Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

und

Schriftliche Beteiligung der wissenschaftlich-medizinischen Fachgesellschaften und der Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ) zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2020-B-244 Inclisiran

Stand: Oktober 2020

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA

Inclisiran
primäre Hypercholesterinämie (heterozygot familiär und nicht familiär) oder gemischte Dyslipidämie

Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	Siehe Übersicht „II. Zugelassene Arzneimittel im Anwendungsgebiet“.
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	LDL-Apherese
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	<u>LDL-Apherese:</u> Richtlinie des G-BA zu Untersuchungs- und Behandlungsmethoden der vertragsärztlichen Versorgung - Ambulante Durchführung der Apheresen als extrakorporales Hämotherapieverfahren <u>Ezetimib</u>: – Therapiehinweis zu Ezetimib vom 17. Dezember 2009 mit Beschluss vom 22. November 2018 aufgehoben – IQWiG-Rapid Report zu Ezetimib <u>Beschlüsse über die Nutzenbewertung nach 35 a SGBV</u> Evolocumab vom 2. September 2018 und 9. März 2016 Alirocumab vom 2. Mai 2019 und 4. Mai 2016 <u>Verordnungseinschränkungen und -ausschlüsse in der Arzneimittelversorgung AM-RL Anlage III</u> 35. Lipidsenker 35a. Evolocumab 35b. Alirocumab
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	Siehe systematische Literaturrecherche

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Inclisiran	geplantes Anwendungsgebiet: Inclisiran ist angezeigt zur Behandlung erwachsener Patienten mit primärer Hypercholesterinämie (heterozygot familiär und nicht-familiär) oder gemischter Dyslipidämie, zusätzlich zu einer diätetischen Therapie: • in Kombination mit einem Statin oder einem Statin mit anderen lipidsenkenden Therapien bei Patienten, die mit der maximal tolerierbaren Statin-Dosis die LDL-C-Ziele nicht erreichen, oder • allein oder in Kombination mit anderen lipidsenkenden Therapien bei Patienten mit Statin-Intoleranz oder für welche ein Statin kontraindiziert ist.
HMG-CoA-Reduktase-Hemmer (Statine), wie z.B.:	
Pravastatin C10AA03 generisch	<u>Hypercholesterinämie</u> Behandlung von primärer Hypercholesterinämie oder gemischter Dyslipidämie, zusätzlich zu einer Diät, wenn das Ansprechen auf eine Diät und andere nicht-pharmakologische Maßnahmen (z. B. körperliche Betätigung, Gewichtsabnahme) nicht ausreichend ist <u>Primäre Prävention</u> Verringerung der kardiovaskulären Mortalität und Morbidität zusätzlich zu einer Diät bei Patienten mit mittlerer oder schwerer Hypercholesterinämie, und mit einem hohen Risiko eines ersten kardiovaskulären Ereignisses (siehe Abschnitt 5.1). <u>Sekundäre Prävention</u> Verringerung der kardiovaskulären Mortalität und Morbidität bei Patienten mit einem Myokardinfarkt (MI) oder instabiler Angina pectoris in der Anamnese, und entweder normalen oder erhöhten Cholesterinwerten zusätzlich zur Korrektur anderer Risikofaktoren (siehe Abschnitt 5.1). (FI Pravastatin Heumann 2017-08)
Atorvastatin C10AA05 generisch	<u>Hypercholesterinämie</u> Die Anwendung von Atorvastatin Hennig ist zusätzlich zu einer Diät angezeigt zur Senkung erhöhter Gesamtcholesterin-, LDLCholesterin-, Apo-Lipoprotein-B- und Triglyzeridspiegel bei Erwachsenen, Jugendlichen und Kindern ab zehn Jahren mit Primärer Hypercholesterinämie, einschließlich Familiärer Hypercholesterinämie (heterozygote Variante) oder Kombinierter (gemischter) Hyperlipidämie (entsprechend Typ IIa und IIb nach Fredrickson), wenn Diät und andere nicht pharmakologische Maßnahmen keine ausreichende Wirkung erbringen. Atorvastatin Hennig ist auch zur Senkung von Gesamt- und LDL-Cholesterin bei Erwachsenen mit Homozygoter Familiärer

II. Zugelassene Arzneimittel im Anwendungsgebiet

	Hypercholesterinämie angezeigt – entweder zusätzlich zu anderen lipidsenkenden Maßnahmen (z. B. LDL-Apherese) oder falls solche Behandlungsmöglichkeiten nicht verfügbar sind. Vorbeugung kardiovaskulärer Erkrankungen zur Vorbeugung kardiovaskulärer Ereignisse bei erwachsenen Patienten, deren Risiko für ein erstes kardiovaskuläres Ereignis als hoch eingestuft wird (siehe Abschnitt 5.1), zusätzlich zur Behandlung weiterer Risikofaktoren. (FI Atorvastatin Hennig® 2020-03)
Fluvastatin C10AA04 generisch	Dyslipidämie Behandlung von Erwachsenen mit primärer Hypercholesterinämie oder gemischter Dyslipidämie, als Zusatz zu einer Diät, wenn das Ansprechen auf die Diät und andere nichtpharmakologische Maßnahmen (z. B. körperliches Training, Gewichtsreduktion) unzureichend ist. Sekundarprävention bei koronarer Herzkrankheit Sekundarprävention schwerwiegender unerwünschter kardialer Ereignisse bei Erwachsenen mit koronarer Herzkrankheit nach perkutaner Koronarintervention (siehe Abschnitt 5.1). (FI Fluvastatin ratiopharm® 2018-07)
Rosuvastatin C10AA07 Rosuvastatin Heumannr®	Behandlung von Hypercholesterinämie Erwachsene, Jugendliche und Kinder ab 6 Jahren mit primärer Hypercholesterinämie (Typ IIa einschließlich heterozygoter familiärer Hypercholesterinämie) oder gemischter Dyslipidämie (Typ IIb), zusätzlich zu einer Diät, wenn das Ansprechen auf eine Diät und andere nicht pharmakologische Maßnahmen (z. B. Bewegung, Gewichtsreduktion) nicht ausreichend sind. Homozygote familiäre Hypercholesterinämie Erwachsene, Jugendliche und Kinder ab 6 Jahren mit homozygoter Hypercholesterinämie zusätzlich zu einer Diät und anderen lipidsenkenden Maßnahmen (z. B. LDL-Apherese) oder wenn solche Maßnahmen nicht geeignet sind. Vorbeugung kardiovaskulärer Ereignisse Vorbeugung schwerwiegender kardiovaskulärer Ereignisse bei Patienten mit erwartet hohem Risiko für erstmalige kardiovaskuläre Ereignisse (siehe Abschnitt 5.1), in Ergänzung der Korrektur anderer Risikofaktoren. (FI Rosuvastatin Heumann® 2018-10)
Simvastatin C10AA01 generisch	Hypercholesterinämie Zur Behandlung der primären oder gemischten Hyperlipidämie begleitend zu Diät, wenn Diät und andere nicht pharmakologische Maßnahmen (z. B. körperliches Training und Gewichtsabnahme) allein nicht ausreichen. Zur Behandlung der homozygoten familiären Hypercholesterinämie (HoFH). Simva-Hennig® wird begleitend zu Diät und anderen lipidsenkenden Maßnahmen (z. B. LDL [low density lipoprotein]-Apherese) angewandt oder wenn solche Maßnahmen nicht geeignet sind. Kardiovaskuläre Prävention

II. Zugelassene Arzneimittel im Anwendungsgebiet	
	Zur Senkung kardiovaskulärer Mortalität und Morbidität bei Patienten mit manifester atherosklerotischer Herzerkrankung oder Diabetes mellitus, deren Cholesterinwerte normal oder erhöht sind. Begleitend zur Korrektur anderer Risikofaktoren und kardioprotektiver Therapie (siehe Abschnitt 5.1). (FI Simva-Hennig® 2020-02)
Pitavastatin C10AA08 LIVAZO	Zur Senkung erhöhter Gesamtcholesterin (TC)- und LDL-C-Werte bei erwachsenen Patienten mit primärer Hypercholesterinämie — einschließlich der heterozygoten familiären Hypercholesterinämie — und kombinierter (gemischter) Dyslipidämie, wenn sich mit diätetischen und sonstigen nicht-medikamentösen Maßnahmen kein ausreichendes Ansprechen erzielen lässt. (Lauer Taxe Bearbeitungsstand 2020-09)
Lovastatin C10AA02 Lovastatin ratiopharm®	Zur Senkung erhöhter Gesamt- und LDL-Cholesterin-Spiegel im Plasma zusammen mit einer diätetischen Behandlung in Fällen, wenn der Patient primäre Hypercholesterin-ämie hat und sich eine Diät und andere nicht-pharmakologische Maßnahmen allei-ne als unzureichend erwiesen haben Zur Senkung erhöhter Cholesterin-Spiegel im Plasma bei der kombinierten Hypercho-lesterinämie und Hypertriglyceridämie, wenn der erhöhte Cholesterin-Spiegel im Plasma der hauptsächliche Grund für die Behand-lung ist. (FI Lovastatin ratiopharm® 2015-11)
Fibrate	
Fenofibrat C10AB05 generisch	Fenofibrat 200 Heumann ist angezeigt als unterstutzende Behandlung neben einer Diät oder anderen nicht-medikamentösen Therapien (z. B. sportlicher Betätigung, Gewichtsabnahme) für folgende Erkrankungen: - schwere Hypertriglyceridämie mit oder ohne niedrige HDL-Cholesterinwerten, - gemischte Hyperlipidämie, wenn ein Statin kontraindiziert ist oder nicht vertragen wird, - bei gemischter Hyperlipidämie bei Patienten mit hohem kardiovaskulären Risiko zusätzlich zu einem Statin, wenn Triglycerid-und HDL-Cholesterinwerte nicht ausreichend kontrolliert werden können. (FI Fenofibrat Heumann® 2018-01)
Bezafibrat C10AB02 generisch	[…] angezeigt als unterstützende Behandlung neben einer Diät oder anderen nicht-medikamentösen Therapien (z. B. sportlicher Betätigung, Gewichtsabnahme) für folgende Erkrankungen: • schwere Hypertriglyceridämie mit oder ohne niedrige HDL-Cholesterinwert • gemischte Hyperlipidämie, wenn ein Statin kontraindiziert ist oder nicht vertragen wird. Die vor der medikamentösen Behandlung eingeleiteten diätetischen Maßnahmen sollen während der Therapie beibehalten werden. (FI Bezafibrat AbZ Pharma® 2014-08)
Gemfibrozil C10AB04 generisch	Gevilon ist angezeigt als unterstützende Behandlung neben einer Diät oder anderen nicht medikamentösen Therapien (z. B. sportlicher Betätigung, Gewichtsabnahme) für folgende Erkrankungen: • schwere Hypertriglyceridämie mit oder ohne niedrige HDL-Cholesterin-Werte

II. Zugelassene Arzneimittel im Anwendungsgebiet

	• gemischte Hyperlipidämie, wenn ein Statin kontraindiziert ist oder nicht vertragen wird • primäre Hypercholesterinämie, wenn ein Statin kontraindiziert ist oder nicht vertragen wird. Primäre Prävention Reduktion der kardiovaskulären Morbidität bei Männern mit erhöhtem Nicht-HDL-Cholesterin, bei denen ein hohes Risiko eines ersten kardiovaskulären Ereignisses besteht, wenn ein Statin kontraindiziert ist oder nicht vertragen wird (siehe Abschnitt 5.1). (FI Gevilon® 2019-10)
Anionenaustauscherharze (Gallensäurebinder)	
Colestyramin C10AC04 generisch	– Die gleichzeitige Anwendung von Colestyramin-ratiopharm® mit einem HMG-CoA-Reduktaseinhibitor (Statin) ist als adjuvante Therapie zur Diät angezeigt, um eine additive Reduktion der LDL-Cholesterin-(LDL-C)-Spiegel bei Patienten mit primärer Hypercholesterinämie zu erzielen, bei denen mit einem Statin allein keine ausreichende Kontrolle möglich ist. – Colestyramin-ratiopharm® als Monotherapie ist als adjuvante Therapie zur Diät zur Reduktion des erhöhten Gesamt- und LDL-Cholesterins bei Patienten mit isolierter primärer Hypercholesterinämie angezeigt, bei denen ein Statin als unangemessen betrachtet wird oder nicht gut vertragen wird. – Chologene Diarrhoen – Pruritus oder Ikterus bei partiellem Gallengangsverschluss Die vor der medikamentösen Behandlung eingeleiteten diätetischen Maßnahmen sollen während der Therapie beibehalten werden. Bisher gibt es keine kontrollierten Langzeitversuche, welche die Wirkung von Colestyramin bei der primären oder sekundären Prävention von Komplikationen der Arteriosklerose belegen. (FI Colestyramin ratiopharm® 2018-08)
Colesevelam C10AC04 Cholestagel®	Die gleichzeitige Anwendung von Cholestagel mit einem 3-Hydroxy-3-Methylglutaryl-Coenzym-A- (HMG-CoA-)Reduktaseinhibitor (Statin) ist als adjuvante Therapie zur Diät angezeigt, um eine additive Reduktion der Low-Density-Cholesterin-(LDL-C-)Spiegel bei erwachsenen Patienten mit primärer Hypercholesterinämie zu erzielen, bei denen mit einem Statin allein keine ausreichende Kontrolle möglich ist. Cholestagel als Monotherapie ist als adjuvante Therapie zur Diät zur Reduktion des erhöhten Gesamt-Cholesterins und LDL-C bei erwachsenen Patienten mit primärer Hypercholesterinämie angezeigt, bei denen ein Statin als unangemessen betrachtet wird oder nicht gut vertragen wird. Cholestagel kann auch in Kombination mit Ezetimib, mit oder ohne ein Statin, bei erwachsenen Patienten mit primärer Hypercholesterinämie einschließlich Patienten mit familiärer Hypercholesterinämie, angewendet werden (siehe Abschnitt 5.1). (FI Cholestagel® 2018-11)
PCSK9-Inhibitoren	
Evolocumab	Hypercholesterinämie und gemischte Dyslipidämie

II. Zugelassene Arzneimittel im Anwendungsgebiet

C10AX13 Repatha®	Repatha wird bei Erwachsenen mit primärer Hypercholesterinämie (heterozygot familiär und nicht-familiär) oder gemischter Dyslipidamie zusätzlich zu diätetischer Therapie angewendet: • in Kombination mit einem Statin oder einem Statin mit anderen lipidsenkenden Therapien bei Patienten, die mit der maximal tolerierbaren Statin-Dosis die LDLC-Ziele nicht erreichen, oder • allein oder in Kombination mit anderen lipidsenkenden Therapien bei Patienten mit Statinintoleranz oder für welche ein Statin kontraindiziert ist. <u>Homozygote familiäre Hypercholesterinämie</u> Repatha wird bei Erwachsenen und Jugendlichen im Alter von 12 Jahren und älter mit homozygoter familiärer Hypercholesterinämie in Kombination mit anderen lipidsenkenden Therapien angewendet. <u>Bekannte atherosklerotische kardiovaskuläre Erkrankung</u> Repatha wird bei Erwachsenen mit bekannter atherosklerotischer kardiovaskulärer Erkrankung (Myokardinfarkt, Schlaganfall oder periphere arterielle Verschlusskrankheit) zur Reduktion des kardiovaskulären Risikos durch Verringerung der LDL-C-Werte zusätzlich zur Korrektur anderer Risikofaktoren angewendet: • in Kombination mit einer maximal tolerierbaren Statin-Dosis mit oder ohne anderen lipidsenkenden Therapien, oder • allein oder in Kombination mit anderen lipidsenkenden Therapien bei Patienten mit Statin-Intoleranz oder für welche ein Statin kontraindiziert ist Zu Studienergebnissen bzgl. der Wirksamkeit auf LDL-C, kardiovaskuläre Ereignisse und die untersuchten Populationen siehe Abschnitt 5.1. (FI Repatha®, 2020-04)
Andere Lipidsenker	
Ezetimib C10AX09 Ezetrol®	<u>Primäre Hypercholesterinämie</u> EZETROL ist zusammen mit einem HMGCoA-Reduktase-Hemmer (Statin) eingenommen begleitend zu Diät angezeigt zur Anwendung bei Patienten mit primärer (heterozygoter familiärer und nicht familiärer) Hypercholesterinämie, bei denen die Therapie mit einem Statin allein nicht ausreicht. Eine Monotherapie mit EZETROL ist begleitend zu Diät angezeigt zur Anwendung bei Patienten mit primärer (heterozygoter familiärer und nicht familiärer) Hypercholesterinämie, bei denen ein Statin als ungeeignet erachtet oder nicht vertragen wird. <u>Prävention kardiovaskulärer Ereignisse</u> EZETROL ist zusätzlich zu einer bestehenden Statintherapie oder initial in Kombination mit einem Statin angezeigt zur Risikoreduktion von kardiovaskulären Ereignissen (siehe Abschnitt 5.1) bei Patienten mit koronarer Herzkrankheit (KHK) und akutem Koronarsyndrom in der Vorgeschichte. <u>Homozygote familiäre Hypercholesterinämie (HoFH)</u> EZETROL ist zusammen mit einem Statin eingenommen begleitend zu Diät angezeigt zur Anwendung bei Patienten mit homozygoter familiärer

II. Zugelassene Arzneimittel im Anwendungsgebiet	
	Hypercholesterinämie. Die Patienten können weitere begleitende Therapien (wie LDL-Apherese) erhalten. Homozygote Sitosterinämie (Phytosterinämie) EZETROL ist begleitend zu Diät angezeigt zur Anwendung bei Patienten mit homozygoter familiärer Sitosterinamie. (FI Ezetrol® 2018-11)
Ezetimib/ Simvastatin C10BA02 Inegy®	Prävention kardiovaskulärer Ereignisse INEGY ist angezeigt zur Risikoreduktion von kardiovaskulären Ereignissen (siehe Abschnitt 5.1) bei Patienten mit koronarer Herzkrankheit (KHK) und akutem Koronarsyndrom in der Vorgeschichte, unabhängig von einer Vorbehandlung mit einem Statin. Hypercholesterinämie INEGY ist begleitend zu Diät angezeigt zur Anwendung bei Patienten mit primärer (heterozygoter familiärer und nicht familiärer) Hypercholesterinämie oder gemischter Hyperlipidämie, für die eine Therapie mit einem Kombinationspräparat geeignet ist: • Patienten, bei denen eine Therapie mit einem Statin allein nicht ausreicht • Patienten, die bereits mit einem Statin und Ezetimib behandelt werden Homozygote familiäre Hypercholesterinämie (HoFH) INEGY ist begleitend zu Diät angezeigt zur Anwendung bei Patienten mit homozygoter familiärer Hypercholesterinämie. Die Patienten können weitere begleitende Therapien (wie LDL[low-density lipoprotein]-Apherese) erhalten. (FI Inegy® 2020-02)
Ezetimib/ Atorvastatin Atozet® C10BA05	Prävention kardiovaskulärer Ereignisse Atozet ist angezeigt zur Risikoreduktion von kardiovaskulären Ereignissen (siehe Abschnitt 5.1) bei Patienten mit koronarer Herzkrankheit (KHK) und akutem Koronarsyndrom in der Vorgeschichte, unabhängig von einer Vorbehandlung mit einem Statin. Hypercholesterinämie Atozet ist begleitend zu einer Diät angezeigt zur Anwendung bei erwachsenen Patienten mit primärer (heterozygoter familiärer und nicht familiärer) Hypercholesterinämie oder gemischter Hyperlipidämie, für die eine Therapie mit einem Kombinationspräparat geeignet ist: • Patienten, bei denen eine Therapie mit einem Statin allein nicht ausreicht • Patienten, die bereits mit einem Statin und Ezetimib behandelt werden Homozygote familiäre Hypercholesterinämie (HoFH) Atozet ist begleitend zu einer Diät angezeigt zur Anwendung bei erwachsenen Patienten mit homozygoter familiärer Hypercholesterinämie. Die Patienten können weitere begleitende Therapien (wie LDL-Apherese) erhalten. (FI Atozet® 2019-09)

Quellen: AMIS-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2020-B-244 (Inclisiran)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	17. September 2020

Inhaltsverzeichnis

Abkürzungsverzeichnis

ACS	akutem Koronarsyndrom
AEs	adverse event
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
BAS	bile acid sequestrants
BEL	Best Evidence Level
CAD	coronary artery disease
CETP	cholesteryl ester transfer protein inhibitors
CVD	cardiovascular disease
DAHTA	DAHTA Datenbank
EZT	ezetimibe
FBT	fibrates
FH	Familiäre Hypercholesterolämie/Familial hypercholesterolaemia
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
HDL	High-density lipoprotein
HDL-C	high density lipoprotein cholesterol
HeFH	Heterozygote familiäre Hypercholesterinämie
HoFH	Homozygote familiäre Hypercholesterinämie
HR	Hazard Ratio
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KHK	Herzkrankheit
KI	Konfidenzintervall
LDL	Low Density Lipoprotein
LDL-C	Low-density lipoprotein cholesterol
LoE	Level of Evidence
Lp(a)	lipoprotein(a)
MACE	major cardiovascular events
MTP	microsomal transfer protein inhibitors
NGC	National Guideline Clearinghouse

NIA	niacin
NICE	National Institute for Health and Care Excellence
NST	non-statin lipid-lowering agents
OMG3	omega-3 fatty acids
OR	Odds Ratio
PCSK	proprotein convertasen subtilisin/kexin-9 inhibitors
RR	Relatives Risiko
SIGN	Scottish Intercollegiate Guidelines Network
ST	Statin
TC	Total cholesterol
TG	Triglyceride
TG	Triglyceride
TRIP	Turn Research into Practice Database
WHO	World Health Organization

1 Indikation

Primäre Hypercholesterinämie (heterozygote familiär und nicht familiär) oder gemischte Dyslipidämie.

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation *primäre Hypercholesterinämie (heterozygot familiär und nicht familiär) und gemischte Dyslipidämie* durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 02.09.2020 abgeschlossen. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews), MEDLINE (PubMed), AWMF, ERCI, G-BA, NICE, TRIP, SIGN, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

In einem zweistufigen Screening wurden die Ergebnisse der Literaturrecherche bewertet. Die Recherche ergab 1352 Quellen. Im ersten Screening wurden auf Basis von Titel und Abstract nach Population, Intervention, Komparator und Publikationstyp nicht relevante Publikationen ausgeschlossen. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Im zweiten Screening wurden die im ersten Screening eingeschlossenen Publikationen als Volltexte gesichtet und auf ihre Relevanz und methodische Qualität geprüft. Dafür wurden dieselben Kriterien wie im ersten Screening sowie Kriterien zur methodischen Qualität der Evidenzquellen verwendet. Basierend darauf, wurden insgesamt 37 Quellen eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 IQWiG Berichte/G-BA Beschlüsse

G-BA, 2017 [15].

Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL):

Anlage III - Übersicht über Verordnungseinschränkungen und –ausschlüsse Nummer 35a – **Evolocumab**

Vom 20. April 2017

Der Gemeinsame Bundesausschuss (G-BA) hat in seiner Sitzung am 20. April 2017 beschlossen, die Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (Arzneimittel-Richtlinie) in der Fassung vom 18. Dezember 2008 / 22. Januar 2009 (BAnz Nr. 49a vom 31. März 2009), zuletzt geändert am 18. Mai 2017 (BAnz AT 16.06.2017 B2), wie folgt zu ändern:

I. Die Anlage III der Arzneimittel-Richtlinie wird wie folgt geändert:

In Nummer 35a wird in der linken Spalte im letzten Satz nach der Angabe „Fachärzte für Innere Medizin und Angiologie“ die Angabe „Fachärzte für Kinder- und Jugendmedizin mit Zusatz-Weiterbildung Kinder-Endokrinologie und –Diabetologie, Kinder-Nephrologie oder Schwerpunkt Kinder-Kardiologie“ eingefügt.

Siehe auch: ***G-BA, 2019 [14].***

Anlage III Stand (letzte Änderung in Kraft getreten am): 13. September 2019

Übersicht über Verordnungseinschränkungen und -ausschlüsse in der Arzneimittelversorgung durch die Arzneimittel-Richtlinie und aufgrund anderer Vorschriften (§ 34 Absatz 1 Satz 6 und Absatz 3 SGB V), Hinweise zur wirtschaftlichen Verordnungsweise von nicht verschreibungspflichtigen Arzneimitteln für Kinder bis zum vollendeten 12. Lebensjahr und für Jugendliche mit Entwicklungsstörungen bis zum vollendeten 18. Lebensjahr sowie Verordnungseinschrän-kungen und -ausschlüsse von sonstigen Produkten

35. Lipidsenker, Arzneimittel und sonstige Produkte

- ausgenommen bei bestehender vaskulärer Erkrankung (KHK, cerebrovaskuläre Manifestation, pAVK)
- ausgenommen bei hohem kardiovaskulärem Risiko (über 20% Ereignisrate/ 10 Jahre auf der Basis der zur Verfügung stehenden Risikokalkulatoren).

Rechtliche Grundlagen und Hinweise:

Verordnungsausschluss aufgrund von Rechtsverordnung für Aluminiumclofibrat, Orotsäure bei Hyperlipidämie.[1]

Verordnungseinschränkung verschreibungspflichtiger Arzneimittel nach dieser Richtlinie.[2]

35a. Evolocumab

Dieser Wirkstoff ist nicht verordnungsfähig, solange er mit Mehrkosten im Vergleich zu einer Therapie mit anderen Lipidsenkern (Statine, Fibrate, Anionenaustauscher, Cholesterinresorptionshemmer) verbunden ist. Das angestrebte Behandlungsziel bei der Behandlung der Hypercholesterinämie oder gemischten Dyslipidämie ist mit anderen Lipidsenkern ebenso zweckmäßig, aber kostengünstiger zu erreichen. Für die Bestimmung der Mehrkosten sind die der zuständigen Krankenkasse tatsächlich entstehenden Kosten maßgeblich.

Dies gilt nicht für Patienten

- mit familiärer, homozygoter Hypercholesterinämie, bei denen medikamentöse und diätetische Optionen zur Lipidsenkung ausgeschöpft worden sind, oder
- mit heterozygot familiärer oder nichtfamiliärer Hypercholesterinämie oder gemischter Dyslipidämie bei therapierefraktären Verläufen, bei denen grundsätzlich trotz einer über einen Zeitraum von 12 Monaten dokumentierten maximalen diätetischen und medikamentösen lipidsenkenden Therapie (Statine und/oder andere Lipidsenker bei Statin-Kontraindikation) der LDL-C-Wert nicht ausreichend gesenkt werden kann und daher davon ausgegangen wird, dass die Indikation zur Durchführung einer LDL-Apherese besteht. Es kommen nur Patienten mit gesicherter vaskulärer Erkrankung (KHK, cerebrovaskuläre Manifestation, pAVK) sowie regelhaft weiteren Risikofaktoren für kardiovaskuläre Ereignisse (z.B. Diabetes mellitus, Nierenfunktion GFR unter 60 ml/min) infrage sowie Patienten mit gesicherter familiärer heterozygoter Hypercholesterinämie unter Berücksichtigung des Gesamtrisikos familiärer Belastung.

Die Einleitung und Überwachung der Therapie mit Evolocumab muss durch Fachärzte für Innere Medizin und Kardiologie, Fachärzte für Innere Medizin und Nephrologie, Fachärzte für Innere Medizin und Endokrinologie und Diabetologie, Fachärzte für Innere Medizin und Angiologie, Fachärzte für Kinder- und Jugendmedizin mit Zusatz-Weiterbildung Kinder-Endokrinologie und –Diabetologie, Kinder-Nephrologie oder Schwerpunkt Kinder-Kardiologie oder durch an Ambulanzen für Lipidstoffwechselstörungen tätige Fachärzte erfolgen.

35b. Alirocumab

Dieser Wirkstoff ist nicht verordnungsfähig, solange er mit Mehrkosten im Vergleich zu einer Therapie mit anderen Lipidsenkern (Statine, Fibrate, Anionenaustauscher, Cholesterinresorptionshemmer) verbunden ist. Das angestrebte Behandlungsziel bei der Behandlung der Hypercholesterinämie oder gemischten Dyslipidämie ist mit anderen Lipidsenkern ebenso zweckmäßig, aber kostengünstiger zu erreichen. Für die Bestimmung der Mehrkosten sind die der zuständigen Krankenkasse tatsächlich entstehenden Kosten maßgeblich.

Dies gilt nicht für Patienten

- mit heterozygot familiärer oder nicht-familiärer Hypercholesterinämie oder gemischter Dyslipidämie bei therapierefraktären Verläufen, bei denen grundsätzlich trotz einer über einen Zeitraum von 12 Monaten dokumentierten maximalen diätetischen und medikamentösen lipidsenkenden Therapie (Statine und/oder andere Lipidsenker bei Statin-Kontraindikation) der LDL-C-Wert nicht ausreichend gesenkt werden kann und daher davon ausgegangen wird, dass die Indikation zur Durchführung einer LDL-Apherese besteht. Es kommen nur Patienten mit gesicherter vaskulärer Erkrankung (KHK, cerebrovaskuläre Manifestation, pAVK) sowie regelhaft weiteren Risikofaktoren für kardiovaskuläre Ereignisse

(z.B. Diabetes mellitus, Nierenfunktion GFR unter 60 ml/min) infrage sowie Patienten mit gesicherter familiärer heterozygoter Hypercholesterinämie unter Berücksichtigung des Gesamtrisikos familiärer Belastung.

Die Einleitung und Überwachung der Therapie mit Alirocumab muss durch Fachärzte für Innere Medizin und Kardiologie, Fachärzte für Innere Medizin und Nephrologie, Fachärzte für Innere Medizin und Endokrinologie und Diabetologie, Fachärzte für Innere Medizin und Angiologie oder durch an Ambulanzen für Lipidstoffwechselstörungen tätige Fachärzte erfolgen.

[1] *Verordnungsausschluss aufgrund der Rechtsverordnung nach § 34 Abs. 3 SGB V (sog. Negativliste)*

[2] *Verordnungseinschränkung nach dieser Richtlinie (§ 92 Abs. 1 Satz 1 Halbsatz 3 SGB V in Verbindung mit § 16 Abs. 1 und 2 AM-RL).*

G-BA, 2019 [16].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 4. Mai 2016 / 2. Mai 2019 - Alirocumab

Zugelassenes Anwendungsgebiet vom 23. September 2015:

Praluent® ist, begleitend zu einer Diät, angezeigt zur Behandlung bei Erwachsenen mit primärer Hypercholesterinämie (heterozygote familiäre und nicht familiäre) oder gemischter Dyslipidämie:

- in Kombination mit einem Statin oder mit einem Statin und anderen lipidsenkenden Therapieprinzipien bei Patienten, die mit einer maximal verträglichen Statintherapie die LDL-C-Zielwerte nicht erreichen, oder
- als Monotherapie oder in Kombination mit anderen lipidsenkenden Therapieprinzipien bei Patienten mit einer Statin- Unverträglichkeit oder wenn Statine kontraindiziert sind.

Zugelassenes neues Anwendungsgebiet vom 11. März 2019[1]:

Established atherosclerotic cardiovascular disease Praluent is indicated in adults with established atherosclerotic cardiovascular disease to reduce cardiovascular risk by lowering LDL-C levels, as an adjunct to correction of other risk factors:

- in combination with the maximum tolerated dose of a statin with or without other lipidlowering therapies or,
- alone or in combination with other lipid-lowering therapies in patients who are statinintolerant, or for whom a statin is contraindicated

For study results with respect to effects on LDL-C, cardiovascular events and populations studied see section 5.1.

a) Erwachsene Patienten mit primärer (heterozygoter familiärer und nicht familiärer) Hypercholesterinämie oder gemischter Dyslipidämie, die mit der maximal tolerierbaren Statin-Dosis die LDL-C-Ziele nicht erreichen und für die Statine infrage kommen:

a1) Erwachsene Patienten (ohne bekannte atherosklerotische kardiovaskuläre Erkrankung (Myokardinfarkt, Schlaganfall oder periphere arterielle Verschlusskrankheit))

mit primärer Hypercholesterinämie (heterozygot familiär und nicht-familiär) oder gemischter Dyslipidämie, die mit der maximal tolerierbaren Statin-Dosis die LDL-C-Ziele nicht erreichen und für die Statine infrage kommen:

zweckmäßige Vergleichstherapie

- maximal tolerierte medikamentöse und diätetische Therapie zur Lipidsenkung

Ausmaß und Wahrscheinlichkeit des Zusatznutzens von Alirocumab gegenüber der zweckmäßigen Vergleichstherapie:

Ein Zusatznutzen ist nicht belegt.

a2) Erwachsene Patienten (mit bekannter atherosklerotischer kardiovaskulärer Erkrankung (Myokardinfarkt, Schlaganfall oder periphere arterielle Verschlusskrankheit)) mit primärer Hypercholesterinämie (heterozygot familiär und nicht-familiär) oder gemischter Dyslipidämie, die mit der maximal tolerierbaren Statin-Dosis die LDL-C-Ziele nicht erreichen und für die Statine infrage kommen:

zweckmäßige Vergleichstherapie

- maximal tolerierte medikamentöse und diätetische Therapie zur Lipidsenkung

Ausmaß und Wahrscheinlichkeit des Zusatznutzens von Alirocumab gegenüber der maximal tolerierten medikamentösen und diätetischen Therapie zur Lipidsenkung:

Ein Zusatznutzen ist nicht belegt.

b) Patienten mit primärer (heterozygoter familiärer und nicht familiärer) Hypercholesterinämie oder gemischter Dyslipidämie, für die eine Statintherapie aufgrund von Kontraindikationen oder therapielimitierenden Nebenwirkungen nicht infrage kommt:

b1) Erwachsene Patienten (ohne bekannte atherosklerotische kardiovaskuläre Erkrankung (Myokardinfarkt, Schlaganfall oder periphere arterielle Verschlusskrankheit)) mit primärer (heterozygoter familiärer und nicht familiärer) Hypercholesterinämie oder gemischter Dyslipidämie, für die eine Statintherapie aufgrund von Kontraindikationen oder therapielimitierenden Nebenwirkungen nicht infrage kommt:

zweckmäßige Vergleichstherapie

- andere (als Statine) Lipidsenker (Fibrate oder Anionenaustauscher oder Cholesterinresorptionshemmer) als Monotherapie und diätetische Therapie zur Lipidsenkung

Ausmaß und Wahrscheinlichkeit des Zusatznutzens von Alirocumab gegenüber der zweckmäßigen Vergleichstherapie:

Ein Zusatznutzen ist nicht belegt.

b2) Erwachsene Patienten (mit bekannter atherosklerotischer kardiovaskulärer Erkrankung (Myokardinfarkt, Schlaganfall oder periphere arterielle Verschlusskrankheit)) mit primärer (heterozygoter familiärer und nicht familiärer) Hypercholesterinämie oder gemischter Dyslipidämie, für die eine Statintherapie aufgrund von Kontraindikationen oder therapielimitierenden Nebenwirkungen nicht infrage kommt:

zweckmäßige Vergleichstherapie

- andere (als Statine) Lipidsenker (Fibrate oder Anionenaustauscher oder Cholesterinresorptionshemmer) als Monotherapie und diätetische Therapie zur Lipidsenkung

Ausmaß und Wahrscheinlichkeit des Zusatznutzens von Alirocumab gegenüber der zweckmäßigen Vergleichstherapie:

Ein Zusatznutzen ist nicht belegt.

c) Für Patienten, bei denen medikamentöse und diätetische Optionen zur Lipidsenkung ausgeschöpft worden sind:

- LDL-Apherese (als „ultima ratio“ bei therapierefraktären Verläufen) ggf. mit begleitender medikamentöser lipidsenkender Therapie.

Ausmaß und Wahrscheinlichkeit des Zusatznutzens von Alirocumab gegenüber der zweckmäßigen Vergleichstherapie für Patienten, bei denen medikamentöse und diätische Optionen zur Lipidsenkung ausgeschöpft worden sind:

Ein Zusatznutzen ist nicht belegt.

Fazit / Ausmaß des Zusatznutzens / Ergebnis

a), a1), a2), b), b1), b2), c): Ein Zusatznutzen ist nicht belegt.

G-BA, 2018 [17].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 9. März 2016 / 16. Juni 2016 / 6. September 2018 - Evolocumab

Zugelassenes Anwendungsgebiet vom 08. Mai 2018:

Hypercholesterinämie und gemischte Dyslipidämie

Repatha wird bei Erwachsenen mit primärer Hypercholesterinämie (heterozygot familiär und nicht-familiär) oder gemischter Dyslipidämie zusätzlich zu diätetischer Therapie angewendet:

- in Kombination mit einem Statin oder einem Statin mit anderen lipidsenkenden Therapien bei Patienten, die mit der maximal tolerierbaren Statin-Dosis die LDL-C-Ziele nicht erreichen, oder
- allein oder in Kombination mit anderen lipidsenkenden Therapien bei Patienten mit Statinintoleranz oder für welche ein Statin kontraindiziert ist.

Homozygote familiäre Hypercholesterinämie

Repatha wird bei Erwachsenen und Jugendlichen im Alter von 12 Jahren und älter mit homozygoter familiärer Hypercholesterinämie in Kombination mit anderen lipidsenkenden Therapien angewendet.

Bekannte atherosklerotische kardiovaskuläre Erkrankung

Repatha wird bei Erwachsenen mit bekannter atherosklerotischer kardiovaskulärer Erkrankung (Myokardinfarkt, Schlaganfall oder periphere arterielle Verschlusskrankheit) zur Reduktion des kardiovaskulären Risikos durch Verringerung der LDL-C-Werte zusätzlich zur Korrektur anderer Risikofaktoren angewendet:

- in Kombination mit einer maximal tolerierbaren Statin-Dosis mit oder ohne anderen lipidsenkenden Therapien, oder
- allein oder in Kombination mit anderen lipidsenkenden Therapien bei Patienten mit Statin-Intoleranz oder für welche ein Statin kontraindiziert ist.

Praluent® ist, begleitend zu einer Diät, angezeigt zur Behandlung bei Erwachsenen mit primärer Hypercholesterinämie (heterozygote familiäre und nicht familiäre) oder gemischter Dyslipidämie:

- in Kombination mit einem Statin oder mit einem Statin und anderen lipidsenkenden Therapieprinzipien bei Patienten, die mit einer maximal verträglichen Statintherapie die LDL-C-Zielwerte nicht erreichen, oder
- als Monotherapie oder in Kombination mit anderen lipidsenkenden Therapieprinzipien bei Patienten mit einer Statin- Unverträglichkeit oder wenn Statine kontraindiziert sind.

Zugelassenes neues Anwendungsgebiet vom 11. März 2019[1]:

Established atherosclerotic cardiovascular disease Praluent is indicated in adults with established atherosclerotic cardiovascular disease to reduce cardiovascular risk by lowering LDL-C levels, as an adjunct to correction of other risk factors:

- in combination with the maximum tolerated dose of a statin with or without other lipidlowering therapies or,
- alone or in combination with other lipid-lowering therapies in patients who are statinintolerant, or for whom a statin is contraindicated

For study results with respect to effects on LDL-C, cardiovascular events and populations studied see section 5.1.

a) Erwachsene Patienten mit primärer (heterozygoter familiärer und nicht familiärer) Hypercholesterinämie oder gemischter Dyslipidämie, die mit der maximal tolerierbaren Statin-Dosis die LDL-C-Ziele nicht erreichen und für die Statine infrage kommen:

a1) Erwachsene Patienten (ohne bekannte atherosklerotische kardiovaskuläre Erkrankung (Myokardinfarkt, Schlaganfall oder periphere arterielle Verschlusskrankheit)) mit primärer Hypercholesterinämie (heterozygot familiär und nicht-familiär) oder gemischter Dyslipidämie, die mit der maximal tolerierbaren Statin-Dosis die LDL-C-Ziele nicht erreichen und für die Statine infrage kommen:

zweckmäßige Vergleichstherapie

- maximal tolerierte medikamentöse und diätetische Therapie zur Lipidsenkung

Ausmaß und Wahrscheinlichkeit des Zusatznutzens von Alirocumab gegenüber der zweckmäßigen Vergleichstherapie:

Ein Zusatznutzen ist nicht belegt.

a2) Erwachsene Patienten (mit bekannter atherosklerotischer kardiovaskulärer Erkrankung (Myokardinfarkt, Schlaganfall oder periphere arterielle Verschlusskrankheit)) mit primärer Hypercholesterinämie (heterozygot familiär und nicht-familiär) oder gemischter Dyslipidämie, die mit der maximal tolerierbaren Statin-Dosis die LDL-C-Ziele nicht erreichen und für die Statine infrage kommen:

zweckmäßige Vergleichstherapie

- maximal tolerierte medikamentöse und diätetische Therapie zur Lipidsenkung

Ausmaß und Wahrscheinlichkeit des Zusatznutzens von Alirocumab gegenüber der maximal tolerierten medikamentösen und diätetischen Therapie zur Lipidsenkung:

Ein Zusatznutzen ist nicht belegt.

a3) Erwachsene Patienten mit primärer Hypercholesterinämie (heterozygot familiär und nicht-familiär) oder gemischter Dyslipidämie, bei denen medikamentöse und diätetische Optionen zur Lipidsenkung (außer Alirocumab) ausgeschöpft worden sind

Zweckmäßige Vergleichstherapie:

- Alirocumab oder LDL-Apherese (als „ultima ratio“ bei therapierefraktären Verläufen) ggf. mit begleitender medikamentöser lipidsenkender Therapie.

Ausmaß und Wahrscheinlichkeit des Zusatznutzens von Evolocumab gegenüber der LDL-Apherese:

Ein Zusatznutzen ist nicht belegt.

b) Homozygote familiäre Hypercholesterinämie

b1) Patienten, bei denen medikamentöse und diätetische Optionen zur Lipidsenkung nicht ausgeschöpft worden sind

Zweckmäßige Vergleichstherapie:

- maximal tolerierte medikamentöse und diätetische Therapie zur Lipidsenkung.

Ausmaß und Wahrscheinlichkeit des Zusatznutzens von Evolocumab gegenüber der zweckmäßigen Vergleichstherapie für Patienten, bei denen medikamentöse und diätetische Optionen zur Lipidsenkung nicht ausgeschöpft worden sind:

Ein Zusatznutzen ist nicht belegt.

b2) Patienten, bei denen medikamentöse und diätetische Optionen zur Lipidsenkung ausgeschöpft worden sind und die keine LDL-Apheresebehandlung erhalten bzw.

b3) die zugleich eine LDL- Apheresebehandlung erhalten

Zweckmäßige Vergleichstherapie:

- LDL-Apherese (als „ultima ratio“ bei therapierefraktären Verläufen) ggf. mit begleitender medikamentöser lipidsenkender Therapie.

Ausmaß und Wahrscheinlichkeit des Zusatznutzens von Evolocumab gegenüber der zweckmäßigen Vergleichstherapie für Patienten, bei denen medikamentöse und diätetische Optionen zur Lipidsenkung ausgeschöpft worden sind:

Ein Zusatznutzen ist nicht belegt.

Fazit / Ausmaß des Zusatznutzens / Ergebnis

a), a1), a2), a3), b), b1), b2), b3): Ein Zusatznutzen ist nicht belegt.

G-BA, 2009 [15].

Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL) - Anlage IV: Aufhebung des Therapiehinweises zu Ezetimib vom 22. November 2018

Der Gemeinsame Bundesausschuss (G-BA) hat in seiner Sitzung am 22. November 2018 beschlossen, die Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (Arzneimittel-Richtlinie) in der Fassung vom 18. Dezember 2008 / 22. Januar 2009 (BAnz. Nr. 49a vom 31. März 2009), zuletzt geändert am 6. Dezember 2018 (BAnz AT 01.02.2019 B2), wie folgt zu ändern:

I. In Anlage IV wird der Therapiehinweis zu „Ezetimib (z.B. Ezetrol®, Inergy®)“ in der Fassung des Beschlusses vom 17. Dezember 2009 (BAnz. Nr.45 (S.1090) aufgehoben.

IQWiG, 2019 [21].

Ezetimib zur Prävention kardiovaskulärer Ereignisse; Rapid Report; Auftrag A18-83; Version 2.0

Fragestellung

Die Ziele der vorliegenden Untersuchung sind

- die Nutzenbewertung einer Behandlung mit Ezetimib in Kombination mit einem Statin im Vergleich zu einer Behandlung mit einem Statin allein (Fragestellung 1) und
- die Nutzenbewertung einer Behandlung mit Ezetimib in Kombination mit einem Statin im Vergleich zu einer Behandlung mit einer Kombination eines Statins mit einem anderen den Lipidstoffwechsel beeinflussenden Wirkstoff (Fragestellung 2)

zur Risikoreduktion kardiovaskulärer Ereignisse bei Patientinnen und Patienten mit koronarer Herzkrankheit (KHK) oder akutem Koronarsyndrom (ACS) in der Vorgeschichte hinsichtlich patientenrelevanter Endpunkte.

Ergebnisse der umfassenden Informationsbeschaffung

Die Informationsbeschaffung identifizierte insgesamt 8 randomisierte kontrollierte Studien, 7 für Fragestellung 1 (Ezetimib + Statin vs. Statin) und 1 für Fragestellung 2 (Ezetimib + Statin vs. Statin + ein anderer den Lipidstoffwechsel beeinflussender Wirkstoff), die den Einschlusskriterien der Nutzenbewertung entsprechen. Für Fragestellung 1 wurde durch die Informationsbeschaffung keine zusätzliche Evidenz im Vergleich zur aktuellen systematischen Übersichtsarbeit von Zhan et al. 2018 identifiziert. Des Weiteren wurden 3 laufende Studien identifiziert, die relevant für Fragestellung 1 sind. Die letzte Suche fand am 04.02.2019 statt.

Die Studie HIJ-PROPER wurde, anders als geplant, nicht für die Nutzenbewertung berücksichtigt, da die Auswirkungen der unterschiedlichen LDL-C-Zielwertstrategien zwischen den Behandlungsgruppen auf die Ergebnisse der Studie nicht abgeschätzt werden können und somit unklar ist, inwiefern beobachtete Effekte auf Ezetimib zurückzuführen sind. Deshalb wurden alle weiteren durch die Informationsbeschaffung eingeschlossenen Studien daraufhin überprüft, ob sie in der Lage sind, die Ergebnisse der Studie IMPROVE-IT infrage zu stellen oder die Aussagesicherheit zu erhöhen.

Die Bewertung der Fragestellung 1 erfolgt letztlich nur auf Basis der Studie IMPROVE-IT. Die Bewertung der Fragestellung 2 erfolgt auf Basis der Studie COMBO II.

Ergebnisse zu Fragestellung 1

Studien, deren Ergebnisse nicht in der Nutzenbewertung betrachtet werden

Aufgrund der Studiengröße und der jeweils nur mäßigen qualitativen Ergebnissicherheit kann keine der weiteren 6 identifizierten Studien das Ergebnis der Nutzenbewertung zu Fragestellung

1 auf Basis der Studie IMPROVE-IT infrage stellen oder die Aussagesicherheit erhöhen. Die Ergebnisse dieser Studien werden deshalb nicht in der Nutzenbewertung betrachtet.

Studiencharakteristika der in die Bewertung eingeschlossenen Studie

Die Studie IMPROVE-IT ist eine randomisierte, doppelblinde, aktiv kontrollierte, 2-armige Parallelgruppenstudie, in der Ezetimib in Kombination mit Simvastatin mit einer Behandlung mit Simvastatin und der zusätzlichen Gabe von Placebo verglichen wurde. Eingeschlossen wurden erwachsene Patientinnen und Patienten, die innerhalb von 10 Tagen vor der Randomisierung wegen eines ACS (instabile Angina Pectoris, Myokardinfarkt ohne ST-Streckenhebung oder Myokardinfarkt mit ST-Streckenhebung) hospitalisiert wurden. Die LDL-C-Werte von Patientinnen und Patienten, die vor dem qualifizierenden ACS-Ereignis noch keine lipidsenkende Therapie erhalten hatten, sollten zwischen 50 und 125 mg/dl liegen. Patientinnen und Patienten, die vor dem ACS-Ereignis schon eine lipidsenkende Therapie erhalten hatten, sollten LDL-C-Werte zwischen 50 und 100 mg/dl aufweisen.

Insgesamt wurden 9067 Patientinnen und Patienten in den Ezetimib/Simvastatin-Arm und 9077 in den Simvastatin + Placeboarm der Studie randomisiert. Die Behandlung der Patientinnen und Patienten in den beiden Studienarmen erfolgte gemäß den Fachinformationen. Eine lipidsenkende Vorbehandlung war in der Studie IMPROVE-IT grundsätzlich erlaubt, deren Stärke zur LDL-C-Senkung vor der Hospitalisierung die von 40 mg/Tag Simvastatin jedoch nicht überschreiten durfte.

Der primäre Endpunkt der Studie IMPROVE-IT war ein kombinierter Endpunkt aus kardiovaskulärer Mortalität, nicht tödlichem Myokardinfarkt, nicht tödlichem Schlaganfall, Hospitalisierung wegen instabiler Angina Pectoris und Revaskularisation mittels perkutaner koronarer Intervention oder koronararterieller Bypassoperation mindestens 30 Tage nach der Randomisierung. Sekundäre Endpunkte waren weitere Endpunkte aus den Kategorien Morbidität, Mortalität und Nebenwirkungen.

Die Studiendauer sollte mindestens 2,5 Jahre betragen, vorausgesetzt es war zu diesem Zeitpunkt ein Ereignis des primären Endpunkts bei mindestens 5250 Patientinnen und Patienten eingetreten. Die tatsächliche mediane Beobachtungsdauer betrug 6 Jahre. Die mediane Behand-lungsdauer lag bei 4,4 Jahren.

Verzerrungspotenzial

Das endpunktübergreifende Verzerrungspotenzial wird für die Studie IMPROVE-IT als niedrig eingestuft. Das endpunktspezifische Verzerrungspotenzial wird für die Ergebnisse des kombinierten Endpunkts schwerwiegendes unerwünschtes kardiovaskuläres Ereignis (MACE) aufgrund hoher und zwischen den Behandlungsgruppen zeitlich differenzieller Abbruchraten als hoch bewertet. Für die Ergebnisse aller weiteren relevanten Endpunkte wurde das endpunktspezifische Verzerrungspotenzial als niedrig bewertet. Somit können aus den vorhandenen Daten für den Endpunkt MACE maximal Anhaltspunkte, für alle weiteren relevanten Endpunkte maximal Hinweise auf einen höheren oder geringeren Nutzen bzw. Schaden abgeleitet werden.

Ergebnisse zu patientenrelevanten Endpunkten

Der zur Bewertung herangezogene kombinierte Endpunkt MACE setzt sich zusammen aus den Einzelkomponenten kardiovaskulärer Tod (definiert als KHK-Tod, Tod durch atherosklerotische vaskuläre Erkrankung oder Tod durch andere, nicht atherosklerotische kardiovaskuläre Erkrankungen), nicht tödlicher Myokardinfarkt und nicht tödlicher Schlaganfall. Der kombinierte kardiovaskuläre Endpunkt MACE ist operationalisiert als die Zeit bis zum 1. Auftreten eines

Ereignisses für 1 der 3 Einzelkomponenten. Für den Endpunkt MACE zeigt sich ein statistisch signifikanter Unterschied zwischen den Behandlungsgruppen zum Vorteil von Ezetimib/Simvastatin im Vergleich zu Simvastatin. Dieser zeigt sich in einem statistisch signifikanten Unterschied zwischen den Behandlungsgruppen zum Vorteil von Ezetimib/Simvastatin im Vergleich zu Simvastatin für die Einzelkomponenten nicht tödlicher Myokardinfarkt und nicht tödlicher Schlaganfall. Für die Einzelkomponente kardiovaskulärer Tod zeigt sich hingegen kein statistisch signifikanter Unterschied zwischen den Behandlungsgruppen und die Effektschätzung beträgt HR = 1,00 mit dem 95 %-Konfidenzintervall [0,89; 1,13]. Für den kombinierten kardiovaskulären Endpunkt MACE ergibt sich aufgrund des endpunktspezifisch hohen Verzerrungspotenzials ein Anhaltspunkt für einen höheren Nutzen von Ezetimib / Simvastatin im Vergleich zu Simvastatin.

Für die weiteren Endpunkte Gesamtmortalität, Hospitalisierung wegen instabiler Angina Pectoris, Hospitalisierung wegen Herzinsuffizienz, SUEs, Abbruch wegen UEs, Myopathie und Rhabdomyolyse zeigt sich in der Studie IMPROVE-IT jeweils kein statistisch signifikanter Unterschied zwischen den Behandlungsgruppen. Daraus ergibt sich jeweils kein Anhaltspunkt für einen höheren oder geringeren Nutzen bzw. Schaden von Ezetimib/Simvastatin im Vergleich zu Simvastatin. Der Endpunkt gesundheitsbezogene Lebensqualität wurde in der Studie nicht erhoben. Patientenrelevante Endpunkte zur gefäßbedingten nicht kardiovaskulären und nicht zerebrovaskulären Morbidität wurden ebenfalls nicht erhoben. Für den Endpunkt schwere Lebertoxizität lagen keine verwertbaren Daten vor.

Zusammenfassung der Beleglage

Für den kombinierten Endpunkt MACE ergibt sich ein Anhaltspunkt für einen höheren Nutzen von Ezetimib/Simvastatin gegenüber Simvastatin. Dies zeigt sich in statistisch signifikanten Unterschieden für die Einzelkomponenten nicht tödlicher Myokardinfarkt und nicht tödlicher Schlaganfall.

Für die Endpunkte Gesamtmortalität, Hospitalisierung wegen instabiler Angina Pectoris, Hospitalisierung wegen Herzinsuffizienz, SUEs, Abbruch wegen UEs, Myopathie und Rhabdomyolyse ergibt sich jeweils kein Anhaltspunkt für einen höheren oder geringeren Nutzen bzw. Schaden von Ezetimib/Simvastatin gegenüber Simvastatin. Zur gefäßbedingten nicht kardiovaskulären und nicht zerebrovaskulären Morbidität sowie zur gesund-heitsbezogenen Lebensqualität wurden keine Daten berichtet. Für den Endpunkt schwere Lebertoxizität lagen keine verwertbaren Daten vor.

Ergebnisse zu Fragestellung 2

Studiencharakteristika

Die Studie COMBO II ist eine randomisierte, doppelblinde, aktiv kontrollierte, 2-armige Parallelgruppenstudie, in der Ezetimib und Alirocumab, jeweils in Kombination mit einem Statin, verglichen wurden. Eingeschlossen wurden Patientinnen und Patienten mit einem hohen bis sehr hohen kardiovaskulären Risiko (KHK oder periphere arterielle Verschlusskrankheit, ischämischer Schlaganfall, moderate Niereninsuffizienz, Diabetes mellitus Typ 1 oder 2 mit mindestens 2 weiteren Risikofaktoren), deren LDL-C-Werte mit einer bestehenden Statin-therapie nicht ausreichend kontrolliert waren (≥ 70 mg/dl).

Insgesamt wurden 241 Patientinnen und Patienten in den Ezetimib-Arm und 479 in den Alirocumab-Arm im Verhältnis 1:2 randomisiert.

Die Dosierung von Ezetimib und Alirocumab entsprach den Vorgaben der jeweiligen Fachinformation. Die vorliegende Nutzenbewertung basiert auf den Daten der finalen Analyse nach 104 Wochen Behandlungsdauer.

Primärer Endpunkt der Studie war die Änderung der LDL-C-Konzentration nach 24 Wochen im Vergleich zur LDL-C-Konzentration zu Studienbeginn. Patientenrelevante Endpunkte wurden hauptsächlich anhand der Auswertungen zu UEs erhoben.

Für die Nutzenbewertung relevante Teilpopulation

Alirocumab ist nur für Patientinnen und Patienten zugelassen, die mit einer maximalen bzw. maximal tolerierten Statin-Vortherapie die LDL-C-Zielwerte nicht erreichen. Eine zulassungskonforme Behandlung mit Ezetimib zur Prävention kardiovaskulärer Ereignisse setzt eine KHK oder ein ACS in der Vorgeschichte der Patientinnen und Patienten voraus.

In der Studie COMBO II ist jedoch für mindestens 40 % der Patientinnen und Patienten der Gesamtpopulation nicht nachgewiesen, dass sie mit einer für sie maximal verträglichen Statindosis vorbehandelt waren. Für die Gesamtpopulation der Studie COMBO II ist daher kein zulassungskonformer Einsatz von Alirocumab gewährleistet. Für das Verfahren der frühen Nutzenbewertung zum Auftrag A18-74 wurden jedoch Auswertungen zu einer Teilpopulation herangezogen, die zu Studienbeginn mit einer maximalen Statintherapie vorbehandelt wurde (Maximale-Statintherapie[mST]-Population). In der mST-Population hatten zudem über 90% der Patientinnen und Patienten eine KHK, sodass auch ein zulassungskonformer Einsatz von Ezetimib gewährleistet war. Daher wurden beim Hersteller Sanofi-Aventis die für das Verfahren der frühen Nutzenbewertung zum Auftrag A18-74 angefertigten Auswertungen zu der oben beschriebenen Teilpopulation angefordert, da diese eine hinreichende Annäherung an die relevante Population für die Fragestellung 2 der vorliegenden Nutzenbewertung darstellt.

Die vorliegende Nutzenbewertung stützt sich somit auf die mST-Population als relevante Teilpopulation der Studie COMBO II. Diese umfasst 140 Patientinnen und Patienten im Ezetimib-Arm und 262 im Alirocumab-Arm. Alle nachfolgend dargestellten Daten beziehen sich auf die mST-Population.

Verzerrungspotenzial

Das endpunktübergreifende Verzerrungspotenzial wird für die Studie COMBO II als niedrig eingestuft. Das endpunktspezifische Verzerrungspotenzial wird für die Ergebnisse aller relevanten Endpunkte ebenfalls als niedrig bewertet. Somit können aus den vorhandenen Daten für alle relevanten Endpunkte maximal Hinweise auf einen höheren oder geringeren Nutzen bzw. Schaden abgeleitet werden.

Ergebnisse zu patientenrelevanten Endpunkten

Der kombinierte Endpunkt schwerwiegendes unerwünschtes kardiovaskuläres Ereignis (MACE) setzt sich zusammen aus den Einzelkomponenten KHK-bedingter Tod, nicht tödlicher Myokardinfarkt, tödlicher oder nicht tödlicher ischämischer Schlaganfall und Hospitalisierung aufgrund instabiler Angina Pectoris. Für den kombinierten kardiovaskulären Endpunkt MACE liegen jedoch keine Daten für die relevante Teilpopulation vor. Daher werden die Einzelkomponenten separat zur Nutzenbewertung herangezogen. Die Komponente KHK-bedingter Tod wird allerdings nicht separat bewertet, da der Endpunkt Gesamtmortalität Todesfälle jeglicher Ursache abbildet und daher ein umfassenderes Bild bietet als die Mortalität aufgrund spezifischer Ursachen.

Für die Einzelkomponenten nicht tödlicher Myokardinfarkt, tödlicher und nicht tödlicher Schlaganfall und Hospitalisierung wegen instabiler Angina Pectoris zeigt sich jeweils kein statistisch signifikanter Unterschied zwischen den Behandlungsgruppen. Daraus ergibt sich kein Anhaltspunkt für einen höheren oder geringeren Nutzen von Ezetimib + Statin im Vergleich zu Alirocumab + Statin.

Auch für die Endpunkte Gesamtmortalität, Hospitalisierung wegen Herzinsuffizienz, SUEs, Abbruch wegen UEs, Myopathie, Rhabdomyolyse, allergische Reaktionen und lokale Reaktionen an der Injektionsstelle zeigt sich jeweils kein statistisch signifikanter Unterschied zwischen den Behandlungsgruppen. Daraus ergibt sich jeweils kein Anhaltspunkt für einen höheren oder geringeren Nutzen bzw. Schaden von Ezetimib + Statin im Vergleich zu Alirocumab + Statin. Der Endpunkt gesundheitsbezogene Lebensqualität wurde in der Studie nicht erhoben. Patientenrelevante Endpunkte zur gefäßbedingten nicht kardiovaskulären und nicht zerebrovaskulären Morbidität wurden ebenfalls nicht erhoben. Für den Endpunkt schwere Lebertoxizität lagen keine verwertbaren Daten vor.

Zusammenfassung der Beleglage

Für keinen der relevanten Endpunkte ergibt sich ein Anhaltspunkt für einen höheren oder geringeren Nutzen bzw. Schaden von Ezetimib + Statin gegenüber Alirocumab + Statin. Für die Endpunkte Gesamtmortalität, nicht tödlicher Myokardinfarkt, tödlicher und nicht tödlicher ischämischer Schlaganfall, Hospitalisierung wegen instabiler Angina Pectoris sowie Hospitalisierung wegen Herzinsuffizienz ist die Datenlage zudem unzureichend, da das 95 %-Konfidenzintervall so unpräzise ist, dass weder eine Halbierung noch eine Verdopplung des Effekts ausgeschlossen werden kann. Zur gefäßbedingten nicht kardiovaskulären und nicht zerebrovaskulären Morbidität sowie zur gesundheitsbezogenen Lebensqualität wurden keine Daten berichtet. Für den Endpunkt schwere Lebertoxizität lagen keine verwertbaren Daten vor.

Fazit

Für **Fragestellung 1** ergab sich für Patientinnen und Patienten mit KHK oder ACS in der Vorgeschichte ein Anhaltspunkt für einen höheren Nutzen einer Behandlung mit Ezetimib in Kombination mit einem Statin im Vergleich zu einer Behandlung mit einem Statin allein zur Risikoreduktion kardiovaskulärer Ereignisse für den kombinierten kardiovaskulären Endpunkt MACE. Dieser Vorteil zeigte sich in statistisch signifikanten Unterschieden für die 2 Einzelkomponenten nicht tödlicher Myokardinfarkt und nicht tödlicher Schlaganfall. Für die 3. Einzelkomponente kardiovaskulärer Tod zeigte sich hingegen kein statistisch signifikanter Unterschied, wobei hier die Punktschätzung (Hazard Ratio) auf dem Nulleffekt lag. Für die weiteren patientenrelevanten Endpunkte ergab sich jeweils kein Anhaltspunkt für einen höheren oder geringeren Nutzen bzw. Schaden einer Behandlung mit Ezetimib in Kombination mit einem Statin im Vergleich zu einer Behandlung mit einem Statin allein zur Risikoreduktion kardiovaskulärer Ereignisse.

Für **Fragestellung 2** ergab sich für Patientinnen und Patienten mit KHK oder ACS in der Vorgeschichte für keinen der patientenrelevanten Endpunkte ein Anhaltspunkt für einen höheren oder geringeren Nutzen bzw. Schaden einer Behandlung mit Ezetimib in Kombination mit einem Statin im Vergleich zu einer Behandlung mit Alirocumab in Kombination mit einem Statin zur Risikoreduktion kardiovaskulärer Ereignisse. Insbesondere für die Endpunkte zu kardiovaskulären Ereignissen sowie für den Endpunkt Gesamtmortalität war die Datenlage dabei unzureichend.

3.2 Cochrane Reviews

Adams S et al., 2020 [1].

Pitavastatin for lowering lipids.

Fragestellung

To quantify the effects of various doses of pitavastatin on the surrogate markers: LDL cholesterol, total cholesterol, HDL cholesterol and triglycerides in participants with and without cardiovascular disease.

Methodik

Population:

- Participants may be of any age, with and without cardiovascular disease. They could have normal lipid parameters or any type of hyperlipidaemia or dyslipidaemia. We included participants with various comorbid conditions, including type 2 diabetes mellitus, hypertension, metabolic syndrome, chronic renal failure or cardiovascular disease.

Intervention:

- Pitavastatin

Komparator:

- Control (siehe Ergebnisse)

Endpunkte:

- LDL cholesterol, Total cholesterol, HDL cholesterol, Triglycerides, Withdrawals due to adverse effects (WDAEs)

Recherche/Suchzeitraum:

- up to March 2019

Qualitätsbewertung der Studien:

- Cochrane approach / GRADE

Ergebnisse

Anzahl eingeschlossener Studien:

- Forty-seven studies (five RCTs and 42 before-and-after studies) in 5436 participants

Charakteristika der Population:

- The participants were of any age with and without cardiovascular disease, and pitavastatin effects were studied within a treatment period of three to 12 weeks.

Qualität der Studien:

- The summary of all 'Risk of bias' tools for the lipid effects suggests a high risk of bias. However, the lipid parameter outcomes are probably relatively resistant to bias. If anything, a high risk of bias would lead to an overestimate of the lipidlowering effects rather than an underestimate. However, because of the objectivity of the measurement of the lipid

parameters, we think that the lipid measures effects are reasonably accurate. This view is strengthened by the fact that we could not show evidence of funding bias. Comparing Kowa-funded trials with non-Kowafunded trials showed no differences. Furthermore, review of funnel plots did not suggest any publication bias.

Studienergebnisse:

- There was no dose-related effect of pitavastatin on blood HDL cholesterol, which was increased by 4% on average by pitavastatin.
- Pitavastatin 1 mg/day to 16 mg/day reduced LDL cholesterol by 33.3% to 54.7%, total cholesterol by 23.3% to 39.0% and triglycerides by 13.0% to 28.1%. For every two-fold dose increase, there was a 5.35% (95% CI 3.32 to 7.38) decrease in blood LDL cholesterol, a 3.93% (95% CI 2.35 to 5.50) decrease in blood total cholesterol and a 3.76% (95% CI 1.03 to 6.48) decrease in blood triglycerides. The certainty of evidence for these effects was judged to be high.
- When compared to other statins for its effect to reduce LDL cholesterol, pitavastatin is about 6-fold more potent than atorvastatin, 1.7-fold more potent than rosuvastatin, 77-fold more potent than fluvastatin and 3.3-fold less potent than cerivastatin.
- For the placebo group, there were no participants who withdrew due to an adverse effect per 109 subjects and for all doses of pitavastatin, there were three participants who withdrew due to an adverse effect per 262 subjects.

Anmerkung/Fazit der Autoren

Pitavastatin lowers blood total cholesterol, LDL cholesterol and triglyceride in a dose-dependent linear fashion. Based on the effect on LDL cholesterol, pitavastatin is about 6-fold more potent than atorvastatin, 1.7-fold more potent than rosuvastatin, 77-fold more potent than fluvastatin and 3.3-fold less potent than cerivastatin. There were not enough data to determine risk of withdrawal due to adverse effects due to pitavastatin.

3.3 Systematische Reviews

Hsu HY et al., 2020 [19].

Efficacy of more intensive lipid-lowering therapy on cardiovascular diseases: a systematic review and meta-analysis.

Fragestellung

to investigate whether intensive lipid-lowering therapies reduce greater cardiovascular disease risks in primary prevention settings.

Methodik

Population:

- population without clinically evident coronary artery disease

Intervention:

- intensive lipid-lowering group

Komparator:

- standard lipid-lowering group

Endpunkte:

- cardiovascular events of interest and all-cause mortality rate

Recherche/Suchzeitraum:

- MEDLINE, EMBASE, and Cochrane Library databases were searched from inception to March 2019

Qualitätsbewertung der Studien:

- Cochrane Risk of Bias Tool

Ergebnisse

Anzahl eingeschlossener Studien:

- A total of 18 randomized controlled trials were included.
- A total of 103,864 participants were randomly allocated to the more intensive lipid-lowering (N= 52, 008) and control (N= 51,856) groups.

Charakteristika der Population:

- Mean follow-up duration was 4.0 years (range 1–7.4 years). Mean baseline LDL-C level was 144.7 mg/dL (range 106.1–205.3 mg/dL). Greater LDL-C reduction (19.0–49.1%) was noted in the intensive lipid-lowering group than in the standard lipid-lowering group (− 6.5–15.3%) at 1–2 years of follow-up. Mean age of participants was 60 years (range 30–80 years). The proportion of women varied from 0 to 87.4% within studies. Six trials had total diabetes participants, and the prevalence of diabetes population for the rest of the trials was between 1.2 and 24.6%.

Qualität der Studien:

Study	Overall risk of bias
LRC-CPPT, 1984	Low
HHS, 1987	Some Concerns
ACAPS, 1994	Low
WOSCOPS, 1995	Low
AFCAPS/TexCAPS, 1998	Low
Sasaki et al., 2002	High
ASCOT-LLA, 2003	Low
Beishuizen et al., 2004	Low
CARDS, 2004	Low
FIELD, 2005	Low
MEGA, 2006	Low
ASPEN, 2006	Some Concerns
JUPITOR, 2008	Low
Heljic et al., 2009	Some Concerns
SHARP, 2011	Low
HOPE-3, 2016	Low
EMPATHY, 2018	High
Kitas et al., 2019	Low

Studienergebnisse:

- The risk reductions in cardiovascular outcomes and all-cause mortality associated with more intensive vs. standard lipid-lowering therapy across all trials were 24 and 10%, respectively (RR 0.76, 95% confidence interval 0.68–0.85; RR 0.90, 95% confidence interval 0.83–0.97); however, the risk reduction varied by baseline LDL-C level in the trial. A greater risk reduction was noted with higher LDL-C level.

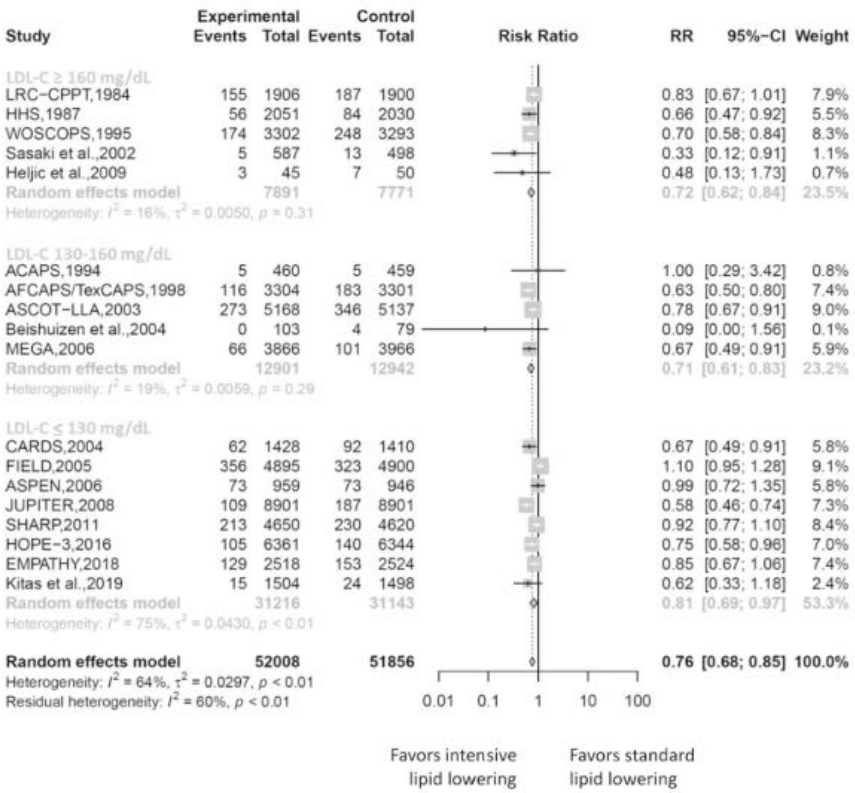


Fig. 3 Forest plot of subgroup analyses of coronary event risks according to baseline LDL-C levels

- Intensive lipid-lowering for coronary heart disease protection was more pronounced in the nondiabetic populations than in the diabetic populations.

Anmerkung/Fazit der Autoren

In summary, our study indicates that more intensive LDL-C lowering was associated with a greater reduction in risk of CVD and all-cause mortality in trials of patients with higher baseline LDL-C levels. Intensive lipidlowering among patients without diabetes remains an important strategy for cardiovascular risk reduction. Further studies are urgently needed to clarify the benefits of intensive lipid-lowering on diabetes populations.

Ida S et al., 2019 [20].

Efficacy and safety of pemafibrate administration in patients with dyslipidemia: a systematic review and meta-analysis

Fragestellung

To investigate the efficacy and safety of pemafibrate, a novel selective peroxisome proliferator-activated receptor α modulator, in patients with dyslipidemia.

Population:

- Patients with dyslipidemia

Intervention/Komparator:

- Pemafibrate versus placebo

- Pemafibrate versus fenofibrate
- The dose of pemafibrate was 0.025, 0.05, 0.1, 0.2, or 0.4 mg/day. The comparison group was placebo and fenofibrate (100, 106.6, or 200 mg/day).

Endpunkte:

- Lipid and glucose metabolism-related parameters
- Total AEs, the increase in hepatobiliary enzyme activities [aspartate aminotransferase (AST), alanine aminotransferase (ALT), and γ-glutamyl transpeptidase (γGTP) activities above the normal upper limit], kidney disorder (creatinine 1.5 mg/dL or more), and creatine kinase (CK) increase (above the normal upper limit).

Recherche/Suchzeitraum:

- Literature search was performed on November 1, 2018, using MEDLINE (from 1960), Trials Registry (from 1960), and ClinicalTrials.gov.

Qualitätsbewertung der Studien:

- Cochrane's risk of bias tool
- Subgroup analysis including: (1) baseline TG ≥ 300 mg/dL and TG < 300 mg/dL type, (2) presence/ absence of diabetes type and (3) presence/absence of concomitant statin use type.

Ergebnisse

Anzahl eingeschlossener Studien:

- Seven RCTs (n = 1623 patients)

Charakteristika der Population:

- Mean patient age was 52 years, the mean ratio of female patients was 16.9%, and the mean examination period was 16 weeks.

Table 1 Characteristics of pemafibrate interventions included in the present meta-analysis compared with placebo or fenofibrate interventions

No.	References	Year	Region	No. of patients	Age (years)	% women	BMI (kg/m^2)	Diabetes (%)	Hypertension (%)	Statin (%)	Study duration (weeks)	TG (mmol/L)
1	Ishibashi et al. [11]	2016	Japan	224	48	2.9	26.8	11.4	25.7	0	12	3.4
2	Arai et al. [17]	2017	Japan	423	55	20	26.2	29.3	58.5	100	24	4.3
3	Arai et al. [12]	2018	Japan	526	49	12	26.9	16.3	34.9	0	12	346 (mg/dL)
4	Araki et al. [18]	2018	Japan	166	61	34	26	100	37	40.4	24	3.2
5	Ishibashi et al. [19]	2018	Japan	225	53	21	26.1	6.8	24.7	0	24	2.7
6	Matsuba et al. [20]	2018	Japan	27	46	0	25.8	0	18.2	0	12	3.4
7	Yamashita et al. [21]	2018	Japan	32	52	29	25	12.5	31.3	0	4	2.9

Unless indicated otherwise, data are shown as mean values

BMI body mass index, *TG* triglycerides

Qualität der Studien:

No	Reference	Randomization procedure	Allocation concealment	Blinding of personnel and participants	Blinding of outcome assessment	Incomplete outcome assessment	Selective reporting
1	[11]	L	L	L	L	L	L
2	[17]	U	U	U	U	L	L
3	[12]	L	L	L	L	L	L
4	[18]	L	L	L	L	L	L
5	[19]	L	L	L	L	L	L
6	[20]	L	L	L	L	H	L
7	[21]	L	L	L	L	L	L

Studienergebnisse:

Effect on TG level

- In the pemafibrate group, TG level decreased significantly compared with the placebo group (SMD, − 1.38; 95% CI, − 1.63 to − 1.12; P < 0.001; I^2 = 78% (P < 0.001)).
- Regardless of the dose of pemafibrate, TG in the pemafibrate group decreased significantly compared to the placebo group.
- On the other hand, there was no significant difference in TG level between the pemafibrate and fenofibrate groups (SMD, − 0.16; 95% CI, − 0.36 to 0.03; P = 0.10; I^2 = 75% (P < 0.001)).

Effect on HDL-C level

- In the pemafibrate group, HDL-C level increased significantly compared with the placebo group (SMD, 0.77; 95% CI, 0.66–0.89; P < 0.001; I^2 = 0% (P = 0.45)).
- Regardless of the dose of pemafibrate, HDL-C level in the pemafibrate group decreased significantly compared to the placebo group.
- On the other hand, there was no significant difference in HDL-C level between the pemafibrate and fenofibrate groups.

Effect on LDL-C level

- In the pemafibrate group, LDL-C level increased significantly, compared with the placebo group (SMD, 0.19; 95% CI, 0.06–0.33; P = 0.006; I^2= 28% (P = 0.17)).
- In the pemafibrate group, the LDL-C level was significantly higher than in the fenofibrate group, an effect which was particularly marked at the 0.4 mg dose pemafibrate group.

Effect on non-HDL-C level

- The non-HDL-C level was significantly lower in the pemafibrate group than in the placebo group (SMD, − 0.39; 95% CI, − 0.51 to − 0.28; P < 0.001; I^2= 0% (P = 0.58).
- No significant difference in non-HDLC level was observed between the pemafibrate and fenofibrate groups.

Effect on homeostasis model assessment for insulin resistance (HOMA-IR)

- In the pemafibrate group, the HOMA-IR as significantly lower than in the placebo group (SMD, − 0.27; 95% CI, − 0.39 to − 0.14; P < 0.001); I^2 = 0% (P = 0.94).
- no significant difference in HOMA-IR between the pemafibrate and fenofibrate groups.

Effect on HbA1c level

- No significant difference in HbA1c level between the pemafibrate group and the placebo group (SMD, 0.03; 95% CI, − 0.15 to 0.20; P = 0.76; I^2= 0% (P = 0.94).), and between the pemafibrate group and the fenofibrate group.

Subgroup analysis on the effect on TG level

- in the pemafibrate and placebo groups, the TG level decreased significantly in the pemafibrate group compared with the placebo group, regardless of the baseline TG value, the presence or absence of diabetes nd the presence or absence of the concomitant use of statin.

Adverse Events

- no significant difference in total AEs between the pemafibrate group and the placebo group (OR, 0.92; 95% CI, 0.74–1.14; P = 0.45; I^2 =0% (P=0.83)).
- total AEs in the pemafibrate group was significantly lower than in the fenofibrate group (OR, 0.60; 95% CI, 0.49–0.73; P < 0.001; I^2 =0% (P=0.49)).
- The frequency of hepatobiliary enzyme activity increase was significantly lower in the pemafibrate group as compared with either the placebo group (OR, 0.33; 95% CI, 0.21– 0.52; P < 0.001; I^2 =0% (P=0.61)) or the fenofibrate group (OR, 0.14; 95% CI, 0.10–0.20; P < 0.001; I^2 =48.6% (P=0.10)).).
- In particular, ALT activity decreased significantly following administration of pemafibrate as compared with the placebo group while γGTP activity decreased significantly as compared with both the placebo group and the fenofibrate group.
- no difference in the frequency of kidney dysfunction when comparing the pemafibrate group and the placebo group (OR, 1.67; 95% CI, 0.63–4.42; P = 0.30; I^2 =0% (P=0.99)) or when comparing with the fenofibrate group (OR, 0.51; 95% CI, 0.20–1.32; P = 0.19; I^2 =0% (P=0.80)). However, although Cre level increased in the pemafibrate group compared with the placebo group, the increase in Cre level in the pemafibrate group was significantly lower than in the fenofibrate group.
- No significant difference was found in the frequency of CK activity increase between the pemafibrate group and the placebo group (OR, 0.50; 95% CI, 0.24–1.05; P = 0.07; I^2 =0% (P=0.58)) nor between the pemafibrate and fenofibrate groups (OR, 0.55; 95% CI, 0.21–1.45; P = 0.23; I^2 =0% (P=0.98)).

Anmerkung/Fazit der Autoren

In summary, using a meta-analysis of RCTs, we investigated the efficacy and safety of pemafibrate administration in patients with dyslipidemia. The lipid profile significantly improved in the pemafibrate group than in the placebo group. Apart from the fact that the pemafibrate group showed a lipid-improving effect equivalent to that in the fenofibrate group, the total AEs was significantly fewer in the pemafibrate group than in the fenofibrate group and the hepatobiliary enzyme activity was actually improved. However, the clinical data of daily medical practice and the long-term efficacy and safety of pemafibrate administration need to be investigated in future studies.

Karatasakis A et al., 2017 [22].

Effect of PCSK9 Inhibitors on Clinical Outcomes in Patients With Hypercholesterolemia: A Meta-Analysis of 35 Randomized Controlled Trials

Siehe auch: **Qian LJ et al., 2017 [27].**

Fragestellung

We sought to examine the efficacy and safety of 2 PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitors: alirocumab and evolocumab.

Methodik

Population:

- Adults with hypercholesterolemia

Intervention:

- PCSK9 antibodies: evolocumab, alirocumab

Komparator:

- No PCSK9 antibodies

Endpunkte:

- All-cause and cardiovascular mortality, myocardial infarction (MI), unstable angina requiring hospitalization, congestive heart failure exacerbation requiring hospitalization, stroke, coronary revascularization, neurocognitive adverse events, new onset or worsening of preexisting diabetes mellitus, increase in serum creatine kinase level, increase in serum alanine or aspartate aminotransferase levels, myalgia, and treatment-emergent serious adverse events, lipid end points.

Recherche/Suchzeitraum:

- PubMed/Medline, Embase, CENTRAL, and ClinicalTrials.gov up to March 18, 2017.

Qualitätsbewertung der Studien:

- Cochrane risk of bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- Alirocumab was used in 18 studies (28 treatment arms)
- Evolocumab used in 17 studies (39 treatment arms)
- placebo was the most common control used (52 control arms), with ezetimibe used in 17 arms, and standard therapy in 2 arms

Charakteristika der Population:

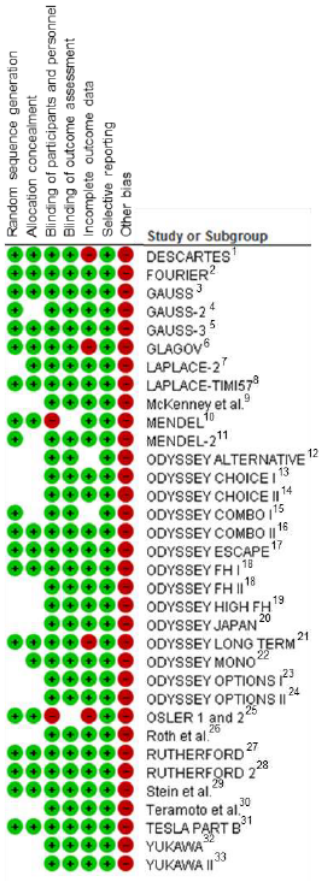
- Eight studies were of an exclusively familial hypercholesterolemia (FH) population
  - seven studies with only heterozygous familial hypercholesterolemia
  - one study with only homozygous familial hypercholesterolemia
- Five studies included only patients intolerant to statins
- One study with coronary artery disease + hypercholesterolemia
- Mean age was 61.0 - 2.8 years, and 67.6% of participants were men
- Mean baseline LDL-C was 106.0-22.3 mg/dL (2.7-0.6 mmol/L)

- The majority of study participants (91.8%) were on stable statin therapy at baseline, and 58.4% were on an intensive statin regimen.

Qualität der Studien:

- "Other Bias" in all studies detected (without explanation)
- two trials with incomplete outcome data.
- Not all items presented.

Figure S2. Risk of bias assessment of included studies



Studienergebnisse:

All-cause Mortality

- Evolocumab: OR = 1.03 (95% CI: 0.90, 1.18); I^2 = 0%, P = 0.43
- Alirocumab: OR = 0.46 (95% CI: 0.24, 0.89); I^2 = 18%, P = 0.26

Cardiovascular Mortality

- Evolocumab: OR = 1.04 (95% CI: 0.87 , 1.24); I^2 = 0%, P = 0.83
- Alirocumab: OR = 1.01 (95% CI: 0.85, 1.19); I^2 = 0%, P = 0.74

Myocardial infarction

- Evolocumab: OR = 0.73 (95% CI: 0.64, 0.82); I^2 = 0%, P = 0.99
- Alirocumab: OR = 0.72 (95% CI: 0.64, 0.81); I^2 = 0%, P = 0.77

Stroke

- Evolocumab: OR = 0.79 (95% CI: 0.66, 0.95); I^2 = 0%, P = 0.87

- Alirocumab: OR = 1.53 (95% CI: 0.52, 4.52); I^2 = 0%, P = 0.92

Coronary revascularization

- Evolocumab: OR = 0.76 (95% CI: 0.70, 0.84); I^2 = 0%, P = 0.60
- Alirocumab: OR = 1.21 (95% CI: 0.81, 1.81); I^2 = 0%, P = 0.82

Unstable angina

- Evolocumab: OR = 0.98 (95% CI: 0.82, 1.17); I^2 = 0%, P = 0.83
- Alirocumab: OR = 0.73 [95% CI: 0.11, 4.65); I^2 = 0%, P = 0.55

Congestive heart failure exacerbation:

- Evolocumab: OR =0,99 (95% CI: 0,86, 1,13); I^2 = 0%, P = 0.86
- Alirocumab: OR = 0.84 (95% CI: 0.37, 1.92); I^2 =0%, P = 0.80

Neurocognitive adverse events:

- Evolocumab: OR = 1.26 (95% CI: 0.64, 2.48); I^2 = 53%; P = 0.10
- Alirocumab: OR = 1.04 (95% CI: 0.56, 1.94); I^2 = 0%, P = 0.65

Anmerkung/Fazit der Autoren

In conclusion, our comprehensive meta-analysis of 35 RCTs shows that, compared with no PCSK9 inhibitor administration, treatment with PCSK9 inhibitors results in improvement in cardiovascular outcomes, including MI, stroke, and coronary revascularization; no statistically significant change in the rate of adverse events, including neurocognitive adverse events, and incident or worsening of pre-existing diabetes mellitus; and dramatic reductions in atherogenic lipid fractions. Although there was no statistically significant improvement in mortality, metaregression analysis revealed an association between higher baseline LDL-C and an allcause mortality benefit, which needs further evaluation in RCTs.

Kommentare zum Review

- Risk of Bias Assessment unvollständig: nicht alle Items angegeben. Bei allen Studien wurde „Other Bias“ beobachtet. Allerdings findet sich keine Ausführung zur Art dieses Bias.
- Die Autoren berichten Interessenskonflikte von moderat bis beträchtlich.
- Eine Studie schloss Patienten mit HoFH ein.

Toth PP et al., 2017 [33].

Systematic Review and Network Meta-Analysis on the Efficacy of Evolocumab and Other Therapies for the Management of Lipid Levels in Hyperlipidemia

Fragestellung

Systematic review and network meta-analysis to compare LDL-C reduction with evolocumab to other lipid-lowering therapies (including alirocumab) in patients receiving statin background therapy.

Methodik

Population:

- Patients with hypercholesterolemia whose condition is not adequately controlled according to European lipid goals with moderate- to high-intensity statin background therapy and who remain at risk of cardiovascular events

Intervention:

- Evolocumab and other pharmacologic agents for the management of hypercholesterolemia

Komparator:

- Placebo (ie, background statin therapy alone) and all other therapies that share a common comparator

Endpunkt:

- Percentage change from baseline in LDL-C, high-density lipoprotein cholesterol (HDL-C), non-HDL-C, apolipoprotein B (ApoB), and lipoprotein (a) [Lp(a)] and cardiovascular events, adverse event (AE), treatment-related AE, and serious AE

Recherche/Suchzeitraum:

- MEDLINE, Embase, the Cochrane Databases of Systematic Reviews and Controlled Trials CENTRAL, the Database of Abstracts of Reviews of Effects, and the Health Technology Assessment Database from inception to August 2016.

Qualitätsbewertung der Studien:

- Cochrane Collaboration Risk of Bias Assessment Tool
- Network meta-analysis was conducted using Bayesian models

Ergebnisse

Anzahl eingeschlossener Studien:

69 trials of lipid-lowering therapies enrolled patients requiring further LDL-C reduction while on maximally tolerated medium- or high-intensity statin, of which 15 could be relevant for inclusion in LDL-C reduction networks with evolocumab, alirocumab, ezetimibe, and placebo as treatment arms were found.

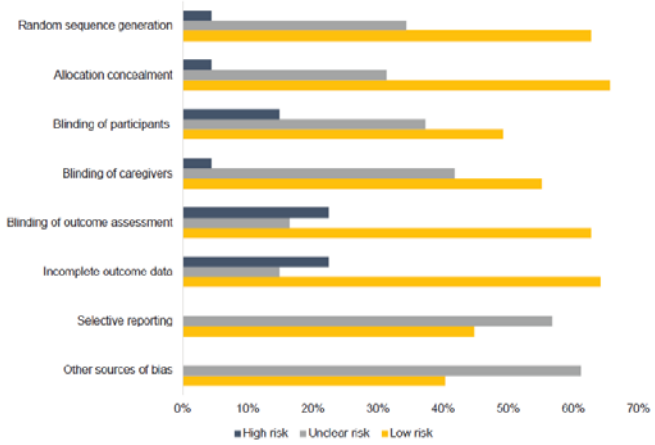
- 5 studies of Evolovumab (all vs Placebo, one additionally vs. Ezetimibe)
- 9 studies of Alirocumab (nicht relevant für diese Synopse)
- 1 study comparing Ezetimibe vs. Placebo
- Netzwerk der Metaanalyse siehe Abbildung 1 im Anhang

Charakteristika der Population:

- Patients requiring further LDL-C reduction while on maximally tolerated medium- or high-intensity statin
- Studiencharakteristika siehe Tabelle 1 im Anhang

Qualität der Studien:

Figure S2. Risk of Bias Assessed in 69 Trials



Studienergebnisse:

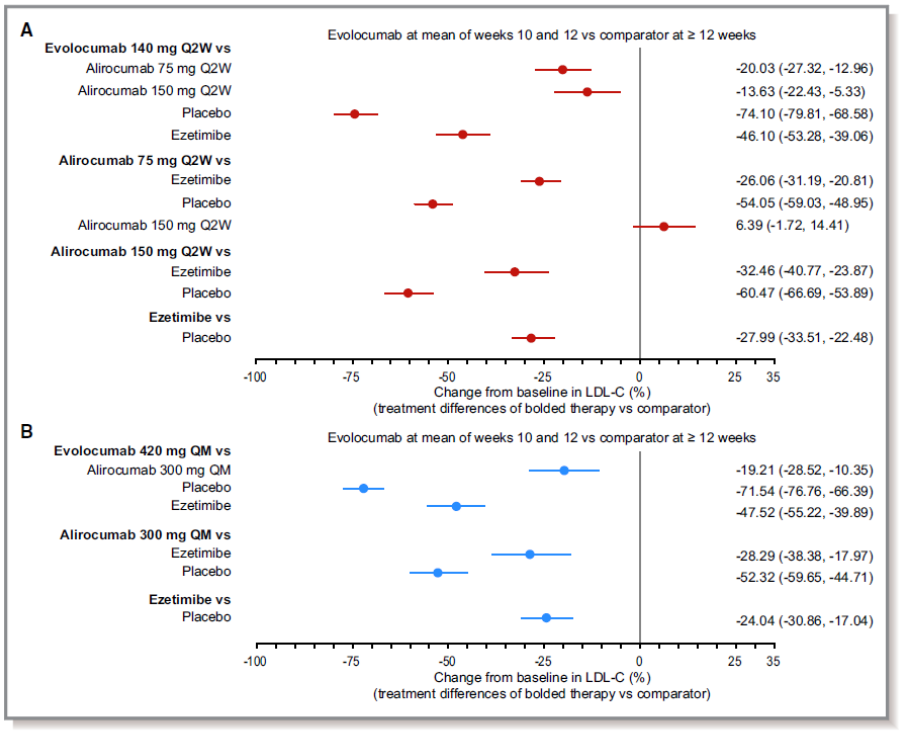
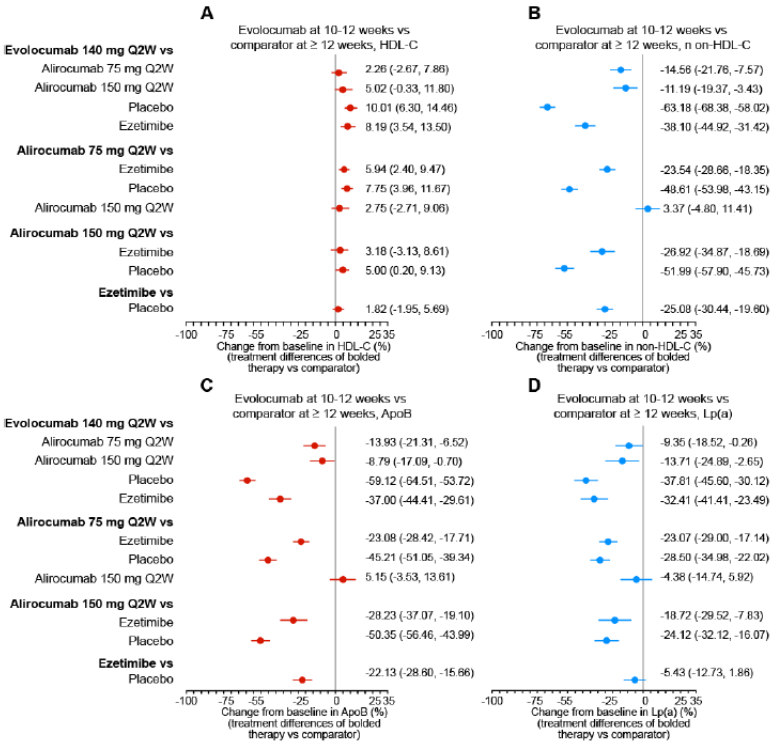


Figure 3. Treatment difference in percentage LDL-C change (95% credible interval) in response to evolocumab 140 mg Q2W network (A) or evolocumab 420 mg QM network (B): evolocumab at the mean of weeks 10 and 12 vs comparator at ≥12 weeks. LDL-C indicates low-density lipoprotein cholesterol; Q2W, every 2 weeks; QM, every month.

Network meta-analysis of HDL-C, ApoB und Lp(a)

Figure S7. Treatment Difference in Percent (95% Credible Interval) Change from Baseline, Evolocumab 140 mg Q2W at the Mean of Weeks of 10 and 12 vs Comparator at ≥ 12 Weeks: Panel A, HDL-C; Panel B, Non-HDL-C; Panel C, ApoB; Panel D, Lp(a).



LDL-C indicates low-density liprotein cholesterol; Q2W, every 2 weeks; QM, every month.

Safety

Table 2. Risk Ratio (95% CI) for Occurrence of Any AE, Treatment-Related AE, and Serious AE

Comparison	Any AE	Treatment-Related AE	Serious AE
Evolocumab 140 mg Q2W vs placebo	1.10 (0.93-1.29)	1.10 (0.42-2.85)	0.96 (0.44-2.09)
Evolocumab 420 mg QM vs placebo	1.03 (0.91-1.18)	1.47 (1.03-2.09)	0.91 (0.38-2.16)
Alirocumab 75 mg Q2W vs placebo	1.06 (0.92-1.22)	1.25 (0.87-1.81)	1.00 (0.74-1.34)
Alirocumab 150 mg Q2W vs placebo	1.25 (0.76-2.08)	NR	1.05 (0.40-2.75)
Alirocumab 300 mg QM vs placebo	1.26 (0.89-1.79)	1.17 (1.01-1.35)	1.03 (0.07-15.78)
Ezetimibe vs placebo	1.04 (0.89-1.21)	1.17 (0.68-2.00)	0.77 (0.44-1.36)

AE indicates adverse event; CI, confidence interval; NR, not reported; Q2W, every 2 weeks; QM, monthly.

Anmerkung/Fazit der Autoren

- Based on network meta-analyses, the PCSK9 inhibitors evolocumab and alirocumab were associated with reductions in LDL-C of 54% to 74% versus placebo and 26% to 46% versus ezetimibe in patients not adequately controlled by statins alone. Recognizing the limitations of indirect comparison, our synthesis of the available data shows a greater reduction with evolocumab in LDL-C versus alirocumab 75 mg Q2W with evidence also suggesting more intense LDL-C reduction versus alirocumab 150 mg Q2W. There was some evidence to suggest that evolocumab may also significantly increase HDLC and decrease non-HDL-C, ApoB, and Lp(a) levels in comparison to alirocumab and other treatments. Further research is needed into the effects of evolocumab and alirocumab on the risk of cardiovascular events.

Kommentare zum Review

- Ein Großteil der eingeschlossenen Studien war von kurzer Dauer (häufig 12 oder 24 Wochen)

Shaya FT et al., 2019 [30].

Lipid-Lowering Efficacy of Ezetimibe in Patients with Atherosclerotic Cardiovascular Disease: A Systematic Review and Meta-Analyses

Fragestellung

„[…] we conducted a systematic literature review and meta-analyses to assess the LDL-C-lowering efficacy of ezetimibe in patients with ASCVD and the high-risk subgroup of patients with recent (event in the last 1 year) ACS."

Methodik

Population:

- Patients with atherosclerotic cardiovascular disease and/or acute coronary syndrome:
  - o defined as those with a prior history of myocardial infarction, stable or unstable angina, coronary or other arterial revascularization, stroke, transient ischemic attack, or peripheral arterial disease.

Intervention:

- Ezetimibe therapy, received with or without other lipid-lowering therapies (LLTs)

Komparator:

- Nicht eingeschränkt.

Endpunkte:

- Primary: mean change in LDL-C from baseline at 6 months, with sensitivity analyses at 1-, 3-, 9-, and 12-month timepoints (or closest reported timepoint to those).

Recherche/Suchzeitraum:

- MEDLINE (via the PubMed platform), Embase (via OVID), and the Cochrane Central Database of Controlled Trials (via the Wiley platform), starting date through to 27 August 2018 for MEDLINE and to 28 August 2018 for Embase and the Cochrane Central Database of Controlled Trials.
- Manual search on the reference lists of identified eligible studies and published systematic literature reviews and for conference abstracts listed in Embase and specific congress proceedings from January 2015 through August 2018

Qualitätsbewertung der Studien:

- Cochrane Collaboration Risk of Bias Assessment Tool for systematic reviews

Ergebnisse

Anzahl eingeschlossener Studien:

- 14 records matching the eligibility criteria were identified through the systematic literature review, 12 studies included in the meta-analysis

- All included studies compared combination ezetimibe plus statin therapy with statin monotherapy

Charakteristika der Population:

- Mean age of participants ranged from 57 to 71 years
- key difference between the 12 studies was the definition of cardiovascular history used as an inclusion criterion:

Study reference	Cardiovascular inclusion criterion	Study definition
Brohet C et al. *Curr Med Res Opin*. 2005;21:571–578.	CHD	NR
Cannon CP et al. *N Engl J Med*. 2015;372:2387–2397.	ACS	ST-segment elevation myocardial infraction; non-ST-segment elevation myocardial infarction, unstable angina
Hibi K et al. *Circ J*. 2018;82:757–766.	ACS	Unstable angina pectoris, non-ST-segment elevation myocardial infarction, ST-segment elevation myocardial infarction
Joshi S et al. *J Clin Diagn Res*. 2017;11:OC28–OC31.	CAD	CAD was diagnosed on the basis of clinical history and electrocardiography (ECG) changes (ST depression/elevation, T wave inversion)
Masuda J et al 2015. *Int Heart J*. 2015;56:278–285.	CAD	Clinically stable angina pectoris undergoing elective PCI
Ran D et al. *Int J Cardiol*. 2017;235:49–55.	ACS	Non-ST-segment elevation ACS (including unstable angina and non-ST-elevation myocardial infarction) undergoing PCI
Ren Y et al. *Exp Ther Med*. 2017;14:4942–4950.	AMI	Hospitalized within preceding 24 hours for AMI, including ST-segment elevation myocardial infarction (STEMI) with or without non-ST-segment elevation myocardial infarction (NSTEMI). STEMI was defined as an AMI with dynamic changes in the electrocardiogram and at least one instance of elevated levels of cardiac enzymes or myocardial necrosis biomarkers, defined as total creatine phosphokinase or creatine kinase major basic fraction >2-fold the upper limit of the normal range and/or positive troponin I or troponin T
Ueda Y et al. *Circ J*. 2017;81:1611–1619.	CAD	Patients with stable CAD who underwent elective PCI and had yellow plaques (≥1 yellow plaque of grade ≥2)

Wang J et al. *Int Angiol*. 2017;36:467–473.	CAS, CHD	Patients with CAS confirmed by ultrasound and with type 2 diabetes mellitus and CHD. CHD defined as at least one major coronary artery stenosis rate heavier than 50% in coronary angiography
Wang X et al. *Heart Lung Circ*. 2016;25:459–465.	CHD	Atherosclerotic lesions identified by coronary angiography near the middle of the coronary arteries (borderline lesions, 40–70% stenosis; severe lesions, >75% stenosis)
West AM et al. *Atherosclerosis*. 2011;218;156–162.	PAD	NR
Zou YC et al. *J Am Geriatr Soc*. 2016;64:S328.	CAS and CHD	NR

ACS acute coronary syndrome, *AMI* acute myocardial infarction, *CAS* carotid atherosclerosis, *CAD* coronary artery disease, *CHD* coronary heart disease, *NR* not reported, *PAD* peripheral arterial disease, *PCI* percutaneous coronary intervention

Qualität der Studien:

- Across the 12 trials, the risk of selection bias was mainly unclear for random sequence generation and allocation concealment,
- The risk of selection bias was mainly low for random sequence generation and unclear for allocation concealment
- The risk of performance bias, pertaining to blinding of participants and personnel, was assessed as high among four trials, low among two trials, and unclear among six trials.
- The risk of detection bias, pertaining to blinding of outcome assessment, was rated as high for one trial.
- The risk of attrition bias (pertaining to incomplete outcome data) and the risk of reporting bias (pertaining to selective reporting of outcomes) was predominantly low across all trials.
- The risk of other sources of bias was predominantly unclear across all trials.

Studienergebnisse:

- Efficacy of Low-Density Lipoprotein Cholesterol Lowering of Ezetimibe:
  - Patients receiving combination ezetimibe were likely to experience an additional decrease in LDL-C (− 21.86 mg/dL; 95% confidence interval [CI] − 26.56 to − 17.17; p < 0.0001; I^2=81,7%, p=0,00) compared with those receiving statin monotherapy.
  - Analyses of studies according to whether patients were statin naïve or had a history of statin therapy at enrolment showed that patients receiving combination ezetimibe plus statin therapy had greater LDL-C reduction than those receiving statin monotherapy, irrespective of prior history of statin therapy (496 participants, 6 studies, mean difference − 25.07 mg/dL; 95% CI − 31.73 to − 18.41; I^2=45,4 and 18,908 participants, 6 studies, mean difference − 19.54 mg/dL; 95% CI − 25.56 to − 13.53; I^2=87,2%, respectively)
- Subgroup Analysis of Patients with a History of Recent Acute Coronary Syndrome:
  - Patients receiving combination ezetimibe plus statin were more likely to experience a decrease in LDL-C levels than those receiving statin monotherapy (LDL-C mean difference of − 19.19 mg/dL; 95% CI − 25.22 to − 13.16, p < 0.0001; I^2=52,3%, p=0,10)

Anmerkung/Fazit der Autorinnen und Autoren

The evidence from this systematic literature review and meta-analyses showed that patients with ASCVD receiving combination ezetimibe plus statin therapy experienced an additional 22 mg/dL reduction in LDL-C compared with patients receiving statin therapy alone. The modest incremental reduction in LDL-C suggests that patients with ASCVD and LDL-C levels more than 20–25 mg/dL from the desired threshold despite statin therapy may need other LLT options such as PCSK9 inhibitors

Kommentare zum Review

- "Funding: This analysis was funded by Sanofi and Regeneron Pharmaceuticals, Inc."
- Auffällige Heterogenität, die von den Autorinnen und Autoren nicht erklärt werden konnte.

Zhao Z et al., 2019 [37].

Comparative efficacy and safety of lipid-lowering agents in patients with hypercholesterolemia

Fragestellung

We, therefore, conducted an update network meta-analysis by summarizing up both direct and indirect evidence to evaluate and rank the comparative efficacy and safety among PCSK9 inhibitors, statins, and ezetimibe in patients with hypercholesterolemia.

Methodik

Population:

- patients with hypercholesterolemia

Intervention:

- statins, ezetimibe, and PCSK9 inhibitors monotherapy

Komparator:

- against each other or placebo

Endpunkte:

- Percentage change from baseline in LDL-C, highdensity lipoprotein (HDL) cholesterol, and total cholesterol (TC) level. Efficacy endpoints were CV events, all-cause mortality CV mortality. Safety outcomes were serious adverse events, neurocognitive event, new-onset diabetes, and elevation of serum CK (3 to 10 folds increase) and ALT level (3 to 10 folds increase).

Recherche/Suchzeitraum:

- January 1, 2000 and June 1, 2018 (PubMed, Embase, and the Cochrane Library Central Register of Controlled Trials)

Qualitätsbewertung der Studien:

- risk of bias in the Cochrane Collaboration guidelines

Ergebnisse

Anzahl eingeschlossener Studien:

- 84 Studien (RCTs from phase 2 or higher; n= 246.706 patients)

Charakteristika der Population:

- Statin-related trials had the largest number (33 trials with 152,037 patients) compared with those of ezetimibe (22 trials with 27,567 patients), and PCSK9 inhibitors (29 trials with 67,102 patients).
- median duration of statin-related trials was 3.2 years, longer than those of ezetimibe (0.3 years) and PCSK9 inhibitor (0.5 years)
- nähere Informationen siehe Anhang 2

Qualität der Studien:

- generally judged as low risk of bias

Studienergebnisse:

- **Lipid-Level**
  - Seventy-one trials involving 210,068 participants provided the outcome data for LDL-C, 60 with 204,432 participants for HDL cholesterol, and 60 with 204,432 participants for TC.
  - Compared with placebo, PCSK9 inhibitor ranked first (probabilities of ranking first for lipid levels were all 100%) for improving LDL-C (SMD -50.76, 95% CI -58.26 to -43.26), HDL cholesterol (7.73, 6.11–8.63), and TC levels (-35.81, -39.53 to -32.09), followed by statin that ranked second for improving LDL-C (-34.03, -44.21 to -23.84), HDL cholesterol (4.17, 2.78–5.57), and TC levels (-24.75, -28.66–-20.85) and ezetimibe that ranked last for improving LDL-C (-18.70,-25.80 to11.59), HDL-cholesterol (2.43, 1.32–3.53), and TC levels (-13.75, -16.73 to -10.78).
- **CV Ereignisse**
  - Fifty-eight trials with 226,368 participants for CV events with no direct comparisons between statin and PCSK9 inhibitor
  - No firm ranking results could be made based on rankograms, but generally statin ranked first (OR 0.80, 95% CI 0.76–0.85; probability of ranking first = 60.6%), PCSK9 inhibitor second (0.82, 0.74–0.92; probability of ranking first = 37.1%), and ezetimibe (0.88, 0.76–1.01; probability of ranking first = 2.3%) last for decreasing CV events as compared with placebo.
- **All-cause and CV mortality**
  - Seventy-two trials involving 228,992 participants provided the outcome data for all-cause mortality, and 61 with 223,356 participants for CV mortality.
  - Statins (0.90, 0.85–0.96) ranked first, PCSK9 inhibitors (0.90, 0.79–1.04) second and ezetimibe (0.96, 0.83–1.11) last for improving all-cause mortality compared with placebo.
  - Statins were not superior to PCSK9 inhibitors for improving allcause mortality (1.00, 0.87–1.16) and CV mortality (0.88, 0.69–1.11).
- **Serious adverse events and neurocognitive events**
  - Clinical data for the 3 agents were lacking in analysis of neurocognitive adverse event, especially for ezetimibe.

- Although ezetimibe ranked first in reducing serious adverse events, none of the PCSK9 inhibitors (0.98, 0.94–1.03), statins (0.99, 0.94–1.03), or ezetimibe (0.87, 0.67–1.13) were associated with significant increase of serious adverse events as compared with placebo.
- However, compared with placebo, ezetimibe (3.94, 1.18–13.12) was associated with increased rate of neurocognitive adverse events while PCSK9 inhibitors (1.26, 0.80–2.00) and statin were not (0.97, 0.51–1.86). Statins ranked first in reducing neurocognitive adverse events compared with other interventions.

- **Statin-related side effects and new-onset diabetes**
  - Seventy-one trials involving 210,068 participants provided the outcome data for outcome of CK, 60 with 204,432 participants for outcome of ALT, and rare data were available for analysing outcome of new-onset diabetes.
  - Generally, statin ranked first in increasing the incidences of statin-related sideeffects and newonset diabetes as compared with other interventions.
  - Compared with placebo, only statins were associated with elevation of ALT (1.89, 1.42–2.51) and CK levels (1.45 1.09–1.93), and increase of new-onset diabetes (1.13, 1.02–1.26), while PCSK9 inhibitor and ezetimibe were not.

Pairwise and network estimates of the 3 lipid-lowering agents on major clinical outcomes.

	Direct comparisons/participants (n/N)	Odds ratio (95% CI)	
		Pairwise meta-analysis	Network meta-analysis
Cardiovascular events			
Statins vs Placebo	29/139233	0.80 (0.76, 0.85)	0.80 (0.76, 0.85)
PCSK9 inhibitor vs Placebo	15/62714	0.79 (0.68, 0.92)	0.82 (0.74, 0.92)
Ezetimibe vs Placebo	17/23977	0.91 (0.85, 0.96)	0.88 (0.76, 1.01)
Statins vs Ezetimibe	5/1969	NA	0.92 (0.79, 1.06)
PCSK9 inhibitor vs Ezetimibe	8/3134	1.18 (0.65, 2.16)	0.83 (0.79, 1.11)
Statins vs PCSK9 inhibitor	0/0	NA	0.98 (0.87, 1.11)
All-cause mortality			
Statins vs Placebo	36/143995	0.91 (0.86, 0.96)	0.90 (0.85, 0.96)
PCSK9 inhibitor vs Placebo	20/60169	0.87 (0.71, 1.07)	0.90 (0.79, 1.04)
Ezetimibe vs Placebo	17/24312	0.92 (0.75, 1.14)	0.96 (0.83, 1.11)
Statins vs Ezetimibe	5/1969	NA	0.94 (0.81, 1.09)
PCSK9 inhibitor vs Ezetimibe	11/3999	0.23 (0.05, 1.03)	0.94 (0.77, 1.14)
Statins vs PCSK9 inhibitor	0/0	NA	1.00 (0.87, 1.16)
Cardiovascular mortality			
Statins vs Placebo	27/134059	0.83 (0.75, 0.92)	0.83 (0.75, 0.91)
PCSK9 inhibitor vs Placebo	20/63501	0.99 (0.87, 1.13)	0.94 (0.76, 1.17)
Ezetimibe vs Placebo	17/24312	1.00 (0.89, 1.12)	1.02 (0.79, 1.30)
Statins vs Ezetimibe	5/1969	NA	0.81 (0.62, 1.06)
PCSK9 inhibitor vs Ezetimibe	11/3999	0.44 (0.08, 2.37)	0.93 (0.67, 1.28)
Statins vs PCSK9 inhibitor	0/0	NA	0.88 (0.69, 1.11)

The 3 lipid-lowering agents including statin, ezetimibe, and PCSK9 inhibitor. Major clinical outcomes were all-cause mortality, cardiovascular events, and cardiovascular mortality. CI = confidence interval, NA = not applied, PCSK9 = proprotein convertase subtilisin/kexin type 9.

Anmerkung/Fazit der Autoren

The current network meta-analysis (comprising 84 trials with 246,706 patients) provides unified hierarchies of evidence for statins, ezetimibe, and PCSK9 inhibitors in patients with hypercholesterolemia, overcoming the lack of comparative data in head to head trials. Our findings were summarized as follows:

1) of the 3 lipid-lowering agents, PCSK9 inhibitors were the most effective agent in improving lipid levels;
2) furthermore, PCSK9 inhibitors were associated with similar decreased risk of CV events as statins;

3) however, no significant CV protective effect of ezetimibe was identified as compared with placebo;
4) only statins were associated with reduced risks of all-cause and CV death;
5) compared with placebo, all the lipid-lowering agents conferred an equal risk profile regarding safety outcomes, except that statins significantly increase the levels of ALT and CK and incidence of new-onset diabetes.

Wang S et al., 2019 [34].

Relative Effect of Current Intensive Lipid-Lowering Drugs on Cardiovascular Outcomes in Secondary Prevention.

Fragestellung

to investigate the comparative cardiovascular benefits of high-dose statin, ezetimibe-statin, and PCSK9 inhibitor-statin treatments in secondary prevention patients

Methodik

Population:

- ≥ 60% were as follows: (1) 0% participants were secondary prevention patients (defined by a history of atherosclerosis cardiovascular disease (CVD), i.e., coronary artery disease [CAD] cerebrovascular disease, or peripheral artery disease)

Intervention/ Komparator:

- compared more intensive lipid-lowering therapy with less-intensive statin therapy

Endpunkte:

- major cardiovascular events (MACE), myocardial infarction (MI), stroke, coronary revascularization, all-cause death, and cardiovascular death

Recherche/Suchzeitraum:

- Bis Juni 2018 (PubMed and Embase)

Qualitätsbewertung der Studien:

- Cochrane Collaboration’s risk of bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- N=12

Charakteristika der Population:

Table 1. Baseline Characteristics of Included Trials

Study and date	Duration, year	Sample size	Female, %	Mean age, years	DM, %	Participants
PROVE-IT (2004)[3]	2.0	2,099/2,063	21.9	58.2	17.6	ACS
A to Z (2004)[4]	2.0	2,265/2,232	24.5	61.0	23.5	ACS
TNT (2005)[5]	4.9	4,995/5,006	19.0	61.0	15.0	Stable coronary disease
IDEAL (2005)[6]	4.8	4,439/4,449	19.2	61.7	12.1	MI
SEARCH (2010)[7]	6.7	6,031/6,033	NR	64.2	NR	MI
IMPROVE-IT (2015)[8]	6.0	9,067/9,077	24.3	63.6	27.2	ACS
ODYSSEY LONG TERM (2015)[15]	1.5	1,550/788	37.7	62.8	34.5	69% CAD
HIJ-PROPER (2017)[16]	3.9	864/857	24.5	65.6	30.2	ACS
SPIRE2 (2017)[17]	0.8	5,312/5,309	34.6	62.4	46.8	CVD
FOURIER (2017)[9]	2.2	13,784/13,780	24.5	62.5	36.6	CVD
ODYSSEY OUTCOMES (2018)[19]	2.8	9,462/9,462	NR	NR	NR	ACS
REAL-CAD (2018)[18]	3.0	6,199/6,214	15.0	68.1	40.1	Stable coronary disease

Study and date	More intensive lipid-lowering			Less-intensive lipid-lowering			Background statin therapy, %
	Intervention	Baseline LDL-C	Achieved LDL	Intervention	Baseline LDL-C	Achieved LDL	
PROVE-IT (2004)[3]	Atorvastatin 80 mg	106.0	62.0	Pravastatin 40 mg	106.0	95.0	25.2
A to Z (2004)[4]	Simvastatin 40–80 mg	112.0	66.0	Simvastatin 20 mg[a]	111.0	81.0	0.0
TNT (2005)[5]	Atorvastatin 80 mg	97.0	77.0	Atorvastatin 10 mg	98.0	101.0	0.0
IDEAL (2005)[6]	Atorvastatin 80 mg	121.6	81.0	Simvastatin 20 mg	121.4	104.0	75.5
SEARCH (2010)[7]	Simvastatin 80 mg	96.7	83.1	Simvastatin 20 mg	96.7	96.7	NR
IMPROVE-IT (2015)[8]	Simvastatin 40 mg+ Ezetimibe 10 mg	93.8	53.7	Simvastatin 40 mg	93.8	69.5	34.5
ODYSSEY LONG TERM (2015)[15]	Alirocumab 150 mg[b]	122.7	58.5	Placebo	121.9	126.4	99.9
HIJ-PROPER (2017)[16]	Pitavastatin 2 mg+ Ezetimibe 10 mg	134.8	65.1	Pitavastatin 2 mg	135.6	84.6	17.5
SPIRE2 (2017)[17]	Bococizumab 150 mg[c]	133.9	93.0	Placebo	133.4	136.2	83.2
FOURIER (2017)[9]	Evolocumab 140 mg or 420 mg[d]	92.0	30.0	Placebo	92.0	92.0	99.8[e]
ODYSSEY OUTCOMES (2018)[19]	Alirocumab q2 weeks	87.0	42.3	Placebo	87.0	96.4	89.0[e]
REAL-CAD (2018)[18]	High-dose pitavastatin	87.7	73.7	Low-dose pitavastatin	88.1	89.4	90.9

[a]A to Z Placebo titrated to simvastatin 20 mg. [b]Alirocumab 150 mg subcutaneously every 2 weeks. [c]Bococizumab 150 mg every 2 weeks. [d]Evolocumab either 140 mg every 2 weeks or 420 mg every month. [e]High-dose statin with or without ezetimibe. A to Z, Phase Z of the A to Z trial. FOURIER, Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk. HIJ-PROPER, Heart Institute of Japan Proper level of lipid lowering with Pitavastatin and Ezetimibe in acute coronary syndrome trial. IDEAL, Incremental Decrease in End Points Through Aggressive Lipid Lowering Study Group. IMPROVE-IT, The Improved Reduction of Outcomes: Vytorin Efficacy International Trial. ODYSSEY LONG TERM, Long-term Safety and Tolerability of Alirocumab in High Cardiovascular Risk Patients with Hypercholesterolemia Not Adequately Controlled with Their Lipid Modifying Therapy. ODYSSEY OUTCOMES, Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab. PROVE-IT, Pravastatin or Atorvastatin Evaluation and Infection Therapy. SEARCH, Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine. SPIRE2, Studies of PCSK9 Inhibition and the Reduction of Vascular Events program 2. TNT, Treating to New Targets. REAL-CAD, High-Dose Versus Low-Dose Pitavastatin in Japanese Patients With Stable Coronary Artery Disease. CAD, coronary artery disease; CVD, cardiovascular disease; DM, diabetes mellitus; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; NR, not reported.

Qualität der Studien:

- All the trials were conducted on multicenter and according to the intention-to-treat principle. Blinded procedures were applied to the processes of randomized assignment and outcome assessment. There was no significant difference among the trials regarding the risk of bias identified. No publication bias was identified by visually inspected the funnel plot or by Begg's test in analyzing the outcomes of MACE, revascularization, MI, and stroke. However, potential biases were presented in analyzing all-cause and cardiovascular deaths.

Studienergebnisse:

- The relative effects of high-dose statin, ezetimibe-statin, and PCSK9 inhibitor-statin on major cardiovascular events (MACE), and revascularization were varied and decreased gradually, of which high-dose statin resulted in lower risk of MACE and revascularization than PCSK9 inhibitor-statin per 1 mmol/L reduction of low-density lipoprotein cholesterol (LDL-C): risk ratio (RR) for MACE, 0.86 (95% confidence interval (CI), 0.81–0.90) for high-dose statin, 0.90 (95% CI, 0.83–0.96) for ezetimibe-statin, and 0.94 (95% CI, 0.92–0.96) for PCSK9 inhibitorstatin; RR for revascularization, 0.84 (95% CI, 0.77–0.90) for high-dose statin, 0.91 (95% CI, 0.81–1.00) for ezetimibe-statin, and 0.94 (95% CI, 0.90–0.97) for PCSK9 inhibitor-statin.

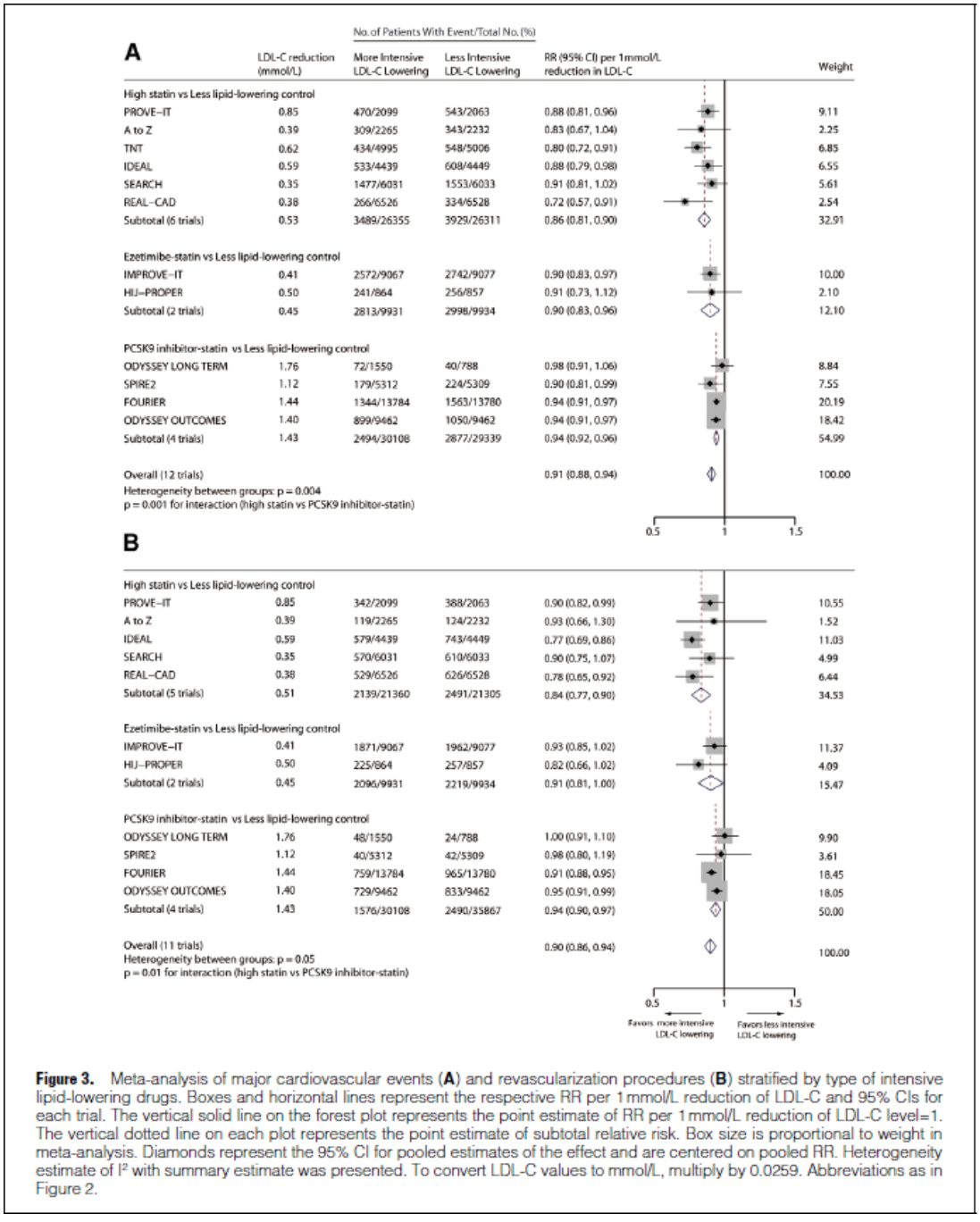


Figure 3. Meta-analysis of major cardiovascular events (**A**) and revascularization procedures (**B**) stratified by type of intensive lipid-lowering drugs. Boxes and horizontal lines represent the respective RR per 1 mmol/L reduction of LDL-C and 95% CIs for each trial. The vertical solid line on the forest plot represents the point estimate of RR per 1 mmol/L reduction of LDL-C level=1. The vertical dotted line on each plot represents the point estimate of subtotal relative risk. Box size is proportional to weight in meta-analysis. Diamonds represent the 95% CI for pooled estimates of the effect and are centered on pooled RR. Heterogeneity estimate of I^2 with summary estimate was presented. To convert LDL-C values to mmol/L, multiply by 0.0259. Abbreviations as in Figure 2.

- Similar relative effects of intensive lipid-lowering treatment were also observed in analyses of myocardial infarction and stroke, although no significant difference between groups was identified.

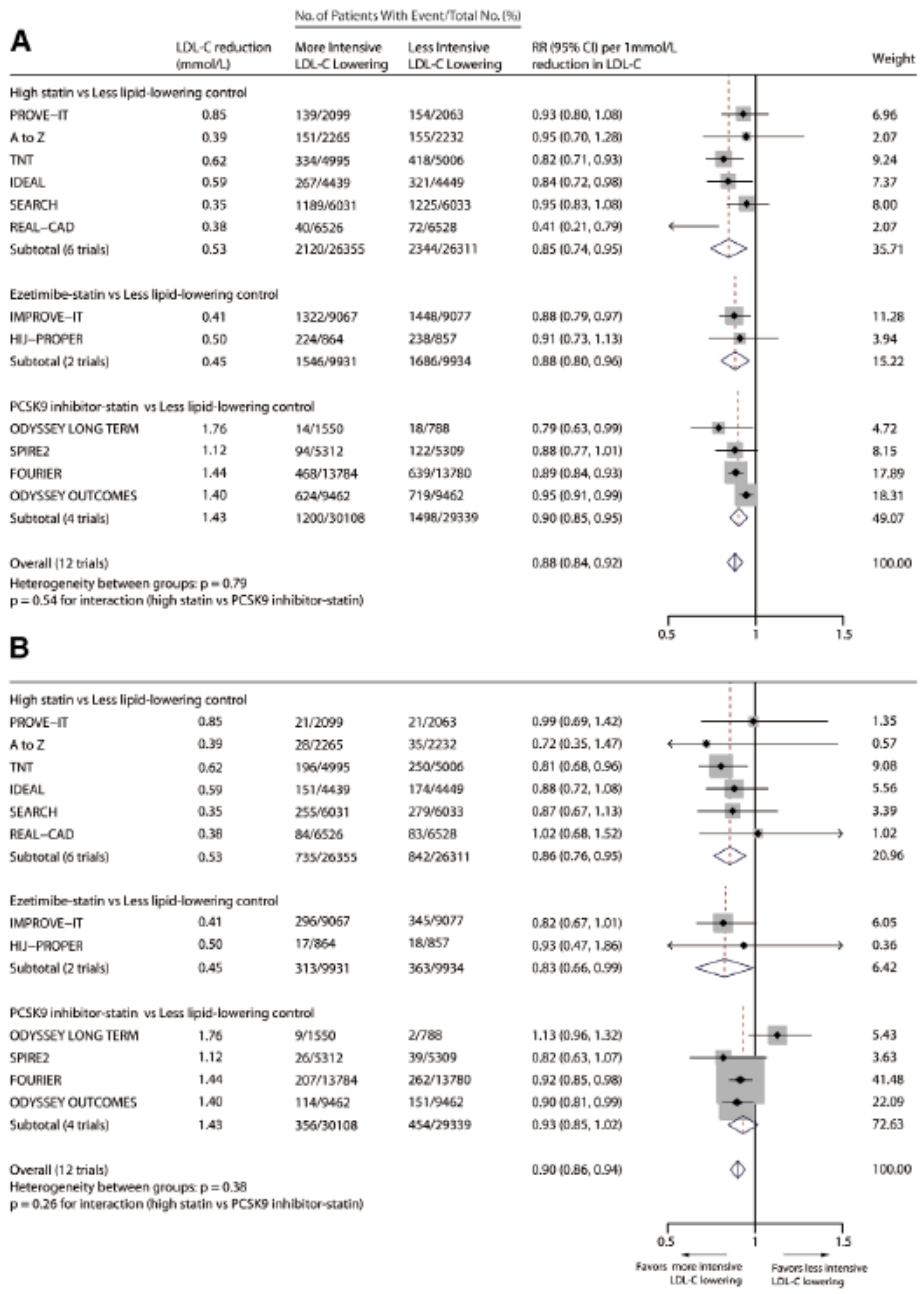


Figure 4. Meta-analysis of myocardial infarction (**A**) and stroke (**B**) stratified by type of intensive lipid-lowering drugs. See Figure 3 for explanations.

- All-Cause Death
  - The overall risk reduction in all-cause death with more vs. less-intensive therapy across all trials was 0.94 (95% CI, 0.89–0.99) per 1 mmol/L reduction of the LDL-C level, and did not vary by the type of intensive lipid-lower- ing drugs.
  - In the predefined subgroup analyses, all-cause death risk was associated with an RR of 0.90 (95% CI, 0.79–1.00), 0.86 (95% CI, 0.55–1.17), 0.98 (95% CI, 0.92–1.04) per 1

mmol/L reduction of the LDL-C level, respectively, in the subgroups with high-dose statin, ezetimibe-statin, and PCSK9 inhibitor-statin as the intervention (Figure 5); findings were generally unchanged intervenstratified by baseline LDL-C level

- Cardiovascular Death
  - The overall risk reduction in cardiovascular death with more vs. less-intensive therapy across all trials was 0.95 (95% CI, 0.89–1.01) per 1 mmol/L reduction of the LDL-C level, and did not vary by the type of intensive lipid-lowering drugs.
  - In the predefined subgroup analyses, cardiovascular death risk was associated with an RR of 0.88 (95% CI, 0.75–1.00), 0.99 (95% CI, 0.85–1.14), and 0.99 (95% CI, 0.93–1.04) per 1 mmol/L reduction of the LDL-C level, respectively, in the subgroups with high-dose statin, ezetimibe-statin, and PCSK9 inhibitor-statin as the intervenstratified reduction; findings were generally unchanged stratified by baseline LDL-C level.

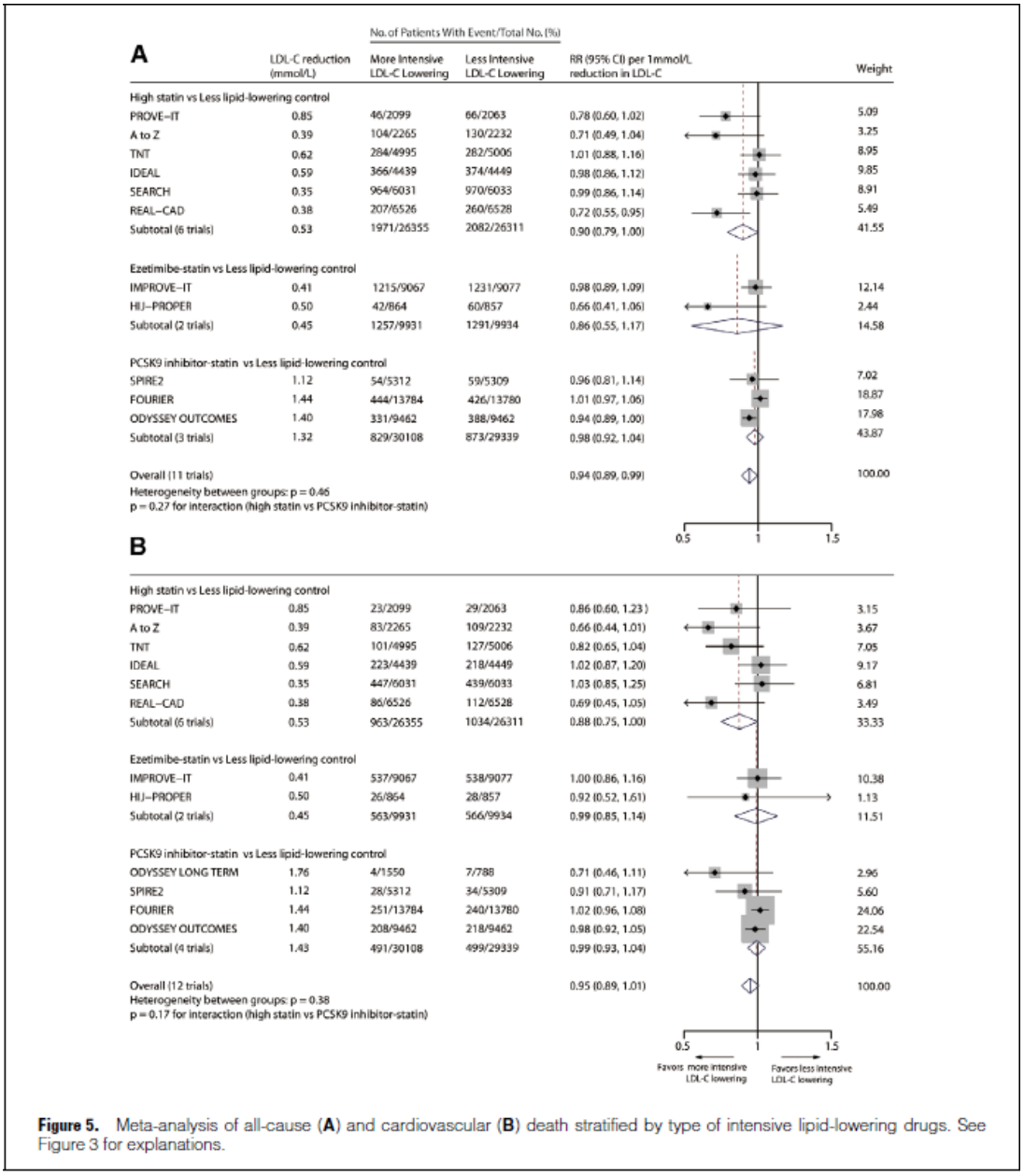


Figure 5. Meta-analysis of all-cause (**A**) and cardiovascular (**B**) death stratified by type of intensive lipid-lowering drugs. See Figure 3 for explanations.

Anmerkung/Fazit der Autoren

We newly found that the beneficial effects of high-dose statin, ezetimibe-statin, and PCSK9 inhibitor-statin on the risks of cardiovascular events were varied and decreased gradually in secondary prevention patients, for whom high-dose statin was significantly better than PCSK9 inhibitor-statin against MACE and revascularization per 1 mmol/L reduction in the LDL-C level. High-dose statin was also superior to ezetimibe-statin and PCSK9 inhibitorstatin for improvement in all-cause and cardiovascular deaths. These findings may inform clinicians to select highdose statins as first-line lipid-lowering drugs for secondary prevention of CVD.

Kommentare zum Review

- investigated the relative effect of different intensive lipidlowering drugs in secondary prevention patients; whether our conclusions also apply to primary prevention patients remains unknown.
- only obtained data that compared the relative effects among high-dose statins, ezetimibestatin, and PCSK9 inhibitor-statin on cardiovascular outcomes; the comparative benefits and harms among statins, ezetimibe, and PCSK9 inhibitors are not yet known.

Shin J et al., 2019 [31].

Achieved low-density lipoprotein cholesterol level and stroke risk: A meta-analysis of 23 randomised trials.

Fragestellung

This meta-analysis of RCTs evaluated whether a lower achieved LDL-cholesterol level is associated with a lower stroke risk by analysing stroke risk reduction: (a) per 1mmol/L decrease in achieved LDL-cholesterol level; (b) stratified by achieved LDL-cholesterol levels; and (c) with pharmacological interventions added to background statin therapy to reduce LDL-cholesterol level further.

Methodik

Population:

- Patients receiving cholesterol-lowering pharmacological therapies

Intervention:

- LDL-cholesterol lowering drugs

Komparator:

- placebo or intensive and less intensive LDL-cholesterol-lowering pharmacological therapies

Endpunkte:

- primary outcome: any stroke
- secondary outcomes: ischaemic stroke, haemorrhagic stroke, MI, cardiovascular mortality and MACE.

Recherche/Suchzeitraum:

- MEDLINE, EMBASE and the Cochrane Library (January 2002 to May 2017)

Qualitätsbewertung der Studien:

- Cochrane risk of bias

Ergebnisse

Anzahl eingeschlossener Studien:

- 26 studies in 52 arms with 6345 stroke events (=222149)
- Studies for quantitative analysis: n=23
- Studies for qualitative analysis: n=17

Charakteristika der Population:

- Among the 52 arms, eight arms of four trials were secondary stroke prevention trials exclusively enrolling patients with a stroke history,5,6,13,14 while 44 arms of 22 trials (two trials were overlapped with secondary stroke prevention trials) were classified as primary stroke prevention trials.5–12,15–28

Qualität der Studien:

- all trials were at low or unclear risk of bias for most of the assessed domains

Studienergebnisse:

Table 2. Summary of meta-regression analyses on the effect of achieved LDL-cholesterol level.

	All studies			Primary stroke prevention			Secondary stroke prevention		
	No.	Slope (95% CI)	*P* value	No.	Slope (95% CI)	*P* value	No.	Slope (95% CI)	*P* value
Any stroke	52	0.235 (0.007, 0.464)	0.044	44	0.196 (0.034, 0.357)	0.019	8	0.309 (−0.308, 0.648)	0.068
Ischaemic stroke	26	0.286 (−0.019, 0.591)	0.065	18	0.148 (−0.078, 0.375)	0.184	8	0.159 (−0.335, 0.652)	0.461
Haemorrhagic stroke	26	0.011 (−0.068, 0.089)	0.779	18	−0.003 (−0.105, 0.098)	0.943	8	−0.018 (−0.149, 0.113)	0.747
MI	52	−0.083 (−0.520, 0.353)	0.703	44	−0.006 (−0.482, 0.471)	0.981	8	−0.513 (−1.903, 0.878)	0.402
Cardiovascular mortality	44	0.079 (−0.704, 0.861)	0.840	38	0.135 (−0.758, 1.027)	0.761	6	−0.392 (−0.984, 0.201)	0.140
MACE	46	0.268 (−0.713, 1.250)	0.585	40	0.339 (−0.781, 1.458)	0.544	6	0.151 (−1.745, 1.442)	0.805

LDL: low-density lipoprotein; CI: confidence interval; MI: myocardial infarction; MACE: major adverse cardiovascular event.

Anmerkung/Fazit der Autoren

In conclusion, this meta-analysis demonstrates that lowering of the LDL-cholesterol level reduces stroke events to a very low level. Additional non-statin LDL-cholesterol lowering drugs such as ezetimibe or PCSK9 inhibitors could be used for further reduction of the LDL-cholesterol level to decrease the rate of stroke events.

Riaz H et al., 2019 [28].

Effects of high-density lipoprotein targeting treatments on cardiovascular outcomes: A systematic review and meta-analysis

Fragestellung

We performed a systematic review and meta-analysis to assess the impact of HDL cholesterol increasing therapies on the risk of cardiovascular outcomes.

Methodik

Population:

- patients receiving high-density lipoprotein cholesterol modifiers

Intervention vs Komparator:

- HDL cholesterol targeting treatments (niacin, fibrates and CETP inhibitors)

Endpunkte:

- Primary outcome: cardiovascular mortality.
- Secondary endpoints: myocardial infarction (MI), stroke, all-cause mortality, change in HDL cholesterol, LDL cholesterol and triglyceride levels.

Recherche/Suchzeitraum:

- MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials (CENTRAL) databases from inception to 15 January 2018.

Qualitätsbewertung der Studien:

- Cochrane risk of bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 31 RCTs (154 601 patients)

Charakteristika der Population:

- Overall, 10 trials (78,542 patients) assessed CTEP inhibitors,20–29 16 trials (41,765 patients) assessed fibrates5,6,19,30–42 and six trials(34,294 patients) assessed niacin.7,19,43–46
- Sixteen trials used background statin therapy20–29,40,42–46 and 15 had no statin therapy. 5–7,19,30–39,41 The mean age of study participants was 58.4±6.7 years and 78% were men. The pooled mean baseline HDL cholesterol was 42.7±4.9 mg/dL. The mean follow-up duration was 3.2±1.6 years.

Qualität der Studien:

- Cochrane risk of bias tool

Studienergebnisse:

Cardiovascular mortality

- Twenty-five trials (151,900 patients) reported 5190 events of cardiovascular mortality.
- HDL cholesterol modifiers had no statistically significant effect on cardiovascular mortality (RR 0.94, 95% CI 0.89–1.00, P=0.05, I2=13%).

Myocardial infarction

- Thirty trials (154,332 patients) reported 7687 events of MI.
- HDL cholesterol modifiers reduced the relative risk of MI by 13% (RR 0.87, 95% CI 0.82–0.93, P<0.001, I2=37%).

- Every 1 mmol (38.5 mg) reduction in LDL cholesterol generated a 39% relative risk reduction in MI in fibrates trials (RR 0.61, 95% CI 0.39–0.94, P=0.03).

Stroke

- Twenty-two trials (137,069 patients) reported 3980 events of stroke.
- The use of HDL cholesterol had a neutral effect on the relative risk of stroke compared to control (RR 1.00, 95% CI 0.93–1.09, P=0.94, I2=25%)

All-cause mortality

- Twenty-five trials (150,196 patients) reported 10,014 events of all-cause mortality.
- HDL cholesterol modifiers did not reduce the relative risk of all-cause mortality compared to control (RR 1.02, 95% CI 0.97–1.08, P=0.48, I2=49%

Subgroup analysis

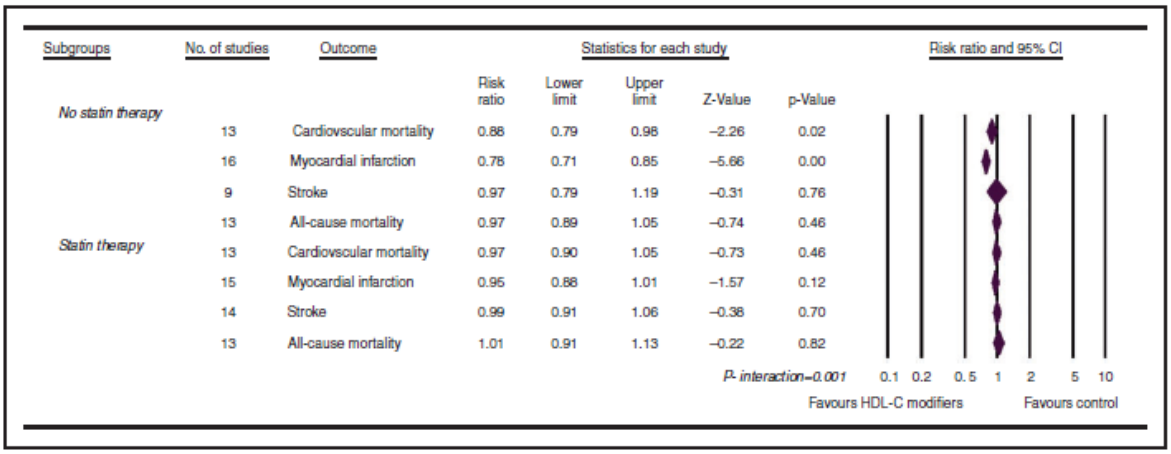


Figure 4. Forest plot showing effect of high-density lipoprotein (HDL) cholesterol modifiers on all endpoints in subgroups of patients with concomitant background statin therapy or no statin therapy.

Anmerkung/Fazit der Autoren

In conclusion, we report that three classes of drugs that raise HDL cholesterol by distinct mechanisms failed to reduce cardiovascular mortality, stroke or all-cause mortality significantly. […] Meta-regression analyses confirmed that the observed MI benefit by fibrates was due to LDL cholesterol reduction and there is a lack of association between HDL cholesterol and a reduction in the outcomes of interest. Our findings refute the efficacy of HDL cholesterol modifiers on hard clinical endpoints.

Liu H et al., 2018 [23].

Effect of pitavastatin and atorvastatin on regression of atherosclerosis assessed using intravascular ultrasound: a meta-analysis

Fragestellung

Thus, this study was designed to evaluate the effects of pitavastatin and atorvastatin on IVUS evaluation in patients with dyslipidaemia, find the difference between these two statins, and provide instructions for future clinical practice.

Methodik

Population:

- Patients with dyslipidaemia

Intervention:

- Pitavastatin

Komparator:

- Atorvastatin

Endpunkte:

- total cholesterol, LDL-C, HDL-C, triglycerides, glycated hemoglobin (HbA1c), intravascular ultrasound (IVUS) profiles

Recherche/Suchzeitraum:

- PubMed, Elsevier, Springer LINK, and Whiley Interscience till 1 October 2016.

Qualitätsbewertung der Studien:

- Cochrane risk of bias

Ergebnisse

Anzahl eingeschlossener Studien:

- 11 studies (n=2129)

Charakteristika der Population:

Table 1 **Characteristics of included studies**

References	Country	Patients	Sample size	Follow-up (weeks)	Lost to follow-up (%)	Blinding
Yokote *et al.* [8] (CHIBA)	Japan	Hypercholesterolemia	204	12	NR	Open-label
Gumprecht *et al.* [18]	Poland	Hypercholesterolemia with DM	418	56	47.8	Double-blind
Hiro *et al.* [13] (JAPAN-ACS)	Japan	Dyslipidemia with ACS	252	32–48	2.0	Open-label
Lee *et al.* [19]	Korea	Hypercholesterolemia	268	8	NR	Open-label
Liu *et al.* [20] (PAPAGO-T)	Taiwan of China	Hypercholesterolemia with DM	251	12	1.1	Double-blind
Sansanayudh *et al.* [21]	Japan	Hypercholesterolemia	100	8	2.0	Open-label
Sasaki *et al.* [22]	Japan	Hypercholesterolemia with glucose intolerance	207	52	8.7	Open-label
Tani *et al.* [23]	Japan	Hypercholesterolemia	104	24	NR	Open-label
Toi *et al.* [17]	Japan	Hypercholesterolemia with ACS	160	2–3	NR	Open-label
Yoshida *et al.* [24] (VISION)	Japan	Hypercholesterolemia	47	12	10.6	Open-label
Matsushita *et al.* [25] (YOKOHAMA-ACS)	Japan	Hypercholesterolemia with ACS	118	40	6.8	Open-label

ACS, acute coronary syndrome; DM, diabetes mellitus; NR, not reported.

Qualität der Studien:

Some of the eligible studies were characterized by lack of information about the random sequence generation and allocation concealment. Allocation concealment was adequate in five (29.4%) trials and unclear in the remainder. Double blinding was undertaken in two (11.7%) trials, and the remainder were open-labeled studies. Incomplete data were addressed in seven (41.1%) trials and unclear in the remainder

Studienergebnisse:

Effects of pitavastatin and atorvastatin on low-density lipoprotein cholesterol

- For the head-to-head comparison of pitavastatin and atorvastatin, the MD in change from baseline for LDL-C was 2.51 (95% CI: 1.17–3.86; I2=48%; P=0.0003) (Fig. 3).

Effects of pitavastatin and atorvastatin on high-density lipoprotein cholesterol

- The change for head-to-head comparison of pitavastatin and atorvastatin was 2.17 (95% CI: 1.42–2.91; I2= 40%; P <0.00001) (Fig. 4).

Effects of pitavastatin and atorvastatin on glycated hemoglobin

- The head-to-head comparison of pitavastatin and atorvastatin was −0.15 (95% CI: −1.44–1.15; I2=0%; P=0.83) (Fig. 5).

Anmerkung/Fazit der Autoren

The present meta-analysis suggests that atorvastatin is more effective than pitavastatin in lowering LDL-C, but there was no significant difference between these two statins in HDL-C, HbA1c, and IVUS-based volume parameters.

Kommentare zum Review

- Gemäß Autoren fokussiert der Review sich auf asiatische (japanische) Studien: In addition, the studies included were mostly restricted to Asia area (especially Japan), thereby the outcomes of our study represent the outcome of pitavastatin versus atorvastatin in Asian people especially Japanese population.

Chou R et al., 2016 [11].

Statins for Prevention of Cardiovascular Disease in Adults Evidence Report and Systematic Review for the US Preventive Services Task Force

Fragestellung

To systematically review benefits and harms of statins for prevention of CVD to inform the US Preventive Services Task Force.

Methodik

Population:

- Adults ≥40 y without prior CVD events. Studies were limited to those in which fewer than 10% of the participants had prior CVD events to include only trials that predominantly enrolled the population of interest

Intervention:

- Statin therapy

Komparator:

- Placebo or no statin therapy or usual care without statin

Endpunkte:

- all-cause mortality, coronary heart disease, stroke-related morbidity or mortality, or harms of treatment (including muscle injury, cognitive loss, incident diabetes, and hepatic injury)

Recherche/Suchzeitraum:

- Cochrane Central Register of Controlled Trials (from 1991), the Cochrane Database of Systematic Reviews (from 2005), and Ovid MEDLINE (from 1946) to June 2016

Qualitätsbewertung der Studien:

- Methods developed by the USPST based on the number, quality, and size of studies; consistency of results between studies; and directness of evidence.

Criteria	Descriptions
Study limitations	• Study design • Quality: Graded good, fair, or poor, based on the aggregate quality of the individual studies • Precision: Graded precise or imprecise based on the width of the confidence interval of the pooled estimate, whether it encompasses a relative risk of 1, and whether the clinical action would differ if the upper versus lower boundary of the confidence interval represents the truth
Consistency	• Graded consistent (I^2 for pooled estimate <30%, or I^2≥30% to <60% and >75% of trials report same direction of estimates) or inconsistent (I^2≥60%, or I^2≥30% to <60% and ≤75% of trials report same direction of estimates)
Applicability	• Graded based on the applicability of studies to expected U.S. primary care settings, based on the populations enrolled, interventions evaluated, and settings in which the studies were conducted

Overall Quality Ratings and Definitions

Good: Evidence consists of studies without important limitations in study design, quality, or precision; consistent findings across studies; and highly applicable to U.S. primary care settings. More evidence is unlikely to change the magnitude or direction of findings.

Fair: Evidence consists of studies with some limitations in study design, quality or precision; some inconsistency across studies; and/or limited applicability to U.S. primary care settings. More evidence may change the magnitude or direction of the findings.

Poor: Evidence consists of studies with serious limitations in study design, quality, or precision; serious inconsistency across studies; and/or poor applicability to U.S. primary care settings. More evidence is likely to change the magnitude or direction of the findings.

Ergebnisse

Anzahl eingeschlossener Studien:

- 21 studies: 19 Trials included for KQ1a, 0 Trials included for KQ1b, 7 Trials included for KQ1c, 17 Trials and 2 observational studies for KQC 2

Charakteristika der Population:

- Mean ages ranged from 51 to 66 years. Duration of follow-up ranged from 6 months to 6 years.
- All trials enrolled patients at increased cardiovascular risk. In 6 trials, the main criterion for enrollment was presence of dyslipidemia19,24,30,31,33,35; in 3 trials, early cerebrovascular disease18,25,32; in 4 trials, diabetes21,23,26,27; in 2 trials, hypertension20,28; and in 1 trial each, mild to moderate aortic stenosis,22 microalbuminuria, and elevated C-reactive protein (CRP) level (≥20 mg/L [to convert CRP values to nmol/L, multiply by 9.524]).29

Qualität der Studien:

- Six trials were rated as of good quality,14,22,26,29,30,35 1 trial as of poor quality,27 and 12 trials as of fair quality .18-21,23-25,28,31-34
- Methodological limitations in the fair quality trials included unclear randomization and allocation concealment methods and unclear blinding status. The poor-quality trial also did not report attrition.Twotrials18,33 reported noindustry funding; the rest were fully or partially industry funded.
- The trials were judged to have high applicability to general US primary care settings based on the characteristics of the patients enrolled, the statin therapies evaluated, and study settings.

Studienergebnisse:

Key Question 1a What are the benefits of statins in reducing the incidence of CVD-related morbidity or mortality or all-cause mortality in asymptomatic adults 40 years or older without prior CVD events?

All-cause mortality

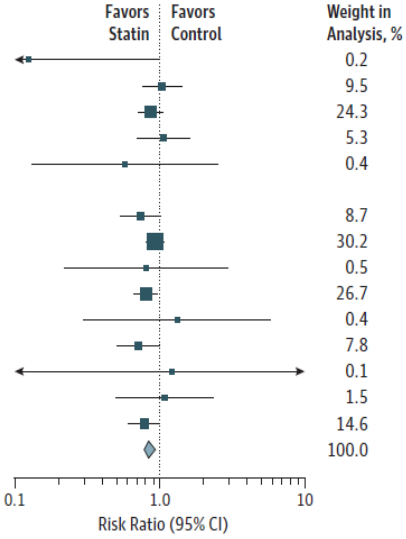
Figure 3. Meta-analysis: Statins vs Placebo and All-Cause Mortality, Cardiovascular Mortality, and Incident Diabetes

A All-cause mortality

Study	Follow-up, y	Statins: Patients With Events, No./Total (%)	Control: Patients With Events, No./Total (%)	Risk Ratio (95% CI)	Weight in Analysis, %
ACAPS,[18] 1994	3	1/460 (0.22)	8/459 (1.7)	0.12 (0.02-0.99)	0.2
AFCAPS/TexCAPS,[19] 1998	5	80/3304 (2.4)	77/3301 (2.3)	1.04 (0.76-1.41)	9.5
ASCOT-LLA,[20] 2003	3	185/5168 (3.6)	212/5137 (4.1)	0.87 (0.71-1.05)	24.3
ASPEN,[21] 2006	4	44/959 (4.6)	41/946 (4.3)	1.06 (0.70-1.60)	5.3
Beishuizen et al,[23] 2004	2	3/103 (2.9)	4/79 (5.1)	0.58 (0.13-2.50)	0.4
Bone et al,[24] 2007	1	0/485 (0)	0/119 (0)	Not estimable	
CARDS,[26] 2004	4	61/1428 (4.3)	82/1410 (5.8)	0.73 (0.53-1.01)	8.7
HOPE-3,[14] 2016	6	334/6361 (5.3)	357/6344 (5.6)	0.93 (0.81-1.08)	30.2
HYRIM,[28] 2005	4	4/283 (1.4)	5/285 (1.8)	0.81 (0.22-2.97)	0.5
JUPITER,[29] 2008	2	198/8901 (2.2)	247/8901 (2.8)	0.80 (0.67-0.96)	26.7
KAPS,[30] 1995	3	4/214 (1.9)	3/212 (1.4)	1.32 (0.30-5.83)	0.4
MEGA,[31] 2006	5	55/3866 (1.4)	79/3966 (2.0)	0.71 (0.51-1.00)	7.8
METEOR,[32] 2007	2	1/700 (0.14)	0/281 (0)	1.21 (0.05-29.5)	0.1
Prevend-IT,[34] 2004	4	13/433 (3.0)	12/431 (2.8)	1.08 (0.50-2.34)	1.5
WOSCOPS,[35] 1995	5	106/3302 (3.2)	135/3293 (4.1)	0.78 (0.61-1.01)	14.6
Total (95% CI)		1089/35967 (3.0)	1262/35164 (3.6)	0.86 (0.80-0.93)	100.0

Heterogeneity: $\tau^2 = 0.00$; $\chi^2_{13} = 11.07$, ($P = .60$); $I^2 = 0\%$

Test for overall effect: $Z = 3.63$ ($P < .003$)

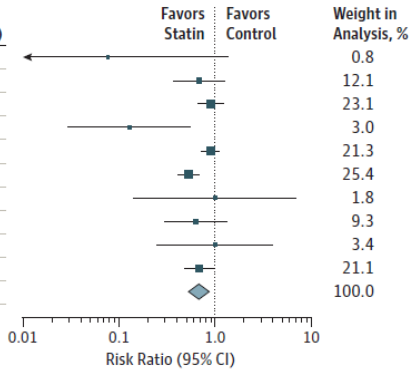


Cardiovascular mortality

B Cardiovascular mortality

Study	Follow-up, y	Statins: Patients With Events, No./Total (%)	Control: Patients With Events, No./Total (%)	Risk Ratio (95% CI)	Weight in Analysis, %
ACAPS,[18] 1994	3	0/460 (0)	6/459 (1.3)	0.08 (0.004-1.36)	0.8
AFCAPS/TexCAPS,[19] 1998	5	17/3304 (0.51)	25/3301 (0.76)	0.68 (0.37-1.26)	12.1
ASCOT-LLA,[20] 2003	3	74/5168 (1.4)	82/5137 (1.6)	0.90 (0.66-1.23)	23.1
ASTRONOMER,[22] 2010	4	2/103 (1.9)	12/79 (15.2)	0.13 (0.03-0.55)	3.0
HOPE-3,[14] 2016	6	154/6361 (2.4)	171/6344 (2.7)	0.90 (0.72-1.11)	21.3
JUPITER,[29] 2008	2	83/8901 (0.93)	157/8901 (1.8)	0.53 (0.41-0.69)	25.4
KAPS,[30] 1995	3	2/214 (0.93)	2/212 (0.94)	0.99 (0.14-6.97)	1.8
MEGA,[31] 2006	5	11/3866 (0.28)	18/3966 (0.45)	0.63 (0.30-1.33)	9.3
Prevend-IT,[34] 2004	4	4/433 (0.92)	4/431 (0.93)	1.00 (0.25-3.95)	3.4
WOSCOPS,[35] 1995	5	50/3302 (1.5)	73/3293 (2.2)	0.68 (0.48-0.98)	21.1
Total (95% CI)		397/32 112 (1.2)	550/32 123 (1.7)	0.69 (0.54-0.88)	100.0

Heterogeneity: $\tau^2 = 0.06$; $\chi^2_9 = 19.46$, ($P = .02$); $I^2 = 54\%$
Test for overall effect: $Z = 3.00$ ($P = .003$)

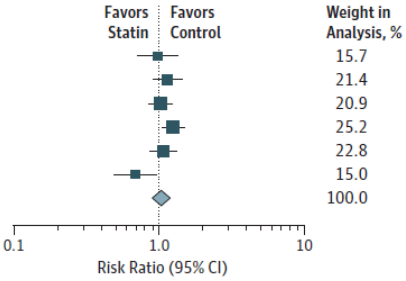


Incident diabetes

C Incident diabetes

Study	Follow-up, y	Statins: Patients With Events, No./Total (%)	Control: Patients With Events, No./Total (%)	Risk Ratio (95% CI)	Weight in Analysis, %
AFCAPS/TexCAPS,[19] 1998	5	72/3094 (2.3)	74/3117 (2.4)	0.98 (0.71-1.35)	15.7
ASCOT-LLA,[20] 2003	3	154/5168 (3.0)	134/5137 (2.6)	1.14 (0.91-1.44)	21.4
HOPE-3,[14] 2016	6	232/6361 (3.6)	226/6344 (3.6)	1.02 (0.86-1.23)	20.9
JUPITER,[29] 2008	2	270/8901 (3.0)	216/8901 (2.4)	1.25 (1.05-1.49)	25.2
MEGA,[31] 2006	5	172/3013 (5.7)	164/3073 (5.3)	1.07 (0.87-1.32)	22.8
WOSCOPS,[35] 1995	5	57/2999 (1.9)	82/2975 (2.8)	0.69 (0.49-0.96)	15.0
Total (95% CI)		957/29 536 (3.2)	896/29 547 (3.0)	1.05 (0.91-1.20)	100.0

Heterogeneity: $\tau^2 = 0.02$; $\chi^2_5 = 10.46$, ($P = .06$); $I^2 = 52\%$
Test for overall effect: $Z = 0.64$ ($P = .52$)



Key Question 1b. What are the benefits of statin treatment to achieve target LDL-C levels vs other treatment strategies?

- No trial directly compared statin treatment titrated to attain target cholesterol levels vs fixed-dose treatment.
- There were no clear differences in estimates between 3 trials[18,19,31] of statins vs placebo that permitted limited dose titration (RR for cardiovascular mortality, 0.61 [95% CI, 0.37 to 1.02], I2 = 9%; and RR for composite cardiovascular outcomes, 0.63 [95%CI, 0.53 to 0.76]; I2 = 0%)

Key Question 1c. Do the benefits vary in subgroups defined by demographic or clinical characteristics?

- Seven trials reported results stratified according to various subgroups, primarily focusing on composite cardiovascular events.[14,19,20,26,29,31,35]
- There were no clear differences in relative risk estimates based on sex (6 trials),[14,19,20,26,29,31] age (7 trials),[14,19,20,26,29,31,35] race/ethnicity (2 trials),[14,29,36] baseline lipid levels (6 trials),[14,19,20,26,31,37] cardiovascular risk score (3 trials),[14,19,29] presence of hypertension (3 trials),[14,29,31] renal dysfunction (2 trials),[19,20] diabetes (2 trials),[20,31] or the metabolic syndrome (2 trials)

Key Question 2. What are the harms of statin treatment?

- Compared with placebo, statin therapy was not associated with increased risk of withdrawal due to
  - adverse events (9 trials;RR,0.95 [95% CI, 0.75 to 1.21]; I2 = 86%) [14,18,19,30-34,39]
  - serious adverse events (7 trials;RR,0.99[95%CI,0.94to 1.04]; I2 = 0%) [14, 19, 22, 24, 28, 29, 32,39]
  - any cancer (10 trials;RR, 1.02 [95% CI,0.90to 1.16]; I2 = 43%) [4,19,22,23,25,29-31,37,39]
  - fatal cancer (5 trials;RR,0.85 [95%CI, 0.59 to 1.21]; I2 = 61%),[14,18,19,26,29]
  - myalgias (7 trials; RR,0.96 [95% CI, 0.79 to 1.16]; I2 = 42%) ,[19,23,24,30,32,37,39]
  - elevated aminotransferase levels (11 trials; RR, 1.10 [95%CI, 0.90 to 1.35]; I2 = 0%)
- Statin therapy was also not associated with
  - increased risk of rhabdomyolysis (4 trials; RR, 1.57 [95%CI, 0.41 to 5.99]; I2 = 0%)[14,19,29,40] or
  - myopathy (3 trials; RR, 1.09 [95% CI, 0.48 to 2.47]; I2 = 0%;),[14,19,39] but estimates were imprecise.
- Evidence on renal dysfunction and cognitive harms was sparse but showed no clear associations.

Anmerkung/Fazit der Autoren

In adults at increased CVD risk but without prior CVD events, statin therapy was associated with reduced risk of all-cause and cardiovascular mortality and CVD events, with greater absolute benefits in patients at greater baseline risk.

Choi HD et al., 2018 [10].

Comparison of efficacy and safety of combination therapy with statins and omega-3 fatty acids versus statin monotherapy in patients with dyslipidemia A systematic review and meta-analysis

Fragestellung

We performed a systematic review and metaanalysis to determine the changes in lipid concentrations and the number of adverse events in the reported studies by comparing the effects of statin monotherapy versus combination therapy with statins and omega-3 fatty acids.

Methodik

Population:

- patients with dyslipidemia

Intervention:

- statins or fibrates

Komparator:

- placebo

Endpunkte:

- changes in lipid concentrations, including changes in total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, and other related lipid concentrations

Recherche/Suchzeitraum:

- MEDLINE (OVID and PubMed) and the Cochrane Library on January 15, 2017

Qualitätsbewertung der Studien:

- Jadad scale

Ergebnisse

Anzahl eingeschlossener Studien:

- 6 RCTs

Charakteristika der Population:

- 2 studies were classified as low quality (a score of ≤2) and 4 studies as high quality (scores of ≥3)

Qualität der Studien:

General characteristics of included studies.

Study	Study design	Population	Patients: Total (M/F)	Patients: Ages*	Treatments	Jadad score
Davidson (2007)[7]	Randomized, double-blind, placebo-controlled study	Triglyceride 200–500 mg/dL and LDL-C >10% of the subject's NCEP ATP II goal	254 (146/108)	59.8±10.4	Simvastatin 40 mg + placebo or simvastatin 40 mg + omega-3 4g daily for 8 weeks	5
Maki (2008)[8]	Randomized, crossover study	Triglycerides 200–600 mg/dL and non-HDL-C higher than the subject's NCEP ATP II goal	39 (14/267)	58.0±1.6	Simvastatin 20 mg + placebo or simvastatin 20 mg + omega-3 4 g daily for 6 weeks	2
Maki (2009)[9]	Randomized, crossover study	Triglycerides 200–600 mg/dL and non-HDL-C higher than the subject's NCEP ATP II goal	14 (5/9)	60.1±2.7	Simvastatin 20 mg + placebo or simvastatin 20 mg + omega-3 4 g daily for 6 weeks	2
Bays (2010)[10]	Randomized, double-blind, placebo-controlled study	Triglycerides 250–599 mg/dL and non-HDL-C higher than 160 mg/dL	255 (142/113)	56.0±10.8a; 56.3±9.6b	Atorvastatin 10–40 mg + placebo or atorvastatin 10–40 mg + omega-3 4 g daily for 16 weeks	5
Maki (2013)[11]	Randomized, double-blind, placebo-controlled study	Triglycerides 200–500 mg/dL	646 (382/264)	61.5±9.6a; 60.9±10.0b; 60.1±9.2c	Low-potency statins + placebo, low-potency statins + omega-3 2g or low-potency statins + omega-3 4g daily for 6 weeks*	5
Ballantyne (2015)[12]	Randomized, double-blind, placebo-controlled study	Triglycerides 200–500 mg/dL and LDL-C 40–115 mg/dL	456 (287/169)	61.2±9.4a; 61.1±10.0	Statins + placebo, statins + omega-3 2g or statins + omega-3 4g for 12 weeks*	5

apoB = apolipoprotein B, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, NCEP ATP = National Cholesterol Education Program-Adults Treatment Panel.
*Values are presented mean (range or standard deviation).

Studienergebnisse:

LDL cholesterol (A) and Total cholesterol/HDL cholesterol ratio (B)

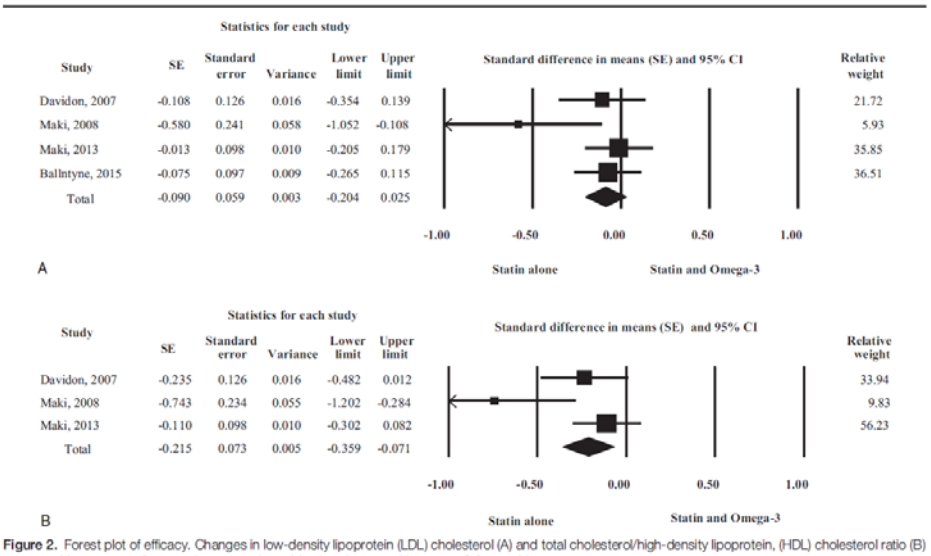


Figure 2. Forest plot of efficacy. Changes in low-density lipoprotein (LDL) cholesterol (A) and total cholesterol/high-density lipoprotein, (HDL) cholesterol ratio (B) compared between statin monotherapy and combination therapy with omega-3 fatty acid.

Total adverse events

- Two hundred fifty-two adverse events occurred in 620 patients (40.6%) treated with statin alone, and 265 adverse events occurred in 611 patients (43.4%) treated with statin plus omega- 3 fatty acid.
- There were no significant differences in total adverse events between the 2 groups.

[1] [7] Davidson MH, Stein EA, Bays HE, et al. Efficacy and tolerability of adding prescription omega-3 fatty acids 4g/d to simvastatin 40mg/d in hypertriglyceridemic patients: An 8-week, randomized, double-blind, placebo-controlled study. Clin Ther 2007;29:1354–67.
[2] [8] Maki KC, McKenney JM, Reeves MS, et al. Effects of adding prescription omega-3 acid ethyl esters to simvastatin (20 mg/day) on lipids and lipoprotein particles in men and women with mixed dyslipidemia. Am J Cardiol 2008;102:429–33.
[3] [9] Maki KC, Lubin BC, Reeves MS, et al. Prescription omega-3 acid ethyl esters plus simvastatin 20 and 80mg: effects in mixed dyslipidemia. J Clin Lipidol 2009;3:33–8.
[4] [10] Bays HE, McKenney J, Maki KC, et al. Effects of prescription omega-3- acid ethyl esters on non-high-density lipoprotein cholesterol when coadministered with escalating doses of atorvastatin. Mayo Clin Proc 2010;85:122–8.
[5] [11] Maki KC, Orloff DG, Nicholls SJ, et al. A highly bioavailable omega-3 free fatty acid formulation improves the cardiovascular risk profile in high-risk, statin-treated patients with residual hypertriglyceridemia (the ESPRIT trial). Clin Ther 2013;35:1400.e1-3–11.e1-3.
[6] [12] Ballantyne CM, Bays HE, Kastelein JJ, et al. Efficacy and safety of eicosapentaenoic acid ethyl ester (AMR101) therapy in statin-treated patients with persistent high triglycerides (from the ANCHOR study) Am J Cardiol 2012;110:984–92.

Anmerkung/Fazit der Autoren

Overall, we suggest that combination therapy with statins and omega-3 fatty acid enhances the lipid profile, except LDL cholesterol, when compared with statin monotherapy. However, controlling LDL cholesterol levels is important for preventing cardiovascular diseases and related deaths. Furthermore, safety issues with the concomitant use of statins and omega-3 fatty acid should be considered. Thus, combination therapy with statins and omega-3 fatty acid should be cautiously recommended after assessing the benefits and risks.

Chaiyasothi T et al., 2019 [9].

Effects of Non-statin Lipid-Modifying Agents on Cardiovascular Morbidity and Mortality Among Statin-Treated Patients: A Systematic Review and Network Meta-Analysis

Fragestellung

Therefore, we conducted a systematic review and a network meta-analysis to evaluate the relative treatment effects and safety of NST on cardiovascular morbidity and mortality among statin users.

Methodik

Population:

- Adults (age ≥ 18 years)

Intervention + Komparator:

- Non-statin lipid modifying agents (bile acid sequestrants (BAS), cholesteryl ester transfer protein inhibitors (CETP), ezetimibe (EZT), fibrates (FBT), microsomal transfer protein inhibitors (MTP), niacin (NIA), omega-3 fatty acids (OMG3), proprotein convertasen subtilisin/kexin-9 inhibitors (PCSK), or miscellaneous agents) among statin-treated patients, where statin was used either as monotherapy or as a part of combination therapy

- Combinations of non-statin lipid-lowering agents (NST) were also evaluated.
- Statin (ST) was used as the reference for network meta-analysis.

Endpunkte:

- CV mortality, all-cause mortality, individual (not composite) events of coronary heart disease (CHD) mortality or non-fatal myocardial infarction (MI), any stroke, or coronary revascularization

Recherche/Suchzeitraum:

- April 2018: PubMed, Embase, Cochrane Central Register of Control Trials (CENTRAL), and ClinicalTrials.gov

Qualitätsbewertung der Studien:

- GRADE, Cochrane risk of bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

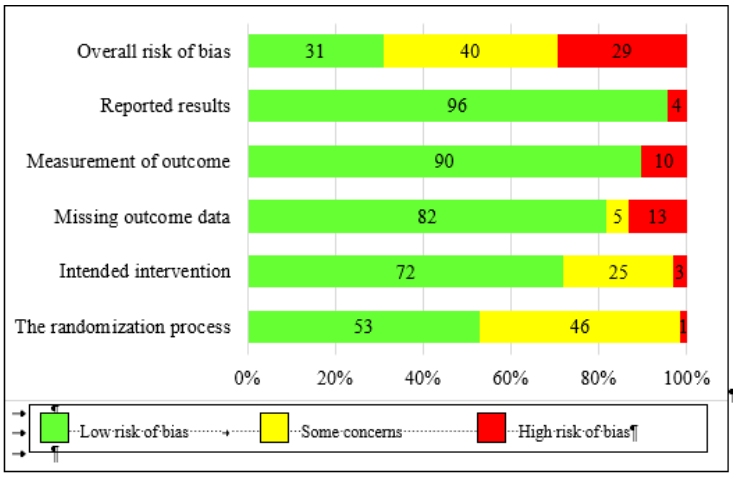
- 67 studies with 259,429 participants

Charakteristika der Population:

- Six different classes of NST including CETP, EZT, FBT, NIA, OMG3, and PCSK were used among 67 included studies. For trial design, the majority (74%) were double-blind RCT.
- Studied population in these trials were mostly high risk patients under the age of 65 who were receiving moderate to high intensity statin with mean age ranged from 45.9 to 84.1 years. It is important to note that 40% of the trial used moderate intensity of statin while another 40% used moderate to high intensity of statin. Proportion of male patients ranged from 31.5 to 93.7%.
- Most trials were secondary prevention or mixed prevention trials with small contribution (9%) of primary prevention trials. Two thirds of the trials were with a follow-up period of ≥1 year with a range of 6–72 (0.5–6 years) months of treatment duration.

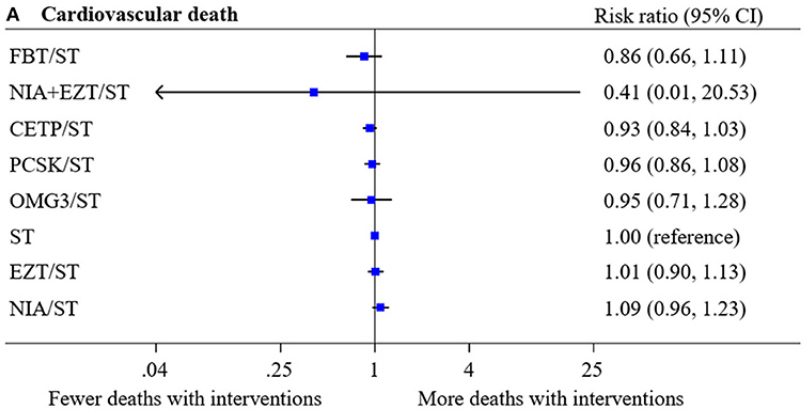
Qualität der Studien:

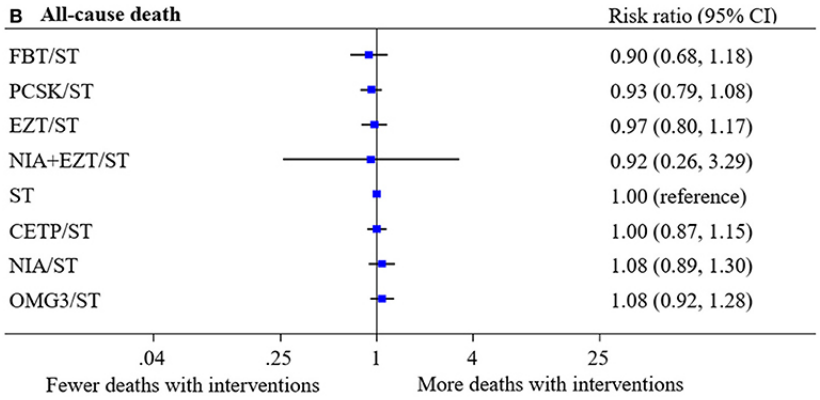
- Based on the Revised Cochrane Risk of Bias Tool for randomized trials (RoB 2.0) (Higgins et al., 2016) and 29% of studies were considered as at low risk, some concerns, and high risk of bias, respectively.
- Among five domains evaluated, inadequate description of allocation concealment and blinding process along with missing outcome data were the three most common reasons for potential bias.
- For trials with high risk of bias (20 trials with 10,812 patients which represented about 4% of total population), the majority were relatively small trials with <1,000 patients in each trial.



Studienergebnisse:

CV death and all-cause death





Only NIA/ST and NIA + EZT/ST showed a significant increase in the risk of all-cause discontinuation. Most NST significantly increased the risk of treatment discontinuations due to adverse events except PCSK/ST and EZT/ST compared with ST. A three-drug combination of NIA + EZT/ST was ranked the lowest for both safety endpoints

Anmerkung/Fazit der Autoren

In summary, our network meta-analysis suggested that none of NST significantly reduce the risk of CV death and all-cause death when added to moderate to high intensity statin therapy.

However, PCSKs and to a lesser extent, ezetimibe may help reduce cardiovascular events with acceptable tolerability profile among broad range of patients. Fibrate, CETPs, niacin, and OMG3 did not show any positive effects on CV outcomes in broad range of high risk patients. Moreover, these agents when combined with statin were associated with higher incidence of adverse reactions. Further research into the risk-benefit along with cost-effectiveness analysis of these therapeutic options should be warranted.

Ai C et al., 2018 [2].

Comparing the combination therapy of ezetimibe and atorvastatin with atorvastatin monotherapy for regulating blood lipids: a systematic review and meta-analyse

Fragestellung

The purpose of our study was to compare the combination therapy of Ezetimibe and Atorvastatin (E + A) with Atorvastatin monotherapy (A) for regulating blood lipids in the clinical application dose, and summarize the results of comparisons

Methodik

Population:

- All participants were 18 to 90 years old.

Intervention:

- Ezetimibe and Atorvastatin (E + A)

Komparator:

- Atorvastatin monotherapy (A)

Endpunkte:

- Low-density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), Total Cholesterol (TC) and Triglyceride (TG) indicators

Recherche/Suchzeitraum:

- database of PubMed, Cochrane Library and Embase from inception through October 2017

Qualitätsbewertung der Studien:

- Cochrane risk ob bias

Ergebnisse

Anzahl eingeschlossener Studien:

- 11 studies (5206 participants)

Charakteristika der Population:

- All trials were randomized, parallel-group studies and 9 trials were double-blind. The patients with LDL-C level > 70 mg/dL (at high risk of CHD) or with hypercholesterolaemia were included in the trials.

Qualität der Studien:

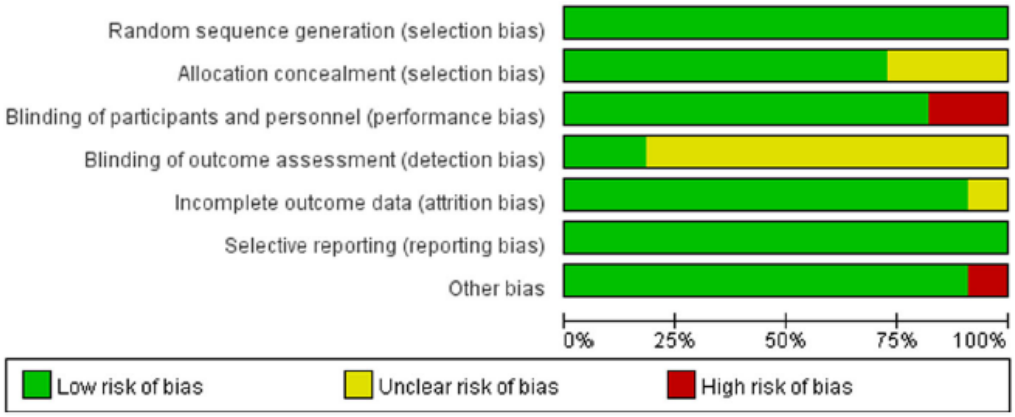


Fig. 2. Risk of bias in the included studies

Studienergebnisse:

Low-density lipoprotein cholesterol (LDL-C)

- Seventeen studies (11 publications)
- Pooled data using a fixed-effects model displayed that combination therapy led to a significant reduction in LDL-C (MD = − 15.38, 95% CI: -16.17 to −14.60, P < 0.0001) with moderate heterogeneity (P = 0.12,I2 = 26.2%)
- The results showed that the four doses were significant and the Ezetimibe 10mg (E10) + Atorvastatin 20mg (A20) vs. A40 group was the most obvious (MD = − 19.94, 95% CI: -23.61 to − 16.27, P < 0.0001), by subgroup.

High-density lipoprotein cholesterol (HDL-C)

- Seventeen studies (11 publications)
- Pooled estimates using a fixed-effects model displayed that, no heterogeneity existed among studies (P = 0.539, I2 = 0%). The results showed that the overall efficacy was significant difference between combination and monotherapy (MD = 0.95, 95% CI: 0.34 to 1.57, P = 0.002)
- The results showed that the overall efficacy was significant difference between combination and monotherapy (MD = 0.95, 95% CI: 0.34 to 1.57, P = 0.002) and the E10 + A10 vs. A20 group was the most obvious (MD = 1.58, 95% CI: 0.72 to 2.44, P = 0.0003), by subgroup.

Total cholesterol (TC)

- Seventeen studies (11 publications)
- Random-effects model was used to analyze the outcome because of the moderate heterogeneity among studies (P = 0.086, I2 = 33.7%). There was significant difference between combination and monotherapy (MD = − 9.51, 95% CI: -10.28 to − 8.74, P < 0.0001).
- The results showed that there was significant difference in the four doses and the E10 + A20 vs. A40 group was the most obvious (MD= − 12.11, 95% CI: -14.65 to − 9.58, P < 0.0001), by subgroup.

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[8] 20. Teramoto T, Sawada T, Iwamoto K, Daida H. Clinical efficacy and tolerability of ezetimibe in combination with atorvastatin in Japanese patients with hypercholesterolemia-ezetimibe phase iv randomized controlled trial in patients with hypercholesterolemia. Curr Ther Res Clin Exp. 2012;73(1–2):16–40.
[9] 21. Ben-Yehuda O, Wenger NK, Constance C, Zieve F, Hanson ME, Lin JX, et al. The comparative efficacy of ezetimibe added to atorvastatin 10 mg versus uptitration to atorvastatin 40 mg in subgroups of patients aged 65 to 74 years or greater than or equal to 75 years. J Geriatr Cardiol. 2011;8(1):1–11.
[10] 22. Zieve F, Wenger NK, Ben-Yehuda O, Constance C, Bird S, Lee R, et al. Safety and efficacy of ezetimibe added to atorvastatin versus up titration of atorvastatin to 40 mg in patients > or = 65 years of age (from the Zetia in the elderly [Zeteld] study). Am J Cardiol. 2010;105(5):656–63.
[11] 23. Stein E, Stender S, Mata P, Sager P, Ponsonnet D, Melani L, et al. Achieving lipoprotein goals in patients at high risk with severe hypercholesterolemia: efficacy and safety of ezetimibe co-administered with atorvastatin. Am Heart J. 2004;148(3):447–55.
[12] 24. Padhy BM, Yadav R, Gupta YK. Hypolipidaemic and anti-inflammatory effects of fixed dose combination of atorvastatin plus ezetimibe in Indian patients with Dyslipidaemia. Singap Med J. 2013;54(2):90–5.
[13] 25. Blagden MD, Chipperfield R. Efficacy and Safety of Ezetimibe Co-Administered with Atorvastatin in Untreated Patients with Primary Hypercholesterolaemia and Coronary Heart Disease. Curr Med Res Opin. 2007;23(4):767–75.
[14] 26. Bays HE, Conard SE, Leiter LA, Bird SR, Lowe RS, Tershakovec AM. Influence of age, gender, and race on the efficacy of adding ezetimibe to atorvastatin vs. atorvastatin up-titration in patients at moderately high or high risk for coronary heart disease. Int J Cardiol. 2011;153(2):141–7.
[15] 27. Conard SE, Bays HE, Leiter LA, Bird SR, Rubino J, Lowe RS, et al. Efficacy and safety of ezetimibe added on to atorvastatin (20 mg) versus uptitration of atorvastatin (to 40 mg) in Hypercholesterolemic patients at moderately high risk for coronary heart disease. Am J Cardiol. 2008;102(11):1489–94.
[16] 28. Conard S, Bays H, Leiter LA, Bird S, Lin J, Hanson ME, et al. Ezetimibe added to atorvastatin compared with doubling the atorvastatin dose in patients at high risk for coronary heart disease with diabetes mellitus, metabolic syndrome or neither. Diabetes Obes Metab. 2010;12(3):210–8.
[17] 29. Leiter LA, Bays H, Conard S, Bird S, Rubino J, Hanson ME, et al. Efficacy and safety of ezetimibe added on to atorvastatin (40 mg) compared with uptitration of atorvastatin (to 80 mg) in Hypercholesterolemic patients at high risk of coronary heart disease. Am J Cardiol. 2008;102(11):1495–501.

Anmerkung/Fazit der Autoren

The overall efficacy and subgroup's efficacy of combination therapy of Ezetimibe and Atorvastatin on lowering LDL-C, TC and TG was significantly better than Atorvastatin monotherapy's. The overall and the E10 + A10/ A20 group's effectiveness of combination therapy on rasing HDL-C were significantly.

AlTurki A et al., 2019 [4].

Siehe auch: Bai J et al., 2018 [7]; Dicembrini 2019 [12]**.**

Meta-analysis of Randomized Controlled Trials Assessing the Impact of Proprotein Convertase Subtilisin/Kexin Type 9 Antibodies on Mortality and Cardiovascular Outcomes

Fragestellung

We aim to evaluate the impact of PCSK9 inhibition on mortality and CV outcomes by pooling data from all available randomized controlled trials (RCTs).

Methodik

Population:

Patients with hypercholesterolemia or coronary artery disease receiving maximally tolerated statin

Intervention:

PCSK9 inhibitors

Komparator:

control (either placebo or lipid lowering therapy)

Endpunkte:

Primary: MACE defined as CV death, nonfatal MI, and nonfatal stroke

Secondary: CV death, MI, stroke, and coronary revascularization.

Recherche/Suchzeitraum:

MEDLINE, PubMed, Embase, ClinicalTrials.gov, and Web of Science up to December 1, 2018

Qualitätsbewertung der Studien:

Cochrane Risk of Bias Assessment Tool

Ergebnisse

Anzahl eingeschlossener Studien:

We included all RCTs with at least 6 months of follow-up.

There were 16 studies evaluating the effects of alirocumab and 5 for evolocumab

Table 1
Study characteristics

Study	Enrollment period	N	PCSK9 inhibitor	Comparator	CAD	Statin use	Ezetimibe (PCSK9 group/ comparator group	Mean or median follow-up (months)
DESCARTES	2012-2013	901	Evolocumab	Placebo	+ 16%	Atorvastatin 88%	21%/21%	12
FOURIER	2013- 2015	27564	Evolocumab	Placebo	+ 80%	Atorvastatin 69%	5%/5%	26
GAUSS-3	2013-2014	218	Evolocumab	Ezetemibe	+ 32%	0%	0%/100%	6
GLAGOV	2013-2015	968	Evolocumab	Placebo	+	Any statin 100%	2%/2%	18
ODYSSEY ALTERNATIVE	2012 −2013	251	Alirocumab	Ezetemibe	+ 47%	0%	0%/100%	6
ODYSSEY CHOICE I	2013-2014	803	Alirocumab	Placebo	+ 52%	Any statin 68%	14%/14%	7
ODYSSEY CHOICE II	2014	233	Alirocumab	Placebo	+ 57%	0%	60%/60%	4
ODYSSEY COMBO I	2012-2014	316	Alirocumab	Placebo	+ 78%	Any statin 100%	7%/10%	6
ODYSSEY COMBO II	2012-2013	720	Alirocumab	Ezetemibe	+ 90%	Any statin 100%	0%/100%	12
ODYSSEY DM-DYSLIPIDEMIA	2016- 2016	413	Alirocumab	Usual Care*	+ 34%	Any statin 81%	38%/38%	6
ODYSSEY DM-INSULIN		517	Alirocumab	Placebo	+ 35%	Any statin 74%	14%/8%	6
ODYSSEY FH I		486	Alirocumab	Placebo	+ 46%	Any statin 100%	56%/60%	6
ODYSSEY FH II		248	Alirocumab	Placebo	+ 36%	Any statin 100%	67%/65%	6
ODYSSEY HIGH FH	2012-2015	104	Alirocumab	Placebo	0%	Any statin 100%	14%/12%	18
ODYSSEY JAPAN	2014-2015	215	Alirocumab	Placebo	0%	Any statin 100%	-	12
ODYSSEY KT		199	Alirocumab	Placebo,	+ 97%	Any statin 100%	14%/12%	6
ODYSSEY LONG TERM		2338	Alirocumab	Placebo	+	Any statin 100%	14%/15%	20
ODYSSEY OPTIONS I	2012-2014	205	Alirocumab	Ezetimibe	+	Any statin 100%	0%/100%	6
ODYSSEY OPTIONS II	2012-2014	204	Alirocumab	Ezetimibe	+	Any statin 100%	0%/100%	6
ODYSSEY OUTCOMES	2012-2015	18924	Alirocumab	Placebo	+	Any statin 100%	3%/3%	36
OSLER	2011-2014	4465	Evolocumab	Placebo	+ 10%	Any statin 70%	13%/15%	12
SPIRE I	2013-2016	16817	Bococizumab	Placebo	+	Any statin 100%	8%/8%	10
SPIRE II	2013-2016	10621	Bococizumab	Placebo	+	Any statin 83%	13%/14%	10

N = number; PCSK9 = Proprotein convertase subtilisin/kexin type 9; CAD = coronary heart disease; FH = familial hypercholesterolemia; NR = not reported.
* Including ezetimibe, fenofibrate and omega-3 fatty acids.

Charakteristika der Population:

Table 2
Baseline patient characteristics

Study	PCSK9 inhibitor						Control					
	Age (mean) (years)	Men	HTN	DM	CAD	Mean LDL, (mg/dl)	Age (mean) (years)	Men	HTN	DM	CAD	Mean LDL, (mg/dl)
DESCARTES	56	48%	48%	10%	16%	104	57	46%	49%	14%	14%	104
FOURIER	63	75%	80%	37%	81%	92	63	76%	80%	37%	81%	92
GAUSS-3	59	54%	48%	11%	33%	218	59	47%	59%	14%	29%	221
GLAGOV	60	72%	82%	20%	100%	93	60	72%	84%	22%	100%	92
ODYSSEY ALTERNATIVE	64	56%	68%	29%	51%	179	63	54%	62%	19%	43%	188
ODYSSEY CHOICE I	61	56%		26%		127	61	61%		29%		122
ODYSSEY CHOICE II	63	57%	69%	17%	32%	158	63	53%	64%	16%	47%	159
ODYSSEY COMBO I	63	63%		45%	79%	95	63	72%		39%	78%	100
ODYSSEY COMBO II	62	75%		31%	91%	108	61	71%		32%	88%	104
ODYSSEY DM-DYSLIPIDEMIA	63	53%	87%	51%		155	63	50%	90%	58%		162
ODYSSEY DM-INSULIN	62	55%		100%	32%	114	63	55%		100%	31%	126
ODYSSEY FH I	52	56%	43%	10%	46%	143	52	58%	44%	15%	48%	143
ODYSSEY FH II	53	52%	34%	4%	35%	135	53	55%	29%	4%	38%	135
ODYSSEY HIGH FH	50	49%	56%	13%	43%	196	52	63%	60%	17%	63%	201
ODYSSEY JAPAN	60	58%		73%	32%	143	62	65%		60%	38%	143
ODYSSEY KT	60	69%		42%	54%	143	60	74%		40%	69%	140
ODYSSEY LONG TERM	60	63%		35%	68%	122	61	60%		34%	70%	121
ODYSSEY OPTIONS I	63	60%					63	60%				
ODYSSEY OPTIONS II		60%						60%				
ODYSSEY OUTCOMES	59	75%	65%	29%	100%	92	59	75%	36%	71%	100%	92
OSLER	58	50%	52%	13%	20%	120	58	51%	52%	15%	21%	121
SPIRE I	63	78%	81%	48%		94	63	78%	81%	47%		94
SPIRE II	62	66%	80%	48%		134	63	65%	81%	46%		133

PCSK9 = Proprotein convertase subtilisin/kexin type 9; HTN = hypertension; DM = diabetes mellitus; CAD = coronary heart disease; LDL = low-density lipoprotein.

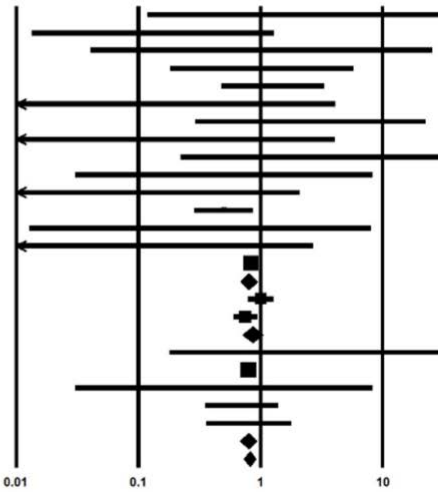
Qualität der Studien:

- All included studies had a low risk of bias as assessed by the Cochrane Collaboration bias detection tool

Studienergebnisse:

- All-cause mortality: PCSK9 inhibition was not associated with reduction in either all-cause mortality (OR 0.91, 95% CI 078 to 1.06; p = 0.22; I2 = 21%) nor in CV deaths (OR 0.95, 95% CI 0.84 to 1.07; p = 0.37; I2 = 0%) compared to controls.
- MACE: PCSK9 inhibition was associated with a 18% reduction in MACE (OR 0.82, 95% CI 0.77 to 0.87; p <0.0001; I2 = 0%) and MI (OR 0.80, 95% CI 0.71 to 0.91; p <0.0001; I2 = 20%). Results for drug subgroups:

Group by Drug	Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	PCSK9I	Control
	ODYSSEY ALTERNATIVE	2.976	0.120	73.759	0.666	0.505	1 / 126	0 / 124
	ODYSSEY CHOICE I	0.132	0.014	1.273	-1.752	0.080	1 / 573	3 / 229
	ODYSSEY CHOICE II	1.017	0.041	25.319	0.011	0.992	1 / 173	0 / 58
	ODYSSEY COMBO I	1.024	0.185	5.684	0.028	0.978	4 / 209	2 / 107
	ODYSSEY COMBO II	1.266	0.485	3.306	0.482	0.630	15 / 479	6 / 241
	ODYSSEY DM-INSULIN	0.164	0.007	4.047	-1.105	0.269	0 / 344	1 / 170
	ODYSSEY FH I	2.547	0.295	21.984	0.850	0.395	5 / 323	1 / 163
	ODYSSEY FH II	0.160	0.006	3.976	-1.118	0.264	0 / 167	1 / 81
	ODYSSEY HIGH FH	4.270	0.223	81.699	0.964	0.335	4 / 72	0 / 32
	ODYSSEY JAPAN	0.500	0.031	8.111	-0.488	0.626	1 / 143	1 / 72
	ODYSSEY KT	0.099	0.005	2.067	-1.492	0.136	0 / 345	2 / 172
	ODYSSEY LONG TERM	0.500	0.291	0.858	-2.516	0.012	27 / 1550	27 / 788
	ODYSSEY OPTIONS I	0.321	0.013	7.962	-0.694	0.488	0 / 104	1 / 101
	ODYSSEY OPTIONS II	0.136	0.007	2.666	-1.314	0.189	0 / 103	3 / 101
	ODYSSEY OUTCOMES	0.836	0.764	0.916	-3.867	0.000	977 / 9462	1145 / 9462
Alirocumab		0.802	0.690	0.932	-2.872	0.004		
	SPIRE I	1.000	0.798	1.253	0.001	0.999	154 / 8408	154 / 8409
	SPIRE II	0.752	0.605	0.934	-2.577	0.010	148 / 5312	195 / 5309
Bococizumab		0.864	0.719	1.037	-1.570	0.116		
	DESCARTES	3.550	0.183	68.946	0.837	0.403	3 / 599	0 / 302
	FOURIER	0.798	0.729	0.873	-4.916	0.000	926 / 13784	1141 / 13780
	GAUSS-3	0.500	0.031	8.110	-0.488	0.626	1 / 145	1 / 73
	GLAGOV	0.705	0.359	1.385	-1.015	0.310	15 / 484	21 / 484
	OSLER 1 and 2	0.799	0.362	1.766	-0.554	0.580	16 / 2976	10 / 1489
Evolocumab		0.795	0.681	0.927	-2.918	0.004		
Overall		0.815	0.743	0.894	-4.324	0.000		



- •Stroke and reduction in coronary revascularization: PCSK9 inhibition was also associated with 25% reduction in stroke (OR 0.75, 95% CI 0.65 to 0.85; p <0.0001; I2 = 0%) and 18% reduction in coronary revascularization (OR 0.82, 95% CI 0.77 to 0.88; p <0.0001; I2 = 0%). The results remained similar in sensitivity analyses with evaluation of either evolocumab or alirocumab separately

Anmerkung/Fazit der Autoren

In conclusion, PCSK9 inhibition was associated with reductions in MACE including MI, stroke, and coronary revascularization. There was no observed mortality benefit associated with these medications in primary and secondary prevention in patients with and without established CAD. Future analyses may identify high-risk patients who may benefit more from these agents and longer follow-up of current or new trials may show a mortality benefit.

Kommentare zum Review

- Bococizumab ist nicht zugelassen.
- Sicherheit wurde in dem Review nicht thematisiert.
- In der Arbeit von Dicembrini 2019 [12] befinden sich auch die Studien, die AlTurki in seiner Arbeit berücksichtigte. Dicembrini schloss jedoch auch Studien mit einer Dauer von weniger als 6 Monaten ein. Dadurch fanden 16 zusätzliche Studienberücksichtigung, viele mit einer Studiendauer von nur 12 Wochen. Diese wirkten sich jedoch nicht auf die Studienergebnisse, weshalb die Autoren eine ähnliche Schlussfolgerung zu AlTurki zogen.
- Eine weitere Metaanalyse von Bai 2018 [7] untersuchte eine vergleichbare Fragestellung, zog jedoch nur RCTs heran, deren Follow-up länger als 48 Wochen war. Trotz der geringeren Anzahl an Studien durch das Follow-up Kriterium sowie einer 2017 stattgefundenen Literaturrecherche kommen die Autoren zu einem vergleichbaren Fazit.

Du H et al., 2019 [13].

Proprotein convertase subtilisin/kexin 9 inhibitors in reducing cardiovascular outcomes: a systematic review and meta-analysis

Fragestellung

On the newly released clinical trials, we conducted a systematic review and meta-analysis of randomised controlled trials (RCTs) to determine the effect of PCSK9 inhibitors across all included populations of patients on the prevention of CVD.

Methodik

Population:

- patients for primary and/or secondary prevention of cardiovascular diseases or with hypercholesterolaemia/ hyperlipidaemia

Intervention:

- PCSK9 inhibitors

Komparator:

- placebo, standard care or other active lipid-lowering agents

Endpunkte:

- primary outcome was major adverse cardiovascular events (MACE).
- secondary outcomes: cardiovascular death, non-fatal myocardial infarction (MI), unstable angina, heart failure, any stroke and all-cause mortality.

Recherche/Suchzeitraum:

- MEDLINE (via OVID), EMBASE (via OVID) and Cochrane Central Register of Controlled Trials (CENTRAL, via OVID) from inception to 11 November 2018; additionally Clinicaltrials. gov

Qualitätsbewertung der Studien:

- Cochrane Risk of Bias Assessment Tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 54 trials with 97 910 patients in the analysis
- Six PCSK9 inhibitors were investigated, including alirocumab (22 trials),bococizumab (10 trials), evolocumab (19 trials), inclisiran (1 trial) LY3015014 (1 trial) and RG7652 (1 trial). Fifteen studies were phase II clinical trials and 39 were phase III

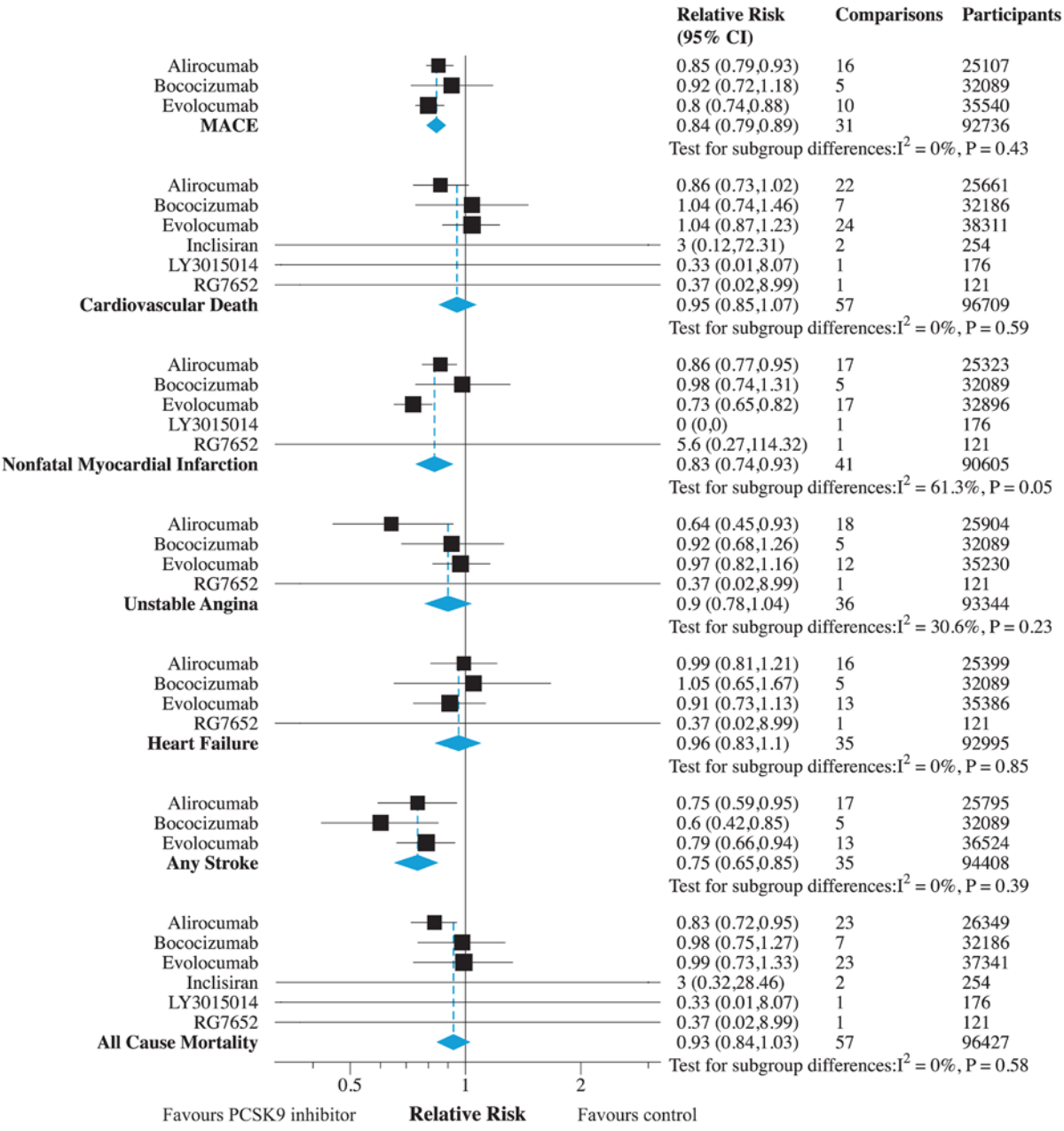
Qualität der Studien:

- All studies adequately reported random sequence generation, allocation concealment, blinding of participants and personnel. All but the open-label trials (ORION-1/2 and ODYSSEY DM-DYSLIPIDEMIA) reported methods for blinding participants and personnel and blinding outcome assessment. 51.8% of the trials were at high risk of incomplete outcome data because of over 10% of patients with missing data. SPIRE trials were at high

risk of other biases because of its premature termination due to the high rate of immunogenicity. The ODYSSEY CHOICE I was also at high risk of other biases because of the imbalanced contamination of statin consumption.

Studienergebnisse:

- Subgroup analyses based on the drug type. MACE, major adverse cardiovascular event; PCSK9, proprotein convertase subtilisin/kexin type



Anmerkung/Fazit der Autoren

In conclusion, our systematic review and meta-analysis demonstrated that PCSK9 inhibitors reduce the risk of MACE, non-fatal MI and stroke. However, pragmatic trials and well-designed observational studies with longer follow-up duration and larger sample size are warranted to further investigate the long-term effect of PCSK9 inhibitors in the real-world practice.

Kommentare zum Review

- Nur Alirocumab und Evolocumab sind in Deutschland zugelassen.
- In dem Review wurden einige Studien mit einem sehr kurzen Follow-up von 12 Wochen eingeschlossen, was geringe Ereignisraten in den Studien und verzerrte Effektschätzer zur Folge haben könnte
- Außerdem umfasst Review teils sehr heterogene Patientenpopulationen (z.B. Primär- und Sekundärprävention)
- Sicherheit wurde in der Studie nicht thematisiert

AlHajri L et al., 2017 [3].

The efficacy of evolocumab in the management of hyperlipidemia: a systematic review.

Fragestellung

To evaluate the efficacy of evolocumab among various populations with hypercholesterolemia.

Methodik

Population:

- Patients diagnosed with hyperlipidemia

Intervention:

- Evolocumab

Komparator:

- Other antidyslipidemic agents

Endpunkt:

- Nicht präspezifiziert, siehe Ergebnisteil.

Recherche/Suchzeitraum:

- ProQuest Health & Medical Complete, Google Scholar, ScienceDirect, and PubMed searched to retrieve relevant studies between the year 2012 and 2016

Qualitätsbewertung der Studien:

- Jadad Scale

Ergebnisse

Anzahl eingeschlossener Studien:

- 8 RCT

Charakteristika der Population:

- Patients with established diagnosis of dyslipidemia.
- Some of these studies used various doses and frequencies of evolocumab, while others investigated one dose only.

- Some studies compared evolocumab with other lipid-lowering agents, while others used placebo as a comparator.

Qualität der Studien:

- All studies had a score above 3 (= high quality)

Studienergebnisse:

- Descriptive analysis:
  - All studies demonstrated a statistically significant reduction in low-density lipoprotein cholesterol (LDL-C) values in the groups that received evolocumab compared with the comparator groups ($p < 0.05$).
  - The decline in LDL-C levels from baseline in the majority of studies ranged from 40% to 80%, whether used alone or in combination with other agents.
  - Also, high-density lipoprotein cholesterol, lipoprotein (a) and apolipoprotein B were improved with the use of evolocumab.

Anmerkung/Fazit der Autoren

In conclusion, the findings of this systematic review decipher the efficacy of evolocumab in dyslipidemia. In fact, the findings brought to light the manifold benefits of the medication for various lipid parameters and subfractions which are receiving more attention lately due to their close association with cardiovascular risks. Furthermore, evolocumab provides an alternative for patients who have refractory disease or develop intolerable side effects, therefore overcoming the stumbling block and helping to achieve optimal lipid management. Finally, the investigated populations represent a broad spectrum of patients (with and without known genetic disorders), hence future studies focusing on substantial populations will provide ample opportunity to learn more about the most responsive population.

Squizzato A et al., 2017 [32].

PCSK9 inhibitors for treating dyslipidemia in patients at different cardiovascular risk: a systematic review and a meta-analysis

Fragestellung

To performe a systematic review and meta-analysis of phase II and III RCTs comparing PCSK9 inhibitors with control arms.

Methodik

Population:

- Patients with dyslipidemia at different cardiovascular risk

Intervention:

- PCSK9 Inhibitoren

Komparator:

- Any comparator

Endpunkte:

Lipid profile percentage variation, cardiovascular events, deaths, and adverse events (e.g., neurocognitive events)

Recherche/Suchzeitraum:

- Up to January 2016: MEDLINE and the EMBASE electronic databases.

Qualitätsbewertung der Studien:

- Cochrane criteria
- Statistical heterogeneity was evaluated using the I2 statistic
- publication bias with Egger's test

Ergebnisse

Anzahl eingeschlossener Studien:

- 22 RCTs (Evolocumab, Bococizumab, Alirocumab)
- 13 relevant RCTs (studies included patients treated with evolocumab)
- Follow-up Period: 12 to 52 weeks

Charakteristika der Population:

- One study was in patients affected by HoFH, 3 studies in patients affected by HeFH or with equivalent cardiovascular risk, 2 studies in patients with statin intolerance, 2 studies in patients statin-naive and 3 studies in patients unable to achieve LDL-C target level despite statin therapy. Of note, 4465 patients were enrolled, after participating in a phase II/III study on evolocumab, in two studies (OSLER 1 and 2), to perform a longer follow-up on safety and efficacy (indication: hypercholesterolaemia)

Qualität der Studien:

- Since all the studies were funded by the company developing the PCSK9 inhibitor, they were all deemed high risk of bias in the ''other bias'' category.

Studienergebnisse:

Evolocumab

- LDL-C: significant reduction (mean = -53.4%; 95% CI -58.6, -48.3; I2 = 91%)
- Cardiovascular events: significant reduction (OR = 0.58; 95% CI 0.39, 0.87; I2 = 0%)
- Death of any cause: (OR = 0.41; 95% CI 0.16, 1.05; I2 = 0%)
- Safety: overall adverse events, OR 1.11 (95% CI 0.94, 1.32; I2 = 50%); serious adverse events, 1.05 (95% CI 0.87, 1.27; I2 = 0%); transaminase elevation, OR 0.75 (95% CI 0.51, 1.11; I2 = 11%); CK elevation, 0.69 (95% CI 0.45, 1.04; I2 = 0%); neurocognitive adverse events, OR 1.08 (95% CI 0.08, 15.58; I2 = 77%)

Subanalysis statin intolerance

- Two studies, totaling 215 patients treated with evolocumab 420 mg 4 W, in one study in monotherapy, in the other on top of ezetimibe, were included in the analysis. Follow-up period was of 12 weeks.

- Overall, evolocumab is associated with a statistically significant reduction of LDL-C (mean = -41.7%; 95% CI -51.9, -31.5; I2 = 66%), compared to control groups. There was one cardiovascular event although not in the treatment group analyzed here. There are no deaths observed in the follow-up period.
- Safety of evolocumab during active treatment, compared to control groups, was analyzed for the overall adverse events, OR 0.92 (95% CI 0.50, 1.71; I2 = 0%); serious adverse events, transaminase elevation, and CK elevation were reported in only one of the two studies, and as such no analysis was carried out

Anmerkung/Fazit der Autoren

In conclusion, PCSK9 inhibitors are superior to currently available lipid lowering drugs in terms of laboratory outcome, i.e., lipid profile markers and, according to data available, on clinical efficacy outcomes. Inferences about the relative efficacy and safety of individual anti-PCSK9 moAbs cannot be made due to the lack of head-to-head comparisons

Kommentare zum Review

In die Evidenzsynopse wurden ausschließlich Ergebnisse von Studien mit Evocolumab aufgenommen. Eine Studie schloss Patienten mit HoFH ein.

3.4 Leitlinien

Grundy SM et al., 2019 [18].

American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines

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

Siehe auch: Mach, F et al., 2019 [24]; Arnett DK et al., 2019 [6]; Arnett DK et al., 2019 [5]; Wong ND et al., 2020 [36]: Wilson, PWF et al., 2019 [35].

Leitlinienorganisation/Fragestellung

k.A.

Methodik

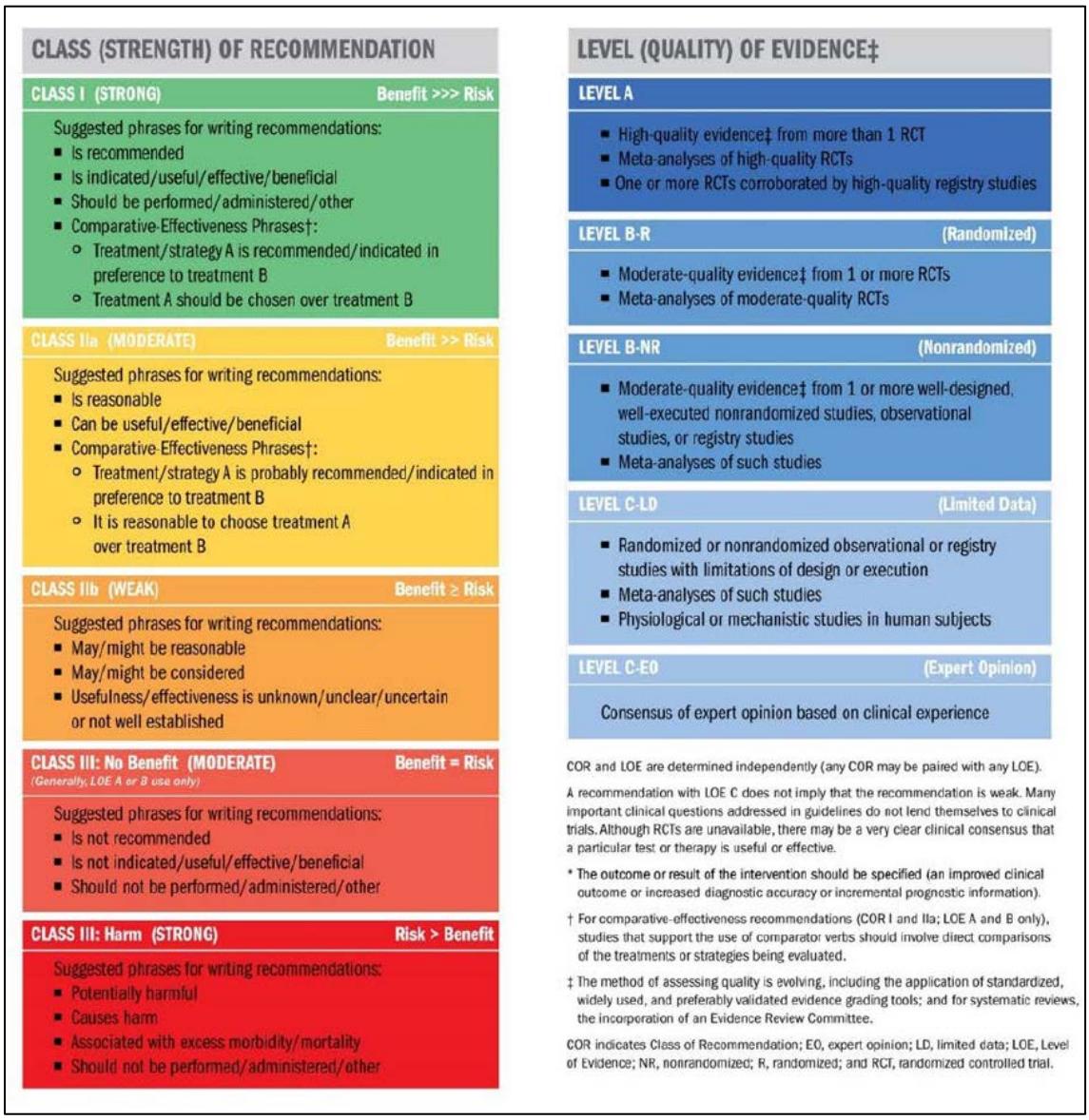
Grundlage der Leitlinie

- Repräsentatives Gremium;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

- from May 1980 to July 2017 (MEDLINE (through PubMed), EMBASE, the Cochrane Library, the Agency for Healthcare Research and Quality, and other selected databases)
- Additional relevant studies published through August 2018 during the guideline writing process, were also considered by the writing committee and added to the evidence tables when appropriate.

LoE/ GoR



CLASS (STRENGTH) OF RECOMMENDATION

CLASS I (STRONG) — Benefit >>> Risk

Suggested phrases for writing recommendations:
- Is recommended
- Is indicated/useful/effective/beneficial
- Should be performed/administered/other
- Comparative-Effectiveness Phrases†:
  - Treatment/strategy A is recommended/indicated in preference to treatment B
  - Treatment A should be chosen over treatment B

CLASS IIa (MODERATE) — Benefit >> Risk

Suggested phrases for writing recommendations:
- Is reasonable
- Can be useful/effective/beneficial
- Comparative-Effectiveness Phrases†:
  - Treatment/strategy A is probably recommended/indicated in preference to treatment B
  - It is reasonable to choose treatment A over treatment B

CLASS IIb (WEAK) — Benefit ≥ Risk

Suggested phrases for writing recommendations:
- May/might be reasonable
- May/might be considered
- Usefulness/effectiveness is unknown/unclear/uncertain or not well established

CLASS III: No Benefit (MODERATE) — Benefit = Risk
(Generally, LOE A or B use only)

Suggested phrases for writing recommendations:
- Is not recommended
- Is not indicated/useful/effective/beneficial
- Should not be performed/administered/other

CLASS III: Harm (STRONG) — Risk > Benefit

Suggested phrases for writing recommendations:
- Potentially harmful
- Causes harm
- Associated with excess morbidity/mortality
- Should not be performed/administered/other

LEVEL (QUALITY) OF EVIDENCE‡

LEVEL A
- High-quality evidence‡ from more than 1 RCT
- Meta-analyses of high-quality RCTs
- One or more RCTs corroborated by high-quality registry studies

LEVEL B-R (Randomized)
- Moderate-quality evidence‡ from 1 or more RCTs
- Meta-analyses of moderate-quality RCTs

LEVEL B-NR (Nonrandomized)
- Moderate-quality evidence‡ from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies
- Meta-analyses of such studies

LEVEL C-LD (Limited Data)
- Randomized or nonrandomized observational or registry studies with limitations of design or execution
- Meta-analyses of such studies
- Physiological or mechanistic studies in human subjects

LEVEL C-EO (Expert Opinion)

Consensus of expert opinion based on clinical experience

COR and LOE are determined independently (any COR may be paired with any LOE).

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

* The outcome or result of the intervention should be specified (an improved clinical outcome or increased diagnostic accuracy or incremental prognostic information).

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

‡ The method of assessing quality is evolving, including the application of standardized, widely used, and preferably validated evidence grading tools; and for systematic reviews, the incorporation of an Evidence Review Committee.

COR indicates Class of Recommendation; EO, expert opinion; LD, limited data; LOE, Level of Evidence; NR, nonrandomized; R, randomized; and RCT, randomized controlled trial.

Empfehlungen

3.2. Lipid-Lowering Drugs

Among lipid-lowering drugs, statins are the cornerstone of therapy, in addition to healthy lifestyle interventions. Other LDL-lowering drugs include ezetimibe, bile acid sequestrants, and PCSK9 inhibitors.

Triglyceride-lowering drugs are fibrates and niacin; they have a mild LDL-lowering action, but RCTs do not support their use as add-on drugs to statin therapy (S3.2-1).

3.2.1. Statin Therapy

The intensity of statin therapy is divided into 3 categories: high-intensity, moderate-intensity, and lowintensity (S3.2.1-1). High-intensity statin therapy typically lowers LDL-C levels by ≥50%, moderateintensity statin therapy by 30% to 49%, and low-intensity statin therapy by <30% (Table 3). Of course, the magnitude of LDL-C lowering will vary in clinical practice (S3.2.1-2).

Certain Asian populations may have a greater response to certain statins (S3.2.1-18). Pharmacokinetic profiles among statins are heterogeneous (Table S4 in the Web Supplement). Statin safety has been extensively evaluated (S3.2.1-19). Statin-associated side effects are discussed in Section 5. Common medications that may potentially interact with statins are listed in Table S5 in the Web Supplement. More information on statin drug–drug interactions can be obtained from the ACC LDL-C Manager (http://tools.acc.org/ldl) (S3.2.1-20).

Table 3. High-, Moderate-, and Low-Intensity Statin Therapy*

	High Intensity	Moderate Intensity	Low Intensity
LDL-C lowering†	≥50%	30%–49%	<30%
Statins	**Atorvastatin (40 mg‡) 80 mg** **Rosuvastatin 20 mg (*40 mg***	**Atorvastatin 10 mg** (20 mg) **Rosuvastatin** (5 mg) **10 mg** **Simvastatin 20–40 mg§**	Simvastatin 10 mg
	…	**Pravastatin 40 mg** (80 mg) **Lovastatin 40 mg** (80 mg) Fluvastatin XL 80 mg **Fluvastatin 40 mg BID** Pitavastatin 1–4 mg	**Pravastatin 10–20 mg** **Lovastatin 20 mg** Fluvastatin 20–40 mg

*Percent reductions are estimates from data across large populations. Individual responses to statin therapy varied in the RCTs and should be expected to vary in clinical practice (S3.2.1-2).
†LDL-C lowering that should occur with the dosage listed below each intensity.
‡Evidence from 1 RCT only: down titration if unable to tolerate atorvastatin 80 mg in the IDEAL (Incremental Decrease through Aggressive Lipid Lowering) study (S3.2.1-3).
§Although simvastatin 80 mg was evaluated in RCTs, initiation of simvastatin 80 mg or titration to 80 mg is not recommended by the FDA because of the increased risk of myopathy, including rhabdomyolysis.
Percent LDL-C reductions with the primary statin medications used in clinical practice (atorvastatin, rosuvastatin, simvastatin) were estimated using the median reduction in LDL-C from the VOYAGER database (S3.2.1-2). Reductions in LDL-C for other statin medications (fluvastatin, lovastatin, pitavastatin, pravastatin) were identified according to FDA-approved product labeling in adults with hyperlipidemia, primary hypercholesterolemia, and mixed dyslipidemia (S3.2.1-4).
Boldface type indicates specific statins and doses that were evaluated in RCTs (S3.2.1-3, S3.2.1-5–S3.2.1-16), and the Cholesterol Treatment Trialists' 2010 meta-analysis (S3.2.1-17). All these RCTs demonstrated a reduction in major cardiovascular events.
BID indicates twice daily; FDA, U.S. Food and Drug Administration; LDL-C, low-density lipoprotein cholesterol; RCT, randomized controlled trial; VOYAGER, an indiVidual patient data meta-analysis Of statin therapY in At risk Groups: Effects of Rosuvastatin, atorvastatin and simvastatin; and XL, extended release.

3.2.2. Nonstatin Therapies

Ezetimibe is the most commonly used nonstatin agent. It lowers LDL-C levels by 13% to 20% and has a low incidence of side effects (S3.2.2-1, S3.2.2-2). Bile acid sequestrants reduce LDL-C levels by 15% to 30% depending on the dose. Bile acid sequestrants are not absorbed and do not cause systemic side effects, but they are associated with gastrointestinal complaints (e.g., constipation) and can cause severe hypertriglyceridemia when fasting triglycerides are ≥300 mg/dL (≥3.4 mmol/L). PCSK9 inhibitors are powerful LDL-lowering drugs. They generally are well tolerated, but long-term safety remains to be proven (S3.2.2-4–S3.2.2-6). Two categories of triglyceride-lowering drugs, niacin and fibrates, may also mildly lower LDL-C levels in patients with normal triglycerides. They may be useful in some patients with severe hypertriglyceridemia, but in the present document they are not listed as LDL-lowering drugs.

3.2.3. Nonstatin Add-on Drugs to Statin Therapy

Under certain circumstances, nonstatin medications (ezetimibe, bile acid sequestrants, and PCSK9 inhibitors) may be useful in combination with statin therapy. The addition of a bile acid sequestrant or ezetimibe to a statin regimen increases the magnitude of LDL-C lowering by approximately 15% to 30% and 13% to 20%, respectively (S3.2.3-1, S3.2.3-2). The addition of a PCSK9 inhibitor to a statin regimen has been shown to further reduce LDL-C levels by 43% to 64% (S3.2.3-3, S3.2.3-4).

4. Patient Management Groups

4.1. Secondary ASCVD Prevention

Synopsis

Clinical ASCVD encompasses ACS, those with history of MI, stable or unstable angina or coronary or other arterial revascularization, stroke, TIA or PAD including aortic aneurysm, all of atherosclerotic origin. The writing group used primarily the Cholesterol Treatment Trialists' (CTT) meta-analysis (S4.1-3, S4.1-4) of statin RCTs plus 4 other RCTs (S4.1-1, S4.1-2, S4.1-38, S4.1-39). Additional RCTs have used nonstatin drugs as add-ons to statin therapy and are included here. As a primary recommendation, high-intensity statin therapy is indicated for clinical ASCVD, but if this cannot be used, moderate-intensity statin therapy can be initiated (Figure 1). The first goal is to achieve a ≥50% reduction in LDL-C levels, but if LDL-C levels remains ≥70 mg/dL (≥1.8 mmol/L) on maximally tolerated statin therapy, adding ezetimibe may be reasonable. In patients >75 years of age with ASCVD, potential benefits versus adverse effects of statin therapy should be considered before initiation of statin therapy. Finally, in very high-risk patients with multiple high-risk clinical factors, ezetimibe can be added to maximally tolerated statin therapy. Furthermore, if LDL-C levels remain ≥70 mg/dL (≥1.8 mmol/L), adding a PCSK9 inhibitor is reasonable if the cost/benefit ratio is favorable. In patients with HF due to ischemic heart disease, moderate-intensity statins may be considered.

Recommendation-Specific Supportive Text

1. CTT meta-analysis (S4.1-3, S4.1-4) showed that LDL-C lowering with statins reduces major ASCVD events. Patients with stroke (S4.1-1) or peripheral artery disease (S4.1-5) also derive these benefits. In a meta-analysis of 5 RCTs (S4.1-3), high-intensity statins compared with moderate-intensity statin therapy, significantly reduced major vascular events by 15% with no significant reduction in coronary deaths. Large absolute LDL-C reduction was associated with a larger proportional reduction in major vascular events (S4.1-4). High-intensity statin therapy generally reduces LDL-C levels by ≥50%. This percentage can be used to judge clinical efficacy. Absolute benefit from statin therapy depends on baseline LDL-C levels; the greatest absolute benefit accrues to patients with the highest baseline LDL-C levels. Percentage reduction of LDL-C levels is the most efficient means to estimate expected efficacy. An alternative to evaluating adequacy of therapy is to examine LDL-C on maximum-intensity statins. In a patient with ASCVD, if LDL-C level is ≥70 mg/dL (≥1.8 mmol/L), adding ezetimibe may be reasonable (see Recommendation 3).

2. Moderate-intensity statin therapy also reduces major vascular events and coronary heart disease (CHD) deaths in patients with ASCVD (S4.1-6, S4.1-7, S4.1-9–S4.1-13, S4.1-40). In RCTs, most of which included moderate-intensity statin therapy, there was a significant reduction in major vascular events even among those >75 years of age. Therefore, an upper age cutoff for moderate-intensity statin therapy was not identified in patients with ASCVD.

3. Patients with clinical ASCVD who are judged to be very high risk include those with a history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions (Table 4). In these patients, additional net benefit from further LDL-C lowering when LDL-C is ≥70 mg/dL (≥1.8 mmol/L) or non–HDL-C ≥100 mg/dL (≥2.6 mmol/L) by ezetimibe and 2 PCSK9 inhibitors (evolocumab and alirocumab) has been demonstrated by 3 RCTs (S4.1-15, S4.1-17, S4.1-18). This guideline makes a strong recommendation (COR I) for clinicians to add ezetimibe to maximally tolerated statin therapy as a first step in lowering LDL-C further. Although no RCT specifically tested the strategy of ezetimibe first and then a PCSK9 inhibitor, ezetimibe was allowed at entry along with statin therapy in both PCSK9 inhibitor trials (FOURIER, ODYSSEY OUTCOMES). Even so, only very small numbers (3% and 5% respectively) were on ezetimibe during these trials. The strategy of ezetimibe before PCSK9 inhibitor is recommended because ezetimibe is widely available as a generic drug and has proven safety and tolerability (S4.1-15). This approach is supported by 2 simulation studies from large populations of very high-risk patients; these reports showed that addition of ezetimibe to statin therapy will lower LDL-C to <70 mg/dL (1.8 mmol/L) in the majority of patients, leaving a minority eligible for a PCSK9 inhibitor (S4.1-41, S4.1-42). These 2 well-designed simulation studies favor the strategy of addition of ezetimibe before PCSK9 inhibitor and warrants an LOE of B-NR.

4. The FOURIER trial (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk) evaluated the PCSK9 inhibitor evolocumab among patients with ASCVD who met at least 1 major or 2 minor criteria (S4.1-17). Recruitment was limited to patients who had LDL-C >70 mg/dL (≥1.8 mmol/L) (or non–HDL-C >100 mg/dL (≥2.6 mmol/L)) on maximal statin + ezetimibe. At a median follow-up of 2.2 years, evolocumab significantly reduced composite ASCVD (15% RRR; 1.5% AAR) without neurocognitive side effects (S4.1-16, S4.1-17), The ODYSSEY OUTCOMES trial (ODYSSEY Outcomes: Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab), tested alirocumab in patients on maximal statin + ezetimibe with ACS over a median of 2.8 years, observed a 15% RRR (1.6% ARR) in composite ASCVD events (S4.1-18). Together, FOURIER and ODYSSEY OUTCOMES justify a COR of IIa for PCSK9 inhibitors (acknowledging efficacy, but at the same time recognizing that there is limited experience

with long-term tolerance of expensive monoclonal antibodies that is also inconvenient because it requires repetitive administration via the parenteral route). Because of the statistically significant results in two large RCTS showing reductions in ASCVD events in patients who had very high risk and LDL-C ≥70 mg/dL (≥1.8 mmol/L) while on maximally tolerated LDL-C lowering therapy this recommendation warrants an LOE of A. There are 2 alternative pathways to initiation of PCSK9 inhibitors: (a) in patients on maximally tolerated statin + ezetimibe; and (b) in those on maximally tolerated statin alone. The strategy of (a) statin + ezetimibe before PCSK9 inhibitor, was graded COR I for reasons given in Recommendation 3. Second, strategy (b), excluding ezetimibe, would expose more patients to the inconvenience of antibody therapy and reduce overall cost effectiveness. If patients develop 2 consecutive LDL-C levels <25 mg/dL while on a PCSK9 inhibitor, clinical judgment should be used to determine whether de-intensification of lipid lowering regimen is warranted as long-term safety of such low levels of LDL-C remains unknown.

5. In IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial) (S4.1-15), addition of ezetimibe to moderate-intensity statin therapy among patients with ACS and LDL-C levels ≥50 mg/dL (≥1.3 mmol/L) resulted in a significant ASCVD risk reduction (7% relative risk reduction [RRR]; 2% absolute risk reduction [ARR]) at a median follow-up of 6 years. The TIMI (Thrombolysis in Myocardial Infarction) Risk Score for Secondary Prevention (TRS 2ºP) is an integer-based risk stratification tool for patients with ASCVD. TRS 2ºP includes 9 readily available clinical high-risk features and was initially developed in a population of patients with MI within 2 weeks to 1 year of randomization to a thrombin receptor agonist (S4.1-43) and further validated in IMPROVE-IT (S4.1- 14). A higher number of these high-risk features was associated with a higher risk of recurrent ASCVD events. In post-ACS patients with ≥3 high-risk features, addition of ezetimibe was associated with substantial risk reduction (19% RRR; 6.3% ARR; number needed to treat, 16); those with 2 high-risk features had some benefit, whereas those with 0 or 1 additional features had no benefit (S4.1-14). Therefore, it is reasonable to initiate ezetimibe in patients with ASCVD who are on maximally tolerated statin therapy and judged to be at very high risk. For the present guideline, a definition of very high risk is amalgamated from TRS 2ºP and the recruitment criteria of 2 trials with PCSK9 inhibitors (Table 4).

6. The cost-effectiveness of using PCSK9 inhibitors for the secondary prevention of ASCVD has been evaluated in 7 published simulation models, as detailed in Section 7 (and Online Data Supplements 44 and 45). The reported incremental cost-effectiveness ratios range from $141,700 to $450,000 per added (QALY), with all but 1 model reporting “low value” (>$150,000 per QALY added). All models agree that the value provided by PCSK9 inhibitors would be significantly improved by price reductions of 70% to 85% from the mid-2018 U.S. list price of roughly $14,000 a year.

7. When high-intensity stain therapy was compared with moderate-intensity statin therapy in patients >75 years of age with ASCVD (S4.1-3), there was no heterogeneity of effect among age groups >75, >65 to ≤75, and ≤65 years. However, analyses of RCTs that compared statin therapy (mostly moderate intensity) with placebo among patients >75 years of age with ASCVD showed statistically significant reduction in major vascular events (S4.1-3). Because older adults may have a higher risk of adverse events (e.g., liver function test abnormalities), lower statin adherence, and higher discontinuation rates with high-intensity therapy (S4.1-44), a moderate-intensity statin may be preferable. Nevertheless, the decision to initiate moderate- or high-intensity statin therapy in patients >75 years of age with ASCVD should be based on expected benefit versus competing comorbidities (S4.1-23– S4.1-31).

8. This recommendation is based on the observation that the age reported in clinical trials of statin therapy in patients with ASCVD represents the patient’s age at study entry. Therefore, it is reasonable to consider continuation of high-intensity therapy in patients >75 years of age with ASCVD if they are tolerating the statin and have a low risk of competing morbidities (S4.1-23, S4.1-26, S4.1-31). RCTs (S4.1-32, S4.1-33, S4.1-35, S4.1-36) have not shown an adverse effect of statin therapy on cognition.

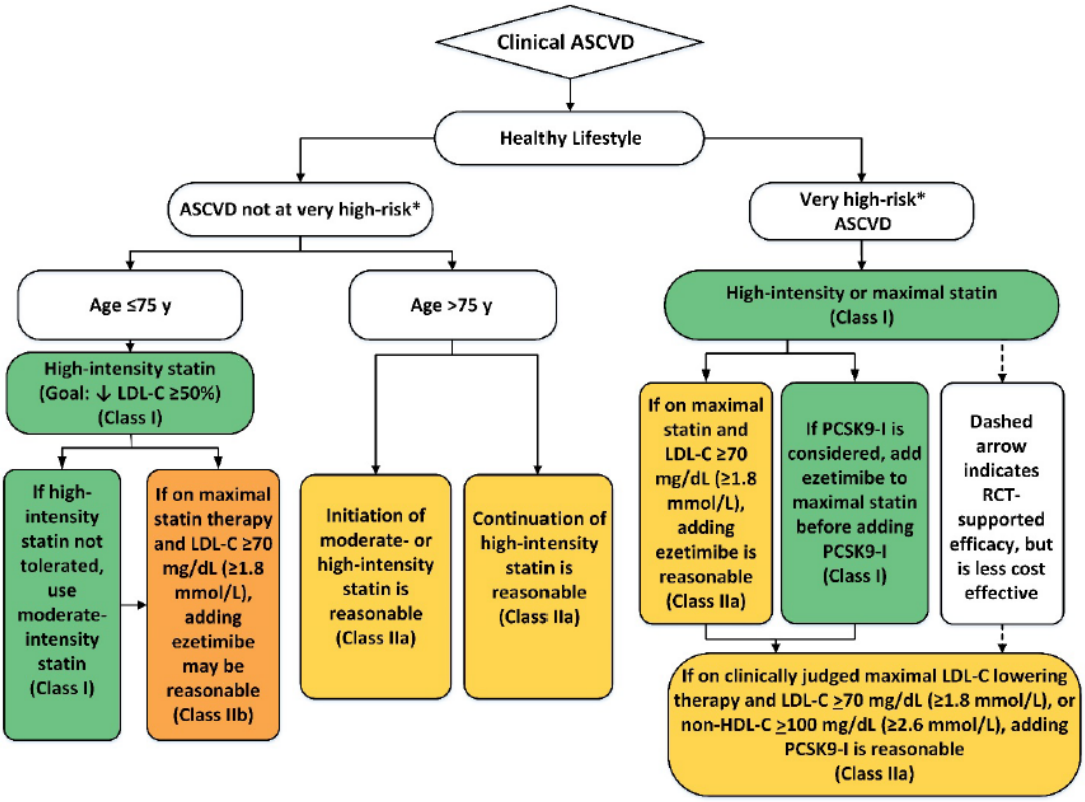
9. Although moderate-intensity statin therapy reduces ASCVD events, it is less effective than high-intensity therapy (S4.1-3). This difference presumably is due to differences in LDL-C–lowering potency. Hence, if ezetimibe were to be added to a moderate-intensity therapy to compensate for the difference in LDL-C–lowering ability between moderate- and high-intensity statins, the combination of moderate-intensity statin and ezetimibe could potentially produce a level of ASCVD risk reduction similar to that produced by high-intensity therapy alone. This hypothesis is supported by the finding that ezetimibe enhanced risk reduction when combined with moderate-intensity therapy in patients after ACS (S4.1-15). Thus, it may be reasonable to add ezetimibe to moderate-intensity therapy in patients with ASCVD for whom high-intensity therapy is indicated but cannot be used, provided their holds for any patient whose LDL-C level remains ≥70 mg/dL (≥1.8 mmol/L) on maximally tolerated statin therapy

10. The CORONA (Controlled Rosuvastatin Multinational Trial in Heart Failure) trial (S4.1-38) (patients with ischemic HF and left ventricular ejection fraction <40%) and GISSI HF trial (Effects of n-3 PUFA and Rosuvastatin on Mortality-Morbidity of Patients With Symptomatic CHF) (S4.1-45) (patients with ischemic and nonischemic HF, 9.8% with left ventricular ejection fraction >40%) evaluated the efficacy and safety of initiation of 10 mg of rosuvastatin daily compared with placebo. Neither trial met its primary outcome. Rosuvastatin reduced the risk of total hospitalizations, hospitalizations for a cardiovascular cause, and hospitalizations for worsening HF in CORONA. A subsequent analysis accounting for repeat HF hospitalizations showed significant reduction in HF hospitalizations (S4.1- 46). Post hoc analyses from CORONA showed that patients randomized to rosuvastatin with less advanced HF with reduced ejection fraction (lowest tertile of NT-proBNP) had a significant reduction in the primary outcome, but no benefit was seen among patients with more advanced HF (S4.1-47). The CORONA and GISSI studies were notable for high overall and cardiovascular mortality rates, with MI occurring in a small minority. A subsequent patient-level analysis (S4.1-37) that pooled data from both these trials and accounted for competing causes of death showed a significant 19% reduction in the risk of MI with rosuvastatin in patients with ischemic HF, although the ARR was small.

Recommendations for Statin Therapy Use in Patients With ASCVD Referenced studies that support recommendations are summarized in Online Data Supplements 6, 7, 8 and in the Systematic Review Report.		
COR	**LOE**	**Recommendations**
I	A	1. In patients who are 75 years of age or younger with clinical ASCVD,* high-intensity statin therapy should be initiated or continued with the aim of achieving a 50% or greater reduction in LDL-C levels (S4.1-1–S4.1-5).
I	A	2. In patients with clinical ASCVD in whom high-intensity statin therapy is contraindicated or who experience statin-associated side effects, moderate-intensity statin therapy should be initiated or continued with the aim of achieving a 30% to 49% reduction in LDL-C levels (S4.1-3, S4.1-6–S4.1-13).
I	B-NR	3. In patients with clinical ASCVD who are judged to be very high risk and *considered for PCSK9 inhibitor therapy,* maximally tolerated LDL-C lowering therapy should include maximally tolerated statin therapy and ezetimibe (S4.1-14, S4.1-15).
IIa	A^{SR}	4. In patients with clinical ASCVD who are judged to be very high risk and who are on maximally tolerated LDL-C lowering therapy with LDL-C 70 mg/dL (≥1.8 mmol/L) or higher or a non–HDL-C level of 100 mg/dL (≥2.6 mmol/L) or higher, it is reasonable to add a PCSK9 inhibitor following a clinician–patient discussion about the net benefit, safety, and cost (S4.1-15–S4.1-19).
IIa	B-R	5. In patients with clinical ASCVD who are on maximally tolerated statin therapy and are judged to be at very high risk and have an LDL-C level of 70 mg/dL (≥1.8 mmol/L) or higher, it is reasonable to add ezetimibe therapy (S4.1-14, S4.1-15).
Value Statement: Low Value (LOE: B-NR)		6. At mid-2018 list prices, PCSK9 inhibitors have a low cost value (>$150,000 per QALY) compared to good cost value (<$50,000 per QALY) (Section 7 provides a full discussion of the dynamic interaction of different prices and clinical benefit) (S4.1-20–S4.1-22).
IIa	B-R	7. In patients older than 75 years of age with clinical ASCVD, it is reasonable to initiate moderate- or high-intensity statin therapy after evaluation of the potential for ASCVD risk reduction, adverse effects, and drug–drug interactions, as well as patient frailty and patient preferences (S4.1-23–S4.1-31).
IIa	C-LD	8. In patients older than 75 years of age who are tolerating high-intensity statin therapy, it is reasonable to continue high-intensity statin therapy after evaluation of the potential for ASCVD risk reduction, adverse effects, and drug-drug interactions, as well as patient frailty and patient preferences (S4.1-3, S4.1-10, S4.1-23, S4.1-26, S4.1-31–S4.1-36).
IIb	B-R	9. In patients with clinical ASCVD who are receiving maximally tolerated statin therapy and whose LDL-C level remains 70 mg/dL (≥1.8 mmol/L) or higher, it may be reasonable to add ezetimibe (S4.1-15).
IIb	B-R	10. In patients with heart failure (HF) with reduced ejection fraction attributable to ischemic heart disease who have a reasonable life expectancy (3 to 5 years) and are not already on a statin because of ASCVD, clinicians may consider initiation of moderate-intensity statin therapy to reduce the occurrence of ASCVD events (S4.1-37).

*Clinical atherosclerotic cardiovascular disease (ASCVD) includes acute coronary syndrome (ACS), those with history of myocardial infarction (MI), stable or unstable angina or coronary or other arterial revascularization, stroke, transient ischemic attack (TIA), or peripheral artery disease (PAD) including aortic aneurysm, all of atherosclerotic origin.

Figure 1. Secondary Prevention in Patients With Clinical ASCVD



Colors correspond to Class of Recommendation in Table 2.

Clinical ASCVD consists of ACS, those with history of MI, stable or unstable angina or coronary other arterial revascularization, stroke, transient ischemic attack (TIA), or peripheral artery disease (PAD) including aortic aneurysm, all of atherosclerotic origin

Very high-risk includes a history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions (Table 4).

ACS indicates acute coronary syndrome; ASCVD, atherosclerotic cardiovascular disease; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; MI, myocardial infarction; and PCSK9-I, PCSK9 inhibitor.

4.2. Severe Hypercholesterolemia (LDL-C ≥190 mg/dL [≥4.9 mmol/L])

Synopsis

Patients with severe hypercholesterolemia have a high lifetime risk, and decisions about statins in these patients do not require ASCVD risk scoring. These patients derive net ASCVD risk reduction benefit from interventions that increase expression of LDL receptors. The strongest data have been derived from statin RCTs, which have demonstrated greater risk reduction with statins than with placebo and greater reduction from higher-intensity statin therapy than with moderate-intensity statin therapy. Ezetimibe plus a moderate-intensity statin is associated with greater LDL-C reduction than is statin monotherapy in patients with heterozygous FH, and the combination reduces ASCVD risk more than moderate-intensity statin monotherapy in patients who have had a recent ACS. In selected patients with severe hypercholesterolemia whose LDL-C is inadequately controlled with drug therapy, LDL apheresis is an option. Referral to a lipid specialist may be indicated.

Recommendation-Specific Supportive Text

1. Patients with primary severe hypercholesterolemia (LDL-C levels ≥190 mg/dL [≥4.9 mmol/L]) have a high-risk of ASCVD (S4.2-2, S4.2-4, S4.2-18) and premature and recurrent coronary events (S4.2-3). Although there have been no randomized, placebo-controlled trials of statin therapy done exclusively in subjects with LDL-C levels ≥190 mg/dL (≥4.9 mmol/L), a placebo-controlled primary prevention study performed in men with a mean baseline LDL-C level of 192±17 mg/dL (4.9±0.4 mmol/L) demonstrated a reduced incidence of MI and cardiovascular death in those receiving pravastatin 40 mg daily (S4.2-5). These findings were extended in a post hoc analysis of 2,560 exclusively primary-prevention subjects in that RCT and in a 20-year observational post-trial long-term follow-up study (S4.2-19). In addition, retrospective cohort studies have demonstrated that statin therapy reduces risk of incident MI (S4.2-6) and of CHD and all-cause death (S4.2-1) in patients with phenotypic or genetically confirmed FH. Because moderate- or high-intensity statins have been shown

to reduce ASCVD risk in both primary- and secondary-prevention trials and because high-intensity statins provide greater ASCVD risk reduction than moderate-intensity statins or placebo (S4.2-7), maximally tolerated statin therapy should be administered to patients with primary severe hypercholesterolemia.

2. A large placebo-controlled RCT examined the effect of simvastatin 80 mg daily, with or without ezetimibe 10 mg daily, on carotid intima-media thickness and plasma lipoproteins over 2 years. Mean LDL-C reduction was greater in the combined-therapy group, but there was no difference in carotid intima-media thickness between the 2 groups. The study was not powered to examine the risk of ASCVD events (S4.2-10). However, a very large placebo-controlled RCT examining ASCVD outcomes in post-ACS patients, performed over a period of 7 years, showed that the addition of ezetimibe 10 mg to simvastatin 40 mg daily resulted in greater ASCVD risk reduction than that produced by statin monotherapy (S4.2-8). Secondary-prevention patients with certain ASCVD risk indicators exhibit greater ASCVD risk reduction from ezetimibe therapy than do patients without these characteristics (S4.2-20). Patients with severe hypercholesterolemia who are adherent to statins, achieve <50% reduction in LDL-C levels with maximally tolerated statin therapy, and have an LDL-C level ≥100 mg/dL (≥2.6 mmol/L) are likely to derive additional ASCVD risk reduction from ezetimibe add-on therapy through additional LDL-C lowering (S4.2-9).

3. When administered to patients with severe hypercholesterolemia who are taking maximally tolerated statins with or without ezetimibe, bile acid sequestrants have demonstrated LDL-C-lowering efficacy (S4.2-11, S4.2-12). However, the clinical utility of bile acid sequestrants is limited by the absence of ASCVD outcomes data when used in combination with statins, as well as by the issues of twice-daily dosing, high pill burden, the absence of well-tolerated generic formulations, drug interactions, and the potential for triglyceride elevation. Nonetheless, in patients with very severe hypercholesterolemia, adding sequestrants to otherwise maximal cholesterol-lowering therapy in patients who are not eligible for a PCSK9 inhibitor may be considered.

4. PCSK9 inhibitors are promising drugs for treatment of FH (S4.2-9, S4.2-13–S4.2-15). Two placebo-controlled RCTs of the efficacy and safety of PCSK9 inhibitors in patients with heterozygous FH who were ≥18 years of age and taking stable, maximally tolerated statin therapy demonstrated favorable safety profiles and an additional ≥50% reduction in LDL-C (S4.2-10, S4.2-15). There are no currently available outcomes trials of PCSK9 inhibitors in patients with ASCVD heterozygous FH. In patients with LDL-C levels ≥190 mg/dL (≥4.9 mmol/L), advancing age is associated with progressively increasing ASCVD risk (S4.2-4), and age-related risk would likely apply to those with heterozygous FH because of their higher lifetime exposure to increased LDL-C concentration (S4.2-18). A long-term prospective cohort registry study of 2,404 patients with heterozygous FH (molecularly defined) taking contemporary statin with or without ezetimibe treatment regimens identified age >30 years, male sex, history of ASCVD, high blood pressure, increased waist circumference, active smoking, Lp(a) ≥50 mg/dL, and LDL-C levels ≥100 mg/dL (≥2.6 mmol/L) as independent predictors of incident ASCVD over a 5.5-year follow-up period (S4.2-14). Because other medical interventions that lower LDL-C levels via increased expression of LDL receptors reduce ASCVD risk (S4.2-9), the use of PCSK9 inhibitors in selected maximally treated patients with heterozygous FH with persistently elevated LDL-C levels may be considered after a clinician–patient discussion of the net benefits versus the cost of such therapy.

5. Regardless of whether a patient with LDL-C levels ≥190 mg/dL (≥4.9 mmol/L) is found to have a genetic mutation associated with FH, those with very high LDL-C values are most likely to achieve the greatest benefit from evidence-based LDL-C–lowering therapy. Consequently, patients who have a baseline LDL-C level ≥220 mg/dL (≥5.7 mmol/L) and an on-treatment LDL-C level ≥130 mg/dL (≥3.4 mmol/L) despite maximally tolerated statin and ezetimibe therapy may be considered for treatment with a PCSK9 inhibitor after a clinician–patient discussion of the net benefits versus the costs of such therapy.

6. The cost-effectiveness of PCSK9 inhibitors for primary prevention among patients with LDL-C levels >190 mg/dL (≥4.9 mmol/L), or with FH, has not been evaluated extensively, and their clinical effectiveness in reducing ASCVD events in these patients has also not been established. The 2 published cost-effectiveness models for primary prevention (see Online Data Supplements 44 and 45 and Section 7.) report very different results, with one suggesting an incremental cost-effectiveness ratio of $503,000 per QALY added, and the other reporting $75,000 per QALY added. Because of the lack of consistent evidence, the use of PCSK9 inhibitors has uncertain value for the primary prevention of ASCVD in patients with severe hypercholesterolemia.

Recommendations for Primary Severe Hypercholesterolemia (LDL-C ≥190 mg/dL [≥4.9 mmol/L]) Referenced studies that support recommendations are summarized in Online Data Supplements 9 and 10.		
COR	**LOE**	**Recommendations**
I	B-R	1. In patients 20 to 75 years of age with an LDL-C level of 190 mg/dL (≥4.9 mmol/L) or higher, maximally tolerated statin therapy is recommended (S4.2-1–S4.2-7).
IIa	B-R	2. In patients 20 to 75 years of age with an LDL-C level of 190 mg/dL (≥4.9 mmol/L) or higher who achieve less than a 50% reduction in LDL-C while receiving maximally tolerated statin therapy and/or have an LDL-C level of 100 mg/dL (≥2.6 mmol/L) or higher, ezetimibe therapy is reasonable (S4.2-8–S4.2-10).
IIb	B-R	3. In patients 20 to 75 years of age with a baseline LDL-C level ≥190 mg/dL (≥4.9 mmol/L), who achieve less than a 50% reduction in LDL-C levels and have fasting triglycerides ≤300 mg/dL (≤3.4 mmol/L). while taking maximally tolerated statin and ezetimibe therapy, the addition of a bile acid sequestrant may be considered (S4.2-11, S4.2-12).
IIb	B-R	4. In patients 30 to 75 years of age with heterozygous FH and with an LDL-C level of 100 mg/dL (≥2.6 mmol/L) or higher while taking maximally tolerated statin and ezetimibe therapy, the addition of a PCSK9 inhibitor may be considered (S4.2-9, S4.2-13–S4.2-15).
IIb	C-LD	5. In patients 40 to 75 years of age with a baseline LDL-C level of 220 mg/dL (≥5.7 mmol/L) or higher and who achieve an on-treatment LDL-C level of 130 mg/dL (≥3.4 mmol/L) or higher while receiving maximally tolerated statin and ezetimibe therapy, the addition of a PCSK9 inhibitor may be considered (S4.2-13–S4.2-17).
Value Statement: Uncertain Value (B-NR)		6. Among patients with FH without evidence of clinical ASCVD taking maximally tolerated statin and ezetimibe therapy, PCSK9 inhibitors provide uncertain value at mid-2018 U.S. list prices.

4.4. Primary Prevention

Primary prevention of ASCVD over the life span requires attention to prevention or management of ASCVD risk factors beginning early in life (Figure 2). One major ASCVD risk factor is elevated serum cholesterol, usually identified clinically as measured LDL-C. Screening can be performed with fasting or nonfasting measurement of lipids. In children, adolescents (10 to 19 years of age), and young adults (20 to 39 years of age), priority should be given to estimation of lifetime risk and promotion of lifestyle risk reduction. Drug therapy is needed only in selected patients with moderately high LDL-C levels (≥160 mg/dL [≥4.1 mmol/L]) or patients with very high LDL-C levels (190 mg/dL [4.9 mmol/L]). Three major higher-risk categories are patients with severe hypercholesterolemia (LDL-C levels ≥190 mg/dL [≥4.9 mmol/L]), adults with diabetes mellitus, and adults 40 to 75 years of age. Patients with severe hypercholesterolemia and adults 40 to 75 years of age with diabetes mellitus are candidates for immediate statin therapy without further risk assessment. Adults with diabetes mellitus should start with a moderate-intensity statin, and as they accrue multiple risk factors, a high-intensity statin may be indicated. In other adults 40 to 75 years of age, 10-year ASCVD risk should guide therapeutic considerations. The higher the estimated ASCVD risk, the more likely the patient is to benefit from evidence-based statin treatment. The risk discussion should also consider several “risk enhancers” that can be used to favor initiation or intensification of statin therapy. When risk is uncertain or if statin therapy is problematic, it can be helpful to measure CAC to refine risk assessment. A CAC score predicts ASCVD events in a graded fashion and is independent of other risk factors, such as age, sex, and ethnicity (S4.4-1). A CAC score equal to zero is useful for reclassifying patients to a lower-risk group, often allowing statin therapy to be withheld or postponed unless higher risk conditions are present. For patients >75 years of age, RCT evidence for statin therapy is not strong, so clinical assessment of risk status in a clinician–patient risk discussion is needed for deciding whether to continue or initiate statin treatment (S4.4-2–S4.4-21).

Primary Prevention Recommendations for Adults 40 to 75 Years of Age With LDL Levels 70 to 189 mg/dL (1.7 to 4.8 mmol/L) Referenced studies that support recommendations are summarized in Online Data Supplement 16.		
COR	**LOE**	**Recommendations**
I	A	1. In adults at intermediate-risk, statin therapy reduces risk of ASCVD, and in the context of a risk discussion, if a decision is made for statin therapy, a moderate-intensity statin should be recommended (S4.4.2-1–S4.4.2-8).
I	A	2. In intermediate-risk patients, LDL-C levels should be reduced by 30% or more, and for optimal ASCVD risk reduction, especially in high-risk patients, levels should be reduced by 50% or more (S4.4.2-1, S4.4.2-4–S4.4.2-9).
I	B-NR	3. For the primary prevention of clinical ASCVD* in adults 40 to 75 years of age without diabetes mellitus and with an LDL-C level of 70 to 189 mg/dL (1.7 to 4.8 mmol/L), the 10-year ASCVD risk of a first "hard" ASCVD event (fatal and nonfatal MI or stroke) should be estimated by using the race- and sex-specific PCE, and adults should be categorized as being at low risk (<5%), borderline risk (5% to <7.5%), intermediate-risk (≥7.5% to <20%), and high-risk (≥20%) (S4.4.2-10, S4.4.2-11).
I	B-NR	4. Clinicians and patients should engage in a risk discussion that considers risk factors, adherence to healthy lifestyle, the potential for ASCVD risk-reduction benefits, and the potential for adverse effects and drug–drug interactions, as well as patient preferences, for an individualized treatment decision (S4.4.2-12-S4.4.2-14).
IIa	B-R	5. In intermediate-risk adults, risk-enhancing factors favor initiation or intensification of statin therapy (S4.4.2-6, S4.4.2-15–S4.4.2-22).
IIa	B-NR	6. In intermediate-risk or selected borderline-risk adults, if the decision about statin use remains uncertain, it is reasonable to use a CAC score in the decision to withhold, postpone or initiate statin therapy (S4.4.2-15, S4.4.2-17, S4.4.2-23).
IIa	B-NR	7. In intermediate-risk adults or selected borderline-risk adults in whom a CAC score is measured for the purpose of making a treatment decision, AND • If the coronary calcium score is zero, it is reasonable to withhold statin therapy and reassess in 5 to 10 years, as long as higher risk conditions are absent (diabetes mellitus, family history of premature CHD, cigarette smoking); • If CAC score is 1 to 99, it is reasonable to initiate statin therapy for patients ≥55 years of age; • If CAC score is 100 or higher or in the 75th percentile or higher, it is reasonable to initiate statin therapy (S4.4.2-17, S4.4.2-23).
IIb	B-R	8. In intermediate-risk adults who would benefit from more aggressive LDL-C lowering and in whom high-intensity statins are advisable but not acceptable or tolerated, it may be reasonable to add a nonstatin drug (ezetimibe or bile acid sequestrant) to a moderate-intensity statin (S4.4.2-9).
IIb	B-R	9. In patients at borderline risk, in risk discussion, the presence of risk-enhancing factors may justify initiation of moderate-intensity statin therapy (S4.4.2-17, S4.4.2-24).

*Definition of clinical ASCVD includes acute coronary syndrome (ACS), those with history of myocardial infarction (MI), stable or unstable angina or coronary or other arterial revascularization, stroke, transient ischemic attack (TIA), or peripheral artery disease (PAD) including aortic aneurysm, all of atherosclerotic origin.

4.4.2. Primary Prevention Adults 40 to 75 Years of Age With LDL-C Levels 70 to 189 mg/dL (1.7 to 4.8 mmol/L)

Synopsis

Adults 40 to 75 years of age in primary prevention can be classified as borderline risk (10-year risk of ASCVD 5% to <7.5%), intermediate-risk (7.5% to <20%), and high-risk (20%). For -intermediate-risk patients, moderate- to high-intensity statin therapy should be considered during risk discussion of treatment options. Additional considerations favoring use of statins in intermediate-risk patients include other independent risk conditions and, in selected individuals, risk-enhancing factors associated with greater ASCVD risk (Table 6). Although the variability of percent LDL-C lowering with high-intensity statin use is wide, its efficacy is proportional to the magnitude of the LDL-C reduction obtained (S4.4.2-18). Systematic reviews indicate that those with higher baseline ASCVD risk derive greater absolute benefit from higher percent LDL-C reduction with evidence-based therapy (S4.4.2-1, S4.4.2-7). Accordingly, if a statin is given, LDL-C levels should be reduced by ≥30% and optimally by ≥50%. When there is uncertainty, consideration of risk-enhancing factors (including family history of premature ASCVD and CAC score), categorical risk factors, and selected biomarkers may inform the decision. CAC scoring is especially useful in older adults to improve specificity (S4.4.2-15). A CAC score of zero revises ASCVD risk downward and selects adults who show little benefit from starting a statin (S4.4.2-20).

Recommendation-Specific Supportive Text

1. Prior guidelines recommended moderate- or high-intensity statins as first-line LDL-C–lowering therapy in primary prevention of ASCVD after a risk discussion of treatment options. This was based on 3 large-scale exclusively primary-prevention RCTs that demonstrated that moderate-intensity statin therapy (S4.4.2-5, S4.4.2-25) and high-intensity statin therapy (S4.4.2-6) were associated with ASCVD risk reduction that outweighed the observable risks. Since those ACC/AHA 2013 guidelines, a large-scale RCT in a racially/ethnically diverse population confirmed statin benefit from a moderate-intensity dose of a statin as compared with placebo in intermediate-risk patients. That RCT enrolled men ≥55 years of age and women ≥65 years of age with at least 1 cardiovascular risk factor. In the placebo group, the 10-year risk of “hard” ASCVD was 8.7%, and the risk of the expanded ASCVD endpoint that included coronary revascularization was 10% (S4.4.2-8). After 5.6 years, those assigned to rosuvastatin 10 mg/d demonstrated significant ARR in both co-primary endpoints with an acceptable safety record. By comparison, after a median follow-up of 1.9 years, those assigned a high-intensity dose of rosuvastatin in the JUPITER RCT achieved greater LDL-C-lowering and greater reductions in ASCVD outcomes. This corroborates meta-analyses demonstrating increased net benefit of evidence-based LDL-C–lowering therapy in those at risk if greater reductions in LDL-C are attained (S4.4.2-1, S4.4.2-9).

2. If in the context of a risk discussion, maximal ASCVD risk reduction is desired, it is reasonable to use a high-intensity statin to lower LDL-C by ≥50%. This provides increased benefit, especially when 10-year ASCVD risk is ≥20%. JUPITER enrolled men ≥50 years of age and women 60 years of age with high-sensitivity C-reactive protein values 2.0 mg/L. Participants randomly assigned to 20 mg/d of rosuvastatin achieved median reductions in LDL-C of 50% and highly significant ASCVD risk reduction at 1.9 years (S4.4.2-6). The trial was stopped prematurely because of a highly significant reduction in cardiovascular death. However, wide individual variability in percent LDL-C reduction was noted. Importantly, the magnitude of the percent LDL-C reduction determined benefit (S4.4.2-18). The U.S. Preventive Services Task Force systematic review of statin therapy in primary prevention showed a reduced risk of all-cause and cardiovascular death and ASCVD events and noted greater absolute benefits in those at greater baseline risk (S4.4.2-4), consistent with other high-quality systematic reviews and meta-analyses (S4.4.2-1, S4.4.2-7, S4.4.2-24). This underscores the need for aggressive and safe risk reduction in the highest-risk groups and the need for follow-up LDL-C testing to determine adherence and adequacy of effect of the prescribed statin (S4.4.2-26).

3. In individuals 40 to 75 years of age, 10-year ASCVD risk assessment begins the clinician–patient risk discussion (S4.4.2-13, S4.4.2-26). Required information includes age, sex, and race/ethnicity; presence of diabetes mellitus or cigarette smoking and treated hypertension; and a current blood pressure level and fasting or nonfasting TC and HDL-C levels. The PCE include a stroke endpoint and race-specific coefficients. This identifies, for example, a black woman who with similar risk factors is at much higher risk than her white counterpart. The PCE were externally validated in a high-quality natural history study published shortly after the 2013 ACC/AHA cholesterol guidelines were presented (S4.4.2-11). These equations may underestimate risk in individuals of South Asian ancestry and other high-risk groups and may overestimate risk in selected lower-risk groups (S4.4.2-10). Unlike other risk estimators, the PCE use only fatal and nonfatal stroke and CHD as endpoints. Other risk estimators that include revascularization and additional cardiovascular endpoints provide risk estimates that cannot be compared directly with those given by the PCE. Finally, the potential for errors in estimating ASCVD risk at both ends of the risk curve (low risk and high-risk) as noted for individuals can be reviewed in the clinician–patient risk discussion (Table 6).

4. The present guidelines continue to emphasize the importance of a clinician–patient risk discussion (S4.4.2-12–S4.4.2-14, S4.4.2-27, S4.4.2-28). In those with a 10-year ASCVD risk of ≥7.5%, it is recommended that the discussion occur before a statin prescription is written (S4.4.2-26). This frank discussion, as recommended in the 2013 ACC/AHA cholesterol guidelines (S4.4.2-26), should consider whether ASCVD risk factors have been addressed, evaluate whether an optimal lifestyle has been implemented, and review the potential for statin benefit versus the potential for adverse effects and drug-drug interactions. Then, on the basis of individual characteristics and including an informed patient preference in shared decision-making, a risk decision about statin therapy can be made (Table 7). Clinicians should indicate that as ASCVD risk increases, so does benefit of evidence-based LDL-C– lowering therapy. They may wish to review the drug and safety sections of the present guideline and stay informed on safety information that is essential for a balanced discussion. Importantly, for those at intermediate-risk, especially those >55 years of age, risk-enhancing factors or CAC can be used to clarify risk if the risk decision is uncertain (S4.4.2-16). Risk-enhancing factors, such as family history of premature

ASCVD or an LDL-C of 160 to 189 mg/dL (4.1–4.8 mmol/L), identify individuals whose ASCVD risk may indicate risk of genetic hypercholesterolemia and hence who may benefit from a moderate- to high-intensity statin (S4.4.2-21) (Table 6).

5. In those with intermediate ASCVD risk, defined as an ASCVD risk of 7.5% to ≤20%, knowledge of risk-enhancing factors is useful in understanding patient characteristics that increase ASCVD risk both short and long-term (Table 6). As in the 2013 ACC/AHA guideline, an ASCVD score does not assign a statin; it begins the decision process, which includes consideration of risk-enhancing factors. For example, in an RCT (S4.4.2-9), a family history of premature ASCVD identified women ≥60 years of age with elevated high-sensitivity C-reactive protein but without ASCVD who benefitted from high-intensity statin therapy. Those with primary elevations of LDL-C ≥160 mg/dL (4.1 mmol/L) have elevated lifetime ASCVD risk and benefit from statin therapy (S4.4.2-21, S4.4.2-22, S4.4.2-25, S4.4.2- 29, S4.4.2-30). Increased ASCVD risk (S4.4.2-2) is seen with metabolic syndrome (S4.4.2-20); inflammatory diseases, including psoriasis (S4.4.2-31) and RA; and HIV when treated with protease inhibitors (S4.4.2-32). In women, a history of pregnancy complicated by preeclampsia and premature menopause (age <40 years) also enhances ASCVD risk (see Section 4.4.5.3.). If measured, ABI <0.9 has been shown to reclassify risk by the 2013 Risk Assessment Guidelines (S4.4.2-33). The presence of risk-enhancing factors may affect the threshold for statin initiation or intensification (see sections 4.4.2, 4.4.4, and 4.5 sections). Finally, in selected individuals, biomarkers, if measured, may identify individuals with increased risk of ASCVD events. Lp(a) levels, especially in those with a family history of premature ASCVD, can increase risk (S4.4.2-16). However, no available RCT evidence supports Lp(a) levels as a target of therapy. Moderate primary elevations of triglycerides, non–HDL-C (TC minus HDL-C), and, if measured, apolipoprotein B (apoB) can improve selection of those at increased ASCVD risk (S4.4.2-22).

6. Evidence shows that a CAC score of zero can “down-risk” individuals who otherwise would qualify for a statin on the basis of their ASCVD 10-year risk. The ability to select those who would benefit greatly from statin therapy, as shown by RCTs in primary-prevention populations (S4.4.2-6, S4.4.2-8) and yet to withhold statin therapy in those least likely to benefit would improve specificity (S4.4.2-34). For example, a CAC score of zero in an analysis of pooled U.S. population-based studies accurately discriminated between lower and higher CHD risk in older adults (S4.4.2-19, S4.4.2-27).The BioImage Study in older adults (S4.4.2-15) and MESA (S4.4.2-17) showed improved detection of individuals not likely to benefit from statins when the CAC score was zero. Selected examples of candidates for CAC scoring who might benefit from knowing their CAC score is zero are listed in Table 8. Clinicians should not down-risk patients who are persistent cigarette smokers, have diabetes mellitus, or have a strong family history of ASCVD, as well as possibly those with chronic inflammatory conditions whose CAC of zero does not rule out risk from noncalcified plaque (S4.4.2-35).

7. In adults at intermediate-risk (predicted 10-year risk of 7.5% to <20%), substantial data indicate how CAC measurement can be effective in meaningfully reclassifying risk in a large proportion of individuals (S4.4.2-15, S4.4.2-17, S4.4.2-36–S4.4.2-49). In such intermediate-risk adults, those with a CAC score ≥100 Agatston units or CAC ≥75th percentile appear to have ASCVD event rates suggesting that statin therapy would be beneficial (S4.4.2-17, S4.4.2-23). Those with a CAC of zero appear to have 10-year event rates in a lower range that suggests statin therapy may be of limited value for these patients, with few exceptions including patients with diabetes mellitus, persistent smoking, and family history or premature ASCVD. Cigarette smoking remains a strong risk factor even in the presence of CAC score of zero (S4.4.2-50, S4.4.2-51). In asymptomatic diabetes mellitus, a CAC score of zero is associated with a favorable 5-year prognosis; but after 5 years, the risk of mortality increases significantly for diabetic individuals even in the presence of a baseline CAC score of zero (S4.4.2-52). In patients with a family history of ASCVD, CAC score of zero and may impart less short-term benefit from statin therapy; but considering a high lifetime risk, long-term benefit cannot be discounted (S4.4.2-53). The same holds for CAC score of zero and a high 10 year risk (e.g., ≥20%) (S4.4.2-34). For those with CAC scores of 1 to 99 Agatston units, 10-year ASCVD event rates are 3.8%, 6.5%, and 8.3% for age groups 45 to 54, 55 to 64, and 65 to 74 years (S4.4.2-23), suggesting that CAC scores in this range favor statin initiation only in adults >55 years of age and indicating that risk reclassification is modest for individuals with CAC scores of 1 to 99. Therefore, for patients with CAC scores of 1 to 99, it is reasonable to repeat the risk discussion. If these patients remain untreated, repeat CAC measurement in 5 to 10 years may have some value in reassessing for CAC progression, but data are limited (S4.4.2-12, S4.4.2-13). A systematic review and meta-analysis suggests that knowledge that a patient’s CAC score is greater than zero is beneficial (S4.4.2-38). Selected examples of candidates for CAC scoring who might benefit from knowing that their CAC score is zero are listed in Table 8. There is an increased likelihood that lifestyle therapies and drug therapy will be started or continued with significant, albeit modest, changes in risk factor levels and predicted risk levels.

8. Clinicians may need to address reducing ASCVD risk in higher-risk primary-prevention patients who either do not wish to take a statin or cannot tolerate the recommended intensity of statin therapy. In such patients, it may be reasonable to use LDL-C–lowering drugs that have been proven safe and effective in RCTs, either as monotherapy or combined with a statin (S4.4.2-9). One alternative is a cholesterol absorption inhibitor. An RCT in adults ≥40 years of age with advanced CKD and without known CHD at baseline found that the addition of ezetimibe to a moderate-intensity statin lowered LDL-C 43 mg/dL (1.1 mmol/L) at 1 year. (S4.4.2-54). After a median 4.9 years, ezetimibe and simvastatin 40 mg per day resulted in a 17% proportional reduction in major atherosclerotic events compared with placebo (S4.4.2-2). Another alternative is a nonsystemic bile acid sequestrant. Bile acid sequestrants used as monotherapy reduced CHD endpoints in a large primary-prevention trial (S4.4.2-55). Bile acid sequestrants can bind other drugs, so other medications must be avoided for 1 hour before and at least 3 to 4 hours after administration. Adding psyllium can minimize constipation and can reduce the bile acid sequestrant dose (S4.4.2-56). These therapies should be considered in the context of a risk discussion that reviews potential for benefit along with tolerability and safety issues.

9. Benefit from statin therapy is seen in lower-risk individuals (S4.4.2-24).. Consideration of enhancing factors in selected younger individuals in this lower risk range, will improve the ability to detect younger patients who develop MI before age 50 years (S4.4.2-58, S4.4.2-59). Nonetheless, the challenge among those in a lower ASCVD risk category is to include those who would benefit yet avoid casting too wide a net, to minimize treating those who would derive little benefit from statin assignment. This risk group benefits greatly from a clinician–patient risk discussion. To arrive at a shared risk

decision, clinicians should assess the patient's priorities for health care, perceived ASCVD risk, and prior risk-reduction experiences and should use best practices to communicate numerical risk (S4.4.2-27). The presence of risk-enhancing factors provides useful information about short term ASCVD risk favoring initiation of statin therapy (Table 6) (S4.4.2-58). Although a CAC score can be useful in selected individuals, it will be positive less often in this lower-risk group than in those with higher levels of ASCVD risk and is not recommended routinely (S4.4.2-17).

4.4.4. Primary Prevention in Other Age Groups

4.4.4.1. Older Adults

Additional recommendations for adults >75 years of age are included in Section 4.1. (Secondary ASCVD Prevention) and Section 4.3. (Diabetes Mellitus in Adults).

Synopsis

Mounting risk factors and subclinical disease are endemic in the rapidly growing population of older adults. Data from RCT (S4.4.4.1-1–S4.4.4.1-4) and a related meta-analysis (S4.4.4.1-5) support primary prevention with statin therapy in older adults up to age 79 years, but some studies do not (S4.4.4.1-12). Nonetheless, data in older subsets (≥80 years of age) remain sparse (S4.4.4.1-6–S4.4.4.1-8). Furthermore, as adults grow older they are more susceptible to statin-related risks (S4.4.4.1-13–S4.4.4.1-15), including those that arise from altered pharmacokinetics and pharmacodynamics, as well as the impact of side effects on health issues such as multimorbidity, polypharmacy, frailty, and cognitive decline. In some patients, the aggregate risks associated with statins may exceed their likely benefits. Limited life spans may also undercut the minimum time for likely statin benefits, especially the 4 to 5 years associated with statins' stroke-reducing benefits (S4.4.4.1-15). Decisions to not initiate statins, or even to deprescribe them, are reasonable in older adults when aggregate risks outweigh potential for meaningful benefit (S4.4.4.1-9, S4.4.4.1-16–S4.4.4.1-18). A shared decision-making process between clinicians and patients that targets individualized decisions is warranted, with regular reassessments over time. CAC determination (S4.4.4.1-10, S4.4.4.1-11) focuses statin therapy on those who benefit most. For older adults with CAC scores of zero, the likelihood of benefits from statin therapy does not outweigh the risks.

Recommendation-Specific Supportive Text

1. An RCT enrolling 5,084 men and women 70 to 82 years of age showed no benefit from pravastatin 40 mg/d versus placebo in the primary-prevention subgroup (S4.4.4.1-12). Another RCT using pravastatin 40 mg per day versus usual care in older adults showed no statin benefit (S4.4.4.1-19) but there were important concerns about both adherence in those assigned to pravastatin and drop-in statin therapy in those assigned to usual care (S4.4.4.1-1, S4.4.4.1-2, S4.4.4.1-4). A recent meta-analysis (S4.4.4.1-3) combining data from JUPITER and HOPE-3 in those ≥70 years of age showed a statistically significant 26% RRR for nonfatal MI, nonfatal stroke, or cardiovascular death. A prospective cohort study (S4.4.4.1-5) comparing healthy older patients (age ≥70 years) who used statins with those who did not showed significantly lower risk of death but nonsignificant cardiovascular event reduction in the statin group. Other recent meta-analyses (S4.4.4.1-6–S4.4.4.1-8) support primary prevention for adults in their 70s. Thus, clinician–patient discussion of risk versus benefit remains particularly important with inconsistent support and few data for adults >80 years of age. Even a small increase in geriatric-specific adverse effects with statins could offset any cardiovascular benefit (S4.4.4.1-20). Statins may be indicated if, after a clinician–patient discussion, the potential for benefit is thought to outweigh the risks of adverse effects, drug–drug interactions, and cost.

2. A counterpoint to the rationale for statin therapy in primary prevention for adults of older ages is the compelling rationale to discontinue therapy in older adults with severe age-related management complexities. Customary risks associated with statins may be intensified by age (e.g., myalgias) (S4.4.4.1-9) and distinctive risks may also develop because of the broader age context (e.g., multimorbidity, polypharmacy, sarcopenia, falls, frailty, and cognitive decline) (S4.4.4.1-15), potentially confounding effective statin therapy. Aggregate risks increase with age and may become disproportionate to the extent that risks outweigh potential for meaningful benefit. Deprescribing statins becomes an important option to be considered (S4.4.4.1-18). Related studies are evolving, particularly in the palliative care domain. One randomized trial (S4.4.4.1-9) and several nonrandomized studies (albeit of relatively lower quality) show feasibility and utility of deprescribing in older adults with significant management complexity (S4.4.4.1-16, S4.4.4.1-17). Nonetheless, these studies also show that decisions about statins are not intuitive because many frailer or more complex patients may prefer to stay on statins precisely because they are at greatest cardiovascular risk (S4.4.4.1-16). Therefore, it is warranted that decisions about statin therapy be individualized and derived from clinician–patient discussions. Moreover, given the predictable fluctuations of health dynamics, such shared decisions should be reconsidered regularly.

3. Multiple studies indicate the utility of CAC measurement in identifying the absence of atherosclerotic pathophysiology in older adults (S4.4.4.1-10, S4.4.4.1-11) Moreover, with reduced costs, the long-term consequences of using low-dose computed tomography for CAC screening are much less concerning for older patients. If CAC score is zero, the patient may be reclassified to a lower-risk status to avoid statin therapy (S4.4.4.1-11).The BioImage study also indicated that scanning for carotid plaque did not down-classify as many individuals as did a CAC score of zero but still improved specificity of statin assignment (S4.4.4.1-11). Limiting statin therapy to those with CAC scores greater than zero, combined with clinical judgment and patient preference, could provide a valuable awareness with which to inform shared decision-making.

Primary Prevention Recommendations for Adults 40 to 75 Years of Age With LDL Levels 70 to 189 mg/dL (1.7 to 4.8 mmol/L) Referenced studies that support recommendations are summarized in Online Data Supplement 16.		
COR	**LOE**	**Recommendations**
I	A	1. In adults at intermediate-risk, statin therapy reduces risk of ASCVD, and in the context of a risk discussion, if a decision is made for statin therapy, a moderate-intensity statin should be recommended (S4.4.2-1–S4.4.2-8).
I	A	2. In intermediate-risk patients, LDL-C levels should be reduced by 30% or more, and for optimal ASCVD risk reduction, especially in high-risk patients, levels should be reduced by 50% or more (S4.4.2-1, S4.4.2-4–S4.4.2-9).
I	B-NR	3. For the primary prevention of clinical ASCVD* in adults 40 to 75 years of age without diabetes mellitus and with an LDL-C level of 70 to 189 mg/dL (1.7 to 4.8 mmol/L), the 10-year ASCVD risk of a first "hard" ASCVD event (fatal and nonfatal MI or stroke) should be estimated by using the race- and sex-specific PCE, and adults should be categorized as being at low risk (<5%), borderline risk (5% to <7.5%), intermediate-risk (≥7.5% to <20%), and high-risk (≥20%) (S4.4.2-10, S4.4.2-11).
I	B-NR	4. Clinicians and patients should engage in a risk discussion that considers risk factors, adherence to healthy lifestyle, the potential for ASCVD risk-reduction benefits, and the potential for adverse effects and drug–drug interactions, as well as patient preferences, for an individualized treatment decision (S4.4.2-12-S4.4.2-14).
IIa	B-R	5. In intermediate-risk adults, risk-enhancing factors favor initiation or intensification of statin therapy (S4.4.2-6, S4.4.2-15–S4.4.2-22).
IIa	B-NR	6. In intermediate-risk or selected borderline-risk adults, if the decision about statin use remains uncertain, it is reasonable to use a CAC score in the decision to withhold, postpone or initiate statin therapy (S4.4.2-15, S4.4.2-17, S4.4.2-23).
IIa	B-NR	7. In intermediate-risk adults or selected borderline-risk adults in whom a CAC score is measured for the purpose of making a treatment decision, AND • If the coronary calcium score is zero, it is reasonable to withhold statin therapy and reassess in 5 to 10 years, as long as higher risk conditions are absent (diabetes mellitus, family history of premature CHD, cigarette smoking); • If CAC score is 1 to 99, it is reasonable to initiate statin therapy for patients ≥55 years of age; • If CAC score is 100 or higher or in the 75th percentile or higher, it is reasonable to initiate statin therapy (S4.4.2-17, S4.4.2-23).
IIb	B-R	8. In intermediate-risk adults who would benefit from more aggressive LDL-C lowering and in whom high-intensity statins are advisable but not acceptable or tolerated, it may be reasonable to add a nonstatin drug (ezetimibe or bile acid sequestrant) to a moderate-intensity statin (S4.4.2-9).
IIb	B-R	9. In patients at borderline risk, in risk discussion, the presence of risk-enhancing factors may justify initiation of moderate-intensity statin therapy (S4.4.2-17, S4.4.2-24).

*Definition of clinical ASCVD includes acute coronary syndrome (ACS), those with history of myocardial infarction (MI), stable or unstable angina or coronary or other arterial revascularization, stroke, transient ischemic attack (TIA), or peripheral artery disease (PAD) including aortic aneurysm, all of atherosclerotic origin.

4.4.4.2. Young Adults (20 to 39 Years of Age)

Much of atherosclerosis begins in young adulthood (S4.4.4.2-1). Progression of atherosclerosis thereafter becomes clinically manifest as ASCVD in middle age or later years. Thus, prevention of clinical ASCVD optimally begins early in life. In children or adolescents, atherosclerosis may begin to appear in those with hypercholesterolemia; in this age range, more aggressive cholesterol-lowering may be indicated. Development of atherosclerosis in young adults most commonly is multifactorial and occurs most rapidly in individuals with multiple risk factors (e.g., hypercholesterolemia, hypertension, cigarette smoking, diabetes mellitus, and obesity) (S4.4.4.2-2).

As discussed in these guidelines (Section 4.2.) FH often goes undiagnosed. Young adults with primary elevations of LDL-C ≥190 mg/dl have a long-term ASCVD burden (S4.4.4.2-3), and statin therapy is recommended. In adults with hypercholesterolemia, cascade screening often identifies other family members with elevated LDL-C (Section 4.2.).

However even moderate hypercholesterolemia can accelerate development of atherosclerosis (S4.4.4.2-4). Secondary causes of elevated cholesterol (hypothyroidism (TSH), obstructive liver disease (liver panel), renal disease and nephrosis (creatinine and urine analysis) as well as dietary and medication history should be addressed appropriately (S4.4.4.2-5). Elevations of LDL-C persisting after excluding secondary causes suggests genetic forms of hypercholesterolemia. Young adults who experience prolonged exposure to hyperlipidemia prior to age 55 are shown to have significantly increased risk of coronary heart disease (S4.4.4.2-6). Intensive lifestyle change has the potential to reduce the hyperlipidemia and associated ASCVD risk factor burden.

A smaller group, but even at higher risk, are young adults with persistent, moderate hypercholesterolemia (LDL-C 160-189 mg/dL), especially when risk-enhancing factors, such as a family history of premature ASCVD, are present. Since there is increased probability of genetic FH in this LDL-C range, clinical judgment would suggest that these high risk young adults will benefit from long-term statin therapy (S4.4.4.2-7) (Section 4.2.). Indeed, it has been shown that those with higher LDL-C can gain as much or more benefit from cholesterol reduction as do those with lower pretreatment LDL-C but at higher risk (S4.4.4.2-8, S4.4.4.2-9).

In young adults without phenotypically severe hypercholesterolemia, risk assessment should begin by estimation of lifetime risk (S4.4.4.2-10). The pooled cohort equations (PCE) can be used to estimate lifetime risk starting at age 21 years (see Section 4.4.2.). This information can inform a focused risk discussion designed to improve high-risk lifestyle behaviors including tobacco use, sedentary lifestyle and/or poor diet (S4.4.4.2-11, S4.4.4.2-12). When young adults with hypercholesterolemia or multiple risk factors are identified, lifestyle intervention is indicated. To date, no long-term RCTs with cholesterol-lowering drugs have been carried out in those 20 to 39 years age. However, a primary prevention RCT in those younger individuals at low to moderate short-term risk, but at high lifetime risk has been proposed (S4.4.4.2-13).

One approach to identifying young adults who could benefit from statins or drug combination would be to detect significant coronary atherosclerosis with coronary artery calcium (CAC) scores. Its use for this purpose has been suggested (S4.4.4.2-14). But again, absence of RCT data precludes guideline recommendations at this time.

4.5.2. Hypertriglyceridemia

Synopsis

Two categories of elevated triglycerides consist of moderate hypertriglyceridemia (fasting or nonfasting triglycerides 150-499 mg/dL [1.6-5.6 mmol/L]) and severe hypertriglyceridemia (fasting triglycerides ≥500 mg/dL [≥5.6 mmol/L]). In the former, excess triglycerides are carried in VLDL. In the latter, most patients

Recommendation-Specific Supportive Text

1. In patients with moderate hypertriglyceridemia, it is reasonable to reduce both atherogenic VLDL and associated risk factors by nonpharmacological means where possible. This can best be achieved by identification and treatment of the multiple underlying causes of elevated triglycerides (e.g., lifestyle causes, secondary disorders, and triglyceride-raising drugs) (S4.5.2-1). Triglyceride-raising drugs include oral estrogens, tamoxifen, raloxifene, retinoids, immunosuppressive drugs (cyclosporine, sirolimus, tacrolimus), beta blockers, interferon, atypical antipsychotic drugs, protease inhibitors, thiazide diuretics, glucocorticoids, rosiglitazone, bile acid sequestrants, L-asparaginase, and cyclophosphamide.

2. Most patients with severe hypertriglyceridemia have multiple ASCVD risk factors and are at enhanced risk of developing atherosclerotic disease (S4.5.2-3–S4.5.2-5, S4.5.2-9). This risk is conveyed by atherogenic VLDL plus other factors, such as obesity, metabolic syndrome, and hyperglycemia. Although chylomicronemia per se may not be atherogenic, in most patients it associates with other atherogenic factors (S4.5.2-10–S4.5.2-13). For this reason, initiation of statin therapy is reasonable. We stress that statins alone cannot prevent increasing levels of triglycerides in the face of secondary causes (see Recommendation 1) from triggering acute hypertriglyceridemic pancreatitis. Indeed, in the pregnant woman with severe hypertriglyceridemia, statins are not part of the treatment regimen because they are not recommended at the present time in pregnancy. (See Section 5., “Statin Safety and Statin-Associated Side Effects.)

3. Epidemiological studies show that patients with moderate hypertriglyceridemia generally are at increased risk of ASCVD (S4.5.2-2–S4.5.2-4). Few studies that primarily recruited patients with hypertriglyceridemia have been carried out with triglyceride-lowering drugs. Statin therapy reduces VLDL similarly to fibrates (S4.5.2-5), and statin trials include hypertriglyceridemic patients. Indeed, there is evidence to show that VLDL excess increases the patient’s ASCVD risk and hence benefit from statin therapy (S4.5.2-6). Therefore, if an adult patient with moderate hypertriglyceridemia has poorly

controlled major risk factors for ASCVD and a 10-year risk of ASCVD ≥7.5% by the PCE, it is reasonable to either initiate or intensify statin therapy. (See Section 4.4.2., "Primary Prevention in Adults 40 to 75 Years of Age.")

4. Most patients with triglycerides ≥500 mg/dL (≥5.6 mmol/L) have elevations of both VLDL and chylomicrons. Elevations of chylomicrons typically are present when triglycerides are ≥500 mg/dL (≥5.6 mmol/L), and chylomicronemia may cause acute pancreatitis. The higher the triglyceride level, the greater is the risk (S4.5.2-7). Patients with triglycerides in the 500- to 999-mg/dL (5.6- to 11.2- mmol/L) range are at risk of developing unrecognized marked increases in triglycerides, leading to pancreatitis. Most cases of severe hypertriglyceridemia have a genetic component, but secondary factors may contribute (S4.5.2-9, S4.5.2-14). To prevent acute pancreatitis, it is reasonable to reduce triglycerides whenever levels exceed 500 mg/dL (5.6 mmol/L). This reduction can be achieved by addressing and eliminating the underlying factors as described in Recommendation 1, implementing a very low-fat diet (S4.5.2-9), and adding fibrates or omega-3 fatty acids for patients with persistently elevated severe hypertriglyceridemia (S4.5.2-15). These are the most reliable pharmacological therapies to reduce triglycerides to a safer level. If a fibrate is necessary in a patient being treated with a statin, it is safer to use fenofibrate than gemfibrozil because of lower risk of severe myopathy (S4.5.2-16). Severe or life-threatening hypertriglyceridemia during pregnancy is best managed in consultation with a lipid specialist (S4.5.2-17).

Recommendations for Hypertriglyceridemia

Referenced studies that support recommendations are summarized in Online Data Supplements 31 and 32.

COR	LOE	Recommendations
I	B-NR	1. In adults 20 years of age or older with moderate hypertriglyceridemia (fasting or nonfasting triglycerides 175 to 499 mg/dL [1.9 to 5.6 mmol/L]), clinicians should address and treat lifestyle factors (obesity and metabolic syndrome), secondary factors (diabetes mellitus, chronic liver or kidney disease and/or nephrotic syndrome, hypothyroidism), and medications that increase triglycerides (S4.5.2-1).
IIa	B-R	2. In adults 40 to 75 years of age with moderate or severe hypertriglyceridemia and ASCVD risk of 7.5% or higher, it is reasonable to reevaluate ASCVD risk after lifestyle and secondary factors are addressed and to consider a persistently elevated triglyceride level as a factor favoring initiation or intensification of statin therapy (see Section 4.4.2.) (S4.5.2-2–S4.5.2-6).
IIa	B-R	3. In adults 40 to 75 years of age with severe hypertriglyceridemia (fasting triglycerides ≥500 mg/dL [≥5.6 mmol/L]) and ASCVD risk of 7.5% or higher, it is reasonable to address reversible causes of high triglyceride and to initiate statin therapy (S4.5.2-3–S4.5.2-5, S4.5.2-7, S4.5.2-8).
IIa	B-NR	4. In adults with severe hypertriglyceridemia (fasting triglycerides ≥500 mg/dL [≥5.7 mmol/L]), and especially fasting triglycerides ≥1000 mg/dL (11.3 mmol/L)), it is reasonable to identify and address other causes of hypertriglyceridemia), and if triglycerides are persistently elevated or increasing, to further reduce triglycerides by implementation of a very low-fat diet, avoidance of refined carbohydrates and alcohol, consumption of omega-3 fatty acids, and, if necessary to prevent acute pancreatitis, fibrate therapy (S4.5.2-7, S4.5.2-9).

Referenzen aus Leitlinien

Bundesärztekammer (BÄK), Kassenärztliche Bundesvereinigung (KBV), Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF), 2019 [8].

Nationale Versorgungs Leitlinie Chronische KHK – Langfassung, 5. Auflage. Version 1. 2019

[Hinweis: Die LL bezieht sich auf das AWG Chronische KHK; jedoch gibt es in Kapitel 7.22 Empfehlungen zu Strategien der Lipidsenkung]

Leitlinienorganisation/Fragestellung

Ziele des NVL-Programms sind insbesondere:

- Empfehlungen zu versorgungsbereichsübergreifenden Vorgehensweisen für prävalente Erkrankungen entsprechend dem besten Stand der medizinischen Erkenntnisse unter Berücksichtigung der Kriterien der Evidenzbasierten Medizin zu erarbeiten und formal zu konsentieren;
- Empfehlungen hinsichtlich der Abstimmung und Koordination der an der Versorgung beteiligten Fachdisziplinen und weiterer Fachberufe im Gesundheitswesen in den verschiedenen Versorgungsbereichen zu geben;
- durch Einbeziehung aller an der Versorgung beteiligter Disziplinen, Organisationen und Patienten eine effektive Verbreitung und Umsetzung der Empfehlungen zu ermöglichen;
- Berücksichtigung von NVL-Empfehlungen in der ärztlichen Aus-, Fort- und Weiterbildung und in Qualitätsma-nagementsystemen sowie bei Verträgen zur Integrierten Versorgung oder strukturierten Behandlungspro-grammen;
- Unterstützung der gemeinsamen Entscheidungsfindung zwischen Arzt und Patient durch qualitativ hochwertige Patienteninformationen und Entscheidungshilfen.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert (Diese Leitlinie wurde am 11. April 2019 durch die Träger des NVL-Programms verabschiedet und ist bis zur nächsten Überarbeitung bzw. spätestens bis Ende April 2024 gültig).

Recherche/Suchzeitraum:

- Strategien der Lipidsenkung: Strategie der festen Dosis (Empfehlung 7-13) und der Zielwertstrategie (Empfehlung 7-14): Expertenkonsens ohne strukturierte oder systematische Recherche
- Strategien der Lipidsenkung: Ezetimib (Empfehlung 7-15) und PCSK-9-Inhibitoren (Empfehlung 7-16): systematische Suche in Medline via Pubmed und der Cochrane-Datenbank (Suche 23.07.2017).

LoE

- Die in der NVL verwendete Graduierung der Empfehlungen orientiert sich, wie im Methodenreport zum Programm für Nationale VersorgungsLeitlinien beschrieben [9], an der Vorgehensweise nach GRADE (Grading of Recommendations, Assessment, Development and Evaluation) [11,12]. Die Vergabe der Empfehlungsgrade berücksichtigt dabei neben der zugrundeliegenden Evidenz z. B. ethische Verpflichtungen, klinische Relevanz der Effektivi-

tätsmaße der Studien, Anwendbarkeit der Studienergebnisse auf die Patientenzielgruppe, Patientenpräferenzen und die Umsetzbarkeit im ärztlichen Alltag [4].

GoR

Tabelle 1: Einstufung von Leitlinien-Empfehlungen in Empfehlungsgrade (Grades of Recommendation) [8]

Empfehlungsgrad	Beschreibung	Formulierung	Symbol
A	Starke Positiv-Empfehlung	soll	⇑⇑
B	Abgeschwächte Positiv-Empfehlung	sollte	⇑
0	Offene Empfehlung	kann	⇔
B	Abgeschwächte Negativ-Empfehlung	sollte nicht	⇓
A	Starke Negativ-Empfehlung	soll nicht	⇓⇓

7.2.1 Statine

Empfehlungen/Statements	Empfehlungs-grad
7-10 Allen Patienten mit KHK soll unabhängig vom Ausgangswert der Blutfettwerte zur Reduktion der Morbidität und der Sterblichkeit dauerhaft ein Statin als Mittel der ersten Wahl empfohlen werden.	⇑⇑

Empfehlungen/Statements	Empfehlungs-grad
7-11 Bei Nebenwirkungen unter Statinen soll durch Reduzierung der Dosis oder Umsetzung auf ein anderes Statinpräparat die Weiterführung der Behandlung versucht werden.	⇑⇑

Empfehlungen/Statements	Empfehlungs-grad
7-12 Bei Auftreten einer Herzinsuffizienz sollte bei Patienten mit KHK eine Statin-Behandlung fortgeführt werden, vor allem in zeitlicher Nähe zu akuten koronaren Ereignissen.	⇑

7.2.2 Strategien der Lipidsenkung

Zur Lipidsenkung stehen zwei verschiedene Strategien zur Verfügung. Trotz der hier aufgeführten Unterschiede der Umsetzung der Statintherapie besteht vollständige Übereinstimmung, dass alle Patienten mit KHK von einer Statintherapie profitieren und entsprechend behandelt werden sollen.

Strategie der Festen Dosis Empfohlen von DEGAM und ACC/AHA 2013	**Zielwertstrategie** Empfohlen von DGIM, DGK, DGPR, DGRW und ESC/EAS
Nach Einschätzung des individuellen Gesamtrisikos wird dem Patienten eine feste Statindosis angeboten. Weitere Lipidbestimmungen oder Adjustierungen entfallen. Bei Patienten mit KHK ist in der Regel eine feste Hochdosisgabe sinnvoll. Andere Lipidsenker sind nur bei teilweiser oder vollständiger Statin-Unverträglichkeit zu erwägen. • In fast allen Lipidstudien wurden feste Dosen gegeben, damit verlässliche Evidenzgrundlage. • Orientiert sich an in Studien nachgewiesener Risikoreduktion. • Als klinische Strategie einfach, praktikabel und mit geringem Aufwand verbunden. • Unzureichend evaluierte Maßnahmen (Medikamente) werden vermieden.	Alle Patienten mit KHK haben ein sehr hohes kardiovaskuläres Risiko, welches umso stärker vermindert wird, je ausgeprägter die Cholesterinsenkung ausfällt. Das LDL-Cholesterin soll auf < 70 mg/dL (< 1,8 mmol/L) gesenkt werden bzw. um > 50% gesenkt werden, falls der LDL-Cholesterin-Ausgangswert im Bereich 70-135 mg/dL (1,8-3,5 mmol/L) liegt. Bei unzureichender LDL-Cholesterinsenkung oder Unverträglichkeiten sollte als Konsequenz individuell eine modifizierte Statindosis, der Wechsel auf ein anderes Statin oder die Kombination mit anderen lipidsenkenden Maßnahmen überlegt werden. • Eine fixe Statindosis bewirkt individuell stark unterschiedliche LDL-Cholesterinsenkungen. • Die Zielwertstrategie ist eine individualisierte Vorgehensweise. • Die Zielwertstrategie steigert Arzt-Patienten-Kontakt und Adhärenz.

Empfehlungen/Statements (DEGAM und ACC/AHA 2013)	Empfehlungsgrad
7-13 Allen Patienten mit koronarer Herzkrankheit sollte eine feste Hochdosis-Statintherapie empfohlen werden, sofern keine Kontraindikationen bestehen.	⇑

Die Zielwert-Strategie (empfohlen von DGIM, DGK, DGPR, DGRW und ESC/EAS)

Empfehlungen/Statements (DGIM, DGK, DGPR, DGRW und ESC/EAS)	Empfehlungsgrad
7-14 Bei Patienten mit einer chronischen KHK soll der LDL-Cholesterinspiegel auf den Zielwert < 70 mg/dl (< 1,8 mmol/l) gesenkt werden oder – wenn der LDL-Cholesterin-Ausgangswert zwischen 70 und 135 mg/dl (1,8 und 3,5 mmol/l) liegt – eine mindestens 50%ige Reduktion erzielt werden.	⇑⇑

7.2.3 Ezetimib

Empfehlungen/Statements	Empfehlungsgrad
7-15 Ezetimib kann Patienten mit KHK angeboten werden, wenn keine Hochdosis-Statintherapie toleriert wird (Strategie der festen Dosis) bzw. wenn der LDL-Cholesterinspiegel unter der maximal verträglichen Statindosis bei > 70 mg/dl bzw. 1,8 mmol/l liegt (Zielwertstrategie).	⇔

7.2.4 PCSK9-Inhibitoren

Empfehlungen/Statements	Empfehlungs-grad
7-16 Patienten mit KHK können PCSK9-Inhibitoren angeboten werden, wenn keine Hochdosis-Statintherapie toleriert wird (Strategie der festen Dosis) bzw. wenn der LDL-Cholesterinspiegel unter der Kombinationstherapie aus maximal verträglicher Statindosis und Ezetimib bei > 140 mg/dl bzw. 3,6 mmol/l liegt (Zielwertstrategie).	⇔

Empfehlungen/Statements	Empfehlungs-grad
Sondervotum der AkdÄ PCSK9-Inhibitoren sollten nicht routinemäßig bei Patienten mit KHK eingesetzt werden, es sei denn, der Einsatz der PCSK9-Inhibitoren erfolgt zur Vermeidung einer Lipid-Apherese (entsprechend AM-RiLi [274–276]).	⇓

Begründung der AkdÄ für das Sondervotum zur Empfehlung 7-16

Nach Einschätzung der AkdÄ ist der klinische Stellenwert der PCSK9-Inhibitoren derzeit nicht abschlie-ßend zu bewerten, da die Effekte der PCSK9-Inhibitoren auf die kardiovaskuläre Morbidität regional inkonsistent und quantitativ gering ausgeprägt sind. In der FOURIER-Studie fand sich bei chronischer KHK ein signifikanter Einfluss der Region auf die Ergebnisse für Evolocumab gegenüber Placebo(Interaktionstests): In der stratifizierten Subgruppe europäischer Patienten (66%) war kein Einfluss auf nicht-tödliche kardiovaskuläre Ereignisse nachzuweisen; die kardiovaskuläre und Gesamtmortalität war numerisch sogar höher als unter Placebo (23% bzw. 17%). Auch im Gesamtkollektiv blieben die kardiovaskuläre und Gesamtmortalität unbeeinflusst (HR 1,05 bzw. 1,04). In der ODYSSEY-Studie fand sich bei Patienten nach akutem Koronarsyndrom unter Alirocumab gegenüber Placebo eine nur geringe Reduktion eines Kombinationsendpunkts aus koronarem Tod, Herzinfarkt, ischämischem Schlaganfall und instabiler Angina pectoris, die zur Krankenhausaufnahme führt, um 1,6% in 2,8 Jahren. Ein Einfluss auf die kardiovaskuläre und Gesamtmortalität war statistisch nicht zu sichern (numerisch -0,4% bzw. -0,6%). Die Ergebnisse für Alirocumab waren abhängig vom Ausgangs-LDL: Bei den Patienten mit einem LDL <100 mg/dl zu Beginn hatte Alirocumab auch auf nicht-tödliche kardiovaskuläre Ereignisse keinen signifikanten Effekt.

NICE, 2008 [26]

National Institute for Health and Care Excellence (NICE)

Familial hypercholesterolaemia: identification and management. Clinical guideline 71

Last updated: October 2019

Leitlinienorganisation/Fragestellung

This guideline gives recommendations to clinicians and others about diagnosis; identification strategies; drug, specific and general treatments; and assessment and monitoring of FH.

Methodik

Grundlage der Leitlinie

- Grundlage der Leitlinie: systematische Evidenzaufbereitung und informale Konsensusprozesse - eigene Checklisten – externes und internes Konsultationsverfahren
- Update: Zuletzt im Dezember 2017; ein Addendum existiert bereits in Form einer Konsultationsfassung
- November 2017: The evidence on case finding, diagnosis and statin monotherapy was reviewed. Some new recommendations were added and some recommendations were updated.
- Nicotinic acid has been removed from the recommendations.
- A new recommendation cross-referring to the technology appraisal guidance on alirocumab and evolocumab has been added to section 1.3.1.
- July 2016: Recommendations 1.3.1.4–1.3.1.9 have been replaced and are adapted from Ezetimibe for treating primary (heterozygous-familial and non-familial) hypercholesterolaemia (NICE technology appraisal 385). TA385 has replaced TA132, the original source for these recommendations. They have been changed to remove reference to non-familial hypercholesterolaemia, which TA385 also covers.
- Minor changes since publication
- December 2017: The definition of high-intensity statin was amended.
- Update: October 2019 → Recommendation 1.1.1 amended to be clearer about when to suspect familial hypercholesterolaemia.
- Update: November 2017: The evidence on case finding, diagnosis and statin monotherapy was reviewed. Some new recommendations were added and some recommendations were updated.
- Nicotinic acid has been removed from the recommendations.

Recherche/Suchzeitraum:

Suchzeitraum der ersten LL-Version: bis Ende 2007

LoE

Level of evidence	Type of evidence
1++	High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1–	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
2++	High-quality systematic reviews of case–control or cohort studies High-quality case–control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal
2+	Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal
2–	Case–control or cohort studies with a high risk of confounding, bias, or chance and a significant risk that the relationship is not causal
3	Non-analytical studies (for example, case reports, case series)
4	Expert opinion, formal consensus

GoR

To avoid giving the impression that higher grade recommendations are of higher priority for implementation, NICE no longer assigns grades to recommendations.

Sonstige methodische Hinweise

Empfehlungen nicht direkt mit Literaturstellen verknüpft

Empfehlungen

1.3.1 Drug treatment

Adults

1.3.1.1 When offering lipid-modifying drug therapy to adults with FH, healthcare professionals should inform the person that this treatment should be lifelong. [2008].

1.3.1.2 Offer a high-intensity statin with the lowest acquisition cost as the initial treatment for all adults with FH and aim for at least a 50% reduction in LDL-C concentration from the baseline measurement. [2017]

1.3.1.3 The dose of statin should be increased to the maximum licensed or tolerated dose to achieve a recommended reduction in LDL-C concentration of greater than 50% from baseline (that is, LDL-C concentration before treatment). [2008]

1.3.1.4 Ezetimibe monotherapy is recommended as an option for treating primary heterozygous-familial hypercholesterolaemia in adults in whom initial statin therapy is contraindicated[2]. [2016]

1.3.1.5 Ezetimibe monotherapy is recommended as an option for treating primary heterozygous-familial hypercholesterolaemia in adults who cannot tolerate statin therapy (as defined in recommendation 1.3.1.9)[2]. [2016]

1.3.1.6 Ezetimibe, co-administered with initial statin therapy, is recommended as an option for treating primary (heterozygous-familial) hypercholesterolaemia in adults who have started statin therapy when[2]:

- serum total or low-density lipoprotein (LDL) cholesterol concentration is not appropriately controlled (as defined in recommendation 1.3.1.8) either after appropriate dose titration of initial statin therapy or because dose titration is limited by intolerance to the initial statin therapy (as defined in recommendation 1.3.1.9) and
- a change from initial statin therapy to an alternative statin is being considered. [2016]

1.3.1.7 When prescribing ezetimibe co-administered with a statin, ezetimibe should be prescribed on the basis of lowest acquisition cost[2]. [2016]

1.3.1.8 For the purposes of this guidance, appropriate control of cholesterol concentrations should be based on individualised risk assessment according to national guidance on managing cardiovascular disease in the relevant populations[2]. [2016]

1.3.1.9 For the purposes of this guidance, intolerance to initial statin therapy is defined as the presence of clinically significant adverse effects that represent an unacceptable risk to the patient or that may reduce compliance with therapy[2]. [2016]

1.3.1.10 Prescribing of drug therapy for adults with homozygous FH should be undertaken within a specialist centre. [2008] 1.3.1.11 Healthcare professionals should offer adults with FH a referral to a specialist with expertise in FH if treatment with the maximum tolerated dose of a highintensity statin and ezetimibe does not achieve a recommended reduction in LDL-C

concentration of greater than 50% from baseline (that is, LDL-C concentration before treatment). [2008]

1.3.1.12 Healthcare professionals should offer adults with FH a referral to a specialist with expertise in FH for consideration for further treatment if they are assessed to be at very high risk of a coronary event, that is, if they have any of the following.

- Established coronary heart disease.
- A family history of premature coronary heart disease.
- Two or more other cardiovascular risk factors (for example, they are male, they smoke, or they have hypertension or diabetes). [2008]

1.3.1.13 For recommendations on managing primary heterozygous familial hypercholesterolaemia in people whose LDL-C levels are not adequately controlled despite maximal tolerated lipid-lowering therapy, see the NICE technology appraisal guidance on alirocumab and evolocumab. [2017]

1.3.1.14 Adults with FH with intolerance or contraindications to statins or ezetimibe should be offered a referral to a specialist with expertise in FH for consideration for treatment with either a bile acid sequestrant (resin) or a fibrate to reduce their LDL-C concentration. [2008, amended 2017]

1.3.1.15 The decision to offer treatment with a bile acid sequestrant (resin) or a fibrate in addition to initial statin therapy should be taken by a specialist with expertise in FH. [2008, amended 2017]

1.3.1.16 Healthcare professionals should exercise caution when adding a fibrate to a statin because of the risk of muscle-related side effects (including rhabdomyolysis). Gemfibrozil and statins should not be used together. [2008, amended 2017]

1.3.3 Specialist treatment

LDL-lowering apheresis

1.3.3.1 Healthcare professionals should consider offering LDL apheresis for the treatment of adults and children/young people with homozygous FH (see recommendations 1.1.8 and 1.1.16). The timing of initiation of LDL apheresis should depend on factors such as the person's response to lipid-modifying drug therapy and presence of coronary heart disease. [2008]

1.3.3.2 In exceptional instances (such as when there is progressive, symptomatic coronary heart disease, despite maximal tolerated lipid-modifying drug therapy and optimal medical and surgical therapy), healthcare professionals should consider offering LDL apheresis for the treatment of people with heterozygous FH. This should take place in a specialist centre on a case-by-case basis and data recorded in an appropriate registry. [2008]

1.3.3.3 Healthcare professionals should recommend arterio-venous fistulae as the preferred method of access for people with FH who are offered treatment with LDL apheresis. People should be counselled about possible benefits and complications of this procedure. [2008]

1.3.3.4 Routine monitoring of the person's iron status should be carried out and iron supplementation initiated as required for people with FH who are receiving treatment with LDL apheresis. [2008]

1.3.3.5 Angiotensin-converting enzyme (ACE) inhibitors should not be used in people with FH who are being treated with LDL apheresis. Instead, ACE inhibitors should be substituted with angiotensin-receptor blocking agents. [2008]

1.3.3.6 People with FH who are receiving blood pressure-lowering drug therapy should have this reviewed and considered for discontinuation on the morning of the day of LDL apheresis. [2008]

1.3.3.7 People with FH who are taking warfarin should have this discontinued approximately 4 days before LDL apheresis and substituted with low molecular weight heparin. [2008]

1.3.3.8 People with FH who are receiving anti-platelet therapy should have this continued if they are receiving treatment with LDL apheresis. [2008]

SIGN, 2017 [29].

Scottish Intercollegiate Guidelines Network

Risk estimation and the prevention of cardiovascular disease

Leitlinienorganisation/Fragestellung

The guideline has attempted to devise effective strategies for the reduction of CVD that take a combined approach using both ‘high-risk’ and population approaches.

Separater Abschnitt zur familiären Hypercholesterolaemia und gemischten Dyslipidämie

Methodik

Grundlage der Leitlinie

- Leitlinie folgt AGREE II Standard
- Update der SIGN 97: Risk estimation and the prevention of cardiovascular disease: Leitlinie vom Februar 2007 (soweit neue Evidenz verfügbar)
- Systematische Literaturrecherche
- Quality of Evidence mittels GRADE
- Evidence to Decision (EtD) tool zur Generierung von Empfehlungen
- Berücksichtigung klinischer und ökonomischer Evidenz

Recherche/Suchzeitraum:

- Update der Evidenz mit Suche von 2009-2015 in CENTRAL, National Institute for Health Research - Health Technology Assessment (NIHR-HTA), Medline, Medline In-Process, Embase, Cinahl, PsycINFO und Cochrane Library
- Zusätzlich Evidenz konnte von den Entwicklungsgruppe eingebracht werden

LoE

KEY TO EVIDENCE STATEMENTS AND RECOMMENDATIONS	
LEVELS OF EVIDENCE	
1++	High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
1-	Meta-analyses, systematic reviews, or RCTs with a high risk of bias
2++	High-quality systematic reviews of case-control or cohort studies High-quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2+	Well-conducted case-control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2-	Case-control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, eg case reports, case series
4	Expert opinion

GoR

RECOMMENDATIONS	
Some recommendations can be made with more certainty than others. The wording used in the recommendations in this guideline denotes the certainty with which the recommendation is made (the 'strength' of the recommendation). The 'strength' of a recommendation takes into account the quality (level) of the evidence. Although higher-quality evidence is more likely to be associated with strong recommendations than lower-quality evidence, a particular level of quality does not automatically lead to a particular strength of recommendation. Other factors that are taken into account when forming recommendations include: relevance to the NHS in Scotland; applicability of published evidence to the target population; consistency of the body of evidence, and the balance of benefits and harms of the options.	
R	For '**strong**' recommendations on interventions that '**should**' be used, the guideline development group is confident that, for the vast majority of people, the intervention (or interventions) will do more good than harm. For '**strong**' recommendations on interventions that '**should not**' be used, the guideline development group is confident that, for the vast **majority** of people, the intervention (or interventions) will do more harm than good.
R	For '**conditional**' recommendations on interventions that should be '**considered**', the guideline development group is confident that the intervention will do more good than harm for most patients. The choice of intervention is therefore more likely to vary depending on a person's values and preferences, and so the healthcare professional should spend more time discussing the options with the patient.

Lipid Lowering

STATIN THERAPY FOR INDIVIDUALS WITHOUT CARDIOVASCULAR DISEASE

Individual RCTs have established that primary prevention with statins reduces major clinical end points. A meta-analysis of 18 trials, including almost 57,000 individuals, demonstrated the magnitude of the clinical effectiveness of this therapy, mostly in those identified as being at relatively high risk of coronary events due to existing risk factors.[216] **(1++)**

In individual patient data meta-analysis of 70,025 statin trial participants, first major vascular events were reduced by 25% per 1 mmol/l lower LDL cholesterol, similar to that achieved in those with pre-existing CHD (21% reduction per 1 mmol/l lower LDL cholesterol).[25] **(1++)**

R Adults who are assessed as being at high cardiovascular risk, but with no established CVD, should be offered treatment with atorvastatin 20 mg/day following an informed discussion of risks and benefits between the individual and their responsible clinician. In those already taking an alternative regimen due to reported intolerance with atorvastatin, there is no need to change their current regimen.

STATIN THERAPY FOR INDIVIDUALS WITH ESTABLISHED CARDIOVASCULAR DISEASE

Individuals with established CVD are at higher risk of future cardiovascular events than those without previous vascular disease. A meta-analysis of data from 170,000 participants in 26 randomised trials of statin therapy showed an annual rate of major vascular events of 1.8% in untreated individuals without previous CVD compared with 5.6% in individuals with established CHD. While CVD event rates are now lower due to secular declines this demonstrates that individuals with CVD are likely to be at significantly higher risk than most individuals without CVD who are estimated to be eligible for preventive treatment by means of formal risk calculation.[25] **(1++)**

R All patients with established atherosclerotic cardiovascular disease should be offered intensive statin therapy with atorvastatin 80 mg/day following an informed discussion of risks and benefits between the individual and responsible clinician.

✓ Consider a lower dose of atorvastatin in patients at increased risk of adverse effects or drug-drug interactions.

EZETIMIBE

The IMPROVE-IT trial investigated the effect of adding 10 mg daily ezetimibe to 40 mg daily simvastatin in 18,144 patients following recent ACS with a baseline LDL cholesterol 1.3–2.6 mmol/l on lipid-lowering therapy, or 1.3–3.2 mmol/l without therapy.[212] During the trial, LDL cholesterol was 0.4 mmol/l lower on ezetimbe plus simvastatin than simvastatin monotherapy. Over a median of six years, the primary end point (composite of cardiovascular death, non-fatal MI, unstable angina requiring rehospitalisation, coronary revascularisation, or non-fatal stroke) was reduced by 6.4% with an HR of 0.94 (95% CI 0.89 to 0.99, p=0.016). No notable side effects occurred. **(1++)**

R Ezetimibe and bile acid sequestrant therapy should only be considered for primary prevention in patients at elevated CVD risk in whom statin therapy is contraindicated, and in patients with familial hypercholesterolaemia.

R Ezetimibe and bile acid sequestrant therapy should be considered for secondary prevention in combination with maximum tolerated statin therapy if LDL cholesterol is considered to be inadequately controlled.

Fibrates

Fibrates are primarily used for lowering triglycerides. Their LDL-cholesterol lowering effects are generally in the range of 10% or less in persons with primary hypercholesterolemia. Trials of fibrate therapy were mostly undertaken in the era prior to routine statin treatment.

R Fibrates are not routinely recommended for primary or secondary prevention of cardiovascular disease.

✓ Individuals with:
- CVD or who are at high cardiovascular risk, and
- marked hypertriglyceridaemia, and
- low HDL cholesterol level

should be considered for treatment with a fibrate.

Nicotinic Acid

Nicotinic acid, or niacin, is a powerful HDL-cholesterol-raising agent.[263] Two forms of niacin are available, crystalline immediate release which is taken three times daily and modified (extended) release taken once daily. Elevations of 15–35% in HDL cholesterol are reported following dosing with 1–3 g of the drug in its crystalline form, and are usually accompanied by a drop of 20–30% in LDL cholesterol and of 35–50% in triglyceride.[264] An RCT that compared the efficacy and safety of treatment with 1.5 g/day of immediate-release (IR) with modified-release (MR) niacin found similar effects on lipids for both preparations.[265] **(1+, 4)**

R Nicotinic acid is not recommended for cardiovascular risk reduction in any group.

PCSK9 Inhibitors

A meta-analysis of 25 short-term studies reported that monthly evolocumab (420 mg) significantly reduced LDL cholesterol by -54.6% compared with placebo (95% CI -58.7 to 50.5%), although significant heterogeneity was noted, I2=80.4%, and by -36.3% (95% CI 38.8 to -33.9%) compared with ezetimibe. There was an increase in HDL cholesterol of 7.6% (95% CI 5.7 to 9.5%) compared with placebo and 6.4% (95% CI 4.3 to 8.4%) compared with ezetimibe. Fortnightly administration of 140 mg evolocumab led to even greater LDL reductions than 420 mg monthly treatment compared with placebo (-60.4%, 95% CI-68.8% to -52.0%). Fortnightly alirocumab (50 to 150 mg) lowered LDL cholesterol by -52.6% (95% CI -58.2 to 47.0%) compared with placebo, by -29.9% (95% CI -32.9 to -26.9%) compared with ezetimibe, and increased HDL cholesterol by 8.0% (95% CI 4.2 to 11.7%) compared with placebo. There was a synergistic effect in those already receiving statin therapy.[238] **(1++)**

R PCSK9 inhibitors should be considered in patients at high risk of vascular events with cholesterol levels remaining above target levels despite other tolerated lipid-lowering therapy.

Familiäre Hypercholesterinämie

Patients with FH based on clinical or genetic evidence should be considered for aggressive statin therapy, irrespective of their calculated cardiovascular risk. Their total cholesterol and LDL cholesterol will usually exceed 8 mmol/l and 4.9 mmol/l respectively and may be substantially higher than this. **(1++)**

Ezetimibe may be added to maximally-tolerated statin therapy where adequate cholesterol lowering has not been achieved with the statin alone, or given as monotherapy in those in whom statin therapy is contraindicated.[236,237] **(4)**

Results of the IMPROVE-IT trial indicated that combination therapy with ezetimibe plus a statin is more clinically effective than a statin alone as shown by lower LDL cholesterol and reduced cardiovascular events.[212] While this trial was conducted in patients with a recent ACS, not FH, and while the baseline LDL-cholesterol level in trial participants was considerably lower than is seen in FH (resulting in a smaller absolute reduction (0.4 mmol/l) in LDL cholesterol), results were consistent with large metaanalyses of statin therapy. Extrapolated to a 1 mmol/l reduction in LDL cholesterol, IMPROVE-IT yielded a similar hazard ratio for cardiovascular events (HR 0.80, 95% CI 0.68 to 0.94) to the meta-analysis (HR 0.78, 95% CI 0.76 to 0.80).[25] **(1++)**

A NICE technology appraisal notes that combination therapy with ezetimibe and a statin is an option for the treatment of FH.[236] **(4)**

R | Individuals with familial hypercholesterolaemia should be offered statin therapy regardless of their calculated cardiovascular risk and may be considered for combination therapy with ezetimibe where LDL cholesterol-lowering is inadequate on maximally-tolerated statin therapy, or for monotherapy where statins are contraindicated.

R | Individuals with heterozygous familial hypercholesterolaemia and elevated LDL cholesterol despite statin monotherapy or statin/ezetimibe combination therapy should be considered for a PCSK9 inhibitor.

Gemischte Dyslipidämie

A number of clinical trials have shown that LDL-cholesterol lowering with statins reduces the risk of vascular events (myocardial infarction, stroke and coronary revascularisation) in participants with diabetes with raised LDL cholesterol.[281,282] The greater the LDL-cholesterol reduction, the greater the benefit.[283] **(1++, 1+)**

The largest vascular end-point trial undertaken with fibrates (FIELD, conducted in participants with diabetes with total-cholesterol/HDL-cholesterol ratio of 4.0 or more and/or plasma triglyceride of 1.0–5.0 mmol/l) provided limited evidence for their benefit in a similar diabetic cohort.[284] Although treatment with fenofibrate did not significantly reduce the risk of a coronary event, it produced a 24% relative reduction (p=0.01) in risk of non-fatal MI. There was a non-significant rise in coronary deaths, but overall cardiovascular disease events (fatal and non-fatal myocardial infarction, stroke and coronary and carotid revascularisation) fell by 11% (p=0.35). Fenofibrate treatment resulted in less albuminuria progression (p=0.002) and fewer cases of retinopathy requiring laser treatment (p=0.0003). Pancreatitis and pulmonary embolism risk rose in the actively-treated group (p=0.031 and 0.022, respectively). **(1+)**

Combined statin/fibrate therapy improves the entire dyslipidaemic profile over that seen with statin therapy alone. Trials have reported a significant increase in HDL-cholesterol levels and significant reductions in triglyceride and LDL-cholesterol levels in patients on combined statin/fibrate therapy compared with patients on statins or fibrate monotherapy.[285,286] **(1+)**

The effect of combined statin/fibrate therapy compared with statin monotherapy was investigated in the ACCORD-Lipid trial.287 In this study 5,518 patients with type 2 diabetes and established CVD or excess risk and with dyslipidaemia (LDL cholesterol 1.55–4.65 mmol/l, HDL cholesterol below about 1.3 mmol/l and triglycerides below 8.5 mmol/l if not receiving lipid therapy or otherwise below 4.5 mmol/l) were randomised to fenofibrate or placebo in addition to ongoing open-label statin therapy. No cardiovascular benefit was noted over 4.7 years. There was, however, a borderline interaction suggesting possible benefit in the subgroup with low HDL

cholesterol (<0.9 mmol/l) and elevated triglycerides (>2.3 mmol/l), similar to what has been found in post hoc analyses of other fibrate trials.[260] **(1++)**

It appears that the potential for impaired metabolism of statins with gemfibrozil [288] is greater than with other fibrates, such as fenofibrate.[289] This is supported by evidence from healthy volunteers that the combination of fenofibrate with statins is associated with minimal differences in the concentrations of either fenofibrate or statin and also by the safety demonstrated by statin plus fenofibrate combination therapy in ACCORDLipid. [287,290] In contrast, the concurrent use of certain statins with gemfibrozil has shown a two- to three fold increase in statin levels.[291] Analyses of the US Food and Drug Administration Adverse Event Reporting System have suggested that the use of fenofibrate with statins results in fewer reports of rhabdomyolysis per million prescriptions than with gemfibrozil and statins.[292] **(1++, 3, 4)**

R	**Statins are the drugs of choice in the management of patients with diabetes with mixed dyslipidaemia and elevated low density lipoprotein cholesterol.**
✓	Combination therapy with a statin and a fibrate may be considered for combined dyslipidaemia.
✓	Statins should not be coadministered with gemfibrozil.
✓	Lifestyle advice involving healthy eating habits and physical activity is particularly important in individuals with combined dyslipidaemia.

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National Institute for Health and Care Excellence (NICE)

Lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease

Last updated: September 2016

Leitlinienorganisation/Fragestellung

Recommendations on lipid modification management and CVD risk assessment.

Methodik

This guidance is a partial update of NICE clinical guideline 67 (published 2008) and will replace it.

New and updated recommendations have been included covering lipid modification management and CVD risk assessment.

Recommendations are marked to indicate the year of the last evidence review [2008] if the evidence has not been updated since the original guideline, [2008, amended 2014] if the evidence has not been updated since the original guideline, but changes have been made that alter the meaning of the recommendation, [2014] if the evidence has been reviewed but no change has been made to the recommendation and [new 2014] if the evidence has been reviewed and the recommendation has been added or updated.

Grundlage der Leitlinie

- Repräsentatives Gremium;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

- Systematic literature searches were undertaken to identify all published clinical evidence relevant to the review questions. Searches were undertaken according to the parameters stipulated within the NICE guidelines manual 2012. 205 Databases were searched using relevant medical subject headings and free-text terms. Studies published in languages other than English were not reviewed. Where possible, searches were restricted to articles published in English. All searches were conducted in MEDLINE, Embase, and The Cochrane Library, and were updated for the final time on 11 November 2013.

LoE/GoR

- Using ‚Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox'

Table 4: Overall quality of outcome evidence in GRADE

Level	Description
High	Further research is very unlikely to change our confidence in the estimate of effect
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low	Any estimate of effect is very uncertain

Sonstige methodische Hinweise

- Empfehlungen nicht direkt mit Literaturstellen verknüpft

Empfehlungen

Lipid modification therapy for the primary and secondary prevention of CVD

- Before starting lipid modification therapy for the primary prevention of CVD, take at least 1 lipid sample to measure a full lipid profile. This should include measurement of total cholesterol, HDL cholesterol, non-HDL cholesterol, and triglyceride concentrations. A fasting sample is not needed. [new 2014]
- Offer atorvastatin 20 mg for the primary prevention of CVD to people who have a 10% or greater 10-year risk of developing CVD. Estimate the level of risk using the QRISK2 assessment tool. [new 2014]
- Start statin treatment in people with CVD with atorvastatin 80 mg[b]. Use a lower dose of atorvastatin if any of the following apply:
  - potential drug interactions
  - high risk of adverse effects
  - patient preference. [new 2014]
- Measure total cholesterol, HDL cholesterol and non HDL cholesterol in all people who have been started on high-intensity statin treatment (both primary and secondary prevention, including atorvastatin 20 mg for primary prevention) at 3 months of treatment and aim for a greater than 40% reduction in non HDL cholesterol. If a greater than 40% reduction in non HDL cholesterol is not achieved:
  - discuss adherence and timing of dose
  - optimise adherence to diet and lifestyle measures
  - consider increasing dose if started on less than atorvastatin 80 mg and the person is judged to be at higher risk because of comorbidities, risk score or using clinical judgement. [new 2014]
- People with primary hypercholesterolaemia should be considered for ezetimibe treatment in line with Ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia (NICE technology appraisal guidance 132). [2008]

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 8 of 12, August 2020) am 31.08.2020

#	Suchfrage
1	[mh ^dyslipidemias]
2	[mh ^hyperlipidemias]
3	[mh hypercholesterolemia]
4	[mh “hyperlipidemia, familial combined”]
5	[mh “hyperlipoproteinemia type ii”]
6	[mh “hyperlipoproteinemia type iii”]
7	(hypercholesterolem* OR hypercholesteremi* OR hypercholesterolaem* OR hypercholesteraemi*):ti,ab,kw
8	(hyperlipidemi* OR hyperlipidaemi* OR hyperlipemi* OR hyperlipaemi* OR hyperlipoproteinemi* OR hyperlipoproteinaemi* OR dysbetalipoprotein*):ti,ab,kw
9	(lipid* OR cholesterol OR lipoprotein* OR ldl OR apolipoprotein*):ti
10	(dyslipidemi* OR dyslipidaemi* OR dyslipoproteinemi* OR dyslipoproteinaemi*):ti
11	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 OR #9 OR #10
12	#11 with Cochrane Library publication date from Aug 2015 to Aug 2020

Systematic Reviews in Medline (PubMed) am 31.08.2020

#	Suchfrage
1	dyslipidemias/therapy[mh:noexp]
2	dyslipidemias/drug therapy[mh:noexp]
3	hyperlipidemias/therapy[mh:noexp]
4	hyperlipidemias/drug therapy[mh:noexp]
5	hypercholesterolemia/therapy[mh]
6	hyperlipidemia, familial combined[mh]
7	hyperlipoproteinemia type II[mh]
8	hyperlipoproteinemia type III[mh]
9	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8
10	((((((hypercholesterolemi*[tiab]) OR hypercholesterolaemi*[tiab]) OR hypercholesteremi*[tiab]) OR hypercholesteraemi*[tiab]) OR hyperlipoproteinemi*[tiab]) OR hyperlipoproteinaemi*[tiab])
11	(((((((((hyperlipidemi*[ti]) OR hyperlipidaemi*[ti]) OR hyperlipemi*[ti]) OR hyperlipaemi*[ti]) OR dyslipidemi*[ti]) OR dyslipidaemi*[ti]) OR dyslipoproteinemi*[ti]) OR dyslipoproteinaemi*[ti]) OR dysbetalipoprotein*[ti])
12	(((((lipid*[ti]) OR cholesterol[ti]) OR lipoprotein*[ti]) OR ldl[ti]) OR apolipoprotein*[ti])
13	#10 OR #11 OR #12
14	(#13) AND ((treatment*[tiab] OR treating[tiab] OR treated[tiab] OR treat[tiab] OR treats[tiab] OR treatab*[tiab] OR therapy[tiab] OR therapies[tiab] OR therapeutic*[tiab] OR monotherap*[tiab] OR polytherap*[tiab] OR pharmacotherap*[tiab] OR effect*[tiab] OR efficacy[tiab] OR management[tiab] OR drug*[tiab]))
15	(#14) NOT medline[sb]

16	#9 OR #15
17	(#16) AND (((Meta-Analysis[ptyp] OR systematic[sb] OR ((systematic review [ti] OR meta-analysis[pt] OR meta-analysis[ti] OR systematic literature review[ti] OR this systematic review[tw] OR pooling project[tw] OR (systematic review[tiab] AND review[pt]) OR meta synthesis[ti] OR meta-analy*[ti] OR integrative review[tw] OR integrative research review[tw] OR rapid review[tw] OR umbrella review[tw] OR consensus development conference[pt] OR practice guideline[pt] OR drug class reviews[ti] OR cochrane database syst rev[ta] OR acp journal club[ta] OR health technol assess[ta] OR evid rep technol assess summ[ta] OR jbi database system rev implement rep[ta]) OR (clinical guideline[tw] AND management[tw]) OR ((evidence based[ti] OR evidence-based medicine[mh] OR best practice*[ti] OR evidence synthesis[tiab]) AND (review[pt] OR diseases category[mh] OR behavior and behavior mechanisms[mh] OR therapeutics[mh] OR evaluation study[pt] OR validation study[pt] OR guideline[pt] OR pmcbook)) OR ((systematic[tw] OR systematically[tw] OR critical[tiab] OR (study selection[tw]) OR (predetermined[tw] OR inclusion[tw] AND criteri* [tw]) OR exclusion criteri*[tw] OR main outcome measures[tw] OR standard of care[tw] OR standards of care[tw]) AND (survey[tiab] OR surveys[tiab] OR overview*[tw] OR review[tiab] OR reviews[tiab] OR search*[tw] OR handsearch[tw] OR analysis[ti] OR critique[tiab] OR appraisal[tw] OR (reduction[tw] AND (risk[mh] OR risk[tw]) AND (death OR recurrence))) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR publication [tiab] OR bibliography[tiab] OR bibliographies[tiab] OR published[tiab] OR pooled data[tw] OR unpublished[tw] OR citation[tw] OR citations[tw] OR database[tiab] OR internet[tiab] OR textbooks[tiab] OR references[tw] OR scales[tw] OR papers[tw] OR datasets[tw] OR trials[tiab] OR meta-analy*[tw] OR (clinical[tiab] AND studies[tiab]) OR treatment outcome[mh] OR treatment outcome[tw] OR pmcbook)) NOT (letter[pt] OR newspaper article[pt])) OR Technical Report[ptyp]) OR (((((trials[tiab] OR studies[tiab] OR database*[tiab] OR literature[tiab] OR publication*[tiab] OR Medline[tiab] OR Embase[tiab] OR Cochrane[tiab] OR Pubmed[tiab])) AND systematic*[tiab] AND (search*[tiab] OR research*[tiab]))) OR ((((((((((HTA[tiab]) OR technology assessment*[tiab]) OR technology report*[tiab]) OR (systematic*[tiab] AND review*[tiab])) OR (systematic*[tiab] AND overview*[tiab])) OR meta-analy*[tiab]) OR (meta[tiab] AND analyz*[tiab])) OR (meta[tiab] AND analys*[tiab])) OR (meta[tiab] AND analyt*[tiab]))) OR (((review*[tiab]) OR overview*[tiab]) AND ((evidence[tiab]) AND based[tiab]))))))
18	((#17) AND ("2015/08/01"[PDAT] : "3000"[PDAT]) NOT "The Cochrane database of systematic reviews"[Journal]) NOT (animals[MeSH:noexp] NOT (Humans[mh] AND animals[MeSH:noexp]))
19	(#18) NOT (retracted publication[pt] OR retraction of publication[pt])

Leitlinien in Medline (PubMed) am 31.08.2020

#	**Suchfrage**
1	dyslipidemias[mh:noexp]
2	hyperlipidemias[mh:noexp]
3	hypercholesterolemia[mh]
4	hyperlipidemia, familial combined[mh]
5	hyperlipoproteinemia type II[mh]
6	hyperlipoproteinemia type III[mh]
7	#1 OR #2 OR #3 OR #4 OR #5 OR #6
8	((((((hypercholesterolemi*[tiab]) OR hypercholesterolaemi*[tiab]) OR hypercholesteremi*[tiab]) OR hypercholesteraemi*[tiab]) OR hyperlipoproteinemi*[tiab]) OR hyperlipoproteinaemi*[tiab])
9	(((((((hyperlipidemi*[tiab]) OR hyperlipidaemi*[tiab]) OR hyperlipemi*[tiab]) OR hyperlipaemi*[tiab]) OR dyslipidemi*[tiab]) OR dyslipidaemi*[tiab]) OR dyslipoproteinemi*[tiab]) OR dyslipoproteinaemi*[tiab] OR dysbetalipoprotein*[tiab])

10	(((((lipid*[ti]) OR cholesterol[ti]) OR lipoprotein*[ti]) OR ldl[ti]) OR apolipoprotein*[ti])
11	#8 OR #9 OR #10
12	#7 OR #11
13	(#12) AND ((Guideline[ptyp] OR Practice Guideline[ptyp] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp]) OR ((guideline*[ti] OR recommendation*[ti]) NOT (letter[ptyp] OR comment[ptyp])))
14	(#13) AND ("2015/08/01"[PDAT] : "3000"[PDAT])
15	(#14) NOT (retracted publication[pt] OR retraction of publication[pt])

Referenzen

1. **Adams S, Alaeiilkhchi N, Wright J.** Pitavastatin for lowering lipids. Cochrane Database of Systematic Reviews [online]. 2020(6). URL: http://dx.doi.org/10.1002/14651858.CD012735.pub2.

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Anhang

Abbildung 1: Netzwerk der Metaanalyse von Toth PP et al., 2017 [33].

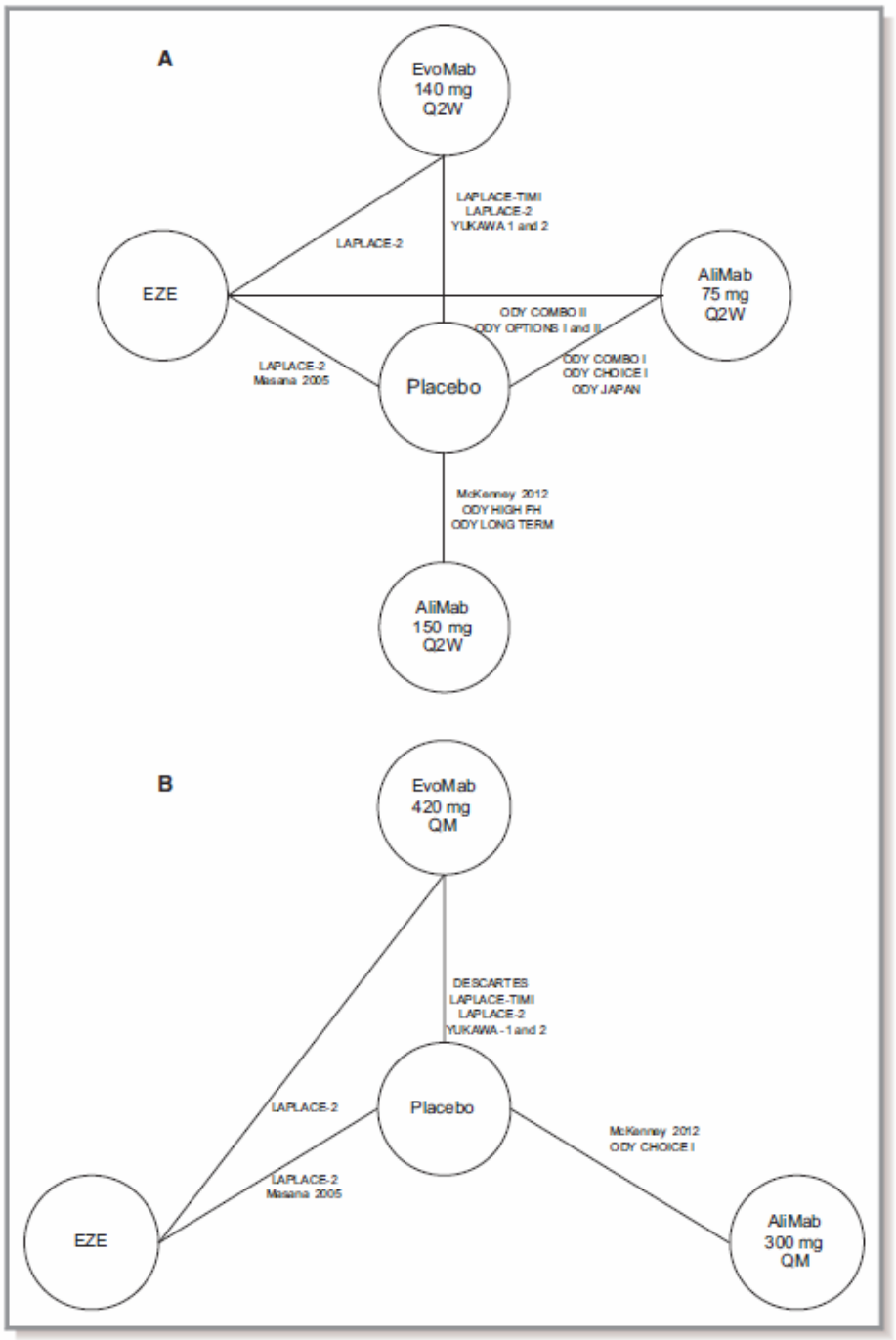

Figure 2. Network of available connections for comparing change in LDL-C. A, Evolocumab 140 mg Q2W (every 2 weeks). B, Evolocumab 420 mg QM (every month). Lines between boxes denote direct comparisons. AliMab indicates alirocumab; EvoMab, evolocumab; EZE, ezetimibe; LDL-C, low-density lipoprotein cholesterol; ODY, ODYSSEY.

Tabelle 1: Studiencharakteristika Toth PP et al., 2017 [33]

Table 1. Specific Details About Studies Included in Main Q2W or QM Network

Study Name	Follow-Up, Weeks	Age, y*	Investigational Drug and Dose	Control	Type HC	CVD Risk Status	FH Status	Type 2 Diabetes Mellitus Status	Obesity Status	Background Therapy
DESCARTES[30]	52	55.9 (10.8)†	EvoMab 420 mg QM	Placebo	Primary or secondary HC	With or without CVD or equivalent	NR/unclear	With and without	All	Diet through 80 mg atorvastatin+ezetimibe
LAPLACE-TIMI 57[34]	12	62.0 (55.0-67.0)	EvoMab 70, 105, or 140 mg Q2W; 280, 350, or 420 mg QM	Placebo	Primary HC	Without prior CVD	NR/unclear	With and without	Overweight	Statin±ezetimibe at physician discretion
LAPLACE-2[29]	12	59.6 (9.9)†	EvoMab 140 mg Q2W; 420 mg QM	Placebo	Mixed dyslipidemia	NR/unclear	NR/unclear	With and without	Overweight	Moderate to high dose atorvastatin or rosuvastatin, moderate dose simvastatin
YUKAWA-1[35]	12	61.5 (9.7)	EvoMab 70 or 140 mg Q2W; 280 or 420 mg QM	Placebo	Primary or secondary HC	With or without CVD or equivalent	NR/unclear	With and without	Overweight	Statin as prescribed by physician
YUKAWA-2[36]	12	62 (11)†	EvoMab 140 mg Q2W; 420 mg QM	Placebo	Primary or secondary HC	With or without CVD or equivalent	HoFH and HeFH eligible	With and without	NR/unclear	20 mg atorvastatin (intensive dose for Japanese population)
McKenney 2012[37]	12	56.7 (10.0)	AliMab 50, 100, 150, or 200 mg Q2W; 300 mg QM	Placebo	Primary HC	NR/unclear	NR/unclear	With and without	Overweight	10, 20, 40 mg atorvastatin
ODYSSEY CHOICE I[41]	56	60.7 (9.1)‡	AliMab 75 mg Q2W or 300 mg QM	Placebo	Primary HC	Moderate- to very-high-risk, no CVD	HoFH excluded	With and without	Normal, overweight, and obese	Maximally-tolerated atorvastatin, rosuvastatin, or simvastatin
ODYSSEY COMBO I[40]	52	63.0 (9.5)§	AliMab 75 mg Q2W	Placebo	Primary or secondary HC	With or without CVD or equivalent	No FH patients	With and without	NR/unclear	Maximally tolerated statin with/without other lipid-lowering therapy
ODYSSEY COMBO II[38]	104	61.7 (9.4)§	AliMab 75 mg Q2W	Ezetimibe	Primary or secondary HC	With or without CVD or equivalent	NR/unclear	NR/unclear	NR/unclear	Stable maximally tolerated statin therapy
ODYSSEY HIGH FH[39]	78	49.8 (14.2)§	AliMab 150 mg Q2W	Placebo	HeFH only	NR/unclear	HeFH only	NR/unclear	NR/unclear	Maximally tolerated statin with/without other lipid-lowering therapy
ODYSSEY JAPAN[45]	24	60.3 (9.7)§	AliMab 75 mg Q2W	Placebo	NR/unclear	With or without CVD	NR/unclear	NR/unclear	NR/unclear	Stable lipid lowering therapy

Continued

Study Name	Follow-Up, Weeks	Age, y*	Investigational Drug and Dose	Control	Type HC	CVD Risk Status	FH Status	Type 2 Diabetes Mellitus Status	Obesity Status	Background Therapy
ODYSSEY LONG TERM[46]	78	60.4 (10.4)	AliMab 150 mg Q2W	Placebo	Primary HC	With or without CVD or equivalent	HeFH included	NR/unclear	NR/unclear	Maximally tolerated statin with/without other lipid-lowering therapy
ODYSSEY OPTIONS I[42]	24	64.2 (10.4)‖	AliMab 75 mg Q2W	Placebo, ezetimibe	Primary or secondary HC	CVD or equivalent	Non-FH or HeFH	With and without	NR/unclear	Statins according to study group assignment
ODYSSEY OPTIONS II[43]	24	57.9 (8.9)¶	AliMab 75 mg Q2W	Placebo, ezetimibe	Primary or secondary HC	CVD or equivalent	Non-FH or HeFH	NR/unclear	NR/unclear	Statins according to study group assignment
Masana 2005[44]	48	61 (28-83)#	Ezetimibe	Placebo	Primary or secondary HC	With or without CVD or equivalent	NR/unclear	With and without	Overweight	Up to 80 mg simvastatin

CVD indicates cardiovascular disease; EvoMab, evolocumab; FH, familial hypercholesterolemia; HC, hypercholesterolemia; HeFH, heterozygous familial hypercholesterolemia; HoFH, homozygous familial hypercholesterolemia; NR, not reported; Q2W, every 2 weeks; QM, monthly.

*Values are mean (standard deviation) or median (interquartile range). Mean age for all patients given unless unavailable, in which case the intervention group was used (marked with footnote). There was no indication in the references that ages were statistically different between groups.

†All evolocumab patients.

‡Alirocumab 75 mg Q2W taking statins.

§All alirocumab patients.

‖Alirocumab 75/150 mg Q2W+atorvastatin 40 mg.

¶Alirocumab 75/150 mg Q2W+rosuvastatin 20 mg.

#All ezetimibe patients. Values in parentheses represent the range of ages observed.

Quelle: Zhao Z et al., 2019 [37]. Comparative efficacy and safety of lipid-lowering agents in patients with hypercholesterolemia

Table S3. Basic characteristics of included trials.

Publication year, Study ID	Setting	Lipid-lowering therapies	No. of patients	Follow-up (year)	Age (mean)	HP history %	DM %	CAD history %	LDL (mg/dL)	HDL (mg/dL)	TG (mg/dL)	Baseline lipid-lowering therapies
Statins-related trials												
2000, SCAT[1]	Multi-center	Simvastatin	460	4	61	36	11	100	130	38	160	Diet therapies
2000, GISSI Prevention[2]	Multi-center	Pravastatin	4,271	2	60	37	14	100	152	46	155	Diet therapies
2002, LIPS [3]	Multi-center	Fluvastatin	1,677	3.9	60	39	12	100	132	38	150	Dietary and lifestyle counseling
2002, FAST[4]	Single center	Pravastatin	164	2	66.1	40	56	NR	166	57	150	Diet therapies
2002, ALLHAT-LLT[5]	Multi-center	Pravastatin	10,355	6	66.4	100	35.1	14.2	146	48	150	Usual care
2002, GREACE[6]	Multi-center	Atorvastatin	1,600	3	58.5	43	19.5	100	180	41	181	Usual care included life-style
2002, Davidson et al.[7]	Multi-center	Rosuvastatin, Atorvastatin	516	0.2	57	NR	NR	NR	186	50	190	Diet therapies
2002, MRC/BHF[8]	Multi-center	Simvastatin	20,536	5	NR	41	19.4	80.6	132	41	280	NR
2002, PROSPER[9]	Multi-center	Pravastatin	5,804	3.2	75.3	61.9	10.7	NR	147	50	120	NR
2003, ASCOT-LLA[10]	Multi-center	Atorvastatin	19,342	3.3	63.1	100	13.1	9.9	132	50	155	NR
2003, Bruckert et al. [11]	Multi-center	Fluvastatin	1,229	0.5	75.5	56	7	NR	200	53	140	Diet therapies
2004, PREVEND IT[12]	Single center	Pravastatin	864	4	51.3	NR	2.5	NR	155	39	155	NR
2004, ALLIANCE[13]	Multi-center	Atorvastatin	2,442	4.3	61.2	NR	22.2	100	147	41	190	Usual care included life-style
2004, JUST[14]	Multi-center	Simvastatin	299	2	58.7	54.8	43.5	100	154	45	165	Diet therapies
2004, PHYLLIS[15]	Multi-center	Pravastatin	508	2.6	58.4	100	NR	100	181	53	140	Low lipid diet
2004, CARDS[16]	Multi-center	Atorvastatin	2,838	3.9	61.7	84	100	0	117	55	175	Additional lipid-lowering treatment on the top of study drug was allowed
2004, PROVE-IT[17]	Multi-center	Pravastatin, Atorvastatin	4,162	2	58.2	50.2	16.7	100	106	39	180	Statins were prescribed both in experimental and control group.
2004, A to Z[18]	Multi-center	Simvastatin	4,497	2	61	49.7	23.8	100	112	39	170	Statins were prescribed both in experimental and control group.

2005, TNT[19]	Multi-center	Atorvastatin	10,001	4.9	61	54.1	15	100	98	47	150	Statins were prescribed both in experimental and control group.
2005, IDEAL[20]	Multi-center	Atorvastatin, Simvastatin	8,888	4.8	61.7	33	12	100	122	46	140	Statins were prescribed both in experimental and control group.
2005, CERDIA[21]	Single center	Cerivastatin	250	2	58.5	50.4	100	0	132	48	162	NR
2005, COMETS[22]	Multi-center	Rosuvastatin, Atorvastatin	397	0.1	57.7	NR	0	0	169	60	115	Diet therapies
2005, MARS[23]	Multi-center	Lovastatin	270	2	58	0	NR	100	153	43	180	Diet therapies
2005, ATHEROMA[24]	Multi-center	Pravastatin	361	3	59.3	42	18.8	100	143	50	165	Diet therapies
2006, ASPEN[25]	Multi-center	Atorvastatin	2,410	4	61.1	55	100	NR	114	47	165	Diet therapies
2007, HYRIM[26]	Single center	Fluvastatin	568	4	57.2	100	NR	NR	150	49	155	Intensive lifestyle intervention or usual care
2008, JUPITER[27]	Multi-center	Rosuvastatin	17,802	1.9	66	57.3	0	11.5	108	49	145	NR
2009, RCASS[28]	Multi-center	Simvastatin	227	2	63	69.2	91.2	100	151	45	165	NR
2009, MEGA[29]	Multi-center	Pravastatin	3,277	5	58.5	100	20.5	0	159	58	135	Diet therapies
2010, SEARCH[30]	Multi-center	Simvastatin	12,064	6.7	64.2	42	11	100	97	40	335	Statins were prescribed both in experimental and control group.
2010,ASTRONOMER[31]	Multi-center	Rosuvastatin	269	3.5	58	28	0	0	122	61	110	NR
2010, METEOR[32]	Multi-center	Rosuvastatin	984	2	57	19.9	NR	10	155	50	120	NR
2016, HOPE3[33]	Multi-center	Rosuvastatin	12,705	5.6	65.8	37.9	5.8	0	128	45	140	Individualized structured lifestyle advice was provided to the participants
Ezetimibe-related trials												
2002, Davidson MH et al.[34]	Multi-center	Ezetimibe, Simvastatin	394	0.2	57.4	NR	4.6	NR	179	51	175	Diet therapies
2002, Dujovne et al.[35]	Multi-center	Ezetimibe	892	0.2	58	33.3	NR	NR	167	52	170	Diet therapies
2003, Ballantyne et al.[36]	Multi-center	Ezetimibe, Atorvastatin	373	0.2	57.5	34	3.5	9	180	53	170	Diet therapies
2003, Kerzner et	Multi-	Ezetimibe,	356	0.2	56.2	30.9	6.5	7	179	52	170	Diet therapies

al.[37]	center	Lovastatin										
2003, Knopp et al.[38]	Multi-center	Ezetimibe	827	0.2	58.1	34.7	5.7	6.8	157	52	200	Diet therapies
2003, Melani et al.[39]	Multi-center	Ezetimibe, Pravastatin	334	0.2	54.2	29.6	5.1	6	178	50	180	Diet therapies
2004, Bays et al.[40]	Multi-center	Ezetimibe, Simvastatin	919	0.2	55.2	36.7	5.7	14.5	178	52	160	Diet therapies
2004, Feldman et al.[41]	Multi-center	Ezetimibe	362	0.4	63	NR	47.8	52.2	172	46	180	Lipid-lowering therapies
2004, Goldberg et al.[42]	Multi-center	Ezetimibe, Simvastatin	534	0.2	NR	31.2	5.6	6.8	175	50	170	Diet therapies
2005, Cruz-Fernandez et al.[43]	Multi-center	Ezetimibe	450	0.2	63.2	55.8	17.5	100	122	52	150	Lipid-lowering therapies
2005, Masana et al.[44]	Multi-center	Ezetimibe	433	1	59.4	NR	NR	NR	136	50	145	Lipid-lowering therapies
2006, Patel et al.[45]	Multi-center	Ezetimibe	152	0.1	65.4	45.4	3.9	100	169	54	40	Lipid-lowering therapies
2006, UK-HARP-II[46]	Multi-center	Ezetimibe, Simvastatin	203	0.5	60.0	NR	10.8	NR	119	40	190	Lipid-lowering therapies
2007, Shankar et al.[47]	Multi-center	Ezetimibe	230	0.2	51.9	33.9	NR	73.9	128	42	460	Lipid-lowering therapies
2008, ENHANCE[48]	Multi-center	Ezetimibe	720	1	45.9	16.4	1.8	NR	318	47	175	Lipid-lowering therapies
2008, Strony et al.[49]	Multi-center	Ezetimibe	109	1	57.3	29.4	5.5	NR	178	49	180	Lipid-lowering therapies
2012, Arimura[50]	Single center	Atorvastatin, Ezetimibe	50	0.5	68	75	30	NR	100	50	150	Lipid-lowering therapies
2015, IMPROVE-IT[51]	Multi-center	Ezetimibe, Simvastatin	18,144	6	63.6	61.4	27.2	100	94	NR	NR	Lipid-lowering therapies
2015, Masuda[52]	Single center	Rosuvastatin, Ezetimibe	51	0.5	67.1	75	47.5	40	127	50	110	Lipid-lowering therapies
2015, PRECISE - IVUS[53]	Multi-center	Atorvastatin, Ezetimibe	202	1	66.5	70.3	29.7	49	109	41	125	Lipid-lowering therapies
2016, Wang[54]	Single center	Rosuvastatin, Ezetimibe	98	1	64	49	35.7	56.1	137	44	70	Lipid-lowering therapies
2016, HIJ-PROPER[55]	Multi-center	Ezetimibe, pitavastatin	1,734	3.9	65.6	NR	NR	100	135	NR	NR	Lipid-lowering therapies
PCSK9 inhibitors-related trials												
2012, LAPLACE-TIMI 57[56]	Multi-center	Evolocumab	315	0.2	63	70.2	17	32	122	54	125	Lipid-lowering therapies
2012, MENDEL[57]	Multi-center	Evolocumab	225	0.2	51	32.9	0	NR	143	53	125	Without lipid-lowering therapies
2012, McKenney et al.[58]	Multi-center	Alirocumab	62	0.2	56.6	48.4	6.5	6.5	127	51	140	Lipid-lowering therapies
2012, RUTHERFORD[59]	Multi-center	Evolocumab	112	0.2	50.6	NR	NR	21.5	156	50	110	Lipid-lowering therapies
2012, Roth et al.[60]	Multi-	Alirocumab	61	0.2	56.9	49.2	16.4	1.5	123	55	125	Lipid-lowering

	center											therapies
2012, Stein et al.[61]	Multi-center	Alirocumab	31	0.2	54	NR	0	35.5	146	52	135	Lipid-lowering therapies
2012, GAUSS[62]	Multi-center	Evolocumab	65	0.2	61	NR	NR	NR	194	57	155	Lipid-lowering therapies
2014, DESCARTES[63]	Multi-center	Evolocumab	901	1	56	48.6	11.5	15.1	104	53	105	Lipid-lowering therapies
2014, YUKAWA[64]	Multi-center	Evolocumab	207	0.2	61	72.9	35	27	139	54	145	Lipid-lowering therapies
2014, MENDEL-2[65]	Multi-center	Evolocumab	614	0.2	53	28.7	0.2	0	143	55	115	Without lipid-lowering therapies
2014, LAPLACE-2[66]	Multi-center	Evolocumab, Ezetimibe	1,897	0.2	60	NR	15	23	109	54	130	Lipid-lowering therapies
2014, GAUSS-2[67]	Multi-center	Evolocumab	307	0.2	62	59	20	29	193	52	NR	Lipid-lowering therapies
2015, ODYSSEY OPTIONS I[68]	Multi-center	Alirocumab, Ezetimibe	206	0.2	64	78.6	NR	NR	104	NR	NR	Lipid-lowering therapies
2015, ODYSSEY COMBO II[69]	Multi-center	Alirocumab, Ezetimibe	720	1	62	NR	31	90	107	46	160	Lipid-lowering therapies
2015, ODYSSEY FHI and FHII[70]	Multi-center	Alirocumab	735	1.5	52.4	39.6	8.2	42.6	139	NR	NR	Lipid-lowering therapies
2015, ODYSSEY COMBO I[71]	Multi-center	Alirocumab	316	1	63	NR	43.1	78.2	102	48	NR	Lipid-lowering therapies
2015, ODYSSEY ALTERNATIVE[72]	Multi-center	Alirocumab, Ezetimibe	314	0.5	63.5	62.7	23.9	47	192	50	153	Without lipid-lowering therapies
2015, RUTHERFORD-2[73]	Multi-center	Evolocumab	331	0.2	51.2	NR	NR	31.3	155	50	106	Lipid-lowering therapies
2015, ODYSSEY LONG TERM[74]	Multi-center	Alirocumab	2,341	1.5	63.5	NR	23.9	47	122	50	NR	Lipid-lowering therapies
2015, ODYSSEY MONO[75]	Multi-center	Alirocumab, Ezetimibe	103	0.5	60.2	NR	3.9	NR	140	57	130	Without lipid-lowering therapies
2015, OSLER-1 (OSLER-1 extension)[76]and OSLER-2[77]	Multi-center	Evolocumab	4,465	1	58	52	13	20	120	51	160	Without lipid-lowering therapies
2016, ODYSSEY OPTIONS II[78]	Multi-center	Alirocumab, Ezetimibe	204	0.5	60.9	71.1	39.7	56.9	112	51	129	Lipid-lowering therapies
2016, YUKAWA-2[79]	Multi-center	Evolocumab	404	0.2	61.5	73.5	48.8	12.9	106	57	123	Lipid-lowering therapies
2016, GAUSS-3[80]	Multi-center	Evolocumab, Ezetimibe	218	0.5	58.8	51.4	11.9	31.7	220	50	185	Without lipid-lowering therapies
2016, ODYSSEY HIGH FH[81]	Multi-center	Alirocumab	107	0.5	50.6	57	14	49.5	198	48	140	Lipid-lowering therapies
2016, GLAGOV[82]	Multi-center	Evolocumab, statins	968	1.5	59.8	83	20.9	NR	93	46	125	Lipid-lowering therapies
		combination										
2017, SPIRE[83]	Multi-center	Bococizumab, statins combination	4,449	1	61.3	78.3	53.3	NR	122	48	160	96% were receiving statin therapy at the time of enrollment
2017, FOURIER[84]	Multi-center	Evolocumab, statins combination	27,564	2.2	62.5	80.1	36.6	100	92	44	135	Lipid-lowering therapies
2018, ODYSSEY OUTCOMES[85]	Multi-center	Alirocuma, statins combination	18,924	2.8	NA	NA	NA	100	87	NA	NA	Lipid-lowering therapies

Table 1: Baseline characteristics of trials included in systematic review

Study	Patients, n	MeanAge, Y	Men%	CAD%	HT%	DM2%	BMI, kg/m²	Mean LDLc level at baseline, mmol/L mean (mg/l)	Total cholesterol	HDL-C	Statin therapy, %	Intensive Statin therapy, %	Statin and Dose (mg)	Non-HDL-C	Apo B	Lp (a)	Fasting TG	ApoA1
ODYSSEY MONO	103	60.2	53.4	NA	NA	3.9	29.3	3.6 (139.7)	224 (0.8)	61 (0.5)	0	0	None					
ODYSSEY COMBO I	316	63	67.3	78.2	88.7	42.5	32.3	2.6 (102.1)	NA	48.3 (14.4)	99.7	62.7	rosuvastatin 20-40, atorvastatin 40-80, or simvastatin 80	130.0 (34.0)	90.8 (21.4)	31.0 (8.0:81.0)	130.0 (92.0:189.0)	
ODYSSEY COMBO II	720	61.5	73.6	90.1	81	30.9	30.2	2.8 (107.7)	4.8 mmols	1.2 mmols	99.9	66.7	rosuvastatin 20-40, atorvastatin 40-80, or simvastatin 80	3.6±1.0	0.9±0.2 g/L	1.0 (0.3, 2.5)	1.5 (1.1, 2.2)	
ODYSSEY LONG TERM	2341	60.5	62.3	68.6	NA	34.4	30.4	3.2 (122.4)	NA	49.8	99.9	44.1	rosuvastatin 20-40, atorvastatin 40-80, or simvastatin 80	152.6	101.9	21.5	133.5	147
ODYSSEY ALTERNATIVE	251	63.5	54.6	47	64.6	23.9	29	5.0 (192.3)	279.7	49.8	0	0	None	230	140	16	152	149.7
ODYSSEY OPTIONS I	112, 94	63.9, 64.1	57.1, 71.3	44.7, 72.3	79.5, 77.6	55.3, 43.6	31.9, 30.3	2.6 (102.2), 2.8 (107.7)	NA	48.7	100	0, 100	atorvastatin 20, atorvastatin 40					
ODYSSEY OPTIONS II	97, 107	61.3, 60.5	50.9, 55.2	NA	NA	NA	32, 30.2	2.7 (104.9, 3.1 (118.7)	NA	NA	100	0, 100	Rosuvastatin 10, Rosuvastatin 20,					
ODYSSEY FH I	486	52.1	55.7	45.5	43.0	9.9	29.0	3.7 (144.6)	NA	NA	100	82.7	rosuvastatin 20-40, atorvastatin 40-80, or simvastatin 80					
ODYSSEY FH II	249	53.2	51.5	34.7	34.1	4.2	28.6	3.5 (134)	NA	NA	100	86.8	rosuvastatin 20-40, atorvastatin 40-80, or simvastatin 80					
ODYSSEY CHOICE I	803	59.3	37.8	100		27	29.7	148.4 (36.8)	233.9 (41.9)	58.2 (15)	68	68	rosuvastatin 20-40, atorvastatin 40-80, or simvastatin 80	-52.7 with 300 vs -0.3 (without statin) -58.8 vs -0.1 (with statin)				
ODYSSEY CHOICE II	233	63.1	53.4	46.6	63.8	15.5	28.5	158.5 (47.3)	244 (50.8)	10.5	0							
ODYSSEY HIGH FH	107	50.6	54.2	49.7	57.1	42.1	28.9	198.6	274.5	47.2			rosuvastatin 20-40, atorvastatin 40-80, or simvastatin 80	227.7	142.4	12.5	126.7	
	6019																	

Beteiligung von AkdÄ und Fachgesellschaften nach §35a Abs. 7 SGB V i.V.m. VerfO 5. Kapitel § 7 Abs. 6

2020-B-244

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zur Behandlung erwachsener Patienten mit primärer Hypercholesterinämie (heterozygot familiär und nicht-familiär) oder gemischter Dyslipidämie, zusätzlich zu einer diätetischen Therapie:

• in Kombination mit einem Statin oder einem Statin mit anderen lipidsenkenden Therapien bei Patienten, die mit der maximal tolerierbaren Statin-Dosis die LDL-C-Ziele nicht erreichen, oder

• allein oder in Kombination mit anderen lipidsenkenden Therapien bei Patienten mit Statin-Intoleranz oder für welche ein Statin kontraindiziert ist.

Was ist der Behandlungsstandard unter Berücksichtigung der vorliegenden Evidenz *"zur Behandlung erwachsener Patienten mit primärer Hypercholesterinämie (heterozygot familiär und nicht-familiär) oder gemischter Dyslipidämie, zusätzlich zu einer diätetischen Therapie"*? Wie sieht die Versorgungspraxis in Deutschland aus?

Es besteht internationaler Konsens zu der kausalen Bedeutung von LDL-Cholesterin für die Pathogenese der Atherosklerose und ihrer Folgeerkrankungen (1). Ohne LDL-C ist die Entstehung von Atherosklerose nicht möglich. Eine monogene, isolierte Erhöhung von LDL-C führt ohne weitere Risikofaktoren zur Entstehung von Atherosklerose (z.B. bei Personen mit Familiärer Hypercholesterinämie). Eine medikamentöse Senkung von LDL-C reduziert das proportional das Risiko der Folgen der Atherosklerose, insbesondere Herzinfarkt, Schlaganfall und kardiovaskulären Tod. Daher richtet sich die lipidsenkende Therapie nach dem LDL-C (1,2).
Der LDL-C Zielwert wird individuell bestimmt und richtet sich nach dem kardiovaskulären Risiko. Das Vorgehen zur Risiko-Bestimmung ist in Quellen 2 und 3 detailliert dargestellt (zusammenfassende Abbildung aus 3):

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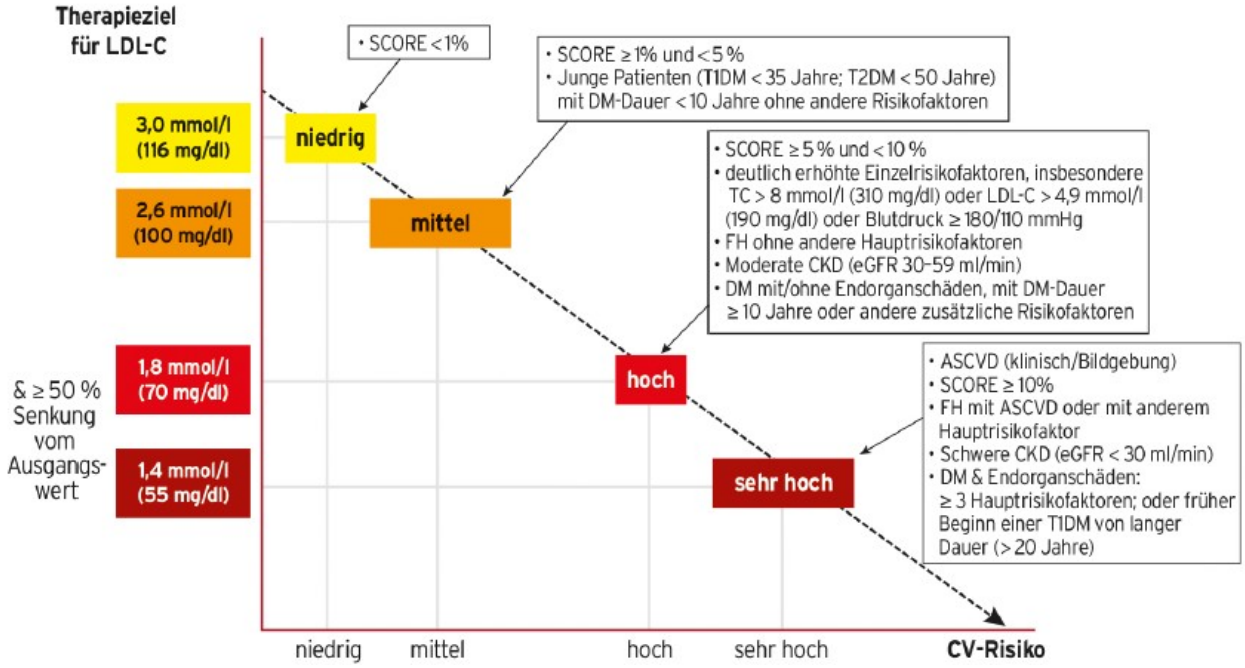
Zentrale Abbildung A) Obere Tafel: LDL-Cholesterin-Therapiezielwerte (LDL-C) in verschiedenen Kategorien des kardiovaskulären Gesamtrisikos.



Therapeutisches Vorgehen:
Die Basis der Therapie stellt die Lebensstil-Modifikation dar (Nikotin-Stop, körperliche Aktivität, Ernährung, Gewichtsreduktion). Das Ziel der Lebensstilmaßnahmen ist die Reduktion des Gesamt-Risikos. Der Einfluss einzelner Komponenten der Lebensstilmaßnahmen auf das LDL-C *per se* hängt von der individuellen Ausgangssituation ab und kann, z.B. bei Patienten mit Familiärer Hypercholesterinämie, gering sein.

Die Basis der pharmakologischen LDL-C Senkung ist die Statin Therapie. Wenn die Zielwerte unter der maximal implementierbaren Statin-Dosis nicht erreicht werden kommt eine Kombinationstherapie zum Einsatz. Hierzu sind Ezetimib und/oder PCSK9 Inhibitoren geeignet (zusammenfassende Abbildung aus

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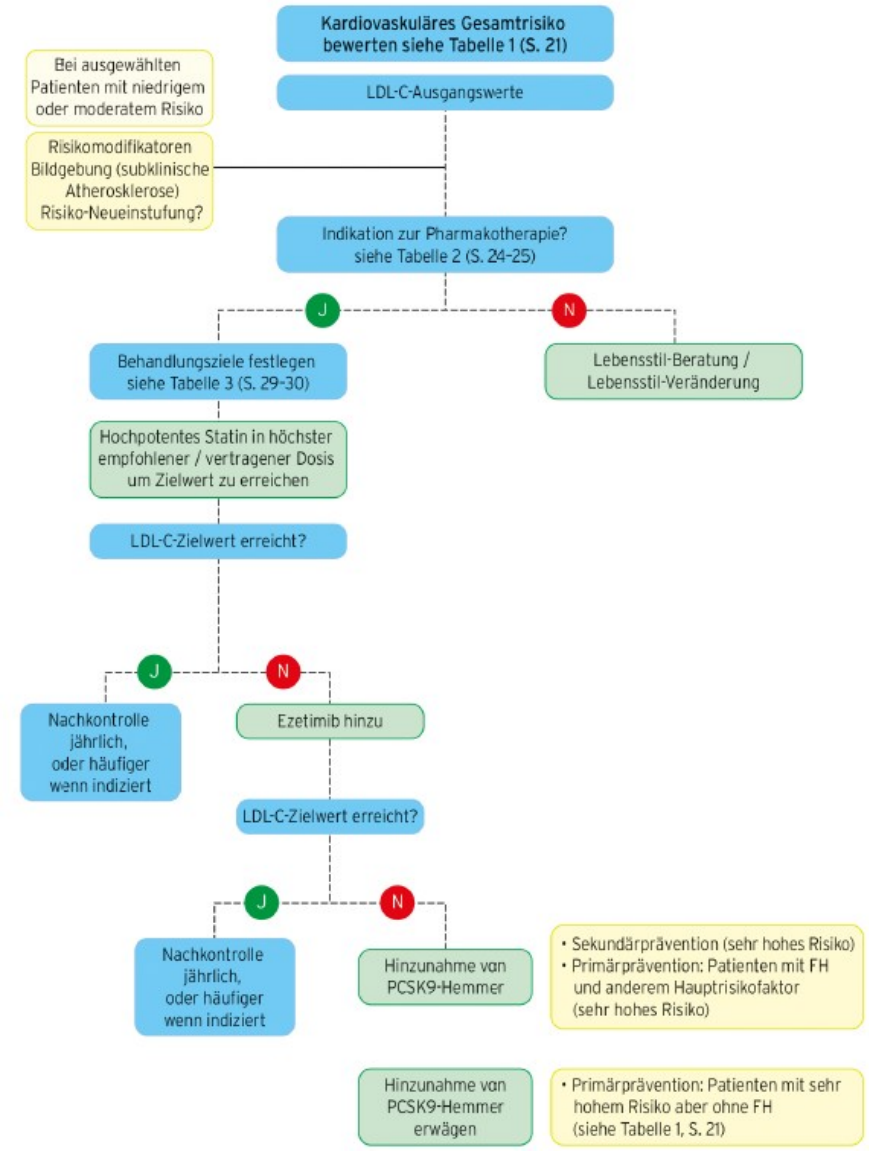
Zentrale Abbildung B) Untere Tafel: Behandlungsalgorithmus zur medikamentösen LDL-C-Senkung



3):

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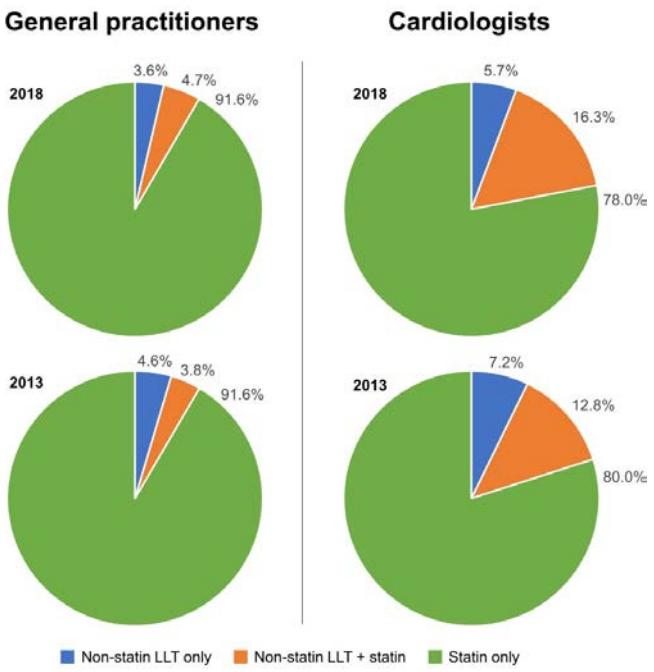
• allein oder in Kombination mit anderen lipidsenkenden Therapien bei Patienten mit Statin-Intoleranz oder für welche ein Statin kontraindiziert ist.

Wie sieht die Versorgungspraxis in Deutschland aus?

Die Auswertung **von** 311.242 Patienten mit sehr hohem Risiko, die in Deutschland zwischen 2013 und 2018 mit einem oralen Lipid-Senker behandelt wurden (Datenquelle: IMS® Disease Analyzer) zeigt, dass in 80-90% eine Monotherapie mit einem Statin erfolgt (Quelle 4):



Quellen:

Quelle 1: Borén J et al., Low-density lipoproteins cause atherosclerotic cardiovascular disease: pathophysiological, genetic, and therapeutic insights: a consensus statement from the European Atherosclerosis Society Consensus Panel. Eur Heart J. 2020;41(24):2313-2330. doi: 10.1093/eurheartj/ehz962.

Quelle 2: 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. ESC Scientific Document Group. Mach F et al. Eur Heart J. 2020;41(1):111-188. doi: 10.1093/eurheartj/ehz455.

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Quelle 3: Pocket-Leitlinie der Deutschen Gesellschaft für Kardiologie – Herz- und Kreislaufforschung e.V. (DGK), Diagnostik und Therapie der Dyslipidämien (Version 2019) Börm Bruckmeier Verlag, 978-3-89862-995-9; https://leitlinien.dgk.org/files/2020_pocket_leitlinie_dyslipidaemie_fuer_homepage_.pdf

Quelle 4: Katzmann JL et al., Non-statin lipid-lowering therapy over time in very high-risk patients: effectiveness of fixed-dose statin/ezetimibe compared to separate pill combination on LDL-C. Clinic Res Cardiol 2020, in press

Gibt es Kriterien für unterschiedliche Behandlungsentscheidungen bei der Behandlung von „*erwachsenen Patienten mit primärer Hypercholesterinämie (heterozygot familiär und nicht-familiär) oder gemischter Dyslipidämie, zusätzlich zu einer diätetischen Therapie*“ die regelhaft berücksichtigt werden? Wenn ja, welche sind dies und was sind in dem Fall die Therapieoptionen?

Unterschiede bzgl. Behandlung von Personen mit Familiärer Hypercholesterinämie im Vergleich zu Personen mit nicht-familiärer oder gemischter Dyslipidämie:
Als Grundprinzip richtet sich die notwendige Intensität der LDL-C Senkung nach dem individuellen Global-Risiko des Patienten und dem LDL-C.
Dabei beeinflussen spezifische Konstellationen des Lipid-Stoffwechsels das Gesamt-Risiko. Ein Beispiel ist die Risiko-Erhöhung durch das Vorliegen einer Familiärer Hypercholesterinämie (FH), da hier eine hohe LDL-C Exposition ab Geburt vorliegt. Daher ist das LDL-C-bezogene Risiko eines Erwachsenen mit FH höher als das Risiko einer Person mit nicht-familiärer LDL-Hypercholesterinämie.

Folgende Empfehlungen gelten für die Familiärer Hypercholesterinämie (FH):

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• allein oder in Kombination mit anderen lipidsenkenden Therapien bei Patienten mit Statin-Intoleranz oder für welche ein Statin kontraindiziert ist.

Empfehlungen zur Diagnose und Behandlung von Patienten mit heterozygoter familiärer Hypercholesterinämie

Empfehlungen	Empf.-grad	Evidenz-grad
Eine Verdachtsdiagnose auf FH besteht bei Patienten mit KHK im Alter <55 Jahre für Männer und <60 Jahre für Frauen, bei Personen mit Verwandten, die frühzeitig eine tödliche oder nicht-tödliche CVD erlitten oder Sehnenxanthome haben, sowie bei Personen mit stark erhöhtem LDL-C (bei Erwachsenen >5 mmol/l [>190 mg/dl], bei Kindern >4 mmol/l [>150 mg/dl]), und bei Verwandten 1. Grades* von FH-Patienten.	I	C
Es wird empfohlen, die FH-Diagnose anhand klinischer Kriterien zu stellen und, wenn verfügbar, mittels DNA-Analyse zu bestätigen.	I	C
Sobald ein Indexpatient mit FH diagnostiziert wurde, wird eine Familienuntersuchung empfohlen.	I	C
Es wird empfohlen, FH-Patienten mit ASCVD oder einem anderen Hauptrisikofaktor als Höchstrisiko und jene ohne vorbestehende ASCVD oder andere Risikofaktoren als Hochrisiko zu behandeln.	I	C

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• allein oder in Kombination mit anderen lipidsenkenden Therapien bei Patienten mit Statin-Intoleranz oder für welche ein Statin kontraindiziert ist.

Empfehlungen zur Diagnose und Behandlung von Patienten mit heterozygoter familiärer Hypercholesterinämie (Fortsetzung)

Empfehlungen	Empf.-grad	Evidenz-grad
Für FH-Patienten mit ASCVD und sehr hohem Risiko sollte die Behandlung eine Senkung um ≥50% vom Ausgangswert und ein LDL-C <1,4 mmol/l (<55 mg/dl) anstreben. Falls diese Ziele nicht erreicht werden, wird eine Kombinationstherapie empfohlen.	I	C
Zur Primärprävention für FH-Patienten mit sehr hohem Risiko sollte eine LDL-C-Senkung um ≥50% vom Ausgangswert und ein LDL-C-Zielwert von <1,4 mmol/l (<55 mg/dl) erwogen werden.	IIa	C
Behandlung mit einem PCSK9-Hemmer wird bei FH-Patienten mit sehr hohem Risiko empfohlen, wenn das Therapieziel trotz maximal vertragener Statin-Dosis plus Ezetimib nicht erreicht wurde.	I	C
Bei Kindern wird eine FH-Diagnostik ab dem Alter von 5 Jahren empfohlen oder früher, falls eine homozygote FH vermutet wird.	I	C
Kinder mit FH sollten dazu erzogen werden, sich richtig zu ernähren, und ab 8-10 Jahren mit einem Statin behandelt werden. Therapieziel sollte ab einem Alter >10 Jahren ein LDL-C <3,5 mmol/l (<135 mg/dl) sein.	IIa	C

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* Abweichend vom sonstigen deutschen Sprachgebrauch sind hierin auch Geschwister eingeschlossen.

Quelle: Pocket-Leitlinie der Deutschen Gesellschaft für Kardiologie – Herz- und Kreislaufforschung e.V. (DGK), Diagnostik und Therapie der Dyslipidämien (Version 2019) Börm Bruckmeier Verlag, 978-3-89862-995-9; https://leitlinien.dgk.org/files/2020_pocket_leitlinie_dyslipidaemie_fuer_homepage_.pdf

Weitere Beispiele für ein erhöhtes Global-Risiko bei Personen gemischter Dyslipidämie, deren Risiko zusätzlich zu dem LDL-C bezogenen Risiko erhöht ist, sind Personen mit hohen Triglyceriden oder Personen mit hohem Lipoprotein (a).

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Triglyceride: Die Lipid-Zielwerte bei erhöhten Triglyceriden richten sich nach dem Non-HDL Cholesterin oder ApoB (Parhofer KG, Laufs U: Diagnose und Therapie der Hypertriglyceridämie. Dtsch Arztebl Int 2019; 116: 825–32. DOI: 10.3238/arztebl.2019.0825):

TABELLE 2

Lipidzielwerte zur Prävention kardiovaskulärer Erkrankungen (5)

kardiovaskuläres Risiko*1	primärer Zielwert		Empfehlungsstufe/ Evidenzklasse	sekundäre Zielwerte		
	LDL-C			Non-HDL-C		Apo B
	mg/dL	mmol/L		mg/dL	mmol/L	mg/dL
niedrig*2	< 116	< 3,0	IIb / A			
moderat*2	< 100	< 2,6	IIa / A	< 130	< 3,4	< 100
hoch	< 70	< 1,8	I / A	< 100	< 2,6	< 80
sehr hoch	< 55	< 1,4	I / A	< 85	< 2,2	< 65

*1 Abschätzung des kardiovaskulären Risikos anhand klinischer Parameter sowie des ESC-Scores (Risiko für ein tödliches kardiovaskuläres Ereignis in den nächsten zehn Jahren); zum Beispiel: „sehr hohes Risiko" bei nachgewiesener Atheroskleroseerkrankung oder Score > 20 %) oder „hohes Risiko" bei Diabetes mellitus ohne nachgewiesenem Endorganschaden.
*2 Diese Zielwerte können erwogen werden.

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Lipoprotein (a): Lp(a) ist ein Risikomarker für Atherothrombose und Herzklappen-Verkalkung. Es sollte einmal im Leben bestimmt werden, um Personen mit hohem genetischen kardiovaskulären Risiko zu identifizieren (IIaC) (2). Lp(a) sollte insbesondere bei Personen mit Familien-Anamnese für prämature Atherosklerose und bei Patienten mit moderatem Risiko (zur Re-Klassifikation) bestimmt werden (IIaC). Ein Lp(a) > 50 mg/dl (75 nmol/L) zeigt ein erhöhtes kardiovaskuläres Risiko an.
Aufgrund der im Wesentlichen genetisch determinierten Lp(a) Pathologie sind die Serum-Konzentrationen unabhängig vom Lebensstil. Aktuell steht kein Wirkstoff zur Verfügung, der Lp(a) bei Personen mit sehr hohen Werten normalisieren könnte. Daher wird zur Reduktion des Lipid-bezogenen Risikos eine LDL-C Senkung empfohlen (2).

Weitere Beispiele für pathogene Lipid-Konstellationen, u.a. Diabetes mellitus oder Niereninsuffizienz, sind in (2) und (3) dargestellt.

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2020-B-244

DEGAM mit zustimmender Kenntnisnahme der Deutschen Gesellschaft für Ernährungsmedizin

Indikation gemäß Beratungsantrag

zur Behandlung erwachsener Patienten mit primärer Hypercholesterinämie (heterozygot familiär und nicht-familiär) oder gemischter Dyslipidämie, zusätzlich zu einer diätetischen Therapie:

• in Kombination mit einem Statin oder einem Statin mit anderen lipidsenkenden Therapien bei Patienten, die mit der maximal tolerierbaren Statin-Dosis die LDL-C-Ziele nicht erreichen, oder

• allein oder in Kombination mit anderen lipidsenkenden Therapien bei Patienten mit Statin-Intoleranz oder für welche ein Statin kontraindiziert ist.

Was ist der Behandlungsstandard unter Berücksichtigung der vorliegenden Evidenz *"zur Behandlung erwachsener Patienten mit primärer Hypercholesterinämie (heterozygot familiär und nicht-familiär) oder gemischter Dyslipidämie, zusätzlich zu einer diätetischen Therapie*"? Wie sieht die Versorgungspraxis in Deutschland aus?

I. Für die Sekundärprävention nach kardiovaskulären Ereignissen ist in Deutschland im Wesentlichen die Nationale Versorgungsleitlinie „chronische KHK"[i] maßgeblich, die von allen relevanten deutschen Fachgesellschaften ratifiziert wurde.
II. Für die Primärprävention ist neben den Arzneimittelrichtlinien (AMR) im hausärztlichen Bereich die S3-Leitlinie der DEGAM[ii] zur „hausärztlichen Beratung zur kardiovaskulären Prävention" maßgeblich.
III. Bei speziellen Fragestellungen wie extrem erhöhten Lipidwerten können ggf. auch aus internationalen Leitlinien relevante Empfehlungen abgeleitet werden.

Gibt es Kriterien für unterschiedliche Behandlungsentscheidungen bei der Behandlung von „*erwachsenen Patienten mit primärer Hypercholesterinämie (heterozygot familiär und nicht-familiär) oder gemischter Dyslipidämie, zusätzlich zu einer diätetischen Therapie*" die regelhaft berücksichtigt werden? Wenn ja, welche sind dies und was sind in dem Fall die Therapieoptionen?

1. Die Therapie des erhöhten kardiovaskulären Risikos besteht im Wesentlichen in Lebensstiloptimierung, Behandlung anderer Risikofaktoren (z.B. Diabetes, Hypertonie) und Gabe von Statinen. Bei Statinunverträglichkeit können leitliniengerecht auch andere lipidsenkende Medikamente verordnet werden.
2. In der Sekundärprävention erfolgt in der Regel die Gabe von Statinen. In der aktuellen NVL KHK werden als Alternativen die Gabe von Standard- bzw. Hochdosis bzw. die Titration auf bestimmte LDL-Zielwerte benannt.
3. In der Primärprävention erfolgt zunächst die Abschätzung des kardiovaskulären Risikos mit einem etablierten Risikokalkulator (arriba, PROCAM, QRISK-3; ggf. Score…) und ggf. Einleitung einer medikamentösen Behandlung bei einem Risiko >20% in 10 Jahren (AMRL). Dabei wird die Hypertriglyceridämie in der Regel nicht berücksichtigt, weil sie in anderen Faktoren abgebildet wird (insbesondere Diabetes, non-HDL-Cholesterin und Adipositas). Ein Lp(A) kann ggf. einmalig

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zusätzlich bei nicht anderweitig erklärbarem erhöhten familiärem oder individuellem Risiko bestimmt werden (kann aber derzeit nicht direkt behandelt werden)

4. Entsprechend der aktuellen Evidenzlage empfiehlt die DEGAM-Leitlinie, dass bei Patienten mit absolutem Gefäßrisiko von 10-20 %/10 Jahre und deutlich erhöhtem altersbezogenem Risiko eine medikamentöse Behandlung nach individueller Beratung erwogen werden kann.
5. Bei Hinweisen (Gesamtcholesterin über 320mg% und LDL über 195mg% und erhöhtes familiäres Risiko) auf familiäre Hypercholesterinämien empfiehlt die DEGAM-Leitlinie die Anwendung der Simon-Broome-Kriterien für die Diagnose.

Zu 1-3) Die Orientierung am kardiovaskulären Risiko spiegelt sich in den gesetzlichen Vorgaben – in Deutschland bestehen im Bereich der gesetzlichen Krankenversicherung (GKV) Richtlinien für eine wirtschaftliche Verordnung. Der gemeinsame Bundesausschuss (G-BA) hat gemäß §92, §16 und §34 des SGB V in der Anlage III zu den Arzneimittelrichtlinien (AMR) die Verordnung lipidsenkender Medikamente zu Lasten der GKV untersagt mit Ausnahmen bei:

- bestehender vaskulärer Erkrankung (KHK, zerebrovaskuläre Manifestation, pAVK)
- hohem kardiovaskularem Risiko (über 20 % Ereignisrate/10 Jahre auf der Basis der zur Verfügung stehenden Risikokalkulatoren und entsprechend Metaanalysen von Interventionsstudien bei Personen ohne vorherige Gefäßereignisse[iii] [iv].
- begründeten Einzelfallen mit besonders hohem Langzeitrisiko (z.B. bei familiärer Hypercholesterinamie)

Zu 4) (Zitate aus DEGAM-Leitlinie) *„…In einer aktuellen Cochrane-Metaanalyse von 14 Primärpräventions-Statinstudien [v] zeigte sich eine signifikante Verringerung kardiovaskularer Ereignisse (RRR 31 %, NNT 50) bereits bei einem durchschnittlichen absoluten Risiko für kardiovaskuläre Ereignisse von 6,4 % in 4,9 Jahren (entspricht ca. 13 % in 10 Jahren). Weitere signifikante Ergebnisse ergaben sich in diesem Risikobereich für Herzinfarkte (RRR 28%, NNT 55), Schlaganfalle (RRR 22 %, NNT 196) sowie die Gesamtsterblichkeit (RRR 16 %, NNT 208) [vi].*
Aktuelle Metaanalysen der CTT auf der Basis individueller Daten von über 170.000 Patienten zeigten eine durchgängige etwa 15%ige relative Risiko-Reduktion kardiovaskulärer Ereignisse und der Gesamtmortalität auch unterhalb eines absoluten Risikos von 10 %/10 Jahren [vii] [viii].

Eine Diskussion über eine Absenkung der Indikationschwelle z.B. auf absolut 10-15 %/10 Jahre ist angesichts der notwendigen Abwägung von Kosten und möglichen unerwünschten Wirkungen der Behandlung noch nicht abgeschlossen [ix] [x] [xi].
Eine Absenkung der Indikationsschwelle von 20 % auf 7,5 % entsprechend der AHA/ACC-Leitlinie von 2013 wurde bei US-amerikanischen Erwachsenen den behandlungsbedürftigen Anteil von 37,5 % auf 48,6 % erhöhen – insbesondere bei 60-75-Jahrigen ohne Vorerkrankungen [xii].

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In Großbritannien wurde in der NICE-Leitlinie von 2014 [xiii]die Schwelle des 10-Jahres-Risikos für 40 bis 74-Jahrige auf 10 % herabgesetzt [xiv]; allerdings bezogen auf den nur in Großbritannien anwendbaren Risikokalkulator QRISK2 bzw. QRISK3.

In den derzeit gültigen Bestimmungen der Arzneimittelrichtlinie findet sich die Option einer individuell zu begründenden Statin-Therapie unterhalb der genannten Risikoschwelle von 20% z.B. bei einem ungewöhnlich hohen relativen Risiko im Vergleich zur altersentsprechenden Population.
„Die behandelnde Ärztin oder der behandelnde Arzt kann die nach dieser Richtlinie in ihrer Verordnung eingeschränkten und von der Verordnung ausgeschlossenen Arzneimittel (Nr. 3 - 6) ausnahmsweise in medizinisch begründeten Einzelfallen mit Begründung verordnen (§ 31 Abs.1 Satz 4 SGB V, § 16 Abs. 5 AM – RL) [xv].
Dies stellt eine praktikable Annäherung an Behandlungsindikationen entsprechend dem kardiovaskulären Lebenszeit-Risiko dar, die derzeit diskutiert wird [xvi] [xvii]…“

Zu 5) familiäre Hypercholesterinämie

(Aus der DEGAM-LL): *„…Bei Patienten mit einer stark ausgeprägten Cholesterinerhöhung liegt in der Regel ein so hohes absolutes Gefäßrisiko vor, dass Modifikationen des Lebensstils (Bewegung, Ernährung) allein nicht ausreichen und eine medikamentöse Behandlung (primär mit einem Statin) sinnvoll ist[xviii] [xix] [xx] und deswegen allgemein empfohlen wird [xxi] [xxii] [xxiii] [xxiv][xxv].*

Als unteren Grenzwert für die direkte Therapieindikation empfehlen die meisten Leitlinien ein Gesamtcholesterin > 8 mmol/l (entsprechend > 310 mg/dl) [xxvi] [xxvii] [xxviii] [xxix].

Die familiäre Hypercholesterinämie ist mit einer Prävalenz von mindestens 1:500 relativ häufig und ist definiert als Kombination von LDL > 4,9 mmol/l (> 190 mg/dl) mit Xanthomen oder mit einer Familienanamnese für vorzeitige KHK (bei Männern vor dem 55 bzw. bei Frauen vor dem 60. Lebensjahr). [xxx]
Durch konsequente Behandlung ab dem Kindesalter insbesondere mit Diät und Statinen (in Studien meist Pravastatin in Standard-Dosis) kann das Risiko für Heterozygote – auch ohne vollständige Cholesterin-Normalisierung – auf das Niveau der Allgemeinbevölkerung abgesenkt werden [xxxi] [xxxii] [xxxiii][xxxiv]

Molekulargenetische Methoden tragen zu einer höheren Spezifität der Diagnostik, Begründung der Behandlungsintensität und Vereinfachung des Screenings von Verwandten Betroffener bei.

Eine einheitliche Definition der familiären Hypercholesterinamie (FH) gibt es derzeit nicht.
Klose et al.[xxxv] schlagen folgende Kriterien für die klinische Diagnose einer familiären Hypercholesterinämie vor:

- *erhöhtes LDL-Cholesterin (> 190 mg/dL, 4,9 mmol/L),*
- *positive Familienanamnese für Hypercholesterinämie oder*
- *entweder frühzeitige koronare Herzerkrankung oder Nachweis von Xanthomen.*

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Die Simon-Broome Kriterien für eine FH sind differenzierter und seit Jahren etabliert [xxxvi] [xxxvii] https://www.akdae.de/Arzneimitteltherapie/TE/A-Z/PDF/Fettstoffwechselstoerungen.pdf

[i] NVL chronische KHK (2019); https://www.leitlinien.de/nvl/khk (zuletzt besucht am 21. 9.2020)
[ii] DEGAM-Leitlinie Hausärztliche Risikoberatung zur kardiovaskulären Prävention https://www.awmf.org/uploads/tx_szleitlinien/053-024l_S3_Hausaerztliche_Risikoberat_kardiovask_Praevention_2018-09.pdf (besucht am 21.09.2020)
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