UC San Diego Health

JOURNAL CLUB

UCSD Geriatric Medicine & Psychiatry Fellowships
Gerontology Research Collaborative (GRC)

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August 27th 2021

UCSD Geriatric Medicine & Psychiatry Fellowships
Gerontology Research Collaborative (GRC)

UC San Diego School of Medicine

GRC GERONTOLOGY RESEARCH COLLABORATIVE

Geriatric Medicine Fellowship
Geriatric Psychiatry Fellowship

San Diego area research institutions:
- UCSD, Salk, SDSU

- **Meetings held every fourth Friday of the month from 3:30-4:30PM**
- **Co-lead: Jordan Kohn, Ph.D.**

Goals for Journal Club

1. Bring together a community of clinicians and researchers in the field of aging to think critically about an article in order to develop a broad yet deep understanding of aging-related research.
2. Facilitate better knowledge awareness through collaborative interdisciplinary group discussion.
3. Promote interest in research while learning from experts about knowledge gaps, future research questions, and the translation of research into clinical practice.
4. To foster collaborations across fields within aging for future papers, studies, and grant proposals.

Research

JAMA Internal Medicine | Original Investigation | LESS IS MORE

Evaluation of Time to Benefit of Statins for the Primary Prevention of Cardiovascular Events in Adults Aged 50 to 75 Years

A Meta-analysis

Lindsey C. Yourman, MD; Irena S. Cenzer, MA; W. John Boscardin, PhD; Brian T. Nguyen, BA; Alexander K. Smith, MD, MPH; Mara A. Schonberg, MD, MPH; Nancy L. Schoenborn, MD, MHS; Eric W. Widera, MD; Ariela Orkaby, MD, MPH; Annette Rodriguez, MA; Sei J. Lee, MD, MAS

Published November 16, 2020

Case Presentation

- Mr. S is a 73-year-old White male.
- **Past Medical History**: HTN, moderate-severe spinal stenosis, mild cognitive impairment.
- **Function**: Functional in all ADLs and IADLs.
- **Family History**: Father died of MI in his late 70s.
- **Medications**: Amlodipine 5 mg, Acetaminophen 500 mg TID, Lidocaine patches, Ibuprofen PRN.
- **Social History:** Retired engineer and served in Vietnam
  - Married, children and grandchildren all nearby
  - Drinks 2-3 drinks a week, former smoker during Vietnam War only
- **Vital Signs:** BP 135/63; HR 78; BMI 29
- **Labs:** A1c 5.7; TC 174, HDL 55, LDL 88

Case Presentation

- Spending time with his family and helping with the grandchildren before his memory worsens.
- Control pain so he can remain functional and not rely on anyone else.
- Would like to minimize medications but will take if it is important.

For an older adult without history of cardiovascular or cerebrovascular disease (but with CV risk factors) and with mild cognitive impairment, does statin therapy for primary prevention improve outcomes that are meaningful to this patient while not exposing him to potentially burdensome risks?

Clinical guideline recommendations

U.S. Preventive Services TASK FORCE

Figure 2. Statin Use for the Primary Prevention of CVD in Adults: Clinical Summary

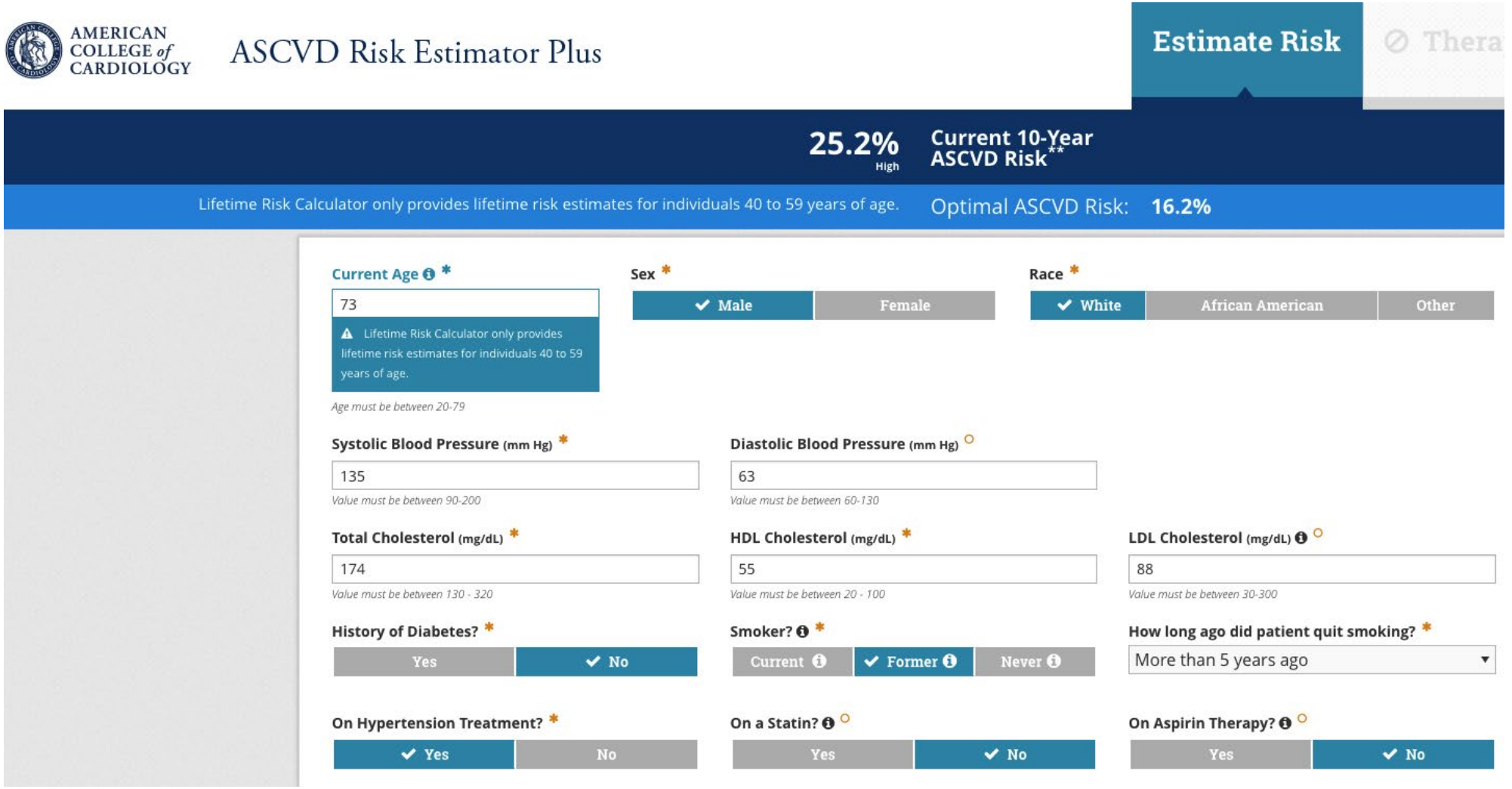
Population	Adults aged 40–75 y with no history of CVD, ≥1 CVD risk factors, and calculated 10-y CVD event risk ≥10%	Adults aged 40–75 y with no history of CVD, ≥1 CVD risk factors, and calculated 10-y CVD event risk of 7.5%–10%	Adults 76 y and older with no history of CVD
Recommendation	Initiate use of low- to moderate-dose statins. Grade: B	Discuss with patient and selectively offer use of low- to moderate-dose statins. Grade: C	No recommendation. Grade: I (insufficient evidence)

CLINICAL PRACTICE GUIDELINE

2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol

In adults 40 to 75 years of age without diabetes mellitus and with LDL-C levels ≥70 mg/dL (≥1.8 mmol/L), at a 10-year ASCVD risk of ≥7.5%, start a moderate-intensity statin if a discussion of treatment options favors statin therapy. Risk-enhancing factors

Atherosclerotic Cardiovascular Disease (ASCVD) Risk?



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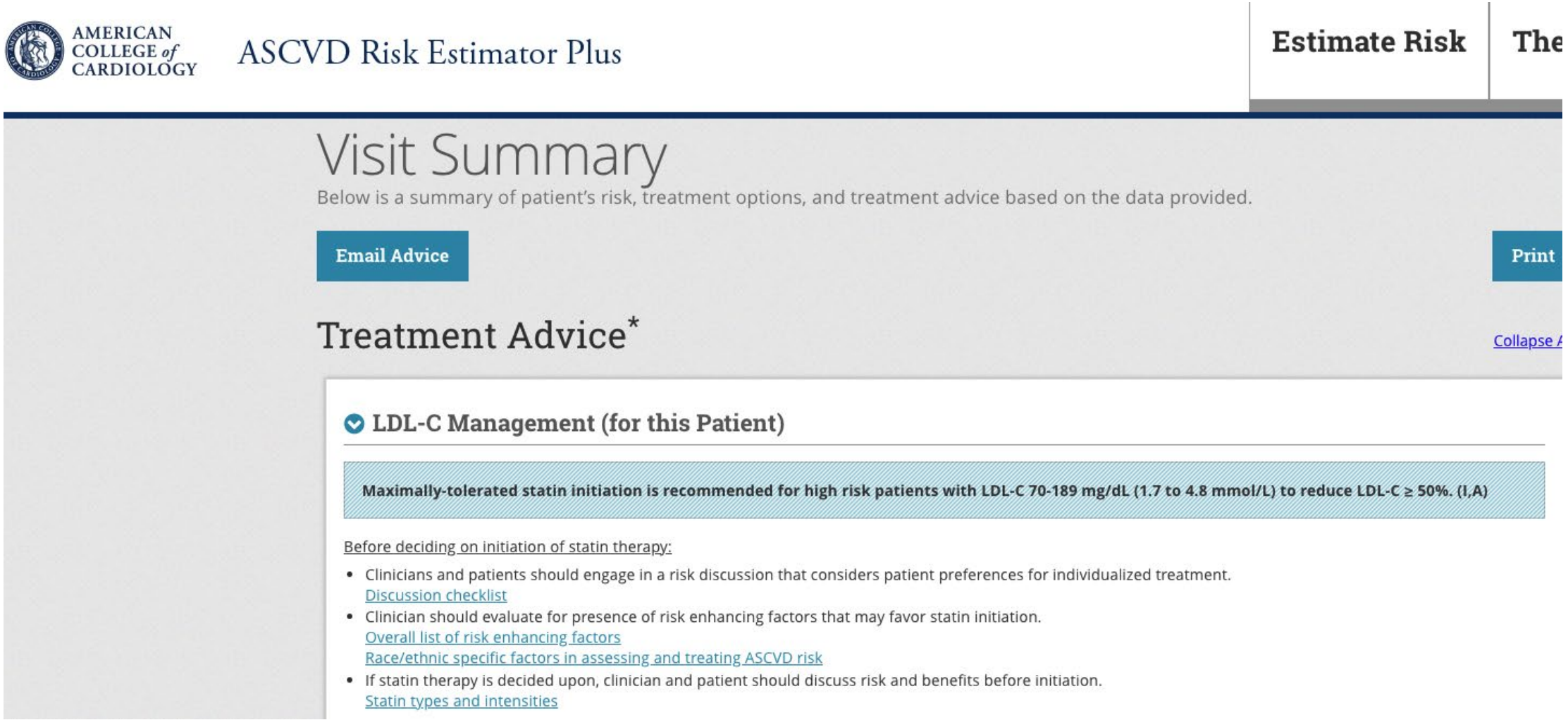
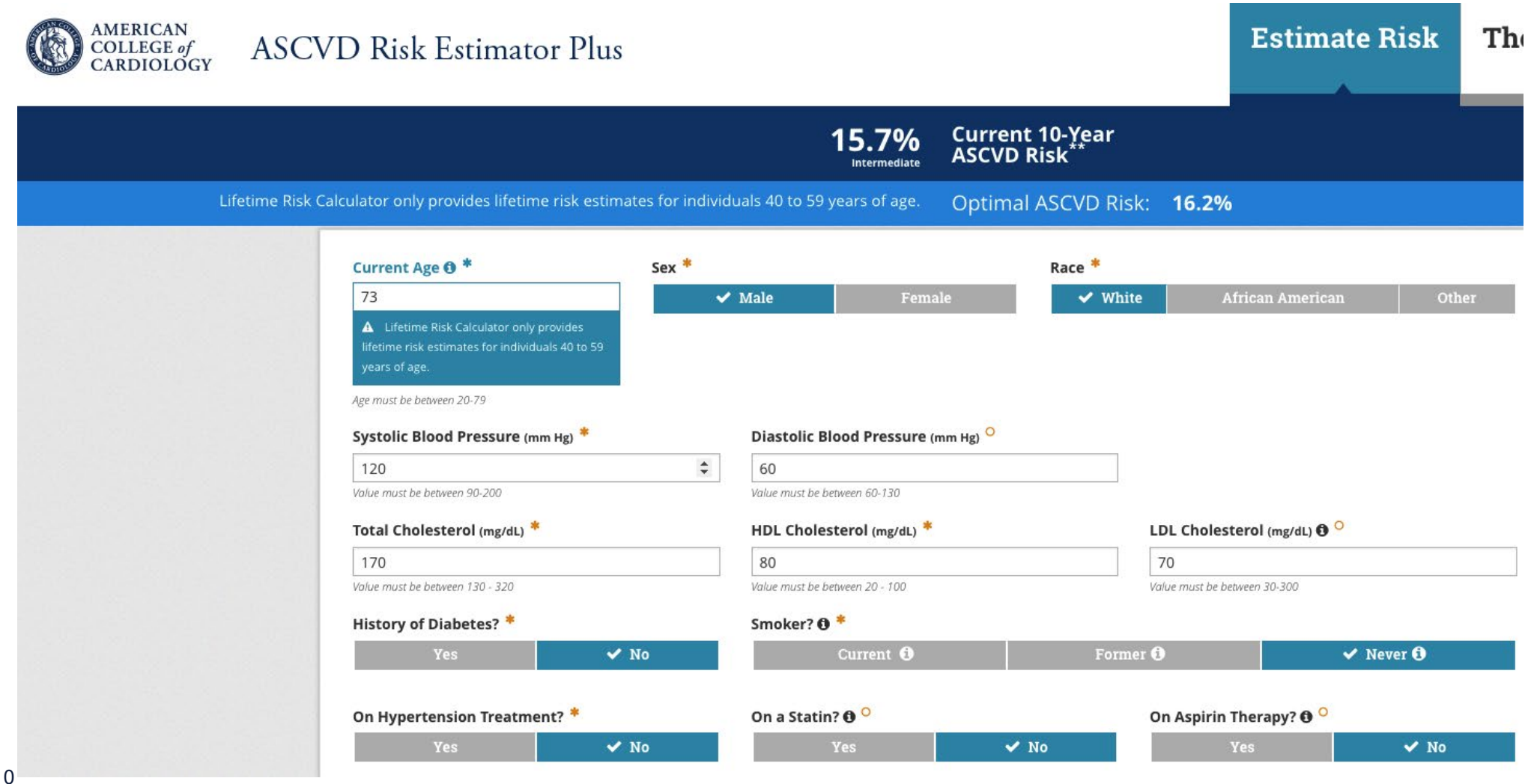
Atherosclerotic Cardiovascular Disease (ASCVD) Risk?



Atherosclerotic Cardiovascular Disease (ASCVD) Risk?



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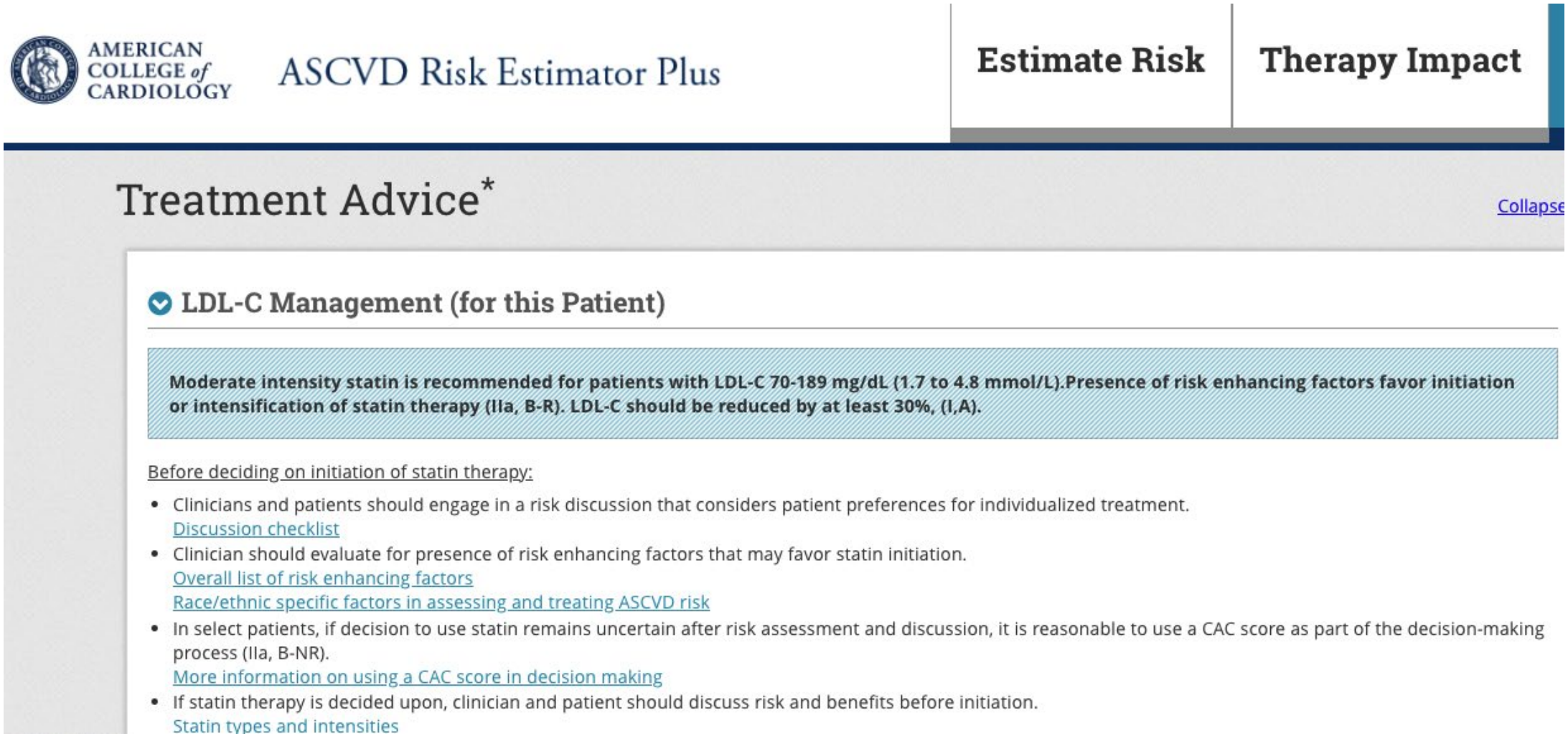
Atherosclerotic Cardiovascular Disease (ASCVD) Risk?



AMERICAN COLLEGE of CARDIOLOGY

ASCVD Risk Estimator Plus

Estimate Risk | Therapy Impact

Treatment Advice*

Collapse

LDL-C Management (for this Patient)

Moderate intensity statin is recommended for patients with LDL-C 70-189 mg/dL (1.7 to 4.8 mmol/L).Presence of risk enhancing factors favor initiation or intensification of statin therapy (IIa, B-R). LDL-C should be reduced by at least 30%, (I,A).

Before deciding on initiation of statin therapy:

- Clinicians and patients should engage in a risk discussion that considers patient preferences for individualized treatment.
  Discussion checklist
- Clinician should evaluate for presence of risk enhancing factors that may favor statin initiation.
  Overall list of risk enhancing factors
  Race/ethnic specific factors in assessing and treating ASCVD risk
- In select patients, if decision to use statin remains uncertain after risk assessment and discussion, it is reasonable to use a CAC score as part of the decision-making process (IIa, B-NR).
  More information on using a CAC score in decision making
- If statin therapy is decided upon, clinician and patient should discuss risk and benefits before initiation.
  Statin types and intensities

Research

JAMA Internal Medicine | Original Investigation | LESS IS MORE

Evaluation of Time to Benefit of Statins for the Primary Prevention of Cardiovascular Events in Adults Aged 50 to 75 Years
A Meta-analysis

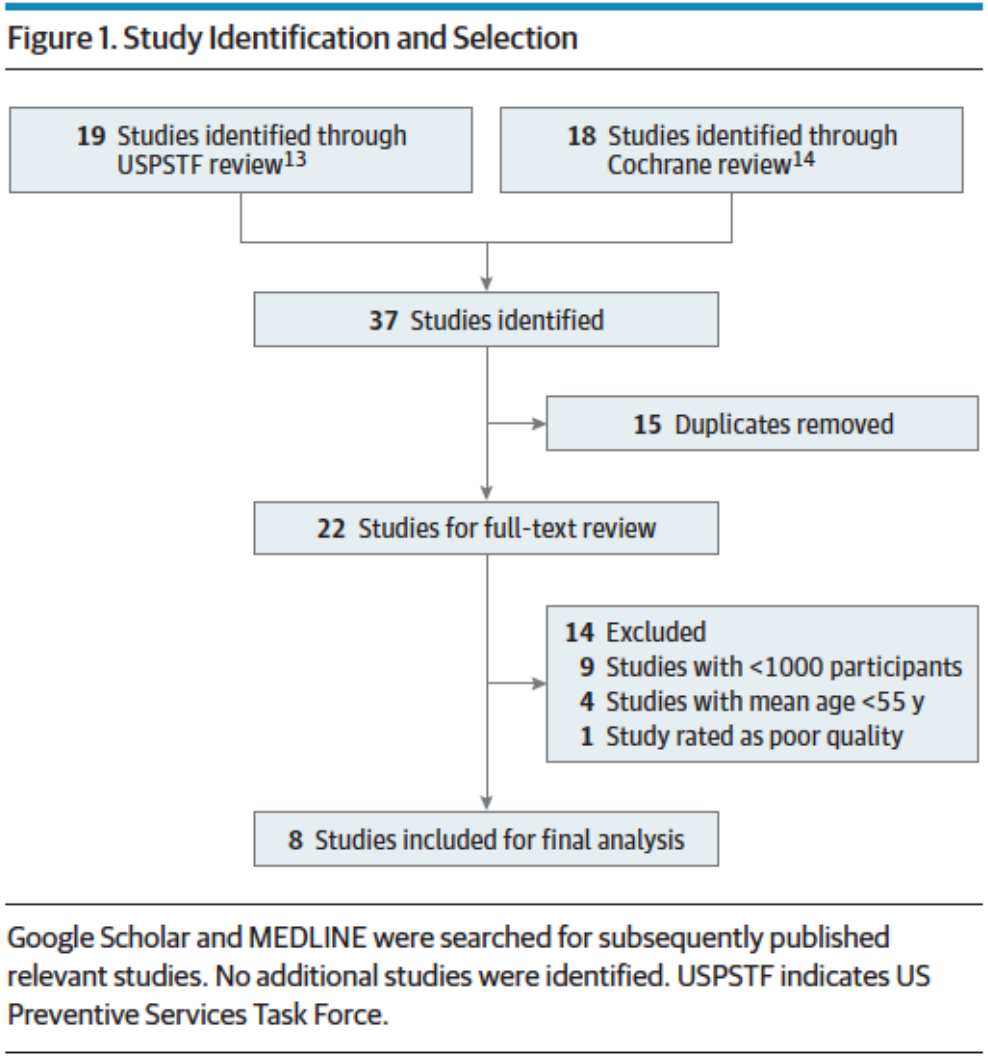
Lindsey C. Yourman, MD; Irena S. Cenzer, MA; W. John Boscardin, PhD; Brian T. Nguyen, BA; Alexander K. Smith, MD, MPH; Mara A. Schonberg, MD, MPH; Nancy L. Schoenborn, MD, MHS; Eric W. Widera, MD; Ariela Orkaby, MD, MPH; Annette Rodriguez, MA; Sei J. Lee, MD, MAS

Published November 16, 2020

In adults aged 50-75 years, what is the time to benefit (TTB) for statins to prevent a first major adverse cardiovascular event (MACE)?

Methods

- Meta-Analysis of randomized clinical trials of statins for primary prevention.
- Eligibility Criteria:
  - Randomized clinical trials with mean patient age of 55+.
  - <15% participants with known pre-existing cardiovascular disease.
  - Larger trials (>1000 participants), high-moderate quality by Cochrane/USPTSF criteria.



Outcomes of Interest

- Time to First Major Cardiovascular Event

eTable. Definition of Major Adverse Cardiovascular Events in the Included Studies

Cardiovascular Events	Studies							
	AFCAPS/ TexCAPS	MEGA	WOSCOPS	ASCOT-LLA	ASPEN	CARDS	HOPE	JUPITER
Myocardial Infarction	X	X	X	X	X	X	X	X
Death from coronary heart disease	X (cardiac & sudden death)	X (cardiac & sudden death)	X	X	X (cardiac & sudden death, & CV death)	X (acute coronary heart disease)	X (CV death)	X (CV death)
Angina	X	X				X		X
Revascularization, recanalization, and coronary artery bypass grafting		X			X (recanalization & coronary artery bypass grafting)	X		X
Stroke					X	X	X	X
Heart Failure					X			
Resuscitated cardiac arrest					X	X		

Statistical Analysis

- For each study:
  - Examined survival curves using annual CV adverse event data for each arm (statin vs. control).
  - Using simulated parameter values by Markov chain Monte Carlo methods to obtain point estimates, SE, 95% CI for rates of CV end points for individual studies.
  - Using models of the survival curves for both control vs statin groups for each study, calculated when specific absolute risk reduction (ARR) thresholds were crossed in each study: 0.002, 0.005, and 0.010.
  - Pooled estimates from each study.

Results

- 8 Randomized Control Trials met inclusion criteria.
  - N=65,383
  - Mean age 55-69 years of age, 66% men
  - Follow up 2-6 years
  - 2 RTCs (n=14,437) evaluated low-intensity statins
  - 5 RTCs (n=33,144) evaluated moderate-intensity statins
  - 1 RTC (n=17,802) evaluated high-intensity statins
  - 7 RTCs had a placebo control
  - 1 RTC compared statin + diet to diet alone

Results

Table 1. Characteristics of Included Studies

Source (study)	No. of partici-pants	Age, y[a]	Women, %	Mean baseline cardiovascular risk factors: BP, mm Hg	LDL-C level, mg/dL	Mean HDL-C level, mg/dL	Treatment	Follow-up duration, y	MACE ARR, % (95% CI)
Low-intensity statin									
Downs et al,[20] 1998 (AFCAPS/TexCAPS)	6605	58 (45-73)	15	138/78	150	36	Lovastatin, 20-40 mg	5	2.0 (1.0 to 3.0)
Nakamura et al,[17] 2006 (MEGA)	7832	58 (40-70)	68	132/78	157	58	Pravastatin sodium, 10-20 mg	5	0.8 (0.2 to 1.5)
Moderate-intensity statin									
Shepherd et al,[27] 1995 (WOSCOPS)	6595	55 (45-64)	0	136/84	192	44	Pravastatin sodium, 40 mg	5	2.3 (1.1 to 3.4)
Sever et al,[28] 2003 (ASCOT-LLA)	10 305	63 (40-79)	19	164/95	133	51	Atorvastatin calcium, 10 mg	3	1.4 (0.6 to 2.1)
Knopp et al,[19] 2006 (ASPEN)	2410	61 (40-75)	34	133/77	114	47	Atorvastatin calcium, 10 mg	4	0.4 (−2.4 to 3.1)
Neil et al,[18] 2006 (CARDS)	1129	69 (65-75)	31	149/82	118	53	Atorvastatin calcium, 10 mg	4	3.9 (NR)
Yusuf et al,[21] 2016 (HOPE-3)	12 705	66 (>55)	46	138/82	128	45	Rosuvastatin calcium, 10 mg	6	1.1 (0.4 to 1.8)
High-intensity statin									
Ridker et al,[16] 2008 (JUPITER)	17 802	66 (>50)[b]	38	134/80	108	49	Rosuvastatin calcium, 20 mg	2	1.2 (0.7 to 1.6)

Abbreviations: AFCAPS/TexCAPS, Air Force/Texas Coronary Atherosclerosis Prevention Study; ARR, absolute risk reduction; ASCOT-LLA, Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm; ASPEN, Atorvastatin Study for Prevention of Coronary Heart Disease End Points in Non-Insulin-Dependent Diabetes Mellitus; BP, blood pressure; CARDS, Collaborative Atorvastatin Diabetes Study; HDL-C, high-density lipoprotein cholesterol; HOPE, Heart Outcomes Prevention Evaluation Study; JUPITER, Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin; LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiovascular event; MEGA, Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese; NR, not reported; WOSCOPS, West of Scotland Coronary Prevention Study.

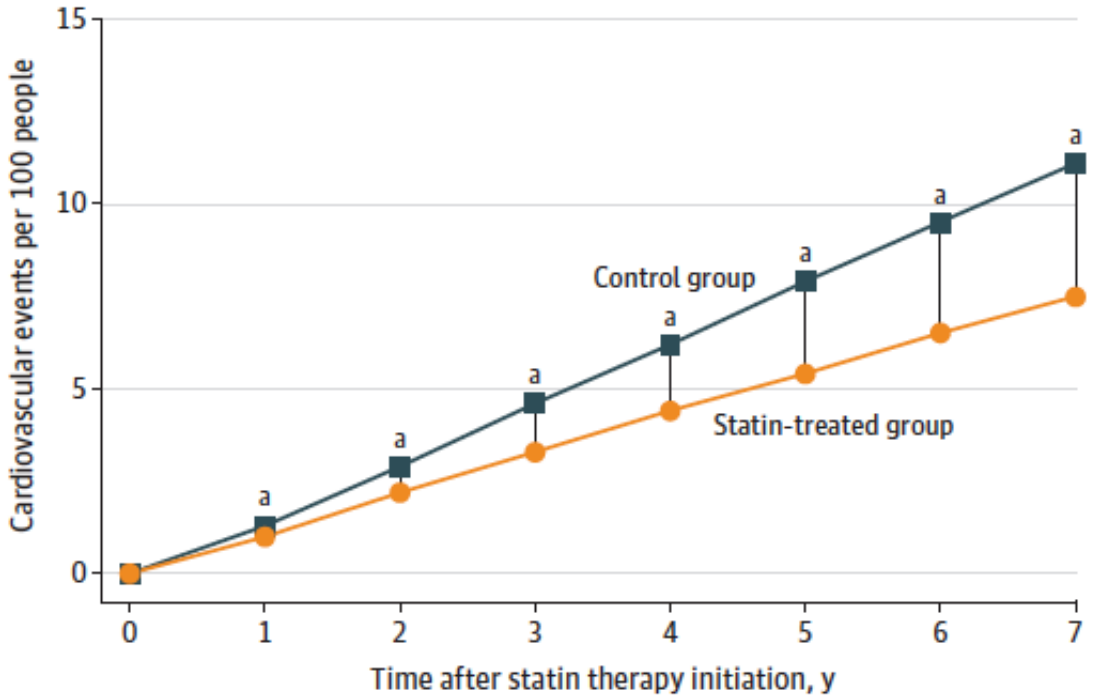
SI conversion factor: To convert cholesterol to mmol/L, multiply by 0.0259.

[a] Unless otherwise indicated, data are expressed as mean (range).

[b] Reported as median.

Results

Figure 2. Pooled Mortality Curves for Major Adverse Cardiovascular Events (MACE)



Values are the difference in MACE rates between control and statin-treated groups, which is equivalent to the absolute risk reduction and the number of cardiovascular events that are prevented per 100 people treated with a statin.

[a] $P < .05$ between groups.

Results

Results: Time to benefit† for preventing a first MACE‡ using statin therapy in older adults without CVD

Absolute risk reduction thresholds	Time to benefit (95% CI)†, *y*	NNT to avoid 1 MACE over time to benefit
1%	2.5 (1.7 to 3.4)	100
0.5%	1.3 (1.0 to 1.7)	200
0.2%	0.8 (0.5 to 1.0)	500

CVD = cardiovascular disease; MACE = major adverse cardiovascular event; other abbreviations defined in Glossary.
†Primary outcome = time from statin initiation to first MACE estimated from survival curves fit using trial annual event data and Markov chain Monte Carlo simulations.
‡Trial-defined MACE included cardiovascular mortality and myocardial infarction in all trials; revascularization, angina, or stroke in 4 trials each; resuscitated cardiac arrest in 2 trials; and heart failure in 1 trial.

- 1 study reported statins decreased all-cause mortality (JUPITER).
- 1 study reported statins decreased CV mortality (WOSCOPS).

Results

Table 2. TTB for the Primary Prevention of Major Adverse Cardiovascular Events for Older Adults

Source (study)	TTB (95% CI), y[a]		
	ARR = 0.002	ARR = 0.005	ARR = 0.010
Downs et al,[20] 1998 (AFCAPS/TexCAPS)	1.1 (0.3-2.8)	1.9 (0.8-3.8)	3.2 (1.7-5.5)
Nakamura et al,[17] 2006 (MEGA)	1.6 (0.4-4.4)	3.5 (1.3-7.8)	6.5 (3.2-11.8)
Shepherd et al,[27] 1995 (WOSCOPS)	0.9 (0.2-2.3)	1.5 (0.6-3.1)	2.5 (1.3-4.4)
Sever et al,[28] 2003 (ASCOT-LLA)	0.6 (0.2-1.3)	1.4 (0.6-2.9)	3.4 (1.3-7.3)
Knopp et al,[19] 2006 (ASPEN)	2.5 (0.5-8.4)	2.9 (0.8-7.7)	3.5 (1.3-7.9)
Neil et al,[18] 2006 (CARDS)	0.7 (0.1-2.9)	1.0 (0.2-3.0)	1.4 (0.5-3.4)
Yusuf et al,[21] 2016 (HOPE-3)	1.9 (0.4-5.2)	3.4 (1.2-7.8)	5.2 (2.8-8.8)
Ridker et al,[16] 2008 (JUPITER)	0.7 (0.4-1.1)	1.2 (0.9-1.7)	1.9 (1.5-2.4)
Summary TTB, y	0.8 (0.5-1.0)	1.3 (1.0-1.7)	2.5 (1.7-3.4)
Test of heterogeneity			
I^2, %	0	0	34.3
P value	.90	.71	.15

Abbreviations: AFCAPS/TexCAPS, Air Force/Texas Coronary Atherosclerosis Prevention Study; ARR, absolute risk reduction; ASCOT-LLA, Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm; ASPEN, Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non–Insulin-Dependent Diabetes Mellitus; CARDS, Collaborative Atorvastatin Diabetes Study; HOPE, Heart Outcomes Prevention Evaluation Study; JUPITER, Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin; MACE, Major Adverse Cardiovascular Event; MEGA, Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese; TTB, time to benefit; WOSCOPS, West of Scotland Coronary Prevention Study.

[a] ARR = 0.002 is the time to prevent 1 cardiovascular event per 500 persons treated with a statin for primary prevention; ARR = 0.005, time to prevent 1 cardiovascular event per 200 persons treated with a statin; and TTB for ARR = 0.010, time to prevent 1 cardiovascular event per 100 persons treated with a statin.

Discussion

- Statin therapy for primary prevention may help prevent major adverse cardiovascular events in adults age 50-75 years old if they have a life expectancy of at least 2.5 years (need to treat 100 to prevent 1).
- No clear mortality benefit (2 of the 8 trials).
- Rigorous methods and selection of major RCT statin studies.
- Helps to better frame conversations about individualized risks and benefits for primary prevention for older adults.

Limitations

- Cardiovascular risk among participants of individual trials are different:
  - Presence of diabetes (CARDS), smoker (ASCOT, HOPE), high-sensitivity C-reactive Protein (hsCRP) level of >2 mg/dL (JUPITER), low HDL (ASCOT), family history CV (HOPE), mild renal dysfunction (HOPE).
- Each study has its own limitations and possible conflicts of interest:
  - JUPITER – early termination, strong commercial conflict of interest.
- Is it okay to use meta-analysis to estimate time to benefit when none of the individual trials directly measured this?
- Mean age groups for most of the studies were younger patients with only 3 studies with a mean age 65+.
- Age group of 50-75 years is a wide range.

Discussion

- ***Mr. S, many of the things we do in medicine we do now to help a patient in the future. For cholesterol medications, if we start now, we may help prevent a heart attack or stroke in the future.***
- *"If you take rosuvastatin 10 mg every day, your hazard ratio for a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke is 0.76 after roughly 5.6 years, in other words, it will reduce your risk for cardiovascular events by 24%."*
- *"From an excellent recent study done by my colleague here at UCSD looking at data from 65,383 people from 8 studies, they estimated that 1 in 100 adults age 50-75 years of age who take cholesterol medicine for primary prevention, may avoid a major adverse cardiovascular event in 2.5 years."*

Discussion

- *"However, it is important to know that while serious adverse effects of cholesterol medicines are rare, they can have other effects that can influence your health and everyday functioning."*

- *"The most frequent adverse event seen in clinical practice is muscular symptoms that can affect up to 25% of people who use statins. You could experience these symptoms much sooner than you receive any possible benefit from this medication."*
- *"Given your lack of other chronic medical diseases and your current level of functioning, you may benefit from this medication. However, what gives me pause is your current issues with memory and that if you do develop muscular symptoms, I worry it would limit you further for your every day activities given your existing chronic pain, and this could be detrimental to your health including cognition and cardiovascular health."*

A Clinical Trial of STAtin Therapy for Reducing Events in the Elderly (STAREE) (STAREE)

ClinicalTrials.gov Identifier: NCT02099123

Recruitment Status : Recruiting
First Posted : March 28, 2014
Last Update Posted : March 12, 2019
See Contacts and Locations

Sponsor:
Monash University

Collaborators:
National Health and Medical Research Council, Australia
National Heart Foundation, Australia

Information provided by (Responsible Party):
Sophia Zoungas, Monash University

Study Description

Go to

Brief Summary:
The STAREE study will examine whether treatment with statin (atorvastatin 40mg) compared with placebo will prolong overall survival or disability free survival amongst healthy elderly people (≥70 years).

Condition or disease	Intervention/treatment	Phase
Independent Living	Drug: Atorvastatin	Phase 4
Disability Free Survival	Drug: Placebo (for Atorvastatin)	

Eligibility Criteria

Information from the National Library of Medicine

Choosing to participate in a study is an important personal decision. Talk with your doctor and family members or friends about deciding to join a study. To learn more about this study, you or your doctor may contact the study research staff using the contacts provided below. For general information, Learn About Clinical Studies.

Ages Eligible for Study:	70 Years and older (Older Adult)
Sexes Eligible for Study:	All
Accepts Healthy Volunteers:	Yes

Criteria

Inclusion Criteria:

- Men and women aged ≥70 years living independently in the community
- Willing and able to provide informed consent and accept the study requirements (Note: competent physical ability to participate in the trial is assessed using the KATZ ADL questionnaire)

Exclusion Criteria:

A history of cardiovascular disease (defined as myocardial infarction, stroke, peripheral vascular disease, angina, transient ischaemic attack, coronary artery angioplasty and/or stenting, coronary artery bypass graftir

- A history of dementia or a 3MS score <78 on screening,
- A history of diabetes,
- Total cholesterol >7.5 mmol/L,
- Moderate or severe chronic kidney disease (persistent proteinuria (Urine albumin:creatinine ratio >30mg/mmol or Urine protein:creatinine ratios >45 mg/mmol)45 and/or eGFR <45ml/min/1.73m2),
- Moderate or severe liver disease (persistent elevations of transaminases of more than 3 times the upper limit of the normal laboratory reference range),
- Serious inter-current illness likely to cause death within the next 5 years such as terminal cancer or obstructive airways disease,
- Current participation in a clinical trial (Note: If yes, this is only an exclusion if other trial involves taking a drug or another intervention)
- Absolute contraindication to statin therapy,
- Current use of statin therapy or other lipid lowering therapy for primary prevention and unwilling to stop therapy,
- Current long term or permanent use of the following cytochrome P450 (CYP) 3A4 inhibitors : Amiodarone, Boceprevir, Cimetidine, Cyclosporin, Danazol, Fosamprenavir, Indinavir, Lopinavir + Ritonavir, Erythromyc

Pragmatic Evaluation of Events And Benefits of Lipid-lowering in Older Adults (PREVENTABLE)

ClinicalTrials.gov Identifier: NCT04262206

Recruitment Status : Recruiting
First Posted : February 10, 2020
Last Update Posted : June 18, 2021

See Contacts and Locations

Sponsor:
Duke University

Collaborators:
National Institute on Aging (NIA)
National Heart, Lung, and Blood Institute (NHLBI)
Wake Forest University Health Sciences

Information provided by (Responsible Party):
Duke University

Study Description

Go to

Brief Summary:
PREVENTABLE is a multi-center, randomized, parallel group, placebo-controlled superiority study. Participants will be randomized 1:1 to atorvastatin 40 mg or placebo. This large study conducted in community-dwelling older adults without cardiovascular disease (CVD) or dementia will demonstrate the benefit of statins for reducing the primary composite of death, dementia, and persistent disability and secondary composites including mild cognitive impairment (MCI) and cardiovascular events.

Condition or disease	Intervention/treatment	Phase
Cognitive Impairment, Mild Dementia Cardiovascular Diseases	Drug: Atorvastatin 40 Mg Oral Tablet Drug: Placebo oral tablet	Phase 4

Eligibility Criteria

Information from the National Library of Medicine

Choosing to participate in a study is an important personal decision. Talk with your doctor and family members or friends about deciding to join a study. To learn more about this study, you or your doctor may contact the study research staff using the contacts provided below. For general information, Learn About Clinical Studies.

Ages Eligible for Study:	75 Years and older (Older Adult)
Sexes Eligible for Study:	All
Accepts Healthy Volunteers:	Yes

Criteria

Inclusion Criteria:

- Community-dwelling adults
- Age ≥75 years
- English or Spanish as primary language

Exclusion Criteria:

- Clinically evident cardiovascular disease defined as prior myocardial Infarction (MI), prior stroke, prior revascularization procedure, or a secondary prevention indication for a statin (clinician determined)
- Hospitalization for a primary diagnosis of heart failure in the prior 12 months (Note: History of heart failure in the absence of recent hospitalization or clinically evident cardiovascular disease is not an exclusion)
- Dementia (clinically evident or previously diagnosed)
- Dependence in any Katz Basic Activities of Daily Living [ADL] (with the exception of urinary or bowel continence)
- Severe hearing impairment (preventing phone follow up)
- Unable to talk (preventing phone follow up)
- Severe visual impairment (preventing cognitive testing)
- Statin use in the past year or for longer than 5 years previously (participant reported)
- Ineligible to take atorvastatin 40 mg (clinician determined)
- Documented intolerance to statins
- Active Liver Disease
- Long-term use of daily colchicine, verapamil at any dose, or diltiazem at a dose >240mg/day.