Management of Dyslipidemia in Latin America

Enrique Cuitlahuac Morales Villegas, MD

Aguascalientes

México
CV Risk Master Class 2015
Management of Dyslipidemia in LatAm

Enrique Morales-Villegas. Lima, Perú October 24 2015
Preamble

Management of Dyslipidemia in LatAm

LatAm Reality

Enrique Morales-Villegas. Lima, Perú October 24 2015
A Latin American Perspective on the New ACC/AHA Clinical Guidelines for Managing Atherosclerotic Cardiovascular Disease

Ada Cuevas · Antonio Arteaga · Attilio Rigotti
Owing to the scarcity of regionally based studies, we propose that a group of experts from Latin American countries with support from panel members producing US and non-US guidelines convene to develop a position statement on how new approaches for risk assessment and statin therapy may be adapted and implemented within the region.
. Abbott
. Aegerión
. Amgen
. Boehringer Ingelheim
. Bristol Myers Squibb
. Genzyme
. Janssen-Cilag
. Lilly
. Merck Sharp and Dohme
. Novartis
. Novo Nordisk
. Pfizer
. Roche
. Sanofi
. Servier
. Takeda
To review with you, what LatAm is, and what is the LatAm Dyslipidemia landscape.
1. What LatAm is?
2. Beyond LatAm Dyslipidemia.
3. H.C Treatment in LatAm:
   a. Risk estimation. The best tool
   b. Tactic. LDL-C reduction
   c. Strategy. ACC-AHA/ESC-EAS/Both
What LatAm Is?
Ethnic group with a mixed genetics from Native Americans -60%-, Europeans -30%-, and Africans -10%-. Population 561,183,291 -2010-
Key Concept 1

LatAm is ethnic diversity.
Beyond LatAm Dyslipidemia

• In three facts
Fact 1:

Heart Disease in Latin America

Risk Factors for Acute Myocardial Infarction in Latin America

The INTERHEART Latin American Study

Fernando Lanas, MSc, MD; Alvaro Avezum, MD, PhD; Leonelo E. Bautista, MD, DrPH; Rafael Diaz, MD; Max Luna, MD; Shofiqul Islam, MSc; Salim Yusuf, DPhil, FRCP; for the INTERHEART Investigators in Latin America

Fernando Lanas et al. Circulation 2007;115:1067-1074
## Risk Factors Prevalence

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Latin-America</th>
<th>Rest-World</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regular eating F-V</td>
<td>84.3%</td>
<td>83.7%</td>
</tr>
<tr>
<td>↑ Waist</td>
<td>48.6%</td>
<td>31.2%</td>
</tr>
<tr>
<td>Smoking</td>
<td>48.1%</td>
<td>48.1%</td>
</tr>
<tr>
<td>▲ ApoB100-▼ ApoAI</td>
<td>42.0%</td>
<td>32.0%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>29.1%</td>
<td>20.8%</td>
</tr>
<tr>
<td>Depression</td>
<td>28.9%</td>
<td>15.8%</td>
</tr>
<tr>
<td>Regular Exercise</td>
<td>22.0%</td>
<td>18.9%</td>
</tr>
<tr>
<td>Alcoholism</td>
<td>19.4%</td>
<td>11.9%</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>09.5%</td>
<td>07.2%</td>
</tr>
<tr>
<td>Permanent stress</td>
<td>06.8%</td>
<td>03.9%</td>
</tr>
</tbody>
</table>
## Population Risk for Myocardial Infarction

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Latin-América</th>
<th>Rest-World</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑ Waist</td>
<td>48.1</td>
<td>30.2</td>
</tr>
<tr>
<td>↑ ApoB100-↓ Apo AI</td>
<td>40.8</td>
<td>44.2</td>
</tr>
<tr>
<td>Smoking</td>
<td>38.4</td>
<td>35.3</td>
</tr>
<tr>
<td>Hypertension</td>
<td>32.9</td>
<td>22.0</td>
</tr>
<tr>
<td>Permanent stress</td>
<td>28.1</td>
<td>7.80</td>
</tr>
<tr>
<td>Regular exercise</td>
<td>28.0</td>
<td>24.8</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>12.9</td>
<td>12.2</td>
</tr>
<tr>
<td>Regular eating F-V</td>
<td>06.9</td>
<td>4.10</td>
</tr>
<tr>
<td>Depression</td>
<td>04.7</td>
<td>8.40</td>
</tr>
<tr>
<td>Alcoholism</td>
<td>-3.2</td>
<td>16.3</td>
</tr>
</tbody>
</table>

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Fernando Lanas et al. Circulation 2007;115:1067-1074
In LatAm, increase of apoB and decrease of apoA1 lipoproteins is a high prevalent dyslipidemic profile -42%-.

The population impact of this profile is similar than in other population -40.8% vs 44.2%-

INTERHEART Lesson

Fernando Lanas et al. Circulation 2007;115:1067-1074
Fact 2:

Cardiovascular Risk and Events in 17 Low-, Middle-, and High-Income Countries


Medium Income Countries

- Argentina
- Brasil
- Colombia
- Chile

In LatAm -Argentina, Brazil, Colombia and Chile- with a lowest cardiovascular risk factor level, the cardiovascular fatality is higher.

Beyond the risk factor level, socioeconomic factors are important.

Educational level, access to, quality and affordability of health care contribute to higher rates of cardiovascular mortality.

Prospective Urban Rural Epidemiologic (PURE) cohort study
Fact 3:

Demographic and Epidemiologic Drivers of Global Cardiovascular Mortality

Gregory A. Roth, M.D., M.P.H., Mohammad H. Forouzanfar, Ph.D., Andrew E. Moran, M.D., M.P.H., Ryan Barber, B.A., Grant Nguyen, B.A., Valery L. Feigin, M.D., Ph.D., Mohsen Naghavi, M.D., Ph.D., George A. Mensah, M.D., and Christopher J.L. Murray, M.D., D.Phil.

Global Burden Disease 2013

Figure 2. Contribution of Changes in Population Growth, Population Aging, and Rates of Age-Specific Cardiovascular Death to Changes in Cardiovascular Mortality, 1990–2013.


<table>
<thead>
<tr>
<th>Year</th>
<th>Global</th>
<th>LatAm</th>
</tr>
</thead>
<tbody>
<tr>
<td>1990-2013</td>
<td>41%</td>
<td>53%</td>
</tr>
</tbody>
</table>
In LatAm cardiovascular mortality has increased, in average 53% from 1990 to 2013.

Population aging and population growth diminishes the positive effect of the medical care improvement.

Beyond the high prevalence of dyslipidemia, LatAm has many others socioeconomic and demographic challenges with a negative medical impact.
H.C Treatment in LatAm
Risk Stratification…
. What tool do we use?
From Framingham 1998 to Globorisk 2015

1. Framingham 1998
2. Framingham-ATP-III 2001
3. Framingham Global 2008
4. PROCAM 2002
5. Euro-SCORE 2003
6. QRISK 2007-2014
7. Reynolds ♀ 2007
8. Reynolds ♂ 2008
9. INTERHEART 2011
10. ACC-AHA Pooled Cohort Equation 2013
11. Globorisk 2015
What Algorithm do we use?

Framingham 2001-2008

ACC-AHA 2013

SCORE 2003

Latin America

## What Algorithm do we use?

<table>
<thead>
<tr>
<th>Country</th>
<th>ASCVD Risk Guideline</th>
<th>HC Treatment Guideline</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Argentina</td>
<td>Framingham/WHO</td>
<td></td>
<td>Lorenzatti A</td>
</tr>
<tr>
<td>Brasil</td>
<td>Framingham 2008</td>
<td></td>
<td>Xavier TH</td>
</tr>
<tr>
<td>Colombia</td>
<td>Framingham calibrado 0.75</td>
<td></td>
<td>Muñoz-Velandía</td>
</tr>
<tr>
<td>Chile</td>
<td>Framingham calibrado</td>
<td></td>
<td>Icaza G</td>
</tr>
<tr>
<td>México</td>
<td>ACC-AHA 2013/Globorisk</td>
<td></td>
<td>Alcocer L</td>
</tr>
<tr>
<td>Perú</td>
<td>Framingham 2008</td>
<td></td>
<td>Bryce A</td>
</tr>
</tbody>
</table>

Pool Cohort Equation 2013:

Estimates cardiovascular death, non-fatal myocardial infarction and non-fatal stroke in naive individuals, without ASCVD with or without Diabetes.
ATP-III 2002-05-Framingham:

Estimates coronary death and non-fatal myocardial infarction in naive individuals without ASCVD or Diabetes.
SCORE:

Estimates cardiovascular death* in naive individuals without ASCVD, Diabetes or CKD.

* A factor x3 in men or x4 in women is equivalent to fatal and non-fatal events
What is the best?

Rotherdam Study

Original Investigation

Comparison of Application of the ACC/AHA Guidelines, Adult Treatment Panel III Guidelines, and European Society of Cardiology Guidelines for Cardiovascular Disease Prevention in a European Cohort

Maryam Kavousi, MD, PhD; Maarten J. G. Leening, MD, MSc; David Nanchen, MD, MSc; Philip Greenland, MD; Ian M. Graham, MD; Ewout W. Steyerberg, PhD; M. Arfan Ikram, MD, PhD; Bruno H. Stricker, MMed, PhD; Albert Hofman, MD, PhD; Oscar H. Franco, MD, PhD
ACC/AHA 2013. Men

Statistic C 0.67 (0.63-0.71)
Calibration 21.5% (20.9-22.1%) vs 12.7% (11.1-14.5%)
ATP-III. Men

Statistic C 0.67 (0.62-0.72)
Calibration 16.1% (15.8-16.5%) vs 6.8% (5.6-8.3%)

<table>
<thead>
<tr>
<th>10-y Predicted Risk Category, %</th>
<th>&lt;10</th>
<th>10 to &lt;20</th>
<th>≥20</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of participants</td>
<td>203</td>
<td>892</td>
<td>336</td>
</tr>
<tr>
<td>No. with hard CHD</td>
<td>3</td>
<td>54</td>
<td>41</td>
</tr>
<tr>
<td>Observed risk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Predicted risk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hard CHD, %</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Maryam Kavousi et al. *JAMA*. 2014; 311:1416-1423
SCORE. Men

Statistic C 0.76 (0.70-0.82)
Calibration 6.8% (5.6-8.3%) vs 3.7% (2.7-4.8%)

Maryam Kavousi et al. JAMA. 2014; 311:1416-1423
Key Concept 3a

All Equations Overestimate
There is not a perfect Equation.
The best Equation is the utilized, choose one and use it with clinical judgment.


Treatment: Tactic…

. LDL colesterol reduction
Compactin, first Statin with Clinical Effect

Fig. 2. Effects of ML-236B on serum lipid concentrations in a case of primary hypercholesterolemia (Y.S.: 30-yr male, FH-heterozygote).

A marked reduction in turorous xanthomas was noticed in a homozygous case of familial hypercholesterolemia, but here the drug was less effective in reducing the serum cholesterol level and a higher dose was required for treatment. Softening of Achilles tendon xanthomas was observed in a case of combined hyperlipidemia.

1976-1980

Akira Endo

1976-1980

Akira Yamamoto, Hiroshi Sudo and Akira Endo

Statin and Atheroregression

Lipid Lowering and Progression of Atherosclerosis

The benefits of statin drugs to reduce lipoprotein levels and cardiovascular morbidity and mortality are well established, but the optimal intensity of therapy is not known. Nissen and colleagues reported results from a multicenter randomized trial examining the progression of atherosclerosis in a target vessel in patients randomly assigned to receive either a moderate lipid-lowering regimen of 40 mg/d of pravastatin or an intensive regimen of 80 mg/d of atorvastatin. At the 18-month follow-up, patients receiving atorvastatin had significantly less increase in atheroma volume in the target vessel and significantly greater reductions in low-density lipoprotein cholesterol and C-reactive protein levels compared with patients receiving pravastatin. In an editorial, Sacks discusses the implications of these results for clinical practice.

Statins and ASCVD Events Reduction

Risk for ASCV at 5 years

- <05%: 43%, RR 0.36-0.89
- ≥05%-%<10%: 30%, RR 0.50-0.74
- ≥10%-%<20%: 23%, RR 0.69-0.85
- ≥20%-%<30%: 23%, RR 0.71-0.83
- ≥30%: 22%, RR 0.72-0.84
- Total: 24%, RR 0.73-0.79

RR for each 39mg/dL LDL-C reduction

Statins plus Ezetimibe and ASCVD Events

Alirocumab plus Statins and ASCVD Events

Cox model analysis
HR = 0.52 (95% CI 0.31 to 0.90)
Nominal P-value = 0.02

No. at risk
Placebo 788 776 731 700 670 653 644 597
Alirocumab 1550 1533 1445 1392 1342 1306 1266 1170

Evolocumab plus Statins and ASCVD Events

Sabatine MS, Giugliano RP, Wiviott SD et al. OSLER I-II. N Engl J Med. 2015, March 15
The New LDL-C Level?

Curing Atherosclerosis

Increasing the Horizon for ASCVD

LDL-C has association, causality and reversibility as risk factor for ASCVD.

Until now, the lower, the better.
Treatment: Strategy…
. Intensity, Goals or Both
What Strategy do we use?

Net Benefit

Statin Intensity

Latin America

LDL-C Goal

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<td>Muñoz-Velandia</td>
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<td>ACC-AHA 2013/Globorisk</td>
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<td>Alcocer L</td>
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<td>Perú</td>
<td>Framingham 2008</td>
<td>LDL-C goals guided</td>
<td>Bryce A</td>
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</tbody>
</table>

Table I Comparison of individuals who should be targeted for lipid modification

<table>
<thead>
<tr>
<th>Clinical risk categories</th>
<th>ACC/AHA (2013) Guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular disease risk in adults</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Those with clinical ASCVD</td>
<td>High-intensity statin therapy. If 50% reduction is not reached drug combination may be considered</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus (Type I or Type II) without ASCVD but with LDL-C between 1.8 and 4.9 mmol/L</td>
<td>Diabetes with high risk: High-intensity statin therapy. Diabetes with low risk: Moderate-intensity statin therapy</td>
<td></td>
</tr>
<tr>
<td>Those with primary elevation of LDL-cholesterol (LDL-C) &gt; 4.9 mmol/L</td>
<td>High-intensity statin therapy, aimed at achieving at least 50% reduction of LDL-C</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical risk categories</th>
<th>ESC/EAS (2011) Guidelines for the management of dyslipidaemias</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Those with CVD</td>
<td>LDL-C &lt; 1.8 mmol/L or 50% reduction in LDL-C</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus (Type I or Type II) with target organ damage</td>
<td>LDL-C &lt; 1.8 mmol/L or 50% reduction in LDL-C</td>
<td></td>
</tr>
<tr>
<td>Familial dyslipidaemia (FH or FCH or chylomicronaemia)</td>
<td>LDL-C &lt; 2.5 mmol/L or maximal reduction in LDL-C with any possible drug combination plus LDL apheresis</td>
<td></td>
</tr>
</tbody>
</table>

If none of the above but with estimated 10-year ASCVD risk of 7.5% or more using a pooled populations risk calculator
If risk-based assessment treatment decision uncertain assessment of 1 or more of family history, hs-C-reactive protein, CAC Score or ABPI may be considered (Class IIb, Level E), contribution of ApoB, CKD, microalbuminuria or cardio-respiratory fitness is uncertain (Level N) and CIMT is not recommended for routine assessment of individual patients (Level N)

Moderate-to-high-intensity statin therapy if ASCVD risk > 7.5%.
If risk 5–7.5% risk of CVD event: Reasonable to consider moderate-intensity statin therapy

Very high risk LDL-C
< 1.8 mmol/L or 50% reduction in LDL-C
High-risk LDL-C<br>2.5 mmol/L, moderate risk<br>LDL-C<br>3.0 mmol/L

Above risk can be modified if additional information is available on:
† TGs, social deprivation, central obesity, † Lipoprotein(a), familial hypercholesterolaemia, subclinical atherosclerosis, CKD, family history of pre-mature CVD (x 1.7 – women, x 2 – men), very high HDL-C, family history of longevity
Health Benefit is Enough?

\[
\frac{\text{NNT}}{\text{NNH}} < 1
\]

Geoffrey Rose 1926-1993


NNT/NNH

Moderate Statin Intensity

Health Benefit/Economic Benefit a new Paradigm

NNT + Save*
NNH + Expense*

* Save and Expense are related with Quality Adjusted Life Year value. In USA an acceptable QALY value is ≤ 50,000 USD (equivalent to annual per-capita income). In LatAm in average the annual per capita income is around 10,000 USD.

<table>
<thead>
<tr>
<th>ACC/AHA ASCVD Risk Threshold, %</th>
<th>Adults Eligible, %</th>
<th>Statin-Induced Diabetes Casesa, b</th>
<th>CVD Eventsa, b</th>
<th>Life Expectancy, y</th>
<th>QALYs c</th>
<th>Costs, 2013 US $c</th>
<th>ICER (US $/QALY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥30.0</td>
<td>34</td>
<td>0.0030</td>
<td>0.4437</td>
<td>81.265</td>
<td>17.287</td>
<td>21 649</td>
<td>Extended dominanced</td>
</tr>
<tr>
<td>≥20.0</td>
<td>36</td>
<td>0.0039</td>
<td>0.4405</td>
<td>81.293</td>
<td>17.299</td>
<td>21 898</td>
<td>Extended dominanced</td>
</tr>
<tr>
<td>≥15.0</td>
<td>39</td>
<td>0.0045</td>
<td>0.4384</td>
<td>81.315</td>
<td>17.309</td>
<td>22 109</td>
<td>24 000/QALY</td>
</tr>
<tr>
<td>≥10.0</td>
<td>44</td>
<td>0.0055</td>
<td>0.4365</td>
<td>81.341</td>
<td>17.320</td>
<td>22 455</td>
<td>30 000/QALY</td>
</tr>
<tr>
<td>≥7.5e</td>
<td>48</td>
<td>0.0062</td>
<td>0.4353</td>
<td>81.356</td>
<td>17.327</td>
<td>22 696</td>
<td>37 000/QALY</td>
</tr>
<tr>
<td>≥5.0</td>
<td>57</td>
<td>0.0072</td>
<td>0.4344</td>
<td>81.371</td>
<td>17.333</td>
<td>23 039</td>
<td>57 000/QALY</td>
</tr>
<tr>
<td>≥4.0</td>
<td>61</td>
<td>0.0076</td>
<td>0.4340</td>
<td>81.377</td>
<td>17.335</td>
<td>23 200</td>
<td>81 000/QALY</td>
</tr>
<tr>
<td>≥3.0</td>
<td>67</td>
<td>0.0080</td>
<td>0.4337</td>
<td>81.382</td>
<td>17.336</td>
<td>23 406</td>
<td>140 000/QALY</td>
</tr>
<tr>
<td>≥2.0</td>
<td>75</td>
<td>0.0085</td>
<td>0.4334</td>
<td>81.386</td>
<td>17.337</td>
<td>23 656</td>
<td>830 000/QALY</td>
</tr>
<tr>
<td>≥1.0</td>
<td>87</td>
<td>0.0091</td>
<td>0.4333</td>
<td>81.389</td>
<td>17.336</td>
<td>23 952</td>
<td>Strong dominancef</td>
</tr>
<tr>
<td>Treat all adults with statins</td>
<td>100</td>
<td>0.0097</td>
<td>0.4332</td>
<td>81.391</td>
<td>17.334</td>
<td>24 225</td>
<td>Strong dominancef</td>
</tr>
</tbody>
</table>

Table ES5. Base-Case Clinical and Economic Outcomes Among Patients with a Prior History of CVD and LDL-Cholesterol ≥ 70mg/dL on Statin Therapy.*

<table>
<thead>
<tr>
<th>Statin</th>
<th>Person-years of treatment (millions)</th>
<th>Total MACE averted</th>
<th>NNT&lt;sup&gt;3&lt;/sup&gt;</th>
<th>QALYs gained&lt;sup&gt;4&lt;/sup&gt;</th>
<th>Incremental Drug Costs&lt;sup&gt;4&lt;/sup&gt; (million $)</th>
<th>Incremental Costs, Other CV Care&lt;sup&gt;4&lt;/sup&gt; (million $)</th>
<th>ICER ($/QALY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>comparator</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statin + Ezetimibe§</td>
<td>199.5</td>
<td>555,300</td>
<td>83</td>
<td>907,100</td>
<td>$382,714</td>
<td>-$45,035</td>
<td>$372,000</td>
</tr>
<tr>
<td>Statin + PCSK9 inhibitor§</td>
<td>201.6</td>
<td>2,235,100</td>
<td>21</td>
<td>3,581,200</td>
<td>$2,173,028</td>
<td>-$179,276</td>
<td>$557,000</td>
</tr>
</tbody>
</table>

QALY 557,000 USD

Institute for Clinical and Economic Review

Institute for Clinical Economic Review, 2015, September 8
LDL-C reduction.
The lower-earliest, the better, but what is the cost/effectiveness of the selected strategy?
Conclusions

5 Key Concepts about Dyslipidemia in LatAm
Key Concept 1

LatAm is ethnic diversity.
Beyond the high prevalence of dyslipidemia, LatAm has many others socioeconomic and demographic challenges with a negative medical impact.
Key Concept 3a

All Equations Overestimate
LDL-C has association, causality and reversibility as risk factor for ASCVD.

Until now, the lower, the better.
LDL-C reduction.

The lower-earliest, the better, but what is the cost/effectiveness of the selected strategy?
LatAm needs a Task Force. This PACE Meeting could be our catalyst.

Enrique Morales-Villegas. Lima, Perú October 24 2015
we anticipate that clinical practice will shift toward more assertive LDL-lowering treatment using both statins and non-statins initiated early in appropriately selected patients.