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Foreword

From the Editor: Is a goal a target?

In using the English language, we often have been careless with words, allowing them to mean different things both written and spoken. This has a positive effect in some circles, giving poets and masters of prose a level of freedom that can add flavor to literature that is both entertaining and at times wondrous–witness Shakespeare. However, I have come to believe this is not a plaything in science or government. There are dangerous consequences in being less careful with our use of words, allowing them to mean very different things in different settings. I believe we have fallen into that trap in the business of writing clinical guidelines. The critical example in our field of clinical lipidology is the confusion over the definitions of target and goal. Both terms are frequently used in sports and perhaps the analogies best used to illustrate the differences between these 2 words can come from their use in many games.

For example, basketball, can illustrate the point that goals should not be called targets. When a player "shoots," he is aiming at the target of a ring suspended in space but he does not score a goal until the ball falls through the ring and the net and usually on the floor. One scores a goal in football when the ball enters the end zone after passing through the imaginary plane above the goal line. In our first guidelines regarding the clinical management of elevated cholesterol in plasma, the Adult Treatment Panel One (ATP I) clearly defined the target of treatment as low-density lipoprotein cholesterol (LDL-C), and treatment of this target was intended to reduce this measure below certain minimal values that were called goals.[1] Goals did not have singularity. They were a range of values defined by an upper limit without a lower limit. These definitions of both target and goal have been adhered to by most guidelines written since. The American College of Cardiology/American Heart Association Guideline Committee somehow did not recognize those definitions and chose to use targets of treatment with the definition that traditionally had meant goals of treatment.[2]

This confusion of the meaning of these words had consequences. Based on this newly adopted definition, we were informed that achieving targets of treatment were not valid because they had not been tested in clinical trials. The implication was that experimental science useful in clinical decision making must be the product of a randomized double-blind clinical trial. Second, we have been informed that achieving targets could actually be dangerous because it would result in the undertreatment of many patients who could benefit from having LDL-C values below the "target" values of 100 or 70 mg/dL. I believe both of these concepts were mistaken. The declaration that randomized clinical trials are necessary for target setting and the implication that goals (not targets) are single values are inconsistent with the use of these words in previous guidelines. The misuse of "targets" instead of "goals" implied that physicians were previously advised to achieve specific LDL-C values with diet and drug therapy.

Targets have traditionally been defined as the lipoprotein measure that is to be treated. Until the last decade, LDL-C has been the major and virtually the sole target in the guidelines used in the United States, Europe, and most of the rest of the world. In the original publication of the National Cholesterol Education Program's ATP Report,[1] LDL-C is clearly defined as the target of treatment. To quote this document in its first use of the word target: "Because most of the cholesterol in the serum is found in the LDL, the concentration of total cholesterol is closely correlated with the concentration of LDL-cholesterol. Thus, while *LDL-cholesterol is the actual target of cholesterol-lowering efforts*, total cholesterol can be used in its place in the initial stages of evaluating a patient's serum lipids." In the last document published in the name of the National Cholesterol Education Program (NCEP) (3), it was stated that: "All ATP reports have identified low-density lipoprotein cholesterol *(LDL-C) as the primary target* of cholesterol lowering therapy."

So there should be no argument regarding the use of the word "targets" for the lipoprotein measures that have demonstrated the power to predict risk and when effectively treated result in a fall in clinical events. More recently, we have discussed the advantages of using non–high-density lipoprotein cholesterol (HDL-C) as an alternative target of therapy in hypertriglyceridemic patients. This recognizes that very low-density lipoprotein (VLDL) remnants are also direct contributors in the mechanisms of atherosclerogenesis. Using non–HDL-C automatically adds the cholesterol content of VLDL remnants to the LDL-C. The variability in cholesterol content of LDL is quite high and therefore many would like to define the particle number of LDL or the apoB content as very valuable measures, particularly in

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patients with low HDL-C and even modestly elevated triglycerides. This consideration of targets is completely independent of how aggressively we should treat any given target. That is where goals come into the discussion.

As with targets, goals were well defined in the original NCEP-ATP I report. The essential and continuing feature through each subsequent publication of the ATP recommendations was the definition of a goal as a range of values below a given lipoprotein value.[3–5] Other organizations even more recently have also used the concept of goals with the same meeting as the NCEP.[6,7] Goals unlike targets are not singular. They are any and all values below the stated goal line. So in the original ATP I publication, two goals were stated for guiding the appropriate reduction of LDL-C: <160 mg/dL for moderate-risk and <130 mg/dL for high-risk individuals. Risk was based on assessment of the integrated risk estimate of all known risk factors identified by the clinician. These goals were the same for dietary treatment and for drug treatment. The issue was to use all effective means in lowering LDL-C considering their safety, cost, and benefit. It is of note that some skepticism was expressed about statin therapy at the time of this publication in 1988[1] since the first drug in this class, lovastatin had been approved by the Food and Drug Administration only 4 months earlier. There had been no trials of effectiveness in preventing vascular disease with statins.

The initial recommendations to reduce LDL-C (below 160 or 130 mg/dL) were derived from observational studies in communities, comparative data from other countries, and clinical experience. The clinical trials with dietary intervention by Leren et al[8] in Norway, Dayton et.al.[9] in the Veterans Administration, and the Lipid Research Clinics Coronary Primary Prevention Trial[10] in the United States (with cholestyramine) showed significant evidence of benefit from changing plasma cholesterol. The event rate reductions without evidence of harm added emphasis to developing guidance to a safer range for LDL-C values in patients. At the time (1970s), the mean LDL-C in middle-aged American males was approximately 130 mg/dL, and this recommendation seemed to invade the "normal range." Much criticism of these goals was offered by clinicians as being overly aggressive. However, as new statins were introduced, compared with placebo or less-effective therapy, benefit was demonstrated in reducing LDL-C to lower and lower values. No value has been found where one can say all benefits possible have been achieved by lowering LDL-C. Fortunately, no value of LDL-C (or non–HDL-C) has been associated with harm if the therapeutic agent itself is not directly causing an adverse response. We are fortunate in that statins and other newer agents such as ezetimibe have shown very uncommon and treatable toxicity.

The fact that we can lower LDL-C and non–HDL-C to extremely low values without evidence of harm provides the clear rationale for our defining goals as a range of values below a defined upper limit. Thus, when we recommend reducing LDL-C to a value of <100 mg/dL, we mean it.

Less than 100 includes all values in the range of 99 to 0. It does not include 100 mg/dL. We are not likely to achieve 0 in the near future with current or envisaged therapy so this number is also mute. This leaves an important question unanswered. Where in that range of values is there a "sweet spot" that is most likely to provide vascular disease risk reduction that balances with cost and safety. A recent meta-analysis examined the relationship of LDL-C, non–HDL-C, and apoB concentrations in 18,677 patients receiving high-dose statin therapy.[11] Trials were included if they contained more than 1000 patients, and the cohort was observed for at least 2 years after beginning therapy. The lipoprotein measures achieved during the trial were arrayed in order by groups and compared with major vascular events in each range of values over the course of the trials. The relationship between LDL-C and vascular disease (Fig. 1) and non–HDL-C (Fig. 2) illustrates a steady reduction in risk with maintenance of lower values for all these measures. It was better to reside in the group with LDL-C between 75 and 50 mg/dL than in that between 100 and 75 mg/dL. Below 50 mg/dL provided a range of values with even lower events. A similar finding is evident with the non–HDL-C measure. However, the cohorts with lowest LDL-C will be somewhat different from comparable percentile reductions in non–HDL-C because elevated VLDL cholesterol is associated with lower LDL-C in many patients. So there is validity in the recent recommendations of the National Lipid Association[6] and the International Atherosclerosis Society[7] recommending that we consider both measures when planning a therapeutic strategy. The same can be said for apoB measures in certain patients, particularly the diabetics and patients with low HDL-C and higher triglycerides.

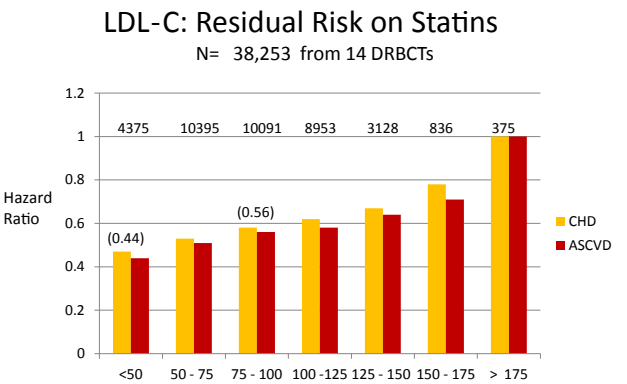

Figure 1 Low-density lipoprotein cholesterol (LDL-C; mg/dL) during statin therapy. The hazard ratio for new incidence of coronary artery disease and for all atherosclerotic vascular disease–related events is plotted for each group of patients ranked by on treatment LDL-C values. Declining incidence is illustrated for each group compared with those with LDL-C of greater than 175 mg/dL to those less than 50 mg/dL. The event rate has been adjusted for sex, age, smoking status, diabetes mellitus, systolic blood pressure, high-density lipoprotein cholesterol and specific trial. The number of patients in each group is listed above respective columns.