intensity statins cannot be tolerated due to side-effects. With the advent of PCSK9 inhibitors (antibodies against the PCSK9 protein that facilitates LDL receptor breakdown), we may be able to achieve LDL levels of <1mmol/L in a large proportion of patients. Whether this will significantly reduce future CVS events remains to be seen. The drug companies are very optimistic and to date, there are now 12 different PCSK9 inhibitors with a number undergoing large phase III randomised controlled trials.
In summary, I believe that treatment targets are important. I also believe in the cholesterol hypothesis that 'lower is better' and that the targets ought to be reduced for high risk patients to further improve on their long term prognosis. This will become more relevant in the coming years when newer and safer drugs become available, as long as they are proven to reduce hard clinical events.

Dr Edmund Lee
AUGUST 2015