Fibrates & Calculated and Direct LDL-C

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Why is the reduction in the calculated LDL-C less with a fibrate like TriCor than when the LDL-C is directly measured by the lab? The numbers can be significantly different. This means that one might see a drop in LDL-C using the calculated LDL-C and would not see a drop in LDL-C using a direct measurement. What gives? Is LDL-C being reduced or is it not? Does it matter when using a fibrate?

This discrepancy can have very real world implications for physicians in the interpretation of the lipid profile as with one method the drop in LDL-C would appear efficacious and with the other method the lack of a drop In LDL-C would make appear that the drug is ineffective.

Only a few clinicians do direct LDL-C measurements as most rely on the labs calculated result. A direct LDL-C measurement accurately assays the cholesterol that exists in all of the LDL particles in a dL of plasma. Since TG are irrelevant to the assay, no fasting is required for direct LDL-C measurements. The Friedewald formula, first described in the 1970's is used by most labs in America to calculate both VLDL-C and LDL-C. The calculation is highly variable depending on TG levels.

Total Cholesterol is the cholesterol content within every lipoprotein particle in a deciliter (100 cc) of plasma). VLDL-C, LDL-C and HDL-C are the cholesterol content within those respective lipoproteins in a dL of plasma. Both the calculated and the directly measured LDL-C are supposed to represent the cholesterol content within the LDL particles. However, as TG levels rise the calculated values looses accuracy and direct measurement does not.

Calculated LDL-C = TC minus (HDL-C plus VLDL-C) Note that both TC and HDL-C are direct laboratory measurements and are usually quite accurate. Neither measurement requires fasting. VLDL-C is estimated by labs using the formula TG/5

This assumption (TG/5) presumes every TG molecule is in VLDL particles and that the lipid composition of VLDL particles has five times more TG than cholesterol. These two assumptions loose accuracy as the TG starts to increase above 130-150 mg/dL. The formula is fairly accurate if the TG is < 70-100 mg/dL. With TG above 130-150 all lipoproteins (not only VLDL) will be transporting TG and the VLDL TG/cholesterol composition changes.

As TG levels rise the composition of VLDL particles changes from a 5:1 to a 10:1 or a 15:1 ratio of TG to cholesterol. So if one has a TG of 200, the standard calculation reports VLDL-C as 200/5 = 40. In reality the VLDL-C is more likely to be 200/10 or 20 mg/dL. This 20 mg/dL error in VLDL-C now carries over to the LDL-C calculation. Using the Friedewald equation, lets now calculate VLDL-C and LDL-C in a patient with a TG of 200 mg/dL using 5:1 and 10:1 ratios

(a) LDL-C = TC minus (HDL-C plus 40) 5:1 ratio used (all labs always use this ratio)
(b) LDL-C = TC minus (HDL-C plus 20) 10:1 ratio used (no labs use this ratio)

The calculated LDL-C would vary by a considerable 20 mg/dL in cases (a) and (b) above. Since in a patient with a TG of 200, the more likely accurate TG/Chol ratio is 10:1 (used in case (b) above, b is the more accurate LDL-C calculation. The direct LDL-C measurement (not dependent on the TG values) would be far more in agreement with the calculated LDL-C in (b) than (a). Obviously a 20 mg/dL difference in LDL-C can easily mean the difference between being at goal and not being at goal.

Practitioners should realize that in all with a TG > 150-200 mg/dL the VLDL-C may be 10-30 mg below what is reported and the LDL-C is actually 10-30 mg higher than the calculated value. The discrepancy increases even more as the TG goes > 200. NCEP addressed these differences between calculated and direct LDL-C in the 2004 addendum. They were explaining that in the Heart protection Study, direct LDL-C measurements were used, not calculated LDL-C vales. They note that a postprandial TG will always be 20-30 mg/dL higher in noninsulin resistant patients and

considerably higher in insulin resistant patients and these calculated cholesterol measurements can be erroneous.

NCEP 2004 ADDENDUM*: Consequently, estimations of baseline fasting LDL-C, if calculated by the Friedewald equation, likely would have been in the range of 150 to 155 mg/dL, or about 15% higher than baseline LDL-C calculated by the direct method. If this difference between direct and calculated LDL-C holds at low LDL-C, a direct LDL-C level of 100 mg/dL would correspond to a calculated LDL-C of 115 mg/dL. Although this difference could be of some significance for treatment decisions, to avoid confusion the distinction will not be emphasized in the guidelines.* Circulation. 2004;110:227-239.

So a fibrate drug like TriCor (fenofibrate), that inhibits TG synthesis and remodels particle composition through its lipase and apoC-III effects, will change the TG and the TG composition within VLDL particles. By changing TG, the drug will also change the VLDL-C and any change in VLDL-C would influence a calculated, but not necessarily a direct LDL-C. Depending on the change in TG, the calculated LDL-C is going to be varying dramatically, than the more accurate direct measurement which will not vary.

If we go back to the cases above: If the patients were started on TriCor, it is very likely the 200 mg/dL of TG will drop. Let's presume (to make the calculations very easy) that the TG levels drops from 200 to 100 mg/dL. With a TG of 100 mg/dL we can assume there is a 5:1 ratio of TG/Cholesterol in the VLDLs. The calculated VLDL-C = 100/5 = 20 mg/dL

The original calculated LDL-C in case (a), using the 5:1 VLDL-C calculations was:
VLDL-C = 200/5 = 40

(a) LDL-C = TC minus (HDL-C plus 40)

Using the formula after the patient received TriCor:
VLDL-C = 100/5 = 20

The LDL-C = TC minus (HDL-C plus 20)

Hooray: The TriCor has reduced the LDL-C by 20 mg/dL.

But wait a minute: The original direct LDL-C was 20 mg/dL less than the calculated value. The direct LDL-C, not being affected by a drop in TG would not have changed on the fibrate TriCor.

Other factors are always at play with the calculated LDL-C:

Calculated LDL-C = TC minus (HDL-C + VLDL-C)

If TriCor raises the HDL-C (which it almost always does to some degree) and reduces the calculated VLDL-C then the reduction in calculated LDL-C would be further enhanced. But again, the Direct LDL-C is not influenced by HDL-C or VLDL-C. So what TriCor does to HDL-C may not affect the direct LDL-C.

Lesson: If you are using the Friedewald-formula derived lipid concentrations (as almost all are) as TG goes up, VLDL-C calculation will rise and LDL-C calculation will fall. A much better way to estimate the atherogenic cholesterol more accurately is to look at the cholesterol content of VLDL and LDL particles. This of course is termed Non-HDL-C. NCEP uses Non-HDL-C as a secondary goal of therapy when treating patients with elevated TG. If one subtracts HDL-C from TC, (which are both accurate measurements even if the patient is not fasting), then one will have a very accurate non-HDL-C.

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Since all apoB particles (LDL and VLDL) are atherogenic (if present in increased quantities), it then becomes irrelevant whether the cholesterol is in LDL (LDL-C) or VLDL (VLDL-C) particles as almost all of that cholesterol is potentially atherogenic. That is why when TG are elevated Non-HDL-C becomes a better surrogate of apoB than is LDL-C. So if you focused everything on Non-HDL-C you would not have to rely on the very variable VLDL-C and LDL-C calculations. Non HDL-C levels do not depend on the variable TG composition of LDL and VLDL particles. When TG are elevated, Non-HDL-C is a much better surrogate or correlate of the all important apoB level, than is LDL-C. Since almost everyone you are prescribing TriCor to has high TG, please focus on apoB when you prescribe TriCor. Non-HDL-C, not LDL-C is your best lipid surrogate in these patients.

In reality, the ultimate bottom line is that neither the direct or calculated LDL-C matters. The only question a clinician has to solve is how many LDL particles does it take to transport any given amount of cholesterol in a specified volume of plasma. Obviously it takes considerably more (up to 40-70%) small LDL particles than large to transport any given level of cholesterol. That is why apoB or LDL-P (from the LipoScience NMR LipoProfile) is a much better predictor of risk than LDL-C. The determining factor on how cholesterol enters the artery wall is how many apoB particles are present, not how much cholesterol is in the particles.

When I prescribe a fibrate like TriCor I know apoB is going down (mostly by its actions on TG-rich remnant lipoproteins), I know LDL size is shifting from small to large, I know HDL particle flux and functionality is improving and I know multiple pleiotropic effects including improving insulin sensitivity, CRP etc are occurring. As Sanders Robbins (author of VA-HIT) remarked, much of the CV protection that a fibrate brings to the table cannot be ascertained by looking at a lipid profile. All of this is why it is very unfair to compare the efficacy of a fibrate to other lipid drugs solely on changes in lipid parameters. Fibrates improve outcomes by affecting lipoproteins in ways not always evident by lipid concentrations and through their pleiotropic effects.