Clinical Pearls in Dyslipidemia Management

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The landscape of lipid referrals has changed. In the past, the bulk of referrals were for decisions to initiate lipid medications and difficulty achieving LDL-C targets with available medications. The evidence-based lipid management guidelines have taken the "guesswork" out of decision-making and the availability of potent 3-hydroxy-3-methylglutaryl-Coenzyme A reductase inhibitor (statin) medications has made target LDL-C levels achievable for more patients. Based on referrals from and questions posed by FPs, more complex issues dominate the field. There are three issues in particular that merit discussion:

- How to manage the patient intolerant to medications
- How to interpret the LDL-C in a high triglyceride patient
- When and how to use combination lipid therapy

Irene's case

Irene is a 58-year-old woman with hypertension and impaired fasting glucose, referred due to "statin-myalgia." She has had myalgia on standard doses of at least four different statin medications and GI upset with fibrates, resins, ezetimibe and niacin. Her baseline lipid profile includes:

- Cholesterol: 10.1
- Triglycerides: 1.9
- HDL-C: 1.55 mmol/L
- LDL-C: 7.66 mmol/L
- Apo B: 1.81 g/L

She is able to tolerate rosuvastatin 20 mg weekly, with modest improvement:

- Cholesterol: 7.0
- Triglycerides: 1.0
- HDL-C: 1.60 mmol/L
- LDL-C: 4.98 mmol/L
- Apo B: 1.2 g/L

Suboptimal but better than nothing.

Case one: Irene

The medication-intolerant patient

Statin medications have the best body of evidence preventing coronary events. Estimates vary, but at least 5% of statin-treated patients will need to stop their medications due to muscle-related side-effects. In the person with very high LDL-C or moderate to high-risk of CVD, this is of major concern. Cytochrome P450 issues need to be verified (drugs competing for elimination with certain statins [*e.g.*, macrolide antibiotics, diltiazem, cyclosporines]). Assuming no allergies or medical contraindications, there are still options. I often will try different members of the statin class, even at subtherapeutic doses. Introducing a medication at lower doses, with gradual

Ron's case

Ron is a 68-year-old man with well-controlled diabetes mellitus, stable coronary artery disease, referred for help in determining adequacy of LDL-C suppression in the presence of high triglycerides.

- Baseline lipids (1993):
  - Cholesterol: 9.0
  - Triglycerides: 22.7
  - HDL-C: 0.7 mmol/L (calculated LDL-C is -2.02)
- On fibrate:
  - Cholesterol: 4.8
  - Triglycerides: 3.93
  - HDL-C: 1.3 mmol/L
  - LDL-C: 1.71 mmol/L (ratio 3.7)

Is he at target levels, or not?

- LDL-C: < 2.0 (ok)
- Non-HDL-C (4.8 - 1.3) = 3.5 (ok)
- Apo B: 1.3 g/L (far from ideal)

Potent statin added with correction to all targets.

increase may allow the patient physically (and sometimes more importantly psychologically) to reach a therapeutic dose. Another therapeutic approach is to use intermittent dosing schedules (alternate day or weekly dosing have been tried for atorvastatin and rosuvastatin). Sometimes we are limited to giving a statin dose without reaching guidelines, but at least patients are receiving statin medication and qualify for some of their benefits. If no statin is tolerated, low doses of a different class may be attempted, understanding that the evidence is lacking for outcome reduction (with the exception of nicotinic acid/niacin). One may also try combining different classes of medications at low enough doses to allow tolerance, recognizing again the limitations on evidence.

Case two: Ron

Interpreting LDL in the high triglyceride patient

Mixed dyslipidemia is a very common occurrence. Before any venture into advanced diagnostics and management, it is crucial to rule out contributing elements (*e.g.*, diet, medications, hyperglycemia) and initiate lifestyle management, as these may identify and correct portions of the dyslipidemia and simplify the case. Although labs will not report LDL-C when triglyceride > 4.5 mmol/L, the correlation between LDL particle number and LDL-C becomes less reliable when the triglyceride > 1.5 mmol/L, so that:

a) LDL-C calculations are less reliable and
b) LDL-C measures are a less meaningful assessment of atherogenic status in those settings.

The evidence-based lipid management guidelines have taken the "guesswork" out of decision-making.

The total cholesterol content on the atherogenic lipid particles correlates with CVD risk, but a better determinant of risk is the number of particles. Atherogenic particles come in different sizes and densities and each LDL particle may have different cholesterol content. What is constant is that there is one molecule of

Larry's case

Larry is a 50-year-old man with metabolic syndrome and angina, referred for inadequate lipid levels on maximal doses of statin or fibrate.

- Baseline lipids:
  - Cholesterol: 6.4
  - Triglycerides: 7.4
  - HDL-C: 0.63 mmol/L
  - Apo B: 1.4 g/L
- On fibrate:
  - Cholesterol: 5.6
  - Triglycerides: 1.5
  - HDL-C: 0.74 mmol/L (ratio > 7)
  - Apo B: 1.0 g/L (ratio and Apo B too high)
- On statin:
  - Cholesterol: 3.9
  - Triglycerides: 3.0
  - HDL-C: 0.74 mmol/L (ratio > 5)
  - Apo B: 0.85 g/L (less high but suboptimal)

He has not tolerated niacin in any form.

Statin and fibrate were combined for him with correction of all lipid parameters and ratios.

Apoprotein B100 (ApoB) for each atherogenic lipid particle; thus, measuring ApoB "counts the particles" and assesses the risk (and the adequacy of treatment) better than calculated or measured LDL-C. Non-HDL-C (total cholesterol minus HDL-C), or calculating a surrogate "residual" lipid level based on the triglyceride have merit, but neither is as robust as looking at ApoB.

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Case three: Larry

Combination treatment for dyslipidemia

When to use combination therapy is a difficult decision. The evidence for combination therapy reducing lipid levels is abundant, but only combinations of statins, niacin and/or bile acid binding resins have evidence of CV outcome, plaque regression or surrogate outcome improvement. The situations for combination therapy are:

- Patients with severe dyslipidemia and inability to reach one or more targets with monotherapy
- Patients with medication intolerance permitting only subtherapeutic dosing on any one type of treatment
- Patients with high CV risk where the practitioner wishes to address multiple lipid parameters beyond those specified in the lipid management guideline targets (*e.g.*, ApoB/Apo A1 ratio, cholesterol/HDL-C ratio).

Although combining medications from different classes may increase the risk of certain complications (*e.g.*, myopathy with statin-

Take-home message

- Looking at the right parameters (ApoB, for example) will be most informative in assessing risk and therapeutic success, especially in the patient with high triglycerides or dysglycemia
- Patients often need individualized care that the guidelines cannot offer

fibrate combinations), the use of combinations may permit multiple lipid targets to be achieved. Perhaps counter-intuitively, the use of multiple drug classes together may reduce side-effects in the medication intolerant individual; small doses of two medications giving fewer side-effects than the full dose of any one medication. Care must be taken to minimize potential drug interactions (*e.g.*, gemfibrozil with certain statins and antidiabetic medications), to be cautious with renal insufficiency (increases myopathy risk with fibrates) and to be cognizant of the side-effect profile of each of the individual medications used.

Conclusion

An evidence-based approach to management of the dyslipidemic individual is always the best approach. Patients, being individuals, often do not fall into the simple algorithms that we would like them to, due to more complex dyslipidemias or due to medication intolerance. There are times when we as physicians must place one foot outside the guidelines with a logical approach that addresses the patient's needs and risk level. In such situations, we try to correct as much of the dyslipidemia as possible (*i.e.*, offer as much risk reduction as possible), while doing as little harm as possible. While we may have to settle for suboptimal treatment (considering the guidelines), at least we are offering treatment to the at-risk individual. Dx

Resources
1. Genest J, McPherson R, Frohlich J, et al: 2009 Canadian Cardiovascular Society/Canadian Guidelines For The Diagnosis And Treatment Of Dyslipidemia And Prevention Of Cardiovascular Disease In The Adult – 2009 Recommendations. Can J Cardiol 2009; 25(10):567-79.
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4. Sniderman A: Targets for LDL-Lowering Therapy. Curr Opin Lipidol 2009; 20(4):282-7.