Rage Against The Risk Factors

(Lipids and Hypertension Masterclass)

Rahul Mohan (GP with Extended role in Diabetes, GP Principal Nottingham)

Hannah Beba (Consultant Pharmacist for Diabetes Leeds Health and Care Partnership)

@rahmoh1 | @hannahbeba

Conflicts of Interest Rahul Mohan

Pharmaceutical and other medical companies for which you have attended an Advisory Board in the past 3 years- None

Pharmaceutical and other medical companies for which you have delivered or received sponsored education in the past 3 years-) Novo Nordisk, Abbott, Astra Zeneca, Eli Lilly, Janssen, Grunenthal, A.Menarini Pharma, Shionogi, Boehringer-Ingelheim, Bayer, Daiichi Sankyo

Roles that you hold a professional contract with (i.e. for which you earn a salary/fee-Not in receipt of any retainer from any Pharmaceutical Company

Professional non-financial roles- PCDS Committee Member (currently co-opted)

SAHF

Other relevant potential conflicts of interest

Partner and Principal –Ruddington Medical Centre

Nottingham and Nottinghamshire ICB- Chair of Task and Finish group, EDEN trainer

Investment in Pharmaceutical companies-None

Conflicts of Interest Hannah Beba

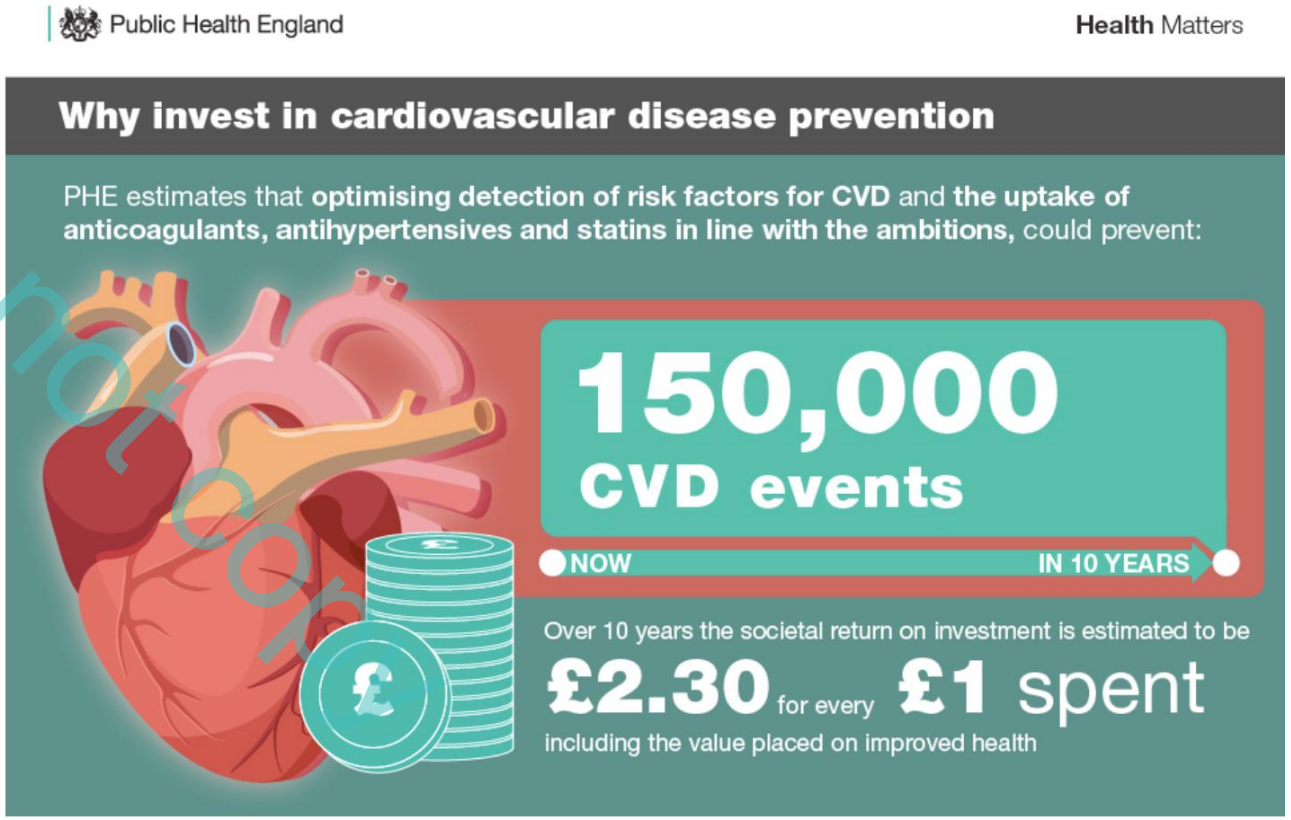
Pharmaceutical and other medical companies for which you have attended an Advisory Board in the past 3 years	ADA virtual attendance 2023 – sponsorship from Lilly EASD attendance 2023 – sponsorship from Daiichi Sankyo ADA virtual attendance 2022 – sponsorship from Lilly EASD in person attendance 2022- sponsorship from Novonordisk EASD virtual attendance 2021 – sponsorship from Novonordisk Since joining Leeds CCG and now Leeds Health and Care Partnership no personal payments have been made to myself from pharmaceutical companies for advisory boards. In the last three years I have taken part in advisory boards for Sanofi, Roche, Abbott, Astra Zeneca, Lilly, Novonordisk, Boehringer, Royal college of Physicians, QiC awards, Diabetes UK, Primary Care Pharmacy Association, Amarin, Manchester University, Leeds University.
Pharmaceutical and other medical companies for which you have delivered or received sponsored education in the past 3 years	Since joining Leeds CCG and now Leeds Health and Care Partnership no personal payments have been made to myself from pharmaceutical companies for education. I have done education linked to: Kings fund, i2i, CPPE, DPC, SPS, Newcastle University, PM Management, PCDS, Amgen, Lilly, Sunderland University, Astra Zeneca, Leeds University, DSN Forum, RPS, PCDE, DUK, Cardiology Professional Care, PCPA, Sanofi, PITSTOP, BHS, BCS
Roles that you hold a professional contract with (i.e. for which you earn a salary/fee)	Consultant Pharmacist for West Yorkshire and Leeds Health and Care Partnership Tutor for Warwick university MSC in Diabetes
Professional non-financial roles	Co-chair of Diabetes UK Council of Healthcare Professionals Member of the UKCPA Diabetes and Endocrinology Committee Member of the Primary Care Diabetes Society Member of Royal Pharmaceutical Society Chair of the Expert Reference Group for Cardio-Renal and Metabolic Medicine at Leeds Health and Care Partnership Chair for the Diabetes Steering Group at Leeds Health and Care partnership Member of the Primary Care Diabetes Transformation and Innovation Group Member of the Expert Working Group for Diabetes Policy
Other relevant potential conflicts of interest	**N/A**

NHS Long Term Plans

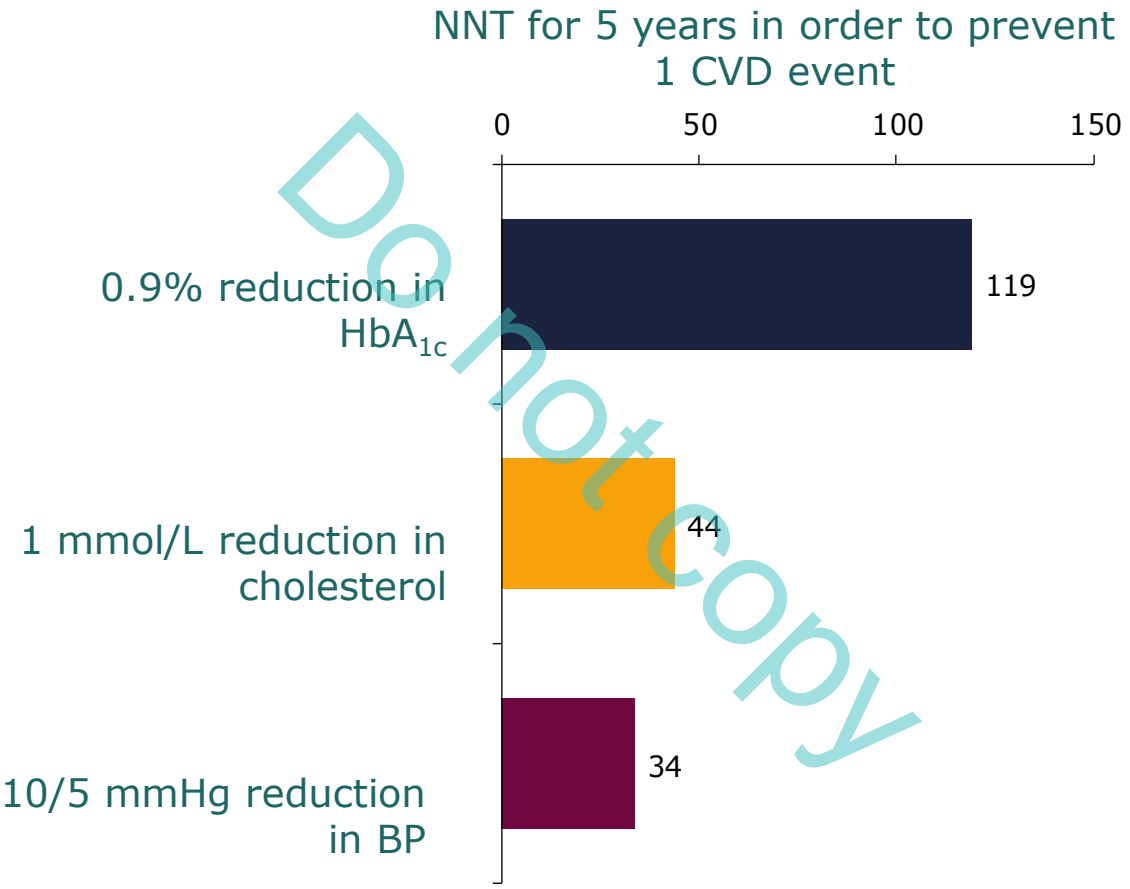
ABC Strategy-

Detection and Management of high-risk conditions-

- Atrial Fibrillation
- **B**lood Pressure
- **C**holesterol



Three Treatment Targets

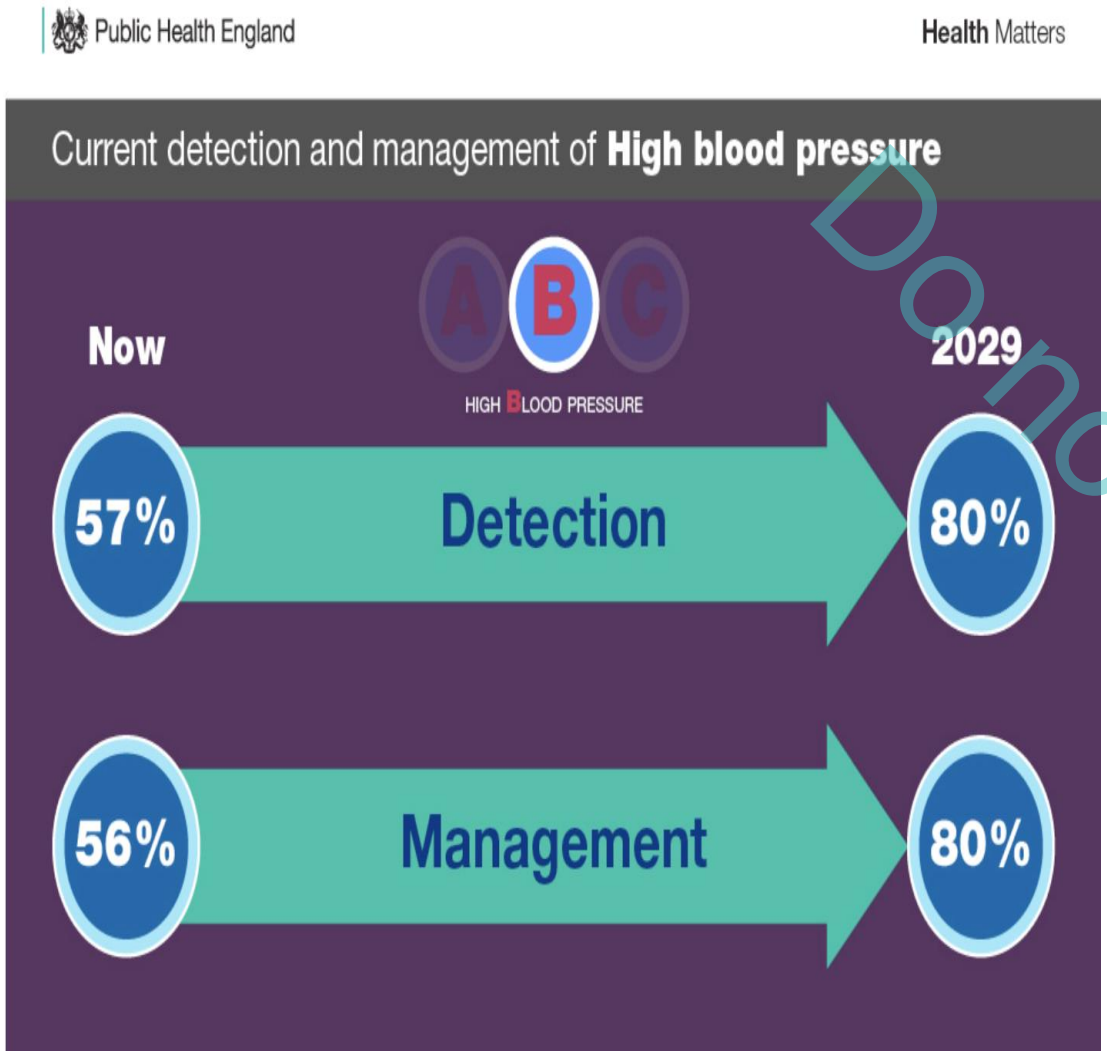


For each variable, data shown are for a change corresponding to the mean change of the variable in intervention studies

BP=blood pressure; CVD=cardiovascular disease; NNT=number needed to treat

20. Adapted from Yudkin JS et al (2010) *Diabetologia* **53**: 2079–85 https://link.springer.com/content/pdf/10.1007%2Fs00125-010-1864-z.pdf
Accessed September 2017

High blood pressure



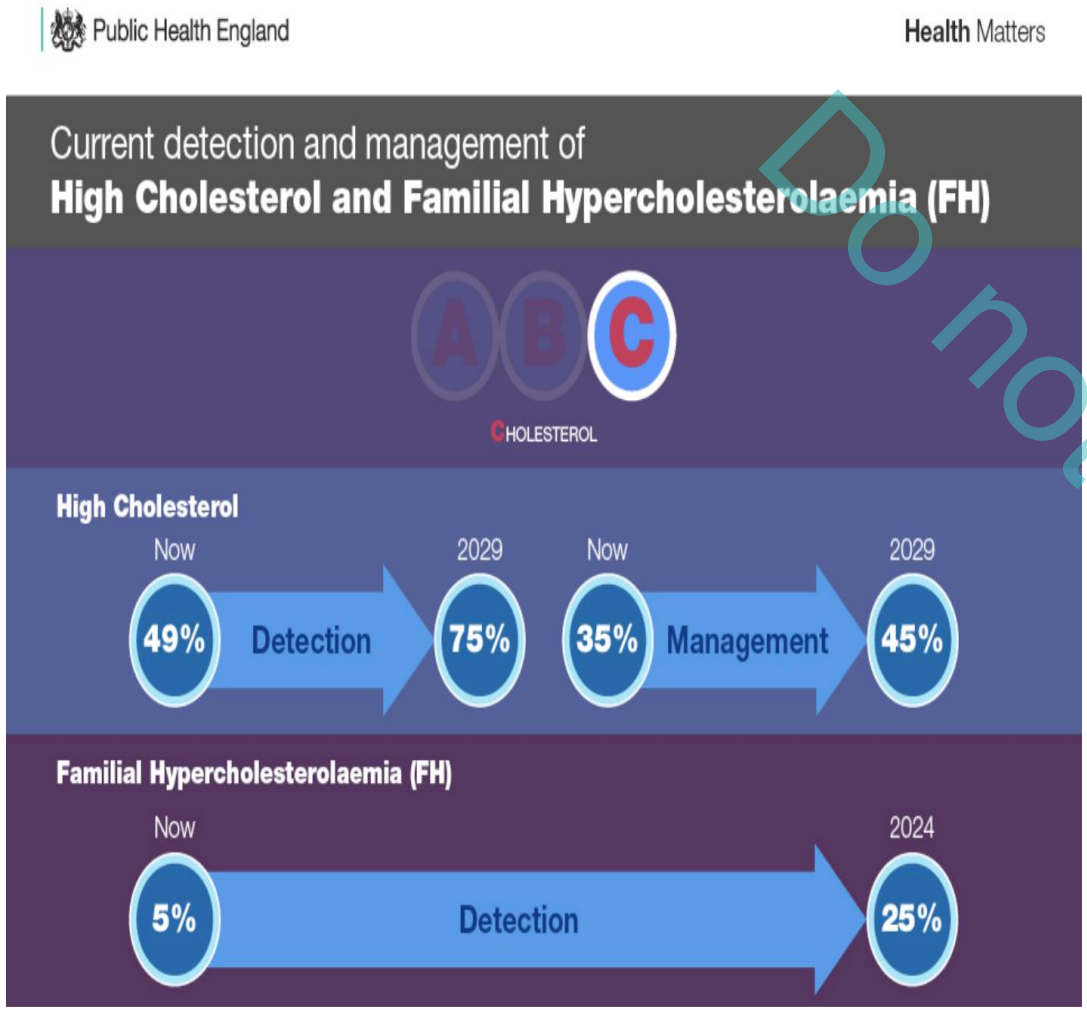
The ambition

The high BP ambitions of the CVDSLF -

- 80% of the expected number of people with high BP are diagnosed by 2029

- 80% of the total number of people diagnosed with high BP are treated to target as per NICE guidelines by 2029

Raised cholesterol



The ambition

The cholesterol ambitions of the CVDSLF

- 75% of eligible people aged 40-74 without established CVD have received a formal validated CVD risk assessment and cholesterol reading recorded on a primary care data system in the last 5 years by 2029
- 45%of people aged 40-74 without established CVD greater 10 year risk of developing CVD are treated by statin by 2029
- 25% of people with Familia Hypercholesterolaemia are diagnosed and treated optimally according to the NICE FH Guidelines by 2024

"I've always been a high achiever, always striving for bigger, faster, greater...and now suddenly I'm expected to settle for *lower* blood pressure and *less* cholesterol?!"

QoF Lipids (CHOL)

QOF		
CHOL001	Percentage of patients on the QOF Coronary Heart Disease, Peripheral Arterial Disease, Stroke/TIA or Chronic Kidney Disease Register who are currently prescribed a statin, or where a statin is declined or clinically unsuitable, another lipid-lowering therapy	14 Points 70-95%
CHOL002	Percentage of patients on the QOF Coronary Heart Disease, Peripheral Arterial Disease, or Stroke/TIA Register, who have a recording of non-HDL cholesterol in 16 20-35% 14 the preceding 12 months that is lower than 2.5 mmol/L, or where non-HDL cholesterol is not recorded a recording of LDL cholesterol in the preceding 12 months that is lower than 1.8 mmol/L	16 Points 20-35%

Therapeutic Inertia in the management of dyslipidaemia and hypertension in primary care

Received: 19 January 2021 | Revised: 15 February 2021 | Accepted: 26 February 2021
DOI: 10.1111/dom.14364

Check for updates

WILEY

ORIGINAL ARTICLE

Therapeutic inertia in the management of dyslipidaemia and hypertension in incident type 2 diabetes and the resulting risk factor burden: Real-world evidence from primary care

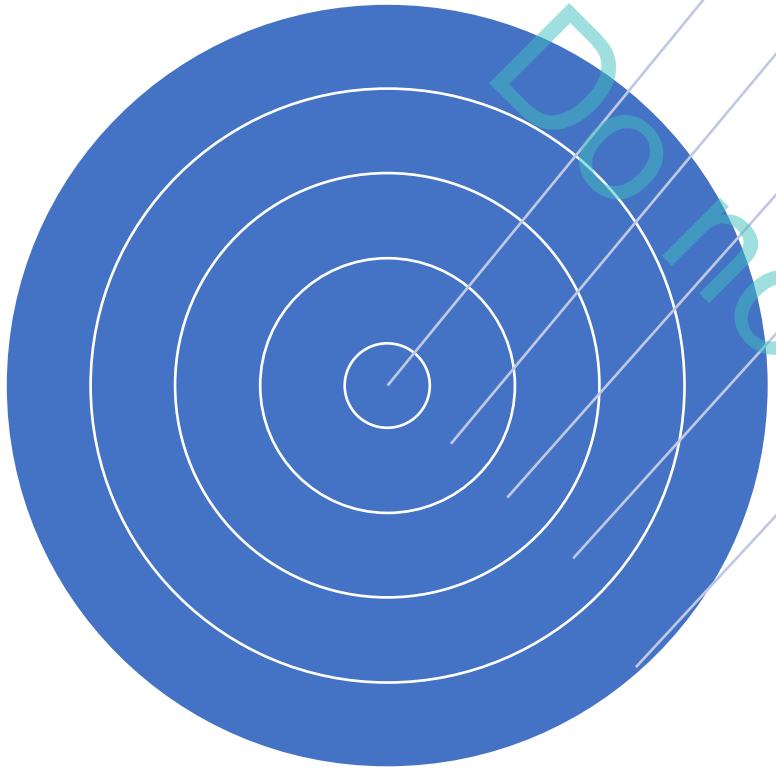
Joanna Z.J. Ling MSc[1,2] | Olga Montvida PhD[1] | Kamlesh Khunti PhD[3] | Anthony L. Zhang PhD[2] | Charlie C. Xue PhD[2] | Sanjoy K. Paul PhD[1,2]

[1]Melbourne EpiCentre, University of Melbourne and Melbourne Health, Melbourne, Victoria, Australia
[2]School of Health and Biomedical Sciences, RMIT University, Melbourne, Victoria, Australia
[3]Department of Health Sciences, University of Leicester, Leicester, UK

Does therapeutic inertia exist when we are managing lipids in primary care?

Fire and forget approach needs to be changed to Treat to target approach

What are the lipid therapies targeting?



Repeat cardiovascular events

Secondary prevention – becoming more important as people are surviving more primary events

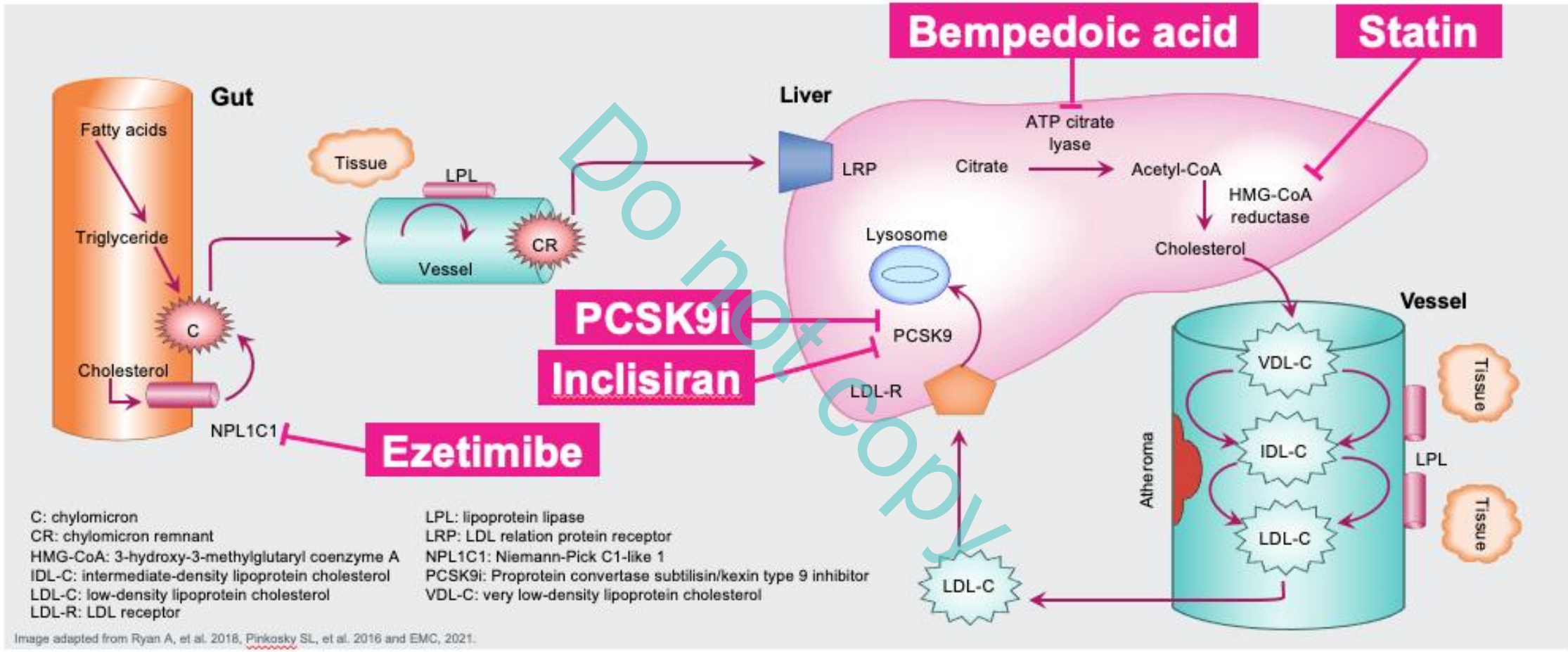
First cardiovascular event

Primary prevention – increased prevalence of cardiovascular risk factors e.g. obesity and diabetes makes this important at population level (promoting health lifestyles) and individual levels (reducing causal risk by addressing unhealthy lifestyle, blood pressure, lipids tec.)

Primordial prevention – all people should be enabled to live a healthy lifestyle

Cooney MT, Dudina A, Whincup P, Capewell S, Menotti A, Jousilahti P, Njolstad I, Oganov R, Thomsen T, Tverdal A, Wedel H, Wilhelmsen L, Graham I; SCORE Investigators. Re-evaluating the Rose approach: comparative benefits of the population and high-risk preventive strategies. Eur J Cardiovasc Prev Rehabil 2009;16:541549.

Catapano AL, Graham I, De Backer G, Wiklund O, Chapman MJ, Drexel H, Hoes AW, Jennings CS, Landmesser U, Pedersen TR, Reiner Z, Riccardi G, Taskinen MR, Tokgozoglu L, Verschuren WMM, Vlachopoulos C, Wood DA, Zamorano JL, Cooney MT; ESC Scientific Document Group. 2016 ESC/EAS Guidelines for the management of dyslipidaemias.Eur Heart J 2016;37:29993058.



C: chylomicron; CR: chylomicron remnant; HMG-CoA: 3-hydroxy-3-methylglutaryl coenzyme A; IDL-C: intermediate-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; LDL-R: LDL receptor; LPL: lipoprotein lipase; LRP: LDL relation protein receptor; LTT: lipid lowering therapy; NPL1C1: Niemann-Pick C1-like 1; PCSK9i: Proprotein convertase subtilisin/kexin type 9 inhibitor; VDL-C: very low-density lipoprotein cholesterol.

ESC European Society of Cardiology

European Heart Journal (2021) **42**, 3227–3337
doi:10.1093/eurheartj/ehab484

ESC GUIDELINES

2021 ESC Guidelines on cardiovascular disease prevention in clinical practice

Developed by the Task Force for cardiovascular disease prevention in clinical practice with representatives of the European Society of Cardiology and 12 medical societies

With the special contribution of the European Association of Preventive Cardiology (EAPC)

Authors/Task Force Members: Frank L.J. Visseren* (Chairperson) (Netherlands), François Mach* (Chairperson) (Switzerland), Yvo M. Smulders† (Task Force Coordinator) (Netherlands), David Carballo† (Task Force Coordinator) (Switzerland), Konstantinos C. Koskinas (Switzerland), Maria Bäck (Sweden), Athanase Benetos[8] (France), Alessandro Biffi[7,10] (Italy), José-Manuel Boavida[9] (Portugal), Davide Capodanno (Italy), Bernard Cosyns (Belgium), Carolyn Crawford (Northern Ireland), Constantinos H. Davos (Greece), Ileana Desormais (France), Emanuele Di Angelantonio (United Kingdom), Oscar H. Franco (Switzerland), Sigrun Halvorsen (Norway), F. D. Richard Hobbs[13] (United Kingdom), Monika Hollander (Netherlands), Ewa A. Jankowska (Poland), Matthias Michal[11] (Germany), Simona Sacco[6] (Italy), Naveed Sattar (United Kingdom), Lale Tokgozoglu[2] (Turkey), Serena Tonstad (Norway), Konstantinos P. Tsioufis[5] (Greece), Ineke van Dis[3] (Netherlands), Isabelle C. van Gelder (Netherlands), Christoph Wanner[4] (Germany), Bryan Williams (United Kingdom), ESC Scientific Document Group

* Corresponding authors: The two chairpersons contributed equally to the document. Frank Visseren, Department of Vascular Medicine, University Medical Center Utrecht, Heidelberglaan 100, 3584 CX Utrecht, Netherlands. Tel: +31 (0)88 7557324, E-mail: F.L.J.Visseren@umcutrecht.nl. François Mach, Cardiology Department, Geneva University Hospital, Perret-Gentil 4, 1211 Geneva, Switzerland. Tel: +41 (0)22 372 71 92, E-mail: francois.mach@hcuge.ch. † The two task force coordinators contributed equally to the document.

Author/Task Force Member affiliations: listed in Author information.

ESC Clinical Practice Guidelines Committee (CPG): listed in the Appendix.

ESC subspecialty communities having participated in the development of this document. Associations: Association of Cardiovascular Nursing & Allied Professions (ACNAP), European Association of Cardiovascular Imaging (EACVI), European Association of Preventive Cardiology (EAPC), European Heart Rhythm Association (EHRA), Heart Failure Association (HFA). **Councils:** Council for Cardiology Practice, Council on Hypertension. **Working Groups:** Aorta and Peripheral Vascular Diseases, Atherosclerosis and Vascular Biology, Cardiovascular Pharmacotherapy.

Patient Forum

The content of these European Society of Cardiology (ESC) Guidelines has been published for personal and educational use only. No commercial use is authorized. No part of the ESC Guidelines may be translated or reproduced in any form without written permission from the ESC. Permission can be obtained upon submission of a written request to Oxford University Press, the publisher of the *European Heart Journal* and the party authorized to handle such permissions on behalf of the ESC (journals.permissions@oup.com).

Disclaimer: The ESC Guidelines represent the views of the ESC and were produced after careful consideration of the scientific and medical knowledge and the evidence available at the time of their publication. The ESC is not responsible in the event of any contradiction, discrepancy and/or ambiguity between the ESC Guidelines and any other official recommendations or guidelines issued by the relevant public health authorities, in particular in relation to good use of healthcare or therapeutic strategies. Health professionals are encouraged to take the ESC Guidelines fully into account when exercising their clinical judgment, as well as in the determination and the implementation of preventive, diagnostic or therapeutic medical strategies; however, the ESC Guidelines do not override, in any way whatsoever, the individual responsibility of health professionals to make appropriate and accurate decisions in consideration of each patient's health condition and in consultation with that patient and, where appropriate and/or necessary, the patient's caregiver. Nor do the ESC Guidelines exempt health professionals from taking into full and careful consideration the relevant official updated recommendations or guidelines issued by the competent public health authorities, in order to manage each patient's case in light of the scientifically accepted data pursuant to their respective ethical and professional obligations. It is also the health professional's responsibility to verify the applicable rules and regulations relating to drugs and medical devices at the time of prescription.

Guidelines for Lipid Management

Summary of National Guidance for Lipid Management for Primary and Secondary Prevention of CVD

ACCELERATED ACCESS COLLABORATIVE

NHS

INITIAL CONSIDERATIONS:
• Measure non-fasting ***full lipid profile*** (total cholesterol, HDL-C, non-HDL-C, triglycerides) and HbA1c as part of an initial baseline assessment. • Consider secondary causes of hyperlipidaemia and manage as needed.
• Ensure appropriate baseline and follow up tests as detailed on page 2. Measure BMI. • Identify and exclude people with contraindications/drug interactions • If non-fasting triglyceride above 4.5mmol/L see page 2.

PRIMARY PREVENTION

Consider statin therapy for adults who do not have established CVD but fall into the categories below. Use QRISK risk assessment tool where appropriate (see page 2, *'Primary Prevention Risk Assessment'*)

- Age ≤84 & QRISK ≥10% over next 10 years
- Type 2 diabetes & QRISK ≥10% over next 10 years
- Type 1 diabetes, if they have one or more of the following:
  - Over 40 years
  - Had diabetes for >10 years
  - Have established nephropathy
  - Have other CVD risk factors
- CKD eGFR < 60 mL/min/1.73m² and/or albuminuria
- Age ≥85 years if appropriate consider comorbidities, frailty & life expectancy

Identify and address all modifiable risk factors - smoking, diet, obesity, alcohol intake, physical activity, blood pressure and HbA1c.

Consider additional risk factors, if present, together with QRISK score (treated for HIV, severe mental illness, taking medicines that cause dyslipidaemia, systemic inflammatory disorder (e.g. SLE), impaired fasting glycaemia, recent change in risk factors)

PRIMARY PREVENTION

If lifestyle modification is ineffective or inappropriate offer statin treatment.
Atorvastatin 20mg daily

- Measure full lipid profile again after 3 months (non-fasting).
- High intensity statin treatment should achieve reduction of non-HDL-C > 40% from baseline. If not achieved after 3 months;
  - discuss treatment adherence, timing of dose, diet and lifestyle
  - If at higher risk (based on comorbidities, risk score or clinical judgement – see page 2 *'Additional Risk Factors'*) consider increasing the dose every 2-3 months up to a maximum dose of atorvastatin 80mg daily,
  - For how to increase in people with CKD see *'Special Patient Populations'* (page 2).
- If patients on a high-intensity statin have side effects, offer a lower dose or an alternative statin (see page 2 *'Extent of lipid lowering with available therapies'*)
- If maximum tolerated dose of statin does not achieve non-HDL-C reduction > 40% of baseline value after 3 months consider adding Ezetimibe 10mg daily (NICE TA385)
- If statin treatment is contraindicated or not tolerated;
  - See AAC Statin Intolerance Algorithm for advice regarding adverse effects (click here)
  - Ezetimibe 10mg monotherapy may be considered. Assess response after 3 months.
  - Ezetimibe 10mg/bempedoic acid 180 mg combination may be considered when ezetimibe alone does not control non-HDL-C/LDL-C well enough (NICE TA694).

If non-HDL-C reduction remains < 40% of baseline despite maximal tolerated lipid lowering therapy (including people with intolerances and contraindications) consider referral to specialist lipid management clinic according to local arrangements

SEVERE HYPERLIPIDAEMIA

If TC>7.5mmol/L and/or LDL-C >4.9mmol/L and/or non-HDL-C >5.9mmol/L, a personal and/or family history of confirmed CHD (<60 years) and with no secondary causes: suspect familial hypercholesterolaemia (possible heterozygous FH)

Do not use QRISK risk assessment tool

DIAGNOSIS AND REFERRAL

Take fasting blood for repeat lipid profile to measure LDL-C.

Use the **Simon Broome** or **Dutch Lipid Clinic Network** (DLCN) criteria to make a **clinical diagnosis of FH.**

Refer to Lipid Clinic for further assessment if **clinical diagnosis of FH** or if TC>9.0mmol/L and/or LDL-C >6.5mmol/L and/or non-HDL-C >7.5mmol/L or Fasting triglycerides > 10mmol/L (regardless of family history) (page 2)

TREATMENT TARGETS IN FH

If clinical diagnosis of FH and/or other risk factors present follow the recommended treatment management pathway for primary or secondary prevention as for non-FH, ***BUT***

Aim to achieve at least a 50% reduction of LDL-C (or non-fasting non-HDL-C) from baseline.

Consider specialist referral for further treatment and/or consideration of PCSK9i therapy IF
- they are assessed to be at very high risk of a coronary event**
- OR therapy is not tolerated
- OR LDL-C remains >5mmol/L (primary prevention)
- OR LDL-C remains >3.5mmol/L (secondary prevention)

despite maximal tolerated statin and ezetimibe therapy.

**defined as any of the following:
• Established coronary heart disease
• Two or more other CVD risk factors

SECONDARY PREVENTION

Offer statin therapy to adults with CVD, this includes CHD, angina, Acute Coronary Syndrome (MI or unstable angina), revascularisation, stroke or TIA, or symptomatic peripheral arterial disease. Do not delay statin treatment if a person has acute coronary syndrome. Take a lipid sample on admission (within 24 hours).

Identify and address all modifiable risk factors - smoking, diet, obesity, alcohol intake, physical activity, blood pressure and HbA1c.

SECONDARY PREVENTION

Do not delay statin treatment in secondary prevention while managing modifiable risk factors.
Prescribe a high intensity statin:
Atorvastatin 80mg daily
Use a lower dose of atorvastatin if there is a potential drug interaction, high risk of or experiencing adverse effects, or patient preference.
Offer atorvastatin 20mg if CKD (people with GFR< 60 mL/min/1.73m²).

- Measure full lipid profile again after 3 months (non-fasting).
- High intensity statin treatment should achieve reduction of non-HDL-C > 40% from baseline. If not achieved after 3 months
  - discuss treatment adherence, timing of dose, diet and lifestyle measures
  - If started on less than atorvastatin 80mg and the person is judged to be at higher risk (based on comorbidities, risk score or clinical judgement - see page 2 *'Additional Risk Factors'*), consider increasing to 80mg atorvastatin. For how to increase in people with CKD see *'Special Patient Populations'* (page 2).
- If non-HDL-C baseline value is not available*, consider target non-HDL-C < 2.5mmol/L (approximately equivalent to LDL-C < 1.8mmol/L) as recommended by Joint British Societies (JBS3).
  **this scenario is not currently covered by NICE CG181. NICE will consider this as part of the guideline update with publication currently expected September 2023*
- If patients on a high-intensity statin have side effects, offer a lower dose or an alternative statin (see page 2 *'Extent of lipid lowering with available therapies'*)

If maximum tolerated dose of statin does not control non-HDL-C/LDL-C well enough after 3 months confirm statin adherence, then consider the following options based on shared decision making* with the patient

If recommended statin treatment is contraindicated or not tolerated - follow AAC Statin Intolerance Algorithm for advice regarding adverse effects (click here).

If statin intolerance is confirmed, consider:
- **Ezetimibe 10mg** monotherapy. Assess response after 3 months (TA385)
- **Ezetimibe 10mg/bempedoic acid 180 mg** combination when ezetimibe alone does not control non-HDL-C sufficiently. (NICE TA694)

If non HDL-C remains > 2.5mmol/L despite other lipid lowering therapies consider Injectable therapies - arrange a fasting blood test and assess eligibility criteria (TA393/394, TA733)

Ezetimibe 10mg daily (NICE TA385). Reassess after three months. If non-HDL-C remains > 2.5mmol/L; consider **injectable therapies** arrange a fasting blood test and assess eligibility

Injectable therapies**
If non-HDL-C > 2.5mmol/L; Arrange fasting blood test to measure LDL-C to assess eligibility:
- **Inclisiran** - if fasting LDL-C ≥ 2.6mmol/L despite maximum tolerated lipid lowering therapy (TA733)

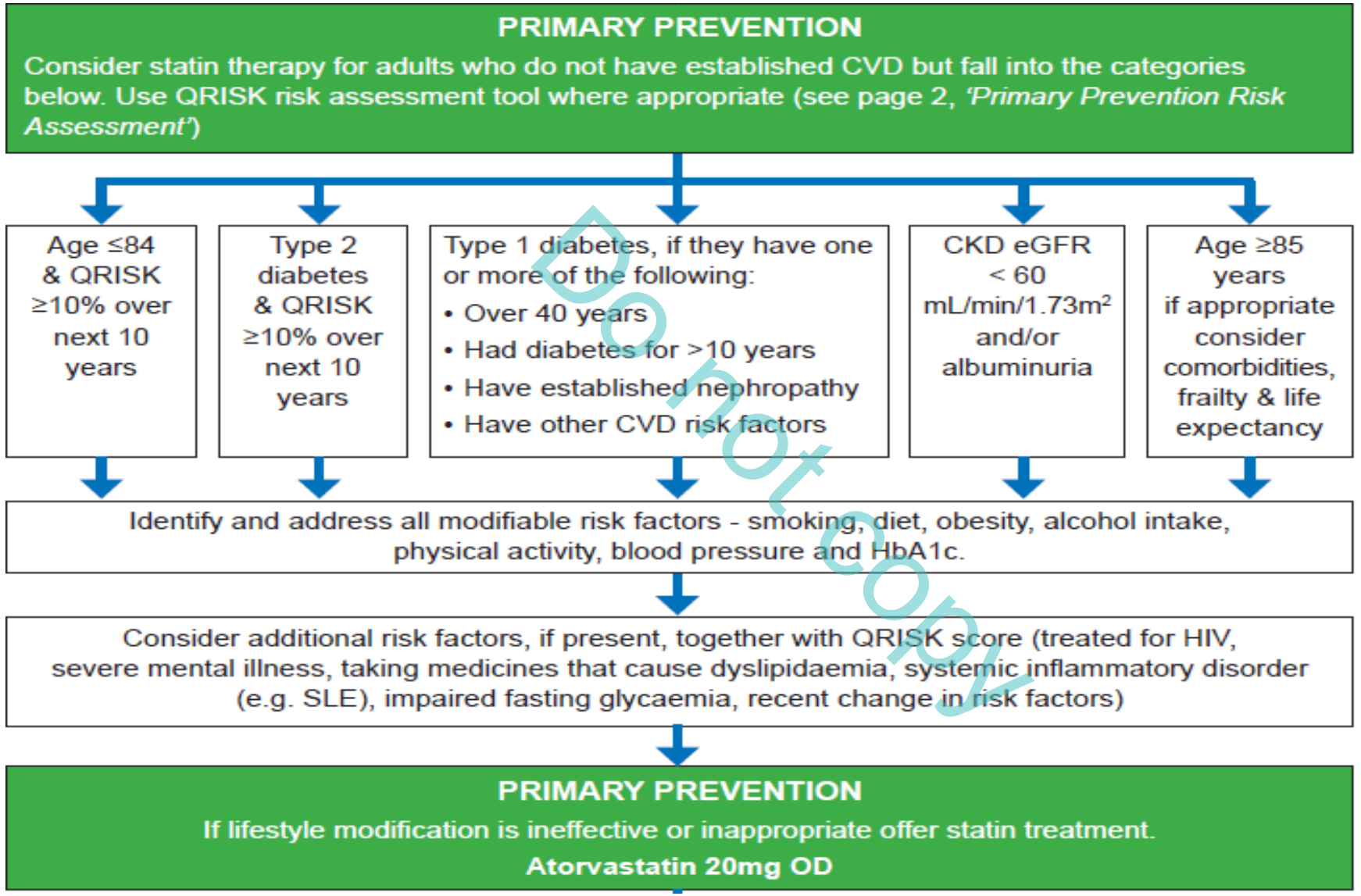
OR

- **PCSK9i** - see overleaf for LDL-C thresholds. (TA393/4)

If eligibility criteria not met, consider **ezetimibe 10mg daily** (if not previously considered)

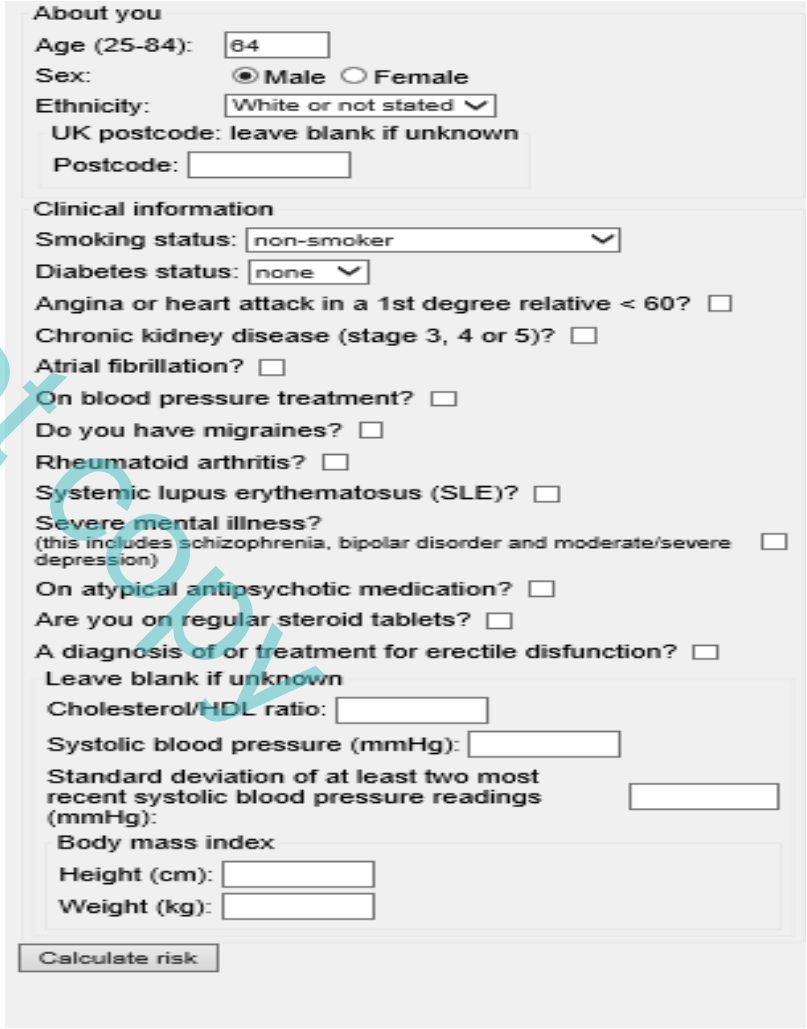
* See overleaf for information to support shared decision making
** Inclisiran and PCSK9i should not be prescribed concurrently

Additional CV risk reduction considerations - check fasting triglycerides levels and consider icosapent ethyl. See triglycerides section overleaf.


PRIMARY PREVENTION
Consider statin therapy for adults who do not have established CVD but fall into the categories below. Use QRISK risk assessment tool where appropriate (see page 2, 'Primary Prevention Risk Assessment')
Age ≤84 & QRISK ≥10% over next 10 years
Type 2 diabetes & QRISK ≥10% over next 10 years
Type 1 diabetes, if they have one or more of the following:
• Over 40 years
• Had diabetes for >10 years
• Have established nephropathy
• Have other CVD risk factors
CKD eGFR < 60 mL/min/1.73m² and/or albuminuria
Age ≥85 years if appropriate consider comorbidities, frailty & life expectancy
Identify and address all modifiable risk factors - smoking, diet, obesity, alcohol intake, physical activity, blood pressure and HbA1c.
Consider additional risk factors, if present, together with QRISK score (treated for HIV, severe mental illness, taking medicines that cause dyslipidaemia, systemic inflammatory disorder (e.g. SLE), impaired fasting glycaemia, recent change in risk factors)
PRIMARY PREVENTION
If lifestyle modification is ineffective or inappropriate offer statin treatment.
Atorvastatin 20mg OD

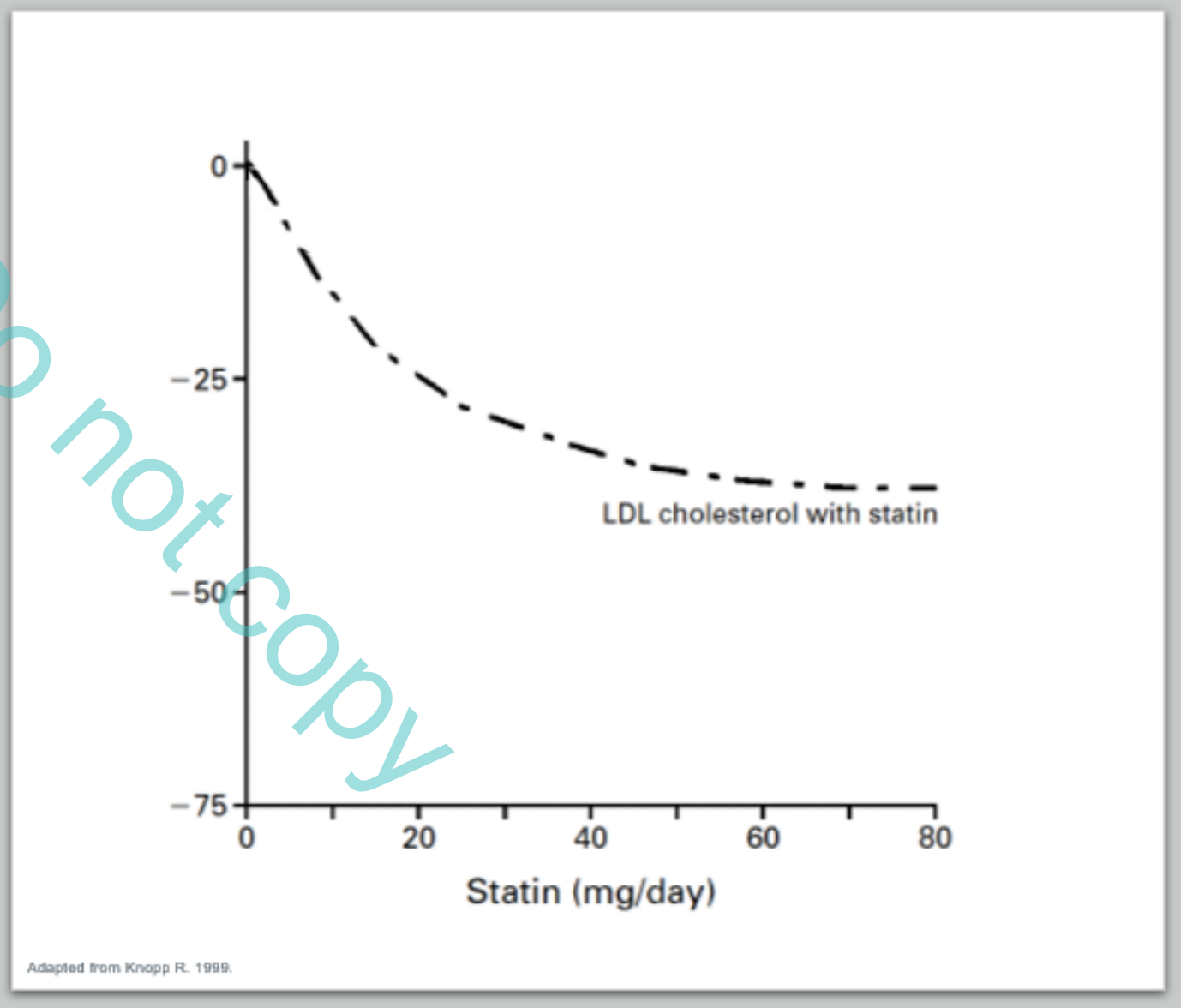
Primary Prevention Risk Assessment

- QRISK 3
- What is new from QRISK 2 ?
  - Chronic kidney disease, which now includes stage 3 CKD
  - Migraine
  - Corticosteroids
  - Systemic lupus erythematosus (SLE)
  - atypical antipsychotics
  - severe mental illness
  - erectile dysfunction
  - a measure of systolic blood pressure variability



Doubling the dose with statins does not double the effect on LDL-C reduction[1]

- The dose required to reduce serum LDL-C concentrations to a similar degree varies substantially among statins
- The response to dose increases is not proportional
- In general, a doubling of the dose above the minimal effective dose, decreases serum LDL-C concentrations by an additional 6%
- The maximal reduction in serum LDL-C concentrations induced by statin treatment ranges from 24–60%



1. Knopp RH. New Engl J Med 1999;341:498–511.

ESC European Society of Cardiology
European Heart Journal Open (2022) 2, 1–3
https://doi.org/10.1093/ehjopen/oeac071

EDITORIAL
Coronary artery disease

Adherence to statin therapy: it seems we know everything, yet we do nothing

Maciej Banach [1,2,3,*] **and Peter E. Penson** [4,5]

[1]Department of Preventive Cardiology and Lipidology, Medical University of Lodz, Rzgowska 281/289, 93-338 Lodz, Poland; [2]Cardiovascular Research Centre, University of Zielona Gora, Zyty 28, 65-417 Zielona Gora, Poland; [3]Department of Cardiology and Congenital Diseases of Adults, Polish Mother's Memorial Hospital Research Institute (PMMHRI), Rzgowska 281/289, 93-338 Lodz, Poland; [4]Clinical Pharmacy & Therapeutics Research Group, School of Pharmacy & Biomolecular Sciences, Liverpool John Moores University, Byrom Street, Liverpool L3 3AF, UK; and [5]Liverpool Centre for Cardiovascular Science, William Henry Duncan Building, 6 West Derby Street, Liverpool L7 8TX, UK

Online publish-ahead-of-print 26 October 2022

This editorial refers to 'Gaps and discontinuation of statin treatment in Norway: potential for optimizing management of lipid-lowering drugs', by I. Engebretsen *et al.* https://doi.org/10.1093/ehjopn/oeac070

Statin discontinuation is one of the most important reasons why such a small proportion of patients reach their LDL cholesterol (LDL-C) goal.[1] In the DaVinci study, only one-third of patients achieved their LDL-C target irrespective of their level of risk. Only 18% of those at very high cardiovascular risk reached targets.[2] The situation is even worse in the Central and Eastern European countries where only 24 and 13% of patients, respectively, from the groups mentioned above of 1.1% since 2010). These data imply that the majority of patients are not aware that they have lipid disorders or are not treated despite a diagnosis. In fact, quite similar results were obtained based on the data from the NATPOL study in Poland, which was performed in 2011. In this study, we showed that amongst subjects with hypercholesterolaemia, almost 60% were not aware of their condition; 22.0% were aware but were not receiving treatment; and only 10.9% were being treated.[8] The authors again confirmed that combination therapy with statin and ezetimibe is highly underused, with only 11% of patients treated with ezetimibe.[6] These results, in fact, reflect the current situation in Europe and worldwide.[3,5,9] To address this problem, the International Lipid Expert Panel, for the first time in April 2021, sug-

- **Statin discontinuation is one of most important reason why only a small proportion of patients reach their LDLc goals**
- **In DaVinci study, only 1/3rd of patients achieved target irrespective of their level of risk. Only 18% of those at very high cardiovascular risk reached targets**
- **Treatment should be started with upfront combination therapy of a statin and ezetimibe for the selected group of patients at very high and extremely high cardiovascular risk.**

Adding ezetimibe to statin therapies produces a further >20% reduction in LDL-C from baseline[1]

Statins alone vs statin + ezetimibe add-on as a second-line therapy across 27 double-blind, placebo and/or active-controlled studies. Studies included:

- **Add-on therapy:** patients on a stable dose of statin randomised to ezetimibe vs placebo while continuing the same dose of statin
- **Uptitration of therapy:** patients on a statin at baseline randomised to ezetimibe + their current statin vs uptitrating (doubling) the statin dose

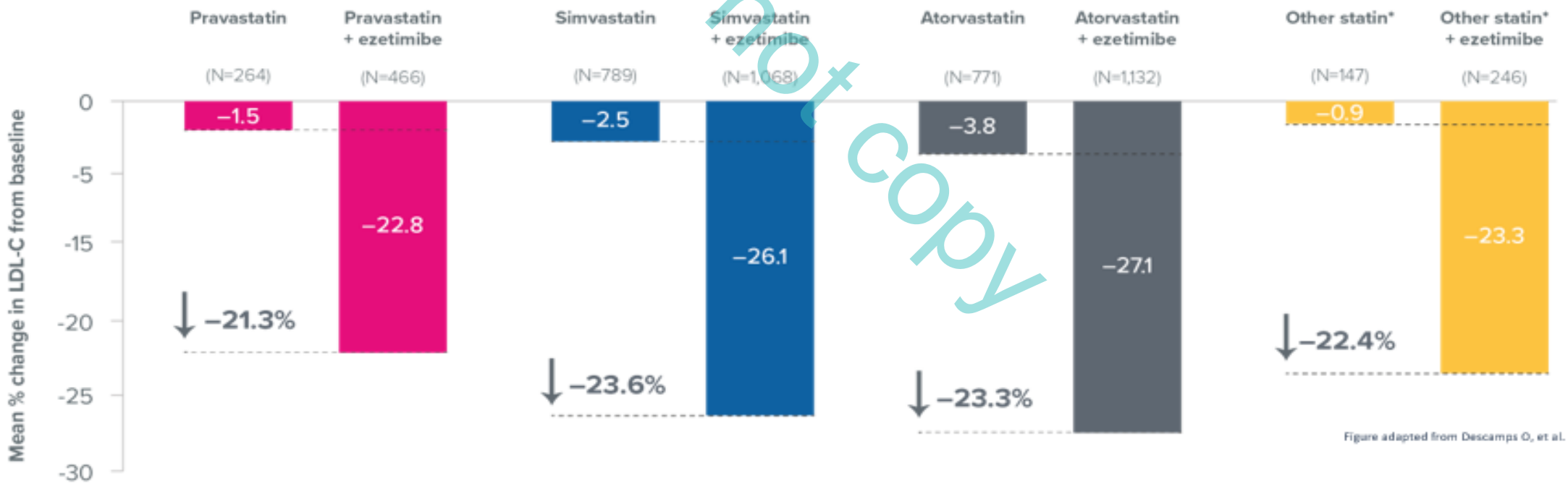


Figure adapted from Descamps O, et al. 2015.

*Lovastatin, fluvastatin, cerivastatin.
LDL-C: low-density lipoprotein cholesterol.

1. Descamps O, et al. Atherosclerosis 2015;240:482–489.

Very High Risk – ESC Guidelines

Descriptor
Previous ACS (heart attack or unstable angina), stable angina, coronary revascularization (PCI, CABG, and other arterial revascularization procedures), stroke and TIA, and peripheral arterial disease.
Significant plaque on coronary angiography or CT scan (multi-vessel coronary disease with two major epicardial arteries having >50% stenosis), or on carotid ultrasound.
Diabetes with target organ damage (microalbuminuria, retinopathy, neuropathy)
Diabetes with at least three major risk factors
Early onset of T1DM of long duration (>20 years).
Severe Chronic Kidney Disease (eGFR <30 mL/min/1.73 m2).
Familial Hypercholesterolaemia with ASCVD (atherosclerotic cardiovascular disease) or with another major risk factor.

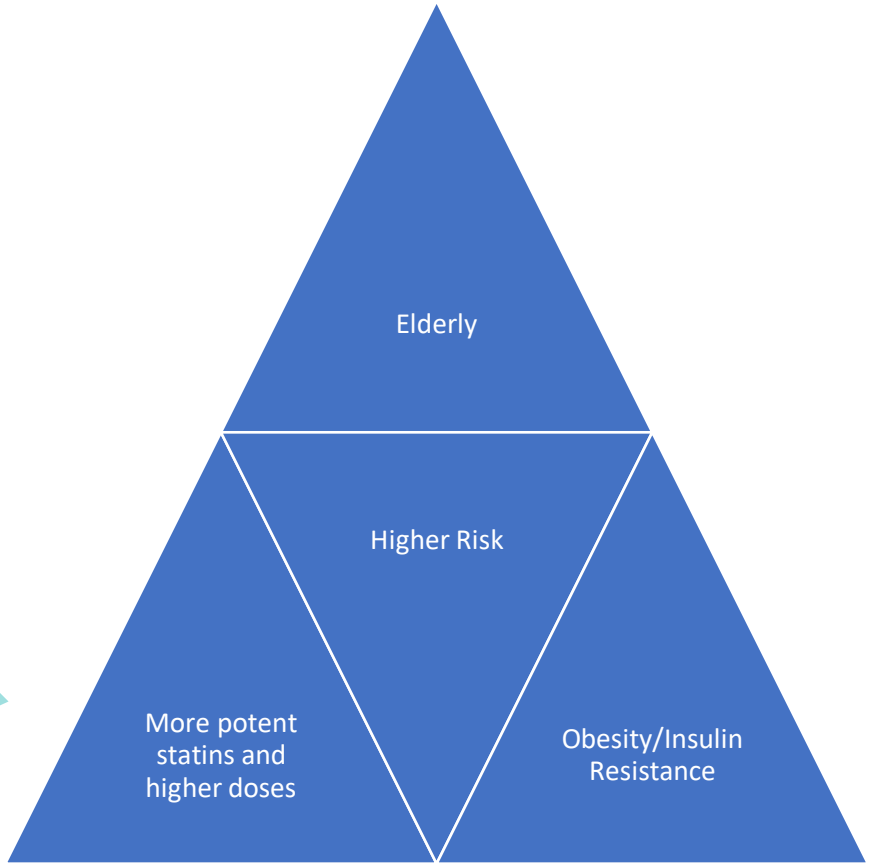
High and Moderate Risk – ESC Guidelines

Descriptor
Markedly elevated single risk factors, in particular TC>8 mmol/L (>310 mg/dL), LDL-C >4.9 mmol/L (>190 mg/dL), or BP >_180/110 mmHg. **Patients with Familial Hypercholesterolaemia without other major risk factors.** **Patients with Diabetes M without target organ damage with Diabetes duration >_10 years or another additional risk factor.** **Moderate CKD (eGFR 30-59 mL/min/1.73 m2).**
Young patients (T1DM <35 years; T2DM <50 years) with Diabetes duration <10 years, without other risk factors.

https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines/Dyslipidaemias-Management-of

Increased Risk of new Onset Diabetes

- Patients on statin treatment have been shown to exhibit an increased risk of dysglycaemia and development of type 2 diabetes mellitus (T2DM).
- Several studies have shown that this is a consistent, dose-related effect.
- A minor, not clinically relevant elevation of glycated haemoglobin (HbA1c) has also been observed.
- The number needed to cause one case of diabetes has been estimated as 255 over 4 years of statin treatment.
- The mechanism of action relates to HMG-CoA reductase inhibition. Polymorphisms of this enzyme also shows increased risk for DM.

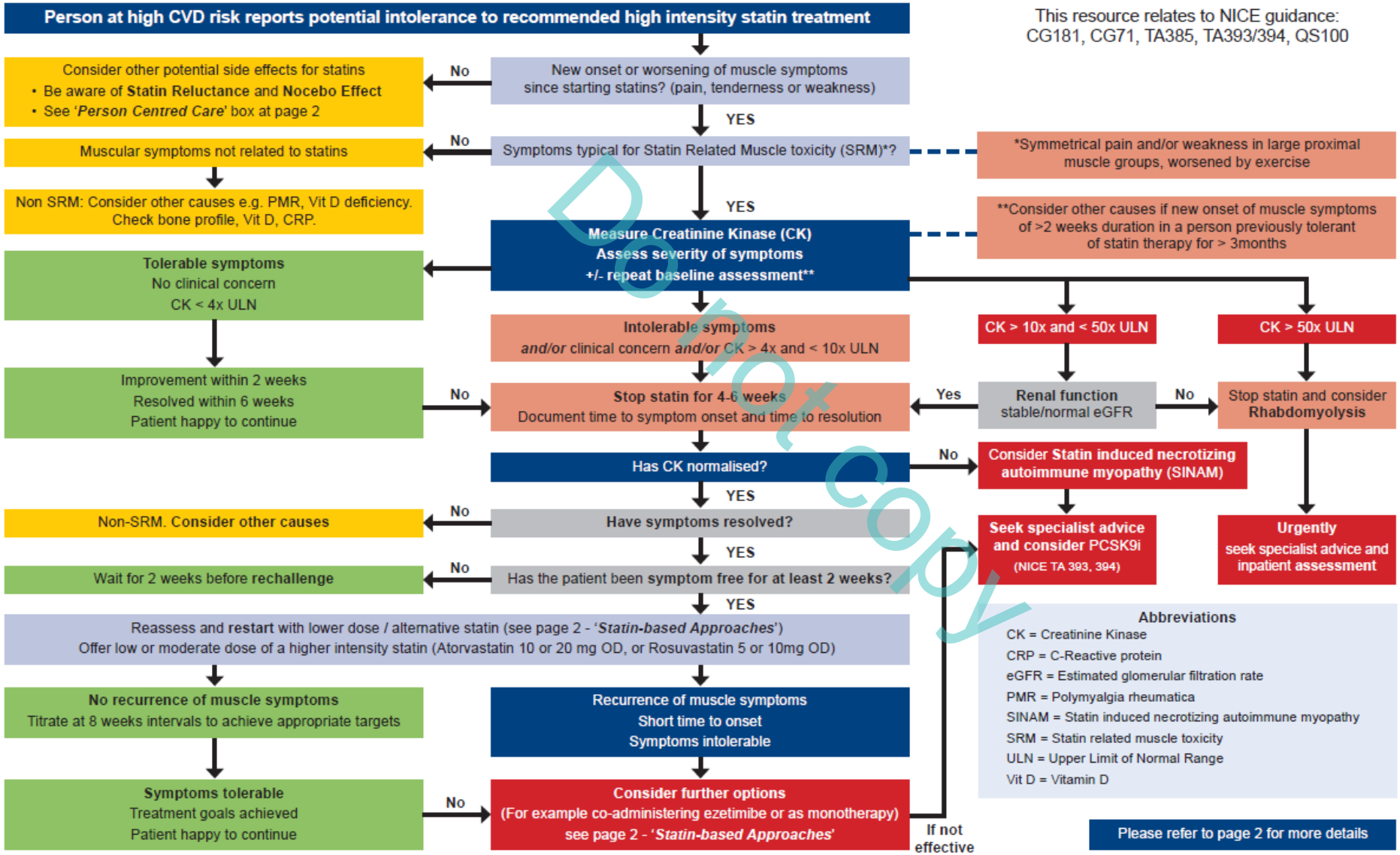


Law M, Rudnicka AR. Statin safety: a systematic review. Am J Cardiol 2006;97:52C60C.
Sattar N, Preiss D, Murray HM et al. 2010. Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. Lancet 375:735742.
Swerdlow DI, Preiss D, Kuchenbaecker KB, Holmes MV et al. HMGcoenzyme A reductase inhibition, type 2 diabetes, and bodyweight: evidence from genetic analysis and randomised trials. Lancet 2015;385:351361.

Statin Intolerance Pathway

ACCELERATED ACCESS COLLABORATIVE

NHS England



https://www.england.nhs.uk/aac/wp-content/uploads/sites/50/2020/09/statin-intolerance-pathway-03092020.pdf

Statin Intolerance Pathways

- Statins are the cornerstone for prevention and treatment of cardiovascular (CV)disease with a substantial evidence of reduction of morbidity and mortality. Refer to Lipid Management Pathway and related NICE guidelines (CG181,CG71) for guidance on initiation, titration and monitoring of statin therapy.
- In clinical trials, statins were found to be largely well tolerated (often with a similar adverse effect (AE) profile to placebo), however this is not reflected in clinical practice where up to 75% of people started on a statin will discontinue treatment within 2 years.
- Stopping statin therapy is associated with an increased risk of major CVevents and there is growing concern that clinicians are labelling patients as‘**statin intolerant**’ too quickly. Indeed statin discontinuation is significantlyassociated with negative media coverage.

https://www.england.nhs.uk/aac/wp-content/uploads/sites/50/2020/04/lipid-management-pathway-guidance.pdf

SRM vs non-SRM

- **Statin-associated muscle symptoms (SAMS)**
  - SAMS are one of the principal reasons for statin non-adherence and/or discontinuation. However, not all such symptoms should lead to a label of‘ statin intolerance’ as they may not be truly statin related muscle toxicity(SRM) as demonstrated by resolution on de-challenge and recurrence with re-challenge.

- **Non-Statin related musculoskeletal symptoms (Non SRM)**
  - If patients report symptoms that are not typical of SRM (e.g. asymmetric distribution, failure to resolve with de-challenge despite normal CK) consider other musculoskeletal disorders, metabolic, degenerative or inflammatory e.g.Vitamin D deficiency, polymyalgia rheumatica. Check Bone profile, Vit D, CRP.

https://www.england.nhs.uk/aac/wp-content/uploads/sites/50/2020/04/lipid-management-pathway-guidance.pdf

Risk Factors for Intolerance

Risk factors for SRM and statin intolerance

Endogenous factors

- Female gender
- Advanced age (> 75 yrs)
- Frailty (reduced lean body mass)
- History of muscle disorder or high CK
- Impaired renal or hepatic function
- Personal or Family history of intolerance to lipid-lowering therapies.
- Hypothyroidism

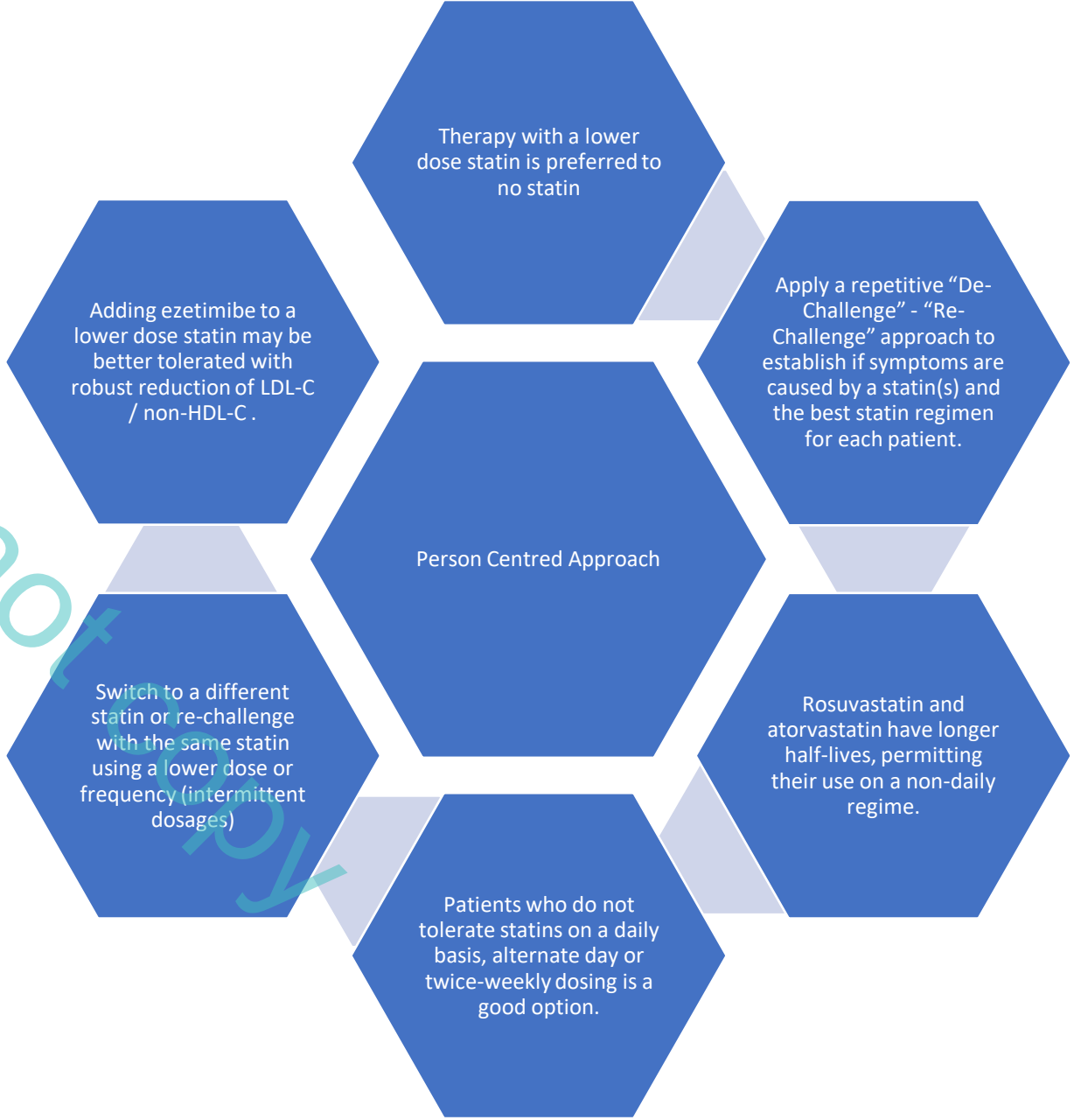
Exogenous Factors

- Excessive alcohol intake
- High intensity exercise
- Dehydration
- Drug interactions with statins (including herbal medicines)
- Vitamin D deficiency

https://www.england.nhs.uk/aac/wp-content/uploads/sites/50/2020/04/lipid-management-pathway-guidance.pdf

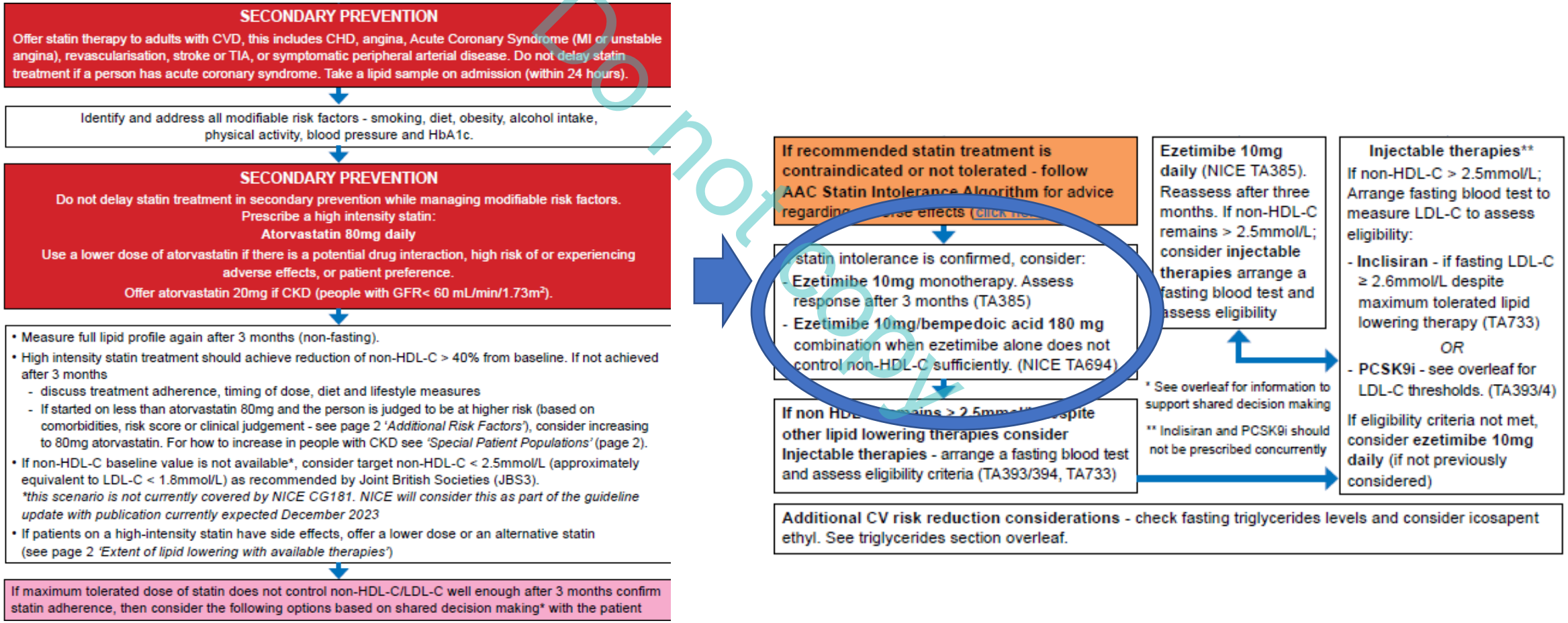
Statin based approaches to manage muscle symptoms

- Once a new regime is tolerated, dose / frequency can be up-titrated slowly to achieve LDL-C / non-HDL-C goals with minimal or no muscle complaints.
- *It is important to note that cardiovascular benefits have not been proven for all the above approaches but any reduction of LDL-C / non-HDL-C is beneficial*



https://www.england.nhs.uk/aac/wp-content/uploads/sites/50/2020/09/statin-intolerance-pathway-03092020.pdf

AAC Guidelines for Lipids



Bempedoic Acid

- Nilemdo is indicated in adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet:
  - in combination with a statin or statin with other lipid-lowering therapies in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin or,
  - alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated.

- Is available in a combination tablet of ezetimibe and bempedoic acid (the ezetimibe is free)
- With or without food
- TA states only to use with ezetimibe only where statins have not been tolerated or are contra-indicated

https://www.medicines.org.uk/emc/product/11743/smpc

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 13, 2023 VOL. 388 NO. 15

Bempedoic Acid and Cardiovascular Outcomes in Statin-Intolerant Patients

S.E. Nissen, A.M. Lincoff, D. Brennan, K.K. Ray, D. Mason, J.J.P. Kastelein, P.D. Thompson, P. Libby, L. Cho, J. Plutzky, H.E. Bays, P.M. Moriarty, V. Menon, D.E. Grobbee, M.J. Louie, C.-F. Chen, N. Li, L.A. Bloedon, P. Robinson, M. Horner, W.J. Sasiela, J. McCluskey, D. Davey, P. Fajardo-Campos, P. Petrovic, J. Fedacko, W. Zmuda, Y. Lukyanov, and S.J. Nicholls, for the CLEAR Outcomes Investigators*

ABSTRACT

BACKGROUND

Bempedoic acid, an ATP citrate lyase inhibitor, reduces low-density lipoprotein (LDL) cholesterol levels and is associated with a low incidence of muscle-related adverse events; its effects on cardiovascular outcomes remain uncertain.

METHODS

We conducted a double-blind, randomized, placebo-controlled trial involving patients who were unable or unwilling to take statins owing to unacceptable adverse effects ("statin-intolerant" patients) and had, or were at high risk for, cardiovascular disease. The patients were assigned to receive oral bempedoic acid, 180 mg daily, or placebo. The primary end point was a four-component composite of major adverse cardiovascular events, defined as death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or coronary revascularization.

RESULTS

A total of 13,970 patients underwent randomization; 6992 were assigned to the

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Nissen can be contacted at nissens@ccf.org or at the Department of Cardiovascular Medicine, Cleveland Clinic, Rm. JB-820, 9500 Euclid Ave., Cleveland, OH 44195.

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

This article was published on March 4, 2023, at NEJM.org.

N Engl J Med 2023;388:1353-64.
DOI: 10.1056/NEJMoa2215024

Presented at ESC Congress, Aug 2023

Three-component MACE (nonfatal MI, nonfatal stroke, CV death): 8.2% vs. 9.5% (p = 0.006)

- Fatal or nonfatal MI: 3.7% vs. 4.8% (p = 0.002)
- Coronary revascularization: 6.2% vs. 7.6% (p = 0.001)
- Fatal or nonfatal stroke: 1.9% vs. 2.3% (p = 0.16)
- All-cause mortality: 6.2% vs. 6.0%
- **Change in LDL-C at 6 months:** -21.1 vs. -0.8 mg/dL (p < 0.06)
- **Change in hsCRP from baseline at 12 months**: -20.6% vs. 0% (p < 0.05)
- **Any muscle disorder:** 15.0% vs. 15.4%
- Hyperuricemia: 10.9% vs. 5.6%
- Gout: 3.1% vs. 2.1%
- Cholelithiasis: 2.2% vs. 1.2%

Bempedoic Acid : CLEAR Outcomes

1. **Bempedoic acid has now entered the list of evidence-based alternatives to statins for primary and secondary prevention in patients at high cardiovascular risk.**

2. **it is a viable alternative for statin-intolerant individuals.**

3. **It was observed that there was a greater effect of Bempedoic acid in the primary-prevention cohort than in the secondary-prevention cohort.**

4. **Adverse effect profile of Bempedoic acid is reassuring and, helpfully, markedly different from statins. Advisable to undertake regular, albeit infrequent, blood monitoring after initiation of Bempedoic acid.**

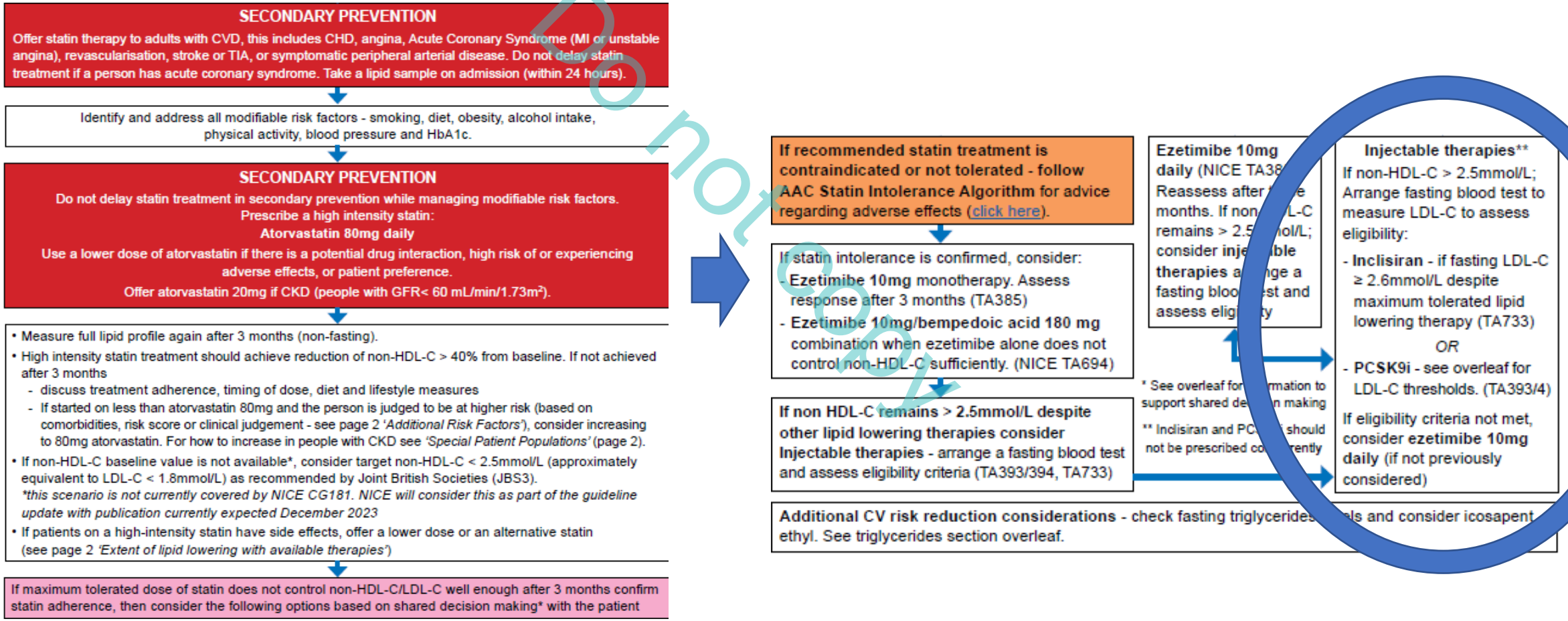
Nissen et al, 2023. Bempedoic Acid and Cardiovascular Outcomes in Satin Intolerant Patients. N Engl J Med 2023; 388:1353-1364
DOI: 10.1056/NEJMoa2215024

Bempedoic Acid - Safety

- Increases in serum transaminases (AST and/or ALT) have been reported with bempedoic acid - monitor LFTs
- Increases in serum uric acid were observed in clinical trials with bempedoic acid possibly related to inhibition of renal tubular OAT2
  - elevations in serum uric acid usually occurred within the first 4 weeks of treatment and returned to baseline following discontinuation
  - IIn both treatment groups, patients who reported gout were more likely to have a medical history of gout and/or baseline levels of uric acid above the ULN.
- Bempedoic acid has been shown to increase serum creatinine and BUN.
  - This effect should be considered when interpreting changes in estimated creatinine clearance in patients on Nilemdo therapy, particularly in patients with medical conditions or receiving medicinal products that require monitoring of estimated creatinine clearance.
- Decreases in haemoglobin were observed in clinical trials with bempedoic acid.

https://www.medicines.org.uk/emc/product/11743/smpc

AAC Guidelines for Lipids



Are there any safety concerns with low cholesterol

ESC European Society of Cardiology
European Heart Journal (2021) **42**, 2154–2169
doi:10.1093/eurheartj/ehaa1080

STATE OF THE ART REVIEW
Dyslipidaemias

How low is safe? The frontier of very low (<30 mg/dL) LDL cholesterol

Angelos D. Karagiannis [1], Anurag Mehta [2], Devinder S. Dhindsa[2], Salim S. Virani[3,4], Carl E. Orringer [5], Roger S. Blumenthal [6], Neil J. Stone[7], and Laurence S. Sperling [2]*

[1]Department of Internal Medicine, Emory University School of Medicine, 1364 Clifton Road NE, Atlanta, GA 30322, USA; [2]Emory Clinical Cardiovascular Research Institute, Division of Cardiology, Department of Medicine, Emory University School of Medicine, 1462 Clifton Way NE, Atlanta, GA 30322, USA; [3]Section of Cardiovascular Research, Department of Medicine, Baylor College of Medicine, 1 Baylor Plaza, Houston, TX 77030, USA; [4]Section of Cardiology, Michael E. DeBakey Veterans Affairs Medical Center, 2002 Holcombe Blvd, Houston, TX 77030, USA; [5]University of Miami Miller School of Medicine, 1600 NW 10th Ave #1140, Miami, FL 33136, USA; [6]Johns Hopkins Ciccarone Center for the Prevention of Cardiovascular Disease, 601 North Caroline Street Suite 7200, Baltimore, MD 21287, USA; and [7]Feinberg School of Medicine, Northwestern University, 420 E Superior St, Chicago, IL 60611, USA

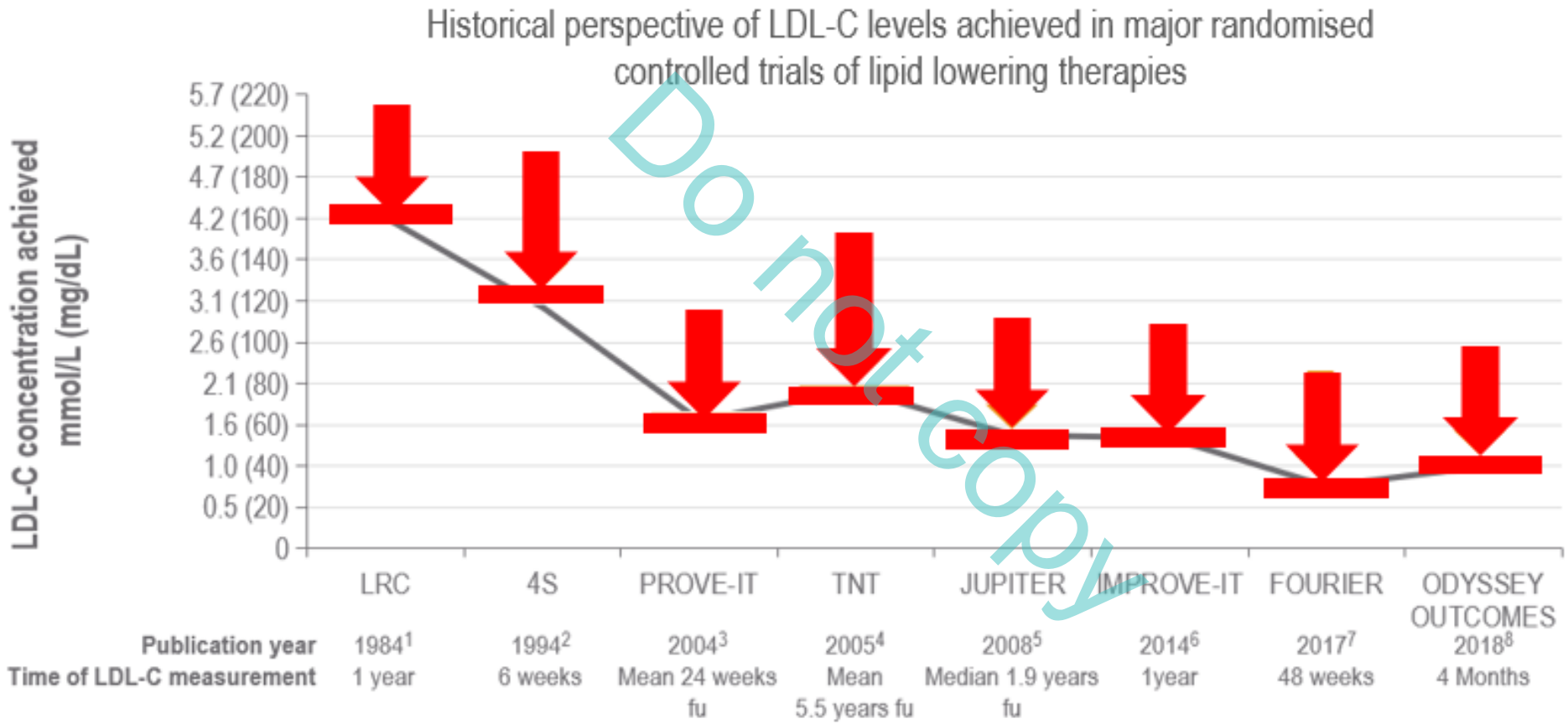
Received 23 August 2020; revised 16 November 2020; editorial decision 16 December 2020; accepted 18 December 2020; online publish-ahead-of-print 19 January 2021

Low-density lipoprotein cholesterol (LDL-C) is a proven causative factor for developing atherosclerotic cardiovascular disease. Individuals with genetic conditions associated with lifelong very low LDL-C levels can be healthy. We now possess the pharmacological armamentarium (statins, ezetimibe, PCSK9 inhibitors) to reduce LDL-C to an unprecedented extent. Increasing numbers of patients are expected to achieve very low (<30 mg/dL) LDL-C. Cardiovascular event reduction increases log linearly in association with lowering LDL-C, without reaching any clear plateau even when very low LDL-C levels are achieved. It is still controversial whether lower LDL-C levels are associated with significant clinical adverse effects (e.g. new-onset diabetes mellitus or possibly haemorrhagic stroke) and long-term data are needed to address safety concerns. This review presents the familial conditions characterized by very low LDL-C, analyses trials with lipid-lowering agents where patients attained very low LDL-C, and summarizes the benefits and potential adverse effects associated with achieving very low LDL-C. Given the potential for cardiovascular benefit and short-term safe profile of very low LDL-C, it may be advantageous to attain such low levels in specific high-risk populations. Further studies are needed to compare the net clinical benefit of non-LDL-C-lowering interventions with very low LDL-C approaches, in addition to comparing the efficacy and safety of very low LDL-C levels vs. current recommended targets.

* Corresponding author. Tel: +1 404 778 2722, Fax: +1 404 325 2796, Email: lsperli@emory.edu

- **Individuals with genetic conditions associated with lifelong very low LDL-C levels can be healthy**
- **Cardiovascular event reduction increases log linearly in association with lowering LDL-C, without reaching any clear plateau even when very low LDL-C levels are achieved.**
- **Given the potential for cardiovascular benefit and short-term safe profile of very low LDL-C, it may be advantageous to attain such low levels in specific high-risk populations.**

LIPID-LOWERING THERAPIES HAVE EVOLVED OVER THE YEARS TO ACHIEVE LOWER LDL-C LEVELS



For illustrative purposes only; individual trials should not be directly compared.

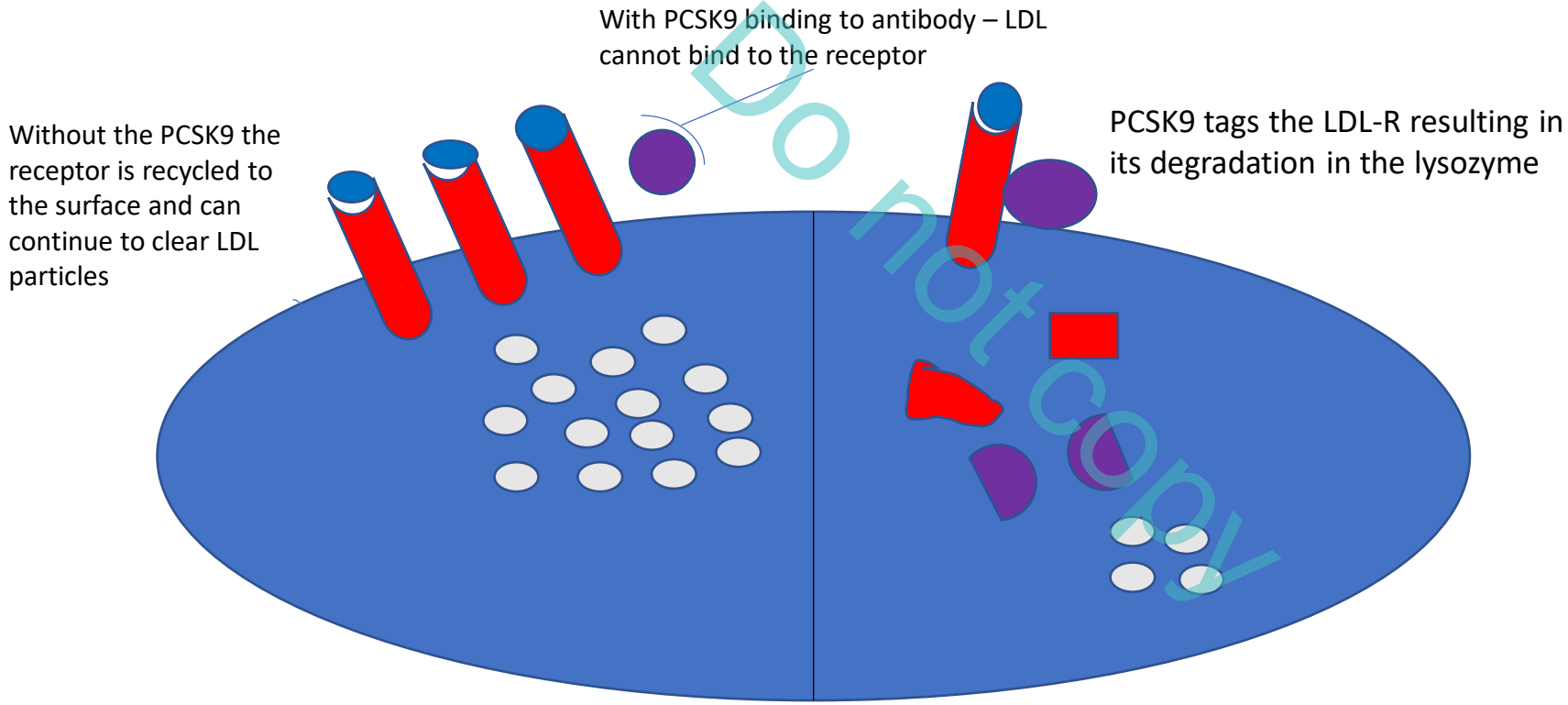
Figure adapted from: Masana, et al. *J Clin Lipidol*. 2018;12(2):292-299.e3. Orange arrows indicate the mean LDL decrease obtained in the study.

fu, follow up; LDL-C, low-density lipoprotein-cholesterol.

1. Lipid Research Clinics. *JAMA*. 1984;251:351–364; 2. Scandinavian Simvastatin Survival Study (4S) Group. *Lancet*. 1994;344:1383–1389; 3. Cannon, et al. *N Engl J Med*. 2004;350:1495–1504; 4. LaRosa, et al. *N Engl J Med*. 2005;352:1425–1435; 5. Ridker, et al. *N Engl J Med*. 2008;359:2195–220; 6. Cannon, et al. *N Engl J Med*. 2015;372:2387–2397; 7. Sabatine, et al. *N Engl J Med*. 2017;376:1713–1722; 8. Schwartz, et al. *N Engl J Med*. 2018;379:2097–2107.

Mechanism of Action – PCSK9i

- Recently, a new class of drugs, PCSK9 inhibitors, has become available that targets a protein (PCSK9) involved in the control of the LDLR.



Abifadel M, Varret M, Rabes JP, Allard D, Ouguerram K, Devillers M, Cruaud C, Benjannet S, Wickham L, Erlich D, Derre A, Villeger L, Farnier M, Beucler I, Bruckert E, Chambaz J, Chanu B, Lecerf JM, Luc G, Moulin P, Weissenbach J, Prat A, Krempf M, Junien C, Seidah NG, Boileau C. Mutations in PCSK9 cause autosomal dominant hypercholesterolemia. Nat Genet 2003;34:154156.
Norata GD, Tibolla G, Catapano AL. Targeting PCSK9 for hypercholesterolemia. Annu Rev Pharmacol Toxicol 2014;54:273293.
Nozue T. Lipid lowering therapy and circulating PCSK9 concentration. J Atheroscler Thromb 2017;24:895907.

Guidelines – Eligibility Criteria

PCSK-9 Eligibility Criteria

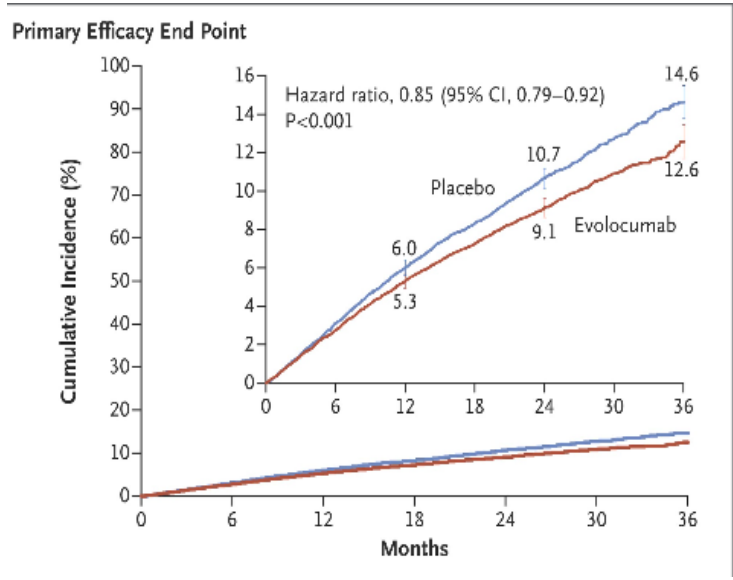
	Without CV	With CVD	
		High Risk	Very High Risk
Primary non-FH or mixed dyslipidaemia	Not recommended	LDL-C >4.0mmol/L	LDL-C >3.5mmol/L
Primary heterozygous FH	LDL-C>5.0mmol/L	LDL-C >3.5mmol/L	

- High risk – ACS, coronary or other arterial revascularisation, PAD, stroke/TIA, CHD
- Very high risk – multiple CV events or events in multiple events in different vascular beds

Inclisiran – for primary non-FH or mixed dyslipidaemia when LDL <2.6mmol/L persistently despite max tolerated other lipid lowering therapy

Fourier Trial

Number of patients	27,564
Patient population	ASCVD – secondary prevention
LDL-C	>1.8mmol/L
Background therapy	statins
Comparator	placebo
LDL-C lowering from baseline at 48 weeks	1.6mmol/L (using median reductions)
Follow up	2.2 years
primary endpoint (composite of CV death, MI, stroke, hospitalization for unstable angina, or coronary revascularization)	significantly reduced the risk of the primary endpoint by 15% [hazard ratio (HR) 0.85, 95%CI 0.79-0.92].
Secondary endpoint (CV death, MI or stroke)	20% reduction in risk 0.80(0.73-0.88)
CV mortality	No evidence of benefit HR 1.05, 95% CI 0.881.25)

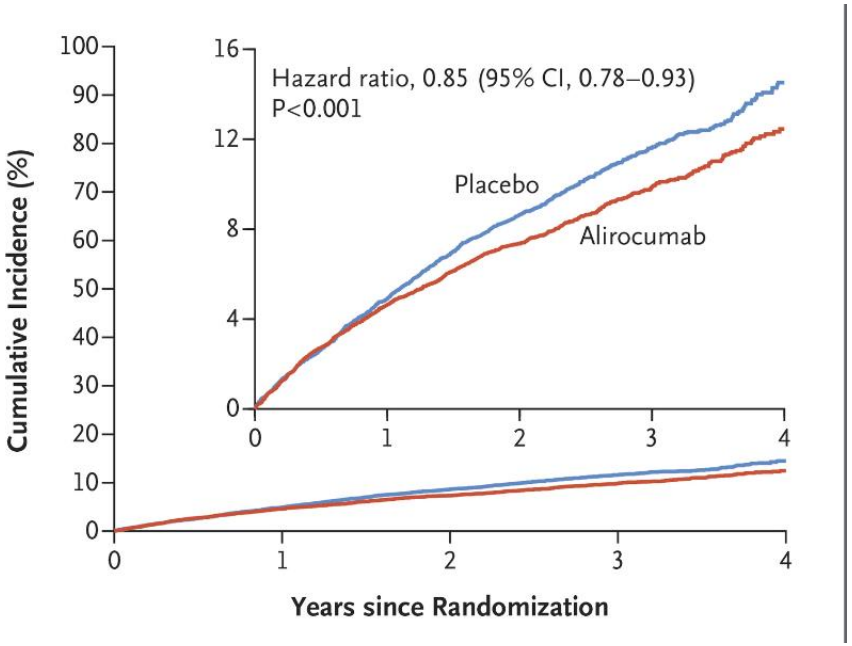


- An analysis of the time to benefit also showed that there was a lower benefit in the first year than in subsequent years, consistent with the effects of statins observed

Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, Kuder JF, Wang H, Liu T, Wasserman SM, Sever PS, Pedersen TR; FOURIER Steering Committee and Investigators. Evolocumab and clinical outcomes in patients with cardiovascular disease. N Engl J Med 2017;376:17131722

Ference BA, Cannon CP, Landmesser U, Luscher TF, Catapano AL, Ray KK. Reduction of low density lipoprotein-cholesterol and cardiovascular events with proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors and statins: an analysis of FOURIER, SPIRE, and the Cholesterol Treatment Trialists Collaboration. Eur Heart J 2018;39:25402545.

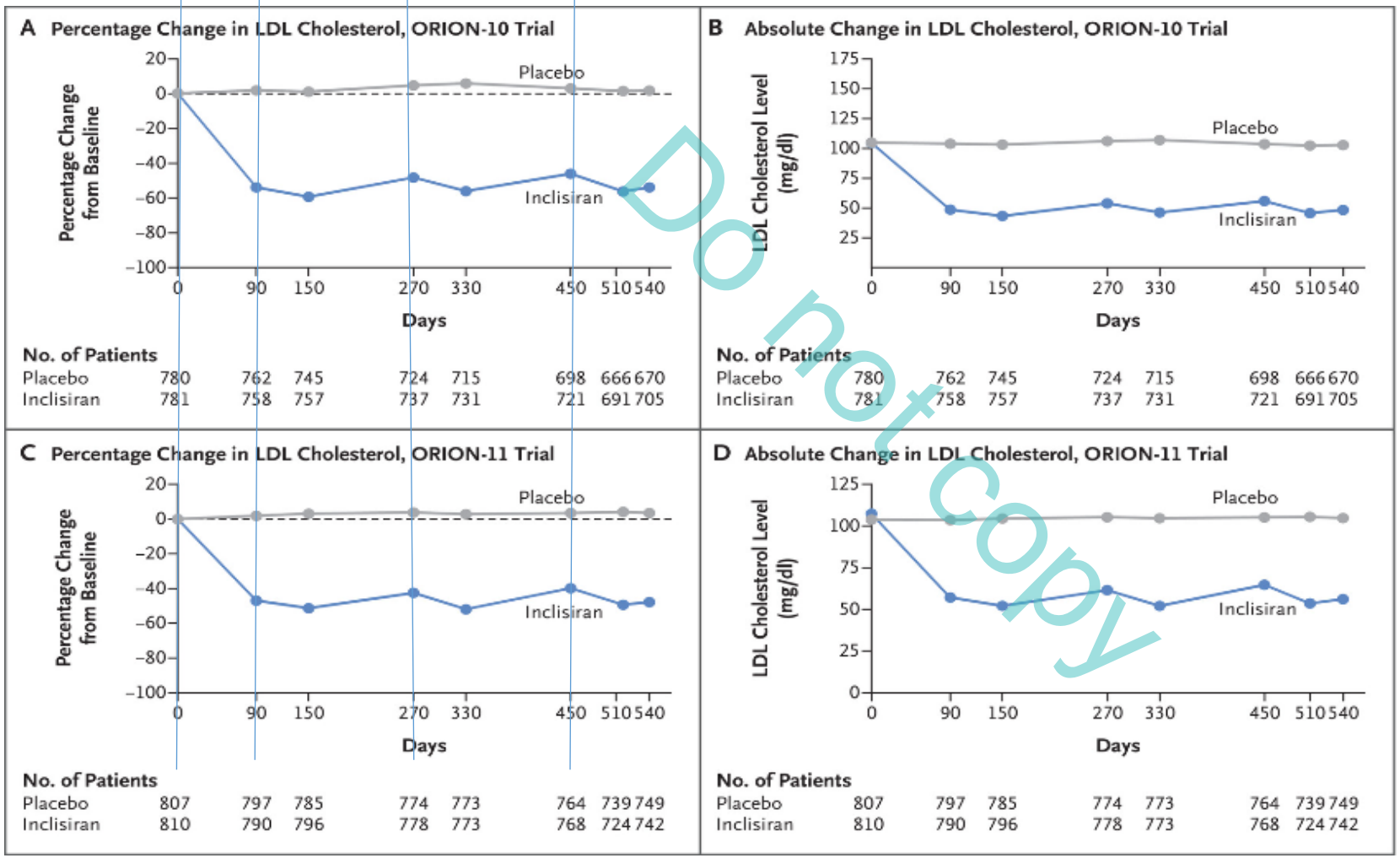
ODYSSEY



Number of patients	18924
Patient population	patients after hospitalization for acute MI or unstable angina
Lipid criteria	LDL >1.8mmol/L, non-HDL>2.6 or ApoB >80mg/dL
Background therapy	statins
Comparator	placebo
LDL-C lowering from baseline at 48 weeks	1.14mmol/L (using mean values)
Follow up	2.8 years
primary outcome (composite of CHD death, nonfatal MI, ischaemic stroke, or unstable angina requiring hospitalization) (	15% relative reduction in the primary outcome. HR 0.85, 95% CI (0.78-0.93)
CV mortality	No evidence of benefit although there was a benefit in all cause mortality

Schwartz GG, Steg PG, Szarek M, Bhatt DL, Bittner VA, Diaz R, Edelberg JM, Goodman SG, Hanotin C, Harrington RA, Jukema JW, Lecorps G, Mahaffey KW, Moryusef A, Pordy R, Quintero K, Roe MT, Sasiela WJ, Tamby JF, Tricoci P, White HD, Zeiher AM; ODYSSEY OUTCOMES Committees and investigators. Alirocumab and cardiovascular outcomes after acute coronary syndrome. N Engl J Med 2018;379:20972107.

Efficacy Trials



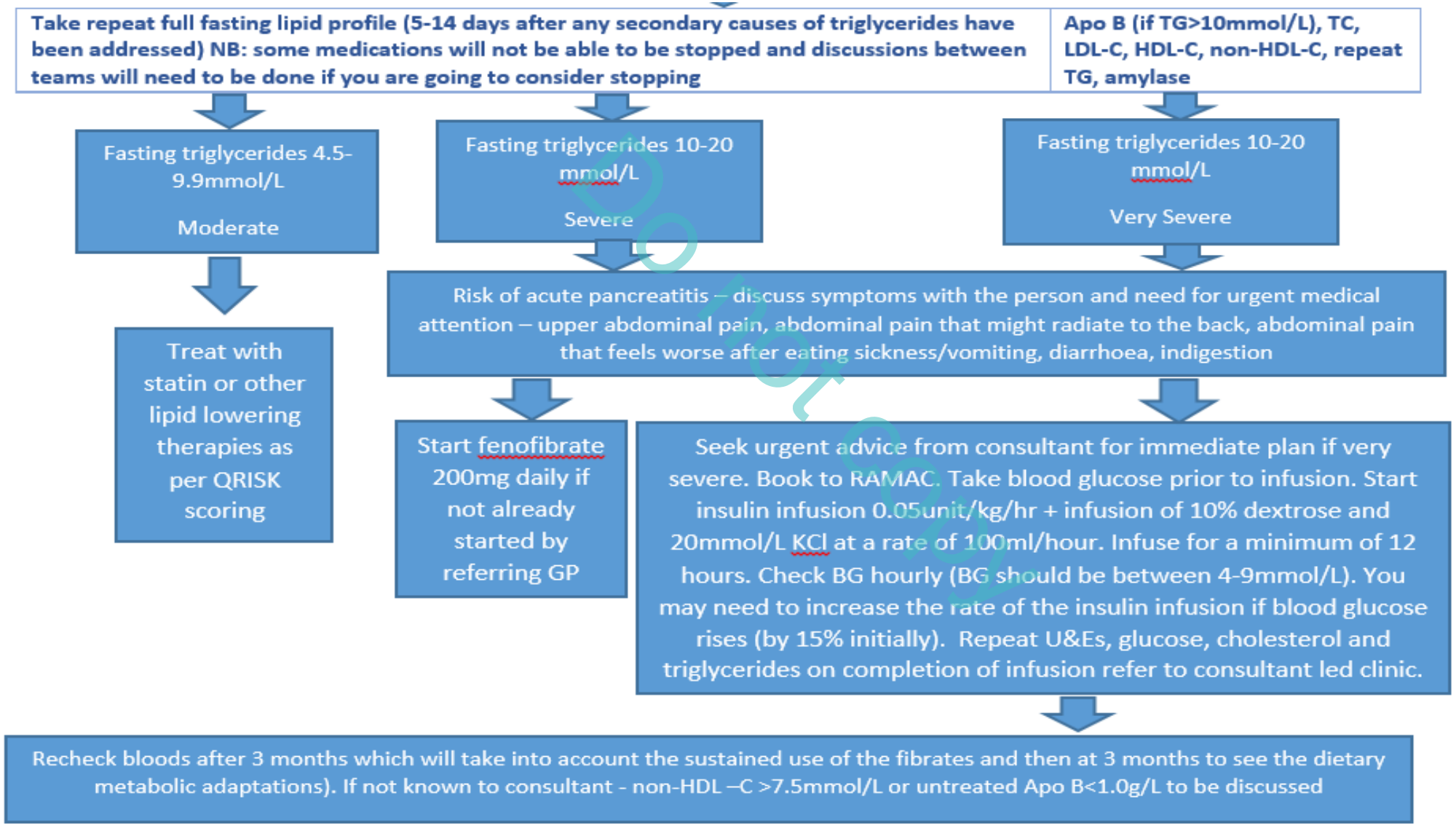
Ray et al. 2020. Phase 3 trials of Incliseran in people with elevated LDL Cholesterol. NEJM. 382:1507-1519. Avaialble from : https://www.nejm.org/doi/full/10.1056/NEJMoa1912387 accessed 23/3/2021

ORION-4 trial

- Set up to interrogate CV outcomes and safety of the medication
- To randomise >15000 participants ages >55 years old with pre-existing CV disease for a median of 5 years
- Pre-existing CV disease – MI, ischaemic stroke, PAD (with revascularisation/aortic aneurysm repair)
- LDL-C - >4mmol/L to proceed (point of care testing)
- Aim for average LDL <2.6mmol/L
- Looking at Primary composite outcome – MACE – CHD death, MI, fatal/non-fatal ischaemic stroke, urgent coronary revascularisation.
- Central appointments made harnessing NHS digital data - feasibility information looking at areas with high CV outcomes

https://www.orion4trial.org/homepage-uk

High Triglycerides



High Triglycerides

1. Discuss BMI and the importance of weight reduction	**Weight reduction increases insulin sensitivity and decreases triglycerides**
2. Discuss alcohol consumption	Significant reductions in alcohol intake should be done
3. Discuss diet	Reduce simple sugar, total carbohydrate and fat. If triglycerides are >9.9mmol/L then the person should make a strict fat-reduced dietary change (<20% of calories as fat). A calorie deficit of 300-500kcal will induce weight loss and this should be done in conjunction with exercise to avoid any muscle or bone depletion.
4. Do a pregnancy test if of child bearing age	
5. Discuss exercise	Increase aerobic activity – give age appropriate exercise advice : https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/832868/uk-chief-medical-officers-physical-activity-guidelines.pdf
6. Medications	Do a medication review and identify any medications which may be causing HTG – corticosteroids, oral oestrogen, tamoxifen, thiazides, non-cardio selective beta blockers, bile acid sequestrants, cyclophosphamide, L-asparaginase, protease inhibitors and second generation antipsychotics (e.g. clozapine, olanzapine)
7. Take bloods to assess for any secondary causes of hypertriglyceridaemia	HbA1c, TFTs, urine albumin: creatinine ratio, LFTs, U&Es, Paraprotein, ANA (refer or discuss any abnormal results with a consultant)

Licenced for:

- Vazkepa is indicated to reduce the risk of cardiovascular events in adult statin-treated patients at high cardiovascular risk with elevated triglycerides (≥ 150 mg/dL [≥ 1.7 mmol/L]) and established cardiovascular disease, or diabetes, and at least one other cardiovascular risk factor.

NICE recommended (TA 805):

- Icosapent ethyl is recommended as an option for reducing the risk of cardiovascular events in adults. It is recommended if they have a high risk of cardiovascular events and raised fasting triglycerides (1.7 mmol/litre or above) and are taking statins, but only if they have:
- established cardiovascular disease (secondary prevention), defined as a history of any of the following:
- acute coronary syndrome (such as myocardial infarction or unstable angina needing hospitalisation)
- coronary or other arterial revascularisation procedures
- coronary heart disease
- ischaemic stroke
- peripheral arterial disease, and
- low-density lipoprotein cholesterol (LDL-C) levels above 1.04 mmol/litre and below or equal to 2.60 mmol/litre.

REDUCE-IT Trial

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 3, 2019 VOL. 380 NO. 1

Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia

Deepak L. Bhatt, M.D., M.P.H., P. Gabriel Steg, M.D., Michael Miller, M.D., Eliot A. Brinton, M.D., Terry A. Jacobson, M.D., Steven B. Ketchum, Ph.D., Ralph T. Doyle, Jr., B.A., Rebecca A. Juliano, Ph.D., Lixia Jiao, Ph.D., Craig Granowitz, M.D., Ph.D., Jean-Claude Tardif, M.D., and Christie M. Ballantyne, M.D., for the REDUCE-IT Investigators*

ABSTRACT

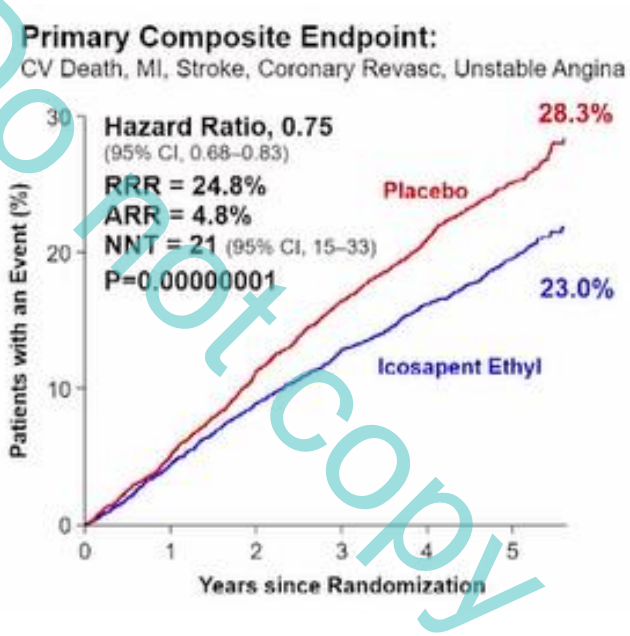
BACKGROUND

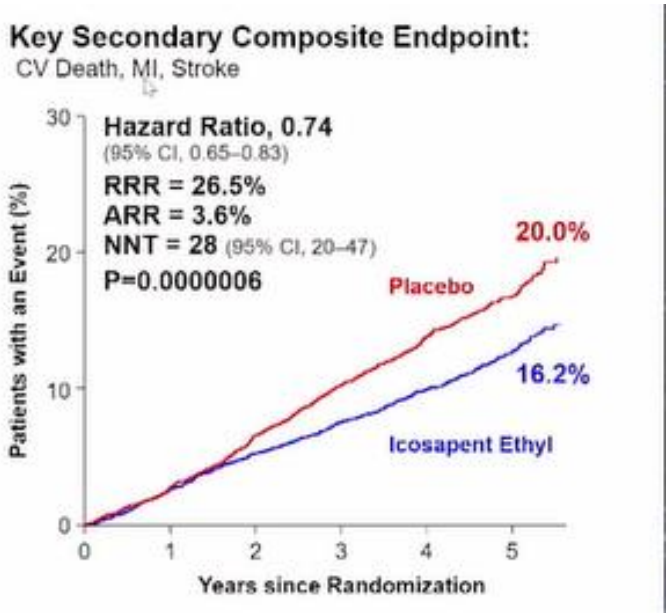
Patients with elevated triglyceride levels are at increased risk for ischemic events. Icosapent ethyl, a highly purified eicosapentaenoic acid ethyl ester, lowers triglyceride levels, but data are needed to determine its effects on ischemic events.

METHODS

We performed a multicenter, randomized, double-blind, placebo-controlled trial involving patients with established cardiovascular disease or with diabetes and other risk factors, who had been receiving statin therapy and who had a fasting triglyceride level of 135 to 499 mg per deciliter (1.52 to 5.63 mmol per liter) and a low-density lipoprotein cholesterol level of 41 to 100 mg per deciliter (1.06 to 2.59 mmol per liter). The patients were randomly assigned to receive 2 g of icosapent ethyl twice daily (total daily dose, 4 g) or placebo. The primary end point was a composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina. The key secondary end point was a composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke.

From Brigham and Women's Hospital Heart and Vascular Center and Harvard Medical School, Boston (D.L.B.); FACT (French Alliance for Cardiovascular Trials), Département Hospitalo-Universitaire FIRE (Fibrose, Inflammation, and Remodeling), Assistance Publique–Hôpitaux de Paris, Hôpital Bichat, Université Paris-Diderot, INSERM Unité 1148, Paris (P.G.S.); National Heart and Lung Institute, Imperial College, Royal Brompton Hospital, London (P.G.S.); the Department of Medicine, University of Maryland School of Medicine, Baltimore (M.M.); the Utah Lipid Center, Salt Lake City (E.A.B.); the Office of Health Promotion and Disease Prevention, Department of Medicine, Emory University School of Medicine





Bhatt et al. 2019. N Engl J Med. Cardiovascular Risk Reduction with Icospent Ethyl for Hypertriglyceridaemia. 380: 11-22. Availabel from : https://www.nejm.org/doi/full/10.1056/NEJMoa1812792 accessed 23/3/2021

Icosapentethyl (IPA) – Safety

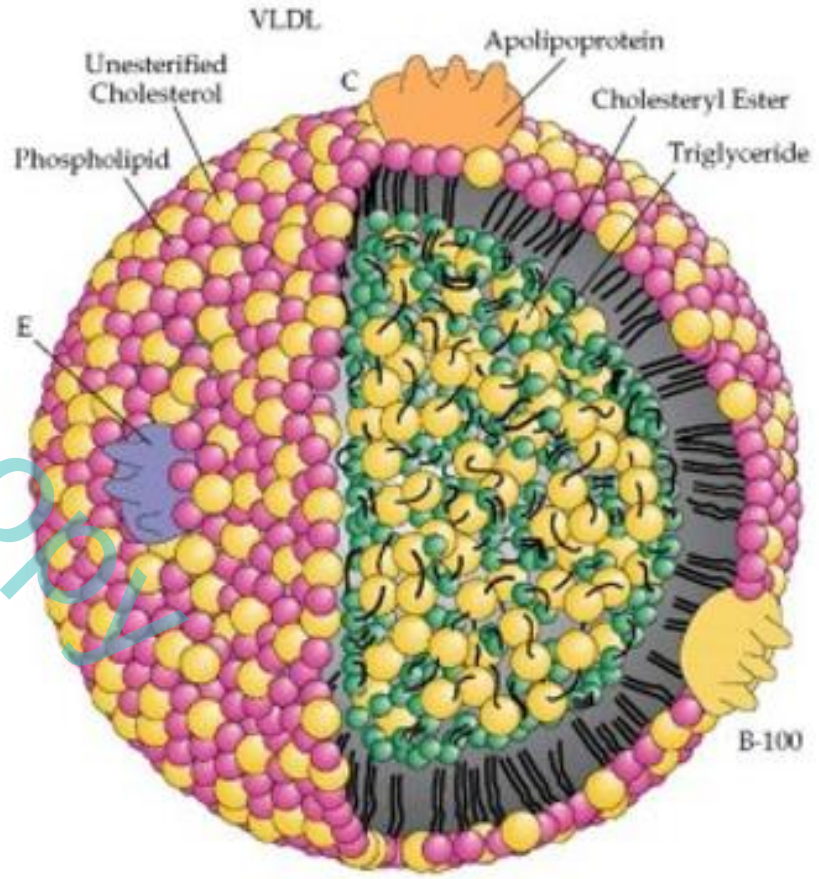
- Significant increase in bleeding – only minor bleeding (no seen for GI bleed, intracranial bleed, haemorrhagic stroke or any other major bleeding events)
- Significant increase in hospitalisation for AF (serious AF/flutter – identical in treatment and placebo)

NB: reduction in stroke in the trial

Bhatt et al. 2019. N Engl J Med. Cardiovascular Risk Reduction with Icospent Ethyl for Hypertriglyceridaemia. 380: 11-22. Availabel from : https://www.nejm.org/doi/full/10.1056/NEJMoa1812792 accessed 23/3/2021

Other Lipoproteins

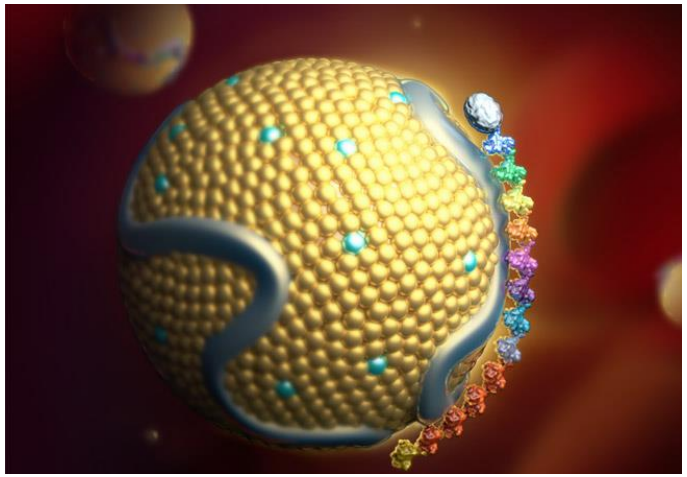
- Apoprotein B – key protein for VLDL, LDL and chylomicrons
- Apoprotein A – key protein in HDL
- Lipoprotein (a)
  - largely decided in our genetic makeup
  - Sticky protein made in the liver
  - High levels increase the risk of circulatory disease and heart disease



https://www.revolutionhealth.org/ldl-p/

Managing residual Cardiovascular risk…. New frontiers

- The causal effect of Lp(a) on the risk of ASCVD is proportional to the absolute change in plasma Lp(a) levels.
- Those with extremely high Lp(a) levels >180 mg/dL (>430 nmol/L) have an increased lifetime risk of ASCVD similar to that of people with heterozygous FH (HeFH)
- 90% of a person's Lp(a) level is inherited
- Extremely elevated Lp(a) may represent a new inherited lipid disorder that is associated with extremely high lifetime risk of ASCVD and is twofold more prevalent than HeFH.
- The Heart Protection Study 2-Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE) trial have shown that large absolute changes in Lp(a) may be needed to produce a clinically meaningful reduction in the risk of ASCVD events.



Burgess S, Ference BA, Staley JR et al. 2018.European Prospective Investigation Into Cancer and Nutrition Cardiovascular Disease (EPIC-CVD) Consortium. Association of LPA variants with risk of coronary disease and the implications for lipoprotein(a)-lowering therapies: a Mendelian randomization analysis. JAMA Cardiol 3:619627.

Parish S, Hopewell JC, Hill MR, Marcovina S, Valdes-Marquez E, Haynes R, Offer A, Pedersen TR, Baigent C, Collins R, Landray M, Armitage J; HPS2-THRIVE Collaborative Group. Impact of apolipoprotein(a) isoform size on lipoprotein(a) lowering in the HPS2-THRIVE Study. Circ Genom Precis Med 2018;11:e001696

Lipoprotein (a)

Lipoprotein (a) level (nmol/l)	ADDITIONAL CONFERED CVD Risk (this is additive from any existing CVD Risk) – manage by addressing risk factors non-HDL, BP and lifestyle (diet, exercise, weight loss, smoking, alcohol intake)
<32	No change
32-90	Minor CVD risk
>90	Moderate CVD risk – everyone from this level upwards should be offered lipid lowering therapy
>200	High CVD risk - everyone from this level upwards should have a non-HDL target <2.5mmol/L
>400	Very high CVD risk

Monitoring

Baseline	Lipid profile : LDL-C, HDL-C, TC, N-HDLC, triglycerides Renal Function : eGFR, creatinine Glucose tolerance : HbA1c Thyroid function : T4 and TSH Liver Function : ALT (or ASP), albumin
3 months	Lipid profile : LDL-C, HDL-C, TC, N-HDLC, triglycerides Liver Function : ALT (or ASP)
6-9 months	If <40% non-HDL-C reduction, up titration required. Repeat full lipid profile and ALT (or AST)within 3 months of each up-titration of statin dose or addition of Ezetimibe as required Lipid profile : LDL-C, HDL-C, TC, N-HDLC, triglycerides Liver Function : ALT (or ASP)
12 months	Lipid profile : LDL-C, HDL-C, TC, N-HDLC, triglycerides Liver Function : ALT (or ASP)
As needed	CK if unexplained muscle pain

Lipid Management: Key Take-Home Messages

i. For every 1 mmol/L ↓ in LDL-C, there is a ↓ in annual CV risk of up to 28%, regardless of the intervention

ii. Growing evidence has driven ↓ target LDL-C levels over time; ESC 2019 recommends <1.4 mmol/L & >50% ↓ baseline for those at very high risk of CVD

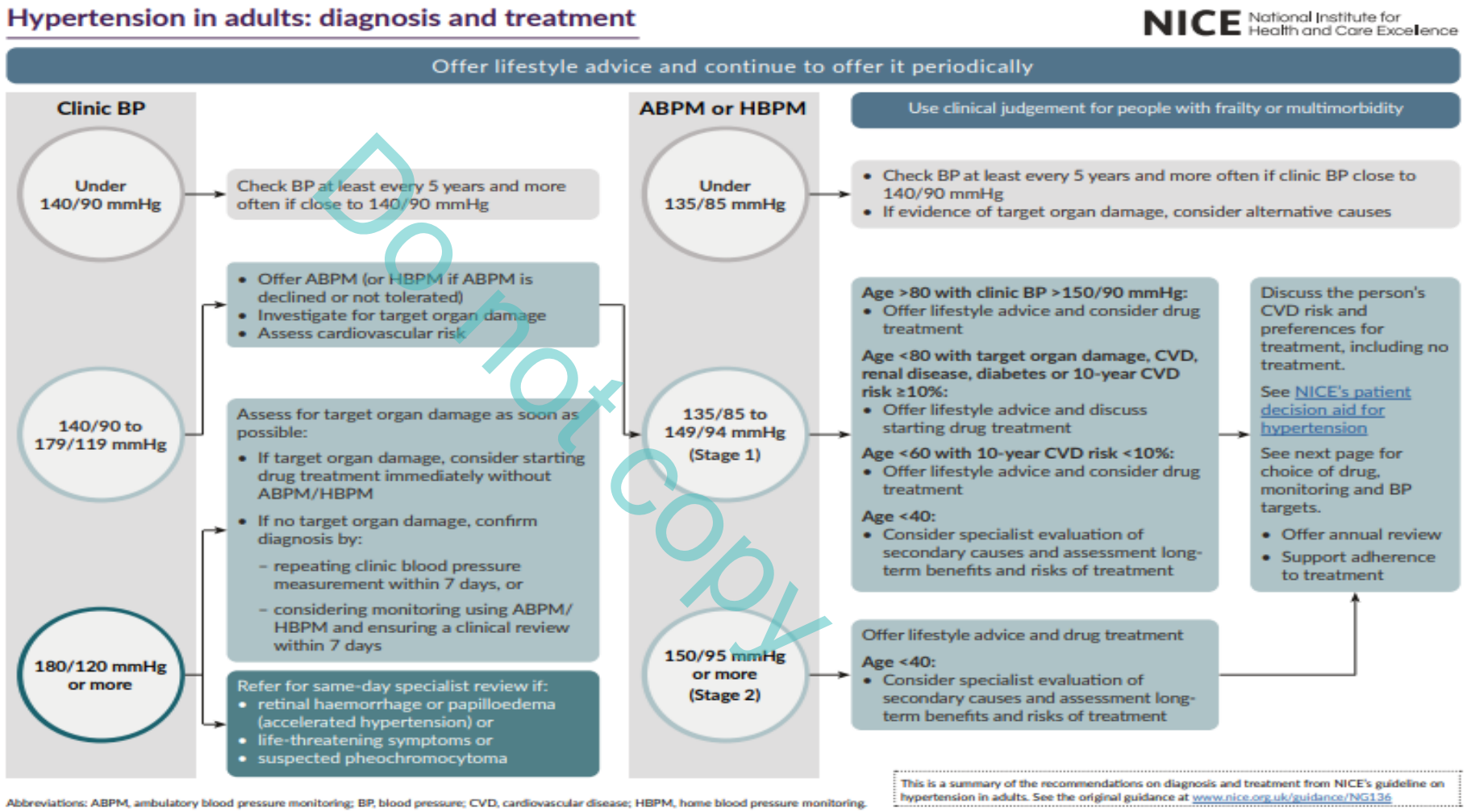
iii. Combination lipid-lowering therapy should now be the norm to achieve these tighter LDL-C targets

"Whenever your cholesterol goes too high, a sensor will send a signal that automatically locks the kitchen door and turns on your treadmill."

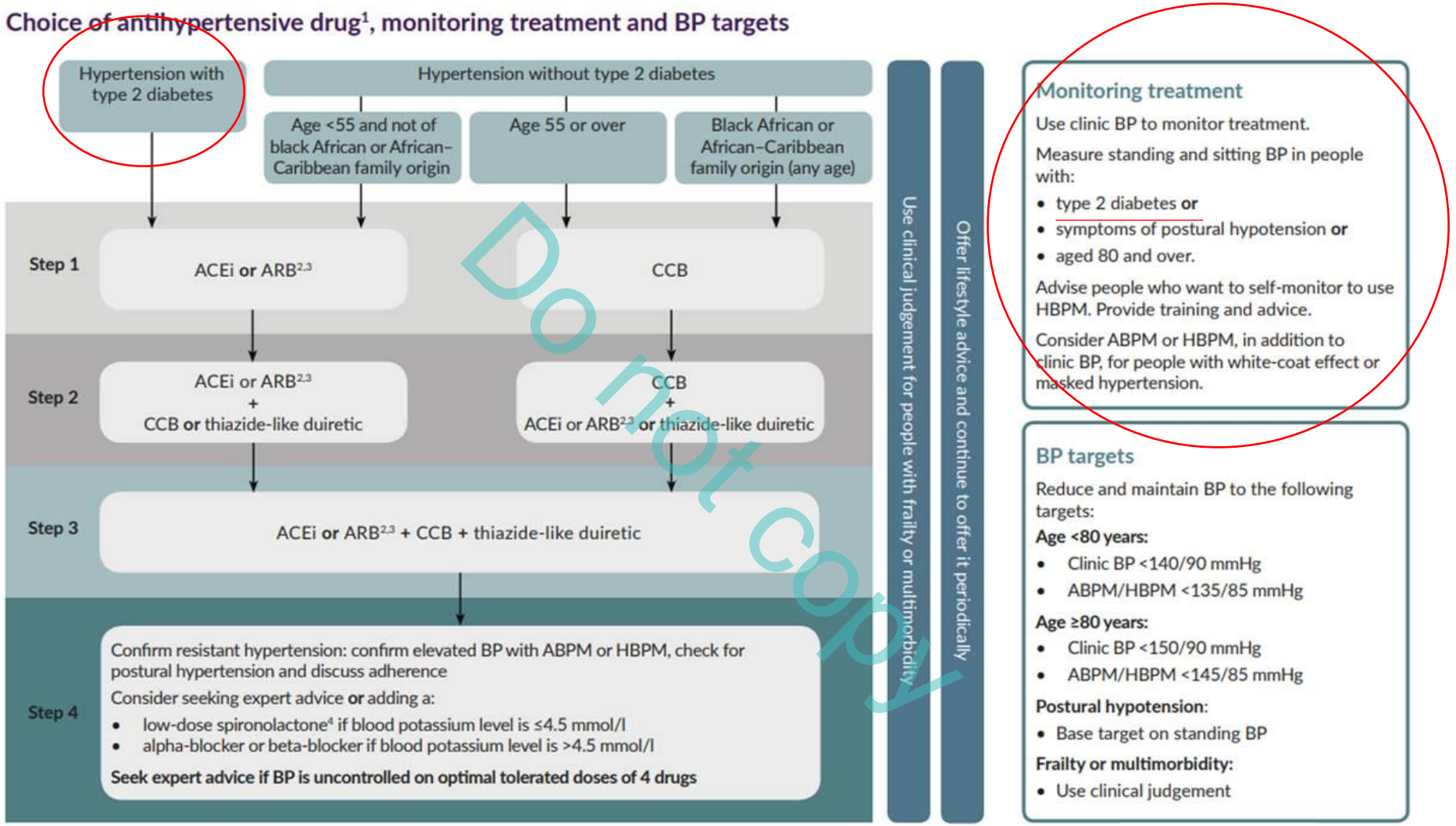
QoF Hypertension (HYP)

QoF		
HYP001	The contractor establishes and maintains a register of those with hypertension	6 points
HYP008	The % of patients aged ≤79 years old with hypertension in whom the last BP reading (measured in the last 12 months) is ≤140/90mmHg (or equivalent HBPM or ABPM)	14 points 40-77%
HYP009	The % of patients aged >80 years with hypertension in whom the last BP readings (measured in the last 12 months) is ≤ 150/90mmg (or equivalent HBPM or ABPM)	5 points 40-80%

NICE Guidelines

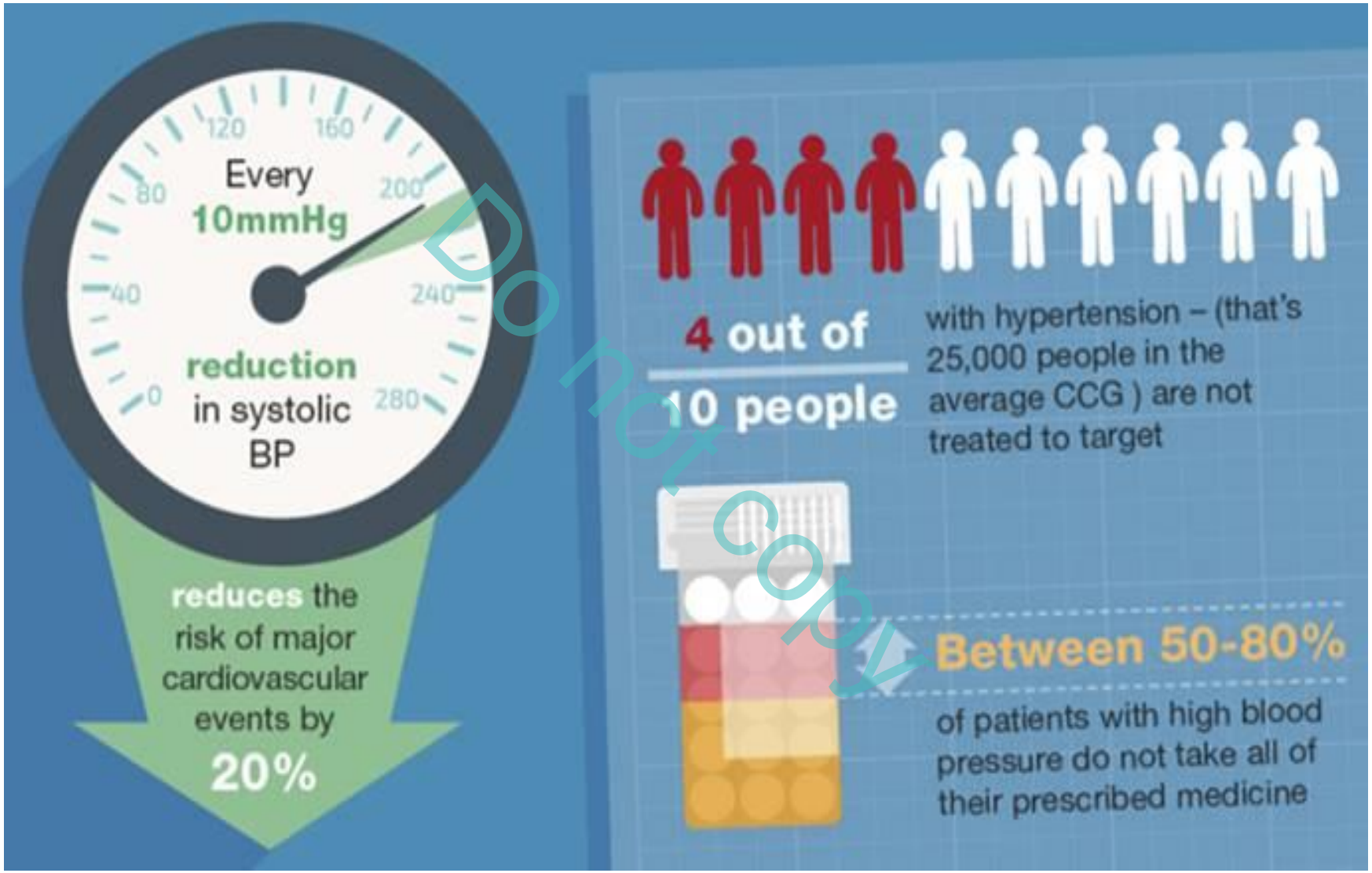


NICE, 2022. NG136. accessed via: https://www.nice.org.uk/guidance/ng136/resources/visual-summary-pdf-6899919517 on 20.08.23



Hypertension in adults: diagnosis and management NICE CG 136 (2019)

2mm/Hg rise in systolic = 10% increased risk of stroke



Hypertension is a Strong Risk Factors for

Atherosclerotic cardiovascular disease (ASCVD)

acute coronary syndrome,

myocardial infarction (MI),

angina,

coronary or other arterial revascularization,

stroke,

transient ischemic attack,

peripheral arterial disease presumed to be of atherosclerotic origin

Heart failure

Microvascular complications.

Large benefits are seen when multiple risk factors are addressed simultaneously (**9**).

Ian H. de Boer, Sripal Bangalore, Athanase Benetos, Andrew M. Davis, Erin D. Michos, Paul Muntner, Peter Rossing, Sophia Zoungas, George Bakris; Diabetes and Hypertension: A Position Statement by the American Diabetes Association. *Diabetes Care* 1 September 2017; 40 (9): 1273–1284. https://doi.org/10.2337/dci17-0026

Mrs DM

Age = 42 years old

Diabetes for 3 years

Medications

Metformin 1g bd

Atorvastatin 20mg once daily

Paracetamol 1g qds prn

Results

BMI=35kg/m2

HbA1c=64mmol/mol

UACR =3.8 mg/mmol(early morning sample – stable microalbuminuria compared to other readings)

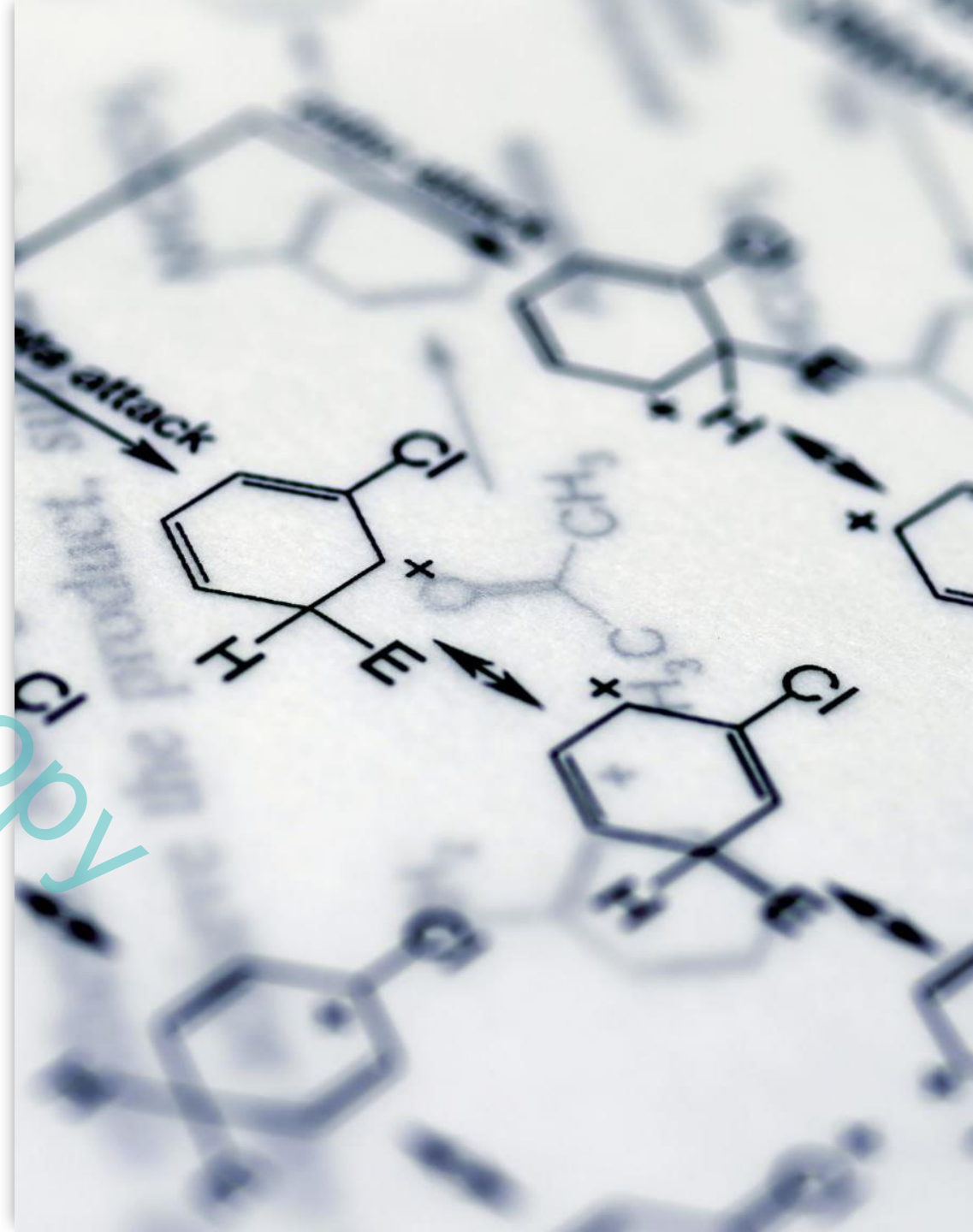
eGFR=88ml/min/1.73m2

LFTs – normal

TFTs – normal

Mrs DM initially has a BP = 158/98mmHg in her left arm, the clinician re-checks the BP in the right arm and BP=162/99mmHg. Her blood pressure has always been in range previously.

What do you do first? Would this be different if the BP was >180/110mmHg?



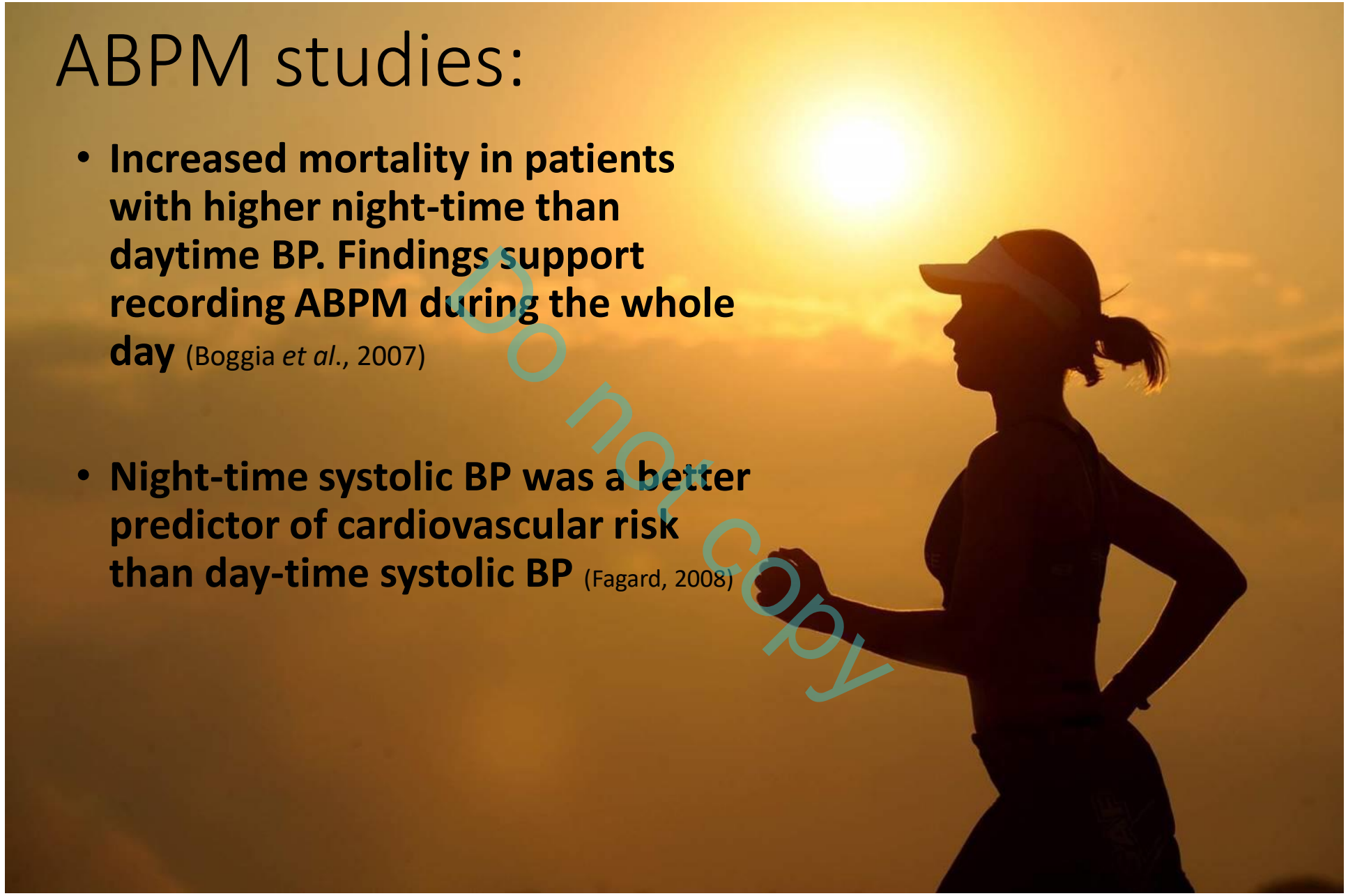
Blood pressure Measurement in Diabetes

Measure	Measure BP at every visit
Allow	Allow people to be sitting comfortably before taking the measurement (approx. 5 mins rest at least)
Take	Take 3 readings 1-2 minutes apart and additional readings if the first 2 readings differ by more than 10mmHg (BP recorded is average of last two readings). With ABPM Ensure that at least 2 measurements per hour are taken during the person's usual waking hours. Use average values (at least 14 BPs) taken during usual waking hours to confirm a diagnosis of hypertension HBPM Educate on correct technique (as per BIHS). BP recorded twice daily (morning & evening)BP recording over at least 4 days, ideally for 7. Discard the measurements on first day: use the average of the remaining measurements
Measure Again	Measure BP 1 min and then 3 minutes after standing on initial visit to rule out orthostatic hypotension

ABPM studies:

- **Increased mortality in patients with higher night-time than daytime BP. Findings support recording ABPM during the whole day** (Boggia *et al*., 2007)

- **Night-time systolic BP was a better predictor of cardiovascular risk than day-time systolic BP** (Fagard, 2008)



Self-monitoring blood pressure

The TASMINH4 Trial: Self-monitoring and self-reporting blood pressure from home works best for long-term control of hypertension

The TASMINH4 randomised controlled trial found that when GPs base their medication adjustments on regular blood pressure readings taken by the patient at home, blood pressure is significantly lower after 12 months compared with those who are managed in the clinic. The trial involved over 1,000 participants aged over 35 on antihypertensive medication for high blood pressure. Participants were recruited from 142 general practices across England, their average age was 67.

Hypertension affects **more than 1 in 4** adults in England

#1

It is the biggest **risk factor for death** & disability internationally

UK 30%

UK 70%

Some people with hypertension already **self-monitor from home**

In the TASMINH4 trial, participants were put into one of three treatment groups:

MEDICATION + USUAL CARE

- BP readings recorded at **routine visits to the clinic**
- GP manually calculates average BP to determine if it is too high or too low
- Medication altered by GP

MEDICATION + SELF-MONITORING

- Home-based BP readings **posted to clinic**
- GP manually calculates average BP to determine if it is too high or too low
- Patient trained to use colour chart to decide when to contact the clinic
- Medication altered by GP

MEDICATION + TELEMONITORING

- Home-based BP readings **texted to clinic**
- GP accesses automated web-based app which calculates average BP
- Automated alerts sent to GP & patient if average BP is too high or too low
- Medication altered by GP

Average blood pressure at the start of the trial: 153mmHg. Average readings were compared at 6 months and 12 months

After 12 months, participants who self-monitored had significantly lower blood pressure than those who were managed in the clinic

UNIVERSITY OF OXFORD · NUFFIELD DEPARTMENT OF PRIMARY CARE HEALTH SCIENCES · UNIVERSITY OF CAMBRIDGE · UNIVERSITY OF BIRMINGHAM · NIHR

McManus RJ, Mant J, Franssen M et al. Efficacy of self-monitored blood pressure, with or without telemonitoring, for titration of antihypertensive medication (TASMINH4): an unmasked randomised controlled trial. Lancet 2018; DOI: 10.1016/S0140-6736(18)30993-X

Monitoring

- Use clinic BP to monitor treatment
- Measure standing and sitting BP in people with:
  - type 2 diabetes or
  - symptoms of postural hypotension or
  - aged 80 and over.

Advise people who want to self-monitor to use HBPM. Provide training and advice. Consider ABPM or HBPM, in addition to clinic BP, for people with white-coat effect or masked hypertension.

The ACCORD and SPRINT trial used automated BP measurements

Arm circumference	Cuff size
22-26cm	Small adults
27-34cm	Adult
35-44cm	Large adult
45-52cm	Adult thigh

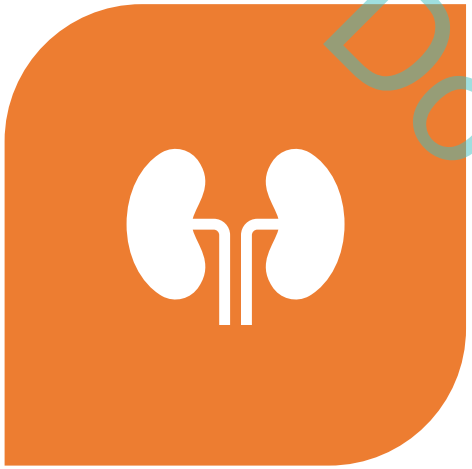
CushmanWC, Evans GW, ByingtonRP, et al.; ACCORD Study Group. Effects of intensive blood-pressure control in type 2 diabetes mellitus. *N Engl J Med*2010;362:1575–1585.

JT Jr, Williamson JD, Whelton PK et al.; SPRINT Research Group A randomized trial of intensive versus standard blood-pressure control *N Engl J Med*2015373:2103–2116

Whilst waiting for results investigate target organ damage:

- LVH: ECG
- CKD: ACR HbA1c/BG U&E LIPIDS
- Hypertensive retinopathy
- Undertake a formal cardio-vascular risk assessment

Mrs DM



SO AFTER PROPERLY ASSESSING THIS PATIENTS BLOOD PRESSURE, HER AVERAGE BLOOD PRESSURE IS 155/95MMHG WITH NO SIGNS OF POSTURAL HYPOTENSION.

WHAT DO YOU DO ? WHAT TARGET BP ARE YOU AIMING FOR? WHAT OTHER INFORMATION DO YOU NEED?

Dietary and Lifestyle

What could you recommend here to help blood pressure?

Dietary and Lifestyle Options

Long-term exercise training intervention modestly but significantly reduces SBP (by −7 mmHg) and DBP (by −5 mmHg). So establishing an exercise regimen that someone can stick to is important.

Ideally, an exercise prescription aimed at lowering BP would include a mix of aerobic exercise with dynamic resistance exercise training.

A marked improvement in CV risk factors (hypertension, dyslipidaemia, diabetes), associated with marked weight loss, was observed after bariatric surgery. We might expect similar results with non- surgical remission… ? Remission programme

Hansen D, Niebauer J, Cornelissen V, Barna O, Neunhäuserer D, Stettler C, *et al.* Exercise prescription in patients with different combinations of cardiovascular disease risk factors: a consensus statement from the EXPERT Working Group. *Sports Med* 2018;**48**:1781–1797. https://doi.org/10.1007/s40279-018-0930-4209.
Beamish AJ, Olbers T, Kelly AS, Inge TH. Cardiovascular effects of bariatric surgery. *Nat Rev Cardiol* 2016;**13**:730–743. https://doi.org/10.1038/nrcardio.2016.162

ACE INHIBITORS WOULD BE FIRST LINE BUT BEFORE YOU CAN COMMENCE THIS YOU NEED TO CHECK ?

WHAT MIGHT YOU NEED TO PREPARE THE PT FOR ?

Pharmacotherapy – with blood pressure medications

- ***ACE inhibitors would be first line but before you can commence this you need to check ?***
- Is this a women of child-bearing potential ? RAS blockers, can have adverse effects on the foetus, especially in early gestation.
- Evidence for RAS inhibition is strong especially for those with signs of renal decline. This lady has microalbuminuria
- A recent meta-analysis indicates that RAS inhibitors were not superior to other classes of anti-hypertensive drugs for reducing total or CV mortality and renal events

- Lindholm LH, Ibsen H, Dahlöf B, Devereux RB, Beevers G, de Faire U, *et al.* Cardiovascular morbidity and mortality in patients with diabetes in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet* 2002;**359**:1004–1010. https://doi.org/10.1016/S0140- 6736(02)08090-X
- Niskanen L, Hedner T, Hansson L, Lanke J, Niklason A; CAPPP Study Group. Reduced cardiovascular morbidity and mortality in hypertensive diabetic patients on first-line therapy with an ACE inhibitor compared with a diuretic/β-blocker–based treatment regimen: a subanalysis of the Captopril Prevention Project. *Diabetes Care* 2001;**24**: 2091–2096. https://doi.org/10.2337/diacare.24.12.2091
- Östergren J, Poulter NR, Sever PS, Dahlöf B, Wedel H, Beevers G, *et al.* The Anglo-Scandinavian Cardiac Outcomes Trial: blood pressure-lowering limb: effects in patients with type II diabetes. *J Hypertension* 2008;**26**:2103–2111. https://doi.org/ 10.1097/HJH.0b013e328310e0d9
- Weber MA, Bakris GL, Jamerson K, Weir M, Kjeldsen SE, Devereux RB, *et al.* Cardiovascular events during differing hypertension therapies in patients with diabetes. *J Am College Cardiol* 2010;**56**:77–85. https://doi.org/10.1016/j.jacc.2010.02.046

Pharmacotherapy – with blood pressure medications

What might you need to prepare the pt for ?

- Often multiple therapies are needed and a long acting calcium channel blocker/diuretic would be a favourable add on.
- What if she did want to have a child in the future?
- Beta blockers are useful – especially in those planning pregnancy.

Kunimura A, Himuro N, Fujiyoshi A, Segawa H, Ohnishi H, Saitoh S. The effects of renin– angiotensin system inhibitors on mortality, cardiovascular events, and renal events in hypertensive patients with diabetes: a systematic review and meta-analysis of randomized controlled trials. *Hypertension Res* 2019;**42**:669–680. https://doi.org/10.1038/s41440-019-0234-6 Wald DS, Law M, Morris JK, Bestwick JP, Wald NJ. Combination therapy versus monotherapy in reducing blood pressure: meta-analysis on 11,000 participants from 42 trials. *Am J Med* 2009;**122**:290–300. https://doi.org/10.1016/j.amjmed.2008.09.038

Pharmacotherapy with glucose lowering agents..

- How might our choice of glucose lowering agent effect BP?

Pharmacotherapy with glucose lowering agents

- SGLT2i therapy may be indicated
- SGLT2 inhibitors induced a larger BP decrease than did GLP-1 Ras without changing heart rate. A recent meta-analysis including seven RCTs demonstrated that SGLT2 inhibitors were associated with an average reduction of 3.6/1.7 mmHg (systolic/diastolic) in 24 h ambulatory BP, which is comparable with efficacy of low-dose hydrochlorothiazide

Mazidi M, Rezaie P, Gao HK, Kengne AP. Effect of sodium-glucose cotransport-2 inhibitors on blood pressure in people with type 2 diabetes mellitus: a systematic review and meta-analysis of 43 randomized control trials with 22 528 patients. *J Am Heart Assoc* 2017;**6**:e004007. https://doi.org/10.1161/JAHA.116.004007
Ye N, Jardine MJ, Oshima M, Hockham C, Heerspink HJ, Agarwal R, *et al.* Blood pressure effects of canagliflozin and clinical outcomes in type 2 diabetes and chronic kidney disease: insights from the CREDENCE trial. *Circulation* 2021;**143**:1735–1749. https:// doi.org/10.1161/CIRCULATIONAHA.120.048740
Kario K, Okada K, Kato M, Nishizawa M, Yoshida T, Asano T, *et al.* 24-hour blood pressure-lowering effect of an SGLT-2 inhibitor in patients with diabetes and uncontrolled nocturnal hypertension: results from the randomized, placebo-controlled SACRA study. *Circulation* 2019;**139**:2089–2097. https://doi.org/10.1161/CIRCULATIONAHA.118.037076

Pharmacotherapy with glucose lowering agents

- GLP-1 therapy may be indicated in the future
- Trials testing GLP-1 RAs have shown a BP decrease with these drugs, partly due to weight loss. A sustained decrease in BP was observed with semaglutide therapy (SBP dose dependent: −1.3 to −2.6 mmHg)
- Similar effects were seen in other studies of GLP-1 Ras and derived from meta-analysis

Wang B, Zhong J, Lin H, Zhao Z, Yan Z, He H, *et al.* Blood pressure-lowering effects of GLP-1 receptor agonists exenatide and liraglutide: a meta-analysis of clinical trials. *Diabetes Obes Metab* 2013;**15**:737–749. https://doi.org/10.1111/dom.12085
Liakos CI, Papadopoulos DP, Sanidas EA, Markou MI, Hatziagelaki EE, Grassos CA, *et al.* Blood pressure-lowering effect of newer antihyperglycemic agents (SGLT-2 inhibitors, GLP-1 receptor agonists, and DPP-4 inhibitors). *Am J Cardiovasc Drugs* 2021;**21**: 123–137. https://doi.org/10.1007/s40256-020-00423-z

NICE guidance for BP with diabetes

Repeat blood pressure measurements within:

- 1 month if BP >150/90 mmHg
- 2 months if BP >140/80 mmHg
- 2 months if BP >130/80 mmHg + kidney, eye or cerebrovascular damage

Provide lifestyle advice (diet and exercise) at the same time

BP targets or BP Limits?

a) T1	a)-135/85
b) T2	b)-140/80
c) Pregnancy with DM	c)-140/80
d) T1 + Micro albuminuria (>70mg/mmol)	d)-130/80
e) T2 + Kidney, eye or cerebrovascular disease	e)130/80

Lifestyle Interventions for Hypertension

Physical Activity	Weight Loss	Sleep Apnoea
30-45 mins brisk walk/day can improve BP Regular exercise may need a reduction in BP meds if well controlled Beta blockers may reduce exercise capacity Diuretics may increase dehydration	1kg weight loss reduced BP by approximately 1mmHg	Treatment of sleep apnoea can decrease blood pressure

ColbergSR Sigal RJ Yardley JE et al. Physical activity/exercise and diabetes: a position statement of the American Diabetes Association *Diabetes Care* 2016 ;39 2065- 2079

SemlitschT, JeitlerK, BergholdA, et al. Long-term effects of weight-reducing diets in people with hypertension*Cochrane Database Syst Rev* 2016 Mar 3:CD008274

ShawJE, PunjabiNM, NaughtonMT, et al. The effect of treatment of obstructive sleep apnea on glycemic control in type 2 diabetes *Am J Respir Crit Care Med* 2016;194:486- 492

Association of systolic and diastolic blood pressure and all cause mortality in people with newly diagnosed type 2 diabetes: retrospective cohort study

In people with cardiovascular disease;

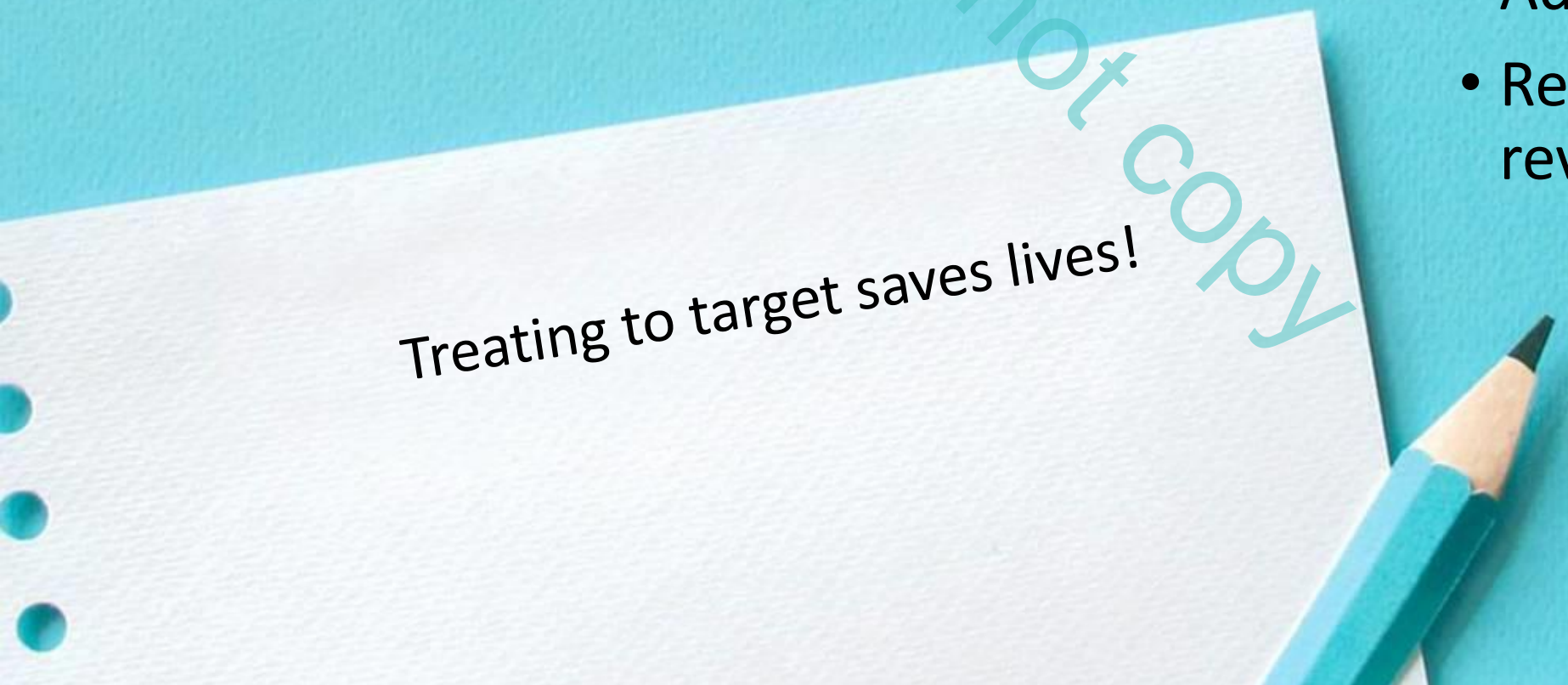
- Tight control of 130/80 **was not associated** with improved survival

- **Low blood pressure** (110/70) was also associated with an **increased risk of all-cause mortality**

Vamos et al BMJ. 2012; 345: e5567.

Top Tips

- Equipment (cuffs and calibration)
- Trained staff following guidelines
- HBPM and ABPM
- Adherence…
- Regular meds review



Thank you for listening

Remember treatments don't work for the patients that don't receive them.

Remember treatments don't work for the patients that don't receive them.