Kanton Bern
Canton de Berne

Gesundheits-, Sozial- und Integrationsdirektion
Generalsekretariat
Rechtsabteilung

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GSI-GS-RA, Rathausplatz 1, Postfach, 3000 Bern 8 (2022.GSI.2729)

A-Post
KSPartner
Kaspar Gehring und Ueli Kieser
Ulrichstrasse 14
8032 Zürich

Kanton Bern
Canton de Berne

Gesundheits-, Sozial- und Integrationsdirektion
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Referenz: 2022.GSI.2729 / stm

Verfügung vom 21. November 2022

in der Beschwerdesache

Dr. med. Michel Romanens, Innere Medizin und Kardiologie FMH, Spitalgasse 9, 4600 Olten

Beschwerdeführer

vertreten durch die Rechtsanwälte Kaspar Gehrig und Ueli Kieser, KSPartner, Ulrichstrasse 14, 8032 Zürich

gegen

Prof Dr. med. Nicolas Rondoni, Inselspital Bern, Universitätsklinik für Allgemeine Innere Medizin, Freiburgstrasse 18, 3010 Bern

Beschwerdegegner

sowie

Kantonale Ethikkommission für die Forschung (KEK), Murtenstrasse 31, 3010 Bern

Vorinstanz

betreffend Akteneinsicht

(Verfügung der Vorinstanz vom 31. August 2022)

wird

verfügt:

1. Von der Beschwerdevernehmlassung der Vorinstanz vom 15. November 2022 wird Kenntnis genommen und gegeben.

2. Vom Eingang der Vorakten wird Kenntnis genommen. Eine Kopie der Vorakten geht an den Beschwerdeführer.

3. Es wird festgestellt, dass der Beschwerdegegner innert Frist keine Stellungnahme eingereicht hat.

4. Zu eröffnen:

   - Rechtsanwälte Gehrig und Kieser, mit Beilage gemäss Ziff. 1 und 2, z. Hd. des Beschwerdeführers, per A-Post
   - Vorinstanz, per A-Post
   - Beschwerdegegner, mit Beilage gemäss Ziff. 1, per A-Post

Generalsekretariat
Rechtsabteilung

Stefan Müller
Rechtsanwalt

Gesundheits- und Fürsorgedirektion des Kantons Bern

Direction de la santé publique et de la prévoyance sociale du canton de Berne

Kantonale Ethikkommission für die Forschung

Commission cantonale d'éthique de la recherche

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Einschreiben

Gesundheits-,Sozial- und Integrationsdirektion des Kantons Bern
Rechtsamt
Rathausplatz 1
Postfach
3011 Bern

Bern, 15.11.2022 /CS/DP

Referenz: 2022.GSI.2729, Beschwerdevernehmlassung

Sehr geehrter Herr Regierungsrat
Sehr geehrter Herr Müller

Die kantonale Ethikkommission (KEK) reicht gemäss Verfügungen vom 05.10.2022 resp. 24.10.2022 der kantonalen Gesundheits-, Sozial- und Integrationsdirektion (GSI) fristgerecht nachfolgende Vernehmlassung zum Beschwerdeverfahren betreffend Akteneinsicht in die Verfahrensakten des bewilligten Gesuchs «*Discontinuing Statins in Multimorbid Older Adults without Cardiovascular Disease (STREAM) – a randomized non-inferiority clinical trial*» ein. Gleichzeitig reichen wir Ihnen die Vorakten ein.

I. Antrag:

Die Beschwerde sei abzuweisen.

II. Begründung:

1. Prozessgeschichte:

Der Beschwerdegegner hat am 14.07.2021 per BASEC die Studie, *Discontinuing Statins in Multimorbid Older Adults without Cardiovascular Disease (STREAM) – a randomized non-inferiority clinical trial*' bei der KEK Bern eingereicht (Verf. Nr. 2021-01513).

Mit Entscheid vom 3. August 2021 wurde das entsprechende Gesuch bedingt bewilligt. Sämtliche Bedingungen wurden erfüllt, so dass das Gesuch seit dem 10. Oktober 2021 bewilligt ist. Zu einem späteren Zeitpunkt beantragte der Beschwerdegegner den Einschluss von weiteren Prüfzentren. Das Projekt ist in der Zwischenzeit als multizentrisches bewilligt.

Mit E-Mail vom 13.06.2022 verlangte der Beschwerdeführer, ihm sei die Eingabe zur Stream Studie und das Votum der Ethikkommission (sowie dazugehörige allfällige Korrespondenz) so bald wie möglich zukommen zu lassen. Andernfalls sei ihm dies zu begründen. Zudem sei die Studie mit einstweiliger Verfügung zu stoppen.

Die KEK antwortete dem Beschwerdeführer brieflich am 15.06.2022, dass sie ein allfälliges Gesuch um Akteneinsicht nur schriftlich entgegennehme. Potenziellen Gefährdungen würde sie nachgehen

die es zu schützen gilt. Daher gehen die Bestimmungen des HFG zur Datenbekanntgabe denjenigen des Informationsgesetzes vor. Diese Einordnung stimmt auch mit dem Anspruch des HFG zur abschliessenden Regelung der Datenbekanntgabe überein.

Das Gesuch um Akteneinsicht des Beschwerdeführers ist daher insbesondere mit Blick auf Art. 59 HFG zu beurteilen.

3. Fehlende Einwilligung für die Bekanntgabe von personenbezogenen Daten (Art. 59 Abs. 4 Bst. b HFG)

Alle Dokumente, in welche der Beschwerdeführer Einsicht beantragt, enthalten personenbezogene Daten, da sie ein einzelnes Bewilligungsgesuch nach dem Humanforschungsgesetz betreffen und auf die Person des Beschwerdegegners (in seiner Rolle als Gesuchsteller für eine Bewilligung nach Art. 45 HFG) bezogen sind. Daher kommen auf den vorliegenden Sachverhalt die Vorgaben gemäss Artikel 59 Absatz 4 HFG zur Anwendung. Da es sich um die Bekanntgabe von personenbezogenen Daten im Sinn von Absatz 4 Buchstabe b handelt, ist die «schriftliche Einwilligung der betroffenen Person im Einzelfall», d.h. vorliegend des Beschwerdegegners, vorausgesetzt. Die Bestimmung vermittelt den betroffenen Personen ein Vetorecht in all jenen Fällen, die nicht unter die Absätze 1 und 2 des Artikel 59 HFG fallen. Der Gesetzgeber stellt damit die Interessen der betroffenen Personen in jedem Fall über die Interessen der Öffentlichkeit bzw. der Vollzugsbehörden an einer Veröffentlichung von personenbezogenen Daten und weicht entsprechend von der allgemeinen Regelung der Koordination von Datenschutz und Öffentlichkeitsinformation im Bereich der aktiven und passiven Behördeninformation ab (vgl. Brunner, a.a.O., Rz. 54). Diese Regelung stellt das Gegenstück zur Registrierungspflicht von klinischen Versuchen nach Artikel 56 HFG dar. Der Gesetzgeber hat damit einen Ausgleich geschaffen zwischen dem Transparenzanliegen einerseits und den berechtigten Geheimhaltungsinteressen der forschenden Personen sowie der Forschungsteilnehmerinnen und -teilnehmer.

Da der Beschwerdegegner im vorinstanzlichen Verfahren beantragt hat, die Akteneinsicht sei zu verweigern und somit im vorliegenden Fall gegenüber der KEK die Einwilligung in die Bekanntgabe seiner Daten an den Beschwerdeführer nicht erteilt hat, musste das vorliegend im Streit liegende Gesuch abgewiesen werden. Es besteht auch weiterhin kein Anspruch auf Akteneinsicht da die Einwilligung des Gesuchstellers fehlt. Die Beschwerde erweist sich daher als unbegründet.

4. Fehlendes öffentliches Interesse resp. fehlendes überwiegendes Interesse

Nach Einschätzung der KEK ist eine Anonymisierung der strittigen Daten ausgeschlossen, da der Beschwerdeführer die Identität des Beschwerdegegners kennt. Ihres Erachtens findet auf das vorliegende Akteneinsichtsgesuch daher Art. 59 Abs. 4 Bst. a HFG keine Anwendung. Wenn die GSI jedoch trotzdem zum Schluss gelangen sollte, dass die vom Akteneinsichtsgesuch betroffenen Dokumente auch resp. insbesondere nicht personenbezogene Daten (anonymisierte Daten oder Informationen zum Verfahren) umfassen sollte, wäre die Bekanntgabe nur dann möglich, wenn sie einem überwiegenden Interesse entspräche.

Dieses überwiegende Interesse wäre von demjenigen geltend zu machen, der Einsicht in die Akten verlangte. Dieser Obliegenheit ist der Beschwerdeführer jedoch nicht nachgekommen, da er kein überwiegendes Interesse an der Einsicht in die Unterlagen dargetan hat: In seiner Eingabe vom 29.Juni 2022 äusserte er sich selber mit keinem Wort zu seinen eigenen Interessen an der Datenbekanntgabe. Hinzu kommt, dass ein solches auch nicht ersichtlich wäre:

Der Beschwerdeführer ist Präsident des Vereins Ethik und Medizin Schweiz (VEMS). Dabei handelt es sich um einen privaten Verein. Weshalb ihm ein speziell geschütztes resp. überwiegendes Interesse zukommen soll, Einsicht in diese Dokumente zu erhalten, ist nicht ersichtlich. Aus seiner Eingabe vom 29. Juni 2022 lässt sich erahnen, dass er prüfen will, ob die Sicherheit für die Patienten im Rahmen der Studie eingehalten ist. Ihm kommt hingegen keine entsprechende Aufgabe zu. Vielmehr überträgt das Gesetz diese Aufgabe der kantonalen Ethikkommission. Diese besteht aus entsprechenden Fachspezialistinnen und Fachspezialisten. Ihr obliegt die Prüfung, ob die Voraussetzungen für die Erteilung einer Bewilligung gegeben sind (Art. 51 HFG). Dabei prüft sie insbesondere, ob der Schutz der betroffenen Personen gewährleistet ist. Weiter klärt sie, ob die Regeln der Guten Klinischen Praxis erfüllt sind (Art. 5 KlinV). Dazu gehört beispielsweise, dass ein unabhängiges data-and safety- monitoring erfolgt (GCP 1.25 und 5.5.2). Zudem sind schwerwiegende unerwünschte Ereignisse, bei denen nicht ausgeschlossen werden kann, dass diese auf die untersuchte Intervention zurückzuführen sind, innerhalb 15 Tage der KEK zu melden (Art. 63 KlinV).

Damit ist das eingangs gestellte Rechtsbegehren gehörig begründet und es wird höflich um dessen Folgegebung gebeten.

Freundliche Grüsse

Prof. Dr. med. Christian Seiler
Präsident

Dr. sc. nat. Dorothy Pfiffner
Leiterin wissenschaftl. Sekretariat/Vizepräsidentin

Beilagen: Vorakten

Kanton Bern
Canton de Berne

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Kantonale Ethikkommission für die Forschung

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GSI-KEK, Murtenstrasse 31, 3010 Bern

Bern, 31.08.2022, FN

Verfügung betreffend Akteneinsicht

Im Verfahren zwischen

Herr Dr. med. Michel Romanens, Innere Medizin und Kardiologie FMH, Spitalstrasse 9, 4600 Olten

Gesuchsteller

und

Herr Prof. Dr. med. Nicolas Rodondi, Universitätsklinik für Allgemeine Innere Medizin, Inselspital Bern, Freiburgstrasse 18, 3010 Bern

Gesuchsgegner

Erwägungen:

Mit Entscheid vom 19.10.2021 hat die KEK Prof. Rodondi die Durchführung der Stream Studie bewilligt. Mit Eingabe vom 29. Juni 2022 hat Dr. Romanens einerseits die KEK aufgefordert, Massnahmen im Sinne von Art. 48 HFG zu ergreifen. Diesen Sachverhalt hat die KEK in einem separaten Verfahren geprüft. Andererseits bittet Dr. Romanens um Einsichtnahme in das Studien Protokoll, die Stellungnahme(n) der KEK Bern, die Patienteninformation und das 'Statistical Analysis Protocol' der entsprechenden Studie resp. des durchgeführten Bewilligungsverfahrens. Diese Bitte hat die KEK als Akteneinsichtsbegehren entgegengenommen und Prof. Rodondi Gelegenheit zur Stellungnahme eingeräumt. In seiner Eingabe vom 15. Juli 2022 äussert sichProf. Rodondi zur Akteneinsicht wie folgt: «Wir sehen keine Veranlassung Hr. Romanens Zugang zu den vertraulichen studienspezifischen Dokumenten zu geben. Durch die Registrierung auf ClinicalTrial.gov und einer öffentlichen Webseite sind alle Informationen, welche für die Öffentlichkeit von Belang sind, zugänglich. Bei allen anderen Dokumenten handelt es sich um vertrauliche Informationen, die lediglich für den Sponsor und die beteiligten Studienzentren gedacht sind.» Damit stellt er sinngemäss den Antrag, die Akteneinsicht sei vollumfänglich zu verweigern.

Gemäss Art. 27 Abs. 1 Informationsgesetzes des Kantons Bern (IG) hat jede Person ein Recht auf Einsicht in amtliche Akten, soweit nicht überwiegende öffentliche oder private Interessen

Die KEK verfügt folgendes:

1. Das Akteneinsichtsgesuch wird abgewiesen. Dr. Romanens werden keine Dokumente zugestellt.
2. Zu eröffnen:
   - Dr. Romanens
   - Prof. Rodondi

Rechtsmittelbelehrung:

Gegen diese Verfügung kann innert 30 Tagen seit Eröffnung bei der Gesundheits-, Sozial- und Integrationsdirektion des Kantons Bern Beschwerde erhoben werden. Die Beschwerdefrist kann nicht verlängert werden. Die Beschwerdeschrift ist im Doppel bei der Gesundheits-, Sozial- und Integrationsdirektion, Rathausgasse 1, Postfach, 3000 Bern 8 einzureichen. Eine allfällige Beschwerde, die in mindesten zwei Exemplaren einzureichen ist, muss einen Antrag, die Angabe von Tatsachen und Beweismitteln, eine Begründung sowie eine Unterschrift enthalten; der angefochtene Entscheid und andere greifbare Beweismittel sind beizulegen. Sie muss (a) angeben, welche Entscheidung anstelle der angefochtenen Verfügung beantragt wird und (b) aus welchen Gründen diese andere Entscheidung verlangt wird sowie (c) die Unterschrift der beschwerdeführenden Partei oder der sie vertretenden Person enthalten. Der Beschwerdeschrift beizulegen sind die Beweismittel, soweit sie greifbar sind, und die angefochtene Verfügung. (Art. 32 und 60 ff. des Gesetzes vom 23. Mai 1989 über die Verwaltungsrechtspflege [VRPG; BSG 155.21]).

Freundliche Grüsse

Prof. Dr. med. Christian Seiler
Präsident KEK Bern

Dr. sc. nat. Dorothy Pfiffner
Vizepräsidentin
Leiterin Wissenschaftliches Sekretariat

Kanton Bern
Canton de Berne

Gesundheits-, Sozial- und Integrationsdirektion
Kantonale Ethikkommission für die Forschung

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Herr
Prof. Dr. med. Nicolas Rodondi
Universitätsklinik für Allgemeine Innere Medizin
Inselspital Bern
Freiburgstrasse 18
3010 Bern

Bern, 29.08.2022, FN

Sehr geehrter Herr Prof. Rodondi

Wir bedanken uns für Ihre ausführliche Stellungnahme vom 15. Juli 2022. Ihre Ausführungen überzeugen und die KEK ist nach Prüfung des relevanten Sachverhalts zum Schluss gekommen, dass keine Gefährdung der Sicherheit oder der Gesundheit der an der Studie beteiligten Patienten vorliegt, die eine Massnahme gemäss Art. 48 HFG erfordert.

Freundliche Grüsse

Prof. Dr. med. Christian Seiler
Präsident KEK Bern

Dr. sc. nat. Dorothy Pfiffner
Vizepräsidentin
Leiterin Wissenschaftliches Sekretariat

Kopie an

☒ Dr. M. Romanens

INSELSPITAL
UNIVERSITÄTSSPITAL BERN
HÔPITAL UNIVERSITAIRE DE BERNE

u^b
Universität Bern
Medizinische Fakultät
Bernes Institut for Hausarztmedizin (BIHAM)

vis Smi 1
09.08.22

Kantonale Ethikkommission Bern
Murtenstrasse 31
Hörsaaltrakt Pathologie, Eingang 43, Büro H372
3010 Bern

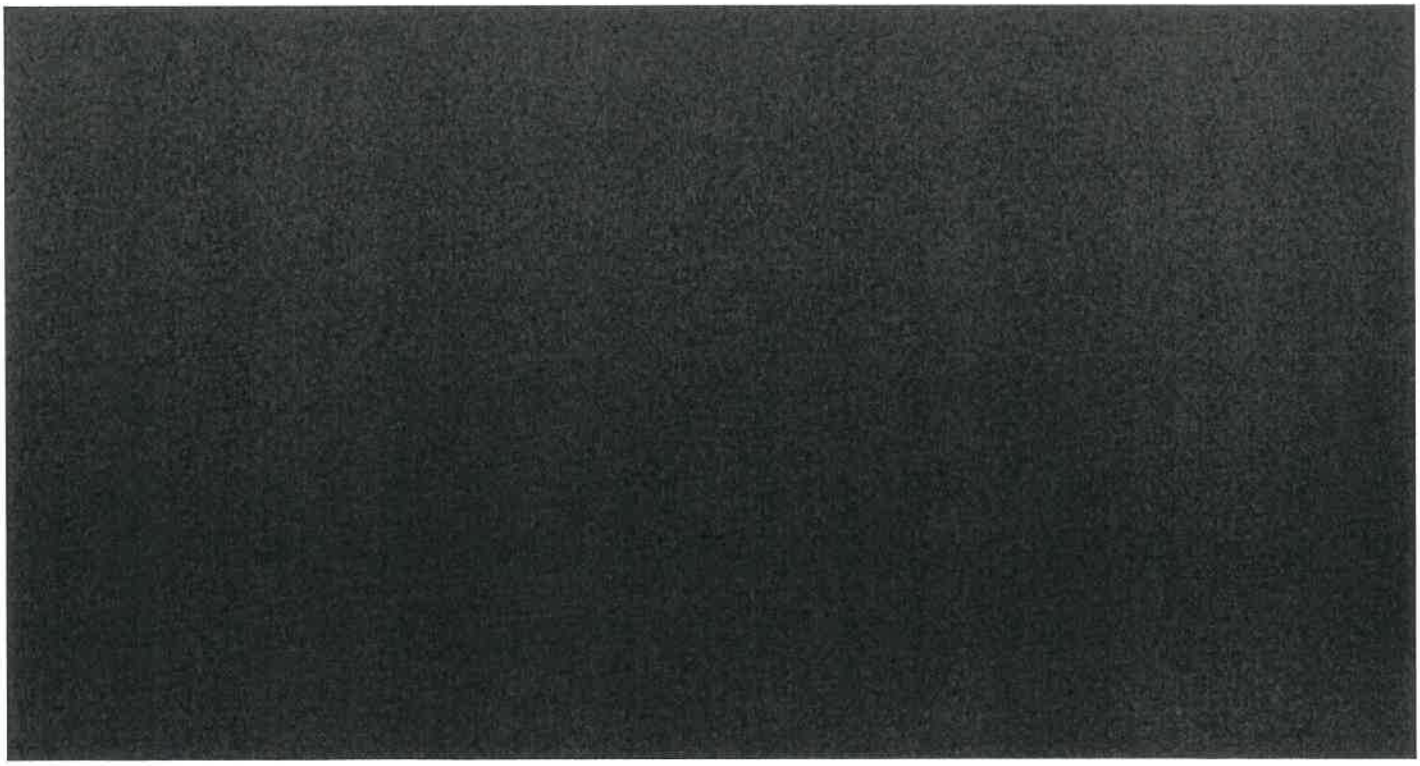
Bern, 15.07.2022

STREAM Studie - BASEC Nr. 2021-01513

Discontinuing Statins in Multimorbid Older Adults without Cardiovascular Disease – a randomized non-inferiority clinical trial

Sehr geehrter Herr Prof. Dr. med. Seiler, Lieber Christian,

Vielen Dank für das Zusenden des der Unterlagen von Dr. Romanens.
Im Folgenden gehen wir mit bestem Wissen und Gewissen auf die unterschiedlichen Kritikpunkte des Antragsstellers ein, aber wir möchten zuerst drei generelle Punkte erwähnen:



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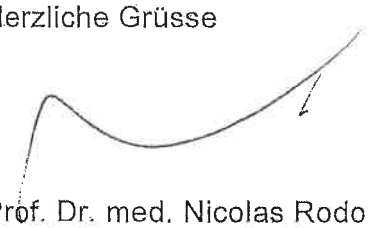
Herzliche Grüsse



Prof. Dr. med. Nicolas Rodondi

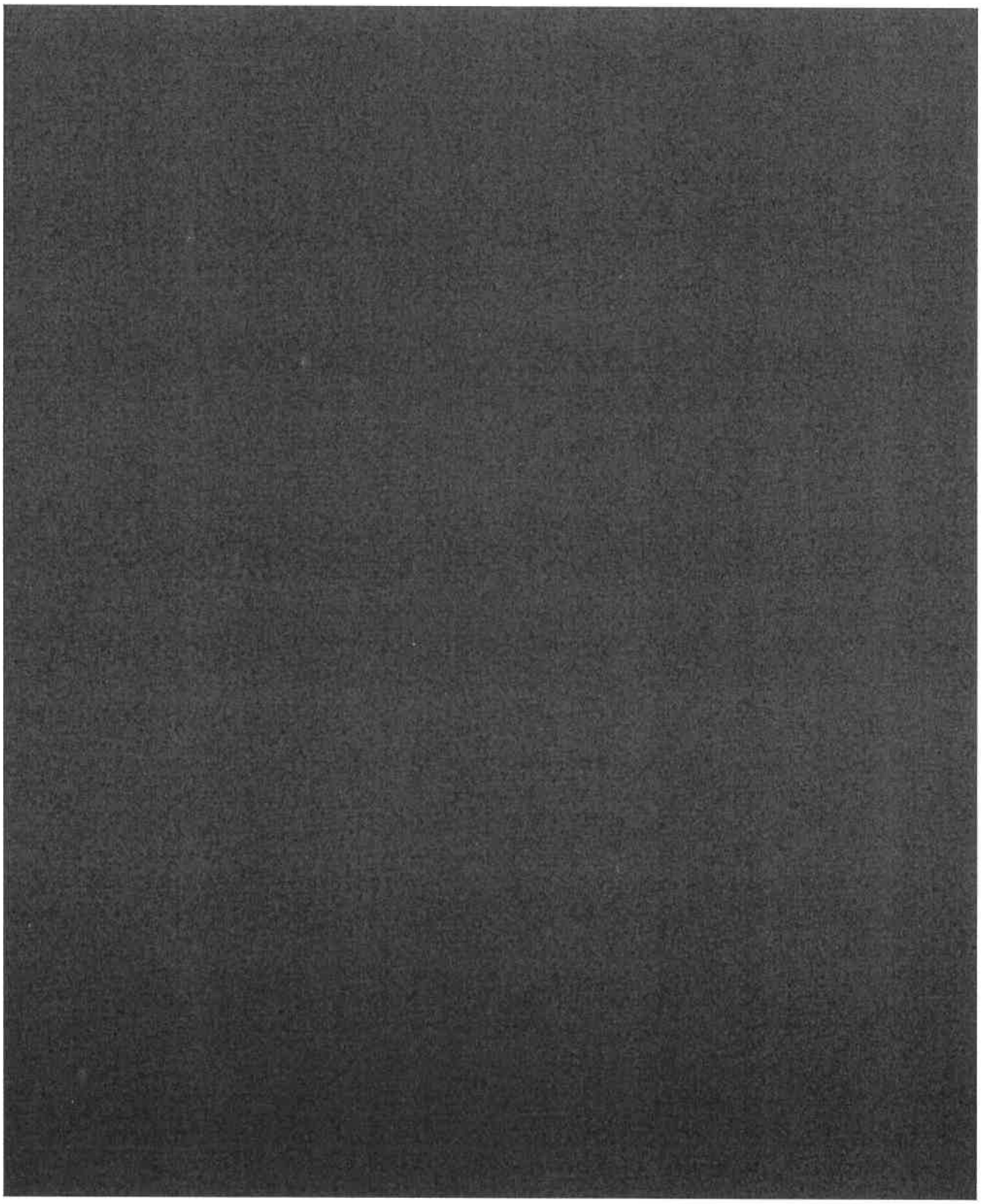
Stellungnahme zu Anträgen (S. 1 Brief Dr. Romanens)

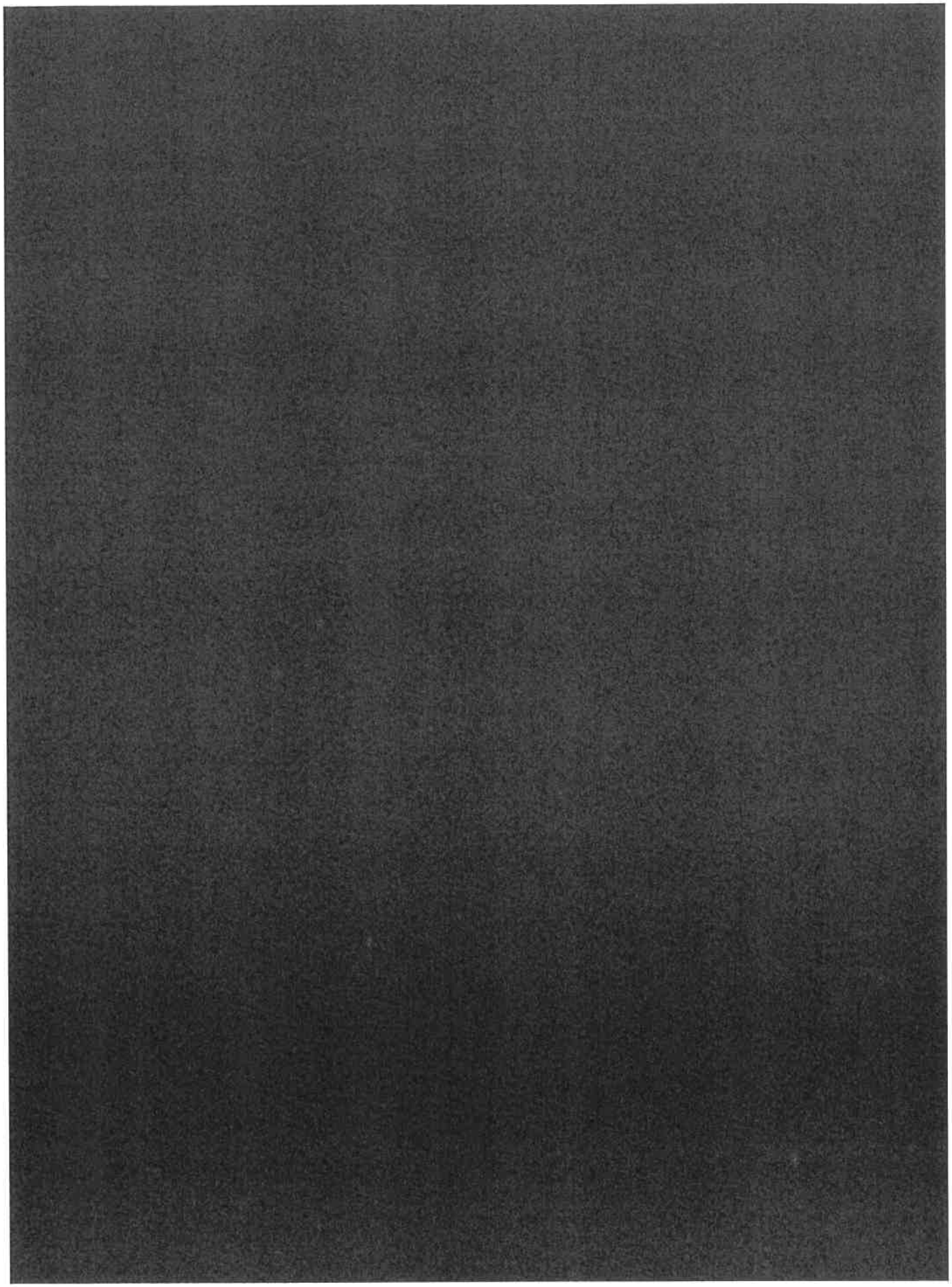
[redacted]

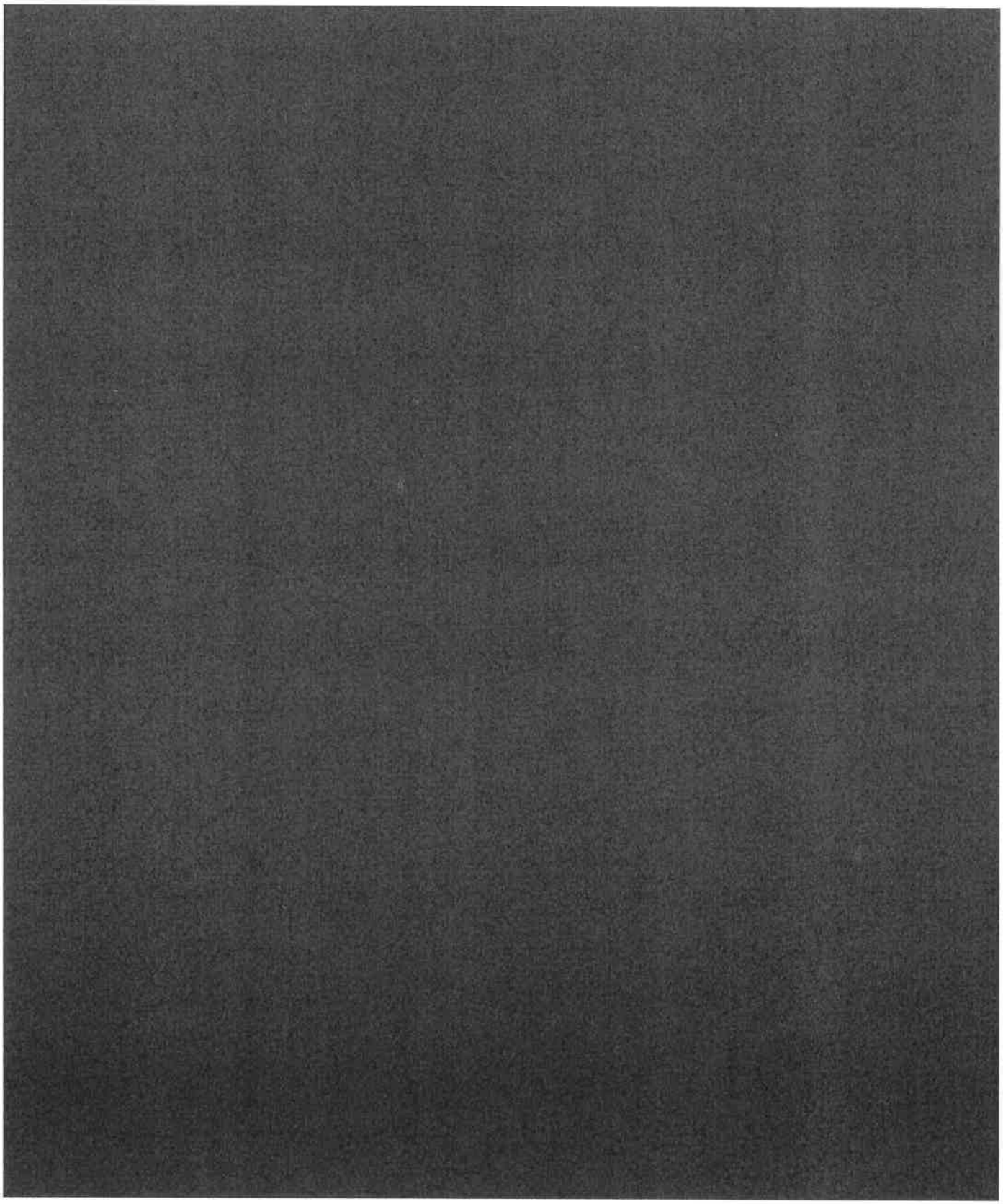
2. *Einsichtnahme in das Study Protocol, die Stellungnahme der KEK Bern, das Informed Consent File und das Statistical Analysis Protocol.*

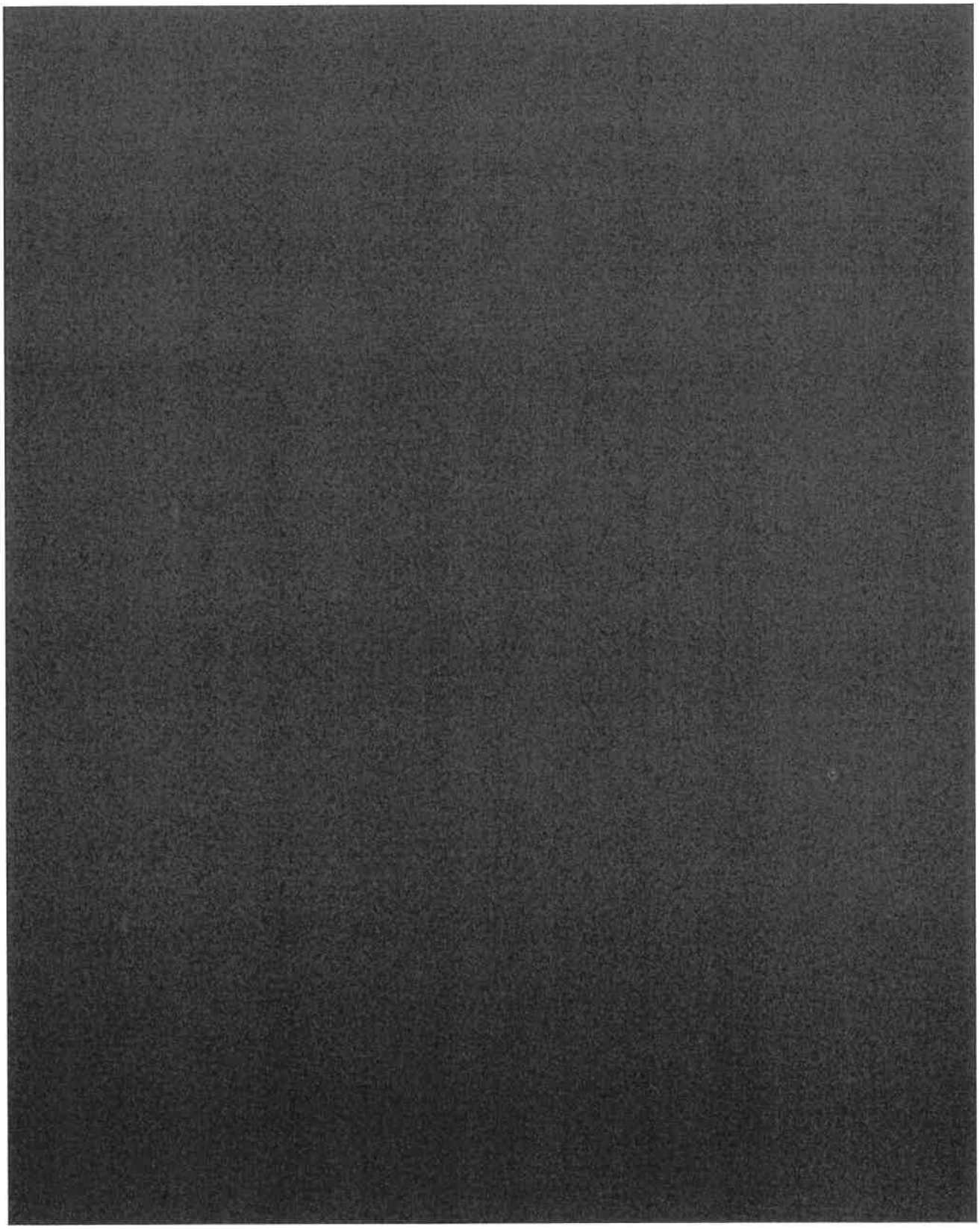
   Antwort: Wir sehen keine Veranlassung Hr. Romanens Zugang zu den vertraulichen studienspezifischen Dokumenten zu geben. Durch die Registrierung auf ClinicalTrial.gov und einer öffentlichen Website sind alle Informationen welche für die Öffentlichkeit von Belang sind zugänglich. Bei allen anderen Dokumenten handelt es sich um vertrauliche Informationen die lediglich für den Sponsor und die beteiligten Studienzentren gedacht sind.

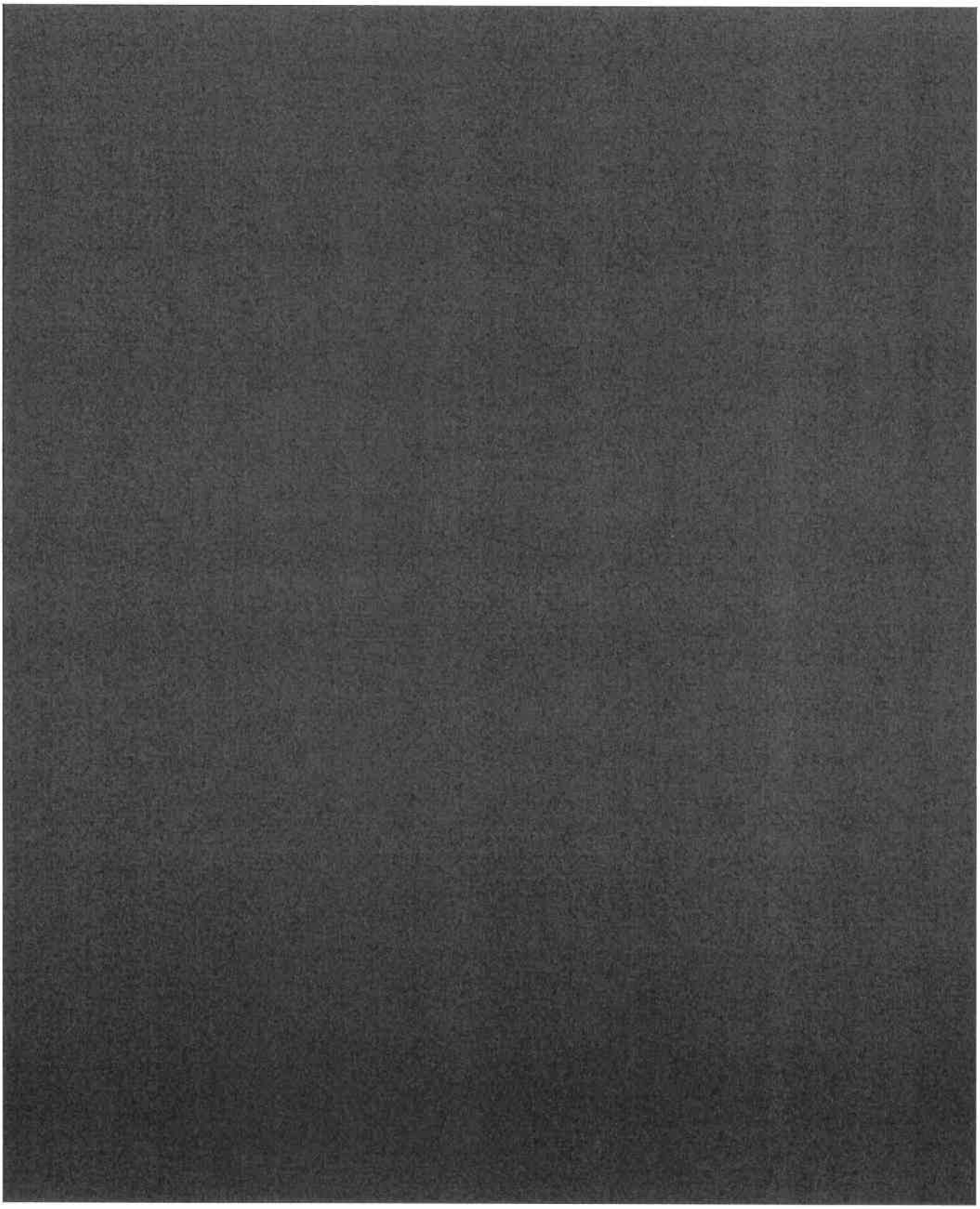
[redacted]

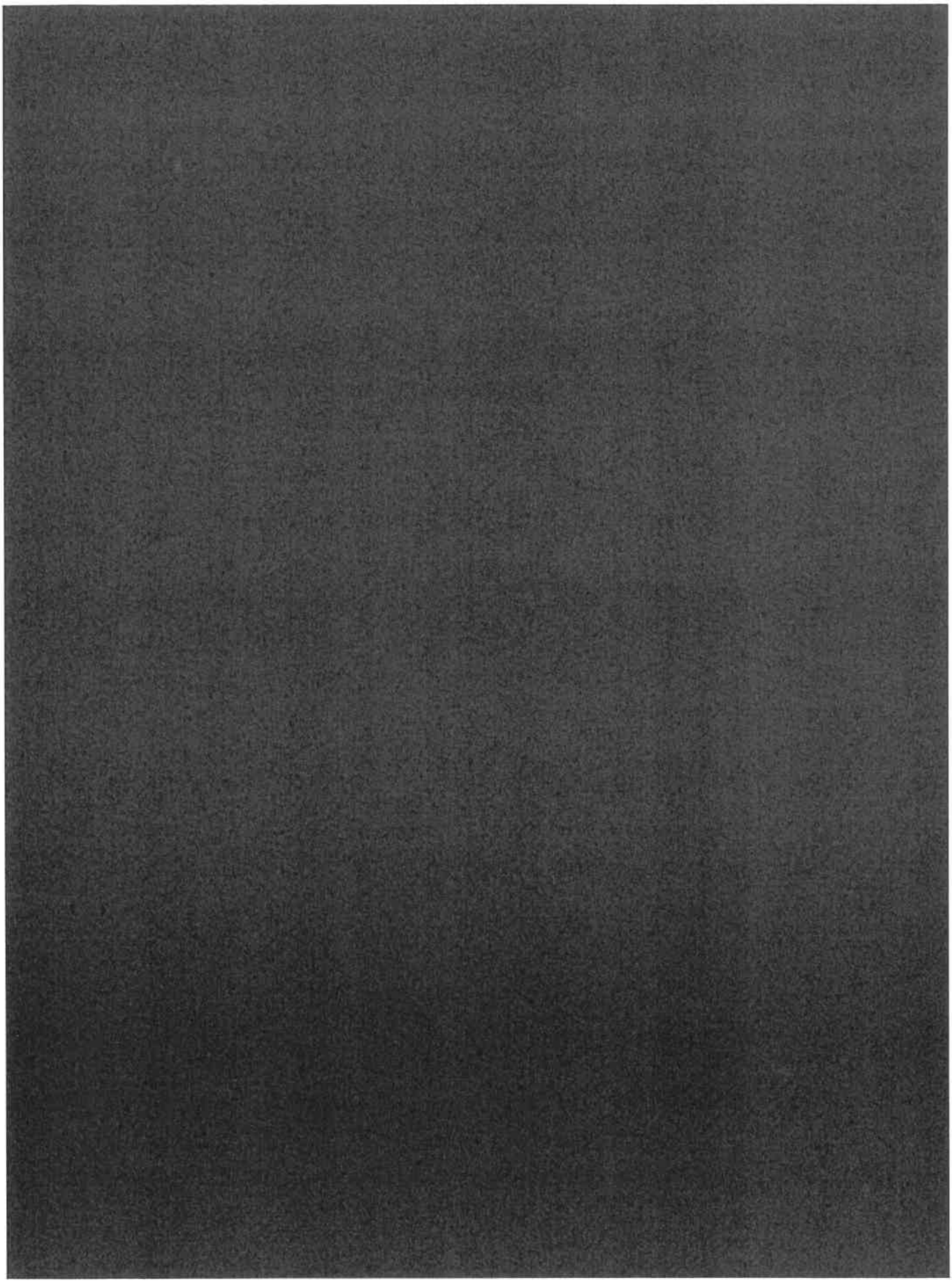












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GSI-KEK, Murtenstrasse 31, 3010 Bern

Herr
Dr. med. Michel Romanens
Innere Medizin und Kardiologie FMH
Spitalstrasse 9
4600 Olten,

Bern, 15.06.2022, FN

Sehr geehrter Herr Dr. Romanens

Besten Dank für Ihre E-Mail vom 13.06.2022. Wir verstehen diese so, dass sie einerseits ein Akteneinsichtsgesuch stellen möchten und uns andererseits auf eine allfällige Gefährdung der Gesundheit der betroffenen Personen aufmerksam machen möchten.

Allfälligen Gefährdungen gehen wir nach, falls wir Kenntnis davon erhalten. Wir würden dann entsprechend prüfen, ob eine Massnahme im Sinne von Art. 48 HFG erforderlich wäre. Ein allfälliges Gesuch um Einsicht in die Akten müssen Sie schriftlich und begründet im Sinne von Art. 59 HFG i.V.m Art. 31 ff. VRPG einreichen.

Freundliche Grüsse

Prof. Dr. med. Christian Seiler
Präsident KEK Bern

Dr. sc. nat. Dorothy Pfiffner
Vizepräsidentin
Leiterin Wissenschaftliches Sekretariat

Kanton Bern
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Einschreiben
Herr
Prof. Dr. med. Nicolas Rodondi
Universitätsklinik für Allgemeine Innere Medizin
Inselspital Bern
Freiburgstrasse 18
3010 Bern

Bern, 12.07.2022, FN

STREAM: Discontinuing Statins in Multimorbid Older Adults without Cardiovascular Disease (STREAM) – a randomized non-inferiority clinical trial (2021-01513):

Sehr geehrter Herr Prof. Rodondi

Wir haben von Dr. M. Romanens am 05.07.2022 Unterlagen zur Stellungnahme erhalten. Wir bitten Sie, zu den Anträgen, Vorwürfen und Kritikpunkten von Dr. Romanens bis am **8. August 2022** Stellung zu nehmen.

Primär geht es um das Risiko, die Behandlung mit Statinen bei über 75-Jährigen in primär-präventiver Absicht zu sistieren. Im Besonderen ist der Fokus auf das Risiko der Polypharmazie bei älteren Menschen zu legen, und das zu vergleichen mit der vorhandenen Evidenz der Wirksamkeit von Statinen in dieser Altersklasse und in primärpräventiver Absicht.

Freundliche Grüsse

Prof. Dr. med. Christian Seiler
Präsident KEK Bern

Dr. sc. nat. Dorothy Pfiffner
Vizepräsidentin
Leiterin Wissenschaftliches Sekretariat

Kopie an

☒ Dr. med. Michel Romanens

Beilagen:
Unterlagen von Dr. M. Romanens, datiert 29.06.2022

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Gesundheits-, Sozial- und
Integrationsdirektion Kantonale
Ethikkommission für die Forschung
Dorothy Pfiffner
dorothy. pfiffner@be.oh
Murtenstrasse 31
3010 Bern

Olten, 29.06.2022

Betreff: Stream Studie Inselspital (Prof. N. Rodondi)

Sehr geehrte Frau Pfiffner

Aufgrund unserer Nachforschung zur nationalen Stream Studie sehen wir Handlungsbedarf seitens der kantonalen Ethikkommission des Kantons Bern und möchten deshalb folgende Anträge stellen:

Anträge

(1) Die KEK des Kantons Bern wird gemäss Artikel 48 HFG ersucht, die erteilte Bewilligung für die Stream Studie zu widerrufen oder nur zu sistieren, falls die KEK der Auffassung ist, dass die Fortführung der Stream Studie von zusätzlichen Auflagen abhängig zu machen ist.

(2) Einsichtnahme in das Study Protocol, die Stellungnahme(n) der KEK Bern, das Informed Consent File und das Statistical Analysis Protocol

Zentrale Kritikpunkte

(1) Non-Inferiority Studien dürfen nicht mit Placebo oder gar keiner Therapie durchgeführt werden, es wird immer ein aktiver Komparator verwendet (1,2). Placebo kontrollierte Studien müssen mit Superiority Studien durchgeführt, um klinisch und statistisch relevante Effekte des aktiven Komparators zu erkennen (2).

(2) Es gibt einen Konsens darüber, dass bei einer Lebenserwartung von über 5 Jahren eine risiko-basierte LDL Behandlung dem heutigen Standard entspricht (3).

(3) Die Statinbehandlung ist auch nach dem 70. Lebensjahr effektiv, hierzu existiert keine Ungewissheit, sondern nur mengenmässig weniger Gewissheit (https://varifo.ch/statin-effekte/).

(4) Die Patienteninformation, wonach Cholesterin ab 70 kein relevanter Risikofaktor darstelle, ist irreführend (4)

Tatsachen und Beweismittel

Öffentlich im Internet zugängliche Angaben zur Stream Studie im Clinical Trials (https://clinicaltrials.gov/ct2/show/NCT05178420.) und online Material zur Stream Studie (https://www.statin-stream.ch/)

Die Studienautoren zitieren als Begründung für die Ungewissheit eine Reihe von Studien, die bei näherer Betrachtung die vermutete Ungewissheit nicht belegen.

1. Die Ökonomin Paula Byrne, führt wegen zahlreicher fehlender Studiendaten eine selektive Analyse durch, welche die vermuteten Zweifel an der Wirksamkeit der Prävention in der Grundversorgung belegen sollen (5). Tatsächlich sind die Statineffekte jedoch trotzdem statistisch signifikant besser als Placebo. Um diese positiven Effekte wegzurechnen, werden Altersgruppen gebildet entsprechend einer nicht zulässigen Subgruppenanalyse, wo dann die Statineffekte für die einzelnen Altersgruppen nicht mehr signifikant sind. Dieses Vorgehen ist unwissenschaftlich und es stellt sich die Frage, warum die Studienautoren diese Byrne Studie überhaupt anführen.
2. Die Shepherd Studie (PROSPER) zeigt signifikante positive Effekte der Statine (6) für 5804 Personen ab 70 Jahren, welche mit 40 mg Pravastatin über 3.2 Jahre behandelt wurden (p=0.014 für den primären Endpunkt aus tödlichem und nicht-tödlichem Myokardinfarkt, NNT 47 für 3.2 Jahre und NNT 15 linear extrapoliert auf 10 Jahre). Pravastatin wurde von dieser Patientenpopulation gut vertragen, die eine große Anzahl von Begleitmedikationen einnahm, und es gab keine Hinweise auf Nebenwirkungen auf die Leberfunktion oder Muskelenzyme. Der fehlende Effekt auf die Verhinderung von Hirnschlägen wurde auf die zu kurze Studiendauer zurückgeführt. Rund 25% der Personen in der Prosper Studie befanden sich wegen stattgehabtem Herzinfarkt oder Hirnschlag jedoch in der Sekundärprävention.
3. Die ALLHAT Statin Studie ist eine post-hoc Analyse mit massivem Confounding durch Crossover in der Behandlung: Personen in der Verum-Gruppe nahmen nach 6 Jahren 22% keine Statine und in der Placebo-Gruppe nahmen nach 6 Jahren 29% ein Statin ein. In dieser Studie, in der 63 % der Patienten > 60 Jahre alt waren, reduzierte Atorvastatin (10 mg) signifikant nicht-tödliche Herzinfarkte und tödliche KHK um 36 % (HR = 0,64; 95 %-KI 0,50–0,83). Interessanterweise zeigte eine Follow-up-Analyse nach ca 8 Jahren langfristige Vorteile bei der Gesamtmortalität (–14 %) und Nicht-CV-Todesfällen (– 15 %); letzteres offenbar aufgrund reduzierter Todesfälle durch Infektionen und Atemwegserkrankungen.

4. In der Übersichtsarbeit von Ruscica (7) geht es gar nicht um die Frage, ob Statine bei älteren Personen eingesetzt werden sollen – da diese wirksam sind -, sondern um die Frage der Dosierung. Ruscica führt jedoch aus, dass im Allgemeinen die ältesten Altersgruppen (> 85 Jahre) wahrscheinlich nicht für eine Cholesterinsenkung in der Primärprävention in Betracht zu ziehen sind. Insbesondere schwer gebrechliche ältere Patienten sollten nicht zur Primärprävention und, sofern nicht unbedingt erforderlich, zur Sekundärprävention behandelt werden
5. Die Studie von Milly zeigt keine neuen Effekt Daten und behandelt die Frage des Deprescribing von Statinen ab dem 80. Lebensjahr in 30 Ländern (8).
6. Die Kutner Studie berichtet, dass am Lebensende das Absetzen von Statinen sicher ist (9).

Die Stream Autoren präsentieren auf dem Online Portal zur Studie «Clinicaltrials.gov» somit entweder Studien mit fehlender Aussagekraft (Paula Byrne) oder Studien, die die positiven Effekte der Statine ab 65 Jahren belegen oder Übersichtsarbeiten zum Deprescribing von Statinen ab 80 Jahren. Zudem werden in fährlässiger Weise zahlreiche weitere Studien, welche im Folgenden aufgeführt sind, verschwiegen. Damit können die Stream Autoren die behauptete Ungewissheit in keiner Weise belegen.

Die Evidenz der Wirksamkeit einer LDL-Senkung zur Senkung des Risikos für Herzinfarkt und Hirnschlag in der Primärprävention ist erwiesen, insbesondere auch für Personen > 75 Jahren (10,11). Wir verweisen hier auf die Ausführungen der AGLA. Zudem haben wir die folgende Studienlage auch online zusammengefasst (https://varifo.ch/statin-effekte/).

Die Metaanalyse von **Gencer** (12) zeigt den Effekt (die Wirkung) von Statinen und anderen Lipidsenkern bei Personen über 75 Jahren pro 1 mmol/l LDL Senkung. Die relative Risikoreduktion von Statinen pro 1 mmol/l LDL Reduktion beträgt mit „random effect metaanalysis" 18% und für die LDL Senkung mit nicht Statinen (PCSK-9 Inhibitoren und Ezetimib) 33%, in der Kombination resultierte ein Effekt von 26%. Zu beachten ist hier, dass in der Regel mit Statinen mehr als 1.0 mmol/l LDL Senkung erzielt wird. Gerade mit der Kombination Statin plus Ezetimib lassen sich auch ab 65 Jahren LDL Senkungen von 2.0 mmol/l problemlos erzielen. Damit verdoppelt sich die Wirkung von 18% auf 36%.

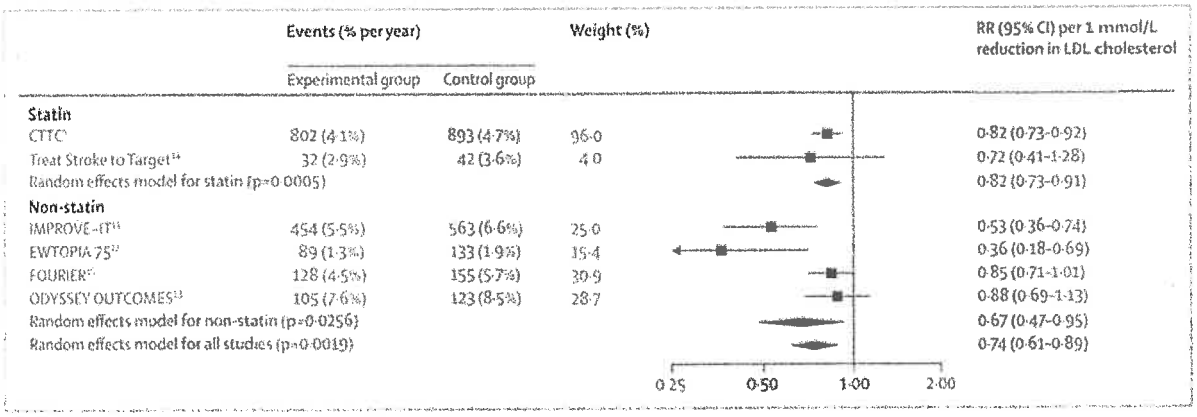
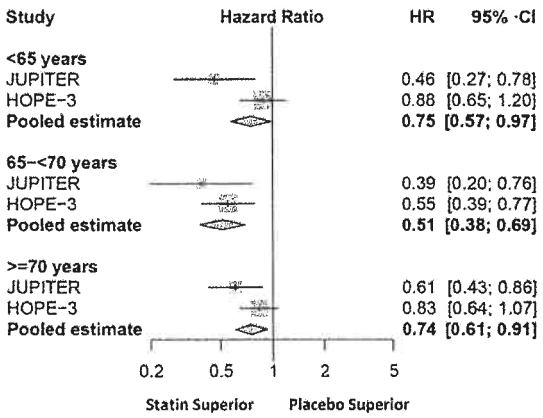


Figure 1: **Effect of LDL cholesterol lowering on the risk of major vascular events with statin and non-statin treatment in older patients**
Older patients were aged 75 years or older. RRs per 1 mmol/L reduction in LDL cholesterol were generated from a random effects model. In the ODYSSEY OUTCOMES trial, the event numbers were provided at 4 years, whereas the RR is for the entire duration of trial. CTTC=Cholesterol Treatment Trialists' Collaboration. EWTOPIA 75=Ezetimibe Lipid-Lowering Trial on Prevention of Atherosclerosclerotic Disease in 75 or Older. FOURIER=Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Patients with Elevated Risk. IMPROVE-IT=Improved Reduction of Outcomes: Vytorin Efficacy International Trial. ODYSSEY OUTCOMES=Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment with Alirocumab. RR=risk ratio.

Daten aus sechs Artikeln wurden in die systematische Übersichtsarbeit und Metaanalyse eingeschlossen, die 24 Studien aus der Metaanalyse der Cholesterol Treatment Trialists' Collaboration sowie fünf Einzelstudien umfasste. Von 244.090 Patienten aus 29 Studien waren 21.492 (8,8 %) mindestens 75 Jahre alt, davon 11.750 (54,7 %) aus Statin-Studien, 6.209 (28,9 %) aus Ezetimib-Studien und 3.533 (16,4 %) aus Studien mit PCSK9-Inhibitoren. Die mediane Nachbeobachtungszeit lag zwischen 2,2 und 6,0 Jahren. Die Senkung des LDL-Cholesterins reduzierte signifikant das Risiko schwerer vaskulärer Ereignisse (n = 3519) bei älteren Patienten um 26 % pro 1 mmol/l Senkung des LDL-Cholesterins (RR 0,74 [95 % KI 0,61–0,89]; p = 0,0019).), ohne statistisch signifikanten Unterschied zur Risikoreduktion bei Patienten unter 75 Jahren (0 85 [0 78–0 92]; P Interaktion = 0 37). Bei älteren Patienten waren die RRs statistisch nicht unterschiedlich für die Statin- (0 82 [0 73–0 91]) und Nicht-Statin-Behandlung (0 67 [0 47–0 95]; P Interaktion = 0 64) . Der Effekt einer Senkung des LDL-Cholesterins bei älteren Patienten wurde für jede Komponente der Kombination beobachtet, einschliesslich kardiovaskulärem Tod (0 85 [0 74–0 98]), Myokardinfarkt (0 80 [0 71–0 90]), Schlaganfall (0 73 [0 61–0 87]) und koronare Revaskularisation (0 80 [0 66–0 96]). Die Autoren dieser Studie kamen zu folgendem Schluss: Bei Patienten ab 75 Jahren war die Lipidsenkung bei der Reduzierung kardiovaskulärer Ereignisse ebenso wirksam wie bei Patienten unter 75 Jahren. Diese Ergebnisse sollten die Leitlinienempfehlungen für den Einsatz von lipidsenkenden Therapien, einschließlich Nicht-Statin-Behandlungen, bei älteren Patienten stärken.

Eine Meta-Analyse von Ridker innerhalb von Altersuntergruppen der Primärpräventionsstudien JUPITER (Justification for Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin) und HOPE-3 (Heart Outcomes Prevention Evaluation), in denen die Auswirkungen von Rosuvastatin auf den kombinierten Endpunkt von nicht tödlichem MI bewertet wurden Infarkt, nicht tödlicher Schlaganfall oder kardiovaskulärer Tod untersucht wurde, zeigte ebenfalls signifikante Effekte der Statinbehandlung bei Personen mit 70 oder mehr Jahren (13).



Eine Metaanalyse von **Savarese** (14,15) zeigt eine signifikante Reduktion von Herz- und Hirnschlag bei 24'674 Personen über 65 Jahren mit 39% weniger Herzinfarkten und 24% weniger Hirnschlägen über eine mittlere Beobachungszeit von 3.5 Jahren.

Zhou hat eine Studie zu gesunden Personen publiziert, welche entweder Statine einnahmen oder nicht (16). Von den 18.096 eingeschlossenen >70 Jahre alten Teilnehmerinnen (Durchschnittsalter 74,2 Jahre, 56,0 % Frauen) nahmen 5.629 zu Studienbeginn Statine ein. Über einen medianen Nachbeobachtungszeitraum von 4,7 Jahren war die Anwendung von Statinen zu Studienbeginn weder mit einem behinderungsfreien Überleben noch mit dem Risiko für Gesamtmortalität oder Demenz verbunden. Es war jedoch mit einem geringeren Risiko für körperliche Behinderung und alle kardiovaskulären Folgen verbunden. Anhaltende Behinderung im Alltag wurde um 25% reduziert ($p=0.02$), es traten 32% weniger Herz- und Hirnschläge auf ($p<0.001$), die kardiovaskuläre Mortalität wurde signifikant um 29% gesenkt, es fanden sich 44% weniger Herzinfarkte und 25% weniger Hirnschläge und Statine erzeugten in einer weiteren Studie von Zhou (https://www.jacc.org/doi/10.1016/j.jacc.2021.04.075) auch kein erhöhtes Risiko für Demenz.

Die Risiken des Statin-Stopps wurden in einer italienischen Studie **untersucht** (17). In diese retrospektive, bevölkerungsbezogene Kohortenstudie wurden 29.047 Einwohner der italienischen Region Lombardei im Alter von 65 Jahren oder älter eingeschlossen, die vom 1. Oktober 2013 bis zum 31. Januar 2015 eine ununterbrochene Behandlung mit Statinen, blutdrucksenkenden, antidiabetischen und Thrombozytenaggregationshemmern erhielten Nachverfolgung bis 30. Juni 2018. Die Daten wurden unter Verwendung der Datenbank zur Nutzung des Gesundheitswesens der

Region Lombardei in Italien erhoben. Die Datenanalyse wurde von März bis November 2020 durchgeführt. EXPOSITIONEN: Kohortenmitglieder wurden nachbeobachtet, um diejenigen zu identifizieren, die Statine absetzten. In dieser Gruppe waren diejenigen, die während der ersten 6 Monate nach dem Absetzen der Statine andere Therapien beibehielten, im Verhältnis 1:1 mit den Patienten verglichen, die weder Statine noch andere Medikamente abgesetzt hatten. WICHTIGSTE ERGEBNISSE UND MASSNAHMEN: Die Patientenpaare, die Statine absetzten und beibehielten, wurden vom ersten Absetzen bis zum 30. Juni 2018 nachbeobachtet, um die Hazard Ratios (HRs) und 95 %-KIs für tödliche und nicht tödliche Folgen im Zusammenhang mit dem Absetzen von Statinen zu schätzen. ERGEBNISSE: Die vollständige Kohorte umfasste 29.047 Patienten, die Polypharmazie ausgesetzt waren (mittleres Alter [SD] 76,5 [6,5] Jahre; 18.257 [62,9 %] Männer). Von ihnen setzten 5819 (20,0 %) Statine ab, während sie andere Medikamente beibehielten, und 4010 (68,9 %) von ihnen wurden mit einem Vergleichspräparat gematcht. In der Abbruchgruppe betrug das mittlere (SD) Alter 76,5 (6,4) Jahre, 2405 (60,0 %) waren Männer und 506 (12,6 %) hatten Multisource Comorbidity Scores von 4 oder 5. In der Erhaltungsgruppe war das mittlere (SD) Alter betrug 76,1 (6,3) Jahre, 2474 (61,7 %) waren Männer und 482 (12,0 %) hatten Multisource-Komorbiditäts-Scores von 4 oder 5. HR, 1,24; 95 % CI, 1,07–1,43) und alle kardiovaskulären Ergebnisse (HR, 1,14; 95 % CI, 1,03–1,26), Todesfälle jeglicher Ursache (HR, 1,15; 95 % CI, 1,02–1,30) und Notaufnahmen aus irgendeinem Grund (HR, 1,12; 95 % KI, 1,05–1,19). SCHLUSSFOLGERUNGEN UND RELEVANZ: In dieser Studie mit Patienten, die Polypharmazie erhielten, war das Absetzen von Statinen unter Beibehaltung anderer medikamentöser Therapien mit einem Anstieg des langfristigen Risikos für tödliche und nicht tödliche kardiovaskuläre Folgen verbunden und auch die Gesamtsterblichkeit war signifikant erhöht.

Die **Eilat Studie** untersucht die Auswirkungen des Absetzens von Statinen (18). Die EILAT-Studie umfasste Primärversorgungspatienten ab 65 Jahren und berichtete 347 Ereignisse bei 1255 Personen, die Statine einnahmen (28 %), und berichtete 4105 Ereignisse bei 7328 Patienten, die keine Statine einnahmen (56 %). Die Analyse umfasste 19.518 ältere Erwachsene, die über einen Zeitraum von 10 Jahren beobachtet wurden (Median = 9,7 Jahre). Die Gesamtmortalitätsraten waren bei denjenigen, die sich an die Statinbehandlung gehalten hatten, um 34 % niedriger als bei denjenigen, die dies nicht getan hatten (Hazard Ratio [HR] = 0,66; 95 % Konfidenzintervall [KI] = 0,56–0,79). Die Einhaltung von Statinen war auch mit weniger atherosklerotischen kardiovaskulären Krankheitsereignissen verbunden (HR = 0,80; 95 % KI = 0,71–0,81). Der Nutzen der Statinanwendung nahm bei über 75-Jährigen nicht ab und war sowohl für Frauen als auch für Männer offensichtlich. Dr. Philippe Giral beobachtete den Effekt das Statin Stop bei Personen über 75 Jahren (19). Das Absetzen von Statinen war bei 75-jährigen Primärpräventionspatienten mit einem um 33 % erhöhten

Risiko für eine Aufnahme wegen kardiovaskulärer Ereignisse verbunden. Zukünftige Studien, einschließlich randomisierter Studien, sind erforderlich, um diese Ergebnisse zu bestätigen und die Aktualisierung und Klärung von Leitlinien zur Verwendung von Statinen zur Primärprävention bei älteren Menschen zu unterstützen.

Orkaby untersuchte die Statineffekte auf die Sterblichkeit ab 75 Jahren (20). **Ergebnisse**: Von 326.981 geeigneten Veteranen (mittleres [SD]-Alter 81,1 [4,1] Jahre; 97 % Männer; 91 % Weiße), 57.178 (17,5 %) neu mit Statinen während des Studienzeitraums begonnen. Während einer mittleren Nachbeobachtungszeit von 6,8 (SD, 3,9) Jahren traten insgesamt 206902 Todesfälle auf, darunter 53296 kardiovaskuläre Todesfälle, mit 78,7 bzw. 98,2 Todesfällen/1000 Personenjahren unter Statinanwendern bzw. Nichtanwendern (gewichtete Inzidenzratendifferenz). [IRD]/1000 Personenjahre, –19,5 [95 % KI, –20,4 bis –18,5]). Es gab 22,6 bzw. 25,7 kardiovaskuläre Todesfälle pro 1000 Personenjahre unter Statinanwendern bzw. Nichtanwendern (gewichtete IRD/1000 Personenjahre, –3,1 [95 KI, –3,6 bis –2,6]). Für den zusammengesetzten ASCVD-Ergebniswert gab es 123379 Ereignisse, mit 66,3 bzw. 70,4 Ereignissen/1000 Personenjahren unter Statinanwendern bzw. Nichtanwendern (gewichtete IRD/1000 Personenjahre, –4,1 [95 % KI, –5,1 bis –3,0]). Nach Anwendung der Überlappungsgewichtung des Neigungs-Scores betrug die Hazard Ratio 0,75 (95 % KI, 0,74–0,76) für die Gesamtmortalität, 0,80 (95 % KI, 0,78–0,81) für die kardiovaskuläre Mortalität und 0,92 (95 % KI, 0,91). -0,94) für eine Zusammenstellung von ASCVD-Ereignissen beim Vergleich von Statin-Anwendern mit Nicht-Anwendern. **Schlussfolgerungen und Relevanz:** Bei US-Veteranen ab 75 Jahren, die zu Studienbeginn frei von ASCVD waren, war die neue Statinanwendung signifikant mit einem geringeren Risiko für Gesamtmortalität und kardiovaskuläre Mortalität verbunden. Weitere Forschung, einschließlich randomisierter klinischer Studien, ist erforderlich, um die Rolle der Statintherapie bei älteren Erwachsenen für die Primärprävention von ASCVD definitiver zu bestimmen.

Betreffend Kosteneffektivität hat das Bundesamt für Gesundheit einen Bericht erstellen lassen (21,22). Sämtliche Korrespondenz und Ergebnisse sind bei uns nachzuverfolgen. Gemäss der Endfassung des HTA Reports betreffen die Kosten pro QALY negative Resultate, somit ein „return on investment" bei gesunden Personen bis 75 Jahre. Da bei Personen ab 75 Jahren häufig ein hohes Risiko für kardiovaskuläre (ASCVD) Ereignisse besteht (rund 5% pro Jahr), besteht kein Grund anzunehmen, dass ab 75 Jahren die positiven kostengünstigen Effekte plötzlich entfallen würden. Die Studie des BAG zeigt auch, dass die narrative Untersuchung des Swiss Medical Boards zur Kosteneffektivität von Statinen falsche Ergebnisse produziert hat (23–27).

Table 5: HTA report about Statins, BAG Nov 2020, regarding cost-efficiency of statins according to level of AGLA risk.

This is an analysis of cost-effectiveness, HTA BAG Nov 2020

The HTA report has been corrected based upon my intervention. The correction factor of the HTA report for AGLAcvd is 1.80, therefore 80% underestimation of risk with AGLAchd.

In slide 3, we found a correction factor of 1.69, which is therefore very similar to the HTA report and suggests, that AGLAcvd is 69% higher than reported by AGLAchd.

This fact shows, that it is inadmissible that AGLA sells CHD for CVD. This is wrong.

The cost-efficacy of Statins is maintained for all patients up from an AGLA risk of at least 5%, probably 3% (< 100 000 / QALY).

This is similar to our calculations published with Prof. Szucs (we found a threshold of 7%). AGLA never fought publicly against the SMB Statin report. This cannot be tolerated.

Age	AGLA risk					
	1%	5%	10%	15%	20%	25%
Males						
40	39,514	4,518	1 088	-105	-748	-1 154
45	59,300	5,799	925	-486	-1,134	-1 542
50	88,152	8,291	800	-913	-1,662	-2 055
55	114,080	12 185	1,316	-1,297	-2,268	-2 714
60	167,037	18,286	2,694	-1,317	-2,832	-3,472
65	204,799	26,356	5,466	-580	-2,999	-4,115
70	274,364	39,396	10 214	1,565	-2,243	-4,206
75	281,012	59,023	19,420	5,692	677	-2,658
Females						
40	14,133	2,757	471	-722	-1,214	-1,573
45	21,095	3,023	383	-702	-1,320	-1,965
50	35,175	3,114	109	-1,009	-1,663	-2,075
55	61,885	4,348	-370	-1,564	-2,178	-2,503
60	91,027	7,937	400	-2,322	-2,993	-3,327
65	139,794	15 349	1 200	-2,509	-3,811	-4,345
70	217,042	28,403	5,726	-997	-3,668	-4,963
75	344,412	51,832	16,038	4,660	-834	-3,512

A major issue reflects the AGLA correction factor of 0.7, which was derived from our observation in 100 patients having had a coronary calcium score in the year 2000 (https://cardiovascmed.ch/article/doi/cvm.2005.01103).

Es besteht somit zu den positiven Statineffekten ab 65, 70 und 75 Jahren weitgehend Gewissheit, jedoch weniger direkte Evidenz aus randomisierten, Placebo-kontrollierten Studien, weswegen in Australien die Staree Studie durchgeführt wird (28). In der Staree Studie werden 18'000 Personen im Alter von 70 Jahren oder mehr untersucht. Die Wirksamkeit von Atorvastatin 40 mg gegenüber Placebo ist doppelt verblindet. Die Studie schliesst noch Personen bis Ende 2022 ein und die Studie wird im Dezember 2023 abgeschlossen werden. Der primäre Endpunkt ist Tod oder Demenz. Sekundäre Endpunkte (insgesamt 12) sind u.a. Herzinfarkt, Hirnschlag, Demenz und Gebrechlichkeit. Eingeschlossen werden alle unabhängig lebenden Personen ab 70. Lebensjahr, ausgeschlossen werden Personen mit bekannten kardiovaskulären Erkrankungen (Herzinfarkt, Hirnschlag, PTCA, PAD, CABG), Demenz, Diabetes mellitus Typ II, Cholesterin > 7.5 mmol/l, Niereninsuffizienz, Leberkrankheiten, Lebenserwartung unter 5 Jahren, Teilnahme in anderen Studien, absolute Kontraindikation für Statine, aktuelle Einnahme von Statinen oder Weigerung, Statine abzusetzen, Einnahme von bestimmten Medikamenten (Langzeitgebrauch von Cytochrome P450 (CYP) 3A4 Inhibitoren.

Die Stream-Studie (29) wurde mit folgender Begründung konzipiert: «Statine gehören zu den am häufigsten verwendeten Medikamenten. Während sie sich bei Probanden mittleren Alters als wirksam (effective) zur Primär- und Sekundärprävention von Herz-Kreislauf-Erkrankungen (CVD) erwiesen haben, ist ihr Nutzen (benefit) für die Primärprävention bei älteren Erwachsenen (im Alter von ≥ 70 Jahren) ohne CVD ungewiss, insbesondere bei Patienten mit Multimorbidität. Das Ziel dieser randomisierten kontrollierten Studie (RCT) ist es, eine Orientierungshilfe zu den Vorteilen und Risiken einer Statin-Absetzung bei multimorbiden älteren Erwachsenen zu geben.»

Die Autoren begründen die Stream-Studie vor folgendem Hintergrund: «Hintergrund: Bisher hat keine RCT, die den Nutzen von Statinen in der Primärprävention untersucht, ausschließlich multimorbide Teilnehmer im Alter von 70 Jahren und älter (70+) rekrutiert, und Teilnehmer über 70 sind in den meisten RCTs unterrepräsentiert, einschließlich derjenigen, die den Nutzen von Statinen in der Primärprävention untersuchen. Nebenwirkungen von Statinen und Arzneimittelwechselwirkungen sind jedoch in Populationen multimorbider älterer Erwachsener häufig und können sich negativ auf die Lebensqualität auswirken. In Beobachtungsstudien wurde gezeigt, dass der Anteil der Patienten, die unter Statinen eine Myalgie entwickeln, bei 5-20 % liegt; höheres Alter und Polypharmazie sind bekannte Risikofaktoren für die Entwicklung von Muskelproblemen unter Statinen. Darüber hinaus treten bei multimorbiden älteren Erwachsenen mit Polypharmazie eher Nebenwirkungen von Statinen (z. B. erhöhte Leberenzyme, Diabetes, Myopathie, Rhabdomyolyse) und Arzneimittelwechselwirkungen (z. B. Antibiotika, Antimykotika) auf, mit den möglichen Folgen einer Arzneimitteltoxizität und einer verringerten körperlichen Wirkung Aktivität, Sarkopenie und Stürze. In der Praxis werden Statine häufig bei multimorbiden älteren Erwachsenen ohne kardiovaskuläre Erkrankungen nach Nebenwirkungen abgesetzt. Der klinische Nettonutzen von Statinen für die Primärprävention bei multimorbiden älteren Erwachsenen über 70 bleibt unklar, und die Wirkung der Multimorbidität könnte die Evidenz dahingehend verschieben, dass keine Statinbehandlung bevorzugt wird, aber keine große RCT untersuchte dieses Thema.»

Studiendesign: «Die Studie ist eine multizentrische, randomisierte Nichtunterlegenheitsstudie, die an mehreren Zentren in der Schweiz durchgeführt wird. Die Studienteilnehmer werden nach dem Zufallsprinzip im Verhältnis 1:1 entweder der Unterbrechung (Interventionsarm) oder der Fortsetzung (Kontrollarm) der Statintherapie zugeteilt. Die Studie ist offen, mit verblindeter Ergebnisbewertung. Nach dem Einschluss werden die Studienteilnehmer zunächst nach 3 Monaten und dann jährlich für durchschnittlich 24 Monate telefonisch nachbeobachtet (min. Nachbeobachtungszeitraum 12 Monate, max. Nachbeobachtungszeitraum 48 Monate). Die Ergebnisse werden bei jedem Follow-up der Studie bewertet.»

Primäre Endpunkte: «Tod aller Ursachen und schweren nicht tödlichen kardiovaskulären Ereignissen (nicht tödlicher Myokardinfarkt, nicht tödlicher ischämischer Schlaganfall) innerhalb von 24 Monaten. Der primäre Endpunkt ist ein zusammengesetzter Endpunkt aus Tod aller Ursachen und schwerwiegenden nicht tödlichen kardiovaskulären Ereignissen (nicht tödlicher Myokardinfarkt, nicht tödlicher ischämischer Schlaganfall). Der Gesamttod (und nicht nur der kardiovaskuläre Tod) wird

gewählt, um eine mögliche Verschiebung von kardiovaskulären Todesursachen zu anderen Todesursachen zu berücksichtigen. Der zusammengesetzte Endpunkt wurde ausgewählt, um den klinischen Nettonutzen in dieser Population mit erwarteter hoher Sterblichkeit zu bewerten. Das Komitee für klinische Ereignisse, das vermutete Ereignisse für die primären und sekundären klinischen Endpunkte klassifiziert, ist verblindet. Der primäre Analysezeitraum liegt bei 24 Monaten, und die Datenerhebung wird bis zu 48 Monate durchgeführt.»

Sekundäre Endpunkte: «Zusammengesetzter Endpunkt aus Tod aller Ursachen und schweren nicht tödlichen kardiovaskulären Ereignissen (nicht tödlicher Myokardinfarkt, nicht tödlicher ischämischer Schlaganfall) innerhalb von 48 Monaten. Zusammengesetzter Endpunkt aus Tod jeglicher Ursache und schwerwiegenden nicht tödlichen kardiovaskulären Ereignissen (nicht tödlicher Myokardinfarkt, nicht tödlicher ischämischer Schlaganfall). Tod jeglicher Ursache [Zeitrahmen: bis zu 48 Monate]. Alle Todesfälle (aus welchem Grund auch immer). Nicht-CV-Tod [Zeitrahmen: bis zu 48 Monate]: Alle Todesfälle mit Ausnahme von Todesfällen aufgrund schwerwiegender CV-Ereignisse. Wichtige CV-Ereignisse [Zeitrahmen: bis zu 48 Monate]. CV Tod, nicht tödlicher Myokardinfarkt und nicht tödlicher ischämischer Schlaganfall. Lebenslaufereignisse insgesamt [Zeitrahmen: bis zu 48 Monate]: CV Tod, nicht tödlicher Myokardinfarkt, Krankenhausaufenthalt wegen instabiler Angina pectoris, nicht tödlicher ischämischer Schlaganfall (einschließlich TIA) und arterielle Revaskularisation (koronare und periphere dringende und nicht dringende Revaskularisation): Zusammengesetzte Ereignisse insgesamt bis zu 48 Monate: Tod jeglicher Ursache, nicht tödlicher Myokardinfarkt, Krankenhausaufenthalt wegen instabiler Angina pectoris, nicht tödlicher ischämischer Schlaganfall (einschließlich TIA) und arterielle Revaskularisation (koronare und periphere dringende und nicht dringende Revaskularisation). EQ-5D-Fragebogen [Zeitrahmen: 3, 12 (Primäranalyse), 24, 36, 48 Monate]. EQ-5D ist der Name des Instruments und kein Akronym. Allgemeine Bewertung der Lebensqualität. Der mögliche Wertebereich reicht von 0 bis 1,0, wobei höhere Werte eine bessere Lebensqualität anzeigen. Verbaler numerischer Schmerzbewertungswert (VNPRS) 3 Monate. Um Statin-assoziierte Muskelsymptome zu beurteilen. Der VNPRS ist eine 11-Punkte-Skala, die von 0-10 bewertet wird, wobei höhere Werte einen höheren Schmerzgrad anzeigen. Selbstberichtete Stürze 12 Monate. Selbstberichtete Stürze, jeder Teilnehmer sammelt und listet alle Stürze während der ersten 12 Monate nach der Randomisierung auf. Umstände und medizinische Folgen jedes Sturzes werden erhoben. Aggregiert als Sturzrate (Stürze pro Person und Jahr). Kraft, Unterstützung beim Gehen, Aufstehen von einem Stuhl, Treppensteigen und Stürzen (SARC-F-Fragebogen) 12 (Primäranalyse), 24, 36, 48 Monate. 5-Punkte-Fragebogen, die Punktzahl reicht von 0 bis 10, wobei höhere Punktzahlen einen höheren Grad an Sarkopenie anzeigen. Girerd-

Medikamenteneinhaltungsskala 12 (Primäranalyse), 24, 36, 48 Monate 6-Punkte-Fragebogen, die Punktzahl reicht von 0 bis 6, höhere Punktzahlen weisen auf eine schlechtere Medikamentenadhärenz hin.»

Einschlusskriterien: «Schriftliche Einverständniserklärung. ≥70 Jahre alt, Multimorbid mit ≥2 koexistierenden chronischen Erkrankungen (definiert durch ICD-10-Codes) mit einer geschätzten Dauer von 6 Monaten oder mehr basierend auf einer klinischen Entscheidung, abgesehen von Dyslipidämie, die mit Statinen behandelt wird. Einnahme eines Statins für ≥80 % der Zeit während des Jahres vor der Einschreibung.»

Ausschlusskriterien: «Kardiovaskuläre Sekundärprävention basierend auf früheren großen Statinstudien, definiert als: Vorgeschichte eines Myokardinfarkts Typ 1 (NSTEMI/STEMI), oder Vorgeschichte einer instabilen Angina pectoris, definiert als symptomatisches ACS in Ruhe, Crescendo oder neu auftretende Angina (CCS 2 oder 3) ohne EKG- oder kardiale Biomarker-Veränderungen (basierend auf verfügbaren Dokumenten), oder stabile Angina pectoris mit einer dokumentierten Ischämie bei einem Belastungstest oder mit einer signifikanten Koronarerkrankung, definiert als Koronarstenose > 50 %, oder Anamnese einer perkutanen Koronarintervention (Ballon oder Stent) oder Koronararterien-Bypass-Operation, oder Geschichte des Schlaganfalls, oder Vorgeschichte einer transienten ischämischen Attacke, definiert als transientes neurologisches Defizit ohne Diffusionsbeschränkung im MRT, oder Karotis-Revaskularisation in der Anamnese (Stent oder Bypass), oder Vorgeschichte einer peripheren arteriellen Verschlusskrankheit, die eine Revaskularisierung erfordert (Stent oder Bypass; Fontaine IV) oder Aortenerkrankung, die eine Gefäßreparatur erforderte, oder Aortenaneurysma mit einem maximalen Durchmesser von > 5,5 cm (Männer) oder > 5,2 cm (Frauen), basierend auf verfügbaren Dokumenten, Diagnose einer familiären Hypercholesterinämie basierend auf dem Dutch Lipid Score ≥6 basierend auf verfügbaren Dokumenten (LDL-Cholesterin, Familienanamnese, persönliche Vorgeschichte), erhöhtes Sterberisiko innerhalb von 3 Monaten nach Studienbeginn, definiert als: hospitalisierte Patienten, die innerhalb von 24 Stunden nach der Aufnahme für Palliativpflege vorgesehen sind oder hospitalisierte Patienten mit einem Palliative Performance Scale (PPS)-Level < 30 % (basierend auf der Situation mindestens 1 Monat vor dem Krankenhausaufenthalt), dies entspricht einer geschätzten Überlebensrate von 43 % nach 3 Monaten; oder Patienten mit einer fortgeschrittenen metastasierten Krebsprognose von ≤20 % Überlebensrate innerhalb von 1 Jahr nach Baseline (basierend auf: https://cancersurvivalrates.com)»

Begründung

Die Sicherheit und Gesundheit der betroffenen Studienteilnehmerinnen sind in der Stream Studie gefährdet. Die medizinische Evidenz zur Effektivität der Lipidtherapie insbesondere mit Statinen ist auch für Personen ab 70 Jahren erwiesen. Die von den Autoren erwähnte Ungewissheit der Statin-Effekte ab 70 Jahren ist eine Falschbehauptung. Es besteht weniger Gewissheit als bei Personen unter 70 Jahren, aber keine Ungewissheit. Zudem hat das Bundesamt für Gesundheit die Kosteneffektivität von Statinen bis 75 Jahren festgestellt.

Kritikpunkte an den Stream Studienautoren zur Studienanlage betreffend:

Begründung: Die Wirksamkeit von Statinen wird zugegeben, aber im Alter ab 70 Jahren als ungewiss bezeichnet, es müsste heissen, weniger gewiss. Statt Wirkung wird der Begriff Nutzen (benefit) verwendet, ohne dass dieser Begriffswechsel begründet wird.

Hintergrund: Die erwähnten Gründe rechtfertigen keine weitere Studie. Bereits im klinischen Alltag werden sämtliche Limitationen der Statinbehandlung berücksichtigt.

Studiendesign: dieses ist falsch gewählt. Eine non-inferiority Studie kann eine fehlende Wirkung nicht ausschliessen, hierfür wird das Studiendesign der Staree Studie verwendet mit ca 80'000 Patientenbeobachtungsjahren (Stream: ca. 1800). Non-inferiority Studien werden aus ethischen Gründen immer mit einem aktiven Komparator durchgeführt, da die Wirkung des Vergleichsmedikaments ja erwiesen ist (1). Placebo-Studien oder gar absetzen von wirksamen Medikamenten sind in non-inferiority Trials deshalb nicht gestattet. Die European Medicines Agency definiert klar: «The objective of a non-inferiority trial is sometimes stated as being to demonstrate that the test product is not inferior to the comparator. However, only a superiority trial can demonstrate this.» (2).

Primäre Endpunkte: das Studiendesign gestattet nicht, die Wirkung von Statinen zu untersuchen. Die Beobachtungsjahre sind viel zu tief gewählt.

Sekundäre Endpunkte: das open-label Studiendesign gestattet keine Aussagen zu den meisten sekundären Endpunkten, insbesondere Lebensqualität, Schmerzbewertung, Kraft, Medikamentenadhärenz. Hierfür sind z.B. N-1 Studien notwendig (30).

Einschlusskriterien: Multimorbidität erhöht das Risiko für das Vorliegen einer präklinischen Atherosklerose und das Risiko für tödlichen und nicht-tödlichen Herz- und Hirnschlag, z.B. betreffend Kombinationen mit Diabetes mellitus Typ II, entzündliche-rheumatische Erkrankungen, Niereninsuffizienz, Nikotin- oder e-Zigaretten Gewohnheit, erhöhtes CRP, Adipositas, Arthrosen und andere Krankheiten mit Bewegungsmangel, arterielle Hypertonie, Dutch Lipid Score 3 bis 5 ist eine familiäre Hypercholesterinämie möglich (z.B. positive Familienanamnese und LDL 5.0 mmol/l = 5 Punkte).

Ausschlusskriterien: In der Staree Studie gelten Diabetes mellitus Typ II, Niereninsuffizienz oder ein Cholesterin von > 7.5 mmol/l als Ausschlusskriterien. Die Stream-Studie schliesst aufgrund des Multimorbiditätskriteriums zahlreiche Personen mit hohem kardiovaskulärem Risiko einschliesslich Cholesterin > 7.5 mmol/l ein. Es sind deshalb weitere Ausschlusskriterien zu fordern, z.B. Vorliegen einer subklinischen Atherosklerose in der Bildgebung (31), dies in Übereinstimmung mit Mortensen (32). Auch existiert weltweit keine Empfehlung, Statine ab 70 Lebensjahren abzusetzen oder nicht einzusetzen. Grund dafür ist die Anzahl erwarteter Lebensjahre. Beträgt diese mehr als 5 Jahre besteht ein Konsens darüber, Statine einzusetzen (3).

Informed consent form (ICF).

Aufgrund der wissenschaftlich falschen Darstellung der Statin Wirksamkeit bei Personen ab 70 Jahren durch die Autoren der Stream Studie ist davon auszugehen, dass die Angaben im ICF nicht korrekt sind oder Tatsachen in der Art verdreht werden, dass die Gefährdung der Studienteilnehmerinnen von diesen zu wenig oder gar nicht erkannt wird.

Die Stream-Studie des Berner Instituts für Hausarztmedizin lädt Ärztinnen und Ärzte ein, Patientinnen und Patienten, die 70 Jahre und älter sind und denen ein cholesterinsenkendes Statin verschrieben wurde, anzufragen, ob sie bereit wären, dieses zu Studienzwecken abzusetzen. Willigen sie ein, so entscheidet ein Computerprogramm zufällig, welche Hälfte von ihnen das verschriebene Medikament weiterhin erhält und welche nicht. Nach 12 bis 45 Monaten will man schauen, ob in jener Gruppe, welche die Behandlung abgesetzt hat, auch wirklich mehr Herzinfarkte und Hirnschläge auftreten.

Hierzu ist festzuhalten: Dafür, dass Statin-Effekte im Alter (https://varifo.ch/statin-effekte/) plötzlich abnehmen sollen, gibt es keinerlei Evidenz. Die wissenschaftliche Situation ist lediglich so, dass für

den Effekt zur Prävention von Herzinfarkt und Hirnschlag durch Statine ab 70 Jahren weniger Evidenz besteht als insgesamt. Die Stream-Studie ist aus diesem Grund problematisch:

- Punkt zwei des Nürnberger Kodex (https://de.wikipedia.org/wiki/N%C3%BCrnberger_Kodex) hält fest: «Der Versuch muss so gestaltet sein, dass fruchtbare Ergebnisse für das Wohl der Gesellschaft zu erwarten sind, welche nicht durch andere Forschungsmittel oder Methoden zu erlangen sind.»
- Verletzung Art. 11 HFG: da bereits die Staree Studie kurz vor dem Abschluss steht, ist ein weiteres Forschungsprojekt nicht notwendig
- Verletzung Art. 12 HFG: der erwartete klinische Effekt eines sicheren und im allgemeinen auch sehr gut verträglichen Statins (33) rechtfertigt die Risiken eines Absetzens von Statinen unabhängig von erwiesenen Nebenwirkungen nicht.
- Verletzung Art. 13 HFG: es besteht keine zwingende oder methodische Begründung für das Absetzen von Statinen (=Placebo Effekt), da der Effekt von Statinen auch ab 70 Jahren erwiesen ist und mit der Studienteilnahme nicht akzeptable Risiken auftreten.
- Verletzung Art. 16b HFG: es muss davon ausgegangen werden, dass die Risiken des Statin-Stop im ICF nicht korrekt wiedergegeben werden.

Es sind von der Stream-Studie keine für das Wohl der Gesellschaft fruchtbaren Ergebnisse zu erwarten. Zu riskieren, dass die Studienteilnehmerinnen und Studienteilnehmer einen Herzinfarkt oder einen Hirnschlag erleiden, ist folglich nicht verantwortbar. Dies insbesondere, weil derzeit internationale Studien laufen, um eben diese kleine verbleibende Evidenzlücke zu schliessen.

Über die Risiken einer Studienteilnahme informiert das Berner Institut für Hausarztmedizin die Studienteilnehmerinnen und Studienteilnehmer wie folgt: «Der Cholesterinspiegel wird ansteigen. Es ist jedoch nicht bewiesen, dass ein erhöhter Cholesterinspiegel ein Risikofaktor für einen Herzinfarkt/Schlaganfall bei 70+ Personen, die nie eine solche Krankheit erlitten haben, darstellt.» Dies ist aufgrund der vorhandenen Evidenz eine Falschaussage (4).

Und weiter: «Ein Herzinfarkt/Schlaganfall kann trotz Statin/tiefem Cholesterinspiegel eintreten.» Mit einer solchen Aussage wir bewusst die positive Wirkung zusätzlich schlecht geredet. Solche Irreführungen nutzen Unsicherheiten der Seniorinnen und Senioren aus, ein weiterer Verstoss gegen den Nürnberger Kodex:

- Punkt eins des Nürnberger Kodex hält fest: «Die freiwillige Zustimmung der Versuchsperson ist unbedingt erforderlich. Das heißt, dass die betreffende Person im juristischen Sinne fähig

sein muss, ihre Einwilligung zu geben; dass sie in der Lage sein muss, unbeeinflusst durch Gewalt, Betrug, List, Druck, Vortäuschung oder irgendeine andere Form der Überredung oder des Zwanges, von ihrem Urteilsvermögen Gebrauch zu machen; dass sie das betreffende Gebiet in seinen Einzelheiten hinreichend kennen und verstehen muss, um eine verständige und informierte Entscheidung treffen zu können.»

Die Studie räumt auf ihrer Website (https://www.statin-stream.ch/infos-fuer-teilnehmer/) Risiken zwar ein: «Es kann jedoch nicht ausgeschlossen werden, dass Stoppen der Statin-Therapie das Risiko eines Herzinfarkts oder Schlaganfalls erhöhen könnte ...» Im Gespräch mit den Patientinnen und Patienten wie es ein Beispielfilm (https://www.youtube.com/watch?v=UYBw1LapqS0&t=1s) zeigt, wird dann aber einseitig informiert und suggestiv gefragt, womit die Seniorinnen und Senioren manipuliert werden könnten. Es stellt sich deshalb die Frage, ob behandelnde Ärztinnen und Ärzte diese Gespräche führen dürfen, oder ob dies vor obigem Hintergrund nicht wissenschaftlichen Mitarbeiterinnen und Mitarbeitern vorbehalten sein sollte, da die Gespräche selbst Teil der Studie sind:

- Punkt acht des Nürnberger Kodex hält fest: «Der Versuch darf nur von wissenschaftlich qualifizierten Personen durchgeführt werden. Größte Geschicklichkeit und Vorsicht sind auf allen Stufen des Versuchs von denjenigen zu verlangen, die den Versuch leiten oder durchführen.»

Mit freundlichen Grüssen

Dr. med. Michel Romanens, Olten
Leitung VEMS, FAIRFOND, VARIFO

Dr. Walter Warmuth, Leipzig.
Mitglied VEMS, FAIRFOND Stiftung

Beilagen: Doppel der Eingabe

Mitunterzeichnung:

Dr. med. Ted Schober, Lützelflüh, Mitglied VEMS, FAIRFOND Stiftung

Flavian Kurth, Basel (Sekretär VEMS, FAIRFOND Stiftung)

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Pfiffner Dorothy, GSI-GA

Von:	Michel Romanens <michel.romanens@hin.ch>
Gesendet:	Montag, 13. Juni 2022 09:30
An:	Info GSI, KEK
Cc:	michel romanens
Betreff:	Eingabe und Votum Stream Studie [SecureMail]
Anlagen:	Mortensen, Falk - 2018 - Primary Prevention With Statins in the Elderly.pdf

Guten Tag

Die Stream Studie (https://www.statin-stream.ch/) unter der Leitung von Prof. Rodondi randomisiert Patienten ab 70 Jahren mit zusätzlichen Komorbiditäten wie Bluthochdruck oder Diabetes II, um lipidsenkende Therapien (z. B. Statine oder Ezetimib) in der Primärversorgung abzusetzen. Diese Kohortenstudie ist eine Nichtunterlegenheitsstudie mit geplantem Einschluss von 1'800 Personen über eine durchschnittliche Beobachtungszeit von 2 Jahren. Der primäre Endpunkt ist Tod aus allen Gründen und nicht-tödlicher Myokardinfarkt oder Schlaganfall. Sekundäre Ergebnismessungen umfassen Fragebögen zu Lebensqualität, Muskelschmerzen, Stürzen und Medikamenteneinnahme. Die STREAM-Studie ist offen und daher nicht therapie-verblindet, und teilnehmende Ärzte mit ihren Patienten sind verpflichtet, während des Studienzeitraums keine LDL-Werte zu kontrollieren.

Zentrale Fehlbehauptung bei der Patientenrekrutierung ist die Aussage, es gäbe zu wenig Evidenz, dass Statine ab 70 genügend wirksam seien. Es müsste heissen: es gibt weniger Evidenz. Die existierende Evidenz zeigt gegenüber jüngeren Personen keine Verminderung der Statin-Effekte. Personen, welche an der Studie teilnehmen sollen, werden somit angelogen. Literatur: https://varifo.ch/wp-content/uploads/2022/06/Rodondi062022.pdf.

Aufgrund dieser Umstände erfolgt diese Anfrage an Sie, uns die Eingabe zur Stream Studie und das Votum der Ethikkommission (und dazugehörige allfällige Korrespondenz) so bald wie möglich zukommen zu lassen. Sollte dies nicht möglich sein, ersuche ich Sie, dies in den nächsten Tagen zu begründen. Zudem bitten wir Sie, die Studie mit einstweiliger Verfügung zu stoppen. Grund dafür sind erhebliche Sicherheitsbedenken für die Teilnehmerinnen, welche multimorbid sein müssen, um in der Studie teilzunehmen (also z.B. aktive Raucher mit Diabetes mellitus Typ II). Das ist komplett unverantwortlich. Ferner muss die Studie als weiteres Ausschlusskriterium das Vorliegen von Atherosklerose beachten: Karotis Plaque > 1.5 mm, Agatston Score > 100, TPA Flächensumme Karotiden > 22 mm2, PAVK, atherosklerotische Plaque in der Aorta. Bei Personen mit Atherosklerose ist das Absetzen von Statinen lebensgefährlich.

Mit bestem Dank und freundlichen Grüssen

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REVIEW TOPIC OF THE WEEK

Primary Prevention With Statins in the Elderly

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ABSTRACT

The burden of atherosclerotic cardiovascular disease (ASCVD) in high-income countries is mostly borne by the elderly. With increasing life expectancy, clear guidance on sensible use of statin therapy to prevent a first and potentially devastating ASCVD event is critically important to ensure a healthy aging population. Since 2013, 5 major North American and European guidelines on statin use in primary prevention of ASCVD have been released by the American College of Cardiology/American Heart Association, the UK National Institute for Health and Care Excellence, the Canadian Cardiovascular Society, U.S. Preventive Services Task Force, and the European Society of Cardiology/European Atherosclerosis Society. Guidance on using statin therapy in primary ASCVD prevention in the growing elderly population (>65 years of age) differs markedly. The authors discuss the discrepant recommendations, place them into the context of available evidence, and identify circumstances in which uncertainty may hamper the appropriate use of statins in the elderly. (J Am Coll Cardiol 2018;71:85–94)

The short-term risk of atherosclerotic cardiovascular disease (ASCVD) increases with age, with the highest incidence rates, number of events, prevalence, and treatment costs in the elderly population. Given the increasing size of this population, it is critically important that guidelines provide clear recommendations for appropriate use of interventions of proven efficacy to reduce the burden of ASCVD in the elderly. Statin therapy represents a substantial potential for safe, effective, and inexpensive primary prevention of ASCVD in elderly individuals (here defined as individuals >65 years of age), as statins have been shown to be generally well tolerated and improve ASCVD outcome across a wide range of population characteristics. However, this potential for meaningful benefits of preventive statin therapy in elderly people is inconsistently utilized in existing guidelines in Europe and North America, as described in this review.

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SCOPE OF THE PROBLEM: DISEASE BURDEN IN THE ELDERLY

The proportion and number of elderly people 65 years of age or older are increasing fast worldwide (1). At 65 years of age, life expectancy is currently estimated to be >20 years for women and >17 years for men in most high-income countries (2). The impact of these demographic changes on the burden of ASCVD is dramatic. It has been projected that the prevalence of coronary heart disease—the most prevalent form of ASCVD—in the United States will increase by as much as 43% (≈5 million more) by year 2030 due to demographic changes alone, while the associated increase in direct costs might be as much as 198% (≈$70 billion more) (3,4). This development poses a major challenge for societies to ensure a healthy elderly population.

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ABBREVIATIONS AND ACRONYMS

ACC/AHA = American College of Cardiology/American Heart Association

ASCVD = atherosclerotic cardiovascular disease

CCS = Canadian Cardiovascular Society

CI = confidence interval

ESC/EAS = European Society of Cardiology/European Atherosclerosis Society

MI = myocardial infarction

NICE = National Institute for Health and Care Excellence

RCT = randomized controlled trial

RR = relative risk

SAS = statin-associated symptoms

SCORE = Systematic COronary Risk Evaluation

STATIN GUIDELINES AND RECOMMENDATIONS FOR THE ELDERLY

Since 2013, 5 major guidelines on statin use to prevent ASCVD have been released, in 2013 by American College of Cardiology/American Heart Association (ACC/AHA) (5), in 2014 by the UK National Institute for Health and Care Excellence (NICE) (6), in 2016 by the Canadian Cardiovascular Society (CCS) (7), in 2016 by the U.S. Preventive Services Task Force (8), and in 2016 by the European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) (9). Although these guidelines are based on the same evidence originating predominantly from randomized controlled trials (RCTs) of statin therapy, the recommendations for using statins to prevent a first ASCVD event differ substantially (**Table 1**). Nevertheless, the guidelines share the same basic concept of allocating statin therapy to those assumed to be at highest risk for ASCVD, either because of a well-defined high-risk condition (i.e., diabetes) or because of a high estimated 10-year risk for a first ASCVD event using guideline-specific risk scores.

One striking difference among the guidelines is their recommendations for statin therapy with advancing age. To facilitate meaningful discussion and highlight important differences, guideline recommendations and evidence pertinent to 3 age groups are reviewed independently—middle aged (40 to 65 years of age), elderly (66 to 75 years of age), and very elderly (>75 years of age)—with the main focus on those individuals >65 years of age.

PRIMARY PREVENTION IN MIDDLE-AGED INDIVIDUALS (40 TO 65 YEARS OF AGE). For apparently healthy individuals 40 to 65 years of age, all 5 statin guidelines provide strong or Class I recommendations for initiation of statin therapy in those at highest risk (**Table 1, Figure 1**). This age group has been well represented in high-quality primary prevention statin trials (**Table 2**) (10-20), and little controversy exists regarding statin efficacy in those at highest risk (21,22). However, the guidelines do not agree on how to define the risk above which statin therapy should be initiated. Although the 2016 ESC/EAS guideline continues to base its recommendations on old "high-risk" considerations (23), the other 4 guidelines have expanded the indication for statin treatment considerably based on a combination of strong RCT evidence, net benefit, and cost-effectiveness analyses (24,25). This is exemplified in the **Central Illustration** by a man who undergoes risk assessment every 10 years. At 56 years of age, his estimated 10-year risk for ASCVD using guideline-recommended risk scores is so high that all but the Systematic COronary Risk Evaluation (SCORE)-based ESC/EAS guideline would recommend initiation of statin therapy (**Table 1**).

PRIMARY PREVENTION IN THE ELDERLY (66 TO 75 YEARS). For apparently healthy individuals 66 to 75 years of age, 4 of the 5 guidelines continue to provide Class I or strong risk-based recommendations for primary prevention with statins in those at highest risk (**Figure 1, Central Illustration**). Only the ESC/EAS guideline on CVD prevention no longer has clear risk-based recommendations because SCORE is not applicable beyond 65 years of age (23). Even more notable, this guideline cautions against "uncritical" initiation of statin therapy in those >60 years of age, even if the estimated risk is very high (>10% 10-year risk for fatal CVD) (9). However, somewhat inconsistent, the ESC/EAS guideline for the management of dyslipidemias recommends that "statin therapy should be considered in older adults free from CVD, particularly in the presence of hypertension, smoking, diabetes and dyslipidaemia" (Class IIa) but without defining what is meant by "older adults" (26). In contrast, the ACC/AHA, CCS, and U.S. Preventive Services Task Force guidelines provide the same risk-based indication for statin therapy up to 75 years of age and NICE up to 84 years of age (**Figure 1, Central Illustration**). Given the strong impact of age on estimated 10-year risk for ASCVD, a progressively higher proportion of elderly individuals become statin eligible with these 4 guidelines. For example, all elderly individuals with optimal risk factors exceed the ACC/AHA 7.5% pooled cohort equation risk threshold by 65 years of age (men) or 71 years of age (women) and the NICE 10% QRISK2 risk threshold by 65 years of age (men) or 68 years of age (women).

Clinical trial evidence supports the use of statin therapy for the primary prevention of nonfatal ASCVD events in elderly individuals 66 to 75 years of age. This age group has been well represented in primary prevention statin trials (**Table 2**), and post hoc analyses from the MEGA (Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese) (27), CARDS (Collaborative Atorvastatin Diabetes Study) (28), JUPITER (Justification for the Use of Statins in prevention: An Intervention Trial Evaluating Rosuvastatin) (20,29) and HOPE-3 (Heart Outcomes Prevention Evaluation-3) (20) trials have shown improved ASCVD outcome also in those individuals older than 65 years of age at enrollment, with relative risk (RR) reductions similar to those

TABLE 1 Eligibility for Primary Prevention With Statins (Class I or Strong Indication)

Indication for Statin Therapy	ACC/AHA 2013 (5)	NICE-UK 2014/2016 (6)	CCS 2016 (7)	USPSTF 2016 (8)	ESC/EAS 2016 (9)
High estimated 10-yr risk					
Age range, yrs	40–75	30–84	30–75*	40–75	40–65†
Risk model	PCE	QRISK2	Modified FRS-CVD	PCE	SCORE
Predicted endpoints	Nonfatal MI, CHD death, stroke	CHD, stroke, TIA (fatal and nonfatal)	MI, angina, CHD death, heart failure, stroke, TIA, PAD	Similar to ACC/AHA	Fatal ASCVD
Risk threshold for therapy	≥7.5%	≥10%	10%–19% (intermediate), ≥20% (high risk)	≥10%	5% to <10% (high risk), ≥10% (very high risk)
Risk factor requirements	No	No	Yes if 10%–19% risk* No if ≥20% risk	≥1‡	No
LDL-C before treatment, mg/dl	70–189	No	≥135 if 10%–19% risk* No if ≥20% risk	≤190	≥155 if high risk ≥100 if ≥10% risk
LDL-C treatment target, mg/dl	No	High intensity: >40%↓§	<77/>50%↓*	No	<100/≥50%↓ if high risk <70/≥50%↓ if ≥10% risk
High-risk clinical condition					
FH and/or high cholesterol, mg/dl	LDL-C ≥190 ≥21 yrs of age	No§	LDL-C ≥190	No‡	FH or TC >310
Diabetes mellitus	40–75 yrs of age LDL-C ≥70	High-risk type 1§	≥40 yrs of age*	No‡	>40 yrs of age
CKD (eGFR), ml/min/1.73 m^2	No	<60§	<60†	No	30–59 = high risk <30 = very high risk†

*The Framingham Risk Score for general cardiovascular disease (FRS-CVD) is not well validated after 75 years of age. In the modified version, the risk is doubled in case of family history of premature cardiovascular disease (CVD). Equivalent values are provided for low-density lipoprotein cholesterol (LDL-C), non–high-density lipoprotein cholesterol (HDL-C), and apolipoprotein B. Required risk factors in intermediate risk: men ≥50 years of age and women ≥60 years of age and 1 additional CVD risk factor. Diabetes: ≥40 years of age or ≥15-year duration for ≥30 years of age (type 1) or microvascular disease. Chronic kidney disease (CKD): ≥50 years of age and estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2 or albumin/creatinine ratio >3 mg/mmol (those on dialysis optional). †Systematic COronary Risk Evaluation (SCORE) is only applicable up to 65 years of age. Statin therapy is not recommended in end-stage renal disease. ‡These recommendations do not pertain to persons with familial hypercholesterolemia (FH) and/or LDL-C >190 mg/dL Required risk factor includes dyslipidemia, diabetes, hypertension, or smoking. §Patients with FH or receiving renal replacement therapy are not covered under this guideline. Diabetes, high risk: type 1 diabetes >40 years of age or diabetes >10 years or nephropathy or cardiovascular risk factors. In type 2 diabetes, QRISK2-guided statin therapy is recommended. CKD: eGFR <60 ml/min/1.73 m^2 and/or albuminuria. Treatment goal: >40% reduction in non–HDL-C.

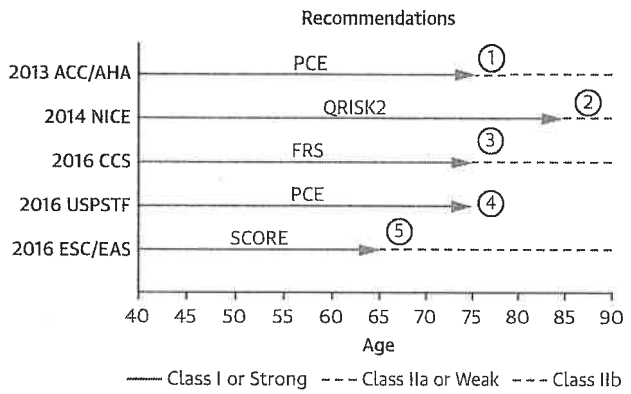
ACC/AHA = American College of Cardiology/American Heart Association; ASCVD = atherosclerotic cardiovascular disease; CCS = Canadian Cardiovascular Society; CHD = coronary heart disease; ESC/EAS = European Society of Cardiology/European Atherosclerosis Society; MI = myocardial infarction; NICE-UK = NICE = UK National Institute for Health and Care Excellence; PAD = peripheral artery disease; PCE = pooled cohort equation; TC = total cholesterol; TIA = transient ischemic attack; USPSTF = U.S. Preventive Services Task Force.

observed in younger individuals. In addition, 2 meta-analyses have provided important insights. Based on 8 RCTs (n = 24,674; ≥65 years of age), Savarese et al. (30) found that primary prevention with statins was highly effective in reducing the risk of myocardial infarction (MI) (RR: 0.60; 95% confidence interval [CI]: 0.43 to 0.85) and stroke (RR: 0.76; 95% CI: 0.63 to 0.93), but not all-cause mortality or cardiovascular death. More recently, Ridker et al. (20) provided age-stratified outcome data from the JUPITER and HOPE-3 trials. In elderly individuals 65 to 70 years of age, rosuvastatin reduced the risk of a composite endpoint (nonfatal MI, nonfatal stroke, or cardiovascular death) substantially by 49% (RR: 0.51; 95% CI: 0.38 to 0.69), and the risk was reduced by 26% (RR: 0.74; 95% CI: 0.61 to 0.91) in those ≥70 years of age. The efficacy was similar in individuals ≥70 and <65 years of age, indicating little heterogeneity in treatment effect by age. Today, nearly all apparently healthy elderly individuals have RCT evidence supporting statin efficacy (31).

PRIMARY PREVENTION IN THE VERY ELDERLY (>75 YEARS OF AGE). For apparently healthy very elderly individuals, only 1 (2014 NICE) of the 5 guidelines continues to provide a strong risk-based recommendation for initiating primary prevention with statins (**Figure 1, Central Illustration**). Thus, although the SCORE-dependent ESC/EAS guidelines provide risk-based indication for statins only up to 65 years of age, the QRISK2-dependent NICE guidelines do so up to 84 years of age. Because everyone >75 years of age exceeds the 10% 10-year QRISK2 threshold for treatment, the NICE guidelines indirectly provide a strong, universal statin indication over the range of 76 to 84 years of age. This guideline also provides a specific treatment recommendation for atorvastatin 20 mg in individuals ≥85 years of age, as "statins may be of benefit in reducing the risk of nonfatal myocardial infarctions" (**Figure 1**).

Very elderly people pose a troubling dilemma for the cardiovascular community, guideline writers, and clinical practitioners. Although they are at high risk of near-term ASCVD by virtue of their age alone, evidence of efficacy for primary prevention with statins is sparse in this age group, as only few have been included in RCTs (**Table 2**). Thus, the decision to initiate primary prevention with statins in people older than 75 years of age cannot be based directly

FIGURE 1 Recommendations for Primary Prevention With Statins in Apparently Healthy People



Guideline Recommendations in Elderly

1. "Statin therapy may be considered in selected individuals" (age >75, Class IIb)
2. "For people 85 years or older consider atorvastatin 20 mg as statins may be of benefit in reducing the risk of non-fatal myocardial infarction"
3. FRS is not well validated beyond age 75, and indications for statins are less well defined in this age group
4. There is no recommendation for statins in people >75 years old
5. SCORE is not applicable beyond age 65, but "statin therapy should be considered in older adults, particularly in the presence of hypertension, smoking, diabetes and dyslipidemia" (Class IIa)

Handling of individuals >65 years of age differs substantially among contemporary European and North American guidelines, partly because of the performance (applicability) of the risk model used. ACC/AHA = American College of Cardiology/American Heart Association; CCS = Canadian Cardiovascular Society; ESC/EAS = European Society of Cardiology/European Atherosclerosis Society; FRS = Framingham Risk Score for general cardiovascular disease; NICE = National Institute for Health and Care Excellence; PCE = pooled cohort equation; SCORE = Systematic COronary Risk Evaluation; USPSTF = U.S. Preventive Services Task Force.

on RCT evidence (32). Further, extrapolation of efficacy and safety data from those ≤75 years of age to those >75 years of age should be done cautiously, considering comorbidity, polypharmacy, potential side effects, and limited life expectancy (33). Efficacy of statin therapy in the very elderly, however, is well documented in secondary prevention trials (34). The PROSPER (Pravastatin in elderly individuals at risk of vascular disease) trial, for example, specifically assessed the benefit of statins in elderly individuals and demonstrated improved outcomes among elderly with known vascular diseases (13).

WHY THE AGE CAP ON RISK-BASED STATIN RECOMMENDATIONS? The risk for ASCVD increases dramatically with age. Why then do all strong risk-based statin recommendations expire at a certain but quite different guideline-dependent age?

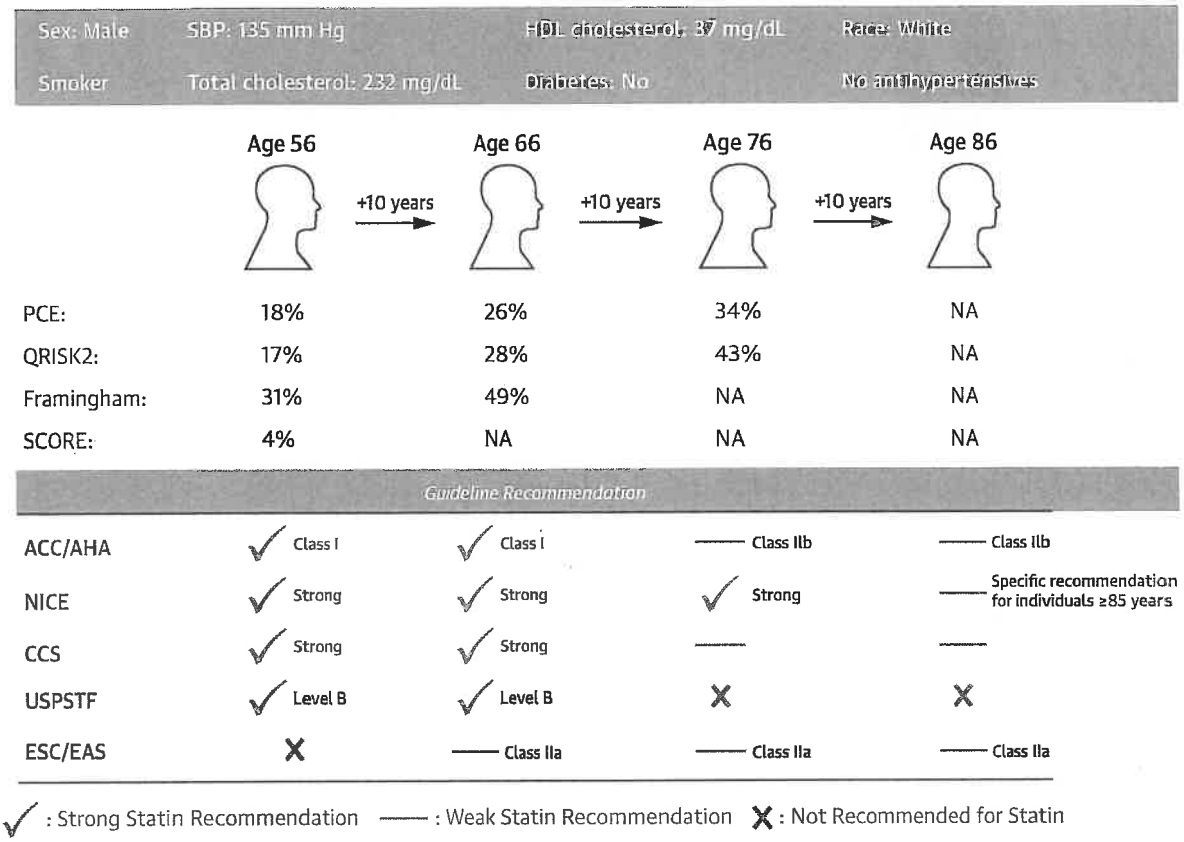
TABLE 2 Enrollment of Elderly and Very Elderly in Primary Prevention Statin Trials

Study Name, Year (Ref. #)	No.	Mean Age (yrs)	Age Range (yrs)	Elderly	Very Elderly (≥75 yrs of Age)
WOSCOPS, 1995 (10)	6,595	55	Men 45–64	0	0
AFCAPS/TexCAPS, 1998 (11)	6,605	Men 58 Women 62	Men 45–73 Women 55–73	Men 20% ≥65 yrs of age Women 33% ≥65 yrs of age	0
ALLHAT-LLT, 2002 (12)	10,355	66	≥55	28% ≥65 yrs of age*	7%*
PROSPER, 2002 (13)	3,239 (no ASCVD)	75 (whole cohort)	70–82 (whole cohort)	100% ≥70 yrs of age	NR
ASCOT-LLA, 2003 (14)	10,305	63	40–79	64% >60 yrs of age 23% >70 yrs of age	NR
CARDS, 2004 (15)	2,838	62	40–75	40% ≥65 yrs of age 12% >70 yrs of age	0
MEGA, 2006 (16)	7,832	58	40–70	23% ≥65 yrs of age	0
JUPITER, 2008 (17)	17,802	66	Men ≥50 Women ≥60	58% ≥65 yrs of age† 32% ≥70 yrs of age†	NR
HOPE-3, 2016 (18)	12,705	66	Men ≥55 Women ≥65/60	52% ≥65 yrs of age† 24% ≥70 yrs of age†	NR

*Primary prevention data reported by Han et al. (19). †Reported by Ridker et al (20).

AFCAPS/TexCAPS = Air Force/Texas Coronary Atherosclerosis Prevention Study; ALLHAT-LLT = Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial-Lipid Lowering Trial; ASCOT-LLA = Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm; CARDS = Collaborative Atorvastatin Diabetes Study; HOPE-3 = Heart Outcomes Prevention Evaluation-3; JUPITER = Justification for the Use of Statins in prevention: An Intervention Trial Evaluating Rosuvastatin; MEGA = Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese; NR = not reported; PROSPER = Pravastatin in elderly individuals at risk of vascular disease; WOSCOPS = West of Scotland Coronary Prevention Study.

CENTRAL ILLUSTRATION **Age-Dependent Implementation of Guidelines in Clinical Practice**



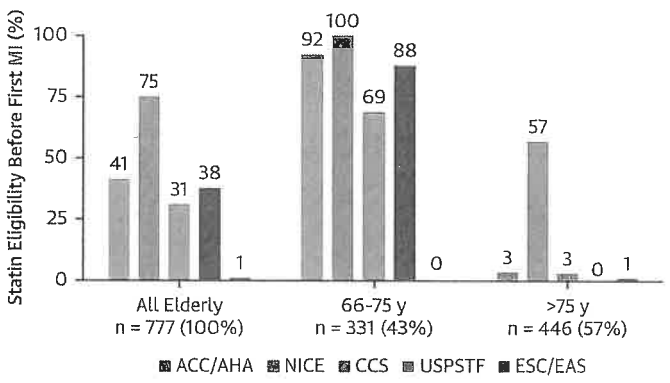
Mortensen, M.B. et al. J Am Coll Cardiol. 2018;71(1):85–94.

In apparently healthy individuals with risk factors shown in the box, all but the European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) guidelines provide a strong indication for statin therapy in the range of 56 to 66 years of age. Above 75 years of age, only the National Institute for Health and Care Excellence (NICE) guideline provides a well-defined indication for statin therapy. See **Table 1** for risks above which statin therapy is recommended. ACC/AHA = American College of Cardiology/American Heart Association; CCS = Canadian Cardiovascular Society; Framingham = Framingham Risk Score for general cardiovascular disease; NA = not applicable; PCE = pooled cohort equation; SCORE = Systematic COronary Risk Evaluation; USPSTF = U.S. Preventive Services Task Force.

Although the pooled cohort equations are applicable up to 79 years of age, the ACC/AHA and U.S. Preventive Services Task Force guidelines clearly state that after 75 years of age there are too few data and inadequate evidence for a strong risk-based statin recommendation. A similar view is found in the CCS guideline, which also emphasizes that the recommended Framingham risk model is not well validated after 75 years of age. Although the NICE guideline recognizes the lack of adequate evidence after 75 years of age, a strong risk-based statin recommendation is provided up to 84 years of age without any explanation—but possibly because QRISK2 is applicable up to this age. The ESC/EAS guideline recommends SCORE for risk assessment, though SCORE is applicable only up to 65 years of age. The appropriateness of this age limitation and not providing an alternative class I statin recommendation after 65 years of age is not discussed.

These discrepant statin recommendations do matter. Evaluated in real-life consecutive nondiabetic patients with a first MI, statin eligibility before the event (detection rate) varied from 1% with the ESC/EAS guideline to 75% with the NICE guideline (**Figure 2**). The SCORE-dependent ESC/EAS guideline is a striking outlier, with an extraordinary low potential to prevent a first MI in people older than 65 years of age. In contrast, only the NICE guideline offers a real potential to prevent such events after 75 years of age. This guideline also provides a weaker statin recommendation specifically for primary prevention of nonfatal MI in people ≥85 years of age.

FIGURE 2 Detection Rate in Elderly Individuals >65 Years of Age With a First MI

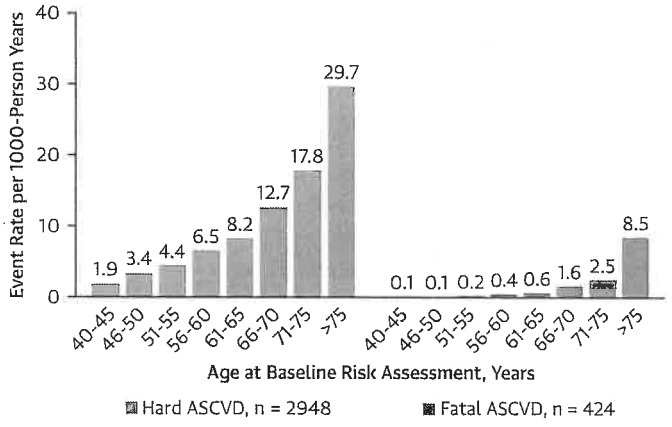


Proportion of apparently healthy elderly patients with first myocardial infarction (MI) who would have qualified for statin therapy (Class I recommendation) before the event. The data are based on 1,399 consecutive patients, of whom 777 (56%) were >65 years of age, hospitalized with a first MI in Denmark in 2010 to 2012 (54). Abbreviations as in **Figure 1**.

SPECIAL CONSIDERATIONS ON STATIN TREATMENT IN THE ELDERLY

For primary prevention with statins, net benefit of treatment is what counts for the individual person and cost effectiveness for the society. Treating acute and chronic ASCVD is costly, and broader use of inexpensive statins to prevent a first ASCVD event in the elderly is most likely cost effective and could very well be cost saving (35).

FIGURE 3 Relationship Between Hard and Fatal ASCVD Events



In apparently healthy individuals from a contemporary general population (the Copenhagen General Population Study, n = 48,814, ≥40 years of age), fatal atherosclerotic cardiovascular disease (ASCVD) events constitute only a minor proportion of hard ASCVD (fatal coronary heart disease and stroke plus nonfatal myocardial infarction and stroke) events. Among elderly people 65 to 75 years of age, the ratio was ≈7 to 8 and among very elderly people >75 years of age was ≈3.5. Adapted with permission from Mortensen et al. (25).

NET BENEFIT CONSIDERATIONS IN THE ELDERLY. The main goal of primary prevention with statins is to achieve net benefit from treatment. Considering potential harms is therefore a crucial part of appropriate decision making (36). As frailty, comorbidity, and polypharmacy may increase the risk for adverse statin-associated symptoms (SAS), the "risk-benefit" balance in the elderly could theoretically tip in favor of withholding statin therapy if such conditions are present. Limited life expectancy for whatever reason may also limit the potential benefit of statin therapy. Thus, initiation of statin therapy should always be preceded by a careful weighing of potential harms and benefits.

Well-documented SAS across all age groups are musculoskeletal issues and diabetes (37). RCT data on adverse effects have the strength of being unbiased, but may not be able to reliable detect rare events. Nevertheless, RCT data indicate that statins are safe and well tolerated in elderly individuals >65 years of age (38), with the caveats that limited data exist on the very old and that the elderly people enrolled in RCTs may be more robust than are those individuals routinely seen in clinical practice. Based on data from primary prevention statin trials (13,28,29) and a meta-analysis (39), muscle discomfort and pain reported in RCTs appear to be unrelated to age and statin therapy. However, because patients treated with statins in clinical practice are told about possible side effect, muscle symptoms will often mistakenly be perceived as statin induced—the so-called nocebo effect (40). Although rare, a higher risk for myopathy, including rhabdomyolysis, has been reported in elderly compared with younger patients treated with high-dose statin therapy, particularly simvastatin 80 mg/day (41).

The modestly increased risk for statin-induced diabetes is possibly age related and occurs almost exclusively among individuals with components of the metabolic syndrome who are already predisposed to develop diabetes (37,42). As new onset diabetes often requires additional drug therapy, this may be problematic especially in elderly patients.

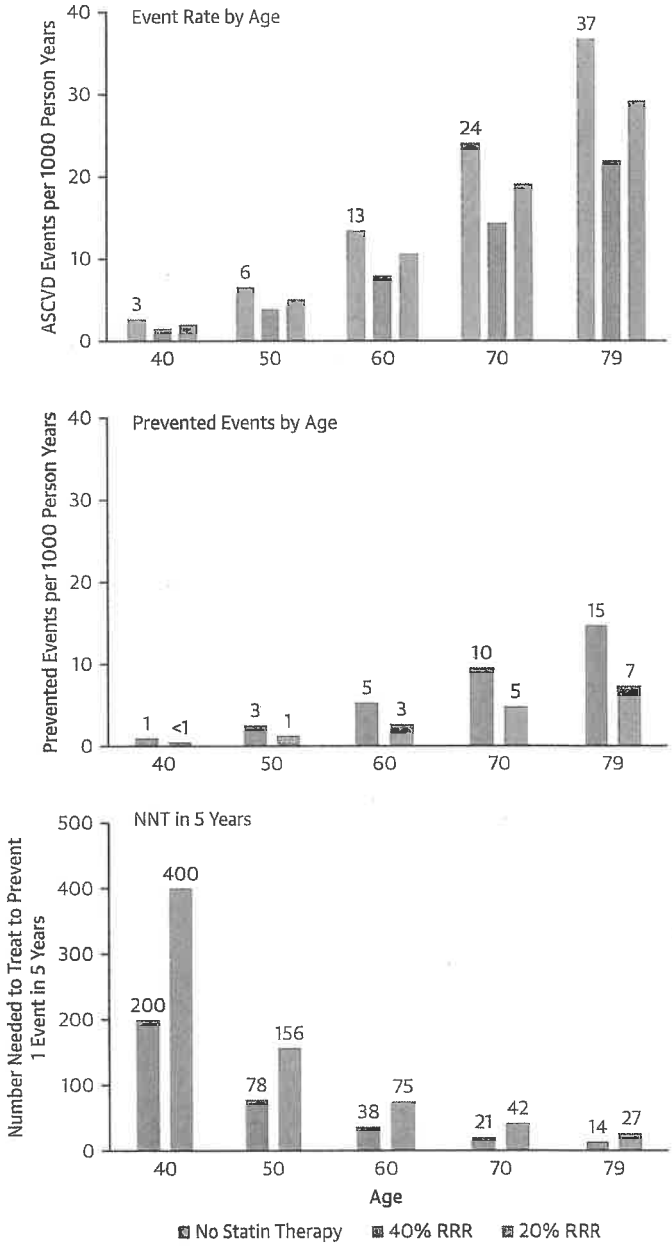
As recently reviewed, current evidence does not support a previous suspicion that statin therapy might cause memory loss, cognitive impairment, or dementia (38,43,44). Important to consider before initiating statin therapy in the elderly is polypharmacy and the associated risk for drug-drug interactions (32,33). This is especially relevant for

statins metabolized by CYP3A4 (i.e., atorvastatin). Close monitoring is important to avoid or treat possible SAS. Importantly, adverse effects of statins usually resolve rapidly after discontinuation of treatment.

MORBIDITY VERSUS MORTALITY BENEFIT IN THE ELDERLY. In primary prevention it is no longer tenable to focus only on longevity and all-cause mortality (45), as ASCVD morbidity and treatment costs are increasing. The majority of ASCVD events in the elderly are nonfatal events (**Figure 3**), and the proportion of elderly individuals >65 years of age living with chronic disease is increasing (46). Thus, patient preferences are critical important for well-informed shared decision making. If a patient only values longevity, there are little data to support primary prevention with statins in people >65 years of age. On the other hand, if preventing nonfatal and potentially disabling MI or stroke is of value to the patient, it might be reasonable to initiate statin therapy. From this perspective, it is noteworthy that the relative importance that people assign to avoiding death compared with avoiding nonfatal events appears to be highly age dependent. Although younger individuals <65 years of age weigh avoiding death highest, elderly individuals ≥65 years put a much higher weight on avoiding MI or stroke than death (47). These differences are compatible with elderly individuals having a greater focus on quality of life and avoiding disability than on extending life (48).

RR, ABSOLUTE RISK, AND NUMBER NEEDED TO TREAT IN THE ELDERLY. There are good reasons to believe that the magnitude of benefit with statins may be substantial in elderly people. As the RR reduction with statin therapy is similar for those at low and high risk of ASCVD, the absolute benefit of treatment with statins is highly dependent on absolute ASCVD risk (49). Thus, even in case of a smaller relative benefit with statin therapy in elderly people, the absolute benefit is likely higher because of the higher risk for ASCVD (**Figure 4**). Assuming different efficacy of statin therapy in various age groups ranging from a RR reduction of 20% to 40% (arbitrarily chosen), it can be estimated that the absolute risk reduction with statin therapy in a 79-year-old person may be considerably higher than in a similar 60-year-old person even if efficacy of treatment should be only one-half of that in the younger person. This translates into much lower number needed to treat in 5 years to prevent 1 event in elderly compared with younger individuals.

FIGURE 4 Conceptual Relationship Between Age and Absolute Benefit of Statin Therapy



Calculations based on the pooled cohort equations assuming a population of nonsmoking men with systolic blood pressure 135 mm Hg, total cholesterol 232 mg/dl, and high-density lipoprotein (HDL) cholesterol 37 mg/dl without diabetes or hypertension. **(Top)** Estimated 10-year risk for atherosclerotic cardiovascular disease (ASCVD) before and after statin therapy assuming 40% and 20% relative risk reduction (RRR). **(Middle)** The absolute risk reduction with statins increases substantially with age. **(Bottom)** The number needed to treat (NNT) in 5 years to prevent 1 ASCVD event becomes lower with aging, even in case of lower efficacy of treatment.

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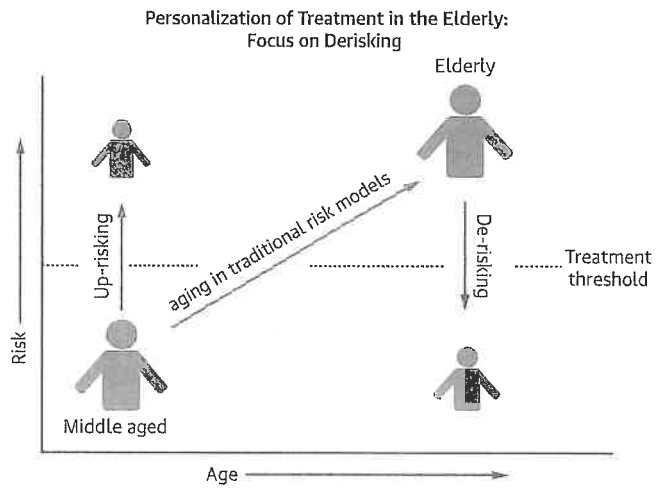
FIGURE 5 The Concept of Derisking in Elderly People



Age is the most important determinant of predicted risk of ASCVD using traditional risk models. Thus, because of increasing age alone, most elderly individuals >65 years of age will eventually exceed the risk-based treatment thresholds for statin therapy by most guidelines. Given the increasing elderly population and the associated concern about overtreatment with statins, the challenge in elderly individuals is therefore to identify those who are at truly low risk for ASCVD despite a high predicted risk with traditional risk models.

DEPRESCRIBING STATIN THERAPY IN THE VERY OLD. In patients at high risk for ASCVD adherence to prescribed statin therapy is critically important. However, discontinuing primary prevention with statin therapy is reasonable to consider in elderly, frail people at increased risk for SAS and low chance of benefit because of limited life expectancy. Quality of life may improve, but RCTs and guidelines provide no or only limited guidance on how to approach and discuss this difficult question (33). The benefit of statin therapy persists after discontinuation of therapy (long-term legacy benefit), without evidence of any rebound adverse effects in primary prevention (50).

FUTURE PERSPECTIVES

As discussed in this review, limited evidence are available on statin therapy for primary prevention of ASCVD in very elderly individuals >75 years of age. The STAREE (STAtins for Reducing Events in the Elderly) trial, a primary prevention trial currently underway, recruits individuals ≥70 years of age to determine efficacy and safety of statin treatment in elderly people (51). This trial will likely provide important insights for the older population.

With the broadened indication for statin therapy in all but the ESC/EAS guideline, most elderly individuals will eventually qualify for treatment. However, the appropriateness of treating all elderly needs reconsideration. Thus, accurate identification of elderly individuals at truly low risk is gaining increasing interest. This situation is the opposite in younger individuals, where the challenge is to identify novel biomarkers that can help "up-risking" those who do not qualify for statins but are at truly high risk for a future ASCVD event. A promising approach to personalize treatment in elderly people is "derisking" by use of negative risk markers (i.e., absence of coronary artery calcification) to identify those at so low risk that statin therapy may safely be withheld (**Figure 5**) (52,53). In the BioImage study of elderly individuals, for example, absence of coronary artery calcification was prevalent (≈1 of 3) and associated with exceptionally low ASCVD event rates (53). Derisking is not considered in current guidelines but deserves to be discussed when the guidelines are updated.

For the ESC/EAS guidelines it is time to address the inherent limitations of SCORE (not applicable beyond 65 years of age, and morbidity does not count) (23).

CONCLUSIONS

The recommendations for statin therapy in elderly >65 years of age differ substantially among the 5 major guidelines currently used in North America and Europe. At one end of the spectrum, the 2016 ESC/EAS guidelines miss great opportunities for safe, cheap, and evidence-based prevention in elderly individuals 66 to 75 years of age. At the other end of the spectrum, the 2014 NICE guideline provides near-universal treatment recommendations well into the very elderly >75 years of age where RCT evidence is sparse and more uncertain. If these guidelines are followed stringently in clinical practice, the large heterogeneity in treatment recommendations will have tremendous variable impact on ASCVD prevention in elderly individuals >65 years of age. Until more evidence is available for those individuals >75 years of age, initiation of primary prevention with statins in this age group must be based on well-informed shared decision making. To curb the increasing burden of ASCVD, guidelines need to address the rapidly changing landscape of population demographics with clear and strong guidance on how to best allocate preventive statin treatment into old age. Indeed, there are reasons to believe that the benefit of statin treatment in elderly people may be

substantial for both the individual patient and for the society.

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REVIEW TOPIC OF THE WEEK

Primary Prevention With Statins in the Elderly

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ABSTRACT

The burden of atherosclerotic cardiovascular disease (ASCVD) in high-income countries is mostly borne by the elderly. With increasing life expectancy, clear guidance on sensible use of statin therapy to prevent a first and potentially devastating ASCVD event is critically important to ensure a healthy aging population. Since 2013, 5 major North American and European guidelines on statin use in primary prevention of ASCVD have been released by the American College of Cardiology/American Heart Association, the UK National Institute for Health and Care Excellence, the Canadian Cardiovascular Society, U.S. Preventive Services Task Force, and the European Society of Cardiology/European Atherosclerosis Society. Guidance on using statin therapy in primary ASCVD prevention in the growing elderly population (>65 years of age) differs markedly. The authors discuss the discrepant recommendations, place them into the context of available evidence, and identify circumstances in which uncertainty may hamper the appropriate use of statins in the elderly. (J Am Coll Cardiol 2018;71:85–94)

The short-term risk of atherosclerotic cardiovascular disease (ASCVD) increases with age, with the highest incidence rates, number of events, prevalence, and treatment costs in the elderly population. Given the increasing size of this population, it is critically important that guidelines provide clear recommendations for appropriate use of interventions of proven efficacy to reduce the burden of ASCVD in the elderly. Statin therapy represents a substantial potential for safe, effective, and inexpensive primary prevention of ASCVD in elderly individuals (here defined as individuals >65 years of age), as statins have been shown to be generally well tolerated and improve ASCVD outcome across a wide range of population characteristics. However, this potential for meaningful benefits of preventive statin therapy in elderly people is inconsistently utilized in existing guidelines in Europe and North America, as described in this review.

Listen to this manuscript's audio summary by *JACC* Editor-in-Chief Dr. Valentin Fuster.

SCOPE OF THE PROBLEM: DISEASE BURDEN IN THE ELDERLY

The proportion and number of elderly people 65 years of age or older are increasing fast worldwide (1). At 65 years of age, life expectancy is currently estimated to be >20 years for women and >17 years for men in most high-income countries (2). The impact of these demographic changes on the burden of ASCVD is dramatic. It has been projected that the prevalence of coronary heart disease—the most prevalent form of ASCVD—in the United States will increase by as much as 43% (≈5 million more) by year 2030 due to demographic changes alone, while the associated increase in direct costs might be as much as 198% (≈$70 billion more) (3,4). This development poses a major challenge for societies to ensure a healthy elderly population.

From the Department of Cardiology, Aarhus University Hospital, Aarhus, Denmark. Both authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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ABBREVIATIONS AND ACRONYMS

ACC/AHA = American College of Cardiology/American Heart Association

ASCVD = atherosclerotic cardiovascular disease

CCS = Canadian Cardiovascular Society

CI = confidence interval

ESC/EAS = European Society of Cardiology/European Atherosclerosis Society

MI = myocardial infarction

NICE = National Institute for Health and Care Excellence

RCT = randomized controlled trial

RR = relative risk

SAS = statin-associated symptoms

SCORE = Systematic COronary Risk Evaluation

STATIN GUIDELINES AND RECOMMENDATIONS FOR THE ELDERLY

Since 2013, 5 major guidelines on statin use to prevent ASCVD have been released, in 2013 by American College of Cardiology/American Heart Association (ACC/AHA) (5), in 2014 by the UK National Institute for Health and Care Excellence (NICE) (6), in 2016 by the Canadian Cardiovascular Society (CCS) (7), in 2016 by the U.S. Preventive Services Task Force (8), and in 2016 by the European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) (9). Although these guidelines are based on the same evidence originating predominantly from randomized controlled trials (RCTs) of statin therapy, the recommendations for using statins to prevent a first ASCVD event differ substantially (**Table 1**). Nevertheless, the guidelines share the same basic concept of allocating statin therapy to those assumed to be at highest risk for ASCVD, either because of a well-defined high-risk condition (i.e., diabetes) or because of a high estimated 10-year risk for a first ASCVD event using guideline-specific risk scores.

One striking difference among the guidelines is their recommendations for statin therapy with advancing age. To facilitate meaningful discussion and highlight important differences, guideline recommendations and evidence pertinent to 3 age groups are reviewed independently—middle aged (40 to 65 years of age), elderly (66 to 75 years of age), and very elderly (>75 years of age)—with the main focus on those individuals >65 years of age.

PRIMARY PREVENTION IN MIDDLE-AGED INDIVIDUALS (40 TO 65 YEARS OF AGE). For apparently healthy individuals 40 to 65 years of age, all 5 statin guidelines provide strong or Class I recommendations for initiation of statin therapy in those at highest risk (**Table 1, Figure 1**). This age group has been well represented in high-quality primary prevention statin trials (**Table 2**) (10-20), and little controversy exists regarding statin efficacy in those at highest risk (21,22). However, the guidelines do not agree on how to define the risk above which statin therapy should be initiated. Although the 2016 ESC/EAS guideline continues to base its recommendations on old "high-risk" considerations (23), the other 4 guidelines have expanded the indication for statin treatment considerably based on a combination of strong RCT evidence, net benefit, and cost-effectiveness analyses (24,25). This is exemplified in the **Central Illustration** by a man who undergoes risk assessment every 10 years. At 56 years of age, his estimated 10-year risk for ASCVD using guideline-recommended risk scores is so high that all but the Systematic COronary Risk Evaluation (SCORE)-based ESC/EAS guideline would recommend initiation of statin therapy (**Table 1**).

PRIMARY PREVENTION IN THE ELDERLY (66 TO 75 YEARS). For apparently healthy individuals 66 to 75 years of age, 4 of the 5 guidelines continue to provide Class I or strong risk-based recommendations for primary prevention with statins in those at highest risk (**Figure 1, Central Illustration**). Only the ESC/EAS guideline on CVD prevention no longer has clear risk-based recommendations because SCORE is not applicable beyond 65 years of age (23). Even more notable, this guideline cautions against "uncritical" initiation of statin therapy in those >60 years of age, even if the estimated risk is very high (>10% 10-year risk for fatal CVD) (9). However, somewhat inconsistent, the ESC/EAS guideline for the management of dyslipidemias recommends that "statin therapy should be considered in older adults free from CVD, particularly in the presence of hypertension, smoking, diabetes and dyslipidaemia" (Class IIa) but without defining what is meant by "older adults" (26). In contrast, the ACC/AHA, CCS, and U.S. Preventive Services Task Force guidelines provide the same risk-based indication for statin therapy up to 75 years of age and NICE up to 84 years of age (**Figure 1, Central Illustration**). Given the strong impact of age on estimated 10-year risk for ASCVD, a progressively higher proportion of elderly individuals become statin eligible with these 4 guidelines. For example, all elderly individuals with optimal risk factors exceed the ACC/AHA 7.5% pooled cohort equation risk threshold by 65 years of age (men) or 71 years of age (women) and the NICE 10% QRISK2 risk threshold by 65 years of age (men) or 68 years of age (women).

Clinical trial evidence supports the use of statin therapy for the primary prevention of nonfatal ASCVD events in elderly individuals 66 to 75 years of age. This age group has been well represented in primary prevention statin trials (**Table 2**), and post hoc analyses from the MEGA (Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese) (27), CARDS (Collaborative Atorvastatin Diabetes Study) (28), JUPITER (Justification for the Use of Statins in prevention: An Intervention Trial Evaluating Rosuvastatin) (20,29) and HOPE-3 (Heart Outcomes Prevention Evaluation-3) (20) trials have shown improved ASCVD outcome also in those individuals older than 65 years of age at enrollment, with relative risk (RR) reductions similar to those

TABLE 1 Eligibility for Primary Prevention With Statins (Class I or Strong Indication)

Indication for Statin Therapy	ACC/AHA 2013 (5)	NICE-UK 2014/2016 (6)	CCS 2016 (7)	USPSTF 2016 (8)	ESC/EAS 2016 (9)
High estimated 10-yr risk					
Age range, yrs	40-75	30-84	30-75*	40-75	40-65†
Risk model	PCE	QRISK2	Modified FRS-CVD	PCE	SCORE
Predicted endpoints	Nonfatal MI, CHD death, stroke	CHD, stroke, TIA (fatal and nonfatal)	MI, angina, CHD death, heart failure, stroke, TIA, PAD	Similar to ACC/AHA	Fatal ASCVD
Risk threshold for therapy	≥7.5%	≥10%	10%-19% (intermediate), ≥20% (high risk)	≥10%	5% to <10% (high risk), ≥10% (very high risk)
Risk factor requirements	No	No	Yes if 10%-19% risk* No if ≥20% risk	≥1‡	No
LDL-C before treatment, mg/dl	70-189	No	≥135 if 10%-19% risk* No if ≥20% risk	≤190	≥155 if high risk ≥100 if ≥10% risk
LDL-C treatment target, mg/dl	No	High intensity: >40%↓§	<77/>50%↓*	No	<100/≥50%↓ if high risk <70/≥50%↓ if ≥10% risk
High-risk clinical condition					
FH and/or high cholesterol, mg/dl	LDL-C ≥190 ≥21 yrs of age	No§	LDL-C ≥190	No‡	FH or TC >310
Diabetes mellitus	40-75 yrs of age LDL-C ≥70	High-risk type 1§	≥40 yrs of age*	No‡	>40 yrs of age
CKD (eGFR), ml/min/1.73 m^2	No	<60§	<60†	No	30-59 = high risk <30 = very high risk†

*The Framingham Risk Score for general cardiovascular disease (FRS-CVD) is not well validated after 75 years of age. In the modified version, the risk is doubled in case of family history of premature cardiovascular disease (CVD). Equivalent values are provided for low-density lipoprotein cholesterol (LDL-C), non–high-density lipoprotein cholesterol (HDL-C), and apolipoprotein B. Required risk factors in intermediate risk: men ≥50 years of age and women ≥60 years of age and 1 additional CVD risk factor. Diabetes: ≥40 years of age or ≥15-year duration for ≥30 years of age (type 1) or microvascular disease. Chronic kidney disease (CKD): ≥50 years of age and estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2 or albumin/creatinine ratio >3 mg/mmol (those on dialysis optional). †Systematic COronary Risk Evaluation (SCORE) is only applicable up to 65 years of age. Statin therapy is not recommended in end-stage renal disease. ‡These recommendations do not pertain to persons with familial hypercholesterolemia (FH) and/or LDL-C >190 mg/dl. Required risk factor includes dyslipidemia, diabetes, hypertension, or smoking. §Patients with FH or receiving renal replacement therapy are not covered under this guideline. Diabetes, high risk: type 1 diabetes >40 years of age or diabetes >10 years or nephropathy or cardiovascular risk factors. In type 2 diabetes, QRISK2-guided statin therapy is recommended. CKD: eGFR <60 ml/min/1.73 m^2 and/or albuminuria. Treatment goal: >40% reduction in non-HDL-C.

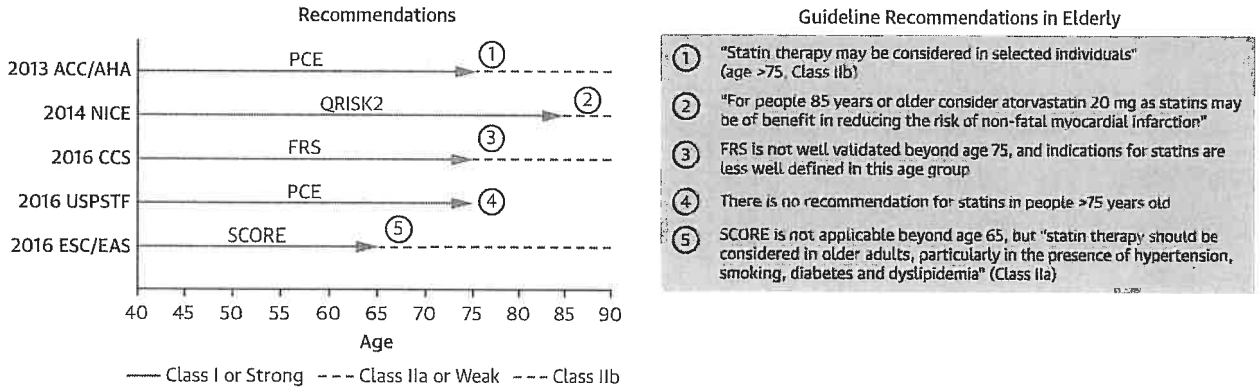
ACC/AHA = American College of Cardiology/American Heart Association; ASCVD = atherosclerotic cardiovascular disease; CCS = Canadian Cardiovascular Society; CHD = coronary heart disease; ESC/EAS = European Society of Cardiology/European Atherosclerosis Society; MI = myocardial infarction; NICE-UK = NICE = UK National Institute for Health and Care Excellence; PAD = peripheral artery disease; PCE = pooled cohort equation; TC = total cholesterol; TIA = transient ischemic attack; USPSTF = U.S. Preventive Services Task Force.

observed in younger individuals. In addition, 2 meta-analyses have provided important insights. Based on 8 RCTs (n = 24,674; ≥65 years of age), Savarese et al. (30) found that primary prevention with statins was highly effective in reducing the risk of myocardial infarction (MI) (RR: 0.60; 95% confidence interval [CI]: 0.43 to 0.85) and stroke (RR: 0.76; 95% CI: 0.63 to 0.93), but not all-cause mortality or cardiovascular death. More recently, Ridker et al. (20) provided age-stratified outcome data from the JUPITER and HOPE-3 trials. In elderly individuals 65 to 70 years of age, rosuvastatin reduced the risk of a composite endpoint (nonfatal MI, nonfatal stroke, or cardiovascular death) substantially by 49% (RR: 0.51; 95% CI: 0.38 to 0.69), and the risk was reduced by 26% (RR: 0.74; 95% CI: 0.61 to 0.91) in those ≥70 years of age. The efficacy was similar in individuals ≥70 and <65 years of age, indicating little heterogeneity in treatment effect by age. Today, nearly all apparently healthy elderly individuals have RCT evidence supporting statin efficacy (31).

PRIMARY PREVENTION IN THE VERY ELDERLY (>75 YEARS OF AGE). For apparently healthy very elderly individuals, only 1 (2014 NICE) of the 5 guidelines continues to provide a strong risk-based recommendation for initiating primary prevention with statins (**Figure 1, Central Illustration**). Thus, although the SCORE-dependent ESC/EAS guidelines provide risk-based indication for statins only up to 65 years of age, the QRISK2-dependent NICE guidelines do so up to 84 years of age. Because everyone >75 years of age exceeds the 10% 10-year QRISK2 threshold for treatment, the NICE guidelines indirectly provide a strong, universal statin indication over the range of 76 to 84 years of age. This guideline also provides a specific treatment recommendation for atorvastatin 20 mg in individuals ≥85 years of age, as "statins may be of benefit in reducing the risk of nonfatal myocardial infarctions" (**Figure 1**).

Very elderly people pose a troubling dilemma for the cardiovascular community, guideline writers, and clinical practitioners. Although they are at high risk of near-term ASCVD by virtue of their age alone, evidence of efficacy for primary prevention with statins is sparse in this age group, as only few have been included in RCTs (**Table 2**). Thus, the decision to initiate primary prevention with statins in people older than 75 years of age cannot be based directly

FIGURE 1 Recommendations for Primary Prevention With Statins in Apparently Healthy People



Handling of individuals >65 years of age differs substantially among contemporary European and North American guidelines, partly because of the performance (applicability) of the risk model used. ACC/AHA = American College of Cardiology/American Heart Association; CCS = Canadian Cardiovascular Society; ESC/EAS = European Society of Cardiology/European Atherosclerosis Society; FRS = Framingham Risk Score for general cardiovascular disease; NICE = National Institute for Health and Care Excellence; PCE = pooled cohort equation; SCORE = Systematic COronary Risk Evaluation; USPSTF = U.S. Preventive Services Task Force.

on RCT evidence (32). Further, extrapolation of efficacy and safety data from those ≤75 years of age to those >75 years of age should be done cautiously, considering comorbidity, polypharmacy, potential side effects, and limited life expectancy (33). Efficacy of statin therapy in the very elderly, however, is well documented in secondary prevention trials (34). The PROSPER (Pravastatin in elderly individuals at risk of vascular disease) trial, for example, specifically assessed the benefit of statins in elderly individuals and demonstrated improved outcomes among elderly with known vascular diseases (13).

WHY THE AGE CAP ON RISK-BASED STATIN RECOMMENDATIONS? The risk for ASCVD increases dramatically with age. Why then do all strong risk-based statin recommendations expire at a certain but quite different guideline-dependent age?

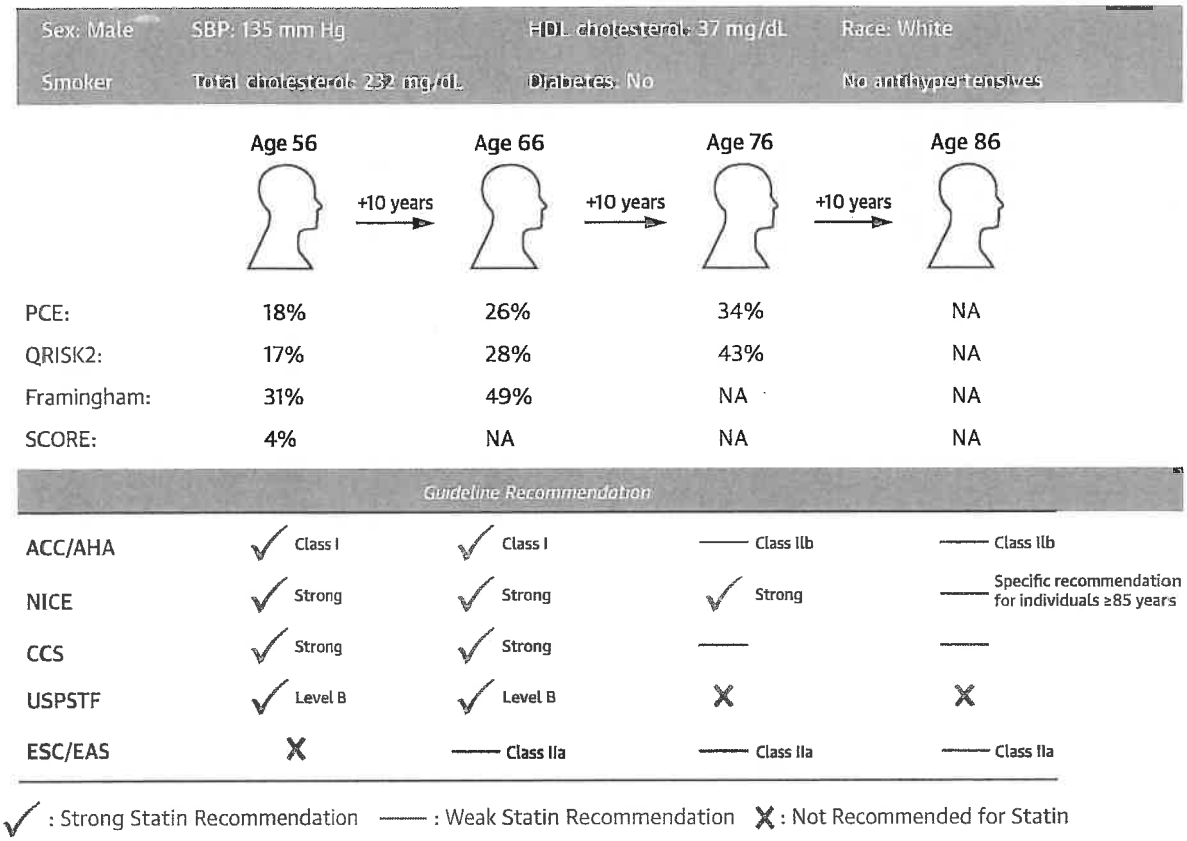
TABLE 2 Enrollment of Elderly and Very Elderly in Primary Prevention Statin Trials

Study Name, Year (Ref. #)	No.	Mean Age (yrs)	Age Range (yrs)	Elderly	Very Elderly (≥75 yrs of Age)
WOSCOPS, 1995 (10)	6,595	55	Men 45–64	0	0
AFCAPS/TexCAPS, 1998 (11)	6,605	Men 58 Women 62	Men 45–73 Women 55–73	Men 20% ≥65 yrs of age Women 33% ≥65 yrs of age	0
ALLHAT-LLT, 2002 (12)	10,355	66	≥55	28% ≥65 yrs of age*	7%*
PROSPER, 2002 (13)	3,239 (no ASCVD)	75 (whole cohort)	70–82 (whole cohort)	100% ≥70 yrs of age	NR
ASCOT-LLA, 2003 (14)	10,305	63	40–79	64% >60 yrs of age 23% >70 yrs of age	NR
CARDS, 2004 (15)	2,838	62	40–75	40% ≥65 yrs of age 12% >70 yrs of age	0
MEGA, 2006 (16)	7,832	58	40–70	23% ≥65 yrs of age	0
JUPITER, 2008 (17)	17,802	66	Men ≥50 Women ≥60	58% ≥65 yrs of age† 32% ≥70 yrs of age†	NR
HOPE-3, 2016 (18)	12,705	66	Men ≥55 Women ≥65/60	52% ≥65 yrs of age† 24% ≥70 yrs of age†	NR

*Primary prevention data reported by Han et al. (19). †Reported by Ridker et al (20).

AFCAPS/TexCAPS = Air Force/Texas Coronary Atherosclerosis Prevention Study; ALLHAT-LLT = Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial-Lipid Lowering Trial; ASCOT-LLA = Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm; CARDS = Collaborative Atorvastatin Diabetes Study; HOPE-3 = Heart Outcomes Prevention Evaluation-3; JUPITER = Justification for the Use of Statins in prevention: An Intervention Trial Evaluating Rosuvastatin; MEGA = Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese; NR = not reported; PROSPER = Pravastatin in elderly individuals at risk of vascular disease; WOSCOPS = West of Scotland Coronary Prevention Study.

CENTRAL ILLUSTRATION **Age-Dependent Implementation of Guidelines in Clinical Practice**



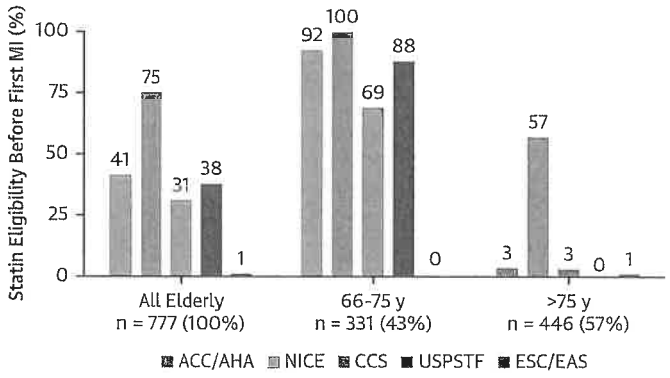
Mortensen, M.B. et al. J Am Coll Cardiol. 2018;71(1):85–94.

In apparently healthy individuals with risk factors shown in the box, all but the European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) guidelines provide a strong indication for statin therapy in the range of 56 to 66 years of age. Above 75 years of age, only the National Institute for Health and Care Excellence (NICE) guideline provides a well-defined indication for statin therapy. See **Table 1** for risks above which statin therapy is recommended. ACC/AHA = American College of Cardiology/American Heart Association; CCS = Canadian Cardiovascular Society; Framingham = Framingham Risk Score for general cardiovascular disease; NA = not applicable; PCE = pooled cohort equation; SCORE = Systematic COronary Risk Evaluation; USPSTF = U.S. Preventive Services Task Force.

Although the pooled cohort equations are applicable up to 79 years of age, the ACC/AHA and U.S. Preventive Services Task Force guidelines clearly state that after 75 years of age there are too few data and inadequate evidence for a strong risk-based statin recommendation. A similar view is found in the CCS guideline, which also emphasizes that the recommended Framingham risk model is not well validated after 75 years of age. Although the NICE guideline recognizes the lack of adequate evidence after 75 years of age, a strong risk-based statin recommendation is provided up to 84 years of age without any explanation—but possibly because QRISK2 is applicable up to this age. The ESC/EAS guideline recommends SCORE for risk assessment, though SCORE is applicable only up to 65 years of age. The appropriateness of this age limitation and not providing an alternative class I statin recommendation after 65 years of age is not discussed.

These discrepant statin recommendations do matter. Evaluated in real-life consecutive nondiabetic patients with a first MI, statin eligibility before the event (detection rate) varied from 1% with the ESC/EAS guideline to 75% with the NICE guideline (**Figure 2**). The SCORE-dependent ESC/EAS guideline is a striking outlier, with an extraordinary low potential to prevent a first MI in people older than 65 years of age. In contrast, only the NICE guideline offers a real potential to prevent such events after 75 years of age. This guideline also provides a weaker statin recommendation specifically for primary prevention of nonfatal MI in people ≥85 years of age.

FIGURE 2 Detection Rate in Elderly Individuals >65 Years of Age With a First MI

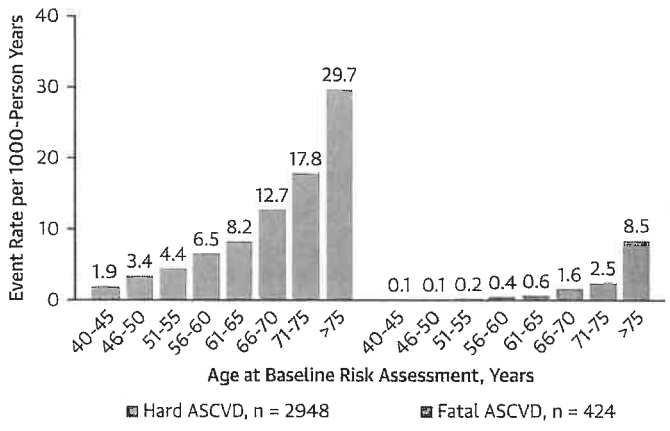


Proportion of apparently healthy elderly patients with first myocardial infarction (MI) who would have qualified for statin therapy (Class I recommendation) before the event. The data are based on 1,399 consecutive patients, of whom 777 (56%) were >65 years of age, hospitalized with a first MI in Denmark in 2010 to 2012 (54). Abbreviations as in **Figure 1.**

SPECIAL CONSIDERATIONS ON STATIN TREATMENT IN THE ELDERLY

For primary prevention with statins, net benefit of treatment is what counts for the individual person and cost effectiveness for the society. Treating acute and chronic ASCVD is costly, and broader use of inexpensive statins to prevent a first ASCVD event in the elderly is most likely cost effective and could very well be cost saving (35).

FIGURE 3 Relationship Between Hard and Fatal ASCVD Events



In apparently healthy individuals from a contemporary general population (the Copenhagen General Population Study, n = 48,814, ≥40 years of age), fatal atherosclerotic cardiovascular disease (ASCVD) events constitute only a minor proportion of hard ASCVD (fatal coronary heart disease and stroke plus nonfatal myocardial infarction and stroke) events. Among elderly people 65 to 75 years of age, the ratio was ≈7 to 8 and among very elderly people >75 years of age was ≈3.5. Adapted with permission from Mortensen et al. (25).

NET BENEFIT CONSIDERATIONS IN THE ELDERLY. The main goal of primary prevention with statins is to achieve net benefit from treatment. Considering potential harms is therefore a crucial part of appropriate decision making (36). As frailty, comorbidity, and polypharmacy may increase the risk for adverse statin-associated symptoms (SAS), the "risk-benefit" balance in the elderly could theoretically tip in favor of withholding statin therapy if such conditions are present. Limited life expectancy for whatever reason may also limit the potential benefit of statin therapy. Thus, initiation of statin therapy should always be preceded by a careful weighing of potential harms and benefits.

Well-documented SAS across all age groups are musculoskeletal issues and diabetes (37). RCT data on adverse effects have the strength of being unbiased, but may not be able to reliable detect rare events. Nevertheless, RCT data indicate that statins are safe and well tolerated in elderly individuals >65 years of age (38), with the caveats that limited data exist on the very old and that the elderly people enrolled in RCTs may be more robust than are those individuals routinely seen in clinical practice. Based on data from primary prevention statin trials (13,28,29) and a meta-analysis (39), muscle discomfort and pain reported in RCTs appear to be unrelated to age and statin therapy. However, because patients treated with statins in clinical practice are told about possible side effect, muscle symptoms will often mistakenly be perceived as statin induced—the so-called nocebo effect (40). Although rare, a higher risk for myopathy, including rhabdomyolysis, has been reported in elderly compared with younger patients treated with high-dose statin therapy, particularly simvastatin 80 mg/day (41).

The modestly increased risk for statin-induced diabetes is possibly age related and occurs almost exclusively among individuals with components of the metabolic syndrome who are already predisposed to develop diabetes (37,42). As new onset diabetes often requires additional drug therapy, this may be problematic especially in elderly patients.

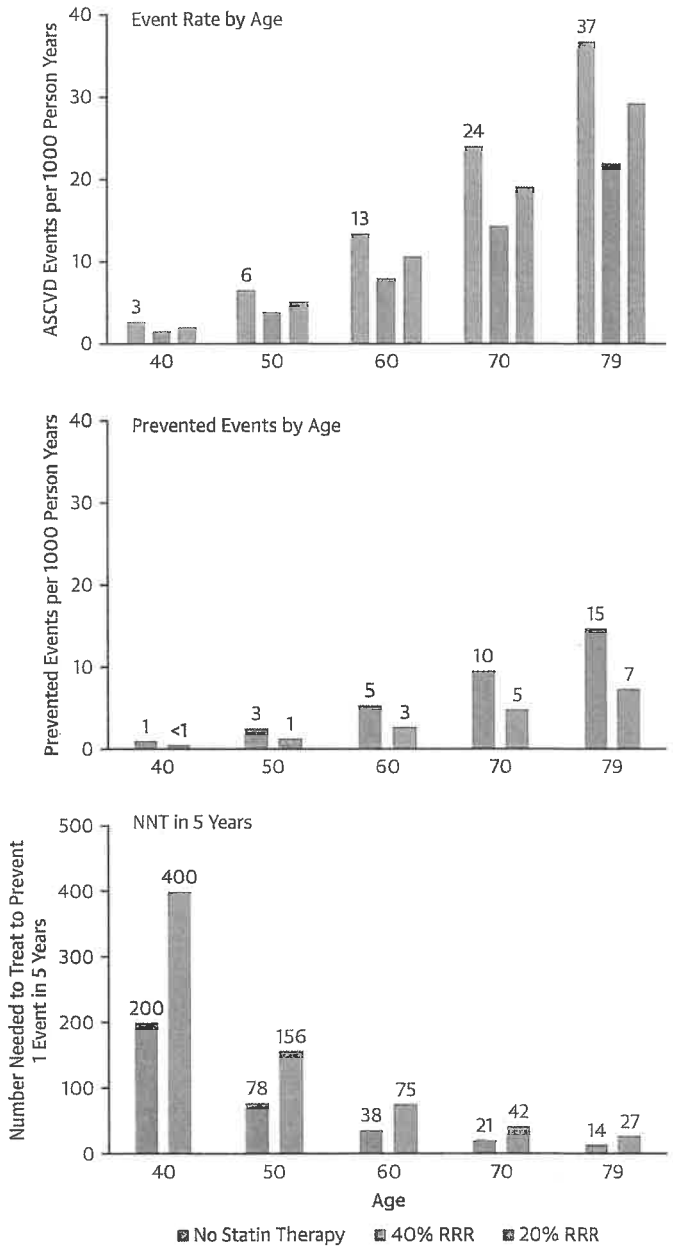
As recently reviewed, current evidence does not support a previous suspicion that statin therapy might cause memory loss, cognitive impairment, or dementia (38,43,44). Important to consider before initiating statin therapy in the elderly is polypharmacy and the associated risk for drug-drug interactions (32,33). This is especially relevant for

statins metabolized by CYP3A4 (i.e., atorvastatin). Close monitoring is important to avoid or treat possible SAS. Importantly, adverse effects of statins usually resolve rapidly after discontinuation of treatment.

MORBIDITY VERSUS MORTALITY BENEFIT IN THE ELDERLY. In primary prevention it is no longer tenable to focus only on longevity and all-cause mortality (45), as ASCVD morbidity and treatment costs are increasing. The majority of ASCVD events in the elderly are nonfatal events (**Figure 3**), and the proportion of elderly individuals >65 years of age living with chronic disease is increasing (46). Thus, patient preferences are critical important for well-informed shared decision making. If a patient only values longevity, there are little data to support primary prevention with statins in people >65 years of age. On the other hand, if preventing nonfatal and potentially disabling MI or stroke is of value to the patient, it might be reasonable to initiate statin therapy. From this perspective, it is noteworthy that the relative importance that people assign to avoiding death compared with avoiding nonfatal events appears to be highly age dependent. Although younger individuals <65 years of age weigh avoiding death highest, elderly individuals ≥65 years put a much higher weight on avoiding MI or stroke than death (47). These differences are compatible with elderly individuals having a greater focus on quality of life and avoiding disability than on extending life (48).

RR, ABSOLUTE RISK, AND NUMBER NEEDED TO TREAT IN THE ELDERLY. There are good reasons to believe that the magnitude of benefit with statins may be substantial in elderly people. As the RR reduction with statin therapy is similar for those at low and high risk of ASCVD, the absolute benefit of treatment with statins is highly dependent on absolute ASCVD risk (49). Thus, even in case of a smaller relative benefit with statin therapy in elderly people, the absolute benefit is likely higher because of the higher risk for ASCVD (**Figure 4**). Assuming different efficacy of statin therapy in various age groups ranging from a RR reduction of 20% to 40% (arbitrarily chosen), it can be estimated that the absolute risk reduction with statin therapy in a 79-year-old person may be considerably higher than in a similar 60-year-old person even if efficacy of treatment should be only one-half of that in the younger person. This translates into much lower number needed to treat in 5 years to prevent 1 event in elderly compared with younger individuals.

FIGURE 4 Conceptual Relationship Between Age and Absolute Benefit of Statin Therapy



Calculations based on the pooled cohort equations assuming a population of nonsmoking men with systolic blood pressure 135 mm Hg, total cholesterol 232 mg/dl, and high-density lipoprotein (HDL) cholesterol 37 mg/dl without diabetes or hypertension. **(Top)** Estimated 10-year risk for atherosclerotic cardiovascular disease (ASCVD) before and after statin therapy assuming 40% and 20% relative risk reduction (RRR). **(Middle)** The absolute risk reduction with statins increases substantially with age. **(Bottom)** The number needed to treat (NNT) in 5 years to prevent 1 ASCVD event becomes lower with aging, even in case of lower efficacy of treatment.

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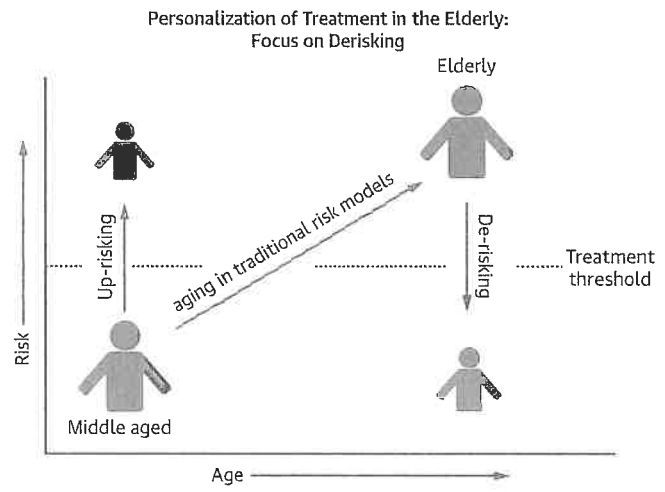
FIGURE 5 The Concept of Derisking in Elderly People



Age is the most important determinant of predicted risk of ASCVD using traditional risk models. Thus, because of increasing age alone, most elderly individuals >65 years of age will eventually exceed the risk-based treatment thresholds for statin therapy by most guidelines. Given the increasing elderly population and the associated concern about overtreatment with statins, the challenge in elderly individuals is therefore to identify those who are at truly low risk for ASCVD despite a high predicted risk with traditional risk models.

DEPRESCRIBING STATIN THERAPY IN THE VERY OLD. In patients at high risk for ASCVD adherence to prescribed statin therapy is critically important. However, discontinuing primary prevention with statin therapy is reasonable to consider in elderly, frail people at increased risk for SAS and low chance of benefit because of limited life expectancy. Quality of life may improve, but RCTs and guidelines provide no or only limited guidance on how to approach and discuss this difficult question (33). The benefit of statin therapy persists after discontinuation of therapy (long-term legacy benefit), without evidence of any rebound adverse effects in primary prevention (50).

FUTURE PERSPECTIVES

As discussed in this review, limited evidence are available on statin therapy for primary prevention of ASCVD in very elderly individuals >75 years of age. The STAREE (STAtins for Reducing Events in the Elderly) trial, a primary prevention trial currently underway, recruits individuals ≥70 years of age to determine efficacy and safety of statin treatment in elderly people (51). This trial will likely provide important insights for the older population.

With the broadened indication for statin therapy in all but the ESC/EAS guideline, most elderly individuals will eventually qualify for treatment. However, the appropriateness of treating all elderly needs reconsideration. Thus, accurate identification of elderly individuals at truly low risk is gaining increasing interest. This situation is the opposite in younger individuals, where the challenge is to identify novel biomarkers that can help "up-risking" those who do not qualify for statins but are at truly high risk for a future ASCVD event. A promising approach to personalize treatment in elderly people is "derisking" by use of negative risk markers (i.e., absence of coronary artery calcification) to identify those at so low risk that statin therapy may safely be withheld (**Figure 5**) (52,53). In the BioImage study of elderly individuals, for example, absence of coronary artery calcification was prevalent (≈1 of 3) and associated with exceptionally low ASCVD event rates (53). Derisking is not considered in current guidelines but deserves to be discussed when the guidelines are updated.

For the ESC/EAS guidelines it is time to address the inherent limitations of SCORE (not applicable beyond 65 years of age, and morbidity does not count) (23).

CONCLUSIONS

The recommendations for statin therapy in elderly >65 years of age differ substantially among the 5 major guidelines currently used in North America and Europe. At one end of the spectrum, the 2016 ESC/EAS guidelines miss great opportunities for safe, cheap, and evidence-based prevention in elderly individuals 66 to 75 years of age. At the other end of the spectrum, the 2014 NICE guideline provides near-universal treatment recommendations well into the very elderly >75 years of age where RCT evidence is sparse and more uncertain. If these guidelines are followed stringently in clinical practice, the large heterogeneity in treatment recommendations will have tremendous variable impact on ASCVD prevention in elderly individuals >65 years of age. Until more evidence is available for those individuals >75 years of age, initiation of primary prevention with statins in this age group must be based on well-informed shared decision making. To curb the increasing burden of ASCVD, guidelines need to address the rapidly changing landscape of population demographics with clear and strong guidance on how to best allocate preventive statin treatment into old age. Indeed, there are reasons to believe that the benefit of statin treatment in elderly people may be

substantial for both the individual patient and for the society.

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KEY WORDS ACC, AHA, atherosclerosis, cardiovascular disease, ESC, guideline

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REVIEW TOPIC OF THE WEEK

Primary Prevention With Statins in the Elderly

Martin Bødtker Mortensen, MD, PhD, Erling Falk, MD, DMSc

ABSTRACT

The burden of atherosclerotic cardiovascular disease (ASCVD) in high-income countries is mostly borne by the elderly. With increasing life expectancy, clear guidance on sensible use of statin therapy to prevent a first and potentially devastating ASCVD event is critically important to ensure a healthy aging population. Since 2013, 5 major North American and European guidelines on statin use in primary prevention of ASCVD have been released by the American College of Cardiology/American Heart Association, the UK National Institute for Health and Care Excellence, the Canadian Cardiovascular Society, U.S. Preventive Services Task Force, and the European Society of Cardiology/European Atherosclerosis Society. Guidance on using statin therapy in primary ASCVD prevention in the growing elderly population (>65 years of age) differs markedly. The authors discuss the discrepant recommendations, place them into the context of available evidence, and identify circumstances in which uncertainty may hamper the appropriate use of statins in the elderly. (J Am Coll Cardiol 2018;71:85–94)

The short-term risk of atherosclerotic cardiovascular disease (ASCVD) increases with age, with the highest incidence rates, number of events, prevalence, and treatment costs in the elderly population. Given the increasing size of this population, it is critically important that guidelines provide clear recommendations for appropriate use of interventions of proven efficacy to reduce the burden of ASCVD in the elderly. Statin therapy represents a substantial potential for safe, effective, and inexpensive primary prevention of ASCVD in elderly individuals (here defined as individuals >65 years of age), as statins have been shown to be generally well tolerated and improve ASCVD outcome across a wide range of population characteristics. However, this potential for meaningful benefits of preventive statin therapy in elderly people is inconsistently utilized in existing guidelines in Europe and North America, as described in this review.

Listen to this manuscript's audio summary by *JACC* Editor-in-Chief Dr. Valentin Fuster.

SCOPE OF THE PROBLEM: DISEASE BURDEN IN THE ELDERLY

The proportion and number of elderly people 65 years of age or older are increasing fast worldwide (1). At 65 years of age, life expectancy is currently estimated to be >20 years for women and >17 years for men in most high-income countries (2). The impact of these demographic changes on the burden of ASCVD is dramatic. It has been projected that the prevalence of coronary heart disease—the most prevalent form of ASCVD—in the United States will increase by as much as 43% (≈5 million more) by year 2030 due to demographic changes alone, while the associated increase in direct costs might be as much as 198% (≈$70 billion more) (3,4). This development poses a major challenge for societies to ensure a healthy elderly population.

From the Department of Cardiology, Aarhus University Hospital, Aarhus, Denmark. Both authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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ABBREVIATIONS AND ACRONYMS

ACC/AHA = American College of Cardiology/American Heart Association

ASCVD = atherosclerotic cardiovascular disease

CCS = Canadian Cardiovascular Society

CI = confidence interval

ESC/EAS = European Society of Cardiology/European Atherosclerosis Society

MI = myocardial infarction

NICE = National Institute for Health and Care Excellence

RCT = randomized controlled trial

RR = relative risk

SAS = statin-associated symptoms

SCORE = Systematic COronary Risk Evaluation

STATIN GUIDELINES AND RECOMMENDATIONS FOR THE ELDERLY

Since 2013, 5 major guidelines on statin use to prevent ASCVD have been released, in 2013 by American College of Cardiology/American Heart Association (ACC/AHA) (5), in 2014 by the UK National Institute for Health and Care Excellence (NICE) (6), in 2016 by the Canadian Cardiovascular Society (CCS) (7), in 2016 by the U.S. Preventive Services Task Force (8), and in 2016 by the European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) (9). Although these guidelines are based on the same evidence originating predominantly from randomized controlled trials (RCTs) of statin therapy, the recommendations for using statins to prevent a first ASCVD event differ substantially (**Table 1**). Nevertheless, the guidelines share the same basic concept of allocating statin therapy to those assumed to be at highest risk for ASCVD, either because of a well-defined high-risk condition (i.e., diabetes) or because of a high estimated 10-year risk for a first ASCVD event using guideline-specific risk scores.

One striking difference among the guidelines is their recommendations for statin therapy with advancing age. To facilitate meaningful discussion and highlight important differences, guideline recommendations and evidence pertinent to 3 age groups are reviewed independently—middle aged (40 to 65 years of age), elderly (66 to 75 years of age), and very elderly (>75 years of age)—with the main focus on those individuals >65 years of age.

PRIMARY PREVENTION IN MIDDLE-AGED INDIVIDUALS (40 TO 65 YEARS OF AGE). For apparently healthy individuals 40 to 65 years of age, all 5 statin guidelines provide strong or Class I recommendations for initiation of statin therapy in those at highest risk (**Table 1, Figure 1**). This age group has been well represented in high-quality primary prevention statin trials (**Table 2**) (10-20), and little controversy exists regarding statin efficacy in those at highest risk (21,22). However, the guidelines do not agree on how to define the risk above which statin therapy should be initiated. Although the 2016 ESC/EAS guideline continues to base its recommendations on old "high-risk" considerations (23), the other 4 guidelines have expanded the indication for statin treatment considerably based on a combination of strong RCT evidence, net benefit, and cost-effectiveness analyses (24,25). This is exemplified in the **Central Illustration** by a man who undergoes risk assessment every 10 years. At 56 years of age, his estimated 10-year risk for ASCVD using guideline-recommended risk scores is so high that all but the Systematic COronary Risk Evaluation (SCORE)-based ESC/EAS guideline would recommend initiation of statin therapy (**Table 1**).

PRIMARY PREVENTION IN THE ELDERLY (66 TO 75 YEARS). For apparently healthy individuals 66 to 75 years of age, 4 of the 5 guidelines continue to provide Class I or strong risk-based recommendations for primary prevention with statins in those at highest risk (**Figure 1, Central Illustration**). Only the ESC/EAS guideline on CVD prevention no longer has clear risk-based recommendations because SCORE is not applicable beyond 65 years of age (23). Even more notable, this guideline cautions against "uncritical" initiation of statin therapy in those >60 years of age, even if the estimated risk is very high (>10% 10-year risk for fatal CVD) (9). However, somewhat inconsistent, the ESC/EAS guideline for the management of dyslipidemias recommends that "statin therapy should be considered in older adults free from CVD, particularly in the presence of hypertension, smoking, diabetes and dyslipidaemia" (Class IIa) but without defining what is meant by "older adults" (26). In contrast, the ACC/AHA, CCS, and U.S. Preventive Services Task Force guidelines provide the same risk-based indication for statin therapy up to 75 years of age and NICE up to 84 years of age (**Figure 1, Central Illustration**). Given the strong impact of age on estimated 10-year risk for ASCVD, a progressively higher proportion of elderly individuals become statin eligible with these 4 guidelines. For example, all elderly individuals with optimal risk factors exceed the ACC/AHA 7.5% pooled cohort equation risk threshold by 65 years of age (men) or 71 years of age (women) and the NICE 10% QRISK2 risk threshold by 65 years of age (men) or 68 years of age (women).

Clinical trial evidence supports the use of statin therapy for the primary prevention of nonfatal ASCVD events in elderly individuals 66 to 75 years of age. This age group has been well represented in primary prevention statin trials (**Table 2**), and post hoc analyses from the MEGA (Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese) (27), CARDS (Collaborative Atorvastatin Diabetes Study) (28), JUPITER (Justification for the Use of Statins in prevention: An Intervention Trial Evaluating Rosuvastatin) (20,29) and HOPE-3 (Heart Outcomes Prevention Evaluation-3) (20) trials have shown improved ASCVD outcome also in those individuals older than 65 years of age at enrollment, with relative risk (RR) reductions similar to those

TABLE 1 Eligibility for Primary Prevention With Statins (Class I or Strong Indication)

Indication for Statin Therapy	ACC/AHA 2013 (5)	NICE-UK 2014/2016 (6)	CCS 2016 (7)	USPSTF 2016 (8)	ESC/EAS 2016 (9)
High estimated 10-yr risk					
Age range, yrs	40–75	30–84	30–75*	40–75	40–65†
Risk model	PCE	QRISK2	Modified FRS-CVD	PCE	SCORE
Predicted endpoints	Nonfatal MI, CHD death, stroke	CHD, stroke, TIA (fatal and nonfatal)	MI, angina, CHD death, heart failure, stroke, TIA, PAD	Similar to ACC/AHA	Fatal ASCVD
Risk threshold for therapy	≥7.5%	≥10%	10%–19% (intermediate), ≥20% (high risk)	≥10%	5% to <10% (high risk), ≥10% (very high risk)
Risk factor requirements	No	No	Yes if 10%–19% risk* No if ≥20% risk	≥1‡	No
LDL-C before treatment, mg/dl	70–189	No	≥135 if 10%–19% risk* No if ≥20% risk	≤190	≥155 if high risk ≥100 if ≥10% risk
LDL-C treatment target, mg/dl	No	High intensity: >40%↓§	<77/>50%↓*	No	<100/≥50%↓ if high risk <70/≥50%↓ if ≥10% risk
High-risk clinical condition					
FH and/or high cholesterol, mg/dl	LDL-C ≥190 ≥21 yrs of age	No§	LDL-C ≥190	No‡	FH or TC >310
Diabetes mellitus	40–75 yrs of age LDL-C ≥70	High-risk type 1§	≥40 yrs of age*	No‡	>40 yrs of age
CKD (eGFR), ml/min/1.73 m^2	No	<60§	<60†	No	30–59 = high risk <30 = very high risk†

*The Framingham Risk Score for general cardiovascular disease (FRS-CVD) is not well validated after 75 years of age. In the modified version, the risk is doubled in case of family history of premature cardiovascular disease (CVD). Equivalent values are provided for low-density lipoprotein cholesterol (LDL-C), non-high-density lipoprotein cholesterol (HDL-C), and apolipoprotein B. Required risk factors in intermediate risk: men ≥50 years of age and women ≥60 years of age and 1 additional CVD risk factor. Diabetes: ≥40 years of age or ≥15-year duration for ≥30 years of age (type 1) or microvascular disease. Chronic kidney disease (CKD): ≥50 years of age and estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2 or albumin/creatinine ratio >3 mg/mmol (those on dialysis optional). †Systematic COronary Risk Evaluation (SCORE) is only applicable up to 65 years of age. Statin therapy is not recommended in end-stage renal disease. ‡These recommendations do not pertain to persons with familial hypercholesterolemia (FH) and/or LDL-C >190 mg/dl. Required risk factor includes dyslipidemia, diabetes, hypertension, or smoking. §Patients with FH or receiving renal replacement therapy are not covered under this guideline. Diabetes, high risk: type 1 diabetes >40 years of age or diabetes >10 years or nephropathy or cardiovascular risk factors. In type 2 diabetes, QRISK2-guided statin therapy is recommended. CKD: eGFR <60 ml/min/1.73 m^2 and/or albuminuria. Treatment goal: >40% reduction in non-HDL-C.

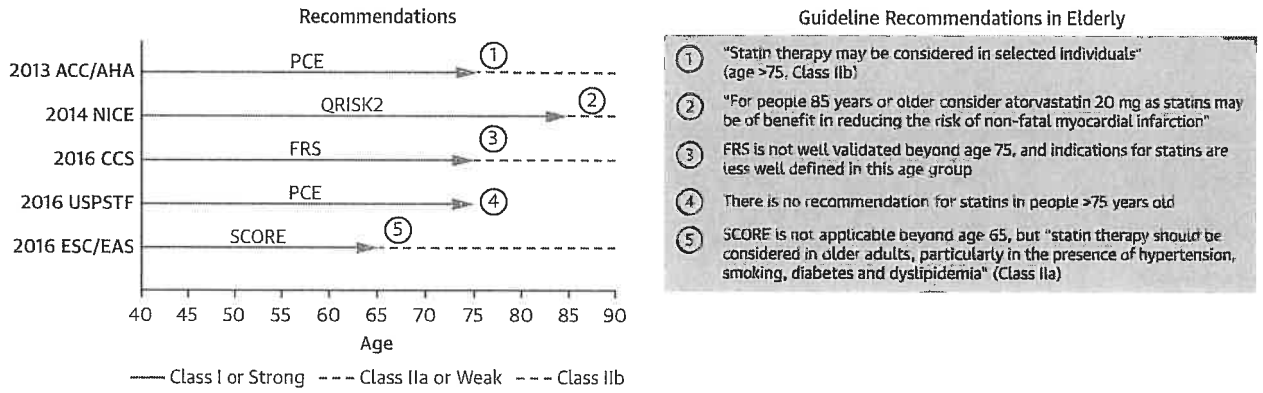
ACC/AHA = American College of Cardiology/American Heart Association; ASCVD = atherosclerotic cardiovascular disease; CCS = Canadian Cardiovascular Society; CHD = coronary heart disease; ESC/EAS = European Society of Cardiology/European Atherosclerosis Society; MI = myocardial infarction; NICE-UK = NICE = UK National Institute for Health and Care Excellence; PAD = peripheral artery disease; PCE = pooled cohort equation; TC = total cholesterol; TIA = transient ischemic attack; USPSTF = U.S. Preventive Services Task Force.

observed in younger individuals. In addition, 2 meta-analyses have provided important insights. Based on 8 RCTs (n = 24,674; ≥65 years of age), Savarese et al. (30) found that primary prevention with statins was highly effective in reducing the risk of myocardial infarction (MI) (RR: 0.60; 95% confidence interval [CI]: 0.43 to 0.85) and stroke (RR: 0.76; 95% CI: 0.63 to 0.93), but not all-cause mortality or cardiovascular death. More recently, Ridker et al. (20) provided age-stratified outcome data from the JUPITER and HOPE-3 trials. In elderly individuals 65 to 70 years of age, rosuvastatin reduced the risk of a composite endpoint (nonfatal MI, nonfatal stroke, or cardiovascular death) substantially by 49% (RR: 0.51; 95% CI: 0.38 to 0.69), and the risk was reduced by 26% (RR: 0.74; 95% CI: 0.61 to 0.91) in those ≥70 years of age. The efficacy was similar in individuals ≥70 and <65 years of age, indicating little heterogeneity in treatment effect by age. Today, nearly all apparently healthy elderly individuals have RCT evidence supporting statin efficacy (31).

PRIMARY PREVENTION IN THE VERY ELDERLY (>75 YEARS OF AGE). For apparently healthy very elderly individuals, only 1 (2014 NICE) of the 5 guidelines continues to provide a strong risk-based recommendation for initiating primary prevention with statins (**Figure 1, Central Illustration**). Thus, although the SCORE-dependent ESC/EAS guidelines provide risk-based indication for statins only up to 65 years of age, the QRISK2-dependent NICE guidelines do so up to 84 years of age. Because everyone >75 years of age exceeds the 10% 10-year QRISK2 threshold for treatment, the NICE guidelines indirectly provide a strong, universal statin indication over the range of 76 to 84 years of age. This guideline also provides a specific treatment recommendation for atorvastatin 20 mg in individuals ≥85 years of age, as "statins may be of benefit in reducing the risk of nonfatal myocardial infarctions" (**Figure 1**).

Very elderly people pose a troubling dilemma for the cardiovascular community, guideline writers, and clinical practitioners. Although they are at high risk of near-term ASCVD by virtue of their age alone, evidence of efficacy for primary prevention with statins is sparse in this age group, as only few have been included in RCTs (**Table 2**). Thus, the decision to initiate primary prevention with statins in people older than 75 years of age cannot be based directly

FIGURE 1 Recommendations for Primary Prevention With Statins in Apparently Healthy People



Handling of individuals >65 years of age differs substantially among contemporary European and North American guidelines, partly because of the performance (applicability) of the risk model used. ACC/AHA = American College of Cardiology/American Heart Association; CCS = Canadian Cardiovascular Society; ESC/EAS = European Society of Cardiology/European Atherosclerosis Society; FRS = Framingham Risk Score for general cardiovascular disease; NICE = National Institute for Health and Care Excellence; PCE = pooled cohort equation; SCORE = Systematic COronary Risk Evaluation; USPSTF = U.S. Preventive Services Task Force.

on RCT evidence (32). Further, extrapolation of efficacy and safety data from those ≤75 years of age to those >75 years of age should be done cautiously, considering comorbidity, polypharmacy, potential side effects, and limited life expectancy (33). Efficacy of statin therapy in the very elderly, however, is well documented in secondary prevention trials (34). The PROSPER (Pravastatin in elderly individuals at risk of vascular disease) trial, for example, specifically assessed the benefit of statins in elderly individuals and demonstrated improved outcomes among elderly with known vascular diseases (13).

WHY THE AGE CAP ON RISK-BASED STATIN RECOMMENDATIONS? The risk for ASCVD increases dramatically with age. Why then do all strong risk-based statin recommendations expire at a certain but quite different guideline-dependent age?

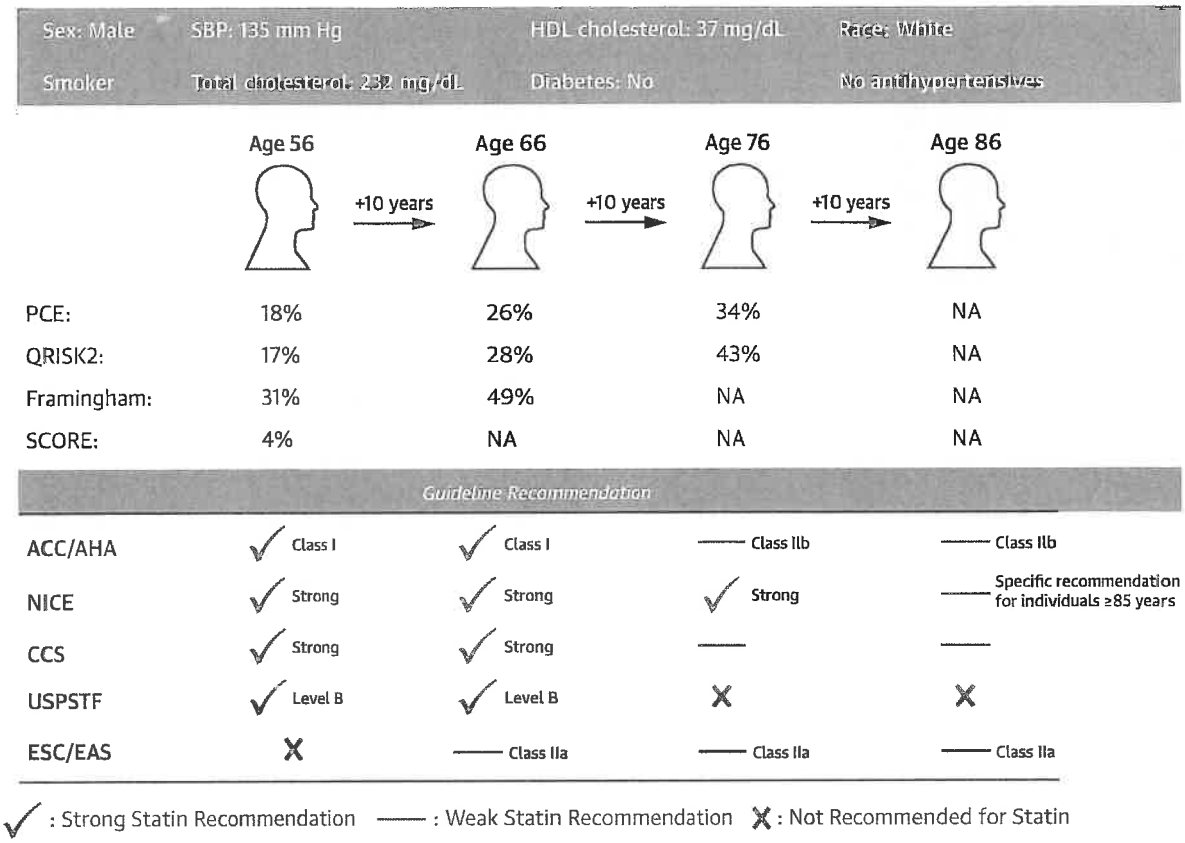
TABLE 2 Enrollment of Elderly and Very Elderly in Primary Prevention Statin Trials

Study Name, Year (Ref. #)	No.	Mean Age (yrs)	Age Range (yrs)	Elderly	Very Elderly (≥75 yrs of Age)
WOSCOPS, 1995 (10)	6,595	55	Men 45–64	0	0
AFCAPS/TexCAPS, 1998 (11)	6,605	Men 58 Women 62	Men 45–73 Women 55–73	Men 20% ≥65 yrs of age Women 33% ≥65 yrs of age	0
ALLHAT-LLT, 2002 (12)	10,355	66	≥55	28% ≥65 yrs of age*	7%*
PROSPER, 2002 (13)	3,239 (no ASCVD)	75 (whole cohort)	70–82 (whole cohort)	100% ≥70 yrs of age	NR
ASCOT-LLA, 2003 (14)	10,305	63	40–79	64% >60 yrs of age 23% >70 yrs of age	NR
CARDS, 2004 (15)	2,838	62	40–75	40% ≥65 yrs of age 12% >70 yrs of age	0
MEGA, 2006 (16)	7,832	58	40–70	23% ≥65 yrs of age	0
JUPITER, 2008 (17)	17,802	66	Men ≥50 Women ≥60	58% ≥65 yrs of age† 32% ≥70 yrs of age†	NR
HOPE-3, 2016 (18)	12,705	66	Men ≥55 Women ≥65/60	52% ≥65 yrs of age† 24% ≥70 yrs of age†	NR

*Primary prevention data reported by Han et al. (19). †Reported by Ridker et al (20).

AFCAPS/TexCAPS = Air Force/Texas Coronary Atherosclerosis Prevention Study; ALLHAT-LLT = Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial-Lipid Lowering Trial; ASCOT-LLA = Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm; CARDS = Collaborative Atorvastatin Diabetes Study; HOPE-3 = Heart Outcomes Prevention Evaluation-3; JUPITER = Justification for the Use of Statins in prevention: An Intervention Trial Evaluating Rosuvastatin; MEGA = Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese; NR = not reported; PROSPER = Pravastatin in elderly individuals at risk of vascular disease; WOSCOPS = West of Scotland Coronary Prevention Study.

CENTRAL ILLUSTRATION **Age-Dependent Implementation of Guidelines in Clinical Practice**



Mortensen, M.B. et al. J Am Coll Cardiol. 2018;71(1):85–94.

In apparently healthy individuals with risk factors shown in the box, all but the European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) guidelines provide a strong indication for statin therapy in the range of 56 to 66 years of age. Above 75 years of age, only the National Institute for Health and Care Excellence (NICE) guideline provides a well-defined indication for statin therapy. See **Table 1** for risks above which statin therapy is recommended. ACC/AHA = American College of Cardiology/American Heart Association; CCS = Canadian Cardiovascular Society; Framingham = Framingham Risk Score for general cardiovascular disease; NA = not applicable; PCE = pooled cohort equation; SCORE = Systematic COronary Risk Evaluation; USPSTF = U.S. Preventive Services Task Force.

Although the pooled cohort equations are applicable up to 79 years of age, the ACC/AHA and U.S. Preventive Services Task Force guidelines clearly state that after 75 years of age there are too few data and inadequate evidence for a strong risk-based statin recommendation. A similar view is found in the CCS guideline, which also emphasizes that the recommended Framingham risk model is not well validated after 75 years of age. Although the NICE guideline recognizes the lack of adequate evidence after 75 years of age, a strong risk-based statin recommendation is provided up to 84 years of age without any explanation—but possibly because QRISK2 is applicable up to this age. The ESC/EAS guideline recommends SCORE for risk assessment, though SCORE is applicable only up to 65 years of age. The appropriateness of this age limitation and not providing an alternative class I statin recommendation after 65 years of age is not discussed.

These discrepant statin recommendations do matter. Evaluated in real-life consecutive nondiabetic patients with a first MI, statin eligibility before the event (detection rate) varied from 1% with the ESC/EAS guideline to 75% with the NICE guideline (**Figure 2**). The SCORE-dependent ESC/EAS guideline is a striking outlier, with an extraordinary low potential to prevent a first MI in people older than 65 years of age. In contrast, only the NICE guideline offers a real potential to prevent such events after 75 years of age. This guideline also provides a weaker statin recommendation specifically for primary prevention of nonfatal MI in people ≥85 years of age.

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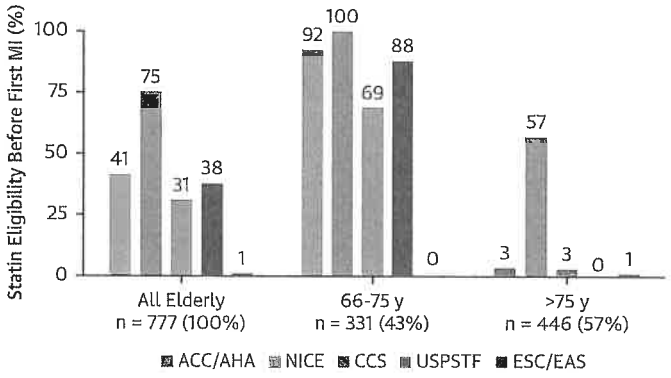
FIGURE 2 Detection Rate in Elderly Individuals >65 Years of Age With a First MI

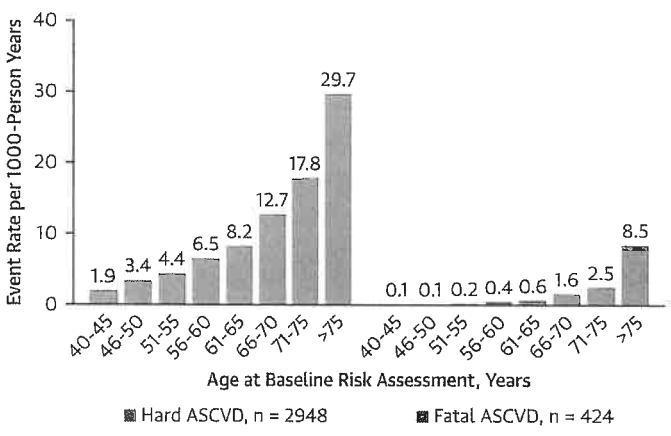


Proportion of apparently healthy elderly patients with first myocardial infarction (MI) who would have qualified for statin therapy (Class I recommendation) before the event. The data are based on 1,399 consecutive patients, of whom 777 (56%) were >65 years of age, hospitalized with a first MI in Denmark in 2010 to 2012 (54). Abbreviations as in **Figure 1**.

SPECIAL CONSIDERATIONS ON STATIN TREATMENT IN THE ELDERLY

For primary prevention with statins, net benefit of treatment is what counts for the individual person and cost effectiveness for the society. Treating acute and chronic ASCVD is costly, and broader use of inexpensive statins to prevent a first ASCVD event in the elderly is most likely cost effective and could very well be cost saving (35).

FIGURE 3 Relationship Between Hard and Fatal ASCVD Events



In apparently healthy individuals from a contemporary general population (the Copenhagen General Population Study, n = 48,814, ≥40 years of age), fatal atherosclerotic cardiovascular disease (ASCVD) events constitute only a minor proportion of hard ASCVD (fatal coronary heart disease and stroke plus nonfatal myocardial infarction and stroke) events. Among elderly people 65 to 75 years of age, the ratio was ≈7 to 8 and among very elderly people >75 years of age was ≈3.5. Adapted with permission from Mortensen et al. (25).

NET BENEFIT CONSIDERATIONS IN THE ELDERLY. The main goal of primary prevention with statins is to achieve net benefit from treatment. Considering potential harms is therefore a crucial part of appropriate decision making (36). As frailty, comorbidity, and polypharmacy may increase the risk for adverse statin-associated symptoms (SAS), the "risk-benefit" balance in the elderly could theoretically tip in favor of withholding statin therapy if such conditions are present. Limited life expectancy for whatever reason may also limit the potential benefit of statin therapy. Thus, initiation of statin therapy should always be preceded by a careful weighing of potential harms and benefits.

Well-documented SAS across all age groups are musculoskeletal issues and diabetes (37). RCT data on adverse effects have the strength of being unbiased, but may not be able to reliable detect rare events. Nevertheless, RCT data indicate that statins are safe and well tolerated in elderly individuals >65 years of age (38), with the caveats that limited data exist on the very old and that the elderly people enrolled in RCTs may be more robust than are those individuals routinely seen in clinical practice. Based on data from primary prevention statin trials (13,28,29) and a meta-analysis (39), muscle discomfort and pain reported in RCTs appear to be unrelated to age and statin therapy. However, because patients treated with statins in clinical practice are told about possible side effect, muscle symptoms will often mistakenly be perceived as statin induced—the so-called nocebo effect (40). Although rare, a higher risk for myopathy, including rhabdomyolysis, has been reported in elderly compared with younger patients treated with high-dose statin therapy, particularly simvastatin 80 mg/day (41).

The modestly increased risk for statin-induced diabetes is possibly age related and occurs almost exclusively among individuals with components of the metabolic syndrome who are already predisposed to develop diabetes (37,42). As new onset diabetes often requires additional drug therapy, this may be problematic especially in elderly patients.

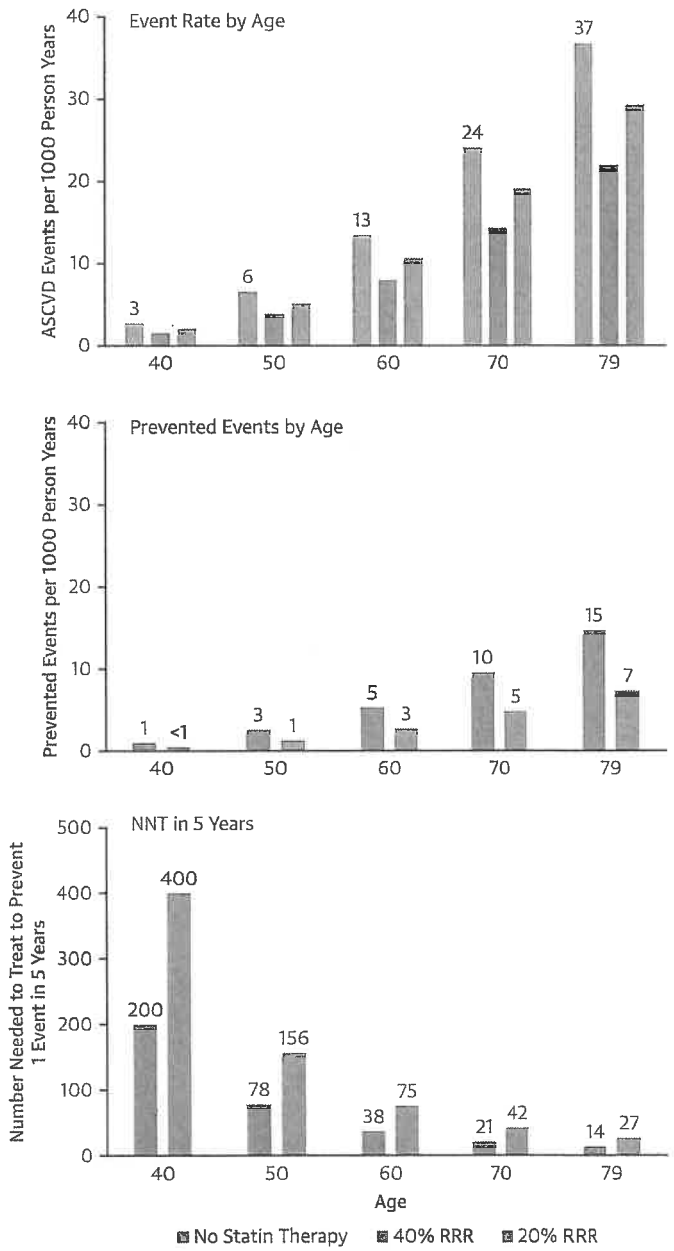
As recently reviewed, current evidence does not support a previous suspicion that statin therapy might cause memory loss, cognitive impairment, or dementia (38,43,44). Important to consider before initiating statin therapy in the elderly is polypharmacy and the associated risk for drug-drug interactions (32,33). This is especially relevant for

statins metabolized by CYP3A4 (i.e., atorvastatin). Close monitoring is important to avoid or treat possible SAS. Importantly, adverse effects of statins usually resolve rapidly after discontinuation of treatment.

MORBIDITY VERSUS MORTALITY BENEFIT IN THE ELDERLY. In primary prevention it is no longer tenable to focus only on longevity and all-cause mortality (45), as ASCVD morbidity and treatment costs are increasing. The majority of ASCVD events in the elderly are nonfatal events (**Figure 3**), and the proportion of elderly individuals >65 years of age living with chronic disease is increasing (46). Thus, patient preferences are critical important for well-informed shared decision making. If a patient only values longevity, there are little data to support primary prevention with statins in people >65 years of age. On the other hand, if preventing nonfatal and potentially disabling MI or stroke is of value to the patient, it might be reasonable to initiate statin therapy. From this perspective, it is noteworthy that the relative importance that people assign to avoiding death compared with avoiding nonfatal events appears to be highly age dependent. Although younger individuals <65 years of age weigh avoiding death highest, elderly individuals ≥65 years put a much higher weight on avoiding MI or stroke than death (47). These differences are compatible with elderly individuals having a greater focus on quality of life and avoiding disability than on extending life (48).

RR, ABSOLUTE RISK, AND NUMBER NEEDED TO TREAT IN THE ELDERLY. There are good reasons to believe that the magnitude of benefit with statins may be substantial in elderly people. As the RR reduction with statin therapy is similar for those at low and high risk of ASCVD, the absolute benefit of treatment with statins is highly dependent on absolute ASCVD risk (49). Thus, even in case of a smaller relative benefit with statin therapy in elderly people, the absolute benefit is likely higher because of the higher risk for ASCVD (**Figure 4**). Assuming different efficacy of statin therapy in various age groups ranging from a RR reduction of 20% to 40% (arbitrarily chosen), it can be estimated that the absolute risk reduction with statin therapy in a 79-year-old person may be considerably higher than in a similar 60-year-old person even if efficacy of treatment should be only one-half of that in the younger person. This translates into much lower number needed to treat in 5 years to prevent 1 event in elderly compared with younger individuals.

FIGURE 4 Conceptual Relationship Between Age and Absolute Benefit of Statin Therapy



Calculations based on the pooled cohort equations assuming a population of nonsmoking men with systolic blood pressure 135 mm Hg, total cholesterol 232 mg/dl, and high-density lipoprotein (HDL) cholesterol 37 mg/dl without diabetes or hypertension. **(Top)** Estimated 10-year risk for atherosclerotic cardiovascular disease (ASCVD) before and after statin therapy assuming 40% and 20% relative risk reduction (RRR). **(Middle)** The absolute risk reduction with statins increases substantially with age. **(Bottom)** The number needed to treat (NNT) in 5 years to prevent 1 ASCVD event becomes lower with aging, even in case of lower efficacy of treatment.

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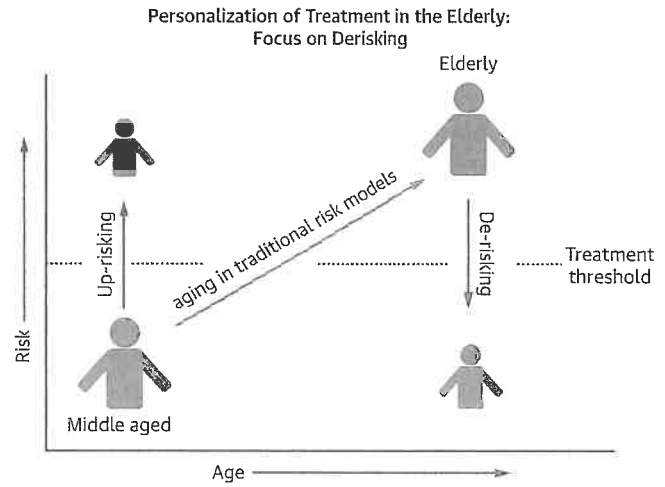
FIGURE 5 The Concept of Derisking in Elderly People



Age is the most important determinant of predicted risk of ASCVD using traditional risk models. Thus, because of increasing age alone, most elderly individuals >65 years of age will eventually exceed the risk-based treatment thresholds for statin therapy by most guidelines. Given the increasing elderly population and the associated concern about overtreatment with statins, the challenge in elderly individuals is therefore to identify those who are at truly low risk for ASCVD despite a high predicted risk with traditional risk models.

DEPRESCRIBING STATIN THERAPY IN THE VERY OLD. In patients at high risk for ASCVD adherence to prescribed statin therapy is critically important. However, discontinuing primary prevention with statin therapy is reasonable to consider in elderly, frail people at increased risk for SAS and low chance of benefit because of limited life expectancy. Quality of life may improve, but RCTs and guidelines provide no or only limited guidance on how to approach and discuss this difficult question (33). The benefit of statin therapy persists after discontinuation of therapy (long-term legacy benefit), without evidence of any rebound adverse effects in primary prevention (50).

FUTURE PERSPECTIVES

As discussed in this review, limited evidence are available on statin therapy for primary prevention of ASCVD in very elderly individuals >75 years of age. The STAREE (STAtins for Reducing Events in the Elderly) trial, a primary prevention trial currently underway, recruits individuals ≥70 years of age to determine efficacy and safety of statin treatment in elderly people (51). This trial will likely provide important insights for the older population.

With the broadened indication for statin therapy in all but the ESC/EAS guideline, most elderly individuals will eventually qualify for treatment. However, the appropriateness of treating all elderly needs reconsideration. Thus, accurate identification of elderly individuals at truly low risk is gaining increasing interest. This situation is the opposite in younger individuals, where the challenge is to identify novel biomarkers that can help "up-risking" those who do not qualify for statins but are at truly high risk for a future ASCVD event. A promising approach to personalize treatment in elderly people is "derisking" by use of negative risk markers (i.e., absence of coronary artery calcification) to identify those at so low risk that statin therapy may safely be withheld (**Figure 5**) (52,53). In the BioImage study of elderly individuals, for example, absence of coronary artery calcification was prevalent (≈1 of 3) and associated with exceptionally low ASCVD event rates (53). Derisking is not considered in current guidelines but deserves to be discussed when the guidelines are updated.

For the ESC/EAS guidelines it is time to address the inherent limitations of SCORE (not applicable beyond 65 years of age, and morbidity does not count) (23).

CONCLUSIONS

The recommendations for statin therapy in elderly >65 years of age differ substantially among the 5 major guidelines currently used in North America and Europe. At one end of the spectrum, the 2016 ESC/EAS guidelines miss great opportunities for safe, cheap, and evidence-based prevention in elderly individuals 66 to 75 years of age. At the other end of the spectrum, the 2014 NICE guideline provides near-universal treatment recommendations well into the very elderly >75 years of age where RCT evidence is sparse and more uncertain. If these guidelines are followed stringently in clinical practice, the large heterogeneity in treatment recommendations will have tremendous variable impact on ASCVD prevention in elderly individuals >65 years of age. Until more evidence is available for those individuals >75 years of age, initiation of primary prevention with statins in this age group must be based on well-informed shared decision making. To curb the increasing burden of ASCVD, guidelines need to address the rapidly changing landscape of population demographics with clear and strong guidance on how to best allocate preventive statin treatment into old age. Indeed, there are reasons to believe that the benefit of statin treatment in elderly people may be

substantial for both the individual patient and for the society.

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