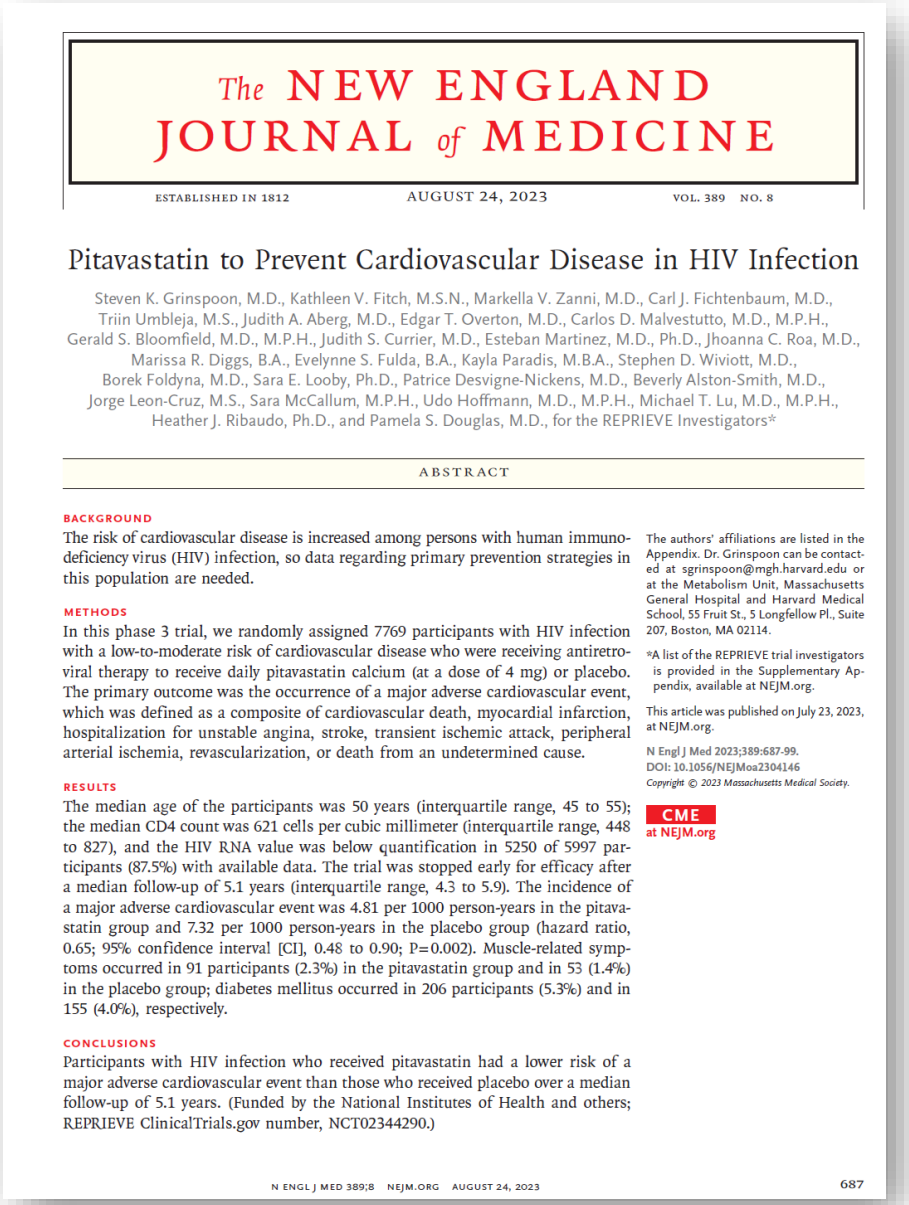


The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 24, 2023 VOL. 389 NO. 8

Pitavastatin to Prevent Cardiovascular Disease in HIV Infection

Steven K. Grinspoon, M.D., Kathleen V. Fitch, M.S.N., Markella V. Zanni, M.D., Carl J. Fichtenbaum, M.D., Triin Umbleja, M.S., Judith A. Aberg, M.D., Edgar T. Overton, M.D., Carlos D. Malvestutto, M.D., M.P.H., Gerald S. Bloomfield, M.D., M.P.H., Judith S. Currier, M.D., Esteban Martinez, M.D., Ph.D., Jhoanna C. Roa, M.D., Marissa R. Diggs, B.A., Evelynne S. Fulda, B.A., Kayla Paradis, M.B.A., Stephen D. Wiviott, M.D., Borek Foldyna, M.D., Sara E. Looby, Ph.D., Patrice Desvigne-Nickens, M.D., Beverly Alston-Smith, M.D., Jorge Leon-Cruz, M.S., Sara McCallum, M.P.H., Udo Hoffmann, M.D., M.P.H., Michael T. Lu, M.D., M.P.H., Heather J. Ribaudo, Ph.D., and Pamela S. Douglas, M.D., for the REPRIEVE Investigators*

ABSTRACT

BACKGROUND

The risk of cardiovascular disease is increased among persons with human immunodeficiency virus (HIV) infection, so data regarding primary prevention strategies in this population are needed.

METHODS

In this phase 3 trial, we randomly assigned 7769 participants with HIV infection with a low-to-moderate risk of cardiovascular disease who were receiving antiretroviral therapy to receive daily pitavastatin calcium (at a dose of 4 mg) or placebo. The primary outcome was the occurrence of a major adverse cardiovascular event, which was defined as a composite of cardiovascular death, myocardial infarction, hospitalization for unstable angina, stroke, transient ischemic attack, peripheral arterial ischemia, revascularization, or death from an undetermined cause.

RESULTS

The median age of the participants was 50 years (interquartile range, 45 to 55); the median CD4 count was 621 cells per cubic millimeter (interquartile range, 448 to 827), and the HIV RNA value was below quantification in 5250 of 5997 participants (87.5%) with available data. The trial was stopped early for efficacy after a median follow-up of 5.1 years (interquartile range, 4.3 to 5.9). The incidence of a major adverse cardiovascular event was 4.81 per 1000 person-years in the pitavastatin group and 7.32 per 1000 person-years in the placebo group (hazard ratio, 0.65; 95% confidence interval [CI], 0.48 to 0.90; P=0.002). Muscle-related symptoms occurred in 91 participants (2.3%) in the pitavastatin group and in 53 (1.4%) in the placebo group; diabetes mellitus occurred in 206 participants (5.3%) and in 155 (4.0%), respectively.

CONCLUSIONS

Participants with HIV infection who received pitavastatin had a lower risk of a major adverse cardiovascular event than those who received placebo over a median follow-up of 5.1 years. (Funded by the National Institutes of Health and others; REPRIEVE ClinicalTrials.gov number, NCT02344290.)

The authors' affiliations are listed in the Appendix. Dr. Grinspoon can be contacted at sgrinspoon@mgh.harvard.edu or at the Metabolism Unit, Massachusetts General Hospital and Harvard Medical School, 55 Fruit St., 5 Longfellow Pl., Suite 207, Boston, MA 02114.

*A list of the REPRIEVE trial investigators is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on July 23, 2023, at NEJM.org.

N Engl J Med 2023;389:687-99.
DOI: 10.1056/NEJMoa2304146

CME at NEJM.org

Should we treat all PWH above 40 years with a statin?

No way!

Professor Georg Behrens
Department of Rheumatology and Immunology
Hannover Medical School

REPRIEVE Study

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 24, 2023 VOL. 389 NO. 8

Pitavastatin to Prevent Cardiovascular Disease in HIV Infection

Steven K. Grinspoon, M.D., Kathleen V. Fitch, M.S.N., Markella V. Zanni, M.D., Carl J. Fichtenbaum, M.D., Triin Umbleja, M.S., Judith A. Aberg, M.D., Edgar T. Overton, M.D., Carlos D. Malvestutto, M.D., M.P.H., Gerald S. Bloomfield, M.D., M.P.H., Judith S. Currier, M.D., Esteban Martinez, M.D., Ph.D., Jhoanna C. Roa, M.D., Marissa R. Diggs, B.A., Evelynne S. Fulda, B.A., Kayla Paradis, M.B.A., Stephen D. Wiviott, M.D., Borek Foldyna, M.D., Sara E. Looby, Ph.D., Patrice Desvigne-Nickens, M.D., Beverly Alston-Smith, M.D., Jorge Leon-Cruz, M.S., Sara McCallum, M.P.H., Udo Hoffmann, M.D., M.P.H., Michael T. Lu, M.D., M.P.H., Heather J. Ribaudo, Ph.D., and Pamela S. Douglas, M.D., for the REPRIEVE Investigators*

ABSTRACT

BACKGROUND
The risk of cardiovascular disease is increased among persons with human immunodeficiency virus (HIV) infection, so data regarding primary prevention strategies in this population are needed.

METHODS
In this phase 3 trial, we randomly assigned 7769 participants with HIV infection with a low-to-moderate risk of cardiovascular disease who were receiving antiretroviral therapy to receive daily pitavastatin calcium (at a dose of 4 mg) or placebo. The primary outcome was the occurrence of a major adverse cardiovascular event, which was defined as a composite of cardiovascular death, myocardial infarction, hospitalization for unstable angina, stroke, transient ischemic attack, peripheral arterial ischemia, revascularization, or death from an undetermined cause.

RESULTS
The median age of the participants was 50 years (interquartile range, 45 to 55); the median CD4 count was 621 cells per cubic millimeter (interquartile range, 448 to 827), and the HIV RNA value was below quantification in 5250 of 5997 participants (87.5%) with available data. The trial was stopped early for efficacy after a median follow-up of 5.1 years (interquartile range, 4.3 to 5.9). The incidence of a major adverse cardiovascular event was 4.81 per 1000 person-years in the pitavastatin group and 7.32 per 1000 person-years in the placebo group (hazard ratio, 0.65; 95% confidence interval [CI], 0.48 to 0.90; P=0.002). Muscle-related symptoms occurred in 91 participants (2.3%) in the pitavastatin group and in 53 (1.4%) in the placebo group; diabetes mellitus occurred in 206 participants (5.3%) and in 155 (4.0%), respectively.

CONCLUSIONS
Participants with HIV infection who received pitavastatin had a lower risk of a major adverse cardiovascular event than those who received placebo over a median follow-up of 5.1 years. (Funded by the National Institutes of Health and others; REPRIEVE ClinicalTrials.gov number, NCT02344290.)

The authors' affiliations are listed in the Appendix. Dr. Grinspoon can be contacted at sgrinspoon@mgh.harvard.edu or at the Metabolism Unit, Massachusetts General Hospital and Harvard Medical School, 55 Fruit St., 5 Longfellow Pl., Suite 207, Boston, MA 02114.

*A list of the REPRIEVE trial investigators is provided in the Supplementary Appendix, available at NEJM.org.

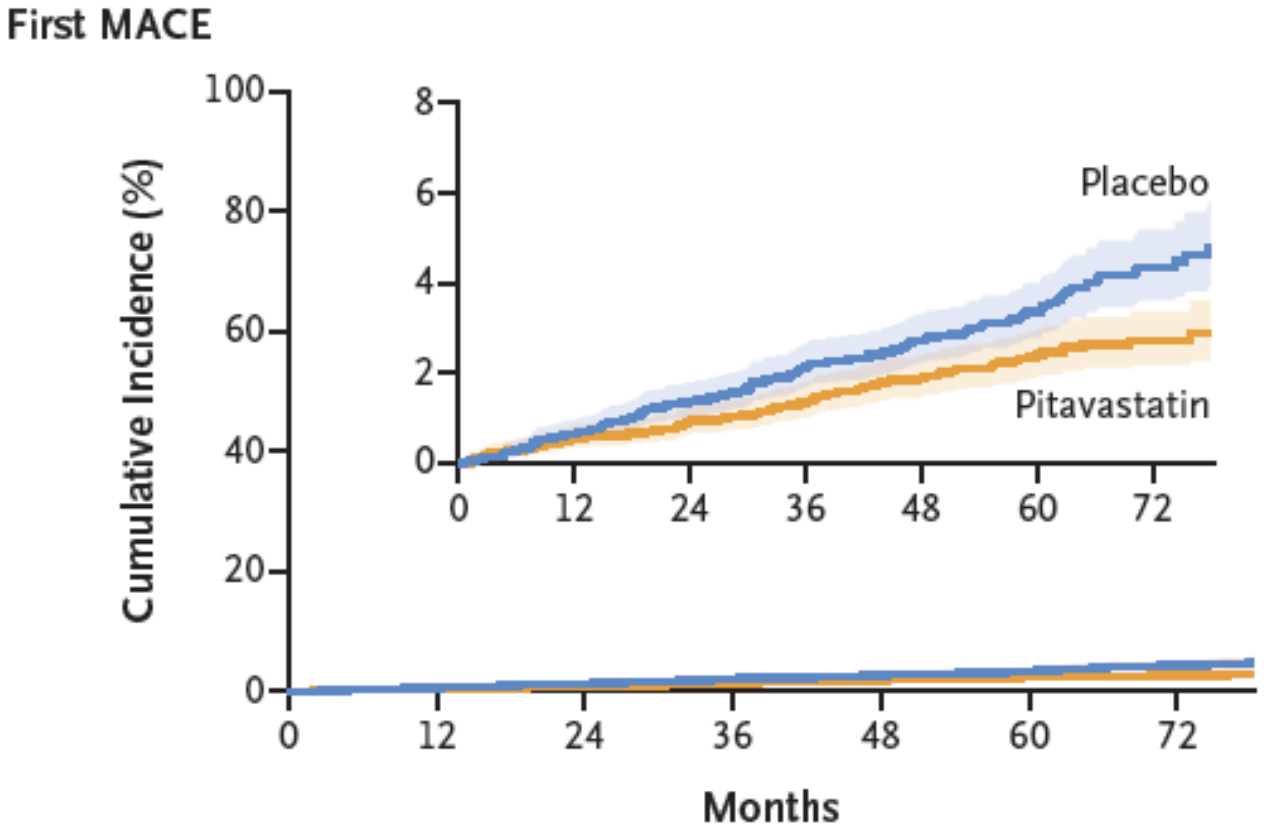
This article was published on July 23, 2023, at NEJM.org.

N Engl J Med 2023;389:687-99.
DOI: 10.1056/NEJMoa2304146

CME at NEJM.org

HR 0.65, 95% CI 0.48-0.90, p=0.002

Pitavastatin prevents MACE in every third patient



Grinspoon SK et al. N Engl J Med 2023

REPRIEVE Study

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 24, 2023 VOL. 389 NO. 8

Pitavastatin to Prevent Cardiovascular Disease in HIV Infection

Steven K. Grinspoon, M.D., Kathleen V. Fitch, M.S.N., Markella V. Zanni, M.D., Carl J. Fichtenbaum, M.D., Triin Umbleja, M.S., Judith A. Aberg, M.D., Edgar T. Overton, M.D., Carlos D. Malvestutto, M.D., M.P.H., Gerald S. Bloomfield, M.D., M.P.H., Judith S. Currier, M.D., Esteban Martinez, M.D., Ph.D., Jhoanna C. Roa, M.D., Marissa R. Diggs, B.A., Evelynne S. Fulda, B.A., Kayla Paradis, M.B.A., Stephen D. Wiviott, M.D., Borek Foldyna, M.D., Sara E. Looby, Ph.D., Patrice Desvigne-Nickens, M.D., Beverly Alston-Smith, M.D., Jorge Leon-Cruz, M.S., Sara McCallum, M.P.H., Udo Hoffmann, M.D., M.P.H., Michael T. Lu, M.D., M.P.H., Heather J. Ribaudo, Ph.D., and Pamela S. Douglas, M.D., for the REPRIEVE Investigators*

ABSTRACT

BACKGROUND
The risk of cardiovascular disease is increased among persons with human immunodeficiency virus (HIV) infection, so data regarding primary prevention strategies in this population are needed.

METHODS
In this phase 3 trial, we randomly assigned 7769 participants with HIV infection with a low-to-moderate risk of cardiovascular disease who were receiving antiretroviral therapy to receive daily pitavastatin calcium (at a dose of 4 mg) or placebo. The primary outcome was the occurrence of a major adverse cardiovascular event, which was defined as a composite of cardiovascular death, myocardial infarction, hospitalization for unstable angina, stroke, transient ischemic attack, peripheral arterial ischemia, revascularization, or death from an undetermined cause.

RESULTS
The median age of the participants was 50 years (interquartile range, 45 to 55); the median CD4 count was 621 cells per cubic millimeter (interquartile range, 448 to 827), and the HIV RNA value was below quantification in 5250 of 5997 participants (87.5%) with available data. The trial was stopped early for efficacy after a median follow-up of 5.1 years (interquartile range, 4.3 to 5.9). The incidence of a major adverse cardiovascular event was 4.81 per 1000 person-years in the pitavastatin group and 7.32 per 1000 person-years in the placebo group (hazard ratio, 0.65; 95% confidence interval [CI], 0.48 to 0.90; P=0.002). Muscle-related symptoms occurred in 91 participants (2.3%) in the pitavastatin group and in 53 (1.4%) in the placebo group; diabetes mellitus occurred in 206 participants (5.3%) and in 155 (4.0%), respectively.

CONCLUSIONS
Participants with HIV infection who received pitavastatin had a lower risk of a major adverse cardiovascular event than those who received placebo over a median follow-up of 5.1 years. (Funded by the National Institutes of Health and others; REPRIEVE ClinicalTrials.gov number, NCT02344290.)

The authors' affiliations are listed in the Appendix. Dr. Grinspoon can be contacted at sgrinspoon@mgh.harvard.edu or at the Metabolism Unit, Massachusetts General Hospital and Harvard Medical School, 55 Fruit St., 5 Longfellow Pl., Suite 207, Boston, MA 02114.

*A list of the REPRIEVE trial investigators is provided in the Supplementary Appendix, available at NEJM.org.

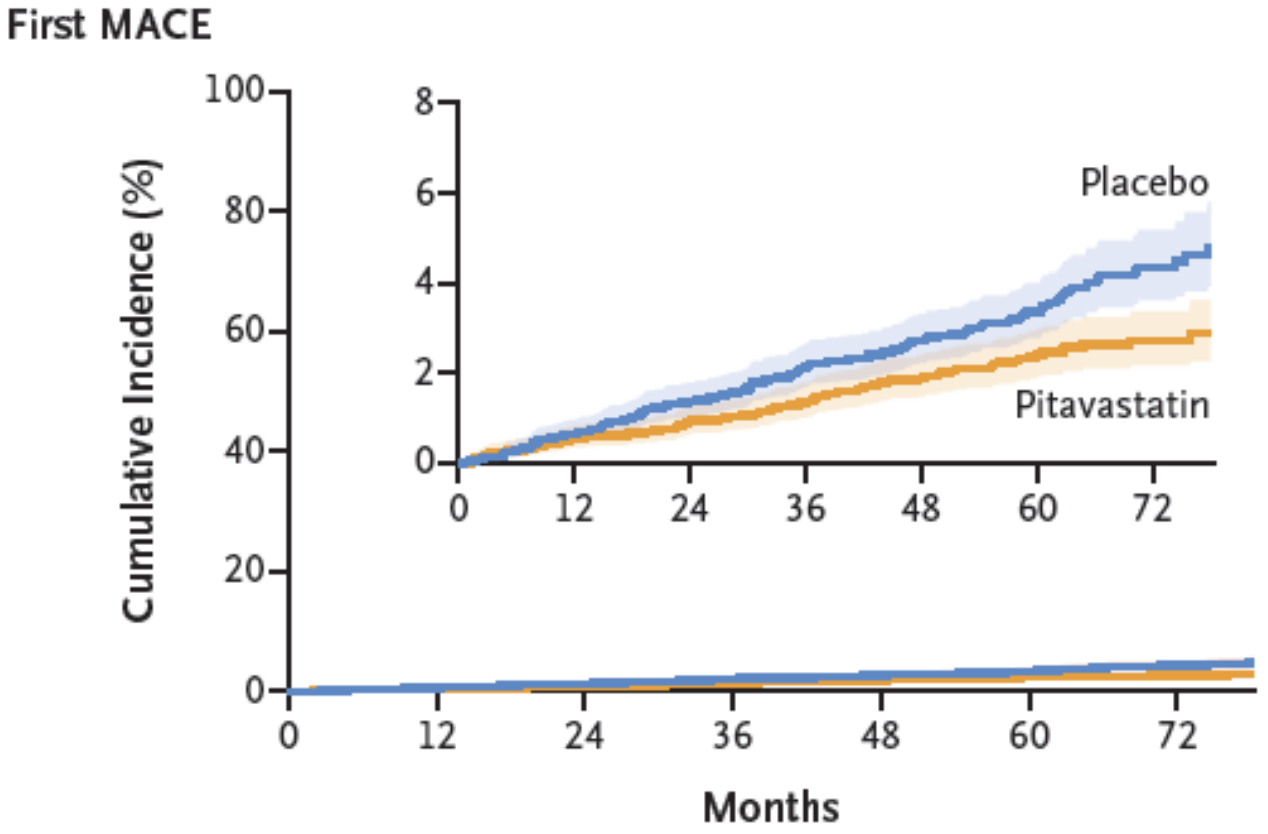
This article was published on July 23, 2023, at NEJM.org.

N Engl J Med 2023;389:687-99.
DOI: 10.1056/NEJMoa2304146

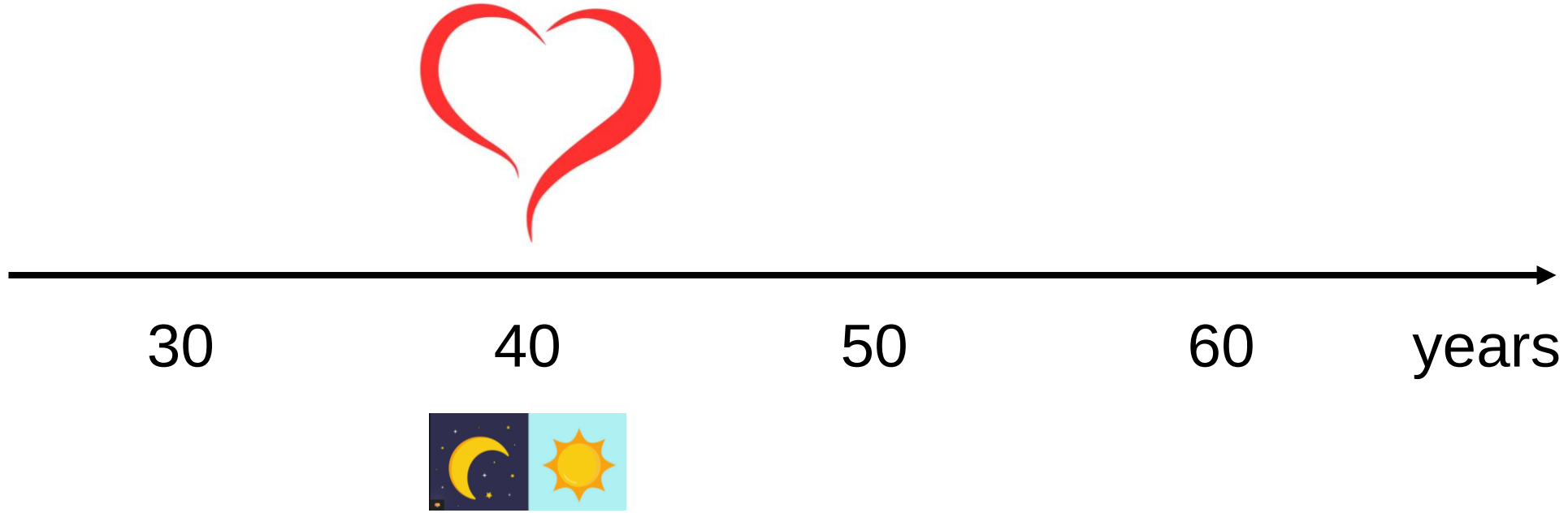
CME at NEJM.org

HR 0.65, 95% CI 0.48-0.90, p=0.002

Pitavastatin **delays** MACE in every third patient



Algorithm medicine, stupid!



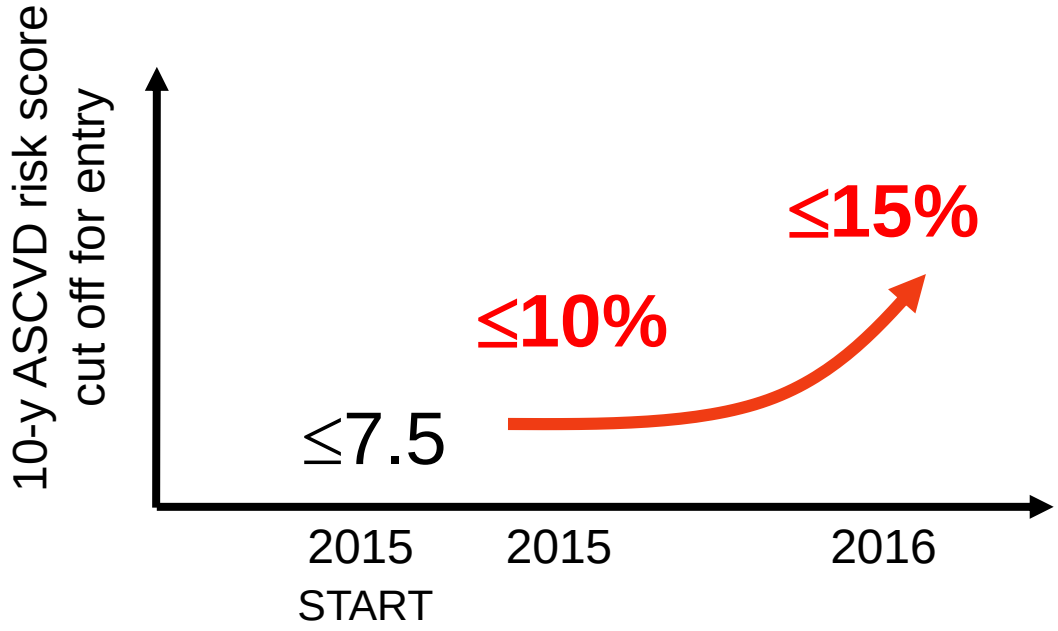
Biologically, nothing bad happens to your heart during the night you turn 40!

REPRIEVE Study required **reanimation** right at the start!

"a number of design changes have been made….

…the upper threshold of risk score for eligibility has been increased and an enrollment limit for participants with the lowest risk estimates has been set."

On the request of the DSMB!



REPRIEVE: The fine-print

Death as primary outcome!??

NIH National Library of Medicine
National Center for Biotechnology Information

ClinicalTrials.gov

Outcome Measure	Measure Description	
Time to the first event of a composite of major cardiovascular events	Includes atherosclerotic or other CVD death, nonfatal myocardial infarction, unstable angina hospitalization, coronary, carotid or peripheral arterial revascularization, nonfatal stroke or transient ischemic attack (TIA), peripheral arterial ischemia	Measured through participants' final study visit, at approximately Month 36 to 96

No!

Primary Outcome Measure

1. Time to the first event of a composite of major cardiovascular events (MACE)
    - Atherosclerotic or other cardiovascular disease death
    - Nonfatal myocardial infarction
    - Unstable angina hospitalization
    - Coronary, carotid, or peripheral arterial revascularization
    - Nonfatal stroke or transient ischemic attack
    - Peripheral arterial ischemia (acute or chronic limb ischemia, amputati

Yes?!

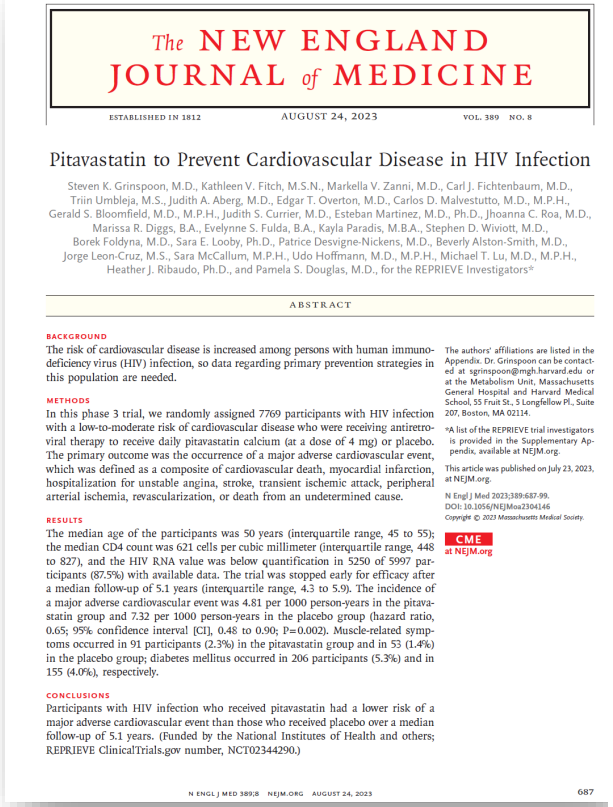
All primary events will be prospectively determined and adjudicated by an exp
Committee (CEC) based on standardized criteria used in prior cardiovascular trials and developed by consensus groups and the FDA.[2]

All deaths classified as undetermined by CEC will be considered primary MACE events for this outcome measure, as specified in the Clinical Event Committee Charter.


The NEW ENGLAND JOURNAL of MEDICINE

Pitavastatin to Prevent Cardiovascular Disease in HIV Infection

MACE?!



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 24, 2023 VOL. 389 NO. 8

Pitavastatin to Prevent Cardiovascular Disease in HIV Infection

Steven K. Grinspoon, M.D., Kathleen V. Fitch, M.S.N., Markella V. Zanni, M.D., Carl J. Fichtenbaum, M.D., Triin Umbleja, M.S., Judith A. Aberg, M.D., Edgar T. Overton, M.D., Carlos D. Malvestutto, M.D., M.P.H., Gerald S. Bloomfield, M.D., M.P.H., Judith S. Currier, M.D., Esteban Martinez, M.D., Ph.D., Jhoanna C. Roa, M.D., Marissa R. Diggs, B.A., Evelynne S. Fulda, B.A., Kayla Paradis, M.B.A., Stephen D. Wiviott, M.D., Borek Foldyna, M.D., Sara E. Looby, Ph.D., Patrice Desvigne-Nickens, M.D., Beverly Alston-Smith, M.D., Jorge Leon-Cruz, M.S., Sara McCallum, M.P.H., Udo Hoffmann, M.D., M.P.H., Michael T. Lu, M.D., M.P.H., Heather J. Ribaudo, Ph.D., and Pamela S. Douglas, M.D., for the REPRIEVE Investigators*.

ABSTRACT

BACKGROUND

The risk of cardiovascular disease is increased among persons with human immunodeficiency virus (HIV) infection, so data regarding primary prevention strategies in this population are needed.

METHODS

In this phase 3 trial, we randomly assigned 7769 participants with HIV infection with a low-to-moderate risk of cardiovascular disease who were receiving antiretroviral therapy to receive daily pitavastatin calcium (at a dose of 4 mg) or placebo. The primary outcome was the occurrence of a major adverse cardiovascular event, which was defined as a composite of cardiovascular death, myocardial infarction, hospitalization for unstable angina, stroke, transient ischemic attack, peripheral arterial ischemia, revascularization, or death from an undetermined cause.

RESULTS

The median age of the participants was 50 years (interquartile range, 45 to 55); the median CD4 count was 621 cells per cubic millimeter (interquartile range, 448 to 827), and the HIV RNA value was below quantification in 5250 of 5997 participants (87.5%) with available data. The trial was stopped early for efficacy after a median follow-up of 5.1 years (interquartile range, 4.3 to 5.9). The incidence of a major adverse cardiovascular event was 4.81 per 1000 person-years in the pitavastatin group and 7.32 per 1000 person-years in the placebo group (hazard ratio, 0.65; 95% confidence interval [CI], 0.48 to 0.90; P=0.002). Muscle-related symptoms occurred in 91 participants (2.3%) in the pitavastatin group and in 53 (1.4%) in the placebo group; diabetes mellitus occurred in 206 participants (5.3%) and in 155 (4.0%), respectively.

CONCLUSIONS

Participants with HIV infection who received pitavastatin had a lower risk of a major adverse cardiovascular event than those who received placebo over a median follow-up of 5.1 years. (Funded by the National Institutes of Health and others; REPRIEVE ClinicalTrials.gov number, NCT02344290.)

The authors' affiliations are listed in the Appendix. Dr. Grinspoon can be contacted at sgrinspoon@mgh.harvard.edu or at the Metabolism Unit, Massachusetts General Hospital and Harvard Medical School, 55 Fruit St., 5 Longfellow Pl., Suite 207, Boston, MA 02114.

*A list of the REPRIEVE trial investigators is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on July 23, 2023, at NEJM.org.

N Engl J Med 2023;389:687-99.
DOI: 10.1056/NEJMoa2304146

CME at NEJM.org

Table S2: Details of First MACE Endpoints

Event type		Total (N=225)	Pitavastatin (N=89)	Placebo (N=136)
All Cerebrovascular Events (Stroke or TIA) — no. (%)		**72 (32)**	**29 (33)**	**43 (32)**
Stroke	Ischemic	43 (19)	15 (17)	28 (21)
	Hemorrhagic	10 (4)	2 (2)	8 (6)
	Undetermined	2 (1)	1 (1)	1 (1)
Transient Ischemic Attack (TIA)		17 (8)	11 (12)	6 (4)
All Cardiac Ischemia or MI Events — no. (%)		**71 (32)**	**25 (28)**	**46 (34)**
Myocardial Infarction	Type 1	50 (22)	16 (18)	34 (25)
	Type 2	13 (6)	7 (8)	6 (4)
Unstable Angina		8 (4)	2 (2)	6 (4)
All Deaths — no. (%)		**63 (28)**	**28 (31)**	**35 (26)**
CV Death	Sudden Cardiac Death	16 (7)	8 (9)	8 (6)
	Cardiovascular Causes	1 (0)	1 (1)	0 (0)
	Cardiovascular Hemorrhage	1 (0)	0 (0)	1 (1)
	Heart Failure	1 (0)	1 (1)	0 (0)
Undetermined		44 (20)	18 (20)	26 (19)
All Cardiac Catheterization or Revascularization Events — no. (%)		**12 (5)**	**5 (6)**	**7 (5)**
Percutaneous (PCI)	Elective	9 (4)	3 (3)	6 (4)
	Urgent	1 (0)	1 (1)	0 (0)
Surgical (CABG)	Elective	2 (1)	1 (1)	1 (1)
All Peripheral Arterial Ischemia Events — no. (%)		**4 (2)**	**2 (2)**	**2 (1)**
Acute Limb Ischemia (ALI)		2 (1)	1 (1)	1 (1)
Critical Limb Ischemia (CLI)		2 (1)	1 (1)	1 (1)
All Peripheral Arterial Revascularization Events — no. (%)		**3 (1)**	**0 (0)**	**3 (2)**
Percutaneous	Elective	2 (1)	0 (0)	2 (1)
Surgical	Elective	1 (0)	0 (0)	1 (1)

MACE = 3 outcomes

MI

Stroke

CV death

The damage: Type 2 Diabetes!

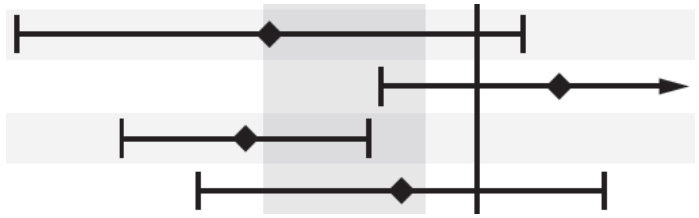
	Placebo Incidence Rate (95%CI)	**Pitavastatin** Incidence Rate (95%CI)	**Incidence Rate Ratio**
T2D	1.13 (0.99-1.30)	0.84 (0.72-0.99)	1.35 (1.09-1.66)

	Placebo n=	**Pitavastatin** n=	
T2D	155	206	**caused n=51!!!!**
MACE	136	89	delayed n=47

	Placebo Incidence Rate (95%CI)	Pitavastatin Incidence Rate (95%CI)	Incidence Rate Ratio
T2D	0.84 (0.72-0.99)	1.13 (0.99-1.30)	**1.35** (1.09-1.66)
Myalgia, muscle weakness, myopathy, grade ≥3 or treatment	0.28 (0.22-0.37)	0.49 (0.40-0.61)	**1.74** (1.24-2.45)

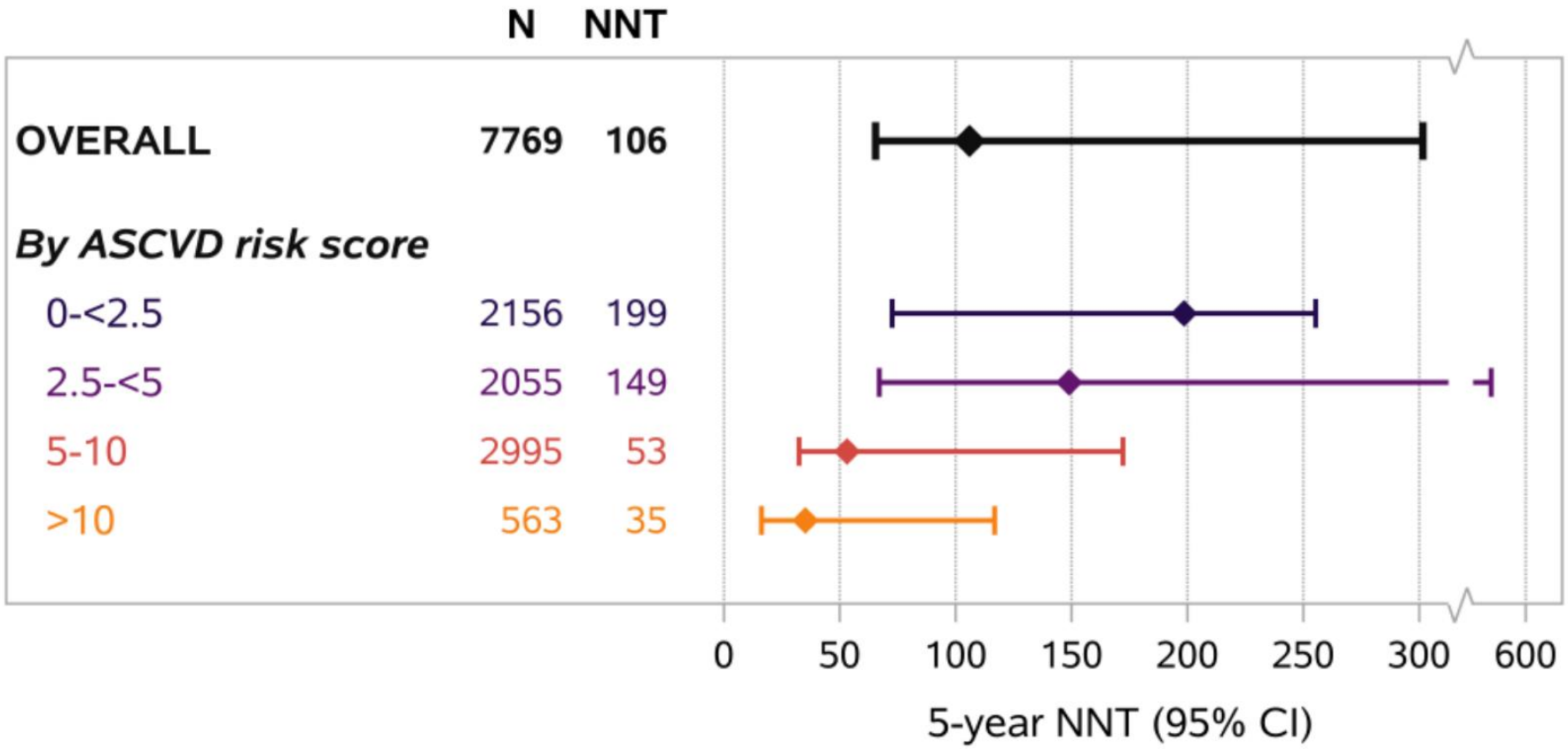
REPRIEVE: Big study, tiny evidence!

ASCVD risk scor	Pitavastatin	Placebo	Pitavastatin	Placebo	Hazard Ratio (95% CI)
	no. of participants		*no./1000 person-yr (no. of events)*		
0 to <2.5%	1096	1060	1.6 (9)	3.1 (17)	0.51 (0.23–1.16)
2.5 to <5%	1030	1025	5.3 (27)	4.1 (21)	1.30 (0.73–2.30)
5 to 10%	1474	1521	5.5 (36)	11.5 (78)	0.48 (0.32–0.71)
>10%	288	275	13.9 (17)	17.5 (20)	0.79 (0.41–1.50)

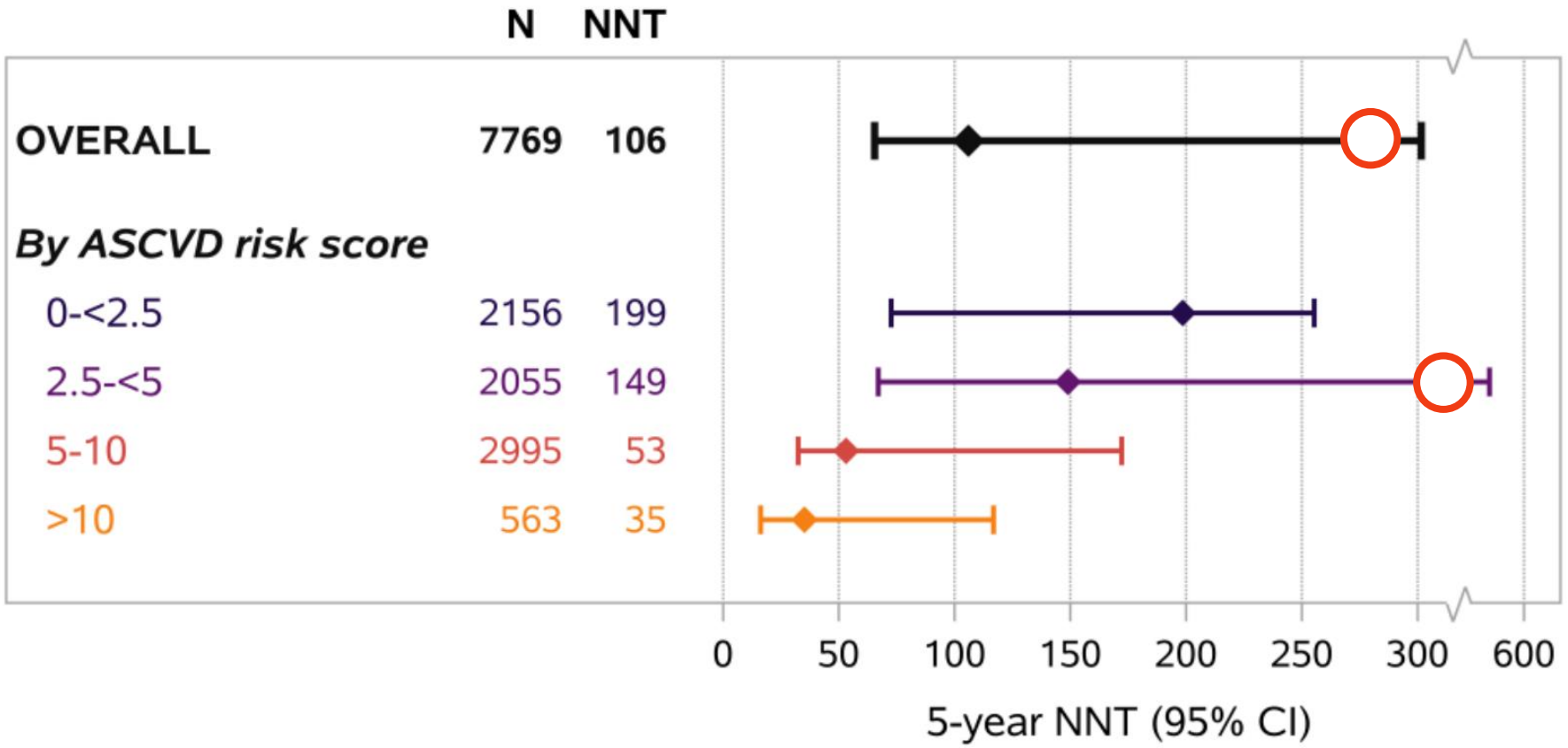


Only 1,474 (of 7,769) PWH were able to benefit from Pitavastatin during the study **(18.9%)!!!**

5-Yr Number Needed To Treat (NNT) to Prevent One MACE



5-Yr Number Needed To Treat (NNT) to Prevent One MACE



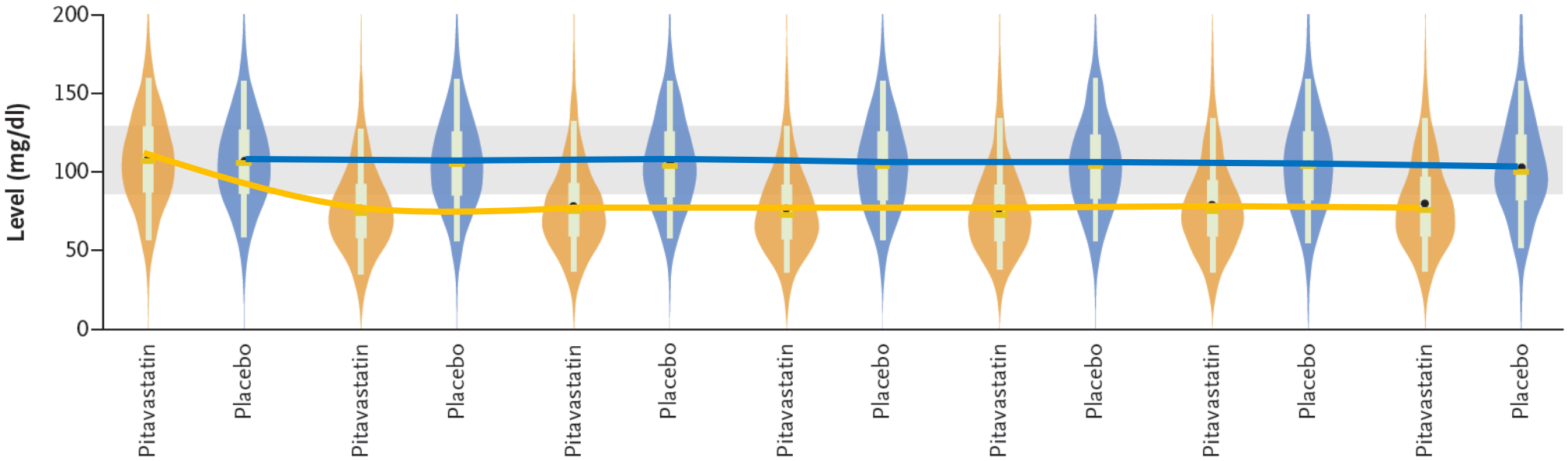
1y NTT=1250

1y NTT=1700

Grinspoon et al. NEJM 2023

Pitavastatin to Prevent Cardiovascular Disease in HIV Infection

LDL-Cholesterol



	Entry		Month 12		Month 24		Month 36		Month 48		Month 60		Month 72	
No.	3681	3666	3340	3321	3079	3117	2790	2770	2371	2352	1458	1454	652	605
Median	107	106	74	105	75	104	73	104	73	104	75	104	76	100
Q1–Q3	87–129	86–127	58–93	85–126	59–93	84–126	57–92	82–126	56–92	83–124	59–95	82–126	59–97	82–124
Mean	108	107	77	106	78	106	77	105	77	105	79	105	80	103
95% CI	107–109	106–108	76–78	105–107	77–79	105–107	76–78	104–106	76–78	104–106	77–80	103–107	78–83	100–106

Real life adherence to statine therapy in prim. prevention

Adherence

VALUE IN HEALTH 18 (2015) 896–905

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/jval

ELSEVIER

Impact of Statin Adherence on Cardiovascular Morbidity and All-Cause Mortality in the Primary Prevention of Cardiovascular Disease: A Population-Based Cohort Study in Finland

Piia K. Ronnanheimo, MSc(Pharm)[1,2], Pekka Tiittanen, MSc[2], Juha Hartikainen, MD[3], Arja Helin-Salmivaara, MD, PhD[1], Risto Huupponen, MD[1,4], Jussi Vahtera, MD[5], Maarit Jaana Korhonen, LicSc(Pharm), PhD[1,*]

[1]Department of Pharmacology, Drug Development and Therapeutics, University of Turku, Turku, Finland; [2]Finnish Medicines Agency, Kuopio, Finland; [3]Heart Center, Kuopio University Hospital, School of Medicine, University of Eastern Finland, Kuopio, Finland; [4]Clinical Pharmacology Unit, Tykslab, Turku University Hospital, Turku, Finland; [5]Department of Public Health, University of Turku, Turku, Finland

ABSTRACT

Objectives: To assess the extent to which adherence to statins is associated with the incidence of cardiovascular (CV) events and all-cause mortality in the primary prevention of CV diseases and whether different analytical approaches influence the observed associations. **Methods:** This population-based cohort study used data from Finnish registers. The cohort included 97,575 new statin users aged 45 to 75 years in 2001 to 2004 with no CV diseases at baseline. Exposure was defined as adherence to statins (proportion of days covered [PDC]). The primary outcome was any CV event or death during a 3-year follow-up. Different analytical approaches, including multivariable-adjusted Cox regression, inverse probability weighting with time-varying adherence, and propensity score calibration, were used. **Results:** During the first year of follow-up, 53% displayed good (PDC ≥ 80%), 26% had intermediate (PDC 40%–79%), and 21% exhibited poor (PDC <40%) adherence. After adjustment for sociodemographic and clinical covariates, a 29% relative risk reduction (hazard ratio [HR] 0.75; 95% confidence interval [CI] 0.71–0.79) was observed in the rate of any CV event or death among good versus poor adherers. Good adherers also had a lower incidence than poor adherers of acute coronary syndrome (HR 0.56; 95% CI 0.49–0.65) and acute cerebrovascular disease events (HR 0.67; 95% CI 0.60–0.76). The different analytical approaches achieved comparable results for all the outcomes. **Conclusions:** The incidence of CV events and mortality was higher in poor versus good adherers. Different analytical methods that took into account changes in adherence and confounding at baseline did not appreciably affect the results.

Keywords: cardiovascular disease, healthy adherer effect, medication adherence, statins.

Introduction

Several large randomized controlled trials (RCTs) and meta-analyses have provided convincing evidence for the benefits of statins in the primary and secondary prevention of cardiovascular (CV) events [1,2]. A recent meta-analysis including 18 RCTs and almost 57,000 high-risk primary prevention patients have demonstrated that statins can reduce the risk of cardiac events by 27% and all-cause mortality by 14% during a median 5 years of follow-up [3].

In RCTs, the adherence to study medication has generally been good. In real life, however, many patients adhere poorly to preventive medications, such as statins, and the benefits observed in highly adherent RCT populations may not be substantiated. A meta-analysis of 44 epidemiological studies estimated that the prevalence of *poor adherence* to statins (defined as consuming <80% of the prescribed medication) is as high as 46%, which would translate to 47 excess CV deaths per 100,000 Americans offered statin therapy per year [4]. Only one of the studies, however, included in that meta-analysis investigated the risk of CV events in relation to statin adherence in primary prevention [5]. This observational study found that good adherers had a 20% lower risk of CV events than poor adherers. In fact, some observational studies of primary prevention populations have reported much larger reductions in the risk of CV events (up to ~40%) and all-cause mortality (up to 45%) for high versus low levels of statin adherence [5–12].

In light of the RCT evidence, the findings of observational studies may exaggerate the risk of CV events and death associated with poor statin adherence. Most of these studies have failed to consider how differences in patients' overall adherence

* Address correspondence to: Maarit Jaana Korhonen, Department of Pharmacology, Drug Development and Therapeutics, 20014 University of Turku, Turku, Finland.
E-mail: maarit.korhonen@utu.fi.

1098-3015$36.00 – see front matter © 2015 Published by Elsevier Inc. on behalf of International Society for Pharmacoeconomics and Outcomes Research (ISPOR).
http://dx.doi.org/10.1016/j.jval.2015.06.002

97,575 new statin users aged 45-75 with no CV diseases at baseline:
53% good adherence

Good adherers 44% less MI
& 33% stroke than poor adherence

CV Health in PLWH Without Existing ASCVD

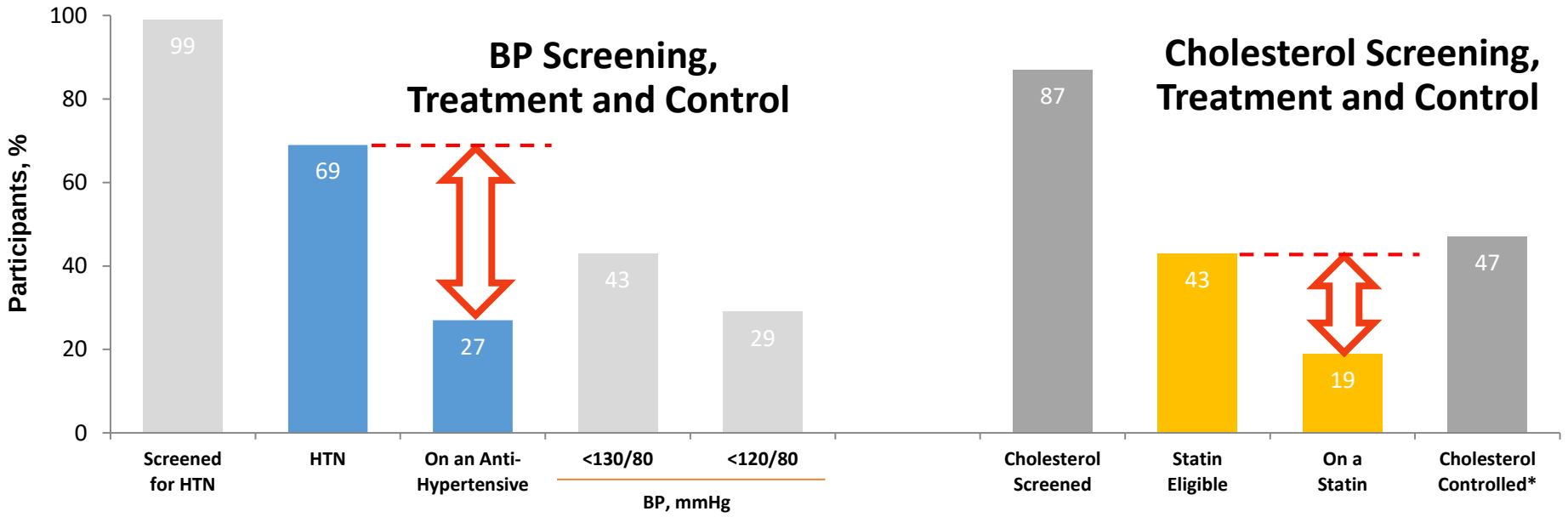
ICD-10 and EHR data: Retrospective analysis (San Francisco), 2019-2022

N=2,567

PLWH aged ≥40 years without documented ASCVD at 3 HIV clinics[1]

Outcome

ASCVD screening, treatment and control; and CV health (defined by AHA Life's Simple 7 metrics[2,3] for nicotine exposure, BMI, total cholesterol, fasting glucose and BP)



*Non-HDL <130 mg/dL. AHA, American Heart Association; ASCVD, atherosclerotic cardiovascular disease; BP, blood pressure; EHR, electronic health record; HTN, hypertension; ICD-10, International Classification of Diseases, 10th Edition. 1. McLaughlin MM, et al. IAS 2023, Poster EPB0167; 2. Lloyd-Jones DM, et al. Circulation 2010;121:586-613; 3. AHA. https://playbook.heart.org/lifes-simple-7/ (accessed July 31, 2023)

Colonoscopy (Europe) 2022

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 27, 2022 VOL. 387 NO. 17

Effect of Colonoscopy Screening on Risks of Colorectal Cancer and Related Death

M. Bretthauer, M. Løberg, P. Wieszczy, M. Kalager, L. Emilsson, K. Garborg, M. Rupinski, E. Dekker, M. Spaander, M. Bugajski, Ø. Holme, A.G. Zauber, N.D. Pilonis, A. Mroz, E.J. Kuipers, J. Shi, M.A. Hernán, H.-O. Adami, J. Regula, G. Hoff, and M.F. Kaminski, for the NordICC Study Group*

ABSTRACT

BACKGROUND

Although colonoscopy is widely used as a screening test to detect colorectal cancer, its effect on the risks of colorectal cancer and related death is unclear.

METHODS

We performed a pragmatic, randomized trial involving presumptively healthy men and women 55 to 64 years of age drawn from population registries in Poland, Norway, Sweden, and the Netherlands between 2009 and 2014. The participants were randomly assigned in a 1:2 ratio either to receive an invitation to undergo a single screening colonoscopy (the invited group) or to receive no invitation or screening (the usual-care group). The primary end points were the risks of colorectal cancer and related death, and the secondary end point was death from any cause.

RESULTS

Follow-up data were available for 84,585 participants in Poland, Norway, and Sweden — 28,220 in the invited group, 11,843 of whom (42.0%) underwent screening, and 56,365 in the usual-care group. A total of 15 participants had major bleeding after polyp removal. No perforations or screening-related deaths occurred within 30 days after colonoscopy. During a median follow-up of 10 years, 259 cases of colorectal cancer were diagnosed in the invited group as compared with 622 cases in the usual-care group. In intention-to-screen analyses, the risk of colorectal cancer at 10 years was 0.98% in the invited group and 1.20% in the usual-care group, a risk reduction of 18% (risk ratio, 0.82; 95% confidence interval [CI], 0.70 to 0.93). The risk of death from colorectal cancer was 0.28% in the invited group and 0.31% in the usual-care group (risk ratio, 0.90; 95% CI, 0.64 to 1.16). The number needed to invite to undergo screening to prevent one case of colorectal cancer was 455 (95% CI, 270 to 1429). The risk of death from any cause was 11.03% in the invited group and 11.04% in the usual-care group (risk ratio, 0.99; 95% CI, 0.96 to 1.04).

CONCLUSIONS

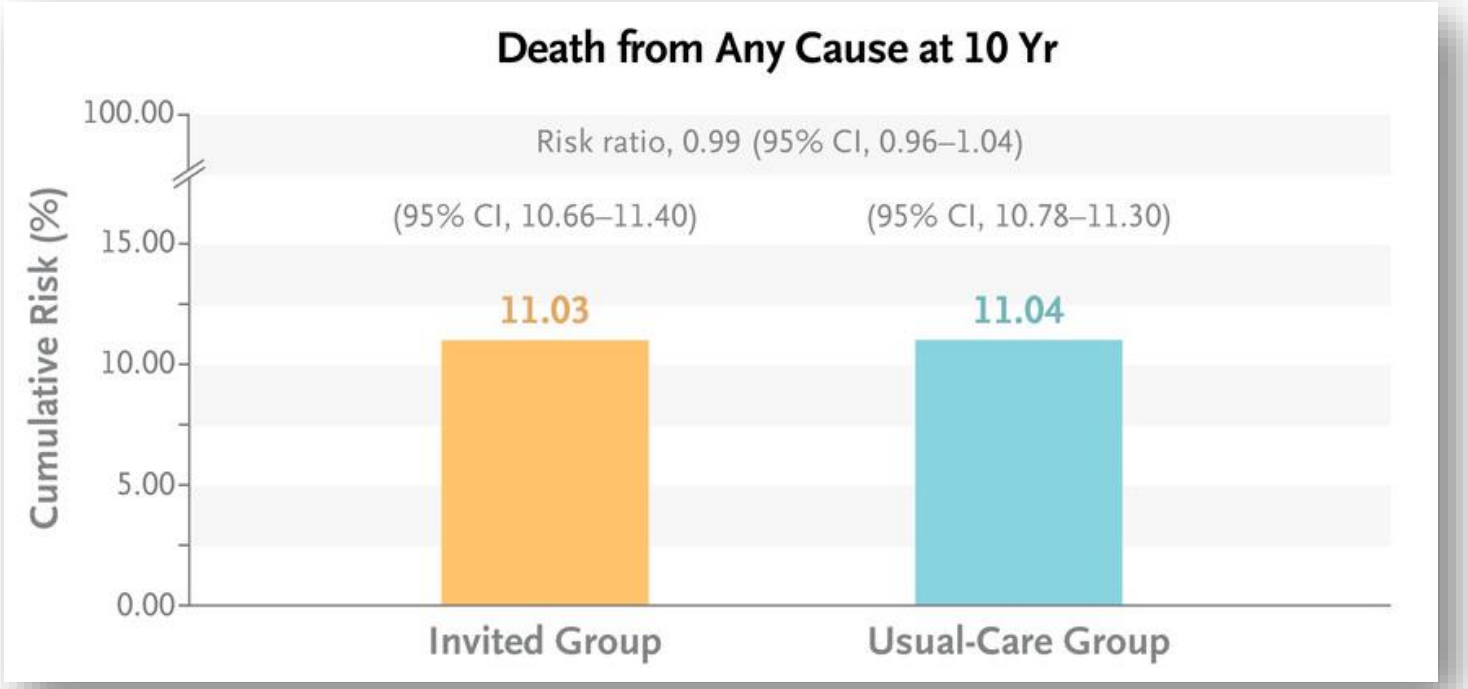
In this randomized trial, the risk of colorectal cancer at 10 years was lower among participants who were invited to undergo screening colonoscopy than among those who were assigned to no screening. (Funded by the Research Council of Norway and others; NordICC ClinicalTrials.gov number, NCT00883792.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Bretthauer can be contacted at michael.bretthauer@medisin.uio.no or at the Clinical Effectiveness Research Group, University of Oslo, Postbox 1089, Blindern, N-0318 Oslo, Norway.

*The members of the NordICC Study Group are listed in the Supplementary Appendix, available at NEJM.org.

This article was published on October 9, 2022, at NEJM.org.

N Engl J Med 2022;387:1547-56.
DOI: 10.1056/NEJMoa2208375



Cardiovascular Screening (Denmark) 2022

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Five-Year Outcomes of the Danish Cardiovascular Screening (DANCAVAS) Trial

Jes S. Lindholt, M.D., D.M.Sc., Rikke Søgaard, Ph.D., Lars M. Rasmussen, M.D., D.M.Sc., Anne Mejldal, Ph.D., Jess Lambrechtsen, Ph.D., Flemming H. Steffensen, Ph.D., Lars Frost, M.D., D.M.Sc., Kenneth Egstrup, M.D., D.M.Sc., Grazina Urbonaviciene, Ph.D., Martin Busk, Ph.D., and Axel Cosmus Pyndt Diederichsen, Ph.D.

ABSTRACT

BACKGROUND

Limited data suggest a benefit of population-based screening for cardiovascular disease with respect to the risk of death.

METHODS

We performed a population-based, parallel-group, randomized, controlled trial involving men 65 to 74 years of age living in 15 Danish municipalities. The participants were randomly assigned in a 1:2 ratio to undergo screening (the invited group) or not to undergo screening (the control group) for subclinical cardiovascular disease. Randomization was based on computer-generated random numbers and stratified according to municipality. Only the control group was unaware of the trial-group assignments. Screening included noncontrast electrocardiography-gated computed tomography to determine the coronary-artery calcium score and to detect aneurysms and atrial fibrillation, ankle–brachial blood-pressure measurements to detect peripheral artery disease and hypertension, and a blood sample to detect diabetes mellitus and hypercholesterolemia. The primary outcome was death from any cause.

RESULTS

A total of 46,611 participants underwent randomization. After exclusion of 85 men who had died or emigrated before being invited to undergo screening, there were 16,736 men in the invited group and 29,790 men in the control group; 10,471 of the men in the invited group underwent screening (62.6%). In intention-to-treat analyses, after a median follow-up of 5.6 years, 2106 men (12.6%) in the invited group and 3915 men (13.1%) in the control group had died (hazard ratio, 0.95; 95% confidence interval [CI], 0.90 to 1.00; P=0.06). The hazard ratio for stroke in the invited group, as compared with the control group, was 0.93 (95% CI, 0.86 to 0.99); for myocardial infarction, 0.91 (95% CI, 0.81 to 1.03); for aortic dissection, 0.95 (95% CI, 0.61 to 1.49); and for aortic rupture, 0.81 (95% CI, 0.49 to 1.35). There were no significant between-group differences in safety outcomes.

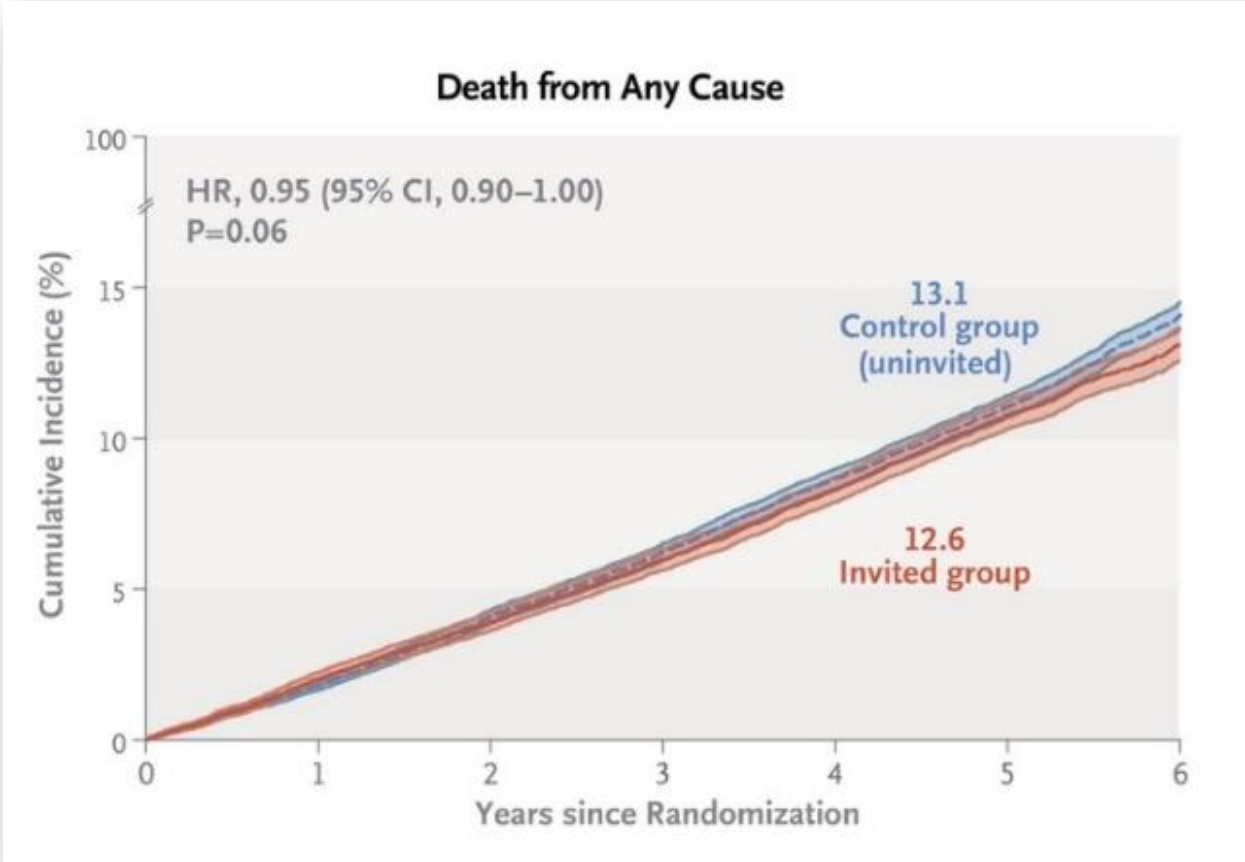
CONCLUSIONS

After more than 5 years, the invitation to undergo comprehensive cardiovascular screening did not significantly reduce the incidence of death from any cause among men 65 to 74 years of age. (Funded by the Southern Region of Denmark and others; DANCAVAS ISRCTN Registry number, ISRCTN12157806.)

From the Departments of Cardiac, Thoracic, and Vascular Surgery (J.S.L., R.S.), Clinical Biochemistry and Pharmacology (L.M.R.), and Cardiology (A.C.P.D.), Elite Research Center for Individualized Medicine in Arterial Diseases, and the Open Patient Data Explorative Network (A.M.), Odense University Hospital, Clinical Institute, University of Southern Denmark (R.S.), Odense, the Department of Cardiology, Odense University Hospital, Svendborg (J.L., K.E.), the Department of Cardiology, Lillebaelt Hospital, Vejle (F.H.S., M.B.), and the Department of Cardiology, Diagnostic Center, Regional Hospital Silkeborg, Silkeborg (L.F., G.U.) — all in Denmark. Dr. Lindholt can be contacted at jes.sanddal.lindholt@rsyd.dk or at the Department of Cardiac, Thoracic, and Vascular Surgery, Odense University Hospital, J.B. Winsløv Vej 4, DK-5000 Odense, Denmark.

This article was published on August 27, 2022, at NEJM.org.

N Engl J Med 2022;387:1385-94.
DOI: 10.1056/NEJMoa2208681



Vitamin D supplementation 2022

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 28, 2022 VOL. 387 NO. 4

Supplemental Vitamin D and Incident Fractures in Midlife and Older Adults

Meryl S. LeBoff, M.D., Sharon H. Chou, M.D., Kristin A. Ratliff, B.A., Nancy R. Cook, Sc.D., Bharti Khurana, M.D., Eunjung Kim, M.S., Peggy M. Cawthon, Ph.D., M.P.H., Douglas C. Bauer, M.D., Dennis Black, Ph.D., J. Chris Gallagher, M.D., I-Min Lee, M.B., B.S., Sc.D., Julie E. Buring, Sc.D., and JoAnn E. Manson, M.D., Dr.P.H.

ABSTRACT

BACKGROUND

Vitamin D supplements are widely recommended for bone health in the general population, but data on whether they prevent fractures have been inconsistent.

METHODS

In an ancillary study of the Vitamin D and Omega-3 Trial (VITAL), we tested whether supplemental vitamin D_3 would result in a lower risk of fractures than placebo. VITAL was a two-by-two factorial, randomized, controlled trial that investigated whether supplemental vitamin D_3 (2000 IU per day), n–3 fatty acids (1 g per day), or both would prevent cancer and cardiovascular disease in men 50 years of age or older and women 55 years of age or older in the United States. Participants were not recruited on the basis of vitamin D deficiency, low bone mass, or osteoporosis. Incident fractures were reported by participants on annual questionnaires and adjudicated by centralized medical-record review. The primary end points were incident total, nonvertebral, and hip fractures. Proportional-hazards models were used to estimate the treatment effect in intention-to-treat analyses.

RESULTS

Among 25,871 participants (50.6% women [13,085 of 25,871] and 20.2% Black [5106 of 25,304]), we confirmed 1991 incident fractures in 1551 participants over a median follow-up of 5.3 years. Supplemental vitamin D_3, as compared with placebo, did not have a significant effect on total fractures (which occurred in 769 of 12,927 participants in the vitamin D group and in 782 of 12,944 participants in the placebo group; hazard ratio, 0.98; 95% confidence interval [CI], 0.89 to 1.08; P=0.70), nonvertebral fractures (hazard ratio, 0.97; 95% CI, 0.87 to 1.07; P=0.50), or hip fractures (hazard ratio, 1.01; 95% CI, 0.70 to 1.47; P=0.96). There was no modification of the treatment effect according to baseline characteristics, including age, sex, race or ethnic group, body-mass index, or serum 25-hydroxyvitamin D levels. There were no substantial between-group differences in adverse events as assessed in the parent trial.

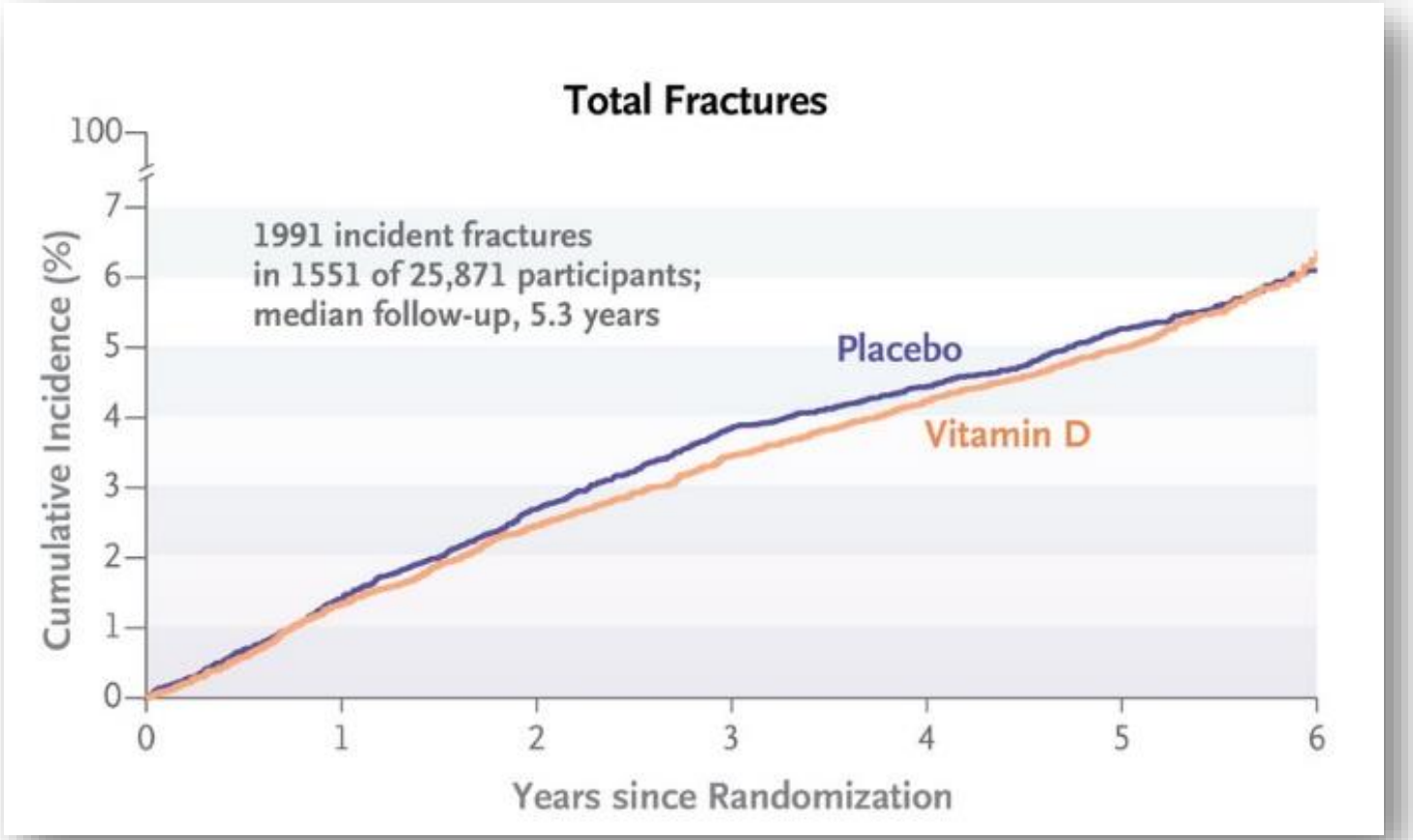
CONCLUSIONS

Vitamin D_3 supplementation did not result in a significantly lower risk of fractures than placebo among generally healthy midlife and older adults who were not selected for vitamin D deficiency, low bone mass, or osteoporosis. (Funded by the National Institute of Arthritis and Musculoskeletal and Skin Diseases; VITAL ClinicalTrials.gov number, NCT01704859.)

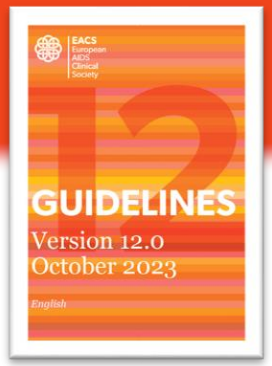
From the Division of Endocrinology, Diabetes, and Hypertension (M.S.L., S.H.C., K.A.R.), the Division of Preventive Medicine (N.R.C., E.K., I.-M.L., J.E.B., J.E.M.), and the Department of Radiology (B.K.), Brigham and Women's Hospital, Harvard Medical School (M.S.L., S.H.C., N.R.C., B.K., I.-M.L., J.E.B., J.E.M.), and the Department of Epidemiology, Harvard T.H. Chan School of Public Health (N.R.C., I.-M.L., J.E.B., J.E.M.) — all in Boston; California Pacific Medical Center Research Institute (P.M.C.), and the Departments of Epidemiology and Biostatistics (P.M.C., D.C.B., D.B.) and Medicine (D.C.B.), University of California, San Francisco — both in San Francisco; and the Department of Endocrinology, Creighton University School of Medicine, Omaha, NE (J.C.G.). Dr. LeBoff can be contacted at mleboff@bwh.harvard.edu or at the Division of Endocrinology, Diabetes, and Hypertension, Brigham and Women's Hospital, 221 Longwood Ave., Boston, MA 02115.

N Engl J Med 2022;387:299-309.
DOI: 10.1056/NEJMoa2202106

CME at NEJM.org



Cardiovascular Disease Risk Assessment: **Bring your own!**



ESC European Society of Cardiology
European Heart Journal (2021) **42**, 2439–2454
doi:10.1093/eurheartj/ehab309

CLINICAL RESEARCH
Epidemiology and prevention

SCORE2 risk prediction algorithms: new models to estimate 10-year risk of cardiovascular disease in Europe

SCORE2 working group and ESC Cardiovascular risk collaboration

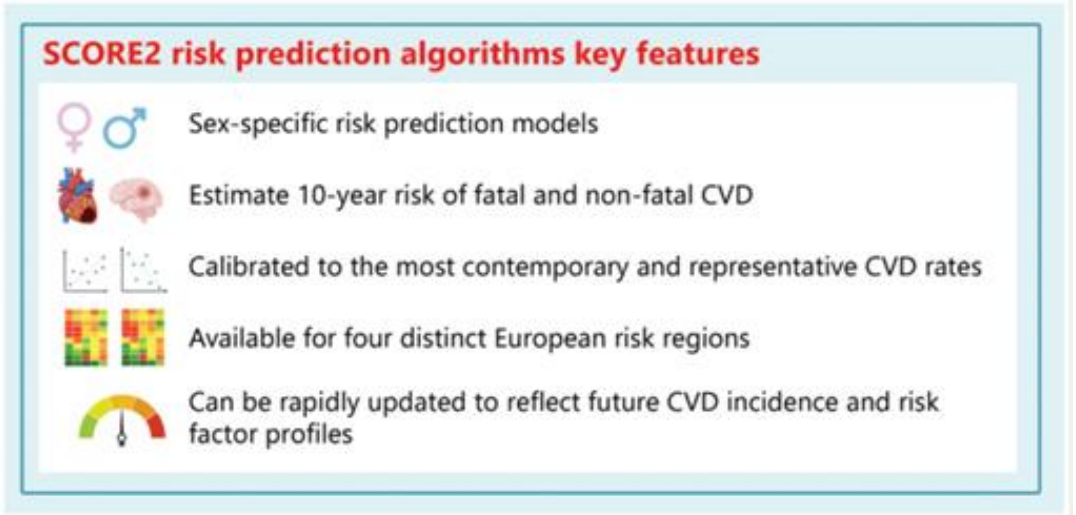
Received 25 January 2021; revised 8 March 2021; editorial decision 4 May 2021; accepted 5 May 2021; online publish-ahead-of-print 13 June 2021

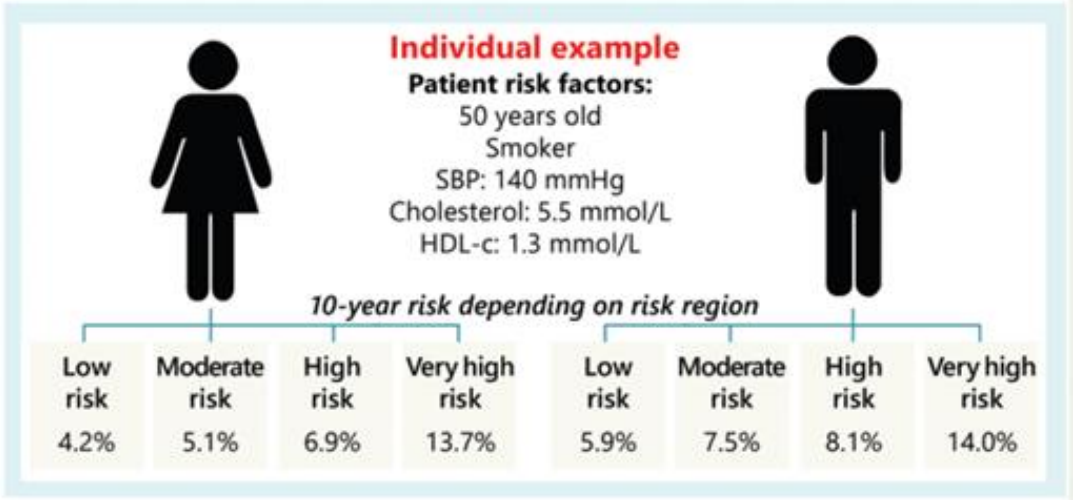
See page 2468 for the editorial comment on this article (doi: 10.1093/eurheartj/ehab310)

Aims The aim of this study was to develop, validate, and illustrate an updated prediction model (SCORE2) to estimate 10-year fatal and non-fatal cardiovascular disease (CVD) risk in individuals without previous CVD or diabetes aged 40–69 years in Europe.

Methods and results We derived risk prediction models using individual-participant data from 45 cohorts in 13 countries (677 684 individuals, 30 121 CVD events). We used sex-specific and competing risk-adjusted models, including age, smoking status, systolic blood pressure, and total- and HDL-cholesterol. We defined four risk regions in Europe according to country-specific CVD mortality, recalibrating models to each region using expected incidences and risk factor distributions. Region-specific incidence was estimated using CVD mortality and incidence data on 10 776 466 individuals. For external validation, we analysed data from 25 additional cohorts in 15 European countries (1 133 181 individuals, 43 492 CVD events). After applying the derived risk prediction models to external validation cohorts, C-indices ranged from 0.67 (0.65–0.68) to 0.81 (0.76–0.86). Predicted CVD risk varied several-fold across European regions. For example, the estimated 10-year CVD risk for a 50-year-old smoker, with a systolic blood pressure of 140 mmHg, total cholesterol of 5.5 mmol/L, and HDL-cholesterol of 1.3 mmol/L, ranged from 5.9% for men in low-risk countries to 14.0% for men in very high-risk countries, and from 4.2% for women in low-risk countries to 13.7% for women in very high-risk countries.

Conclusion SCORE2—a new algorithm derived, calibrated, and validated to predict 10-year risk of first-onset CVD in European populations—enhances the identification of individuals at higher risk of developing CVD across Europe.





CVD risk scores: What a mess!!!

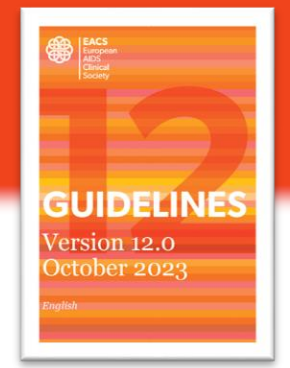
ACC/AHA and ESC 10-Year ASCVD Risk Categories

ESC Risk Category	ESC (SCORE2/SCORE2-OP)	ACC/AHA (PCE)	ACC/AHA Risk Category
Low-moderate	<2.5% (age <50 y) <5% (age 50-69 y) <7.5% (age ≥70 y)	<5% (age 40-75 y)	Low
High	2.5-<7.5% (age <50 y) 5-<10% (age 50-69 y) 7.5%-<15% (age ≥70 y)	5%-<7.5% (age 40-75 y)	Borderline
Very high	≥7.5% (age <50 y) ≥10% (age 50-69 y) ≥15% (age ≥70 y)	7.5%-19.9% (age 40-75 y)	Intermediate
		≥20% (age 40-75 y)	High

PCE: Pooled Cohort Equations

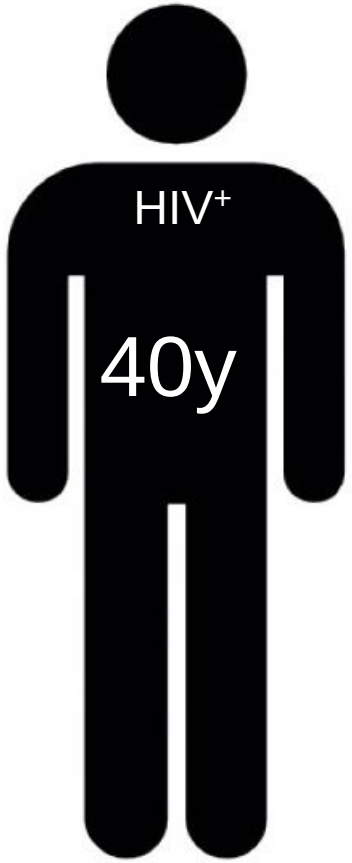
Fegers-Wustrow I et al. J Am Coll Cardiol 2022

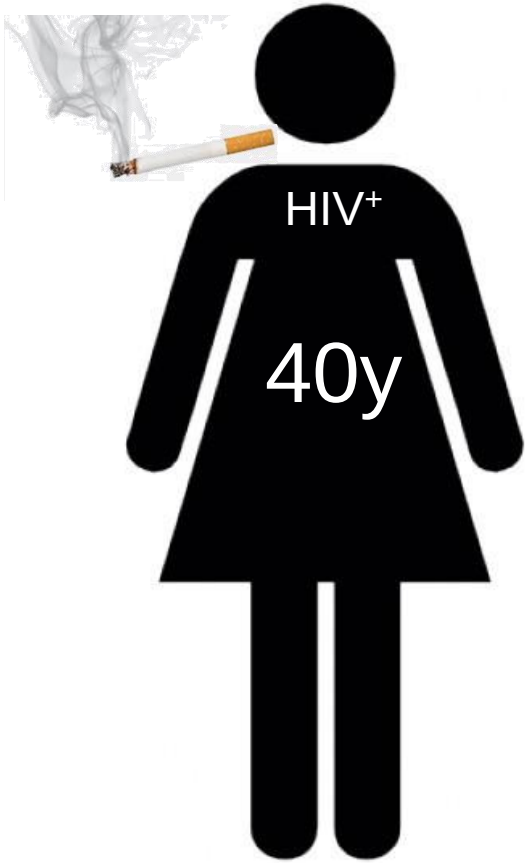
SCORE2: Who‘s risk is above 5%?



T-chol 214 mg/dL
LDL 180 mg/dL
HDL 48 mg/dL
BP 150 mm/Hg
Non-Smoker

2.9 %





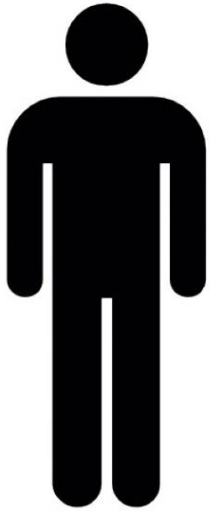
T-chol 214 mg/dL
LDL 160 mg/dL
HDL 48 mg/dL
BP 160 mm/Hg
Smoker

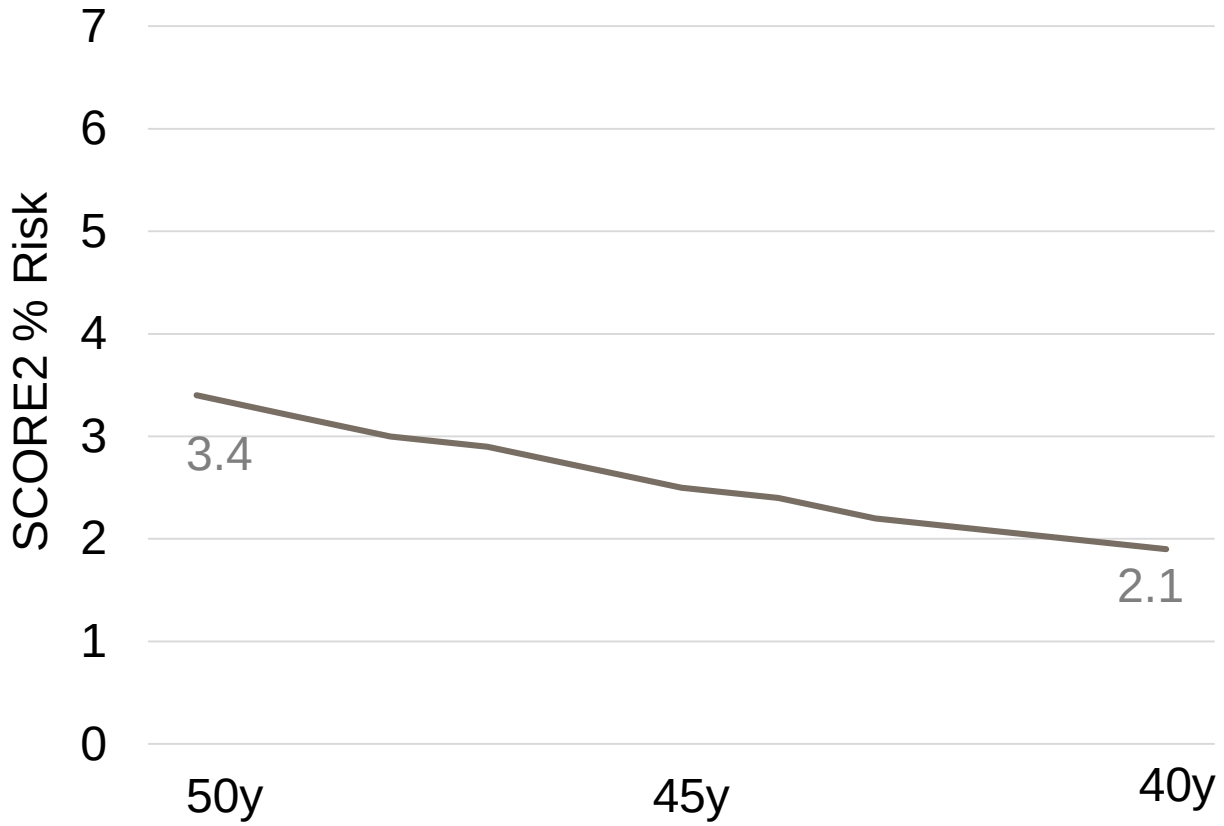
4.4 %

SCORE2 and the relevanc of age

Median REPRIEVE individual

Total Cholesterol	185 mg/dL
LDL Cholesterol	108 mg/dL
HDL Cholesterol	48 mg/dL
Syst. BP	125 mm Hg

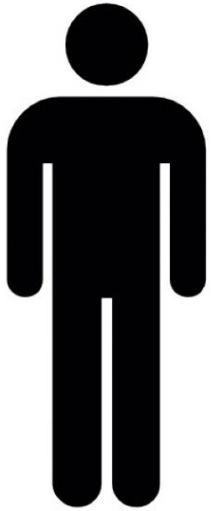


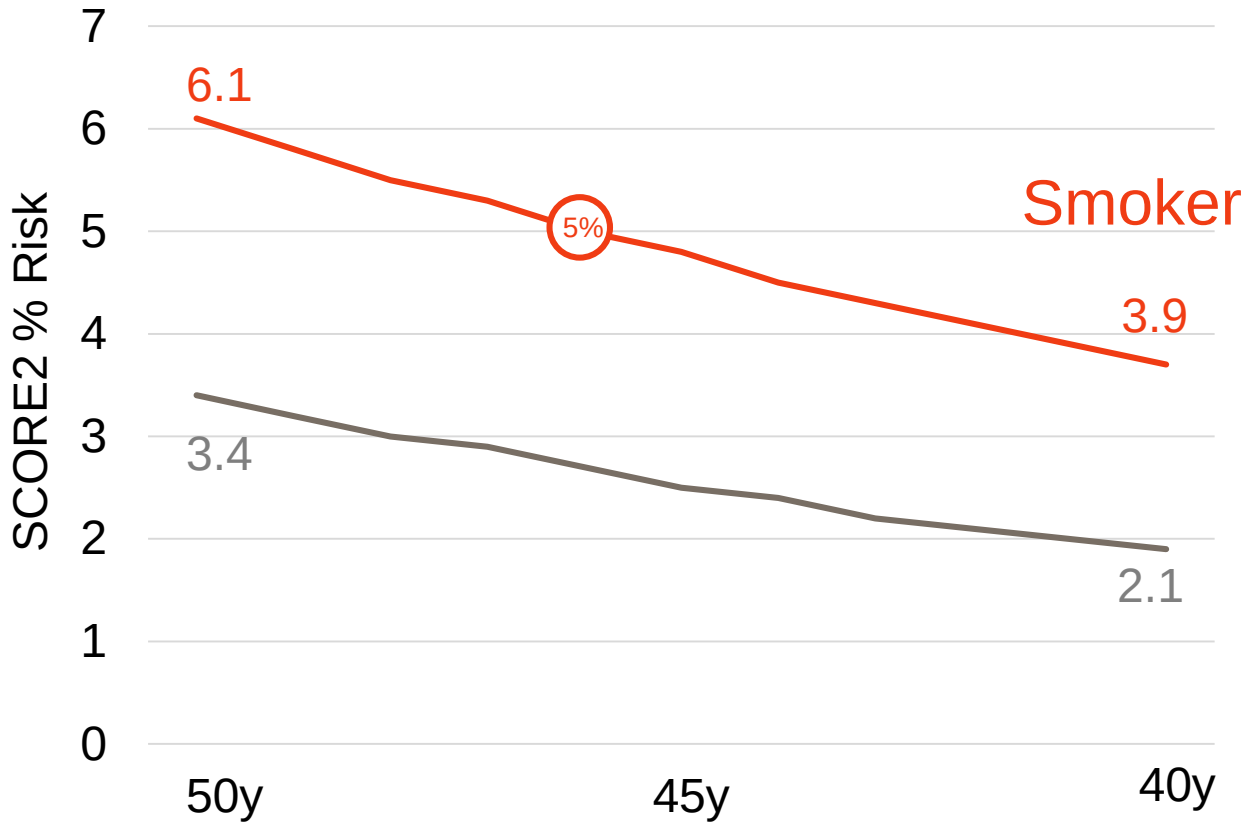


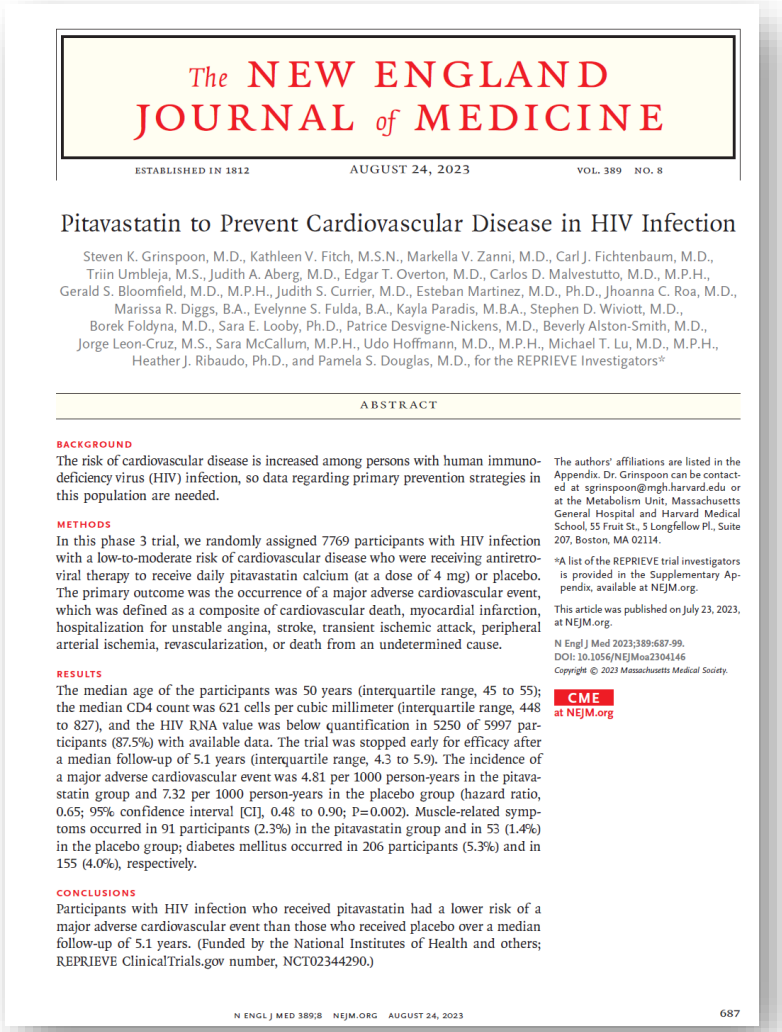
SCORE2 and the relevanc of age

Median REPRIEVE individual

Total Cholesterol	185 mg/dL
LDL Cholesterol	108 mg/dL
HDL Cholesterol	48 mg/dL
Syst. BP	125 mm Hg







The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 24, 2023 VOL. 389 NO. 8

Pitavastatin to Prevent Cardiovascular Disease in HIV Infection

Steven K. Grinspoon, M.D., Kathleen V. Fitch, M.S.N., Markella V. Zanni, M.D., Carl J. Fichtenbaum, M.D., Triin Umbleja, M.S., Judith A. Aberg, M.D., Edgar T. Overton, M.D., Carlos D. Malvestutto, M.D., M.P.H., Gerald S. Bloomfield, M.D., M.P.H., Judith S. Currier, M.D., Esteban Martinez, M.D., Ph.D., Jhoanna C. Roa, M.D., Marissa R. Diggs, B.A., Evelynne S. Fulda, B.A., Kayla Paradis, M.B.A., Stephen D. Wiviott, M.D., Borek Foldyna, M.D., Sara E. Looby, Ph.D., Patrice Desvigne-Nickens, M.D., Beverly Alston-Smith, M.D., Jorge Leon-Cruz, M.S., Sara McCallum, M.P.H., Udo Hoffmann, M.D., M.P.H., Michael T. Lu, M.D., M.P.H., Heather J. Ribaudo, Ph.D., and Pamela S. Douglas, M.D., for the REPRIEVE Investigators*

ABSTRACT

BACKGROUND

The risk of cardiovascular disease is increased among persons with human immunodeficiency virus (HIV) infection, so data regarding primary prevention strategies in this population are needed.

METHODS

In this phase 3 trial, we randomly assigned 7769 participants with HIV infection with a low-to-moderate risk of cardiovascular disease who were receiving antiretroviral therapy to receive daily pitavastatin calcium (at a dose of 4 mg) or placebo. The primary outcome was the occurrence of a major adverse cardiovascular event, which was defined as a composite of cardiovascular death, myocardial infarction, hospitalization for unstable angina, stroke, transient ischemic attack, peripheral arterial ischemia, revascularization, or death from an undetermined cause.

RESULTS

The median age of the participants was 50 years (interquartile range, 45 to 55); the median CD4 count was 621 cells per cubic millimeter (interquartile range, 448 to 827), and the HIV RNA value was below quantification in 5250 of 5997 participants (87.5%) with available data. The trial was stopped early for efficacy after a median follow-up of 5.1 years (interquartile range, 4.3 to 5.9). The incidence of a major adverse cardiovascular event was 4.81 per 1000 person-years in the pitavastatin group and 7.32 per 1000 person-years in the placebo group (hazard ratio, 0.65; 95% confidence interval [CI], 0.48 to 0.90; P=0.002). Muscle-related symptoms occurred in 91 participants (2.3%) in the pitavastatin group and in 53 (1.4%) in the placebo group; diabetes mellitus occurred in 206 participants (5.3%) and in 155 (4.0%), respectively.

CONCLUSIONS

Participants with HIV infection who received pitavastatin had a lower risk of a major adverse cardiovascular event than those who received placebo over a median follow-up of 5.1 years. (Funded by the National Institutes of Health and others; REPRIEVE ClinicalTrials.gov number, NCT02344290.)

The authors' affiliations are listed in the Appendix. Dr. Grinspoon can be contacted at sgrinspoon@mgh.harvard.edu or at the Metabolism Unit, Massachusetts General Hospital and Harvard Medical School, 55 Fruit St., 5 Longfellow Pl., Suite 207, Boston, MA 02114.

*A list of the REPRIEVE trial investigators is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on July 23, 2023, at NEJM.org.

N Engl J Med 2023;389:687-99.
DOI: 10.1056/NEJMoa2304146

CME at NEJM.org

Should we treat all PWH above 40 years with a statin?

REPRIEVE says: No way!