Management Options and Interventions for Elevated Lipoprotein (a)

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Disclosure

Dr. Harold Bays and his affiliated research center do not own pharmaceutical stocks or patents. In the past 12 months, Dr. Harold Bays’ research site has received research grants from Amarin, Amgen, Alere, Allergan, Arisaph, AstraZeneca, Bristol Meyers Squibb, Catabasis, Cymabay, Dr. Reddy, Eisai, Elcelyx, Eli Lilly, Esperion, Ferrer/Chiltern, Gemphire, Gilead, GSK, Janssen, Johnson and Johnson, Kowa, Merck, Necktar, Nichi-Iko, Novartis, NovoNordisk, Orexigen, Pfizer, Pronova, Regeneron, Sanofi, Selecta, Takeda, and TIMI. In the past 12 months, Dr. Harold Bays has served as a consultant/advisor for Alnylam, Akcea, Amgen, AstraZeneca, Eli Lilly, Ionis (ISIS), Janssen, Johnson & Johnson, Merck, Moderna, Novartis, Procter & Gamble, Regeneron, Sanofi, Teva, and Takeda. In the past 12 months, Dr. Harold Bays has served as a speaker for Amarin, Amgen, Astra Zeneca, Eisai, Orexigen, Regeneron, Sanofi and Takeda.
Presentation Outline

- Describe how has lipoprotein (a) [Lp(a)] science and clinical application has / has not advanced for the past quarter century
- Describe who might best benefit from Lp(a) assessment
- Discuss approved agents that lower Lp(a)
- Discuss investigational agents that lower Lp(a)
“Old” thinking
Elevated Lipoprotein (a) Blood Levels as the Single Treatable Atherosclerotic Risk Factor in Patients With Coronary Artery Disease

Harold Boys MD, Carlos A. Dufourne, MD; J. Brent Mays, PA-C

An elevated blood level of lipoprotein (a) (Lp(a)) has been studied as an independent risk factor for coronary artery disease. We report a series of nine consecutive patients with clinical onset or recurrence of coronary artery disease who presented without treatable atherosclerosis risk factors. Five of whom had elevated Lp(a) blood levels. Indications for measuring Lp(a) levels and usefulness of niacin therapy are reviewed.

Reduction in coronary artery disease (CAD) morbidity and mortality has been shown with correction of treatable CAD risk factors such as dyslipidemia, hypertension, cigarette smoking, and/or diabetes mellitus. Other CAD risk factors such as family history of CAD, male gender, and aging are not amenable to intervention.

Recommendations directed towards reducing the progression of atherosclerosis in patients with CAD without treatable CAD risk factors is unclear. It has been suggested, although not shown by controlled trials, that an elevated blood level of lipoprotein(a) (Lp(a)) may be an important CAD risk factor in these patients.1-2

We describe nine consecutively detected patients with clinical onset or recurrence of CAD who presented without treatable CAD risk factors. Their fasting blood levels of “routine” lipoproteins would not have required lipid-lowering drug therapy according to 1988 National Cholesterol Education Program (NCEP) recommendations.3 Five of these nine patients had elevated Lp(a) blood levels.

Patient Selection

Of approximately 2400 patients assessed at our clinic between the years 1986 and 1992, data was evaluated on the first nine consecutive patients who presented with onset or recurrence of CAD and no treatable CAD risk factors (including dyslipidemia, hypertension, diabetes mellitus, and/or cigarette smoking within 10 years of onset or recurrence of CAD).

Fasting total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C) and triglycerides (TG) blood levels were obtained within 1 year prior to recurrence, or 6-12 months after the clinical onset of CAD. Only those patients with CAD, absent treatable CAD risk factors, and fasting LDL-C < 4.14 mmol/L (160 mg/dL), HDL-C > 0.91 mmol/L (35 mg/dL), and/or TG blood levels < 2.82 mmol/L (250 mg/dl) were included in this report.

Lp(a) blood levels were subsequently measured in all nine of these patients by enzyme-linked immunosorbent assay at either of two Lipid Research Center Laboratories within 3 years of the clinical onset or recurrence of CAD. No patients had been treated with lipid-lowering drug therapy prior to the measurement of Lp(a) or other lipoprotein blood levels.

Clinical onset of CAD was defined as a myocardial infarction or documented coronary artery disease by cardiac catheterization occurring in patients without previous history of CAD.

Recurrent CAD was defined as progression of atherosclerotic lesions documented by cardiac catheterization or stress thallium testing in patients with previously clinically successful coronary artery by-pass grafting.

The pertinent clinical and laboratory data are outlined in Table 1.

Discussion

Epidemiologic studies suggest that over 10% of patients who develop CAD have blood TC levels below 5.17 mmol/L (200 mg/dl). Many of these
“An elevated Lp(a) blood level is thought to be an important CAD risk factor because of the potential increased risk of atherosclerosis and/or thrombosis. Elevated Lp(a) blood levels are strongly associated with CAD, stenosis of carotid and cerebral arteries, as well as saphenous vein bypass graphs, independent of other CAD risk factors.”

“Individual Lp(a) blood levels remain constant throughout life, are thought to be generally unaffected by diet and/or lifestyle intervention, and are in large part genetically determined.”
Management of elevated Lp(a) in 1993

“Elevated Lp(a) blood levels have been suggested to be the best discriminator between Familial Hypercholesterolemia (FH) patients with CAD, and FH patients without CAD.”

Management of elevated Lp(a) in 1993

“Aspirin therapy may be especially important in patients with CAD and elevated blood levels of Lp(a) to decrease the potential increased risk of thrombosis.”

“We evaluated nine consecutive patients with clinical onset or recurrence of CAD and no other treatable CAD risk factors. Five of these nine patients were found to have elevated Lp(a) blood levels.”

(All had first degree family member with CAD.)
“Our report suggests that an elevated Lp(a) blood level may be an important measurable and treatable CAD risk factor in the subset of patients with clinical onset or recurrence of CAD, and no other treatable CAD risk factors.”

Management of elevated Lp(a) in 1993

"Therapeutic guidelines are not available, and a reduction in CAD by lowering Lp(a) blood levels awaits confirmation by clinical trials. However, niacin therapy may be justified in these patients to not only lower Lp(a), but to improve other lipoprotein blood levels."

“New” thinking
Current Management: Diagnosis

- Lp(a) is a heterogenous lipoprotein similar to LDL, but metabolically distinct.
- Elevated Lp(a) levels (>50 mg/dL) are associate with increased ASCVD risk.
- Clinical ASCVD outcomes trials have yet to demonstrate that lowering Lp(a) reduces ASCVD risk. However, because of its potential casual role in atherogenesis, in applicable and selected patients, some clinicians may choose to monitor lipoprotein (a) during lipid altering intervention.

Bays HE, Jones PH, Orringer CE, Underberg JA, Jackson EJ, Jacobson TA. National Lipid Association Annual Summary of Clinical Lipidology 2017
Diagnosis

▪ South Asian individuals often have elevated triglyceride and reduced HDL-C levels, increased LDL-P with an increased prevalence of smaller, more dense LDL particles), and increased Lp(a), all which may increase ASCVD risk.

▪ Lp(a) of >= 30 mg/dL and above may be a more appropriate cutoff point to assess ASCVD risk in African Americans, as opposed to a level of >= 50 mg/dL cut-off point sometimes described for Caucasian and Hispanic individuals.

Bays HE, Jones PH, Orringer CE, Underberg JA, Jackson EJ, Jacobson TA. National Lipid Association Annual Summary of Clinical Lipidology 2017
Diagnosis

- Among patients with moderate elevations in LDL-C levels who have calculated LDL-C measurements, marked elevations in Lp(a) and its accompanying cholesterol can increase the cholesterol blood levels to a degree as to result in a phenotypic diagnosis of familial hypercholesterolemia.

- As many as 25% of cases of familial hypercholesterolemia, diagnosed phenotypically, may be largely dependent upon the additional circulating cholesterol carried by marked elevations in Lp(a).

Bays HE, Jones PH, Orringer CE, Underberg JA, Jackson EJ, Jacobson TA. National Lipid Association Annual Summary of Clinical Lipidology 2017
Langsted A, Kamstrup PR, Benn M, Tybjaerg-Hansen A, Nordestgaard BG. High lipoprotein(a) as a possible cause of clinical familial hypercholesterolaemia: a prospective
Diagnosis

Although little to no evidence exists to support clinical benefit, diagnostically, agents suggested to mildly reduce Lp(a) include:

- Androgens
- Angiotensin converting enzyme inhibitors
- Ascorbic acid combined with L-lysine
- Aspirin
- Calcium channel antagonists
- L-carnitine
- Neomycin
- N-acetylcysteine
- Tamoxifen
- Thyroxine replacement in hypothyroid patients
- Tranexamic acid
Approved agents that lower Lp(a)

- PCSK9 inhibitors (~20 - 30%)
- Niacin (~20 - 30%)
- Mipomersen (apo B antisense) (~20 – 30%)
- Lomitapide (~10 – 15%)
- Lipoprotein apheresis
  - Single = ~60 – 75%; weekly/biweekly = ~ 25 – 40%
- Estrogen (variable reduction)

Bays HE, Jones PH, Orringer CE, Underberg JA, Jackson EJ, Jacobson TA. National Lipid Association Annual Summary of Clinical Lipidology 2017
Reduction in lipoprotein(a) with PCSK9 monoclonal antibody evolocumab (AMG 145): a pooled analysis of more than 1,300 patients in 4 phase II trials

- Mean age 56.4 years
- 56.2% women
- 60.3% patients taking statin therapy
- Median baseline Lp(a) concentration was 40.0 nmol/l (16 mg/dL using 2.5 conversion factor)
- Mean baseline LDL-C concentration was 140.6 mg/dL
Reduction in lipoprotein(a) with PCSK9 monoclonal antibody evolocumab (AMG 145): a pooled analysis of more than 1,300 patients in 4 phase II trials

- Evolocumab for 12 weeks significantly reduced Lp(a) for all treatment groups (25 – 30%), irrespective of dose regimen (140 mg every 2 weeks or 420 mg every 4 weeks), age, or gender, with a trend toward greater reduction in those patients taking statins.

- While the mean percentage of reduction was significantly greater in those patients with baseline Lp(a) of ≤125 nmol/l, the absolute reduction was substantially larger in those with levels >125 nmol/l.
Challenges in interpreting reports of Lp(a)

Lp(a) = Usually a nonparametric variable reported as median

1 mg/dL = 10 mg/L  
50 mg/dL = 500 mg/L

1 mg/dL = 2.5 nmol/L  
50 mg/dL = 125 nmol/L

1 mg/dL = 0.357 umol/L  
50 mg/dL = 1.785 umol/L
Challenges in interpreting reports of Lp(a)

- Serum concentrations of lipoprotein (a) [Lp (a)] were determined in two groups of elderly males suffering from prostatic carcinoma, who were randomized to treatment with estrogen (n = 15) or orchidectomy (n = 16).
- Estrogen was given as oral ethinylestradiol, 150 micrograms daily, combined with intramuscular polyestradiol phosphate, 80 mg/mo.
- 6 mo after initiation of therapy, serum Lp (a) levels were decreased approximately 50% in the estrogen-treated group (P less than 0.001) in contrast to a 20% increase (P less than 0.01) in the orchidectomized group.
- Concomitantly, LDL cholesterol decreased by 30% and HDL cholesterol increased by almost 60% in the estrogen-treated patients.
- In conclusion, Lp (a) levels in males were found to drastically decrease upon estrogen treatment and to increase after orchidectomy, suggesting that sex hormones, and particularly estrogens, exert a regulatory role on the serum Lp (a) level in man.

## Challenges in interpreting reports of Lp(a)

<table>
<thead>
<tr>
<th>Changes in Lp(a) with therapeutic agents</th>
<th>Increase Lp(a)</th>
<th>Decrease Lp(a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statins (0–50%)</td>
<td></td>
<td>Clinically available</td>
</tr>
<tr>
<td>Ezetimibe (~20%)</td>
<td></td>
<td>LDL apheresis (acutely 60–80%, time-averaged 30–35%)</td>
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<tr>
<td>Low-fat diets (20–30%)</td>
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<td>Niacin (20–30%)</td>
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<tr>
<td>Garlic supplements</td>
<td></td>
<td>Mipomersen (20–40%)</td>
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<tr>
<td></td>
<td></td>
<td>IL-6 antagonists (30%)</td>
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<td></td>
<td></td>
<td>PCSK9 Inhibitors (20–40%)</td>
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<td>Aspirin</td>
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<td>Insulin</td>
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<td>Investigational</td>
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<td>Antisense to apo(a) (80–99%)</td>
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<td></td>
<td></td>
<td>CETP Inhibitors (20–35%)</td>
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<tr>
<td></td>
<td></td>
<td>Other</td>
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<tr>
<td></td>
<td></td>
<td>Thyroid analogues</td>
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<td>Oral estrogen/tamoxifen</td>
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<td>Anabolic steroids</td>
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<td></td>
<td>N-acetylcysteine</td>
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<td></td>
<td>L-carnitine</td>
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</tbody>
</table>

Tsimikas CV Endo Diab Obes 2016
RESULTS:
The mean levels of total cholesterol (TC), LDL-C, triglycerides (TG), and apolipoprotein (apo) B, respectively, showed a significant decrease from 229+/-39 to 191+/-37 mg/dL (-16%, p<0.0001), from 151+/-34 to 118+/-33 mg/dL (-22%, p<0.0001), from 162+/-82 to 135+/-55 mg/dL (-7%, p<0.01), and from 116+/-22 to 94+/-21 mg/dL (-18%, p<0.0001) after 12 weeks of treatment with ezetimibe. The mean level of RLP-C and median level of hs-CRP also decreased significantly from 6.8+/-4.0 to 4.8+/-2.5 mg/dL (-21%, p<0.0001) and from 0.6 to 0.4 mg/L (-33%, p<0.05). **The median level of Lp(a) decreased significantly from 14 to 10 mg/dL (-29%, p<0.05) in patients treated with ezetimibe monotherapy.**

CONCLUSIONS: **Ezetimibe could be a potential therapeutic option for decreasing the Lp(a) level.**

CONCLUSION:

Our results suggest that 12-week atorvastatin is effective in reducing Lp(a) in dyslipidaemic patients free of CVD.

CONCLUSIONS:

After atorvastatin treatment, total OxPL on all apoB-100 particles was decreased. However, there was enrichment of OxPL on a smaller pool of apoB-100 particles, in parallel with similar increases in Lp(a).


Apheresis as novel treatment for refractory angina with raised lipoprotein (a): a randomised controlled trial

- Controlled, randomized, cross-over trial of 20 patients without familial hypercholesterolemia,
- Refractory angina
- Lp(a) greater than 500 mg/L; LDL-C less than 4 mmol/L (155 mg/dL)
- 3 months of weekly lipoprotein apheresis, one month washout, and then another 3 months crossover therapy
- Compared to sham procedures, lipoprotein apheresis
  - Improved myocardial perfusion, carotid atheromatous lesions,
  - Exercise capacity, angina symptoms, and quality of life

Germany

• Three separate studies evaluated 300 individuals with ASCVD (95% statin treatment) with elevated Lp(a) in prospective and/or retrospective trials with the treated patients acting as their own control group.
• Mean pre-apheresis lipoprotein(a) and LDL-C levels were 97 and 100 mg/dl, respectively.
• Lipoprotein apheresis therapy resulted in a 70–80% reduction of major adverse cardiac events (MACE) compared with standard lipid modifying therapy.

### Apheresis: Evidence for Clinical Benefit

**Germany:**

| Table 1. Lipoprotein apheresis therapy for increased lipoprotein(a) levels |
|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
|                             | **Jaeger et al. [18]**      | **Rosada et al. [19]**      | **Leebmann et al. [20]**    |
|                             | Before          | After                      | Before          | After                      | Before          | After                      |
| Patients (n)                | 120            | 120                        | 37             | 37                         | 170            | 166                        |
| Duration (years)            | 5.5            | 5.0                        | 5.2            | 6.8                        | 2              | 2                          |
| LDL-C (mg/dl)               | 125            | 45  (−65%)                | 84             | 34  (−60%)                | 100            | 33  (−60%)                |
| Lipoprotein(a) (mg/dl)      | 118            | 33  (−72%)                | 112            | 36  (−68%)                | 87             | 26  (−70%)                |
| MACE total                  | 297            | 57  (−81%)                | 67             | 20  (−70%)                | 142            | 31  (−78%)                |
| MACE per year               | 1.05           | 0.14  (−86%)              | 2.80           | 0.08  (−97%)              | 0.41           | 0.09  (−78%)              |

MACE, major adverse cardiovascular event.

Russia

- In a Russian trial of an apheresis device that only removes Lp(a), patients (n=30) with CHD verified by angiography, LDL-C < 100 mg/dL on chronic statin therapy, and Lp(a) > 50 mg/dL were randomized 1:1 to weekly Lp(a) apheresis and statin or statin alone.

- Following 18 months of treating elevated lipoprotein(a), and not LDL-C, the apheresis group demonstrated a significant regression of coronary atherosclerosis compared with the control group as assessed by quantitative coronary angiography.

Lipoprotein apheresis

- Case report of male child with elevated lipoprotein (a) leading to acute ischemic stroke

- Patrick M. Moriarty¹, Heather Tennant¹, Nandhini Sehar¹, Lauryn Denney¹, Paola Luna², Francesca Perez-Marques², Apurva Panchal², Michael Abraham³, John Leever⁴ (1)Division of Clinical Pharmacology, Department of Internal Medicine, (2) Department of Pediatrics, (3) Department of Neurology, (4) Department of Radiology, University of Kansas Medical Center, Kansas City, Kansas, USA
Investigational Agents that lower Lp(a)

- CETP inhibitors (~40%)
- Interleukin-6 receptor antagonists (~25%)
- Antisense inhibitors of apolipoprotein (a) (~70 – 90%)

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Antisense Oligonucleotides (ASO’s)
Investigational Agents that lower Lp(a)

<table>
<thead>
<tr>
<th>Class of agent and mechanism of action</th>
<th>Name</th>
<th>Sponsor</th>
<th>Sample references (or Clinical Trials.gov Identifiers)</th>
<th>Sentinel, reported safety/tolerability findings</th>
<th>Sentinel lipid effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antisense inhibitor of lipoprotein (a)</td>
<td>IONIS-APO(a)Rx*</td>
<td>Ionis</td>
<td>91, 306, 307</td>
<td>Mild injection site reactions</td>
<td>Dose dependent 66% to 92% reduction in lipoprotein (a)</td>
</tr>
</tbody>
</table>

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* **Ligand-Conjugated Antisense (LICA):** Certain conjugates or ligands may enhance delivery of drugs to particular tissues (e.g., liver), up to 30 fold
Summary

OLD THINKING A QUARTER CENTURY AGO:

“Elevated Lp(a) blood levels have been suggested to be the best discriminator between Familial Hypercholesterolemia (FH) patients with CAD, and FH patients without CAD.” An elevated Lp(a) blood level may be an important measurable and treatable CAD risk factor in the subset of patients with clinical onset or recurrence of CAD, and no other treatable CAD risk factors.”

NEW THINKING:

In patients at higher ASCVD risk, Lp(a) measurement may be considered for selected patients, especially those with:
- Family history of premature ASCVD.
- Recurrent ASCVD events despite therapeutic lifestyle intervention and lipid-altering pharmacotherapy.
- Familial hypercholesterolemia.

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Summary

OLD THINKING A QUARTER CENTURY AGO:

“Therapeutic guidelines are not available, and a reduction in CAD by lowering Lp(a) blood levels awaits confirmation by clinical trials. However, niacin therapy may be justified in these patients to not only lower Lp(a), but to improve other lipoprotein blood levels.”

NEW THINKING:

The determination if lowering Lp(a) is beneficial awaits, definitive, randomized, placebo-controlled, ASCVD outcomes studies. In the interim, patients with elevated Lp(a) should have:

- Aggressive management of non-lipid ASCVD risk factors
- Aggressive management of non-HDL-C and LDL-C levels
- The decision to concomitantly lower Lp(a) via PCSK9 inhibitors, mipomersen, lomitapide, apheresis, or perhaps even niacin, is best determined by the presentation of the patient, and the judgment of the clinician.

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