2013 Cholesterol Guidelines

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Disclosures

- Speaker

  Gilead Sciences

NHLBI Charge to the Expert Panel

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
  - Cholesterol Panel: 3 CQs
  - Risk Assessment Work Group: 2 CQs
  - Lifestyle Management Work Group: 3 CQs
- RCTs and systematic reviews/meta-analyses of RCTs independently assessed as fair-to-good quality
- Develop recommendations based on RCT evidence
- Less expert opinion than in prior guidelines

Guideline Scope

- Focus on treatment of blood cholesterol to reduce ASCVD risk in adults
- Emphasize adherence to a heart healthy lifestyle as foundation of ASCVD risk reduction
  - See Lifestyle Management Guideline
- Identify individuals most likely to benefit from cholesterol-lowering therapy
  - 4 statin benefit groups
- Identify safety issues

Classification of Recommendations and Levels of Evidence

SIZE OF TREATMENT EFFECT

ESTIMATE OF CERTAINTY (PRECISION) OF TREATMENT EFFECT

	CLASS I *Benefit >>> Risk* Procedure/Treatment **SHOULD** be performed/ administered	CLASS IIa *Benefit >> Risk* *Additional studies with focused objectives needed* **IT IS REASONABLE** to perform procedure/administer treatment	CLASS IIb *Benefit ≥ Risk* *Additional studies with broad objectives needed; additional registry data would be helpful* Procedure/Treatment **MAY BE CONSIDERED**	CLASS III *No Benefit* or CLASS III *Harm* Procedure/ Test / Treatment COR III: No benefit — Not Helpful — No Proven Benefit COR III: Harm — Excess Cost w/o Benefit or Harmful — Harmful to Patients
LEVEL A Multiple populations evaluated* Data derived from multiple randomized clinical trials or meta-analyses	■ Recommendation that procedure or treatment is useful/effective ■ Sufficient evidence from multiple randomized trials or meta-analyses	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Sufficient evidence from multiple randomized trials or meta-analyses
LEVEL B Limited populations evaluated* Data derived from a single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is useful/effective ■ Evidence from single randomized trial or nonrandomized studies	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Evidence from single randomized trial or nonrandomized studies
LEVEL C Very limited populations evaluated* Only consensus opinion of experts, case studies, or standard of care	■ Recommendation that procedure or treatment is useful/effective ■ Only expert opinion, case studies, or standard of care	■ Recommendation in favor of treatment or procedure being useful/effective ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation's usefulness/efficacy less well established ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Only expert opinion, case studies, or standard of care
Suggested phrases for writing recommendations	should is recommended is indicated is useful/effective/beneficial	is reasonable can be useful/effective/beneficial is probably recommended or indicated	may/might be considered may/might be reasonable usefulness/effectiveness is unknown/unclear/uncertain or not well established	COR III: No Benefit: is not recommended; is not indicated; should not be performed/ administered/ other; is not useful/ beneficial/ effective COR III: Harm: potentially harmful; causes harm; associated with excess morbid-ity/mortality; should not be performed/ administered/ other
Comparative effectiveness phrases†	treatment/strategy A is recommended/indicated in preference to treatment B treatment A should be chosen over treatment B	treatment/strategy A is probably recommended/indicated in preference to treatment B it is reasonable to choose treatment A over treatment B		

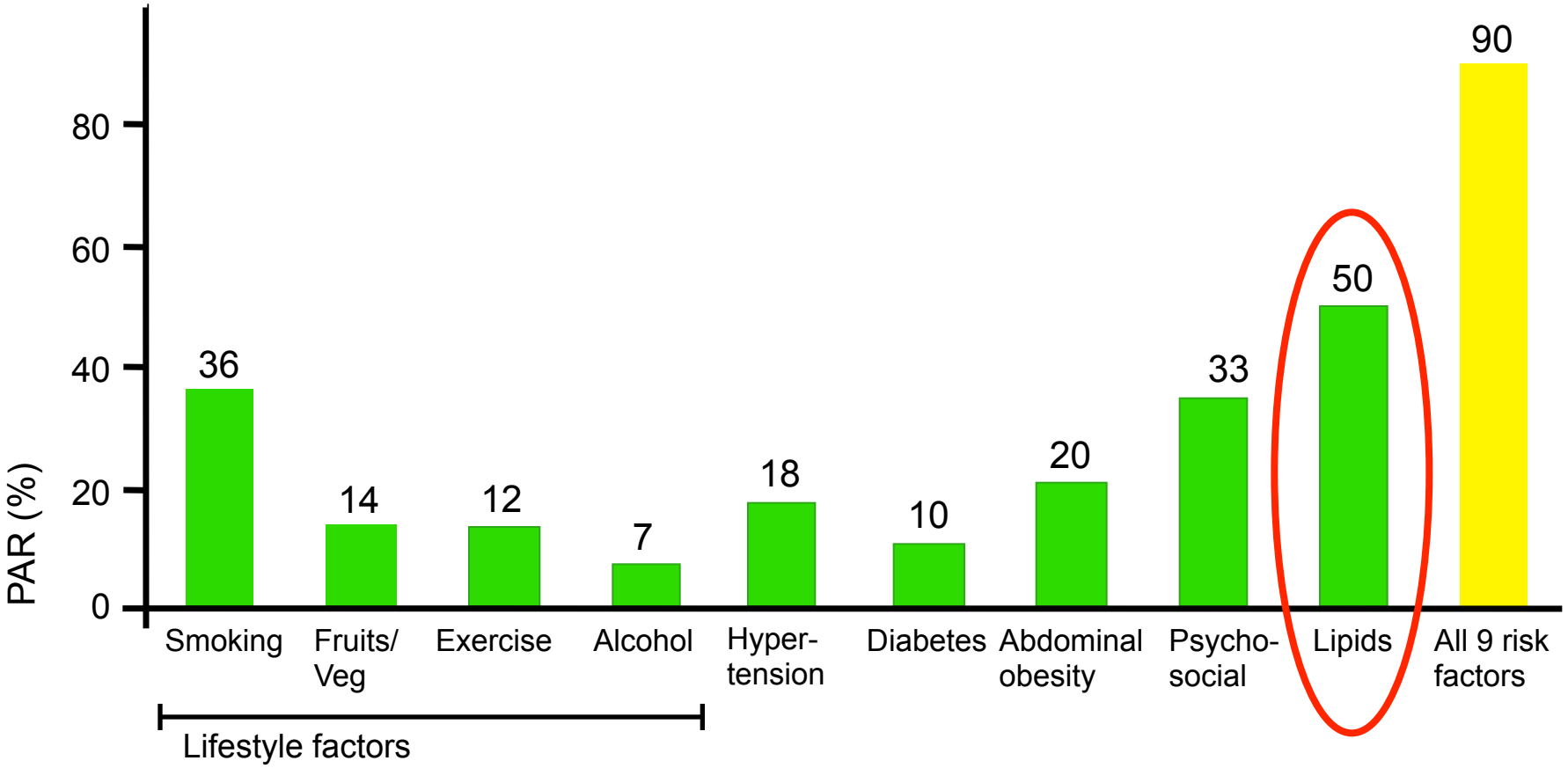
A recommendation with Level of Evidence B or C does not imply that the recommendation is weak. Many important clinical questions addressed in the guidelines do not lend themselves to clinical trials. Although randomized trials are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

*Data available from clinical trials or registries about the usefulness/ efficacy in different subpopulations, such as sex, age, history of diabetes, history of prior myocardial infarction, history of heart failure, and prior aspirin use.

†For comparative effectiveness recommendations (Class I and IIa; Level of Evidence A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

Attributable Risk Factors for a First Myocardial Infarction

INTERHEART Study

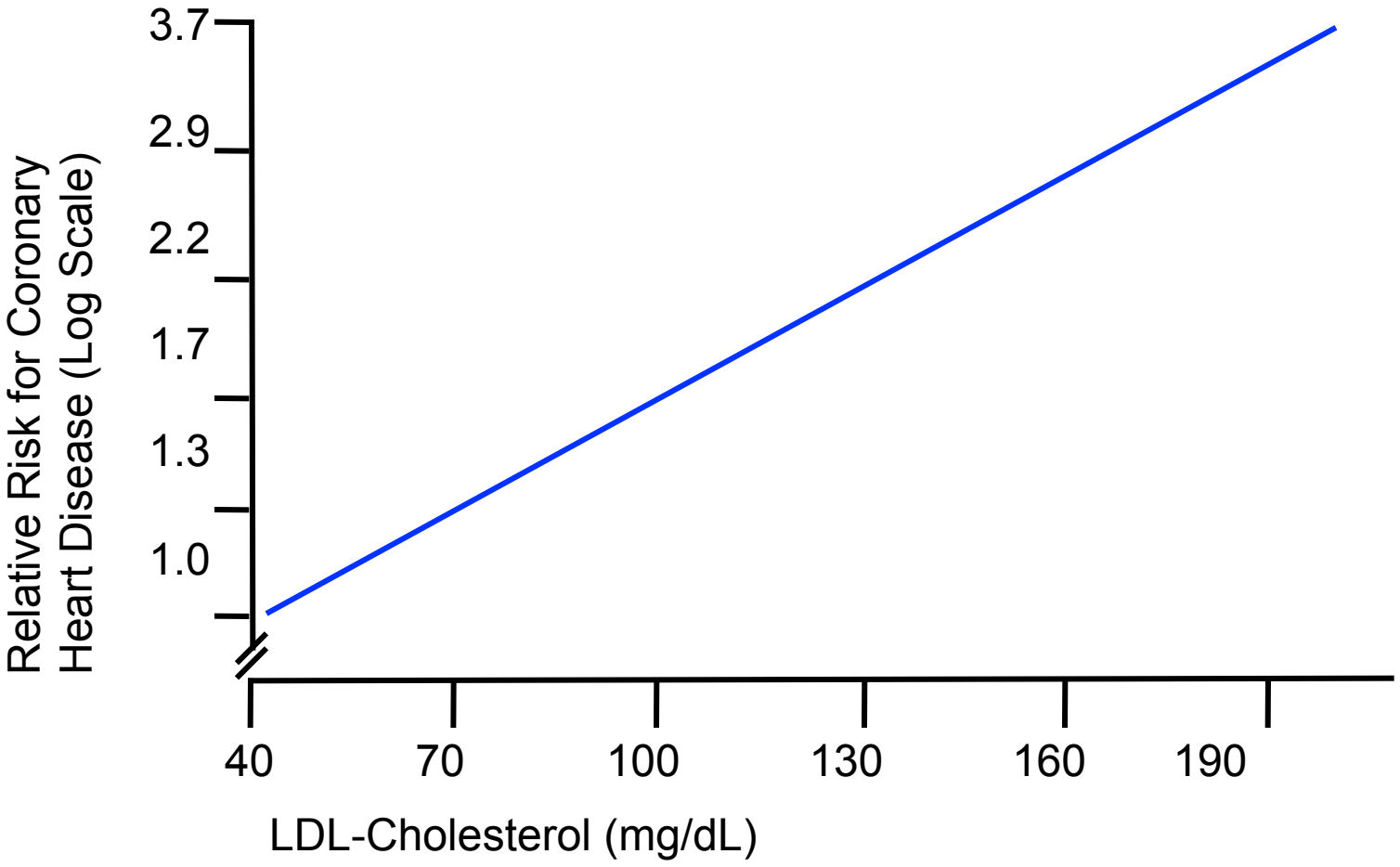


n=15,152 patients and 14,820 controls in 52 countries

MI=Myocardial infarction, PAR=Population attributable risk (adjusted for all risk factors)

Source: Yusuf S et al. *Lancet*. 2004;364:937-952

Coronary Heart Disease Risk According to LDL-C Level

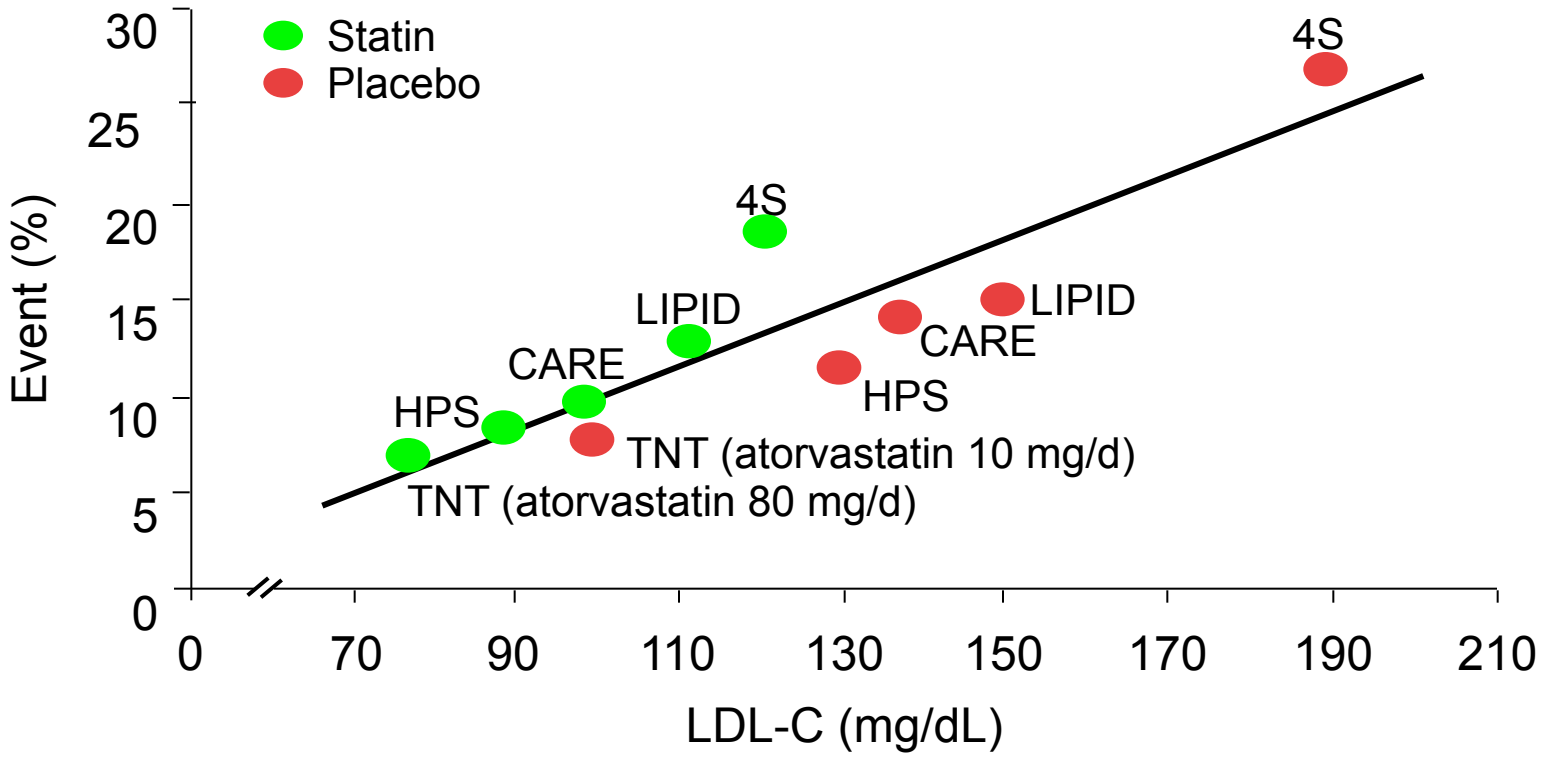


CHD=Coronary heart disease, LDL-C=Low-density lipoprotein cholesterol

Source: Grundy S et al. *Circulation* 2004;110:227-239

HMG-CoA Reductase Inhibitor Evidence: Secondary Prevention

Relationship between LDL-C levels and event rates in secondary prevention statin trials of patients with stable CHD



CARE=Cholesterol and Recurrent Events Trial, CHD=Coronary heart disease, HPS=Heart Protection Study, LDL-C=Low density lipoprotein cholesterol, LIPID=Long-term Intervention with Pravastatin in Ischaemic Disease, 4S=Simvastatin Survival Study, TNT=Treating to New Targets

Source: LaRosa JC et al. *NEJM* 2005;352:1425-1435

4 Statin Benefit Groups

- Clinical ASCVD*
- LDL-C ≥190 mg/dL, Age ≥21 years
- Primary prevention – Diabetes: Age 40-75 years, LDL-C 70-189 mg/dL
- Primary prevention - No Diabetes†: ≥7.5%‡ 10-year ASCVD risk, Age 40-75 years, LDL-C 70-189 mg/dL

*Atherosclerotic cardiovascular disease

†Requires risk discussion between clinician and patient before statin initiation

‡Statin therapy may be considered if risk decision is uncertain after use of ASCVD risk calculator

NCEP, ATP-III: Example of Risk Categories and LDL-C Goals

Risk category	Conditions and risk factors	LDL-C goal
High	Coronary heart disease (CHD), non-coronary atherosclerosis, diabetes	<100 optional <70
Intermediate	Multiple (2+) risk factors*	<130
Low	0–1 risk factors	<160

***Risk factors that modify the LDL-C goal:**

Cigarette smoking; hypertension (BP 140/90 mmHg or on antihypertensive medication); low HDL cholesterol (<40 mg/dL); family history of premature CHD (CHD in male first degree relative <55 years; CHD in female first-degree relative <65 years); age (men 45 years; women 55 years)

HDL cholesterol >60 mg/dL = -1 risk factor (protective factor)

New Perspective on LDL-C & Non–HDL-C

- 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
- Quantitative comparison of statin benefits with statin risk
- Nonstatin therapies – did not provide ASCVD risk reduction benefits or safety profiles comparable to statin therapy

Why Not Continue to Treat to Target?

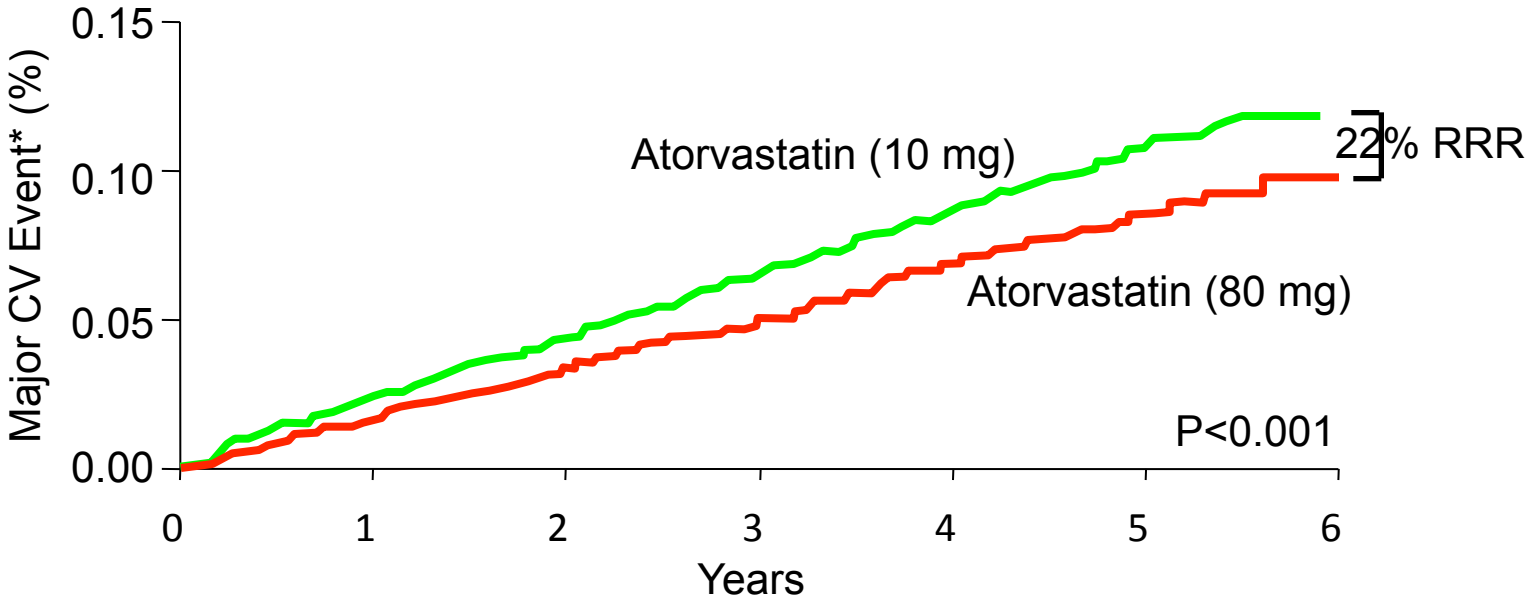
Major difficulties:

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

HMG-CoA Reductase Inhibitor Evidence: Secondary Prevention

Treating to New Targets (TNT) Trial

10,001 patients with stable CHD randomized to atorvastatin (80 mg) or atorvastatin (10 mg) for 4.9 years



High-dose statin therapy provides benefit in chronic CHD

*Includes CHD death, nonfatal MI, resuscitation after cardiac arrest, or stroke

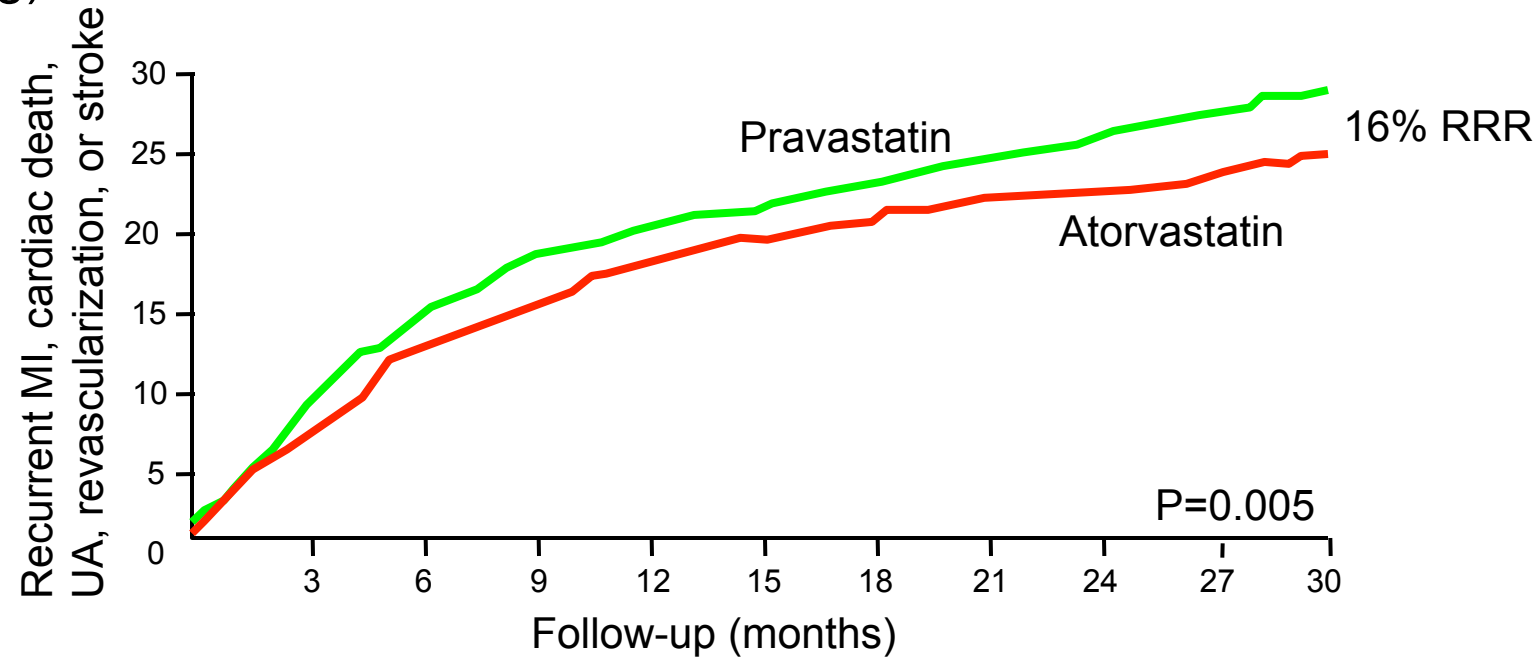
CHD=Coronary heart disease, CV=Cardiovascular, MI=Myocardial infarction, RRR=Relative risk reduction

Source: LaRosa JC et al. *NEJM* 2005;352:1425-35

HMG-CoA Reductase Inhibitor Evidence: Secondary Prevention

Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT)—TIMI 22 Study

4,162 pts with an ACS randomized to atorvastatin (80 mg) or pravastatin (40 mg) for 24 months

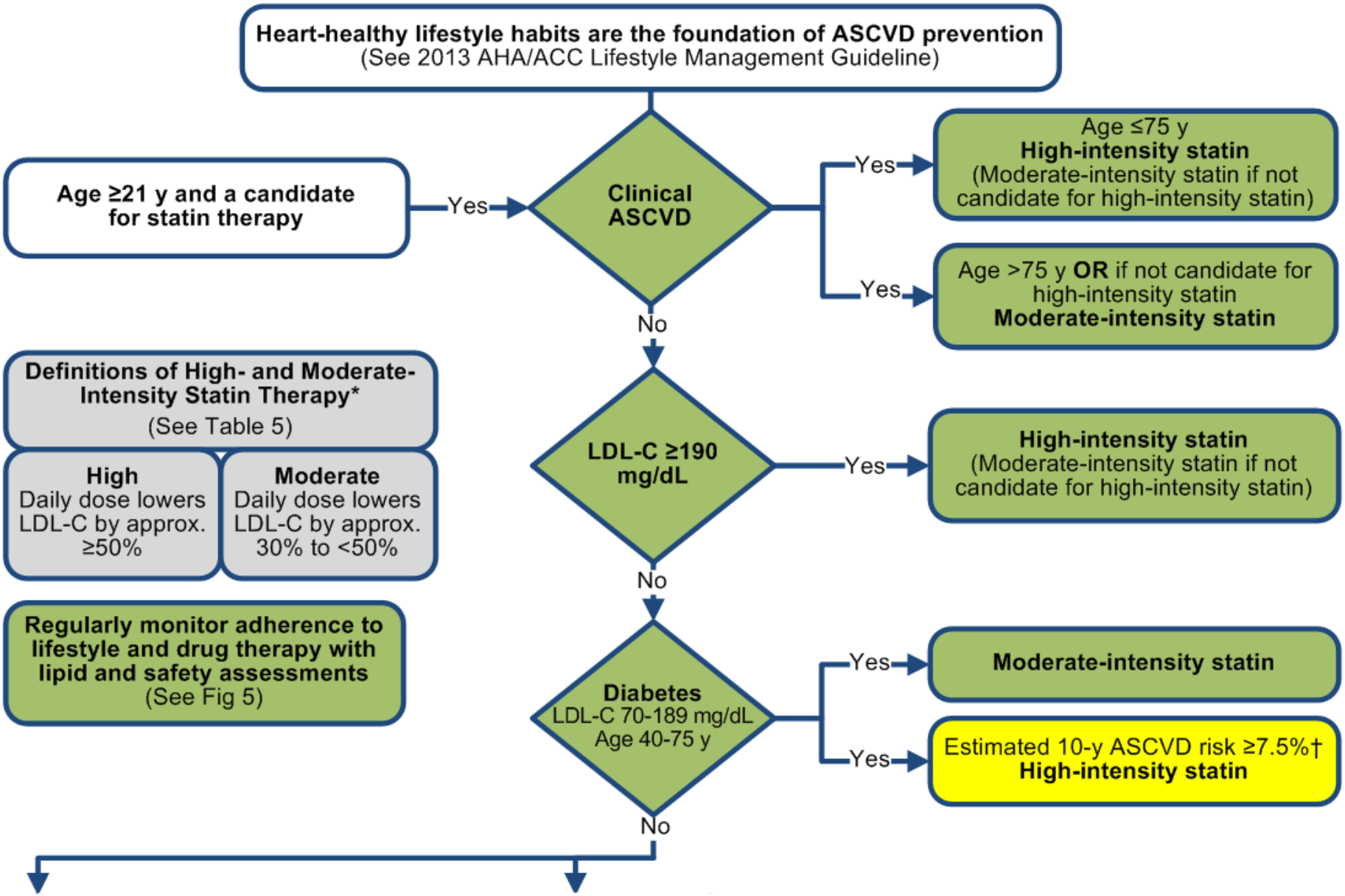


Acute intensive statin therapy provides significant CV benefit

ACS=Acute coronary syndrome, CV=Cardiovascular, MI=Myocardial infarction, RRR=Relative risk reduction, UA=Unstable angina

Source: Cannon CP et al. *NEJM* 2004;350:1495-1504

Summary of Statin Initiation Recommendations to Reduce ASCVD Risk (Revised Figure)



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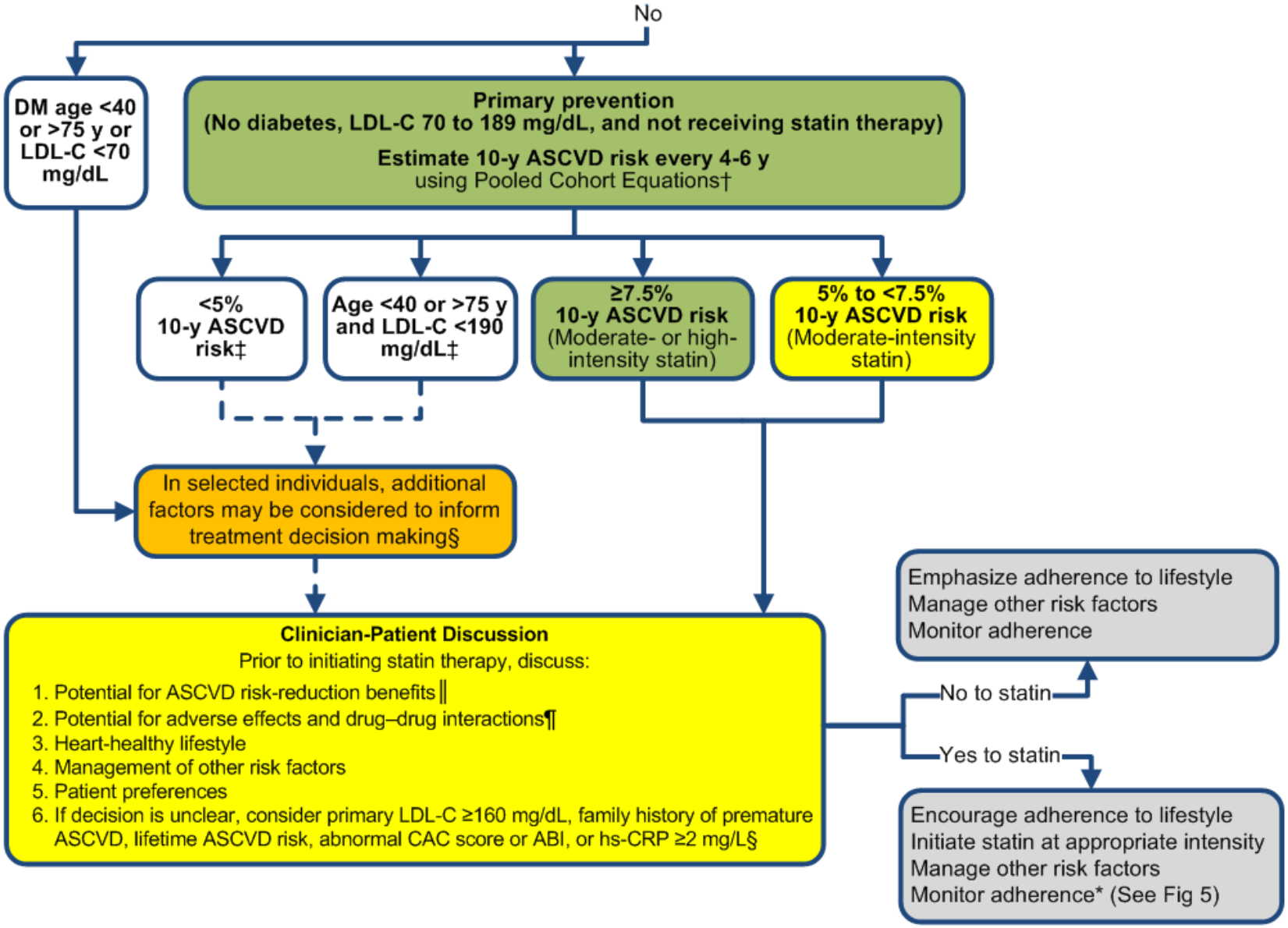


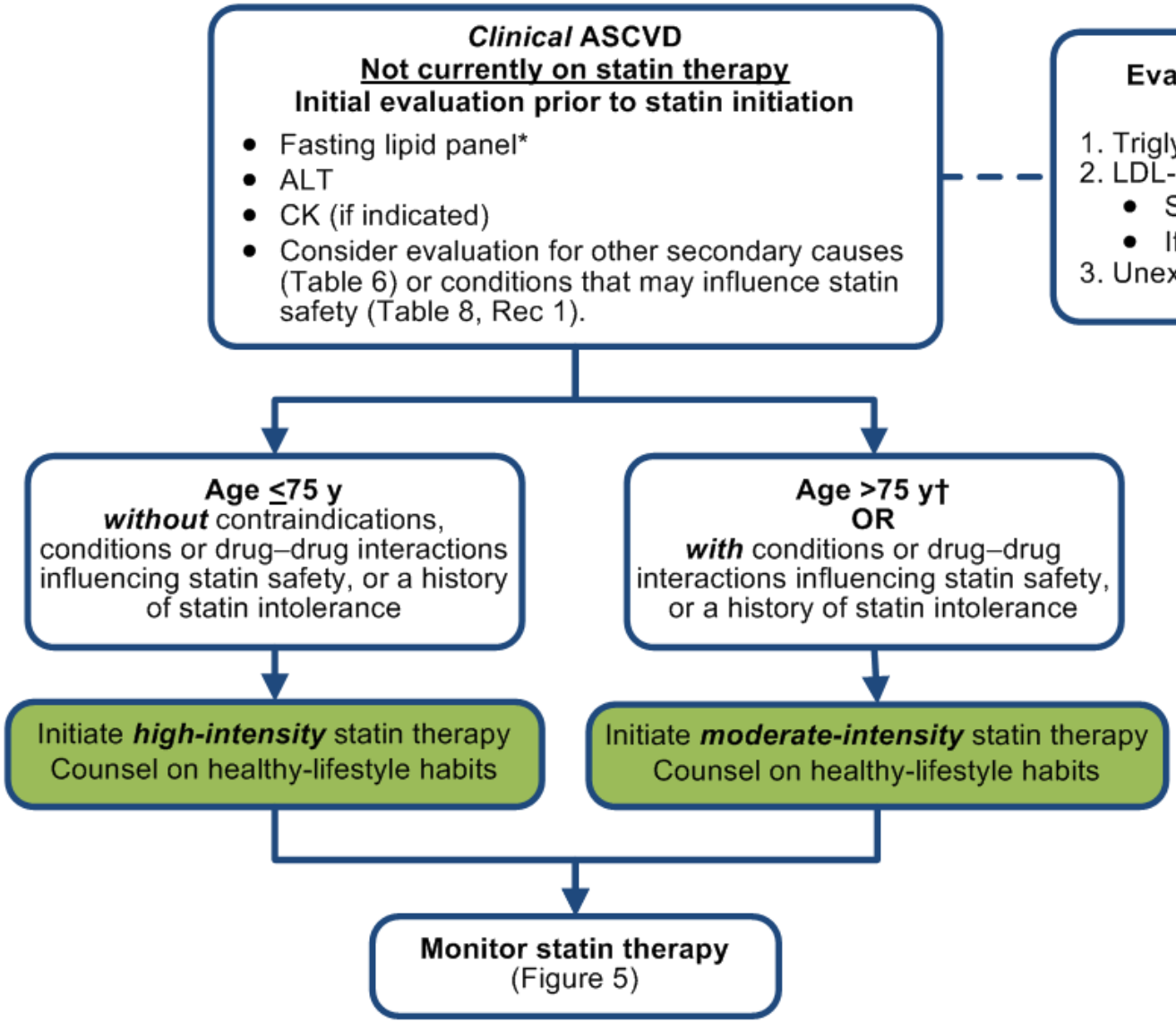
Intensity of Statin Therapy

Table 5. 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 **Rosuvastatin 20 *(40)* mg**	**Atorvastatin 10 *(20)* mg** **Rosuvastatin *(5)* 10 mg** **Simvastatin 20–40 mg‡** **Pravastatin 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 recommended by the FDA due to the increased risk of myopathy, including rhabdomyolysis.

Clinical ASCVD: Initiating Statin Therapy



*Fasting lipid panel preferred. In a nonfasting individual, a nonfasting non-HDL–C ≥220 mg/dL may indicate genetic hypercholesterolemia that requires further evaluation or a secondary etiology. If nonfasting triglycerides are ≥500 mg/dL, a fasting lipid panel is required.

†It is reasonable to evaluate the potential for ASCVD benefits and for adverse effects, and to consider patient preferences, in initiating or continuing a moderate- or high-intensity statin, in individuals with ASCVD >75 years of age.

Primary Prevention Global Risk Assessment

- To estimate 10-year ASCVD* risk
  - New Pooled Cohort Risk Equations
  - White and black men and women
- More accurately identifies higher risk individuals for statin therapy
  - Focuses statin therapy on those most likely to benefit
  - You may wish to avoid initiating statin therapy in high-risk groups found not to benefit (higher grades of heart failure and hemodialysis)

*10-year ASVD: Risk of first nonfatal myocardial infarction, coronary heart disease death, nonfatal or fatal stroke

Individuals Not in a Statin Benefit Group

- In those for whom a risk decision is uncertain, these factors may inform clinical decision making:
  - Family history of premature ASCVD
  - Elevated lifetime risk of ASCVD
  - LDL-C ≥160 mg/dL
  - hs-CRP ≥2.0 mg/L
  - CAC score ≥300 Agaston units
  - ABI <0.9
- Statin use still requires discussion between clinician and patient

Vignettes

What is the optimal intensity of statin therapy for a:

- 63 yo man with STEMI?
- 44 yo woman with diabetes, well-controlled hypertension and micro-albuminuria

Lessons From the Vignettes

Does not need ASCVD risk calculation:

- **Case 1:** ASCVD ≤75 years of age
  - High-intensity statin therapy
    - For optimal risk reduction in those who tolerate it
  - Moderate-intensity statin therapy
    - If >75 yo may be initiated or continued
    - Also use if high-intensity Rx not safe or not tolerated

Lessons From the Vignettes

ASCVD risk calculation useful here:

- **Case 2**: Diabetes, 40-75 yo, LDL-C 70-189 mg/dL
  - Evidence supports moderate-intensity statin Rx to be initiated or continued
  - High-intensity statin Rx reasonable if estimated 10-year ASCVD risk calculated to be >7.5%

Vignettes

38 yo Caucasian man with strong family history of premature coronary artery disease and LDL-C despite diet in the 160-180 mg/dL range. Otherwise normal risk profile.

- What is his lifetime risk of ASCVD?
- Does he have factors that the guidelines recommend can be considered if a risk decision is not certain?
- Does his risk factor burden indicate ASCVD risk that would benefit from statin therapy?
- What are his personal characteristics that would inform the decision regarding safe statin use?
- What is his informed preference?

Lessons From the Vignettes: Primary Prevention

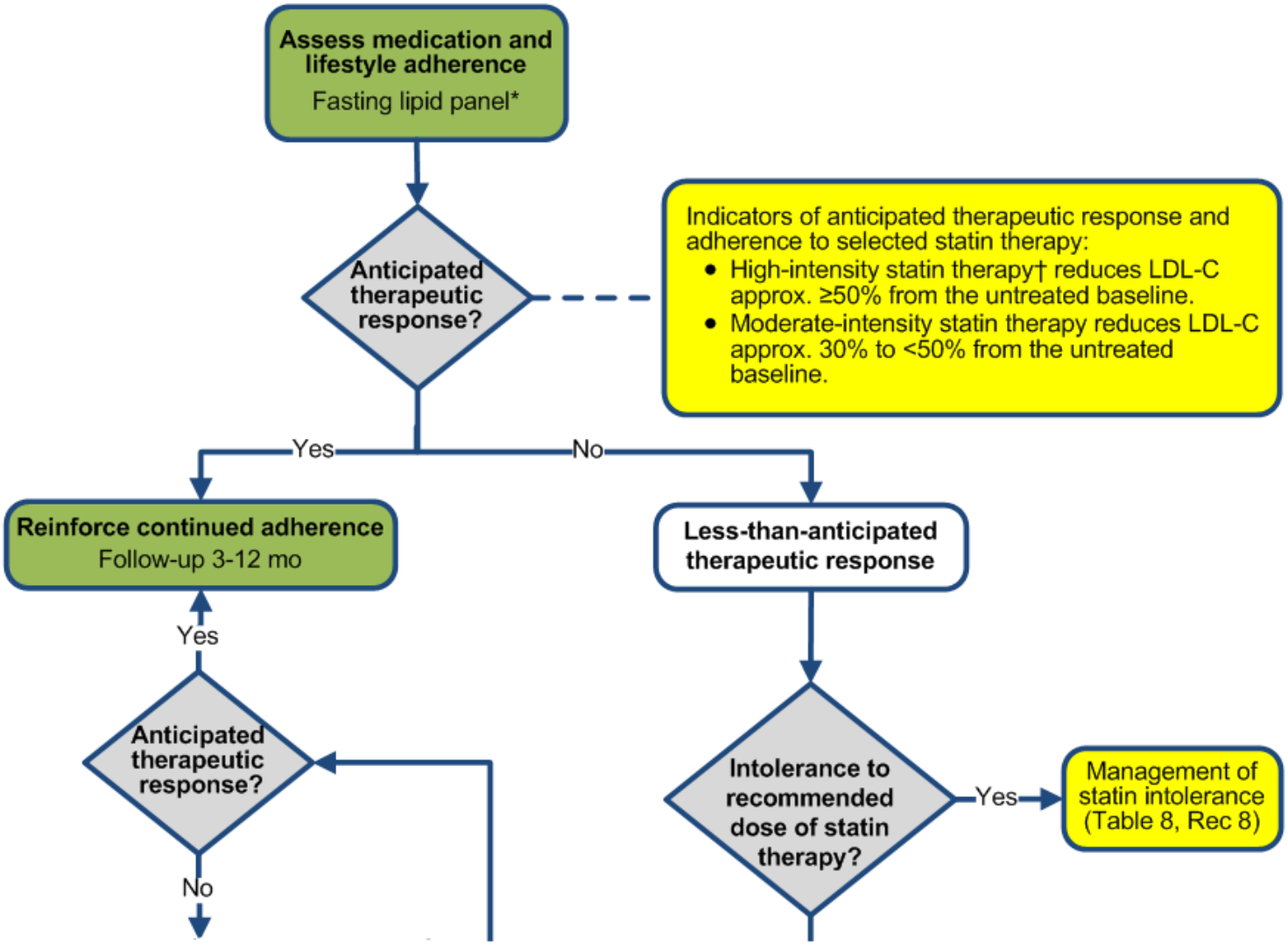
- **Case 3**: LDL-C <190 mg/dL
  - Not otherwise identified in a statin benefit group

    OR
  - After quantitative risk assessment, a risk-based treatment decision is uncertain
- Additional factors that increase risk may be considered. In our case, can use LDL ≥160 mg/dL and family history of premature ASCVD as factors to inform the decision about statin Rx.

Lessons From the Vignettes

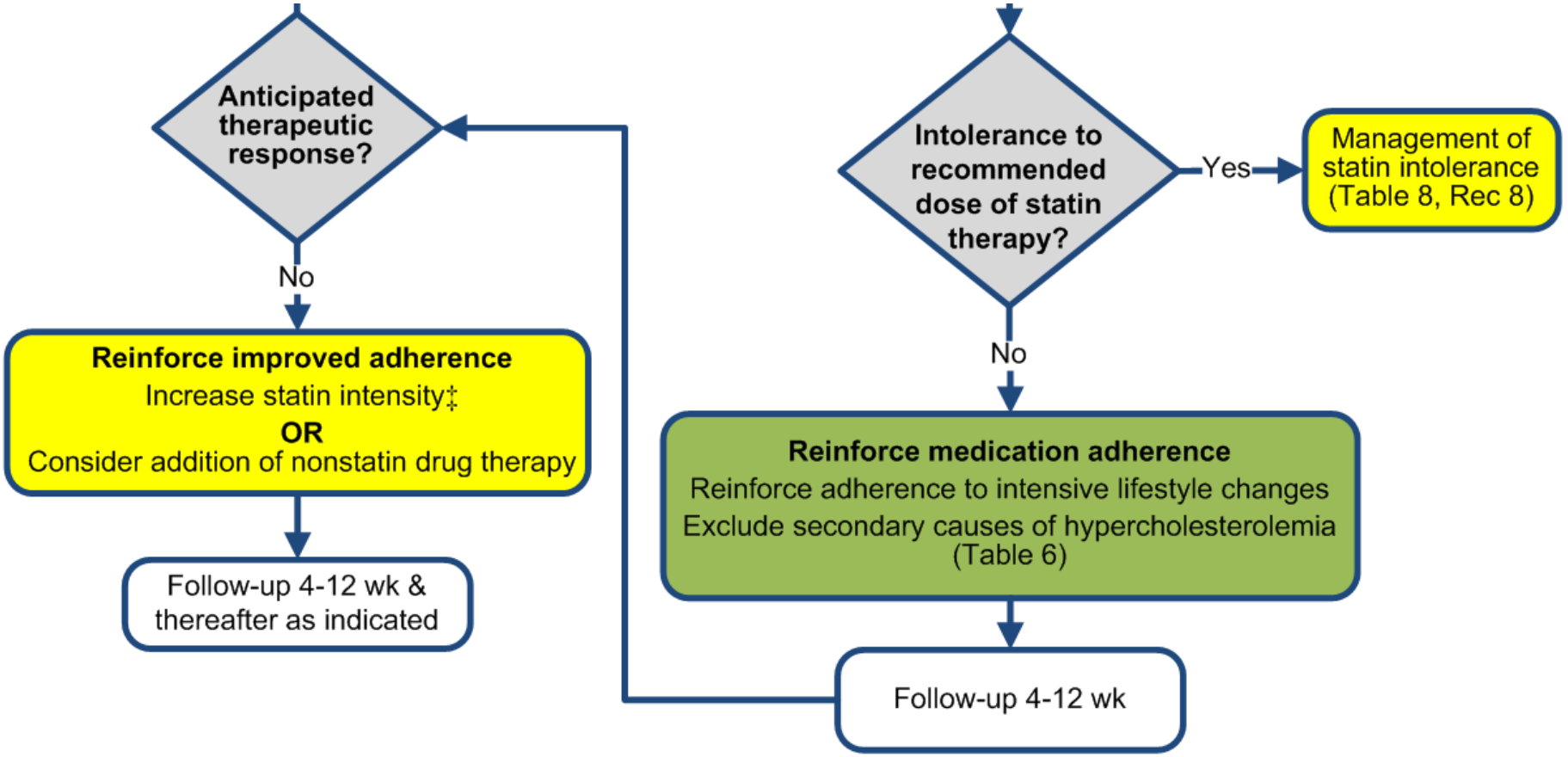
- **Case 3 (cont.)**
  - In these individuals, statin therapy for primary prevention may be considered after evaluating the potential for ASCVD risk reduction benefits, adverse effects, drug-drug interactions, and discussion of patient preferences.
  - Example of where guidelines inform clinical judgment, but do not replace it.

Statin Therapy: Monitoring Response-Adherence



*Fasting lipid panel preferred. In a nonfasting individual, a nonfasting non–HDL-C ≥220 mg/dL may indicate genetic hypercholesterolemia that requires further evaluation or a secondary etiology. If nonfasting triglycerides are ≥500 mg/dL, a fasting lipid panel is required.
†In those already on a statin, in whom baseline LDL-C is unknown, an LDL-C <100 mg/dL was observed in most individuals receiving high-intensity statin therapy in RCTs.

Monitoring Response-Adherence (cont.)



‡See guideline text

Management of Muscle Symptoms on Statin Therapy

- It is reasonable to evaluate and treat muscle symptoms including pain, cramping, weakness, or fatigue in statin-treated patients according to the management algorithm
- To avoid unnecessary discontinuation of statins, obtain a history of prior or current muscle symptoms to establish a baseline before initiating statin therapy

Management of Muscle Symptoms on Statin Therapy (cont.)

If unexplained severe muscle symptoms or fatigue develop during statin therapy:

- Promptly discontinue the statin
- Address possibility of rhabdomyolysis with:
  - CK
  - Creatinine
  - Urinalysis for myoglobinuria

Management of Muscle Symptoms on Statin Therapy (cont.)

If mild-to-moderate muscle symptoms develop during statin therapy:

- Discontinue the statin until the symptoms are evaluated
- Evaluate the patient for other conditions* that might increase the risk for muscle symptoms
- If after 2 months without statin Rx, muscle symptoms or elevated CK levels do not resolve completely, consider other causes of muscle symptoms

*Hypothyroidism, reduced renal or hepatic function, rheumatologic disorders such as polymyalgia rheumatica, steroid myopathy, vitamin D deficiency or primary muscle diseases

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

Three Principles

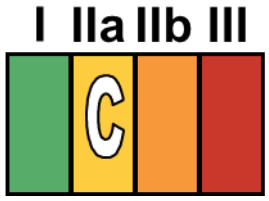
- Do not focus on LDL-C or non–HDL-C levels as treatment goals
  - Although continue to obtain a lipid panel to monitor adherence
- Use medications proven to reduce ASCVD risk
- Risk decisions in primary prevention require a clinician-patient discussion to evaluate the benefits and harms for the individual patient
  - Optimal lifestyle emphasized
  - Clinician-patient discussion needed for appropriate shared decision-making

Statin Treatment: Heart Failure and Hemodialysis

No recommendation

The Expert Panel makes no recommendations regarding the initiation or discontinuation of statins in patients with NYHA class II–IV ischemic systolic heart failure or in patients on maintenance hemodialysis.

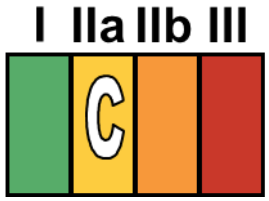
Statin Safety



During statin therapy, it is reasonable to measure CK in individuals with muscle symptoms, including pain, tenderness, stiffness, cramping, weakness, or generalized fatigue.

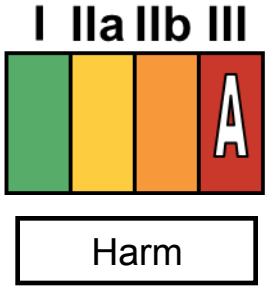
Baseline measurement of hepatic transaminase levels (ALT) should be performed before initiation of statin therapy.

Statin Safety (cont.)



During statin therapy, it is reasonable to measure hepatic function if symptoms suggesting hepatotoxicity arise (e.g., unusual fatigue or weakness, loss of appetite, abdominal pain, dark-colored urine or yellowing of the skin or sclera).

Decreasing the statin dose may be considered when 2 consecutive values of LDL-C levels are <40 mg/dL.



It may be harmful to initiate simvastatin at 80 mg daily or increase the dose of simvastatin to 80 mg daily.

Monitoring Statin Therapy

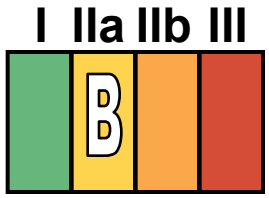
Adherence to medication and lifestyle, therapeutic response to statin therapy, and safety should be regularly assessed. This should also include a fasting lipid panel performed within 4 to 12 weeks after initiation or dose adjustment, and every 3 to 12 months thereafter. Other safety measurements should be measured as clinically indicated.

Optimizing Statin Therapy

The maximum tolerated intensity of statin should be used in individuals for whom a high- or moderate-intensity statin is recommended, but not tolerated.*

* Several RCTs found that low and low-moderate intensity statin therapy reduced ASCVD events. In addition, the CTT meta-analyses of statin trials have shown that each 39 mg/dL reduction in LDL-C reduced CVD events by 22%. Therefore, the Panel considered that submaximal statin therapy should be used to reduce ASCVD risk in those unable to tolerate moderate- or high-intensity statin therapy.

Insufficient Response to Statin Therapy



In individuals who are candidates for statin treatment but are completely statin intolerant, it is reasonable to use nonstatin cholesterol-lowering drugs that have been shown to reduce ASCVD events in RCTs if the ASCVD risk-reduction benefits outweigh the potential for adverse effects.

Summary

- Encourage adherence to a healthy lifestyle
- Statins are recommended in groups with demonstrated benefit
- Utilize the ASCVD risk calculator to more closely estimate burden of ASCVD
- Engage in in clinician-patient discussion before initiating statin therapy, especially for primary prevention in patients with lower ASCVD risk