Presentation to NLA Symposium: May 3 2014

Understanding US Lipid Guidelines-2013:

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Acknowledgements

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Conflict of Interest/Relationships With Industry

1. All panel members disclosed conflict of interest information to the full panel in advance of the deliberations
2. Members with conflicts recused themselves from voting on any aspect of the guideline where a conflict might exist
3. All 16 members of the NHLBI ATP IV Panel transitioned to the ACC/AHA guideline Expert Panel }

4. Independent contractors performed the systematic review with the assistance of the Expert Panel and provided methodological guidance to the Expert Panel

Process:

- *Evaluate higher quality randomized controlled trial (RCT) evidence for cholesterol-lowering drug therapy to reduce ASCVD risk*
  - Use Critical Questions (CQs) to create the evidence search from which the guideline is developed
  - RCTs and systematic reviews/meta-analyses of RCTs *independently* assessed for quality
  - Less expert opinion than in prior guidelines

Systematic Review Process

- The Expert Panel constructed CQs relevant to clinical practice.
- An independent contractor →literature search strategy, based on I/E criteria, for published clinical trial reports for each CQ
- An independent contractor → systematic electronic search of the published literature from relevant bibliographic databases for each CQ
- The date for the overall literature search was from January 1, 1995 through December 1, 2009
- However, RCTs with the ASCVD outcomes of MI, stroke, and cardiovascular death published after that date were eligible for consideration until July 2013

Synopsis of Recommendations

1. Encourage adherence to a healthy lifestyle
2. Statin therapy recommended for adult groups demonstrated to benefit
3. Statins have an acceptable margin of safety when used in properly selected individuals and appropriately monitored
4. Engage in a clinician-patient discussion before initiating statin therapy – especially for primary prevention in patients with lower ASCVD risk

Stone NJ, et al. *Ann Int Med.* 2014 [epub ahead of print]

Synopsis of Recommendations

5. Use the newly developed pooled cohort equations for estimation 10-year ASCVD risk

6. Initiate proper intensity of statin therapy

7. Evidence is inadequate to support treatment to specific LDL-C or non-HDL-C goals

8. Regularly monitor patients for adherence to lifestyle and statin therapy

Stone NJ, et al. *Ann Int Med.* 2014 [epub ahead of print]

Emphasis on healthy lifestyle

- For those 20-59 risk estimator provides lifetime risk estimate
- This is intended to drive discussions of greater adherence to heart-healthy lifestyle and improved risk factors

Statin Benefit Groups

Secondary Prevention

Diabetes – 40 to 75 yrs
LDL-C 70-189 mg/dl
ASCVD risk ≥7.5%

LDL-C ≥ 190 mg/dL

Rx: Optimal benefit with high intensity statins → lower LDL-C ≥ 50%
Use moderate intensity diabetes <7.5%,
if age >75 or can't tolerate high intensity

Primary Prevention –
40 to 75 yrs
LDL-C 70-189 mg/dl
ASCVD Risk ≥ 7.5 %

Rx: Moderate intensity
or high intensity statin

Statin Rx not automatic,
requires clinician-patient discussion

Clinician - Patient Discussion Before Statin Rx

- ✔ Estimate 10 yr ASCVD Risk
  Review other risk factors & risk factor control
- ✔ Review potential for benefit from heart-healthy lifestyle
- ✔ Review potential for
  - benefit from statins and potential for adverse effects & drug-drug interactions
- ✔ Patient Preferences

***Factors if risk decision uncertain**:
LDL-C ≥ 160, family hx premature ASCVD, increased lifetime risk, **hs-CRP≥ 2, CAC score ≥ 300 , ABI < 0.9**

Monitoring and Follow-up:

- ✔ Adherence to a heart healthy lifestyle
  - Optimal adherence to improve lipid profile
- ✔ Review at each visit adherence to statin
  Maximally tolerated statin intensity and lifestyle to keep LDL-c low
- ✔ Measure lipids regularly:
  3-12 weeks after start, then 4-12 months as appropriate to check adequacy of statin Rx;
  - consider secondary causes
  - if high risk and inadequate response, consider non-statin Rx
- ✔ Review safety issues at each visit with history, and labs if appropriate
  - for example:
    some may require CK, FBS, A1c

Areas of Controversy

- ✔ Accuracy of ASCVD Risk Estimator
  Initial concerns not supported by new data from REGARDS
- ✔ Faulty assumption that ASCVD risk ≥ 7.5% risk means automatic statin Rx
  No statin Rx without clinician-patient discussion!
- ✔ No LDL-C/non HDL-C Goals
  Didn't find evidence for or against …
  Lipids followed regularly → therapeutic response & adherence
- ✔ Confusion regarding role for non-statin Rx
  Non-statins may be used in high risk patients to further reduce LDL-C levels per clinician judgment

Intensity of Statin Therapy

High- Moderate- and Low-Intensity Statin Therapy (Used in the RCTs reviewed by the Expert Panel)*

High-Intensity Statin Therapy	Moderate-Intensity Statin Therapy	Low-Intensity Statin Therapy
Daily dose lowers LDL-C on average, by approximately ≥50%	Daily dose lowers LDL-C on average, by approximately 30% to <50%	Daily dose lowers LDL-C on average, by <30%
Atorvastatin (40†)-80 mg **Rosuvasatin 20** *(40)* **mg**	**Atorvastatin 10 (***20)* **mg** **Rosuvastatin** *(5)* **10 mg** **Simvastatin 20-40 mg‡** **Pravstatin 40** *(80)* **mg** **Lovastatin 40 mg** *Fluvastatin XL 80 mg* **Fluvastatin 40 mg bid** *Pitavastatin 2-4 mg*	*Simvastatin 10 mg* **Pravastatin 10-20 mg** **Lovastatin 20 mg** *Fluvastatin 20-40 mg* *Pitavastatin 1 mg*

*Individual responses to statin therapy varied in the RCTs and should be expected to vary in clinical practice. There might be a biologic basis for a less-than-average response.

†Evidence from 1 RCT only: down-titration if unable to tolerate atorvastatin 80 mg in IDEAL (Pedersen et al).

‡Although simvastatin 80 mg was evaluated in RCTs, initiation of simvastatin 80 mg or titration to 80 mg is not

Primary Prevention Statin Therapy

- Thresholds for initiating statin therapy derived from 3 exclusively primary prevention RCTs
  - JUPITER, MEGA, AFCAPS-TEXCAPS
- Saw benefit down to 5%;
- chose 7.5% cutoff instead so if overestimation patient still in a statin benefit group

Pooled Cohort Equations

- Data from 5 population based NHBLI cohort studies on heart and stroke risk
- Includes African American status as an input
- The previous ATP 3 Framingham Score for 10-year CHD risk ->based on earlier data
  - higher estimate of CHD risk in many cases than the more recent Pooled Cohort Equations.
- The Pooled Cohort equations were recently validated in the REGARDS study of 30,000 black and white Americans from a contemporary population-based sample.

Primary Prevention Statin Therapy

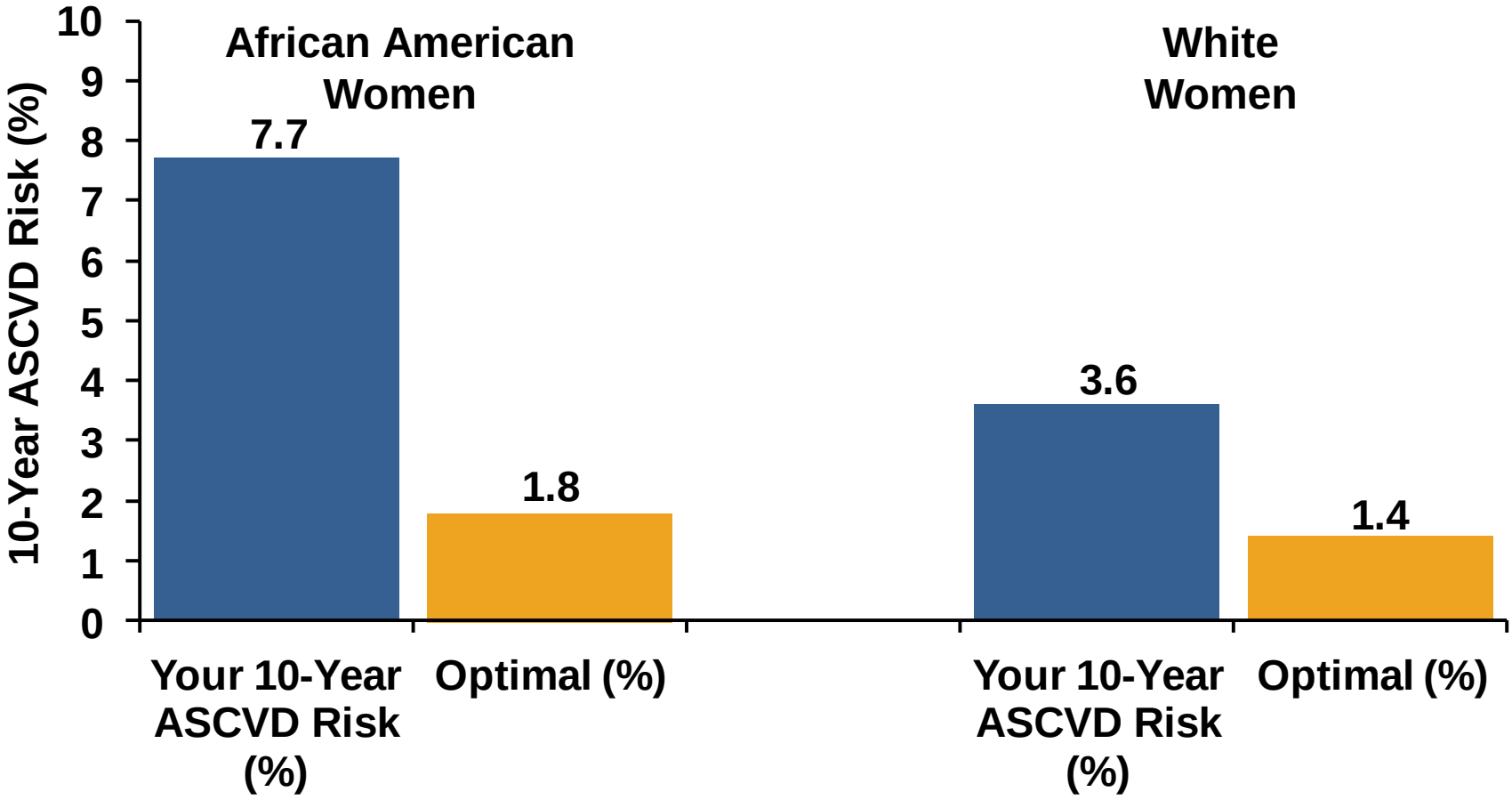
Reviewing the British and new American guidelines

“Both sets of guidelines agree that the primary purpose of risk assessment is to provide the basis for a risk discussion with the patient.

This point is clearly stated in the ACC/AHA document but is often missed or overlooked by the critics.”

Greenland P. Heart 2014

ASCVD Risk Estimator
African American Status makes a difference



ORIGINAL ARTICLE

Application of New Cholesterol Guidelines to a Population-Based Sample

Michael J. Pencina, Ph.D
Ralph B. D'Agostino, Ph.D.,
Allan D. Sniderman, M

BACKGROUND

The 2013 guidelines of the Ameri
Association (ACC–AHA) for the t
statin therapy for the prevention

METHODS

Using data from the National Hea
2010, we estimated the number, a
who would be recommended (i.e.,
guidelines, as compared with th
(ATP III) of the National Cholester
to a population of 115.4 million

RESULTS

As compared with the ATP-III g
number of U.S. adults who are
therapy from 43.2 million (37.5%
numbers (10.4 million of 12.8 m

More adults eligible for statin treatment under the new ACC/AHA guideline:

Statins: **43 million (37.5%) → 56 million (48.6**
(noted that not all may receive statins if 7.5% ris
or greater under our guidelines)

Those who were reclassified upward as contrasted t
those reclassified downward:
1) older
2) more men
3) higher systolic blood pressure,
4) had a significantly lower level of LDL-C
5) higher rate of obesity.

Pencina et al NEJM 2014

Why Not Continue to Treat to Target?

Major difficulties:

1. Current RCT data do not indicate what the target should be
2. Unknown magnitude of additional ASCVD risk reduction with one target compared to another
3. Unknown rate of additional adverse effects from multidrug therapy used to achieve a specific goal
4. Therefore, unknown net benefit from treat-to-target approach

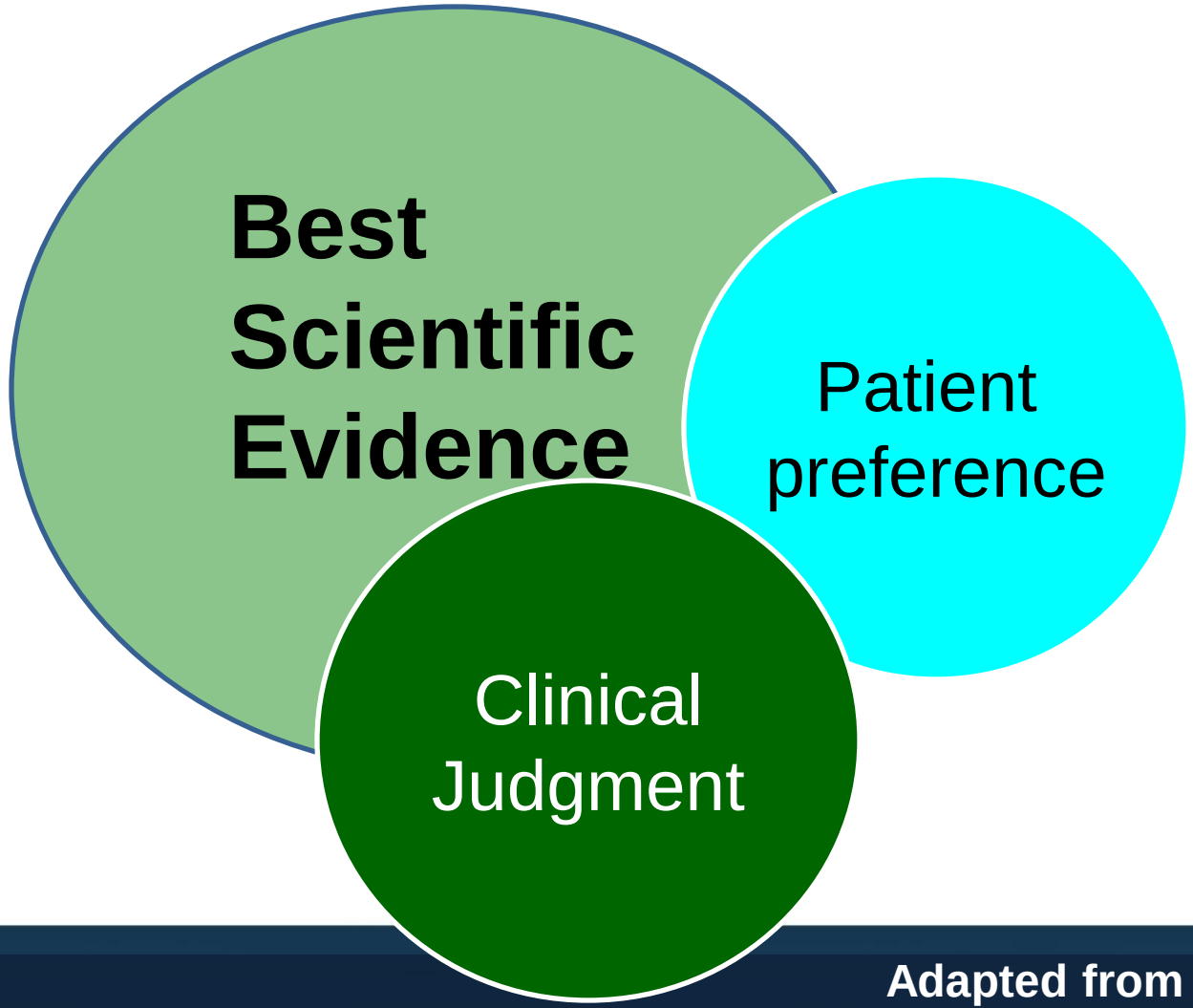
Focus on Appropriate Intensity of Statin Therapy to Reduce ASCVD Risk

- Lack of RCT evidence to support titration of drug therapy to specific LDL–C and/or non-HDL–C goals
- Strong evidence that *appropriate intensity of statin therapy* should be used to reduce ASCVD risk *in those most likely to benefit*
- RCT data allows quantitative comparison of statin benefits with statin adverse effects
    - Important in discussions re benefit/risk of diabetes with statin Rx

Statin-Treated Individuals Nonstatin Therapy Considerations

- Use the maximum tolerated intensity of statin
- Consider addition of a nonstatin cholesterol-lowering drug(s)
  - If a less-than-anticipated therapeutic response persists
  - Only if ASCVD risk-reduction benefits outweigh the potential for adverse effects in higher-risk persons:
    - *Clinical* ASCVD <75 years of age
    - Baseline LDL–C ≥190 mg/dL
    - Diabetes mellitus 40 to 75 years of age
- Nonstatin cholesterol-lowering drugs shown to reduce ASCVD events in RCTs are preferred

Evidence Based To Inform Risk Decisions



Adapted from Dr. Sanjay Kaul with permission

Individuals Not in a Statin Benefit Group

- In those for whom a risk decision is uncertain
- These factors may inform clinical decision making in context of clinician-patient discussion:
  - LDL–C ≥160 mg/dL
  - Elevated lifetime risk of ASCVD *(below added from risk assessment guideline)*
  - Family history of premature ASCVD
  - hs-CRP ≥2.0 mg/L
  - Coronary artery calcium score ≥300 Agatston units
  - Ankle brachial index (ABI)<0.9

The Risk Decision in Young Adults

- 38 yo white man with family history of premature CAD and LDL-C 180 mg/dL
  - Guidelines state that premature CHD and LDL-C of ≥ 160 mg/dL would inform the treatment decision
  - Note if patient was 41 and had a low 10 year ASCVD risk, he still would qualify for Rx
  - Statin therapy would be reasonable in this situation after a risk discussion reviewing potential for benefit, potential for adverse effects, drug-drug interactions and patient preference

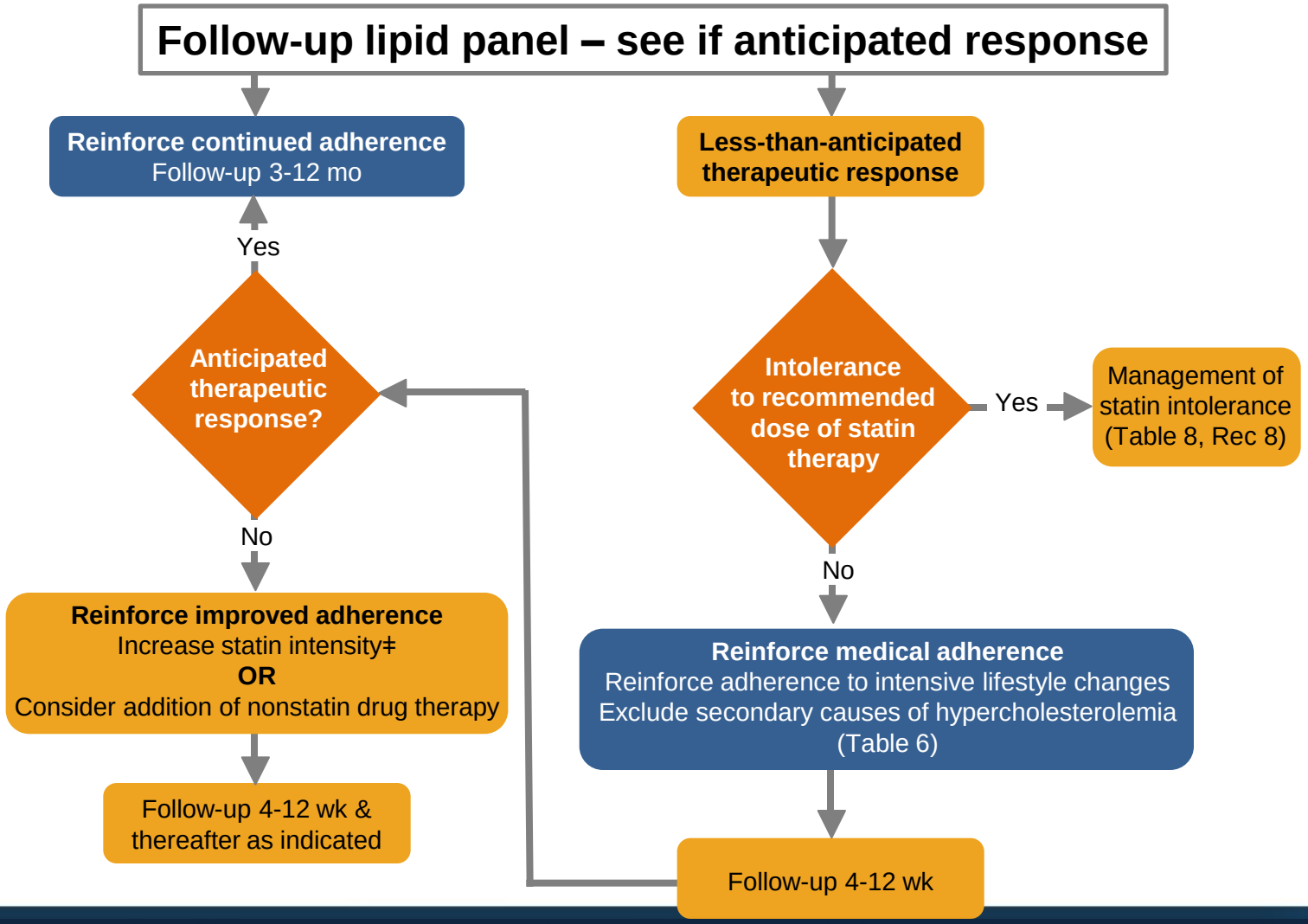
The Risk Decision in Older Adults

- 68 yo white man with average risk factors and estimated 10 year ASCVD risk of >7.5%
- Merits a risk discussion to consider adherence to optimal lifestyle, potential for benefit, potential for adverse effects, drug-drug interactions and informed patient preference
- If clinician or patient felt risk decision uncertain, could order a CAC score, hs-CRP or ABI

Safety

- RCTs & meta-analyses of RCTs used to identify important safety considerations
- Allow estimation of **net benefit** from statin therapy
  - ASCVD risk reduction versus adverse effects
- Expert guidance on management of statin-associated adverse effects, including muscle symptoms
- Recommendations on nonstatin safety issues
- Advise use of additional information including pharmacists, manufacturers prescribing information, & drug information centers for complex cases

Lipids Required for Followup



Four Principles

1. Focus on proven therapy for those shown to benefit

2. To reduce ASCVD, statins are drugs of choice, most are inexpensive & safe when taken as tolerated

3. Focus on proper intensity of statin therapy & monitor for adherence to optimal lifestyle and statin Rx

4. A clinician-patient discussion in primary prevention:
   a. Discuss a global risk reduction strategy
   b. Discuss potential for benefit and adverse effects of statin therapy including drug-drug interactions
   c. Patient preferences (shared decision making)

Future Updates to the Blood Cholesterol Guideline

- These guidelines represent a change from previous guidelines. They align recommendations more closely to the evidence.
- For primary prevention, they focus on shared decision making
- In keeping with the evidence-based approach, these guidelines will be improved by future high quality research

Complex Lipid Disorders

- For the many questions about complex lipid disorders that are beyond the scope of our systematic evidence review, or for which little or no RCT data are available,

  it is anticipated that clinicians with lipid expertise can contribute to their management.